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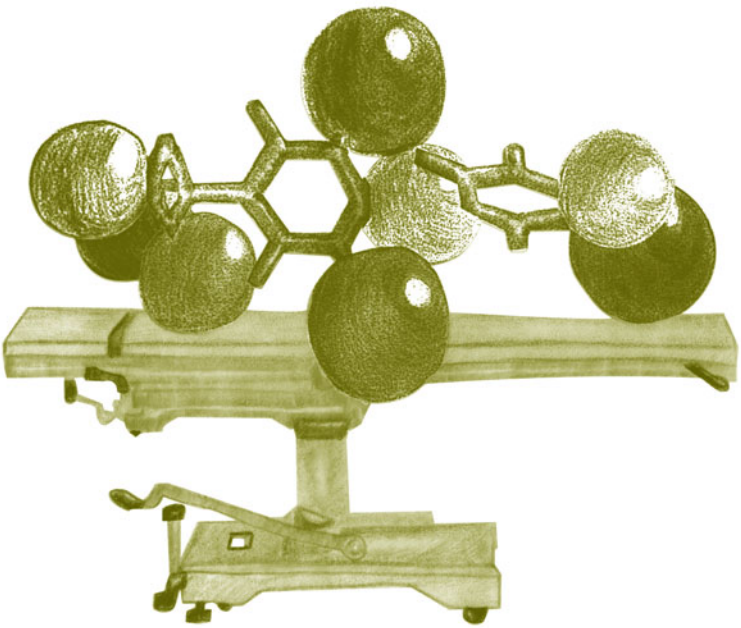
Endocrine Surgery



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v a d e m e c u m

Endocrine Surgery

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Dedication

This book is dedicated to our wives, Lori and Lisa, who have provided the support and encouragement that enabled us to complete this book

and

to our patients who have stimulated our interest in endocrine surgery.

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Preface

Endocrine surgery deals with glands that produce hormones. Understanding the function of these glands and the actions of their hormones has had an impact on all areas of medicine. This handbook is a compact and comprehensive review of the current knowledge of the pathophysiology of surgical disorders of the thyroid, parathyroid and adrenal and endocrine pancreas. The book is intended as a readily available and easy to use reference for those interested in endocrine surgery. It contains practical information about the diagnosis, preoperative, operative, and postoperative management of endocrine surgical disease. We believe it will be a useful tool for students, residents, general surgeons, primary care physicians and endocrinologists who need a concise single source to assist in their understanding of these topics. Hopefully it will help them in providing timely and up to date care of their patients.

CHAPTER 1

Embryology, Anatomy and Physiology of Thyroid

Jacqueline L. Harrison, Edgar D. Staren and Richard A. Prinz

The thyroid gland produces thyroid hormone, which is necessary for normal metabolism, growth, and organ function. Its widespread effects become obvious when derangements of thyroid function occur. Both excess and deficits of thyroid hormone will affect virtually every organ system.

Embryology

The thyroid is the first endocrine gland to develop in the embryo, and starts to form at 24 days. It begins as an endodermal thickening in the midline of the primitive pharynx and grows to extend inferiorly, forming the thyroid diverticulum. As the embryo lengthens and the tongue bud grows, the thyroid descends inferiorly, passing anterior to the hyoid bone and larynx. The thyroglossal duct continues to connect the thyroid to its origin in the tongue until it reaches its destination in the neck. At this point the duct degenerates; this is usually complete by the seventh week, but remnants may persist as thyroglossal duct cysts. These may be located anywhere in the midline along the thyroid's path of descent from the base of the tongue to the mediastinum. Heterotopic thyroid tissue may also be located anywhere along this path. In fact, a pyramidal lobe of the thyroid may occur in 30% of the population and represents a remnant of the inferior end of the thyroglossal duct (see Fig. 1.1A-C).

Histologically, the thyroid diverticulum is hollow at first and then becomes solid. It divides to form the two lobes. The thyroid begins as a solid sheet of endodermal cells. These are then broken up into cords of cells by the ingrowth of surrounding mesenchyme which provides its vascular supply. These cords then divide into smaller cell clusters which form single layers around a lumen. By week 11, colloid and thyroxine are demonstrable in the lumina of these follicles.

Anatomy

The normal adult thyroid gland weighs between 15-20 grams. Lying anterior to the trachea, it is composed of two lateral lobes joined by a bridge of tissue called the isthmus. The superior aspects of the lateral lobes overlie the inferior portion of the thyroid cartilage. The isthmus is located anterior and inferior to the cricoid cartilage and covers the second, third, and fourth tracheal rings. If a pyramidal lobe is present, it remains as a midline finger of tissue extending upward from the isthmus. A thin capsule invests the gland. Posteriorly this capsule blends with the pretracheal fascia.

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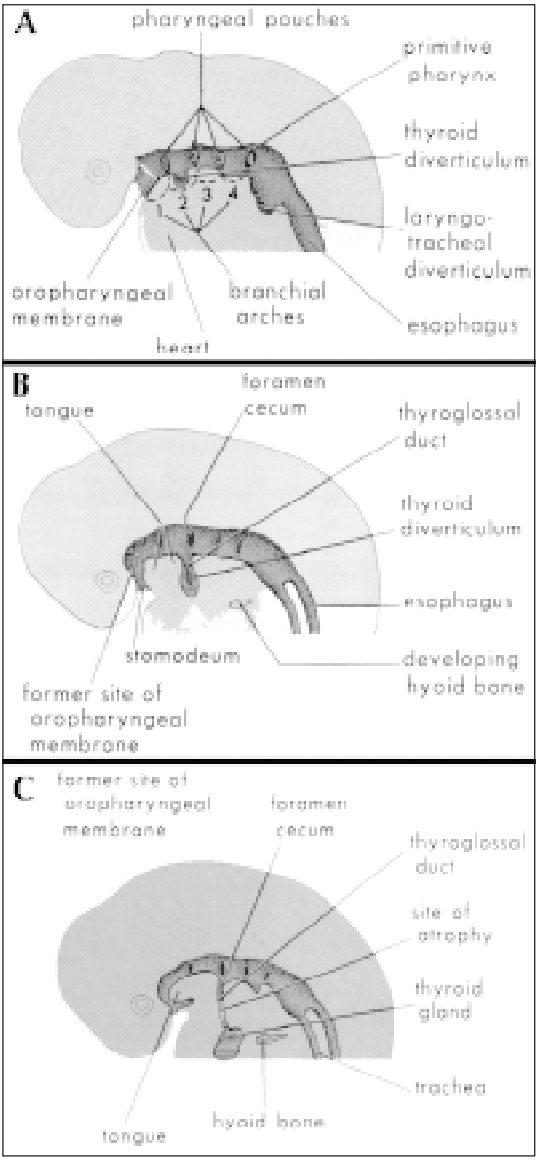

Fig. 1.1. Thyroid embryology. A, B, and C are sagittal views of the head and neck of an embryo at 4, 5, and 6 weeks of development. Note the thyroglossal duct connecting the gland to its origin at the foramen cecum. Reprinted with permission from Moore KL. The developing human clinically oriented embryology. Philadelphia: W.B. Saunders Company, 1988; 185.

This fascia firmly binds the thyroid to the trachea and larynx. As a result the thyroid moves with swallowing, an important clinical point in the evaluation of neck masses. The strap muscles lie superficial to the thyroid. These four paired muscles (sternohyoid, sternothyroid, omohyoid, and thyrohyoid) aid in swallowing even though their function is not essential for this activity. The thyrohyoid muscle is innervated by fibers of cervical nerve 1 (C1) that accompany the hypoglossal nerve. The other strap muscles are supplied by the ansa cervicalis (branches of C2 and C3). The sternothyroid muscle inserts onto the thyroid cartilage. It is this muscular insertion that limits upward extension of the gland if it enlarges. Inferiorly, there is no such anatomic limitation allowing the thyroid to extend into the thorax if it grows larger. The platysma lies anterior to the strap muscles. It is located deep to the superficial fat and skin and its origin and insertion are in the subcutaneous tissue. The fibers of the platysma run obliquely from the clavicle toward the mandible. There is a gap between the two halves of the platysma, leaving the midline uncovered by this muscle except at its uppermost portion below the chin.

As their name implies, the parathyroid glands are in close proximity to the thyroid. The four parathyroid glands are variable in position, but most commonly the superior glands lie adjacent or posterior to the superior portions of the lateral lobes, above the inferior thyroid arteries. The inferior pair of glands are more variable in position, but most often are in close association with the posterior surface of the lower poles, near the entrance of the inferior thyroid artery into the thyroid gland.

The external branch of the superior laryngeal nerve travels with the superior thyroid artery and enters the cricothyroid muscle above the branching of this artery. The external branches of the superior laryngeal nerves innervate the cricothyroid muscle. As such, injury to this nerve may result in a change in voice quality, but its dysfunction may not be very noticeable until the voice is stressed, as in singing or shouting. The recurrent laryngeal nerves innervate all intrinsic laryngeal muscles with the exception of the cricothyroid muscle. Injury to the recurrent laryngeal nerve results in hoarseness due to paralysis of the ipsilateral vocal cord. If both recurrent laryngeal nerves are injured, the patient's vocal cords will both be in a midline position and unable to be abducted. This type of injury often presents with stridor on extubation and necessitates a tracheostomy to provide an airway. Delayed presentation is possible because the splinting effect of the endotracheal tube on a denervated larynx can keep the vocal cords in an abducted position until respiratory demand is increased. The recurrent laryngeal nerves are closely related to the inferior thyroid arteries near the inferior poles of the gland. They usually cross posterior to these arteries before running in the tracheoesophageal grooves, but quite frequently can run anterior to the branches of the inferior thyroid artery.

Arterial Supply

The arterial supply of the thyroid is principally from the superior and inferior thyroid arteries. The superior thyroid arteries are paired vessels that supply the upper poles and anterior surface of the lateral lobes. They are the first branches of the external carotid arteries and pass inferiorly and medially to enter the upper poles. The inferior thyroid arteries arise from the thyrocervical trunks which come off of

the subclavian arteries. They run along the medial border of the scalenus anterior. They then course medially to the lateral lobes and dive posteriorly to the posterior surfaces of the lower poles to supply the lower poles and the posterior surface of the gland. They also usually supply the parathyroid glands.

In less than ten percent of the population, an unpaired thyroidea ima (lowest thyroid) artery arises from the brachiocephalic artery or aortic arch to run along the midline of the trachea to the isthmus (Fig. 1.2).

Venous Supply

The venous drainage of the gland is provided by three paired veins. The superior and middle thyroid veins drain into the ipsilateral internal jugular veins, and the inferior thyroid veins empty into a pretracheal plexus inferior to the isthmus. These veins are valveless and bleed generously when cut.

Lymphatic Drainage

The lymphatic drainage accompanies the arterial supply. The superior lymphatics drain to upper deep cervical lymph nodes, and the inferior lymphatics drain to lower deep cervical lymph nodes. In addition, central compartment nodes including pre-tracheal and tracheo-esophageal nodes receive drainage from the gland. Among these nodes is the delphian node that lies in the midline superior to the isthmus (Fig. 1.3).

Innervation

The nervous supply to the thyroid is limited, consisting of sympathetic fibers that mainly serve to regulate vascular tone. Whether these fibers have other input or function is unclear.

Histology

The thyroid consists of follicular cells that secrete thyroid hormone, and parafollicular cells that secrete calcitonin. The follicular cells are arranged in a single layered sphere, the center is filled with colloid consisting of a thyroglobulin matrix. The amount of colloid in the follicular lumen depends on the level of thyroid activity. It becomes depleted in states of high or excess thyroid activity and accumulates during periods of thyroid inactivity. The eosinophilic layer of follicular cells surrounding the lumen becomes flattened as gland function diminishes. Parafollicular cells are much fewer in number and are located between follicles. There are some occasional parafollicular cells scattered in the follicular wall. These cells are not evenly distributed throughout the gland, being concentrated along the middle and upper thirds of the lateral lobes posteriorly.

Physiology

Thyroid function is regulated by a negative feedback loop involving the hypothalamus, pituitary, and thyroid gland. Thyrotropin releasing hormone (TRH, or thyroliberin) is released from the hypothalamus into the portal circulation of the pituitary, where it stimulates the pituitary to release thyroid stimulating hormone (TSH, or thyrotropin). TSH in turn stimulates the synthesis and release of thyroxine

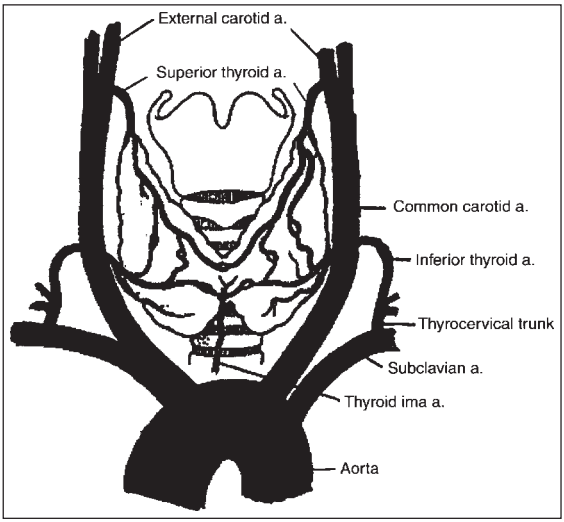

Fig. 1.2. Arterial supply of the thyroid. A thyroid ima artery is present in less than 10% of the population.

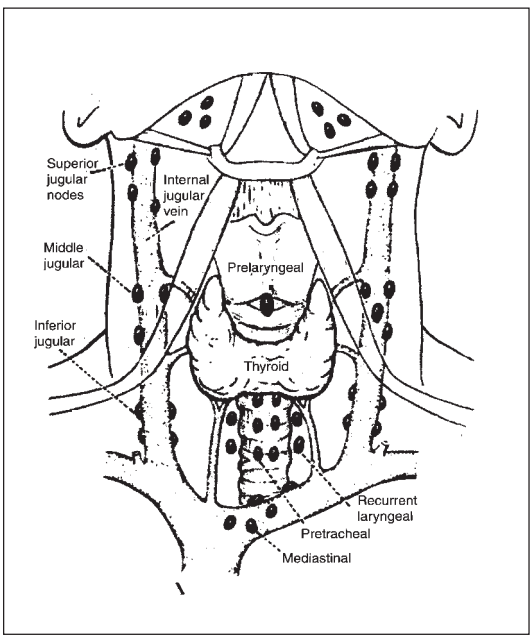

Fig.1.3. Lymphatic drainage of the thyroid.

(T_4) from the thyroid gland. Thyroxine inhibits the release of TRH from the hypothalamus and TSH from the pituitary, thus forming a negative feedback loop. Virtually all steps of thyroid hormone synthesis and release are stimulated by TSH, including the gland's iodine trapping mechanism. TSH binds to membrane receptors on follicular cells and stimulates production of cyclic adenosine monophosphate (cAMP), which leads to increased uptake of iodide (I^-) into the follicular cell. Iodide is actively transported into the follicular cell, against a 20- to 40-fold concentration gradient. This gradient is even higher in the presence of TSH and/or a low extracellular iodine concentration. This increase in active transport of iodide into the follicular cell in the face of low plasma iodide concentration is referred to as thyroid autonomy. Iodide then diffuses into the follicular lumen, where thyroperoxidase uses hydrogen peroxide to oxidize it to form I^-. Thyroperoxidase then catalyzes the binding of I^- to tyrosine residues in the thyroglobulin matrix to produce diiodotyrosine (DIT) or monoiodotyrosine (MIT).

Thyroglobulin is a polypeptide containing an average of 140 tyrosine residues. It is produced in the rough endoplasmic reticulum of the follicular cell and extruded into the follicular lumen. Iodination of tyrosine increases with increasing extracellular concentration of iodine to a maximal rate. Above a certain extracellular iodine concentration (about 25 μg /dl), iodination of tyrosine is inhibited. This phenomenon, called the Wolff-Chaikoff effect, is the basis for acute treatment of hyperthyroidism with exogenous iodine. The thyroid adapts to this high iodine level and escapes this inhibition within several days, so that this treatment is only temporarily effective. A minimum of 75 μg of dietary iodine intake is required daily for adequate thyroid function. The average American ingests 500 μg per day primarily in drinking water, eggs, iodized salt, bread, milk, and seafood. It is absorbed as iodide ion (I^-) after being reduced from inorganic iodine (I°). The normal thyroid contains a reserve of about 8000 g of iodine, with about 1% of this pool turned over per day.

Thyroperoxidase catalyzes the coupling of DIT to DIT to form tetraiodothyronine (T_4 or thyroxine), or the coupling of MIT to DIT to form triiodothyronine (T_3). This coupling takes place in the follicular lumen. TSH stimulates resorption of thyroglobulin into the follicular cell by pinocytosis. This allows lysosomal proteases to split T_4 and T_3 as well as MIT and DIT residues from the thyroglobulin matrix. T_4 and T_3 are released into the circulation from the basal surface of the cell. The MIT and DIT residues released from thyroglobulin are deiodinated so that the iodine can be recycled. Normally, about 80 μg of T_4 and 6 μg of T_3 are made each day. About 70% of both T_4 and T_3 are bound to thyroid binding globulin (TBG), a glycoprotein produced by the liver. This bond is reversible, and each TBG molecule has the capacity to bind one iodothyronine molecule. Prealbumin (transthyretin) and albumin bind almost all of the remaining iodothyronines, leaving only 0.03% of T_4 and 0.30% of T_3 in their free state. Thyroxine has a much higher affinity for these proteins than does T_3, accounting for its longer half-life (7 days, versus 1 day for T_3). The concentration of TBG is influenced by hormones, drugs, and disease states. These states may alter the plasma concentration of total T_4 or T_3 (protein bound + free hormone), even though the concentration of the active forms, free T_4 or T_3, may be unaltered (see Table 1.1). This makes the measurement of total T_4 or

Table 1.1. Conditions affecting TBG concentration

Increase TBG	Decrease TBG
Inherited elevated TBG	Inherited absent or low TBG
Drugs: Oral estrogen	Nephrotic syndrome
Tamoxifen	Cirrhosis
5-Fluorouracil	Androgens
Heroin	Glucocorticoids
Methadone	Major illness
Clofibrate	Protein calorie malnutrition
Perphenazine	Protein losing enteropathy
Hormonal effects: Hyperestrogenic states (pregnancy, birth control pills)	
Viral Hepatitis	
Primary biliary cirrhosis	
Hepatocellular carcinoma	
Myeloma	
Acute intermittent porphyria	
Collagen diseases	

total T_3 unreliable as an indicator of thyroid function, since the total T_4 or total T_3 level may be altered secondary to changes in the level of the bound (inactive) hormone, while the level of free T_4 or free T_3 may be unchanged.

Most free T_4 is converted to T_3 in the peripheral tissues (liver and kidney) by type I 5'deiodinase. Type I 5'deiodinase is inactivated by propylthiouracil. Two other deiodinase enzymes have been isolated. Type II deiodinase is located in the pituitary, brain, and brown fat. It also converts T_4 to T_3. In the pituitary, this serves to inhibit TSH release. Type III 5'deiodinase converts T_4 and T_3 to reverse T_3, an inactive derivative. T_3 is the biologically active form of thyroid hormone. Whether T_4 has any biological effect or is simply a prohormone is not clear.

Both T_4 and T_3 are transported across cellular membranes by a carrier mediated, adenosine triphosphate (ATP)-dependent process. The two iodothyronines do not compete with each other for cellular uptake. Once inside the cell, T_3 is transported into the nucleus where it binds to high affinity thyroid hormone nuclear receptors. The binding of T_3 to these receptors changes the rate of transcription of mRNA from genes containing these receptor binding DNA sequences.

Thyroid Hormone Effects

Virtually no organ or tissue escapes the effects of thyroid hormone. Sufficient amounts are necessary for brain development, normal growth and metabolism. Thyroid hormone affects the rate of synthesis and degradation of many hormones and enzymes.

Thyroid hormone raises the basal metabolic rate and stimulates heat production. This may occur by increasing mitochondrial metabolism, by enhancing Na^+/K^+ ATPase activity, or by increasing futile cycles of carbohydrate or lipid metabolism. Oxygen consumption increases which necessitates an increased ADP/ATP exchange

across the mitochondrial membrane. How this increase is brought about by T_3 is not clear.

Thyroid hormone affects protein, fat, and carbohydrate metabolism through several mechanisms. Protein synthesis is most likely increased by moderate doses of T_3 in humans, as indicated by studies of radiolabeled proteins in hypothyroid patients. In animals, this effect is biphasic, and excess thyroid hormone inhibits protein synthesis. In children, normal amounts of thyroid hormone are necessary for normal growth, with both insufficient and excessive amounts of thyroid hormone leading to growth retardation. Normal amounts of thyroid hormone are necessary for the production and release of growth hormone.

T_3 has multiple effects on carbohydrate metabolism. It increases intestinal absorption of glucose and increases muscle and adipose tissue uptake of glucose. T_3 enhances the glycogenolytic and hyperglycemic effects of adrenaline, and enhances insulin's effects on glycogen production and glucose utilization. However, T_3 speeds up the degradation of insulin. This becomes clinically important in those who cannot produce their own endogenous insulin (type I diabetics). Hyperthyroidism leads to a worsening of blood glucose control in type 1 diabetics and conversely, hypothyroidism leads to an improvement of their glucose regulation.

Lipid synthesis, mobilization, and degradation are all stimulated by thyroid hormone, with degradation being enhanced more than synthesis. This results in a decrease in lipid stores and usually a decrease in plasma lipid concentrations in states of thyroid hormone excess. Clinically, this usually results in a lowering of plasma cholesterol and triglyceride levels.

Vitamin metabolism is also affected by thyroid hormone, with requirements for water-soluble vitamins (vitamin C, vitamin B_{12}, thiamine, riboflavin) increasing in states of thyroid hormone excess. Thyroid hormone is necessary for the synthesis of retinol from vitamin A. Vitamin A, in turn, is synthesized from carotene, another thyroid hormone dependent reaction. This effect is manifested in hypothyroid patients when serum carotene is increased, giving the myxedematous patient a yellowish hue.

Calcitonin

The parafollicular cells (C cells) of the thyroid secrete calcitonin, a polypeptide hormone that inhibits bone resorption and leads to hypocalcemia in lower animals. In humans, physiologic concentrations of calcitonin have never been proven to have an important influence on calcium homeostasis. Exogenous calcitonin is used in the treatment of Paget's disease and hypercalcemia secondary to vitamin D toxicity or hyperparathyroidism. It exerts its effect on the serum calcium level by inhibiting bone resorption. Salmon calcitonin is the most commonly used preparation and is more potent than human calcitonin.

Parafollicular cells are neural crest cells derived from the ultimobranchial bodies of the developing thyroid. As cells of neuroendocrine origin, they may give rise to a neuroendocrine malignancy called medullary thyroid carcinoma. These rare tumors comprise 5% or less of thyroid cancers and are familial in 20% of patients. Medullary thyroid cancer is a component of the Multiple Endocrine Neoplasia Type IIa

and IIb syndromes. Plasma calcitonin can serve as a tumor marker to diagnose and monitor the activity of these tumors.

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CHAPTER 2

Solitary Thyroid Nodule

Michael S. Sabel, Edgar D. Staren

The primary goal in the evaluation of the solitary thyroid nodule is to distinguish those nodules that require surgical excision from those that can be safely observed. Many thyroid diseases can present clinically as a solitary thyroid nodule, such as colloid cysts, adenomas, Graves' disease, thyroiditis, infections, and malignancies (Table 2.1). Given the large numbers of patients with palpable thyroid nodules, i.e., 5-7% of the North American population, it is important for this evaluation to be cost efficient, while avoiding inadvertently missing a thyroid cancer. As many as 10 million people in the United States may be diagnosed with a palpable thyroid nodule; however, only about 16,000 new thyroid cancers are diagnosed per year. While typically minimally aggressive, thyroid cancer can be lethal. Therefore, the most important distinction in working up a solitary thyroid nodule is whether or not the lesion represents a malignancy.

Clinical Considerations

History

The evaluation of the solitary thyroid nodule represents a common and important clinical problem, which has changed considerably over the past 20 years. The first step is a detailed history regarding the mass, the patient's medical history and family history. Several aspects of the history and physical can increase the suspicion of malignancy (Table 2.2). The age of the patient is one strong factor. Most nodules appear between the ages of 30 and 50 years, and most are benign. On the other hand, thyroid nodules are much less common at a young age. Any nodule developing prior to puberty should be viewed with suspicion. It has been estimated that more than half of all thyroid nodules in children prove to be malignant.[1] The incidence of malignancy is also higher in nodules that develop after the age of 65. Benign nodules are more common in both males and females; however, thyroid nodules are five times more frequent in females. The proportion of malignant nodules in males is twice that of females.

One of the most important aspects of the past medical history, is whether the patient has received head or neck irradiation in childhood. Between 1940 and 1960, radiation was used as a treatment for thymic enlargement, recurrent tonsillitis, adenoiditis, otitis media, hemangiomas, ringworm, acne and dermatologic conditions. This therapy has now clearly been associated with an increased incidence of both benign and malignant nodules. If a patient with a solitary nodule has a history of radiation, the prevalence of cancer is 30-50%.[2] Other factors to examine in the

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Table 2.1. Pathology of thyroid nodules

Benign
Adenomatous nodules or colloid nodules
Follicular adenoma
Hurthle cell adenoma
Thyroid cysts
Inflammatory lesions (thyroiditis)
Developmental abnormalities (cystic hygroma, dermoid, teratoma)

Malignant
Papillary carcinoma
Follicular carcinoma
Hurthle cell carcinoma
Mixed papillary/follicular carcinoma
Medullary carcinoma
Anaplastic carcinoma
Lymphoma
Metastatic disease

Table 2.2. Important clinical factors in the diagnosis of thyroid cancer

History
Family history
Gender
Age < 20 or > 60
History of head and neck irradiation
Rapidity of growth
Associated symptoms (pain, dysphagia, dysphonia, dyspnea)
Growth on thyroid hormone suppression

Physical
Solitary vs. multiple nodules
An extremely firm nodule
Fixation to adjacent structures
Diameter 4 cm
Lymphadenopathy

past medical history include symptoms of pheochromocytoma or hyperparathyroidism, long-standing constipation and/or diarrhea, hypertension and/or episodes of nervousness. These should alert the clinician to the possibility of thyroid carcinoma in association with a familial MEN syndrome.

In questioning the patient about the nodule, the time course for its development can be an important piece of information. A nodule that has been stable in size for years is almost always benign. Very rapid development, such as over hours or days, would suggest a thyroid cyst or hemorrhage. Thyroid malignancies usually develop over weeks or months. There are also specific symptoms that would be worrisome of malignancy. Invasion of the thyroid capsule, entrapment of the recurrent laryngeal nerve or spread into adjacent tissues can lead to local pain in the neck or radiating to

the jaw and ear. Dysphagia, dysphonia, dyspnea, hoarseness or hemoptysis may all reflect esophageal or tracheal involvement by a thyroid cancer. These symptoms can also occur with benign causes of thyroid enlargement, such as hemorrhagic degeneration or subacute thyroiditis. Other symptoms that may serve as a clue regard hyperthyroidism (weight loss, nervousness, heat intolerance) or hypothyroidism (weight gain, depression, fatigue, cold intolerance). Nodules associated with hyperthyroidism are usually benign functioning adenomas whereas a nodule in a patient with hypothyroidism is often caused by autoimmune thyroiditis.

Physical

Although it may only give general clues as to the benign or malignant nature of the nodule, a thorough physical examination should be performed. A nodule that is fixed to surrounding structures such as the trachea or strap muscles is most likely malignant. Fixation of the thyroid can also occur with severe chronic thyroiditis, however. Extremely hard thyroid nodules may be malignant, but may also be due to calcifications in benign adenomas. Paralysis of one of the vocal cords strongly suggests an invasive cancer, but again, benign conditions such as Hashimoto's thyroiditis or a multinodular goiter can rarely cause abnormalities of vocal cord function. The most significant physical findings suggestive of malignancy are the characteristically unilateral, firm, mobile, nontender, discrete lymph nodes found in metastatic thyroid cancer. When present, lymphadenopathy is usually located in the anterior cervical chain of the ipsilateral side of the neck and occasionally the posterior cervical triangle.

Laboratory Examination

Most blood tests are usually of little value in the evaluation of a patient with an asymptomatic solitary thyroid nodule. An exception may be thyroid function tests. Blood studies for serum thyroxine (T4), triiodothyronine (T3) resin uptake and thyroid stimulating hormone (TSH) may be obtained in the proper clinical setting to establish hyperthyroidism or hypothyroidism. Abnormalities in thyroid gland function are most often associated with a benign nodule, although most benign nodules have normal thyroid function tests. Malignant thyroid nodules generally have normal thyroid function tests.

Fine Needle Aspiration Biopsy

Fine needle aspiration biopsy (FNAB) has become the diagnostic procedure of choice for solitary thyroid nodules and should be performed before ordering any imaging studies. It is a simple outpatient procedure and complications such as hematoma or infections are rare. It has been shown repeatedly to be a better predictor of malignancy than other preoperative tests and has substantially decreased the number of patients requiring surgery for benign disease.[3]

Cytodiagnostic Categories

It is crucial for the clinician to fully understand the cytopathology report after a fine-needle biopsy. Cytopathology terms may be confusing for the inexperienced individual. The results of FNAB can be divided into four major diagnostic categories:

benign, malignant, indeterminate and nondiagnostic. The results of the FNAB will then guide the management of the thyroid nodule (Fig. 2.1).

Benign

Several benign causes of thyroid nodules can be accurately and reliably diagnosed by cytology. Colloid nodules show flat sheets of follicular epithelium in a honeycomb arrangement against a background of colloid. A report of blood, degenerative debris and histiocytes that are often hemosiderin laden is consistent with degenerating lesions or cysts. Other benign nodules that may be diagnosed on FNAB include some adenomas and different forms of thyroiditis, including Hashimoto's.

Malignant

Fine-needle aspiration biopsy is a very sensitive and specific test for thyroid malignancies. The cytopathologist can usually make a diagnosis of cancer if the nodule is papillary carcinoma, medullary carcinoma, anaplastic carcinoma or a metastatic carcinoma. Thyroid lymphoma can also be diagnosed by FNAB if multiple cells of the lymphoid series with various degrees of maturation are seen. Follicular and Hurthle cell cancers are more difficult to diagnose on FNA, and will more likely be interpreted as indeterminate.

Indeterminate

An aspirate containing small sheets or groups of follicular cells will be labeled as indeterminate, follicular neoplasm, atypical or cellular. This is because it is extremely difficult for the cytopathologist to differentiate between a benign follicular adenoma and a follicular carcinoma. The same situation will arise with a Hurthle cell neoplasm. Occasionally, the cytopathologist will be able to diagnose a cancer by the marked cellularity of the aspirate, overcrowding of nuclei and follicles and the nuclear pleomorphism, although this situation is rare.

Nondiagnostic

An inadequate aspirate will contain too few cells for the cytopathologist to make a diagnosis. In this situation the FNAB should be repeated. Doing another biopsy using a larger-bore needle is not recommended since the accuracy rate is similar to that of fine-needle biopsy.[4] What may be of significant use to the clinician in this situation is the use of ultrasound-guided FNA.

Other Imaging Studies

Ultrasound-Guided Biopsy

Over the past decade, ultrasound has become an extremely useful tool for the surgeon. Ultrasound of the thyroid has been used preoperatively to evaluate thyroid nodules, however, alone, the sensitivity, specificity and positive predictive value for ultrasound is quite low. Despite this, its use in guiding biopsies can be extremely helpful. By using ultrasound in conjunction with FNAB, more information can be obtained about the entire gland. More importantly, ultrasound-guided FNAB can increase the percentage of diagnostic biopsies.[5] Smaller lesions that are more difficult

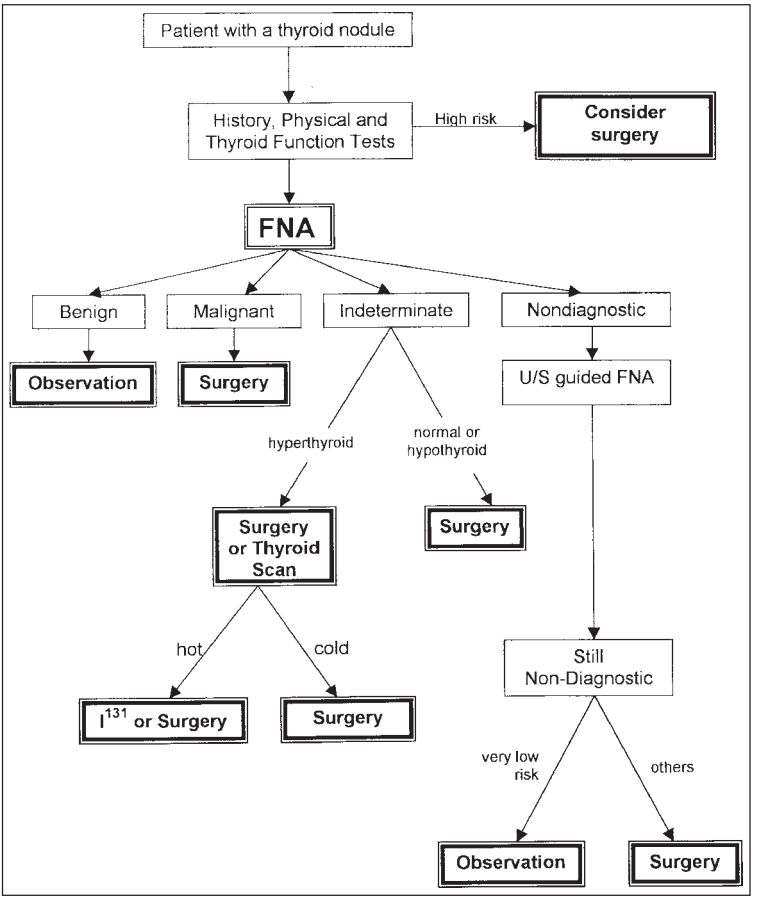

Fig. 2.1. Diagnostic approach to a solitary thyroid nodule.

to biopsy by palpation, are more accessible to ultrasound guided biopsies. The clinician can be assured that the tip of the needle is within the lesion during aspiration. Likewise, nondiagnostic biopsies often result from the tip of the needle sitting in a cystic or degenerative portion of the nodule. Ultrasound can guide the needle into an area of solid tissue. Ultrasound guidance should be considered whenever presented with a patient whose thyroid nodule is difficult to palpate on physical exam, or in whom the initial FNAB was nondiagnostic.

Scintiscan

Until recently, radionuclide scanning had routinely been the first test used in the evaluation of the thyroid nodule. Radioisotopes of iodine or technetium are used

with the theory that malignant thyroid tissue neither traps nor incorporates iodine. They should appear nonfunctioning, or cold, on uptake scan. Normally functioning nodules are warm and hyperfunctioning nodules appear as hot on the scan. The incidence of malignancy is higher in cold nodules as compared with warm or hot nodules. Thyroid scans have generally been replaced as a first-line test by FNAB.

Recognizing that thyroid scanning has fallen out of favor as a first-line test, many still recommend its use as a secondary examination. Thyroid scan has been suggested in those situations in which the FNAB is read as "suspicious" or "follicular neoplasm". In patients with indeterminate cytology, hyperfunctioning or hot nodules are almost always benign; no such differentiation can be made for cold or warm nodules. Unfortunately only a small number of thyroid nodules in this situation will be hot. Because the overwhelming majority of the scans obtained in this situation will be cold, this additional and expensive test will seldom affect the decision to recommend thyroidectomy. As such, surgical excision will still be needed to make a definitive diagnosis. One of the few situations where a radionuclide scan may be useful is when the FNAB is consistent with follicular neoplasm and the patient has thyroid function tests consistent with hyperthyroidism, especially as evidenced by a low or low normal TSH. The presence of the low TSH may increase the yield of hot nodules on a thyroid scan.

Algorithm for Management

Benign Lesions

If the cytologic diagnosis indicates a benign nodule, there are three options for the clinician. These include surgery, observation and hormone suppression. If the nodule is causing symptoms, or is aesthetically displeasing to the patient, surgery may be considered. Thyroid surgery for benign disease is safe with complications being quite rare. Surgery should also be considered in those patients who are at increased risk for thyroid cancer despite a benign FNA.

If the patient does not require surgery, the nodule may either be observed or suppressed with Levothyroxine. The goal of thyroid hormone administration is to eliminate TSH stimulation by total exogenous replacement of the body's need for thyroid hormone. This should either reduce the size of the nodule or prevent its further growth. While this was a more commonly used approach for diagnosis and treatment in the past, it is being used less often. This is probably due in part to the increased diagnostic potential of FNAB, as well as several studies that have failed to demonstrate the efficacy of thyroxine therapy for solitary nodules.[6] Because thyrotoxicosis is a risk factor for osteoporosis, there has also been some concern that the use of thyroxine, especially in postmenopausal women, may lead to osteoporosis.[7] In a patient on thyroxine therapy, nodule growth during this period is suspicious for malignancy, and should be a strong indication for surgery.

Malignant Lesions

Well-differentiated cancers, such as papillary, follicular and mixed papillary-follicular carcinomas are the most common malignancies of the thyroid. In those situations where the diagnosis has been made on FNAB, the patients require no further

work-up prior to surgery. Either an ipsilateral lobectomy with isthmusectomy or a near-total or total thyroidectomy may treat unilobar disease. The extent of thyroid resection is controversial. Supporters of total thyroidectomy argue that lobectomy leads to increased local recurrence, although survival rates are approximately equal. Supporters of conservative surgery feel that the equal survival rates do not justify the increased morbidity of a total thyroidectomy. In the hands of an experienced surgeon however, there is very little increased morbidity between the two approaches. Factors that may push one towards performing a total thyroidectomy include a history of head and neck radiation, increased size of the nodule, palpable lymphadenopathy or plans to use ^{131}I postoperatively in order to ablate any residual thyroid carcinoma cells. In patients with well-differentiated carcinoma, lymph node dissections are only necessary when there is palpable neck disease.

Medullary carcinomas develop from the calcitonin-producing C-cells and make up about 10% of thyroid cancers. Roughly one-quarter are associated with multiple endocrine neoplasia (MEN) syndromes or are familial, non-MEN. Prior to surgery, these patients should have assessment of catecholamine secretion to rule out a pheochromocytoma. In addition, baseline calcitonin levels should be obtained preoperatively. Medullary carcinoma must be treated with a total thyroidectomy since it may be unknown if the patient is part of a familial syndrome and therefore would be expected to have multicentric disease. A central lymph node dissection is suitable for occult cancers detected after family screening, whereas palpable lesions require an ipsilateral modified radical neck dissection.

Anaplastic carcinomas are rare but very aggressive neoplasms. They grow rapidly, and can present with local symptoms including hoarseness and airway obstruction. The prognosis for anaplastic carcinoma is poor; two-thirds of patients die within 1 year of diagnosis. In the rare case that all gross disease can be excised, resection may be appropriate. Chemotherapy and radiotherapy may be used for palliative treatment.

Indeterminate Lesions

When the FNAB demonstrates a cytologic appearance of follicular or Hurthle cell neoplasm, surgery is indicated in order to make the diagnosis. An exception to this rule may be when the nodule is hyperfunctioning, as these are predictably benign. As previously mentioned, when the situation arises of an FNAB consistent with follicular neoplasm and thyroid function tests are consistent with hyperthyroidism, a thyroid scintiscan may be an appropriate test. If the nodule is hot, it may be observed, treated with ^{131}I or surgically excised. If the plan is to treat a hyperfunctioning nodule with surgery, the thyroid scan is not necessary and the patient may proceed directly to surgical excision.

Nondiagnostic Biopsies

The situation may also arise that the results of the FNAB are repeatedly nondiagnostic, despite the use of ultrasound guidance to assure an accurate biopsy of the nodule. Nondiagnostic biopsies occur more often with cystic nodules because of the small amount of cellular material. The rate of malignancy in these nodules is extremely low and observation may be appropriate. However, surgery is the only

method for providing a definitive diagnosis and should be performed after a repeat nondiagnostic FNAB.

If surgery is to be performed without a definite diagnosis, then a lobectomy should be performed. The decision to do a more extensive resection should be based on the patient's history or characteristics of the nodule. Frozen section analysis of the nodule may be of assistance if the FNAB is atypical and depending on the skill of the pathologist. Otherwise, given the low incidence of malignancy in this situation, the routine use of frozen section is excessively costly and false-positive results could lead to unnecessary thyroidectomies.[8]

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CHAPTER 3

Substernal Goiter

Subhash Patel

Introduction

The term 'goiter' is often used to describe enlargement of the thyroid gland. It is derived from the Latin word 'tumidum gutter' meaning the swollen throat. Extension of the goiter beyond the confines of the neck into the thoracic cavity with more than 50% of the mass inferior to the thoracic inlet is called substernal goiter or the intrathoracic goiter. Since the earliest description by Haller in 1749, many distinguished surgeons like Billroth, Kocher, Halsted, Mikulicz, Mayo, Criles, and Lahey have contributed important advances in the treatment of the goiter.[1] Of all the thyroid goiters, the substernal location poses the most unique challenges to the surgeon. Most of these goiters are slow growing and often do not cause symptoms for a considerable period of time. When the mass reaches a critical size, it impinges upon the surrounding structures causing compression symptoms. Although the majority of these lesions are benign, significant numbers may be malignant and a few may exhibit thyrotoxicosis. Multi-nodular goiters in the substernal location are generally refractory to thyroxine therapy and surgery remains the main form of therapy. The extent of surgery is often a subject of controversy. Partial removal of the gland is often followed by recurrence of the lesion. Recently, radioactive iodine therapy is being considered as an alternative form of treatment for patients who have significant medical problems making surgery a prohibitive risk.

Incidence

About 5% of the world population has a goiter. But with the increasing use of iodination programs there has been a substantial decrease in the incidence of endemic goiters. Nevertheless, a large population in the U.S.and in endemic areas of the world continue to have thyroid goiters in the absence of iodine deficiency. Based on routine screnning chest x-rays the incidence of substernal goiter is reported to be about 0.2% in the U.S.[2] This is compared with the year 1921 when Pemberton reported an incidence of 13.6% among 4006 patients undergoing thyroidectomy at the Mayo Clinic.[3] In the recent world literature, the incidence of substernal goiter among patients undergoing thyroid surgery is reported to range from 5-19% (Table 3.1).[4-9] Thyroid goiter accounts for about 5% to 11% of all mediastinal masses.[3]

Anatomical Classification

Substernal goiters are either in the anterior or the posterior superior mediastinum. They are further classified as either primary or secondary goiters. Primary goiters account for less than 1% of all substernal goiters. They originate from ectopic

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Table 3.1. Incidence of the substernal goiter

Author	Country	Year	Thyroidectomies	Substernal goiter
Delbridge L. et al[4]	Australia	1996	10164	17.0%
Mattioli F. et al[5]	Italy	1995	3338	7.1%
Weissberg et al[6]	Israel	1995	222	19.8%
Shaha A et al[2]	USA	1989	370	19.0%
Thompson et al[7]	USA	1983	872	5.7%
Laws HL et al[8]	USA	1980	750	4.1%
DeAndrade MA.[9]	Brazil	1973	9100	15.0%

embryonal thyrocytes that have descended into the chest along with the arch of the aorta. Secondary goiters are cervical goiters that have migrated to the intrathoracic location. Negative mediastinal pressure and the fixation of muscle and soft tissue superiorly favors the downward extension of the goiter into the space of least resistance. Key differences between the primary and secondary goiter are listed in Table 3.2. Secondary goiters in the anterior mediastinum usually originate from the lower pole of the thyroid gland. The goiter descends along the anterolateral aspect of the trachea and anterior to the recurrent laryngeal nerve and the carotid vessel. Occasionally a goiter originating from the posterolateral aspect of the thyroid may descend into the posterior mediastinum pushing the esophagus to the opposite side. It causes forward displacement of the trachea associated with tilting of the larynx. In this case, the recurrent laryngeal nerve, inferior thyroid artery and the carotid vessel lies anterior to the goiter. In a review of 1300 substernal goiters, DeAndrade reported 128 in the posterior mediastinal location.[9]

Pathology and Pathogenesis

Most substernal goiters are benign in nature.[2,5,7,8] The incidence of malignancy varies from 6-16% (Table 3.3). In endemic areas, lack of iodine is the predominant stimulus for its growth. In some areas of the world specific goitrogens are found in the diet. Palm tree fruit in Brazil, seaweed in Japan, cassavas in Nigeria, and millet in Sudan are such examples of goitrogens. A defect in thyroxine synthesis stimulates secretion of thyroid stimulating hormone (TSH), which in turn accelerates the growth of the follicular cells. This mechanism forms the basis for iodine and suppressive thyroxine therapy in the management of endemic goiter.

Recently, understanding of the factors regulating the growth of thyrocytes have alluded to mechanisms other than TSH regulated proliferation of the cells. Studer et al concluded that follicular cells in the goiter grow by episodic proliferation. At any given time only a tiny fraction of the cells proliferate to develop cysts with cell growth occuring in bursts and waves.[10] This may explain why partial removal of the gland is often followed by recurrence of the goiter.

3

Table 3.2. Differences between primary and secondary substernal goiter

	Primary	Secondary
Origin	From ectopically located tissue in chest	Extension of normally located cervical thyroid gland into the chest
Blood supply	Intrathoracic aorta	Inferior thyroid artery
Connection with cervical thyroid gland	None	Yes- usually contiguous with the cervical gland or may be connected with a fibrous band
Cervical mass	None	80%-90% of patients will have associated cervical mass

Table 3.3. Incidence of malignancy in substernal goiter

Author	Year	Total number of patients with substernal goiter	% Malignant lesions
Delbridge L. et al[4]	1996	234	11.0%
Mattioli F et al [5]	1995	237	6.7%
Thompson NW et al [7]	1983	50	16.0%
McElvein RB et al[8]	1982	31	10.0%

Clinical Manifestation

In most reported series 20-35% of patients with substernal goiters are asymptomatic. Generally patients are in their fifth or the sixth decade of their life. The ratio of female to male is 3:1. Since substernal goiters are usually slow growing lesions, several years may pass before a patient experiences symptoms. Forty to fifty percent of patients report a lump in the neck. Other symptoms occur secondary to compression of intrathoracic structures. Compression of the airway may present as dyspnea, stridor or a sensation of choking. About 50% of patients have symptoms of airway compression.[4-7] Shaha et al reported that in 22% of their patients with airway compression, urgent intubation or a semi-urgent operative procedure was needed.[2] In some patients, dyspnea is experienced only when the head is turned toward one side or by lying down flat. Dysphagia is present in about 30-40% and is more common with posterior mediastinal goiters. Hoarseness of the voice has been reported in 13% of patients.[5] Unusual presentations include compression of the vascular system causing downhill esophageal varices leading to upper gastrointestinal bleeding, effort thrombosis of the axillary vein, transient ischemic attacks and cerebral edema.

On physical examination, a palpable lump in the neck can be demonstrated in about 80-90% of patients.[5] When an inferior border of the cervical goiter becomes difficult to define, one should strongly suspect a possibility of substernal goiter.

Other signs that may be present are dilated neck veins and deviation of the trachea. Raising the arms or hyperextension of the neck may result in dilatation of cervical veins and flushing of the face (Pemberton's sign). Patients may even develop respiratory difficulty or stridor with this maneuver. Some of the common signs and symptoms of substernal goiter are listed in Table 3.4.

Diagnosis

The most cost effective test for diagnosis of substernal goiter is a plain chest roentgenogram (CXR). The findings on CXR include deviation of the trachea, which begins high in the neck with an angulation of the larynx. The trachea shows a variable degree of compression. Soft tissue density or a mass effect can be seen with a nodular outline of the tumor. Occasionally calcifications can be noted within the goiter and reflection of the mediastinal pleura can be demonstrated below the trachea (Figs. 3.1 and 3.2).

Both computed tomography (CT) scan and magnetic resonance imaging (MRI) can provide more precise information about the relationship between the various intrathoracic organs and the goiter (Fig. 3.3). This information guides the surgeon in planning the operative approach for ectopic goiters and goiters in the posterior mediastinum. Use of iodinated urographic contrast material during CT scanning may help to differentiate thyroid tissue from other mediastinal masses. However, because iodine uptake in the thyroid is variable, one should expect variable enhancement of the thyroid tissue after a bolus injection of contrast.

Ultrasonography has only limited use in the chest secondary to image interference from the rib cage and sternum and air shadowing. A radionuclide thyroid scan may be useful in differentiating goiter from other mediastinal masses. Nevertheless, a solitary, large cyst may appear as a cold nodule on thyroid scan and thus provide a false negative result. Fine needle aspiration biopsy (FNA) is quite useful for the diagnosis of cervical goiter, but is not indicated for substernal goiter. Risk of bleeding resulting in acute airway compression is the reason cited by most surgeons. Routine indirect laryngoscopy is also not necessary, although it is indicated for patients with a history of voice changes. The presence of unilateral vocal cord paralysis is suggestive of thryoid cancer.

Treatment

Pharmacotherapy

Since the earliest description of goiters physicians have tried different therapies for their management. The ancient Chinese used burnt sponges and seaweed (rich in iodine) for the treatment of thyroid goiter. A patient with elevation of TSH or defects in thyroxine synthesis is a candidate for suppressive therapy. Thyroxine has been utilized by many physicians with the expectation of reduction in the size and volume of the goiter. Data has accumulated in the literature to refute such an expectation. Substernal goiter, especially those that have cystic change and hemorrhage within the gland, do not respond to thyroxine therapy. Overall, only about 20-30% of patients respond to such treatment after one year. Generally, those patients who

Table 3.4. Clinical symptoms and signs

Symptoms	Signs
Asymptomatic	Cervical mass
Airway compression	Dilated cervical veins
Dyspnea	
Stridor	Tracheal deviation
Raspy Cough	
Wheezing	Flushing of skin
Choking sensation	
	Pemberton's sign
Compression of esophagus	
Dysphagia	Horners syndrome
Compression of nerves	
Hoarseness of voice	
Horners syndrome	
Vascular compression	
Superior vena cava syndrome	
TIA	
Cerebral edema	
GI bleeding	
Lump in neck	

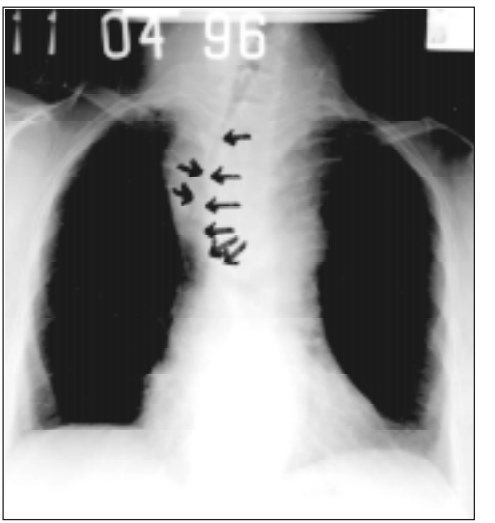

Fig. 3.1. Chest X-ray of a patient with recurrent posterior substernal goiter showing marked deviation of the trachea to the right and compression causing narrowing of its lumen.

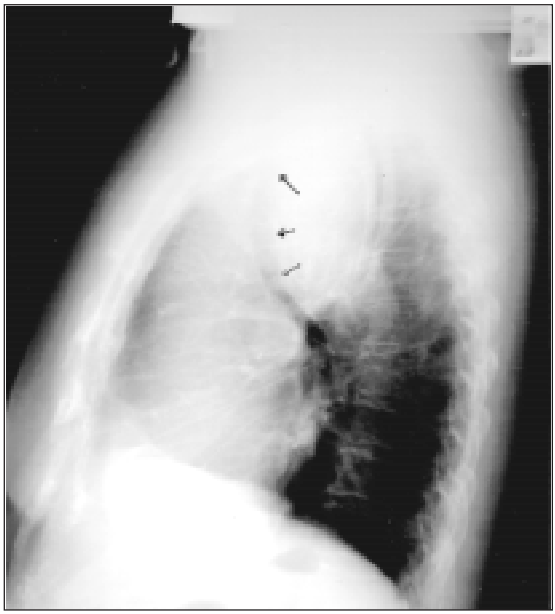

Fig. 3.2. Chest X-ray of the patient from Fig. 3.1 showing forward bowing of the trachea.

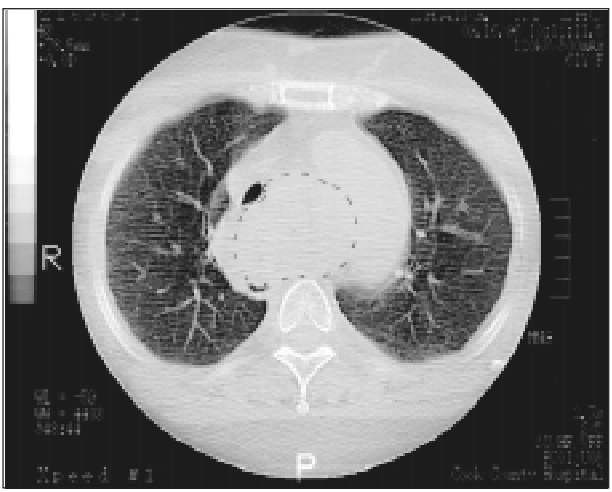

Fig. 3.3. CT Scan of the patient from Fig. 3.1 demonstrating the posterior mediastinal mass which is posterior to the arch of aorta and has displaced the trachea anterolaterally.

respond do so within the first six months of therapy. Presence of cardiac disease and osteoporosis in elderly patients pose an additional hazard to suppressive thyroxine therapy. Unfortunately cessation of therapy is often followed by recurrence of the goiter. If one accepts that the sporadic goiter is a form of non-neoplastic hyperplasia, then one can explain the failure of suppressive therapy based on autonomicity. Recent data have suggested that once stimulated for a long time, autonomous growth occurs, and the hyperplasia is no longer a fully reversible process.

Radioactive Iodine Therapy

Radioactive iodine has been used for the treatment of toxic goiter, however its use in the management of the patients with a non-toxic goiter is a recent event. In 1964 Keiderling first reported the benefits of radioactive iodine therapy in non-toxic goiter in 400 patients. Since then there have been sporadic reports of similar use. Its use in substernal goiter had not been evaluated until 1994 when Huysmans et al reported a prospective study of patients with large compressive goiters.[11] Nine of their 19 patients had intrathoracic extension for more than 2 cm. Using MRI they were able to demonstrate a 40% reduction in the volume of the goiter. They also showed a 10% decrease in both the tracheal narrowing and deviation in three-quarters of their patients. Unfortunately, one-third of their patients did not experience any improvement in their symptoms of dyspnea. Radiotherapy is not without its potential complications. Radiation induced thyroiditis and a transient increase in volume may precipitate an acute airway emergency. Other side effects include neck pain, occasional hyperthyroidism, sore throat, mild dysphagia and dryness of the mouth.

Surgical Therapy

Surgical treatment is the most effective therapy for substernal goiter and the presence of substernal goiter is itself an indication for operation. In rationalizing the operative therapy for substernal goiter, Thompson et al enumerated the following:[7]

1. There is no other treatment for long-standing, large multinodular goiter.
2. Radioactive iodine therapy may precipitate an acute airway emergency, especially in an elderly patient.
3. A long standing history of multinodular goiter does not preclude malignancy, hyperfunction or compressive symptoms.
4. Malignancy occurs in a significant number of these lesions that are inaccessible to FNA.
5. Nearly all substernal goiters can be safely removed via a cervical incision.

The extent of surgical resection for benign disease has remained a focus of debate. In an effort to minimize the risk of injury to the parathyroid glands and the recurrent laryngeal nerve, a partial resection of the gland is often recommended. However we have observed that a significant number of patients are now presenting with recurrent goiter 20-30 years after initial “subtotal thyroidectomy”. In their review of 1819 substernal thyroid glands, Reeve et al noted 234 (12.9%) patients had a previous partial resection of the thyroid.[4] One of our patients who had undergone two previous resections at age 40 and 60 developed a substernal recurrence

associated with tracheal compression at the age of 89; this required a semi-urgent operative intervention.

We feel that a total thyroidectomy is the procedure of choice for any patient whose life expectancy is more than 10 years. With meticulous attention to the details of local anatomy and the technique of capsular hugging one can perform the procedure with minimal risk to the patient. As previously mentioned, in more than 95% of cases, substernal goiters may be removed by a cervical incision. Ligation of the blood vessels close to the thyroid capsule, preservation of the blood supply to the parathyroid gland and minimal dissection of the recurrent laryngeal nerve are the hallmarks of this operaion. Initially the middle thyroid veins are ligated which allows retraction and exposure of the upper lobe. Once the superior pole is mobilized, using a sweeping motion of the finger passed along the carotid vessels posterolateral to the inferior pole, the substernal portion of the goiter may be gently mobilized into the cervical wound. Occasionally, various types of instrumentation may be used to assist in retracting the gland from the chest.[7] During mobilization, careful attention should be paid to the recurrent laryngeal nerve and the parathyroid glands. In difficult situations a sternotomy is preferred over fragmentation or morcellization. Posterolateral thoracotomy, median sternotomy or partial sternal split with a 'T' shaped cervical incision are some of the techniques used for removal of large substernal goiters and goiters that are in the posterior mediastinum. Indications for sternotomy are listed in Table 3.5.

The results after surgical therapy are excellent. Currently substernal goiters can be removed with essentially a zero mortality. Morbidities associated with surgical excision occurs slightly higher than that of cervical thyroid goiter and include hypocalcemia, recurrent laryngeal nerve injury, wound hematoma, bleeding, and wound infection.

Current Research and Its Applications

Evidence suggests that multinodular goiter is a non-neoplastic, hyperplastic proliferation of thyroid cells. Thyroid cells proliferate and form large follicles. The rate of proliferation is not uniform and as one follicle develops, matures and ceases to grow, new follicles develop from new cells. This form of growth explains why a partial resection of a goiter may be followed by a recurrence. Failure of thyroxine therapy to prevent recurrence of the goiter following partial resection has stimulated research for identification of growth factors other than TSH; several growth factors have been identified as possible stimuli for thyroid cell proliferation. Epidermal growth factor (EGF) and an insulin-like growth factor (IGF-1) have been implicated in the pathogenesis of the goiter. While the precise molecular events controlling the thyrocytes' growth have not yet been completely established, transformation of a normal thyroid cell to a proliferative cell is probably secondary to an overexpression of growth related proto-oncogenes. This expression is also modulated by hormones like steroids, estrogen, progesterone and androgens.[10] The increasesd incidence of malignancy in long standing substernal goiters and the occasional finding of microscopic foci of malignancy in multi-nodular goiters raises the possibility of a progressive transformation from hyperplasia to neoplasia. To what extent oncogenes

Table 3.5. Indication for sternotomy for substernal goiter

Goiter size significantly larger than the thoracic inlet
Primary intrathoracic goiter with blood supply derived from intrathoracic vessels
Goiters in the posterior mediastinum that displace or compress the aortic arch
Goiters associated with superior vena cava syndrome
Recurrent substernal goiter
Malignant substernal goiter with lymph node metastasis

responsible for malignant thyroid tumors play a role in the pathogenesis of substernal goiter is yet to be determined. It is possible that in the future manipulation of growth related proto-oncogene and/or growth factors may provide alternative forms of therapy for substernal goiter.

Summary

The presence of goiter in the substernal region is an indication for thyroidectomy even in an asymptomatic patient. Substernal goiters grow slowly and usually present late in life. They remain asymptomatic for long periods of time. The most common symptoms are secondary to compression of the airway and the esophagus. Acute hemorrhage or incarceration of the gland may precipitate an acute airway emergency. A long asymptomatic period does not preclude malignancy or sudden increase in size. The most cost effective test is a CXR. MRI or CT scan can provide important information about the precise anatomic relationship of the goiter with other structures. Subststernal goiters are predominantly in the anterior mediastinum but may occur in the posterior mediastinum and other ectopic locations in the mediastinum. Substernal goiter responds poorly to thyroxine therapy. Surgery is the treatment of choice for substernal goiters and most can be removed via a cervical incision. Sternotomy or a thoracic approach may be used for posterior or ectopic mediastinal goiters. For patients who refuse surgery or have a prohibitive risk for surgery, a trial of radioactive therapy may be considered.

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CHAPTER 4

Thyrotoxicosis

Christopher R. McHenry

Introduction

Thyrotoxicosis refers to a syndrome characterized by signs and symptoms of hypermetabolism and increased sympathetic nervous system activity that result from excessive amounts of thyroid hormone. The incidence of overt thyrotoxicosis has been estimated to be 0.8-1.3 cases per 1000 women and 0.1-0.2 cases per 1000 men per year.[1] Thyrotoxicosis may occur as a result of hyperthyroidism or in the absence of hyperthyroidism (Table 4.1). The term hyperthyroidism is defined as excess synthesis or secretion of thyroid hormone by the thyroid gland. Some patients with thyrotoxicosis, such as those with subacute or silent thyroiditis or excess thyroxine ingestion, do not have hyperthyroidism. The distinction is important in determining the specific etiology and treatment of thyrotoxicosis. The aim of this chapter is to summarize the clinical presentation, pathogenesis, diagnosis and management of patients with spontaneous thyrotoxicosis secondary to: Graves' disease, toxic multinodular goiter, solitary toxic adenoma, thyroiditis and iodine-induced hyperthyroidism.

The clinical manifestations of thyrotoxicosis are diverse (Table 4.2). They are dependent on the underlying etiology of the thyrotoxicosis and its severity, patient age and the involvement of organ systems other than the thyroid gland. Most manifestations are independent of the underlying etiology of thyrotoxicosis. Increased thyroid hormone levels sensitize nerve cells to catecholamines and are responsible for the symptoms of increased sympathetic nervous system activity. The presence of certain features such as extrathyroidal manifestations, the size and shape of the thyroid gland, and the 24 hour radioiodine uptake are important in determining the specific etiology for thyrotoxicosis (Fig. 4.1). Older patients usually have fewer and more subtle symptoms, a phenomenon referred to as apathetic hyperthyroidism. They also more frequently present with cardiovascular manifestations such as atrial fibrillation, dyspnea, angina, or congestive heart failure.

The best screening test for thyrotoxicosis is the third generation thyrotropin (TSH) assay. The TSH level is low in all patients with thyrotoxicosis except in rare cases of TSH-secreting pituitary tumors or pituitary resistance to thyroid hormone (Fig. 4.1). A suppressed TSH level, however, is not entirely specific for thyrotoxicosis. Rare patients with euthyroid sick syndrome secondary to severe nonthyroidal disease may also have a suppressed TSH level without having thyrotoxicosis. When a patient is found to have a low TSH level, a free thyroxine (T_4) and a triodothyronine (T_3) level should be obtained. T_3 levels are important to make a diagnosis of T_3 toxicosis in patients with a suppressed TSH and a normal FT_4 level.

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Table 4.1. Differential diagnosis for thyrotoxicosis

A) Associated with hyperthyroidism
- Graves' disease
- Toxic multinodular goiter
- Solitary toxic adenoma
- Iodine-induced (amiodarone, intravenous contrast material, iodine-containing expectorants, kelp, topical antiseptics)
- Hashimoto's or chronic lymphocytic thyroiditis
- Trophoblastic tumors (hydatiform mole or choriocarcinoma)
- Thyrotropin-producing pituitary tumor
- Thyroid hormone resistance syndromes

B) Not associated with hyperthyroidism
- Subacute, painless, or radiation thyroiditis
- Excess thyroid hormone ingestion (iatrogenic, thyrotoxicosis factitia, "hamburger thyrotoxicosis")
- Struma ovari
- Functioning metastatic thyroid cancer

Table 4.2. Symptoms and signs of thyrotoxicosis

A) Symptoms

Nervousness	Insomnia or sleep disturbances
Anxiety	Fatigue
Irritability	Weakness
Increased appetite	Hair loss
Weight loss or gain	Brittle nails
Palpitations	Dyspnea
Heat intolerance	Increased frequency of bowel movements
Excessive sweating	Impaired fertility, oligomenorrhea or amenorrhea
Tremulousness	Reduced libido

B) Signs

Tachycardia	Warm, moist smooth skin
Systolic hypertension	Thinning hair or hair loss
Supraventricular arrhythmias	Onicholysis
Widened pulse pressure	Muscle weakness
Hyperreflexia	Gynecomastia
Resting tremor	Eyelid retraction, lid lag and stare

Once the diagnosis of thyrotoxicosis is confirmed, a measurement of radioactive iodine uptake may be helpful (Fig. 4.1). The presence of hyperthyroidism is established by an elevated 24-hour radioiodine uptake. A low radioactive iodine uptake is seen in patients with subacute or silent thyroiditis, iodine-induced hyperthyroidism, and excess thyroid hormone ingestion. A thyroid scintiscan, preferably obtained with iodine-123, is important in differentiating a hypofunctioning nodule in a patient with Graves' disease from a solitary toxic nodule. Adjunctive measurement of thyroid

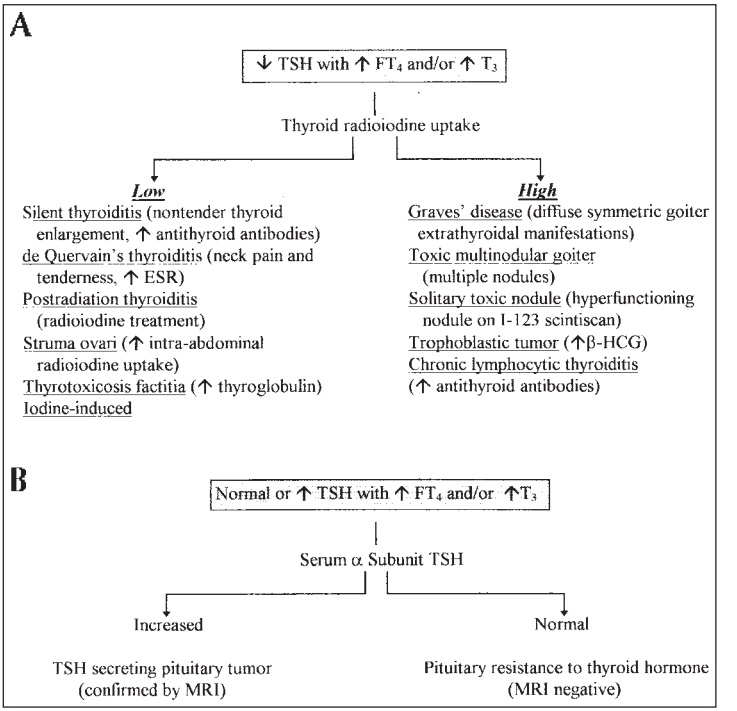


Fig. 4.1. Diagnostic characterization and distinguishing features of patients with thyrotoxicosis. (TSH = thyrotropin, FT_4 = free thyroxine, T_3 = total triiodothyronine, ESR = erythrocyte sedimentation rate, β-HCG = β human chorioric gonadotropin, MRI = magnetic resonance imaging.)

stimulating immunoglobulins and antithyroid antibodies is useful in establishing a diagnosis of Graves' disease or thyroiditis in selected patients. A normal or decreased thyroglobulin level may be helpful in establishing a diagnosis of thyrotoxicosis factitia.

With the development of the third generation TSH assays the diagnosis of subclinical hyperthyroidism has become more precise. Patients with subclinical hyperthyroidism are usually asymptomatic or have very subtle symptoms with normal free T_4 and T_3 levels and a low serum TSH level. Subclinical hyperthyroidism may be associated with increased bone turnover and accelerated bone loss, a significant problem in postmenopausal women who become susceptible to osteoporotic bone fractures. It has also been associated with adverse cardiac consequences such as atrial fibrillation, cardiac hypertrophy, congestive heart failure and aggravation of ischemic heart disease.

Graves' Disease

Graves' disease is the most common cause of spontaneously occurring thyrotoxicosis, accounting for 60-90% of all cases. Graves' disease also referred to as Basedow's disease or Parry's disease, is an autoimmune disorder with a genetic predisposition that typically affects young women 20-40 years of age. The female to male ratio varies from 4:1 to 10:1. Graves' disease has been linked to certain HLA haplotypes, HLA B8 and HLA DR3 in Caucasian populations, HLA BW35 in the Japanese and HLA BW46 in Chinese populations. It frequently occurs in association with other autoimmune diseases such as: chronic lymphocytic thyroiditis, rheumatoid arthritis, Sjogren's syndrome, vitiligo, pernicious anemia, Type I diabetes mellitus, lupus erythematosis, Addison's disease, myasthenia gravis and idiopathic thrombocytopenia purpura.[2]

The specific cause of Graves' disease is unknown. Much of the current research has been directed at the characterization of the autoimmune reaction and determining its etiology. In his review of the pathogenesis of Grave's disease Volpe postulated that the fundamental defect involved reduced activation of suppressor T lymphocytes by specific antigen.[2] This occurs as a result of an inherited abnormality in antigen presentation encoded for by histocompatibility genes. The autoimmune dysfunction may also be precipitated by environmental factors such as stress, infection, or trauma. Environmental factors can convert an occult defect in suppressor T lymphocyte function to an overt one. The defect in suppressor T cell function allows for thyroid-directed B lymphocytes, which are normally suppressed, to produce thyroid antibodies directed against the TSH receptor which stimulates the follicular cells in a manner similar to TSH. This leads to cAMP-mediated increases in thyroid hormone synthesis and growth of the thyroid gland. The thyroid receptor antibodies include a predominance of thyroid stimulating immunoglobulins and to a lesser extent, TSH-receptor inhibiting immunoglobulins. Graves' disease is also characterized by thyroid autoantibodies to other antigens including thyroglobulin and thyroid peroxidase. Rastad and Karlsson postulate that cytotoxic lymphocytes and antibody-dependent cytotoxicity may be responsible for lysis of follicular cells and spontaneous remission which has been observed in some patients with Graves' disease.[3]

The clinical presentation of patients with Graves' disease is characterized by hyperthyroidism, diffuse symmetric goiter, and the variable presence of ophthalmopathy, dermopathy and acropachy (Fig. 4.2). The extrathyroidal manifestations of Graves' disease are related to tissue deposition of glycosaminoglycans in response to the immune reaction against tissue antigens shared with the thyroid gland or antigens which cross react with the TSH receptor. Patients with Graves' disease have the same symptoms as patients with thyrotoxicosis from other causes (Table 4.2). In addition, patients with Graves' disease typically have a diffuse symmetric goiter (Figs. 4.2 and 4.3) often with an audible bruit or a palpable thrill. Elderly patients typically present with more subtle symptoms and are more likely to have cardiovascular manifestations. Approximately 20% of elderly patients will not have a goiter.

Ophthalmopathy occurs in 5-10% of patients with Graves' disease and is mediated by antibody-induced inflammation which affects the extraoccular muscles, the

Fig. 4.2. A patient with Graves' disease manifested by ophthalmopathy and a diffuse symmetric goiter.

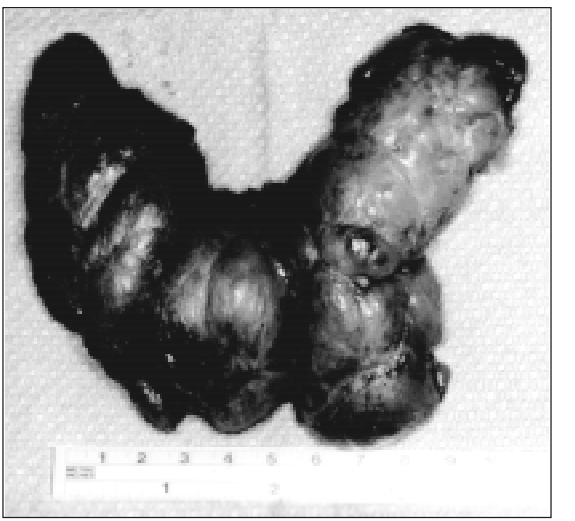


Fig. 4.3. A diffuse, symmetric goiter resected from a patient with Graves' disease with its characteristic absence of nodules.

retroorbital connective tissue and the optic nerve. The etiology is unknown. The retroorbital fibroblast has been suggested as the principle target cell for the antibody-induced inflammation.[2] It has also been established that these fibroblasts express TSH receptors.[2] A higher prevalence of ophthalmopathy has been reported in patients with higher levels of thyroid receptor antibodies.[3] Eyelid retraction, lid lag and stare are nonspecific features that may occur with thyrotoxicosis regardless of its cause and are the consequence of hyperthyroidism-induced sympathetic stimulation of the levater palpebrae superioris muscles of the eyelids. However, periorbital edema, chemosis, exophthalmos, diplopia and decreased visual acuity are more specific for Graves' disease (Fig. 4.2). Graves' ophthalmopathy occurs as a result of edema, glycosaminoglycan deposition, leukocyte infiltration and fibrosis of the orbit and the extraoccular muscles.

Dermopathy and acropachy generally occur in patients with ophthalmopathy. Dermopathy, in the form of pretibial myxedema, occurs in 0.5-4% of patients with Graves' disease. It consists of violaceous, plaque-like thickening or induration of the skin of the lower legs and feet. Patients may complain of associated pain and pruritis. Acropachy is rare, occurring in less than 1% of patients with Graves' disease. It is manifested by thickening or clubbing of the fingers or toes, nail changes and periosteal new bone formation.

The diagnosis of Graves' disease is usually established by the presence of hyperthyroidism, a diffuse symmetric goiter and increased thyroidal radioactive iodine uptake. In most patients with Graves' disease, the serum TSH level is below the detectable limits of the assay used. Measurement of thyroid receptor antibodies is not routinely necessary. However, they may be of value in establishing a diagnosis of Graves' disease in an elderly thyrotoxic patient without a palpable goiter. Documentation of high titers of thyroid stimulating immunoglobulins during pregnancy in women with a history of Graves' disease may be important in predicting the risk of fetal and neonatal thyrotoxicosis.[2]

The thyroid scintiscan is not routinely necessary in the evaluation of patients with Graves' disease. It is used selectively to help differentiate thyrotoxicosis caused by Graves' disease from toxic multinodular goiter or a solitary toxic thyroid nodule (Figs. 4.4, 4.5, and 4.6). It may also be helpful in patients with Graves' disease who have a concomitant dominant thyroid nodule. The thyroid scintiscan in patients with Graves' disease typically reveals increased radioiodine uptake that is diffuse and symmetric (Fig. 4.4).

The management of patients with Graves' disease consists of three therapeutic alternatives: radioiodine, antithyroid drug therapy, or surgery. In the United States the majority of patients with Graves' disease are treated with iodine-131. Iodine-131 emits beta particles which are locally destructive to the follicular cells of the thyroid gland. Nordyke and Gilbert emphasize that delayed hypothyroidism develops in most patients with Graves' disease treated with radioiodine regardless of the dose of iodine-131 used.[4] As a result, definitive treatment of hyperthyroidism is the most important consideration. At our institution, a standard 10 mCi dose of iodine-131 is used for treatment of Graves' thyrotoxicosis. Nordyke and Gilbert reported that 90% of their patients with Graves' disease treated with a 10 mCi dose of

Fig. 4.4. Iodine-123 thyroid scintiscan demonstrating diffuse increased uptake characteristic of Graves' disease.

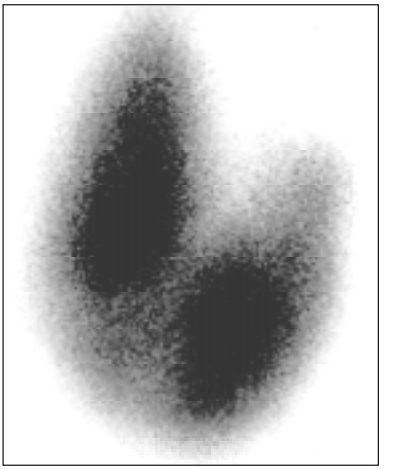
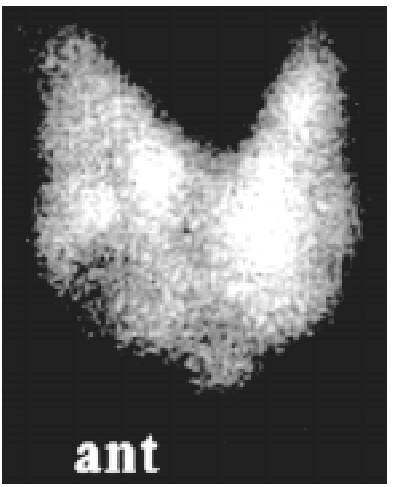


Fig. 4.5. Iodine-123 thyroid scintiscan demonstrating multiple autonomous functioning nodules and characteristic patchy radioiodine uptake.



iodine-131 were cured.[4] Persistent hyperthyroidism was more common in patients with thyroid glands estimated to be greater than 50 grams. A higher dose of iodine-131 may be used in patients with larger thyroid glands. Most patients experience symptomatic improvement 6 to 8 weeks after receiving radioiodine treatment and complications are rare. Serum TSH levels are monitored in all patients and thyroid replacement therapy is begun when TSH levels are elevated. Radioiodine is contraindicated in women who are pregnant or breast feeding. A pregnancy test should be obtained prior to radioiodine administration in all women of child bearing age.

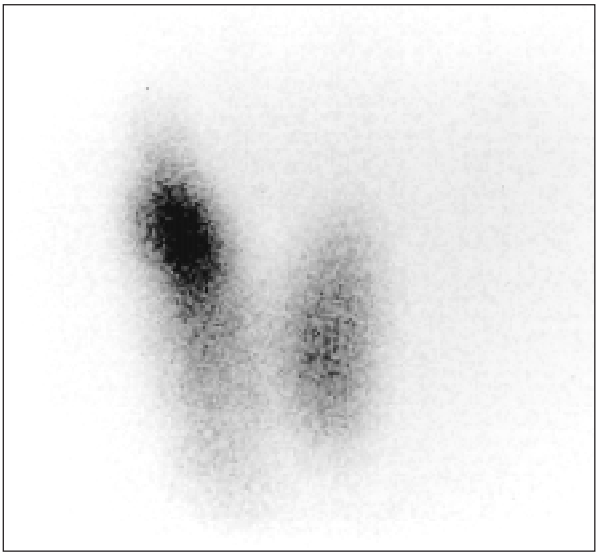


Fig. 4.6. Iodine-123 thyroid scintiscan demonstrating a solitary hyperfunctioning nodule in the superior pole of the right lobe of the thyroid gland. (From McHenry CR, Sandoval BA: Management of follicular and Hürthle cell neoplasms of the thyroid gland. Reprinted with permission from Oncology Clinics of North America (in press)).

Thioamide drugs are used for treatment of Graves' disease in: children, women who are pregnant or breast feeding, elderly patients that have mild to moderate symptoms without a goiter, and for preparation of patients for radioiodine or surgical treatment. The thioamide drugs, propylthiouracil (PTU) and methimazole, both decrease thyroid hormone synthesis by a dose-dependent inhibition of the thyroid peroxidase enzyme. PTU also blocks the peripheral conversion of thyroxine to triiodothyronine. PTU is preferable to methimazole in women who are pregnant or breast feeding because of its greater protein binding which results in less passage across the placenta and the mammary epithelium. PTU has a half life of two hours and is given two to three times per day, whereas methimazole has a half life of six hours and is given one to two times per day. Adverse effects of thioamide drug use can be minor or major. Minor side effects may be dose or agent related and include: skin rash, pruritis, urticaria, nausea, vomiting, myalgias or arthralgias, fever and transient leukopenia. For patients with minor side effects, drug dosage can be reduced or the other thioamide drug can be substituted. However, patients may experience cross sensitivity. Major side effects are idiopathic and include: agranulocytosis, hepatitis, aplastic anemia and vasculitis.

A high thioamide dose is given initially, either 100-200 mg of PTU three times per day or 10-30 mg of methimazole twice a day. Once the free T_4 and T_3 levels have normalized, the thioamide dose is tapered to the lowest dose that will maintain a

euthyroid state. Patients are kept on a maintenance dose usually for one to two years' duration. Remissions are variable and most often last for less than 6 months. Hedley and colleagues reported that 40-80% of patients develop recurrent thyrotoxicosis after discontinuation of antithyroid drugs.[5] However, the fact that 20-60% of patients with Graves' thyrotoxicosis become euthyroid after treatment has prompted investigative efforts to try and identify accurate criteria to select patients for antithyroid drug therapy. An anticipated future application of this research will be the development of recommendations for therapy based on the assessment of a patient's risk for recurrence following thioamide treatment.

4

Surgical treatment of Graves' disease is indicated for: 1) pregnant patients who are intolerant to antithyroid drugs; 2) patients with massive thyroid enlargement and compressive symptoms; 3) patients with a concomitant solitary cold nodule; 4) patients who fail to respond to multiple doses of radioiodine; and 5) patients who prefer surgery. The advantages of surgical treatment of Graves' disease is that patients experience immediate symptomatic improvement. This is in contrast to patients receiving radioiodine who may not experience relief for up to three months from the time they receive their treatment. The standard operation is a bilateral subtotal thyroidectomy leaving a 3 gram remnant of thyroid tissue on either side of the trachea. This operation has traditionally been advocated to try and maintain a euthyroid state postoperatively and reduce the risk of recurrent laryngeal nerve injury and hypoparathyroidism while minimizing the risk of recurrent hyperthyroidism. The incidence of recurrent hyperthyroidism is approximately 10-15% following bilateral subtotal thyroidectomy.

Because it has been demonstrated that a majority of patients become hypothyroid within ten years of undergoing bilateral subtotal thyroidectomy, near total or total thyroidectomy can be performed preferentially to effectively eliminate the risk of recurrent Graves' disease. However, this is only a suitable alternative if it can be performed without an increase in complication rate. Total thyroidectomy has also been recommended for patients with severe or progressive ophthalmopathy and high TSH receptor antibody titers.[3] Total removal of the thyroid gland is advocated to decrease TSH receptor antibodies and other antibodies directed against the extraocular muscles, orbit and optic nerve.[3]

Prior to elective surgery, patients are rendered biochemically euthyroid using a thioamide drug. A beta adrenergic-blocking agent is also used for symptomatic treatment of thyrotoxicosis as well as to maintain the resting heart rate between 60 and 80 beats per minute. β-blockers inhibit the peripheral conversion of T_4 to T_3. The use of a thioamide drug and a β-blocker to prepare a patient for surgery is important in eliminating the risk of perioperative thyroid storm. Once the patient's FT_4 and T_3 levels have been normalized, iodine is administered for 7-10 days prior to surgery, either as Lugol's solution (three drops three times per day) or as a saturated solution of potassium iodide (one drop three times per day). Iodine administration decreases the vascularity of the thyroid gland, reduces operative blood loss and makes the operation easier.

Toxic Multinodular Goiter

Toxic multinodular goiter, also known as Plummer's disease, is characterized by thyrotoxicosis which occurs as a result of multiple autonomous functioning thyroid nodules in a pre-existing multinodular goiter. Toxic multinodular goiter accounts for 5-15% of cases of thyrotoxicosis. It typically occurs in elderly patients with a long-standing history of multinodular goiter. It more commonly affects women. Toxic multinodular goiter is thought to occur as a result of progressive generation of autonomously functioning thyroid follicles overtime that have a greater capacity to synthesize T_4 and T_3. This eventually results in transition from a nontoxic to a toxic multinodular goiter.

Thyrotoxicosis is generally mild in comparison to patients with Graves' disease. Cardiovascular manifestations occur more commonly because the patients are older. The onset of thyrotoxicosis is insidious and often preceded by a long period of subclinical hyperthyroidism. Patients with toxic multinodular goiter often have marked thyroid enlargement (Figs. 4.7 and 4.8) and substernal extension that produces associated compressive symptoms. Patients can complain of dysphagia, hoarseness, coughing or choking spells or dyspnea secondary to compression of the esophagus, recurrent laryngeal nerve or the trachea. Infiltrative ophthalmopathy does not occur in patients with toxic multinodular goiter.

Physical examination reveals multiple nodules affecting both lobes of the thyroid gland, frequently with very marked thyroid enlargement (Fig. 4.7). Laboratory evaluation reveals a low serum TSH level with or without elevated serum FT_4 and/or T_3 levels. Twenty-four hour radioiodine uptake is usually only slightly elevated or in the high normal range. Undetectable TSH levels, marked elevation in serum FT_4 and/or T_3 levels, and marked increases in radioiodine uptake that are characteristic of patients with Graves' disease are rarely seen in patients with toxic multinodular goiter. In most patients, a diagnosis of toxic multinodular goiter can be made solely on the basis of a low serum TSH level and bilateral nodular enlargement of the thyroid gland. Routine scintiscanning is not necessary. Selective scintiscanning may be of value in the rare thyrotoxic patient in whom it is difficult to determine whether thyroid enlargement is nodular or diffuse. The thyroid scintiscan in patients with a toxic multinodular goiter is characterized by a patchy distribution of radioisotope with multiple areas of increased and decreased uptake of radioisotope (Fig. 4.5).

The goal in treatment of toxic multinodular goiter is to eradicate all autonomously-functioning thyroid follicles. This can be accomplished by surgical resection or iodine-131 therapy. Because of the marked thyroid enlargement and frequent associated compressive symptoms, surgical resection is the usual treatment. All abnormal thyroid tissue should be removed. This usually entails performing a near-total thyroidectomy. A subtotal thyroidectomy is performed only when it can be accomplished without leaving abnormal thyroid tissue behind. Patients are pretreated with a thioamide drug preoperatively to normalize their free T_4 or T_3 levels before proceeding with thyroidectomy. Unlike in patients with Graves' disease, iodine is not administered preoperatively because it may worsen thyrotoxicosis. The thyroid gland in patients with toxic multinodular goiter is much less vascular than patients with Graves' disease and significant blood loss is uncommon.

Fig. 4.7. A patient with toxic multinodular goiter manifested by nodules affecting both lobes of the thyroid gland.

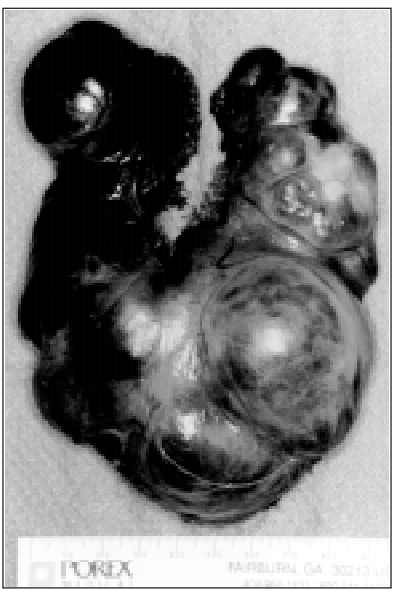


Fig. 4.8. A resected toxic multinodular goiter notable for its massive enlargement and multiple bilateral nodules.

Radioiodine may also be used to treat toxic multinodular goiter. However, toxic multinodular goiters can be resistant to radioiodine therapy. Radioiodine is usually not effective in alleviating compressive symptoms related to thyroid enlargement. Iodine-131 treatment is usually reserved for elderly patients with multiple concurrent medical problems that place them at high risk for surgery. Treatment with antithyroid

drugs should be considered prior to radioiodine administration especially in patients with underlying heart disorders. It must be discontinued 3-5 days prior to treatment to optimize radioiodine uptake and then resumed one week after treatment.

Solitary Toxic Nodule

A solitary toxic nodule is a discrete, autonomous, hyperfunctioning nodule that occurs in an otherwise normal thyroid gland and causes hyperthyroidism. It accounts for approximately 3-10% of all cases of spontaneous thyrotoxicosis. The term hyperfunctioning nodule is used to describe the scintigraphic appearance of a nodule that takes up greater radioiodine than the normal adjacent thyroid tissue (Fig. 4.6). Only 25% of all hyperfunctioning nodules are toxic nodules. A solitary toxic nodule is autonomous, meaning that it functions independently of the hypothalamic-pituitary-thyroid feedback mechanism and secretes thyroid hormone despite suppressed TSH levels.

The manifestations of thyrotoxicosis are generally milder than in patients with Graves' disease. A solitary toxic nodule may occur at any age, although it is more common in women and in patients less than 50 years of age. Physical examination reveals a single, discrete nodule in the thyroid gland. The initial diagnostic test obtained is a third generation TSH level to establish the presence of thyrotoxicosis. A serum free T_4 and T_3 level should be obtained in patients when the serum TSH level is low. Hyperfunctioning nodules preferentially secrete T_3 and as a result serum T_3 levels are more likely to be elevated in patients with an autonomous nodule. An iodine-123 thyroid scintiscan should be performed to confirm the presence of a hyperfunctioning nodule and exclude the presence of a hypofunctioning nodule in a patient with underlying Graves' disease.[6]

Solitary hyperfunctioning thyroid nodules concentrate radioiodine more avidly than normal thyroid tissue. They account for 5-15% of all thyroid nodules. A hyperfunctioning nodule may result in suppression in the uptake of radioiodine by the remaining normal thyroid tissue (Fig. 4.9). Occasionally, the contralateral thyroid lobe will take up no radioiodine and this must be differentiated from congenital thyroid hemiagenesis by demonstration of a normal contralateral lobe either by palpation or ultrasound. The pathology of a toxic solitary nodule is almost uniformly either a follicular adenoma or an adenomatous nodule. Carcinoma occurs in approximately 1% of hyperfunctioning nodules.[6]

Solitary hyperfunctioning nodules are thought to occur as a result of mutation in the gene for the TSH receptor or the gene for the α subunit of the stimulatory guanine nucleotide-binding (G_s) protein which leads to constitutive activation of the TSH receptor or the G_s protein, increased cAMP production and increased thyroid hormone synthesis. Approximately 20% of patients with hyperfunctioning nodules $\geq$ 3 cm in diameter will develop thyrotoxicosis, compared to only 2-5% of patients with hyperfunctioning nodules $\leq$ 2.5 cm in diameter.[7] Thyrotoxicosis is also more likely to occur in patients with serum T_3 levels at the upper limit of normal and patients who are less than 20 or greater than 60 years of age.[7] All patients with hyperfunctioning nodules should be followed for the development of signs and

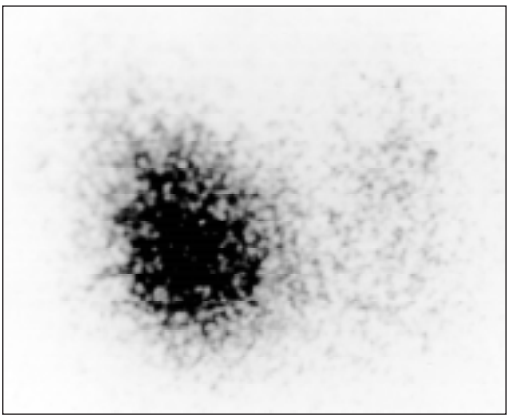


Fig. 4.9. Autonomously hyperfunctioning nodule with suppression of radioiodine uptake in the contralateral lobe of the thyroid gland.

symptoms of thyrotoxicosis. Serum TSH levels should be monitored at yearly intervals.

Patients with a hyperfunctioning thyroid nodule who are not thyrotoxic and are otherwise asymptomatic can be observed. In patients with subclinical hyperthyroidism treatment is recommended for those who are at high risk for cardiac side effects and for postmenopausal women with decreased bone mineral density. Because of the increased risk of hyperthyroidism in patients with hyperfunctioning nodules that are ≥ 3 cm in diameter, treatment is recommended even in the absence of thyrotoxicosis.

The primary therapeutic options for patients with a solitary toxic nodule are radioiodine ablation versus surgical removal. O'Brien and colleagues found that both iodine-131 and surgery are effective treatment of solitary toxic nodules.[8] Surgical treatment, consisting of simple thyroid lobectomy, is associated with a low risk of complications. Both recurrence of hyperthyroidism and hypothyroidism are uncommon. Radioiodine treatment usually requires higher doses of iodine-131 than are normally used for treatment of Graves' disease. The disadvantages of iodine-131 therapy are the delay in symptomatic relief, the exposure of normal thyroid tissue to the effects of radioiodine which may result in hypothyroidism in up to 35% of patients, and concern related to nodule persistence.[8] The advantages of surgical therapy are immediate symptomatic relief and avoidance of radiation exposure to the normal thyroid tissue.

Other less attractive therapeutic alternatives include antithyroid drugs and percutaneous ethanol injection. Antithyroid drugs are not curative. They must be given lifelong because hyperthyroidism recurs when they are discontinued. Their use may be considered in elderly patients with multiple concurrent medical problems that preclude surgical or radioiodine treatment. Antithyroid drugs are also used to prepare patients for surgery or radioiodine therapy. Percutaneous ethanol injection directly

into a toxic nodule using ultrasound guidance is effective in reversing hyperthyroidism. However, it requires multiple injections which are painful. It can be complicated by transient recurrent laryngeal nerve paresis. The long-term efficacy of percutaneous ethanol injection has not been established.

Thyroiditis

Thyrotoxicosis secondary to thyroiditis is uncommon. It is typically transient and self-limited. It may occur as a result of chronic lymphocytic or Hashimoto's thyroiditis, silent or painless thyroiditis, subacute or de Quervain's thyroiditis and radioiodine-induced thyroiditis. Silent, subacute and radioiodine-induced thyroiditis are all characterized by the inability to trap iodine, follicular cell destruction and release of preformed thyroid hormone resulting in thyrotoxicosis with a low radioiodine uptake. In contrast, radioiodine uptake is increased in patients with thyrotoxicosis secondary to chronic lymphocytic or Hashimoto's thyroiditis. The pathogenesis of thyrotoxicosis in chronic lymphocytic thyroiditis is felt to be similar to that of Graves' disease.

Thyrotoxicosis in patients with chronic lymphocytic or Hashimoto's thyroiditis, referred to as Hashitoxicosis, is uncommon. It typically occurs in the early stages of the disease and is transient in nature. It is thought to occur as a result of lymphocyte production of stimulatory anti-TSH receptor antibodies which are present in ten to 25% of all patients with chronic lymphocytic thyroiditis. Patients with chronic lymphocytic thyroiditis have marked elevation of antithyroglobulin and antithyroid peroxidase (antimicrosomal) antibody titers and focal or diffuse lymphocytic infiltration of the thyroid gland. They may also have a firm goiter and rarely ophthalmopathy. Most patients are women between the ages of 30 and 50. As the disease evolves, thyrotoxicosis resolves and hypothyroidism invariably develops. Usually no treatment is necessary for the thyrotoxicosis. When symptoms become problematic, a beta adrenergic-blocking agent or a thioamide drug may be used. Patients are followed clinically and their serum TSH levels are monitored for the inevitable development of hypothyroidism which will require thyroid hormone replacement.

Silent or painless thyroiditis is the major cause of thyrotoxicosis in patients with a low radioiodine uptake. It is an autoimmune disorder which accounts for less than 5% of all cases of thyrotoxicosis. It is a form of lymphocytic thyroiditis that is characterized by single or recurrent episodes of acute inflammation of the thyroid gland resulting in release of stored thyroid hormone. It can occur sporadically or in the postpartum period. Patients are usually women between 30 and 40 years of age. Symptoms of thyrotoxicosis are acute in onset, usually mild and self limited, and last an average of 2 months. Thyrotoxicosis may be followed by transient hypothyroidism which can last for 2-9 months. Most patients eventually recover normal thyroid function. Patients may have a firm, nontender, mild to moderately enlarged thyroid gland. Antithyroid peroxidase and antithyroglobulin antibodies are elevated in approximately 60% and 25% of patients, suggesting an autoimmune etiology.[9]

Patients have a normal or mildly elevated erythrocyte sedimentation rate and a markedly elevated serum thyroglobulin level.

In general, thyrotoxicosis secondary to silent thyroiditis requires no therapy. If the symptoms become problematic, a beta adrenergic antagonist and anti-inflammatory therapy with prednisone can be used. Because increased thyroid hormone synthesis is not the cause for the thyrotoxicosis, the use of thioamide drugs is not effective. Subtotal thyroidectomy or radioiodine ablation may be beneficial in the rare patient with recurrent disabling episodes of silent thyroiditis with thyrotoxicosis. Radioiodine ablation is effective only if administered when thyroidal radioiodine uptake has recovered.

Subacute thyroiditis, also known as de Quervain's, granulomatous, or giant cell thyroiditis, is an acute, self-limited inflammatory condition of the thyroid gland. It is characterized by neck pain, fever, myalgias, malaise, mild to moderate thyroid enlargement, exquisite neck tenderness and symptoms of thyrotoxicosis which occur during the initial phase of inflammation. Most patients have a history of an antecedent flu-like or upper respiratory illness. The cause for subacute thyroiditis is multifactorial. It appears that a viral infection triggers an abnormal cell mediated immune response directed at the thyroid follicular cells causing follicular cell destruction and release of preformed thyroid hormone. In addition to infection and autoimmune factors, a genetic predisposition may also be important in the pathogenesis as suggested by the association of the HLA BW35 haplotype with subacute thyroiditis in certain patients.[9] The diagnosis is supported by the presence of a markedly increased erythrocyte sedimentation rate, an increased serum thyroglobulin level and a suppressed radioactive iodine uptake.

The treatment of patients with subacute thyroiditis is primarily supportive. Aspirin, nonsteroidal anti-inflammatory agents, or prednisone may be used depending on the degree of thyroid inflammation. Thyrotoxicosis usually requires no treatment and resolves after 3-6 weeks. If symptoms become problematic, a beta adrenergic blocking agent may be given. As in silent thyroiditis, antithyroid drugs are not effective. If follicular cell destruction is extensive, hypothyroidism may develop during the recovery phase. However, at least 95% of patients become euthyroid within 6 months of onset.

Iodine-Induced Thyrotoxicosis

Iodine-induced thyrotoxicosis usually occurs in elderly patients with a pre-existing multinodular goiter who are given a large iodine load (Table 4.3). It is the only cause of hyperthyroidism with a low radioiodine uptake. It accounts for less than 1% of all causes of thyrotoxicosis. The pathogenesis is not completely understood. In normal individuals, large doses of iodine lead to an inhibition of iodine transport and a rapid decrease in thyroid hormone synthesis and release, a phenomenon known as the Wolff Chaikoff effect. Iodine-induced thyrotoxicosis may occur as a result of supplying excess iodine to areas of autonomous function in the thyroid gland, the so called Jod Basedow effect. It also may occur as a result of an increase in the iodine set point of the thyroid gland which leads to increased thyroid hormone synthesis at iodine levels which normally reduce synthesis and release of thyroid hormone.

Table 4.3. Sources of large iodine load precipitating iodine-induced thyrotoxicosis

Oral expectorants (iodinated glycerol and saturated solution of potassium iodide)
Amiodarone
Kelp
Topical antiseptics (povidone-iodine, tincture of iodine)
Vaginal douches (povidone-iodine)
Intravenous contrast material

The diagnosis of iodine-induced thyrotoxicosis is suspected by a history of a recent exogenous iodine load in a patient with a goiter. The diagnosis is supported by a serum iodide concentration greater than 1.5 μg/dl and a 24 hour urinary iodide excretion greater than 1000 μg. Treatment most often consists of simple discontinuation of the source of iodide, although this may be problematic in patients with refractory arrhythmias on amiodarone.[10] Thioamide drugs may also be used either alone in combination with potassium perchlorate which competitively inhibits iodine uptake by the thyroid gland. A beta adrenergic antagonist may also be used in conjunction with a thioamide drug. Radioiodine therapy is not an option because the high iodine load suppresses radioiodine uptake by the thyroid gland. A beta adrenergic antagonist may also be used in conjunction with a thioamide drug. Radioiodine therapy is not an option because the high iodine load suppresses radioiodine uptake by the thyroid gland. Near-total thyroidectomy may be indicated in patients with amiodarone-induced thyrotoxicosis that is refractory to medical therapy or as an initial treatment for patients who present with resurgence of life-threatening cardiac arrhythmias.[10]

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CHAPTER 5

Follicular and Hürthle Cell Neoplasms

William B. Inabnet

Introduction

Follicular and Hürthle cell neoplasms are rare tumors of the thyroid gland for which the management remains controversial. Since the follicular cell is the common cell of origin for papillary, follicular, and Hürthle cell neoplasms, it is not uncommon for studies to include patients with all three types of histology in the same analysis, making interpretation of the data difficult.

It has become clear that the histopathologic features, biologic behavior, and prognosis of follicular and Hürthle cell neoplasms are distinct. Nevertheless, sensitivity of fine needle aspiration biopsy (FNA) and frozen section analysis in differentiating their benign and malignant behavior is low. Furthermore, once the diagnosis has been established, there are still divergent opinions regarding the optimal surgical management for both (i.e., thyroid isthmus and lobectomy vs total thyroidectomy).

This chapter provides a concise review of the presentation, diagnosis, and management of follicular and Hürthle cell neoplasms of the thyroid, paying particular attention to the surgical decision-making process. Due to the unique biologic behavior of these neoplasms, each will be reviewed separately.

Follicular Neoplasms

Epidemiology

Follicular neoplasms of the thyroid may be divided into two broad categories: benign follicular adenomas and follicular thyroid carcinomas. Follicular carcinoma of the thyroid is an uncommon tumor with approximately 1350 newly diagnosed cases each year in the United States.[1] Follicular carcinoma makes up 10-25% of thyroid malignancies. Follicular adenomas are much more common than follicular carcinoma, comprising 80-90% of all follicular neoplasms demonstrated by FNA or biopsy.[4] Autopsy and ultrasound studies have shown that the true incidence of thyroid nodules is considerably higher than the 4-7% often cited, reaching close to 50% of the adult population in the United States in some studies.[2] Therefore, the true prevalence of follicular neoplasms is probably higher than previously thought.

Although the etiology of follicular thyroid neoplasms is unknown, several interesting observations have been made. There seems to be a definite relationship between elevated thyroid-stimulating hormone (TSH) levels and the occurrence of follicular thyroid carcinoma, an association not seen in papillary thyroid carcinoma. Disease states that lead to persistent TSH stimulation of the thyroid follicle may contribute to the pathogenesis of follicular carcinoma. For example, in areas of the world where

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iodine deficiency and endemic goiter are prevalent, as in parts of Europe, the incidence of follicular thyroid carcinoma is higher than in areas without iodine deficiency such as in the United States. As is the case with papillary carcinoma, a prior history of radiation exposure is associated with the development of follicular carcinoma. Other important epidemiological factors include a history of previous thyroid cancer, a family history of thyroid malignancy, certain genetic diseases such as Gardner's disease, and a history of breast cancer.[3]

Presentation

A follicular neoplasm typically presents as a firm, nonfunctioning nodule of the thyroid gland with a diameter between 1 and 4 cm. Due to the well-encapsulated nature of follicular adenomas, they often feel rubbery on physical examination. They can occur at any age and are more common in young adults.[4] These lesions are solitary, slow-growing, and equally distributed throughout the thyroid gland and rarely cause symptoms. In fact, the majority are discovered incidentally by the patient or detected during routine physical examination. Occasionally a follicular adenoma will suddenly increase in size due to internal hemorrhage into the center of the lesion, an event that may cause pain. Otherwise, the presence of symptoms should heighten the suspicion of a malignant process.

Follicular carcinoma generally occurs in an older age group than papillary carcinoma, peaking in the fifth decade of life. It is more common in women with a female to male ratio ranging between 2:1 and 5:1. Generally, the clinical presentation is similar to patients with benign follicular adenomas. In a recent review, 60% of patients presented with an asymptomatic thyroid mass. Symptoms occurred in 37% of patients, including hoarseness (15%), dysphagia (8%), and local compressive symptoms (6%).[6] Nodules that are firm or fixed on physical examination are also more suggestive of a malignant process.

Since follicular carcinoma disseminates hematogenously, lymph node metastases are rare, occurring in less than 10% of patients. However, 15-30% of patients will have distant disease at the time of diagnosis and may have associated pathological fractures or pulmonary insufficiency. Bone and lung are the most common sites of metastases, followed by liver and brain.

Diagnosis

The greatest diagnostic challenge in the evaluation of follicular neoplasms is the accurate differentiation between benign follicular adenomas and malignant carcinomas. The hallmark of follicular carcinoma is capsular or vascular invasion, a finding that is not always clear-cut. In fact, follicular carcinomas have been divided into two groups based on the degree of invasion. **Minimally invasive follicular carcinoma**, the least aggressive type of follicular cancer, is extremely difficult to differentiate from follicular adenomas due to histologic similarities.[1,4] Both the follicular adenoma and the minimally invasive follicular carcinoma are encapsulated, but the latter is defined by penetration of the lesion into the capsule or surrounding thyroid parenchyma. The distinction can be difficult due to the fact that in normal patients

the thyroid capsule is not always complete and subtle extensions of extrathyroidal tissue may be present. Minimally invasive lesions have an excellent prognosis.

Widely invasive follicular carcinoma, on the other hand, is more aggressive, often displaying characteristic features of malignancy such as extrathyroidal extension, frequent mitoses, vascular invasion, aneuploidy, and tumor necrosis.[1] Cellular characteristics may range from near normal-appearing follicular cells to anaplastic tissue. The most aggressive variety will often invade surrounding structures, such as the strap muscles and trachea, findings which portend a worse prognosis. The extent of capsular and vascular invasion plays an important role in the decision-making process and is one of several factors that directly influences prognosis. Careful evaluation of these features by both the pathologist and surgeon can not be over emphasized.

In recent years, the follicular variant of papillary carcinoma has received a great deal of attention. Lesions that are follicular in appearance but contain any feature of papillary carcinoma, such as psammoma bodies or optically clear nuclei (Orphan Annie nuclei), are now classified as the follicular variant of papillary carcinoma. The biologic behavior of these lesions is similar to that of pure papillary carcinoma and the management should be the same.

The work up of a thyroid nodule should be approached in a systematic, cost effective manner. When evaluating these patients, the importance of a thorough history and a complete physical examination can not be over emphasized. Historical information and physical findings can have a direct bearing on the decision-making process.

Follicular neoplasms of the thyroid are typically nonfunctioning lesions; therefore, thyroid function tests are usually normal and contribute little to the diagnosis. For the same reason, approximately 90% of follicular nodules appear “cold” on scintigraphy. In recent years, ultrasonography has been used more routinely than in the past, becoming the first-line imaging study at many centers. In particular, ultrasound has greatly improved the detection of nonpalpable thyroid nodules as well as the accuracy of FNA.

Although FNA has revolutionized the work up of differentiated thyroid cancer, it has contributed little to the preoperative decision-making process of follicular neoplasms. The heralding feature of follicular carcinoma—capsular or vascular invasion—can not be readily determined by FNA, a test designated to examine the characteristics of individual cells rather than the relationship of cells to surrounding structures (i.e., blood vessels). Despite these pitfalls, most patients with thyroid nodules should undergo FNA since it is well tolerated, relatively inexpensive, and easily performed in the office setting. Frozen section analysis is often noncontributory to the diagnosis of follicular carcinoma due to its poor ability to determine capsular penetration. Furthermore, frozen section analysis is time-consuming and expensive. Most often, the diagnosis of follicular carcinoma is made by examination of permanent histologic sections whereby the pathologist can accurately access capsular and vascular invasion.

Management

Even though the diagnostic yield of FNA is poor for follicular carcinoma, FNA plays an important role in the identification of follicular neoplasms. Given the difficulty in differentiating benign from malignant lesions, surgical therapy is indicated for the majority of follicular neoplasm. Separating patients into high, intermediate, and low risk groups (Fig. 5.1) may be helpful.[4] A trial of thyroid hormone suppressive therapy and continued observation may be indicated in low risk patients. Radioiodine scanning may be considered for those patients in the intermediate risk group, with surgical excision being indicated for all cold lesions identified on scintigraphy. All patients in the high risk group should undergo thyroid resection. Although clinical judgment, patient preference, and local expertise all play a role in the decision to observe a nodule with indeterminate follicular cytology, the author favors surgical therapy for all intermediate and high risk lesions. If the lesion is found to be benign on analysis of the permanent section, thyroid lobectomy and isthmusectomy are therapeutic. On the other hand, if the tumor is malignant, additional surgical therapy may be indicated as discussed below.

For follicular carcinoma, considerable controversy surrounds the extent of surgery. Several prognostic risk factors have been identified for differentiated thyroid cancer to help determine the optimal extent of surgical resection.[7,8] The Mayo clinic developed the AGES classification system which emphasizes age (> 40 for females, > 50 for males), grade (high vs low), extent (extracapsular vs intracapsular), and size of the tumor (> 4 cm).[7] However, this classification system was developed from a large retrospective analysis of patients with papillary cancer and is not truly applicable to patients with follicular carcinoma. The Lahey Clinic prefers the AMES classification which uses age, distant metastases, extent, and size as prognostic risk factors at the time of diagnosis.[8] Proponents of these systems prefer thyroid lobectomy and isthmusectomy for low risk patients, reserving total thyroidectomy for the high risk group.

Despite the utility of the AGES and AMES classification systems, there are several advantages to performing a total thyroidectomy for follicular carcinoma. Even though the overall mortality of differentiated thyroid cancer is low, a small percentage of low risk patients will die of their disease process. As such some clinicians support more extensive surgical resection for low risk patients, even those with lesions less than 1 cm in diameter.[4,6] Total thyroidectomy has the advantage of eradicating all gross and occult disease from the thyroid bed, thereby lowering the likelihood of local recurrence.[9] Some studies have also shown improved survival using this approach.[4] In addition, multicentric disease is eliminated by total thyroid resection and postoperative surveillance is facilitated. Thyroglobulin levels are easier to follow in the hypothyroid patient and iodine-131 scanning is more sensitive. Furthermore, the postoperative ablation of residual thyroid tissue or distant disease with iodine-131 is more effective following total thyroidectomy. In the hands of an experienced thyroid surgeon, total thyroidectomy can be performed with minimal morbidity.

Generally frozen section is used to confirm a previously suspected carcinoma and may be useful with an “atypical” cytology. The situation may arise where interpretation of a frozen section suggests a benign follicular adenoma but the

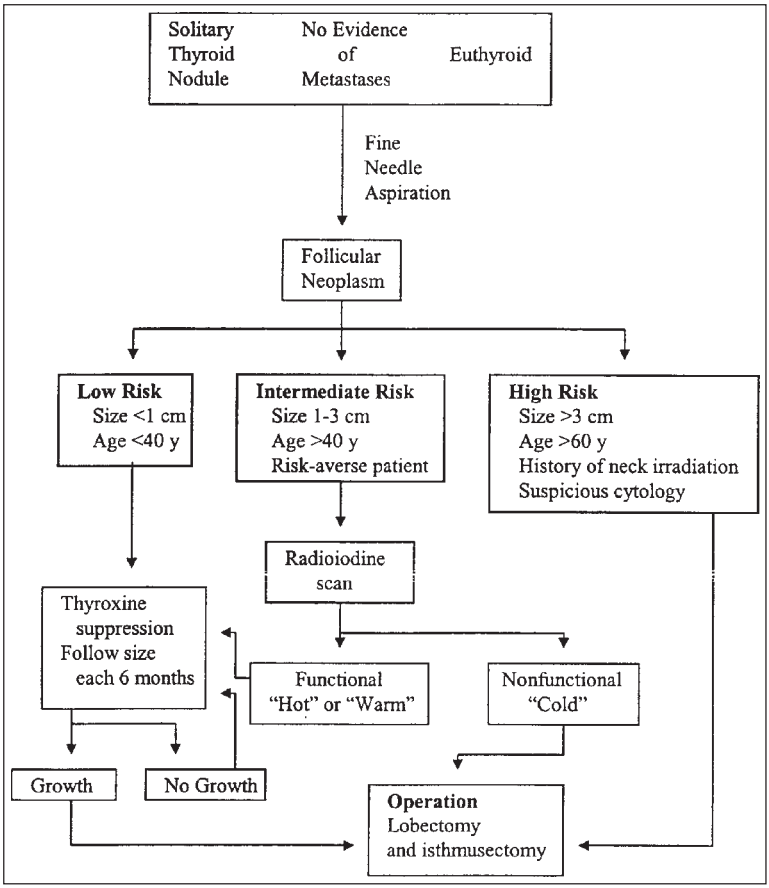

Fig. 5.1. Management scheme for patients with follicular neoplasms. Reprinted with permission from: Doherty G.M. Follicular neoplasms of the thyroid. In: Clark OH, Duh QY, eds. Textbook of Endocrine Surgery. 1st ed. WB Saunders Co., 1997.

permanent section reveals a follicular carcinoma several days following thyroid lobectomy. In this situation, completion thyroidectomy is generally indicated. Exceptions may include patients with the minimally invasive variety of follicular carcinoma or young patients with a primary lesion less than 1 cm in size. The prognosis of this type of follicular carcinoma is excellent and in most cases no further therapy is indicated. Although the incidence of lymph node metastases is low with follicular carcinoma, all grossly abnormal lymph nodes should be excised from the central nodal compartment and the carotid-jugular chain. An ipsilateral modified

neck dissection is preferred to the "berry picking" approach in the presence of palpable cervical adenopathy.

Postoperative Management

All patients with follicular carcinoma require lifelong treatment with exogenous thyroid hormone to suppress TSH synthesis, the production of which can stimulate the growth of differentiated thyroid cancer. Thyroid-stimulating hormone suppression lowers the recurrence rate of follicular carcinoma by diminishing the stimulation of TSH receptors which are present on the surface of differentiated thyroid tumors.[9] Ideally, TSH levels should be suppressed to undetectable levels with the lowest possible dose of thyroid hormone, especially since replacement therapy can cause side effects such as osteoporosis and thyrotoxicosis.[4]

Iodine-131 scanning plays an essential role in the postoperative management of differentiated thyroid cancer. Most authorities agree that iodine-131 scanning is indicated in the vast majority of patients with follicular carcinoma, excluding only young patients with the minimally invasive variety or with primary lesions less than 1 cm in size. There are two basic strategies for obtaining such a scan. The first strategy involves radioiodine scanning six weeks following thyroidectomy. The patient is started on T3 replacement therapy (liothyronine) in the immediate postoperative period, a form of therapy which has a much shorter half-life than that of T4 (thyroxine). Liothyronine is continued for four weeks at which time it is discontinued to induce a state of hypothyroidism in preparation for radioiodine scanning. Once the TSH level has increased to a value greater than 40 U/ml—typically two weeks following the cessation of T3—the iodine-131 scan is performed. The administration of T3 has the advantage of minimizing the duration of hypothyroidism, a state which may cause uncomfortable symptoms.

With the second strategy, iodine-131 scanning is performed 6 months following surgery. The patient is started on T4 immediately after thyroidectomy and maintained on this therapy until 6 weeks before radioiodine scanning. The patient may then be started on T3 as with the first approach. Obtaining the radioiodine scan 6 months following surgical therapy has the theoretic advantage of improved sensitivity by allowing any residual disease to "mature". Currently, the use of recombinant TSH is being investigated in a phase II trial, the preliminary results of which are encouraging. Recombinant TSH, which stimulates residual thyroid tissue by binding to TSH receptors, is administered without having to stop thyroid hormone replacement therapy, thereby avoiding the side effects of hypothyroidism.

During the initial iodine-131 scan, a small dose of radioiodine is used (3-5 mCi). If any residual or distant disease is identified, a larger dose is administered ranging from 100-250 mCi based on the extent of disease and the patient's overall state of health. Subsequent radioiodine scans are performed at 6 month intervals with the administration of therapeutic doses of iodine-131 as indicated. This cycle of scanning and treatment is repeated until there is no evidence of disease, at which time there is no need for further radioiodine scanning.

Serum thyroglobulin is a sensitive tumor marker which is best obtained when the patient is hypothyroid, such as when thyroid hormone therapy has been stopped in preparation for iodine 131-scanning. Serum thyroglobulin can be measured while the patient is on suppressive TSH therapy but the results are less reliable and often harder to interpret. Baseline levels should be obtained following thyroidectomy and again when hormone replacement therapy has been stopped in preparation for radioiodine scanning. An increase in serum thyroglobulin is suggestive of recurrent disease. Serum thyroglobulin levels are obtained annually and serve as the mainstay of long-term surveillance.

Prognosis

The outcome of patients with follicular carcinoma of the thyroid is generally worse than that of papillary carcinoma and is directly related to the stage of disease at the time of diagnosis. Patients are divided into four clinical stages based on the extent of disease at presentation:[3]

Stage I—Intrathyroidal disease
Stage II—With cervical lymph node metastases
Stage III—With extrathyroidal extension
Stage IV—With distant metastases

While overall 10 year survival for follicular carcinoma is felt to be approximately 85%, the true overall 10 year survival for follicular carcinoma is difficult to determine, ranging from 43-95% in several large retrospective series.[4] This wide variability in survival is most likely due to the difference in the patient populations studied, with some series having a higher percentage of patients with metastatic disease at the time of diagnosis.

Several prognostic factors have been identified that influence survival. The most frequently cited factors influencing the prognosis of follicular thyroid carcinoma are the degree of capsular invasion and the presence of angioinvasion.[6] Lesions with high degrees of invasion tend to be more aggressive, carrying a worse prognosis. Age at the time of diagnosis is also an important prognostic factor, with older patients having a lower survival than younger patients. Other risk factors include the presence of metastatic disease at presentation, extrathyroidal extension, lymph node involvement, and an aneuploid DNA pattern.

Hürthle Cell Neoplasms

Introduction

Hürthle cell neoplasms are an uncommon group of thyroid epithelial tumors that continue to generate much controversy. There is ongoing disagreement, for example, regarding the cell of origin of these well differentiated thyroid neoplasms (follicular vs parafollicular). Furthermore, changes in the classification of differentiated thyroid cancer over the last 20 years have added to the controversy surrounding Hürthle cell neoplasms. In 1988, the World Health Organization changed the classification of Hürthle cell carcinoma to follicular carcinoma, oxyphilic cell type. Certain investigators, however, believe that these lesions should be classified separately as

Hürthle cell tumors, citing the unique biologic behavior of Hürthle cell neoplasms when compared to follicular neoplasms.[10] The literature also contains additional names for Hürthle cell neoplasms, such as Askanazy cell or Langhans tumors, but they are most commonly referred to as Hürthle cell neoplasms.

Some surgeons support the notion that all Hürthle cell neoplasms are potentially malignant and therefore warrant aggressive surgical therapy. The proponents of this school of thought cite reports of histologically documented Hürthle cell adenomas that ultimately metastasized, resulting in patient death.[10] Others feel that the biologic behavior of Hürthle cell neoplasms can be adequately predicted by certain histopathologic features which can be used to identify patients for whom a more conservative approach is appropriate.[9] Once an Hürthle cell neoplasm is shown to be malignant, however, most surgeons agree that an aggressive surgical approach is warranted; surgery is the only effective therapy for Hürthle cell carcinoma.

Presentation

Hürthle cell neoplasms occur less commonly than follicular neoplasms, comprising 4.5-10% of all thyroid neoplasms.[1,5,9,10] The incidence of Hürthle cell carcinoma is equally low, representing 10-35% of Hürthle cell neoplasms and 0.4-10% of all thyroid malignancies.[1,9] Close to three-fourths of Hürthle cell carcinomas are confined to the thyroid gland and lymph node metastases occur in 10%. Approximately 15% of patients will have distant metastatic disease at the time of diagnosis.[5,10]

The presentation of Hürthle cell neoplasms is similar to that of follicular neoplasms, appearing as a solitary, nonfunctioning nodule. Symptoms are uncommon and their presence should raise the level of suspicion of a malignant process. Although Hürthle cell neoplasms may present at any age, they generally present later in life than papillary and follicular lesions, most commonly appearing in the sixth decade of life.[10] Hürthle cell neoplasms are more common in females with a female to male ratio ranging from 2:1 to 10:1, but the ratio of malignant lesions is actually higher in men. There is an increased incidence of malignancy with increasing age. Prior exposure to radiation is also associated with a higher incidence of Hürthle cell carcinoma and up to 40% of these patients will have a concomitant papillary or follicular cancer at a site different from the index nodule.[5,10]

One third of patients with Hürthle cell neoplasms will have an additional nonmalignant thyroid disorder such as Graves' disease, multinodular goiter, or Hashimoto's thyroiditis; and accordingly, some patients may present with symptoms of hyperthyroidism. Because of this finding, the mere presence of Hürthle cells does not necessarily signify a neoplastic process. The presence of a capsule surrounding Hürthle cells, on the other hand, is the defining characteristic of Hürthle cell neoplasms.

Diagnosis

Hürthle cells are large, polygonal eosinophilic cells with a fine granular acidophilic cytoplasm containing nuclei that are larger than the nuclei of normal follicular cells.[10] Hürthle cell neoplasms are encapsulated lesions that contain at least a 75% Hürthle

cell component and are generally believed to be a variant of follicular neoplasms.[5,9] Evidence supporting the follicular origin of Hürthle cells includes histologic studies demonstrating the transition of follicular to Hürthle cells, the ability of Hürthle cells to secrete thyroglobulin, and the presence of a functional thyroid-stimulating hormone receptor-adenylate cyclase system.[5,9] In addition, the presence of Hürthle cells in several benign thyroid conditions as previously discussed further supports this theory. However, other authorities believe that Hürthle cell neoplasms represent a distinct entity, citing the unique oncogenic expression and the relative inability of Hürthle cells to absorb radioiodine.[9] The fact that Hürthle cell neoplasms generally display a more aggressive biologic behavior than follicular neoplasms also lends credence to the unique origin of Hürthle cells.

The diagnostic dilemmas that surround follicular neoplasms also apply to Hürthle cell neoplasms. Fine needle aspiration can accurately differentiate Hürthle cell neoplasms from non-neoplastic disorders, but as is true with follicular lesions, the differentiation of a benign from a malignant process is much more difficult. The diagnosis of Hürthle cell carcinoma is based on the presence of capsular or vascular invasion, extrathyroidal extension, or distant disease, features which are not reliably determined by cytopathology. Although frozen section analysis is often utilized by surgeons, multiple sections are often required to fully appreciate capsular or vascular invasion, the presence of which is more reliably determined by permanent sections. The measurement of nuclear DNA content and ploidy patterns have also been disappointing in the differentiation of Hürthle cell adenomas and carcinomas.[10] As a result of these pitfalls, surgical therapy is most often required to secure a correct diagnosis.

Management

Because of the difficulty in differentiating benign from malignant disease and the potential malignant behavior of benign lesions, many surgeons support an aggressive surgical approach for all Hürthle cell neoplasms.[5,10] In addition, the majority of patients with Hürthle cell carcinoma do not respond to iodine-131 ablation therapy, rendering thyroidectomy the only effective treatment for malignant disease. Others, however, support a more conservative approach, recommending total thyroidectomy only for histologically documented malignant disease.[1] Proponents of the conservative approach cite the potential surgical complications that can arise from overtreating benign disease with total thyroidectomy in addition to the lifelong requirement for thyroid hormone replacement therapy.

In an excellent review article on the management of Hürthle cell tumors of the thyroid, McLeod and Thompson provide a concise algorithm for the treatment of Hürthle cell neoplasms.[10] Following FNA, all patients with cytologic confirmation of a Hürthle cell neoplasm, should undergo ipsilateral thyroid lobectomy and isthmusectomy with frozen section analysis. If the results of this analysis shows Hürthle cell nodules in association with a benign thyroid disorder, such as Graves' disease or Hashimoto's thyroiditis or if there are no signs of invasion, the operation is terminated. On the other hand, if frozen section analysis reveals a malignant process, total thyroidectomy is performed. In the setting of malignant disease, subtotal

thyroidectomy is to be avoided due to the higher recurrence rate in patients undergoing lesser procedures when compared to total thyroidectomy.[5,10] If upon interpreting the permanent sections the diagnosis changes from a Hürthle cell adenoma to carcinoma, completion thyroidectomy is performed within a few days of the initial procedure.

There are a number of special circumstances that also warrant an aggressive surgical approach at the initial operation. Up to 50% of patients with a Hürthle cell neoplasm and a history of head and neck irradiation will have a concomitant differentiated thyroid neoplasm; total thyroidectomy is indicated in this patient population.[5] Although the majority of malignant lesions are larger than their benign counterparts, there appears to be no correlation between lesion size and malignant potential. Nevertheless, total thyroidectomy is reasonable in patients with nodules larger than 4 cm in diameter. Palpable contralateral nodules or the presence of an aneuploid DNA pattern in medium-sized benign lesions are also relative indications for total thyroid resection. The presence of an aneuploid nuclear DNA pattern in Hürthle cell neoplasms has been associated with an increased risk of recurrence, distant metastases, and death.[10]

A rare Hürthle cell variant of papillary carcinoma has been identified, comprising about 2-8% of papillary cancers.[1] Unlike the follicular variant of papillary carcinoma whose biologic behavior is similar to pure papillary carcinoma, the biologic behavior of the Hürthle cell variant is more aggressive. Total thyroidectomy should be strongly considered for these lesions.

For the most part, the follow up of patients with Hürthle cell carcinoma is similar to that for follicular carcinoma. The administration of thyroid hormone suppressive therapy and the periodic measurement of thyroglobulin levels play an important role in the postoperative management. Unlike follicular carcinomas, however, Hürthle cells do not concentrate radioiodine, rendering iodine-131 scanning ineffective in the detection and treatment of most patients with metastatic disease.[1,5,9,10] Likewise, chemotherapy and external irradiation have not been shown to be effective and should only be considered on an individualized basis.

Prognosis

Hürthle cell carcinomas are generally more aggressive than follicular and papillary cancers and have a prognosis that falls somewhere between that of follicular and medullary carcinoma (i.e., 10 year survival of 65%). In light of the fact that surgery is the only effective treatment for Hürthle cell carcinoma, the extent of disease as well as the extent of surgery greatly influences outcome. An aneuploid DNA pattern has also been shown to independently correlate with decreased patient survival.[1,2,10] Unlike follicular carcinomas, lesion size, patient age, and histologic grade do not seem to significantly influence prognosis

Summary

Follicular and Hürthle cell neoplasms are uncommon tumors of the thyroid gland. The differentiation of benign and malignant pathology is dependent upon the demonstration of full thickness capsular penetration or angioinvasion, features

which are not easily determined by FNA or frozen section analysis. Once a diagnosis of carcinoma has been established, total thyroidectomy is the treatment of choice in most cases, especially in the case of radio-insensitive Hürthle cell tumors. Postoperative radioiodine scanning is indicated in most patients with follicular carcinoma, but is of little benefit in patients with Hürthle cell carcinoma. Life long thyroid hormone suppressive therapy is recommended in all cases of differentiated, nonmedullary thyroid carcinoma and serum thyroglobulin levels should be monitored on an annual basis to facilitate the early detection of recurrent disease.

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CHAPTER 6

Differentiated Thyroid Carcinoma

Steven A. De Jong

Introduction

Differentiated thyroid carcinoma (DTC) refers to both papillary and follicular carcinomas which arise from the thyroid follicular cell. Thyroid cancers associated with low-dose external radiation exposure to the head or neck are also included, as most of these malignancies are papillary carcinoma. DTC is uncommon but highly curable when compared to other epithelial carcinomas and is usually discovered during the evaluation of a thyroid nodule, cervical mass, and/or cervical lymphadenopathy. Controversy surrounds the extent of surgical treatment required, the indication for use of radioactive iodine and the use of thyroxine for TSH suppression. Important advances have recently been made in understanding the potential causes and tumor biology of DTC, improving methods for diagnosis, staging and management and predicting the clinical behavior and prognosis of individual tumors. Cost effective strategies for early diagnosis have been developed, and treatment and follow up are often tailored to the probability of tumor recurrence or aggressive behavior. The few tumors with the potential for aggressive behavior can usually be identified at the time of diagnosis and properly treated with multimodality therapy.

Epidemiology and Classification

Thyroid carcinoma is classified by many subtypes (Table 6.1) and accounts for 1.5% of all cancers in the United States. The age-adjusted annual incidence for thyroid carcinoma in the U.S. is less than 40 cases per one million people and 12,000-15,000 new cases are diagnosed each year.[1,2] While 4-5% of the population have thyroid nodules, only four% of these nodules actually contain differentiated thyroid carcinoma. Several factors however, can increase this incidence. Patients, for example, who are exposed to low dose irradiation to the head or neck, commonly develop nodular thyroid disease and harbor thyroid carcinoma in 30-40% of these thyroid nodules. Ten percent of all differentiated thyroid carcinomas occur in children and adolescents as they are uniquely sensitive to radiation exposure as a major risk factor for thyroid carcinogenesis. These young patients generally have more aggressive tumors, higher rates of recurrence and are more likely to develop cervical lymph node metastasis (60-90%) when compared to a similar adult population (30-40%).[3]

Papillary thyroid carcinoma accounts for 70-90% of all thyroid malignancies and 90% of all radiation-induced thyroid cancers. Follicular cancers represent 10-15% of thyroid malignancies and are generally present in older patients. Table 6.2 sum-

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Table 6.1. Histologic classification of thyroid carcinoma

Differentiated Thyroid Carcinoma—Follicular thyroid cell origin
- Papillary thyroid carcinoma
  - Follicular, tall cell, mucoid, or insular variant
- Follicular thyroid carcinoma
  - Hürthle cell carcinoma
- Anaplastic thyroid carcinoma

Medullary Thyroid Carcinoma—Parafollicular or C cell origin
- Sporadic medullary thyroid carcinoma
- Non-MEN familial medullary thyroid carcinoma
- Multiple endocrine neoplasia type 2A (MEN 2A)
  - Multifocal medullary thyroid carcinoma
  - Parathyroid hyperplasia
  - Pheochromocytoma
- Multiple endocrine neoplasia type 2B (MEN 2B)
  - Multifocal medullary thyroid carcinoma
  - Pheochromocytoma
  - Marfanoid habitus and mucosal neuromas

Table 6.2. Distinguishing features. Papillary and follicular thyroid carcinoma

Feature	Papillary	Follicular
Mean Age (years)	38-45	48-53
Female:Male Ratio	3-4:1	1:1
Incidence	70-90 %	10-15 %
Radiation induced	Yes	Rare
FNAB accuracy	90-95 %	Difficult to Dx
Pattern of spread	Lymphatic	Hematogenous
Multicentricity	30-50 %	10-15 %
Nodal involvement	30-40 %	10-15 %
Recurrence (20 yr.)	10-15 %	20-30 %
Distant metastasis	5-10 %	20-25 %
Survival (20 yr.)	90-95 %	80-85 %

marizes some of the distinguishing features of papillary and follicular carcinomas of the thyroid gland. The median age at diagnosis for DTC is 40-50 years and papillary thyroid carcinoma is three to four times more common in women than in men. Clinically evident thyroid carcinoma is much less common than incidental occult microscopic thyroid carcinoma which is found in 3-13% of autopsied patients.[3] This demonstrates the benign nature of most of these cancers. Death from thyroid carcinoma is unusual. It accounts for only 1000-1200 deaths annually in the U.S., and it represents less than 1% of all cancer-related deaths. Recent 20 and 30 year mortality rates for papillary carcinoma range from 3-12% with 40 year follow up reported.[1-3,7] The 20 and 30 year mortality rate is slightly higher in men. The overall

prognosis for follicular carcinoma is somewhat less favorable, but is still excellent when compared to other epithelial malignancies.[4]

Pathology, Pathogenesis and Carcinogenesis

The pathology of papillary and follicular thyroid carcinoma differs in many aspects, but both malignancies originate from the thyroid follicular cell. Papillary carcinoma is an unencapsulated tumor with papillary and follicular architecture, consisting of single layers of thyroid cells arranged around vascular stalks that form papillae. The cells are characterized by overlapping nuclei with a ground-glass appearance, longitudinal grooves, and invaginations of cytoplasm into the nuclei. Laminated calcified spheres, known as psammoma bodies, are also seen in 40-50% of tumors. Encapsulated, follicular, tall-cell, columnar-cell, clear-cell, and diffuse sclerosing carcinomas are all recognized histologic variants of papillary thyroid carcinoma. The follicular variant of papillary carcinoma behaves much like papillary carcinoma, but the presence of tall cells within the tumor suggests an aggressive clinical course. Multicentricity is found in 30-50% of these tumors and is commonly seen (70-80%) in radiation-induced papillary thyroid carcinoma. Papillary carcinoma spreads through lymphatic channels and cervical lymph node metastases is present in 30-40% of patients.[3]

Follicular carcinoma is characterized by a follicular appearance without the specific nuclear features seen in papillary cancers. These neoplasms are distinguished from follicular adenomas by the presence of neoplastic invasion of the tumor capsule and adjacent blood vessels. The cytologic appearance of these malignant follicular cells is often quite bland and fine needle aspiration biopsy cytology alone can not distinguish benign follicular adenomas from their malignant counterpart.[3,5] Distinguishing the histologic features of a cellular follicular adenoma from a follicular carcinoma with minimal capsular invasion still remains a challenge for even the most experienced endocrine pathologist and intraoperative frozen section of these tumors has not been uniformly helpful. Likewise, DNA ploidy and cell cycle analysis have not proven reliable in identifying patients with follicular malignancy.

There are several recognized forms of pure follicular carcinoma based on the invasive behavior and metastatic potential of the tumor. Minimally invasive tumors display an indolent course, while tumors with major capsular invasion and angioinvasion behave aggressively with local invasion, frequent recurrence and distant spread. Multicentricity and lymph node involvement are less frequent (10-20%) than in papillary carcinoma, and metastasis to the lungs and bones result from a tendency of these tumors to spread by hematogenous pathways instead of lymphatic channels. Hürthle cell carcinoma is a cytologic variant of follicular carcinoma characterized by the presence of large oncocytic cells with bizarre nuclei, eosinophilic cytoplasm, and abundant mitochondria. Preoperative and intraoperative determination of Hürthle cell malignancy, as in other follicular thyroid malignancies, is difficult or impossible, but histology can usually determine benign adenomas from Hürthle cell carcinoma. The malignant potential of these tumors has been the subject of debate for many years, but Hürthle cell malignancy, in contrast to pure follicular

carcinoma, appears to have a greater propensity for aggressive behavior, lymph node metastasis and resistance to radioiodine therapy.[4]

The major risk factor for developing differentiated thyroid carcinoma is exposure to low-level external radiation. Enlargement of the thymus, scalp ringworm, recurrent tonsillitis, cervical adenopathy, facial acne and other head and neck disorders were commonly treated with 100-1500 cGy of external radiation from 1940 until the late 1960s. A dramatic increase in the diagnosis of differentiated thyroid carcinoma, predominately papillary carcinoma, resulted from these treatments and displayed an average latency period of 5 years from exposure to diagnosis. Young patients exposed between the ages of 5 and 15 seem to be at highest risk for developing radiation-associated thyroid carcinoma.[6] This risk, which is increased after radiation exposure of as little as 10 cGy, is highest at 20 years after exposure and declines gradually thereafter. These same observations have been seen in Hiroshima and Nagasaki after the atomic bomb, in Nevada and in the Marshall Islands after atomic bomb testing and, most recently, in the Ukraine following the Chernobyl nuclear disaster in 1989.[1] Differentiated thyroid carcinoma, especially in children, has increased over 100 fold in these regions of the world as a result of the release of large amounts of external radiation in the form of ^{131}I and other short lived radioactive iodine isotopes. Higher doses of radiation used for the treatment of Hodgkin's disease and other solid organ epithelial malignancies frequently result in cell death and appear to cause a smaller but appreciable increase in the incidence of differentiated thyroid carcinoma.

Other factors such as iodine deficiency, autoimmune thyroid disease, hyperthyroidism, sex hormone status and alcohol intake have all been implicated in the development of thyroid carcinoma, but remain unproven. Possible genetic patterns of differentiated thyroid carcinoma include patients with Gardner's syndrome (familial colonic polyposis) and Cowden's disease (familial goiter and skin hamartomas), but less than 3% of all papillary and/or follicular thyroid carcinomas are truly familial.[3] Cigarette smoking has not caused an increase in the incidence of thyroid carcinoma.

Over the last five years, advances in the identification of oncogenes responsible for thyroid carcinogenesis have provided an outline of possible molecular events leading to the development of DTC. The RET proto-oncogene, which encodes a tyrosine kinase receptor (TRK), is not normally expressed in the normal thyroid follicular cell. Rearrangement of this gene and the TRK gene alters the structure of chromosome 10 and is detectable in 10-30% of papillary carcinomas and 60-80% of radiation-associated thyroid carcinomas.[1,3] The end result is the expression of high levels of tyrosine kinase in the affected follicular cell which may be one trigger point in thyroid carcinogenesis. Point mutations of the RAS gene and p53 tumor-suppressor gene are also seen in thyroid adenomas and follicular thyroid carcinomas with varying degrees of frequency.

Clinical Presentation and Diagnosis

Most patients with differentiated thyroid carcinoma initially present with nodular thyroid disease or a cervical mass. The nodule is more likely to contain carcinoma in children, adolescents, males, patients exposed to low doses of radiation to

the head or neck, and patients older than 60 years of age. Associated symptoms suggesting differentiated thyroid carcinoma include hoarseness from a vocal cord paresis, recent onset or rapid growth of a solitary nodule, dysphagia, hemoptysis, or cervical pain related to the nodule or cervical spine. Uncommon presentations include cervical lymphadenopathy with or without obvious thyroid pathology, symptomatic bone pain from metastatic disease to the spine, pelvis or ribs, asymptomatic pulmonary metastases found radiographically, and focal neurologic abnormalities from distant spread to the brain.

Physical examination may reveal a hard, irregular, solitary, fixed thyroid mass causing local compressive symptoms with or without associated cervical lymphadenopathy. Palpable lymph node metastases, when present, are usually evident along the mid and lower portions of the jugular vein and in the posterior triangle of the neck. Direct laryngoscopy should be performed to identify the existence of a vocal cord paresis or, rarely, tracheal invasion when present. A thyroid mass with an associated ipsilateral vocal cord paresis contains carcinoma until proven otherwise.

There are no effective serum tumor markers useful in screening patients for differentiated thyroid carcinoma. Initial laboratory evaluation includes the measurement of serum ultrasensitive thyroid-stimulating hormone (TSH), free thyroid hormone levels, antithyroid autoantibodies, and serum calcium to exclude coexistent parathyroid disease which can be found in patients with nodular thyroid disease and thyroid carcinoma. Most patients with thyroid nodules and thyroid carcinomas are biochemically euthyroid, but subclinical or biochemical hyperthyroidism associated with uninodular or multinodular thyroid disease can be detected by laboratory screening. Such patients have a 3-6% incidence of associated thyroid carcinoma. The presence of thyroid autoantibodies suggests Hashimoto's thyroiditis which may raise the suspicion of thyroid dysfunction and identify a controversial risk factor for DTC. Patients with a familial history of thyroid carcinoma should be screened for medullary thyroid carcinoma with serum calcitonin and CEA levels. In addition, serum calcium levels, urinary catecholamines, and adrenal gland imaging studies should be obtained in all patients suspected of having medullary thyroid carcinoma to identify a multiple endocrine neoplasia syndrome and the existence of a pheochromocytoma.

Obtaining thyroid imaging studies on all patients with nodular thyroid disease remains controversial. The main options currently available are thyroid scintigraphy and ultrasonography. The use of thyroid scintigraphy has declined in this country because of the accuracy and simplicity of ultrasonography, and the specificity of serum ultrasensitive TSH in identifying the patient with hyperthyroidism. Thyroid scanning and uptake measurement using ^{123}I is useful in patients with diffuse thyromegaly or nodular thyroid disease with clinical and/or biochemical hyperthyroidism to diagnose Graves' disease, an autonomous "hot" solitary nodule or a toxic multinodular goiter. It may also be useful to determine the need for thyroidectomy in patients with "follicular neoplasia" cytology found on fine needle aspiration biopsy (FNAB) of the thyroid nodule. Thyroidectomy may not be mandatory for the follicular nodule that concentrates the radioiodine tracer. The incidence of thyroid malignancy in a "cold" thyroid nodule remains 15-20%.

Ultrasonography, using 5-10 mHz probes, is a good imaging modality for nodular thyroid disease. Cystic and solid characteristics of the nodule are easily identified along with nonpalpable nodular thyroid disease throughout the remainder of the gland. Local invasion of the trachea and/or carotid sheath contents can usually be identified when in addition to the presence of pathologic lateral and central cervical lymphadenopathy. Ultrasonography can also guide the successful fine needle aspiration biopsy of nonpalpable small posterior thyroid nodules. The incidence of thyroid carcinoma in solid solitary thyroid nodules is 15-20% and as high as 10-15% in cystic thyroid nodules that recur after several successful percutaneous needle aspirations.

Staging and Prognostic Factors

There have been several staging and classification systems proposed for characterizing differentiated thyroid carcinoma. The simplest appears to be the AMES classification which divides patients into low risk and high risk for aggressive tumor behavior and recurrence (Table 6.3). Factors such as age, extrathyroidal tumor extension, tumor size, and presence of metastasis are all factors important in this classification system.[7] A modification of this staging system, known as AGES, includes histologic tumor grade in the classification and combines metastases and extrathyroidal extension in the category described as extent of disease at presentation. This classification system is also widely used and can be associated with a scoring system to predict prognosis based on the aforementioned clinical features. Low risk patients have small thyroid carcinomas confined to the gland itself with no lymphatic or distant metastases. Factors placing patients in the high risk group include males older than 41 years, females older than 51 years, extrathyroidal extension of the DTC, high grade tumor histopathology, extensive nodal involvement or distant metastases, and a primary tumor diameter of greater than 5 cm.[1,5] Nearly 90% of patients with papillary thyroid carcinoma are classified in the low risk category with an associated 20-year survival probability of nearly 90-95%. In contrast, high risk patients with DTC are characterized by aggressive and invasive tumor behavior, extensive nodal and/or distant metastasis, frequent local recurrence, and death in nearly 50% of these patients over a 5-10 year follow-up period.

The TNM classification has also been applied to patients with differentiated thyroid carcinoma (Table 6.4). Tumor size, presence of lymph node metastases, and distant metastases comprise the major information of this classification system. Over 80% of patients classified with a TNM system are Stage I with an associated 20-year survival rate of nearly 100%.[3] Stage I is defined as disease limited to the thyroid gland, Stage II includes cervical lymph node metastases, Stage III adds extrathyroidal extension and Stage IV identifies patients with distant metastasis. Only 5% of all patients are classified as Stage IV and have an associated 5-year survival of only 25%.

Despite the many variations in these classification systems, there are certain factors that influence the prognosis of differentiated thyroid carcinoma. The best prognostic group includes younger patients with small primary tumors without nodal and distant metastases, and extrathyroidal extension. Complete tumor resection at the

Table 6.3. AMES/AGES staging classification for DTC (age, metastasis/grade, extent, size)

Low Risk Patient
- Men younger than 41 and women younger than 51years with disease confined to the thyroid and no regional/distant metastases
- Older patients without regional/distant metastases, extrathyroidal extension, or major tumor capsular invasion
- Primary tumor size less than 4 cm in diameter
- Histologically well differentiated low grade tumors

High Risk Patient (All patients who do not meet the "low risk" criteria)
- Young patients (M < 41 and F < 51 years old) with regional/distant metastases and/or extra-thyroidal extension
- Older patients with regional/distant metastases and/or extrathyroidal extension
- Major tumor capsule invasion (usually follicular carcinoma)
- Primary tumor size greater than 4 cm in diameter
- Histologically poorly differentiated high grade tumors (Insular, mucoid, and tall cell variants)

Table 6.4. TMN staging for DTC[3]

Primary Tumor Diameter (T)
- T1 = ≤ 1 cm
- T2 = > 1 cm and ≤ 4 cm
- T3 = > 4 cm,
- T4 = extension beyond thyroid capsule

Lymph Node Involvement (N)
- N0 = no lymph node metastases
- N1 = positive lymph node metastases

Distant Metastases (M)
- MX = metastasis unknown
- M0 = no distant metastases,
- M1 = positive distant metastases

Stage	**Age**	
	< 45 yrs.	≥ 45 yrs.
I	Any T, any N, M0	T1, N0, M0
II	Any T, any N, M1	T2, T3, N0, M0
III		T4 or N1, M0
IV		Any T or N, M1

time of surgery is also an important prognostic feature that predicts a low incidence of tumor recurrence and disease-specific mortality. There is continued controversy over the appropriate treatment for patients with "low risk" tumors, but all are in agreement that high risk tumors or patients with surgically unresectable disease need aggressive therapy to achieve acceptable survival rates.

Surgical and Medical Treatment

A total or near total thyroidectomy remains the gold standard for treating differentiated thyroid carcinoma and achieving the goal of removing all thyroid tissue and involved cervical lymph nodes from the neck. Complications are minimal when meticulous preservation of the recurrent laryngeal nerves and parathyroid tissue is accomplished.[8] Complications such as hypoparathyroidism, unilateral or bilateral recurrent nerve injury, and cervical hematoma should occur in less than 1-2% of all patients undergoing this procedure when meticulous dissection along the thyroid capsule is performed. Liberal use of parathyroid autotransplantation into the sternocleidomastoid muscle or the muscles of the forearm, when anatomic preservation is impossible, will further minimize the incidence of hypoparathyroidism after thyroidectomy.

Total thyroidectomy is associated with the lowest recurrence rates for DTC in the central and lateral neck. Recurrence is a poor prognostic sign as 40-50% of these patients eventually die of DTC. Complete thyroid resection also facilitates the treatment of multicentric DTC, especially when contralateral thyroid lobe involvement is detected. Total thyroidectomy also facilitates effective use of postoperative radioactive iodine therapy for diagnostic and treatment purposes. Finally, complete removal of all thyroid tissue allows the use and accurate interpretation of serial plasma thyroglobulin levels in the early identification of recurrent thyroid carcinoma.

Controversy continues regarding the need for total or near total thyroidectomy in all patients with differentiated thyroid carcinoma. Data exists to support ipsilateral total and contralateral subtotal thyroidectomy in low risk patients with small thyroid carcinomas less than 1.5-4 cm in diameter that are limited to the thyroid gland.[7] Local recurrence, however, in these patients appears to be significantly higher during long term postoperative surveillance. Serum thyroglobulin levels can be followed to detect early tumor recurrence, but are less effective and sensitive when compared to the use of thyroglobulin in patients treated with total thyroidectomy. Radioiodine imaging and therapy may also be less effective with normal thyroid tissue still present in the neck. This procedure is appropriate for surgeons treating low risk patients who are uncomfortable performing a total thyroidectomy with a low rate of associated complications. It also seems quite possible that the surgical cure rates for occult, incidental or minimal papillary thyroid carcinomas, defined as carcinomas less than 10 millimeters in diameter, likely approaches 10%, independent of the extent of thyroidectomy.

Total thyroidectomy is optimal treatment for most patients with preoperative identification of differentiated thyroid carcinoma.[8] Microscopic, occult or minimal papillary thyroid carcinomas noticed incidentally on final histopathologic examination of the surgical specimen may be adequately treated by the complete ipsilateral lobectomy and contralateral subtotal thyroid resection which is the minimal surgical resection recommended for all forms of nodular thyroid disease. Completion thyroidectomy after 8-12 weeks is advisable for certain patients with follicular thyroid carcinomas that could not be identified with preoperative FNAB cytology or intraoperative histopathologic methods. Multicentricity or unexpected cervical lymph node metastases may also mandate completion thyroidectomy in young patients

with long life expectancies. Cervical lymph node metastases in the central and/or lateral neck can be confirmed by preoperative FNAB cytology or intraoperative histopathology. This finding mandates the performance of a total thyroidectomy, central cervical lymphadenectomy, and/or immediate or staged ipsilateral modified radical cervical lymphadenectomy to facilitate postoperative radioiodine imaging and treatment. Finally, patients with distant metastases from DTC usually benefit from total thyroidectomy and postoperative ablative therapeutic radioiodine to treat the pulmonary or osseous metastases.

Lymphatic and Distant Metastasis

Lymphatic metastasis from papillary thyroid cancer can be present in as many as 30-40% of patients. In contrast, follicular thyroid carcinoma spreads preferentially via a hematogenous route and the rate of cervical lymph node metastases for these patients ranges from 10-20%. Preoperative cervical ultrasonography or computerized tomography may identify cervical lymphadenopathy associated with the thyroid tumor and raise the suspicion of cervical lymph node metastasis. Optimal treatment involves an important distinction between central lymph node metastasis located between the jugular veins, and lateral, jugular or posterior cervical lymph node involvement.[1] Central lymph nodes consist primarily of superior pretracheal (Delphian nodes), inferior pretracheal lymph nodes, and the perithyroidal lymph nodes adjacent to the thyroid capsule, inferior thyroid artery and recurrent laryngeal nerve. Lateral lymph nodes consist generally of all jugular, supraclavicular, and posterior triangle cervical lymph nodes.

Enlarged central or lateral cervical lymph nodes encountered during thyroidectomy should be excised and examined with intraoperative frozen section analysis to identify the presence of thyroid carcinoma. Immediate or delayed ipsilateral modified radical neck dissection is recommended for treatment of metastatic lateral cervical lymph nodes as it spares the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein while removing all lymphatic tissue within the boundaries of the anterior and posterior triangles of the neck. There is no evidence that a radical neck dissection that sacrifices these structures improves outcome in the vast majority of patients with DTC. Local extension of the tumor, however, into one or several of these structures may require that a radical dissection be performed. Central cervical lymph node metastasis from DTC is treated by excision and node dissection during total thyroidectomy. Prophylactic cervical lymph node dissections are not performed routinely for differentiated thyroid carcinoma.

Distant metastasis from DTC occurs in 10-15% of patients and is usually discovered initially in the lungs or bones. Pulmonary metastasis is more frequent in young patients while osseous metastases predominate in older patients with follicular thyroid carcinomas. Symptoms from pulmonary metastases are uncommon as the process is diffuse and dyspnea occurs at a late stage. Symptoms from osseous metastases include bone pain, swelling, and pathologic fracture at the affected site. Severe spinal radiculopathy from the vertebral osseous metastases can occasionally be the first clinical sign of DTC and palliative neurosurgical decompression and external radiotherapy can be required for the associated cervical, thoracic or lumbar

vertebral body destruction and associated nerve compression. Osseous metastases are usually osteolytic in nature and are readily identified using radioactive iodine scanning. Computerized tomography, magnetic resonance imaging and bone scintigraphy have also been used as modalities to detect these lesions. Patients with distant metastases from DTC usually have an associated elevation in their serum thyroglobulin.

The overall ten year survival rate for patients with distant metastases of differentiated thyroid carcinoma ranges between 25 and 40%.[3] Young patients with distant metastases that concentrate radioactive iodine have the most favorable prognosis. Older patients with bulky tumors and several areas of lung and/or osseous metastases that do not concentrate radioactive iodine have a poorer prognosis. Clearly, patients with distant metastasis that concentrate radioactive iodine are best treated with 100-200 mCi of radioactive iodine every 4-6 months until a cumulative dose of 500-600 mCi has been reached.[9] External beam radiotherapy has been helpful as an additional palliative measure. Chemotherapy, consisting largely of Adriamycin, is not particularly effective and should be reserved for patients with distant metastasis that do not concentrate radioactive iodine.

Diagnostic and Therapeutic Radioactive Iodine-131

Postoperative total body radioactive iodine scanning is recommended for all high-risk patients with DTC as this modality decreases the local recurrence and death rates (Table 6.5). Most low risk patients are also candidates but, selective use is acceptable in low-risk node negative patients with small, occult, minimal, or incidentally discovered differentiated thyroid carcinoma. Figure 6.1 illustrates the protocol for performing a total body radioiodine scan 6-12 weeks after thyroidectomy that begins by withholding thyroid hormone medication (LT_4) from the patient for approximately 4 weeks. The use of a LT_3 hormone preparation such as Cytomel for the first two of these four weeks can alleviate the problems of symptomatic hypothyroidism. The serum TSH level is checked at the end of four weeks and should be greater than 30-50 IU prior to radioisotope administration.[2] This is also the best time to establish an accurate baseline for serum thyroglobulin levels for use as a future surveillance tool for these patients. Two to five mCi of ^{131}I is administered and a total-body scan is performed 48 hours later. Ablative doses of ^{131}I, ranging from 100-200 mCi depending on the location and magnitude of uptake, are administered for uptake greater than 2% of the administered dose to destroy any residual or metastatic thyroid carcinoma. The scan is repeated four to seven days after administration of therapeutic radioiodine and thyroid hormone supplementation for TSH suppression is restarted. The total body radioiodine scan is usually repeated in treated patients in 6-12 months after treatment to confirm total ablation of all thyroid tissue. Additional treatment doses of ^{131}I can be administered to a total dose of 500-600 mCi in patients with persistent isotope concentration.[9] Recent experience with recombinant TSH stimulating radioiodine uptake and the use of Sestamibi scanning after thyroidectomy for DTC, suggest that cessation of thyroid hormone therapy prior to radioiodine imaging and treatment may be unnecessary in the future.

Table 6.5. Indications for diagnostic and therapeutic ^{131}I

Incomplete excision of primary thyroid tumor
Patients at "high risk" for local tumor recurrence
Cervical lymph node metastasis which cannot be surgically removed
Distant metastasis (usually lung or bone)
Elevated serum thyroglobulin levels > 3 months after surgery (Selective use acceptable in most incidental, minimal, and occult DTC and in some "low risk" patients)

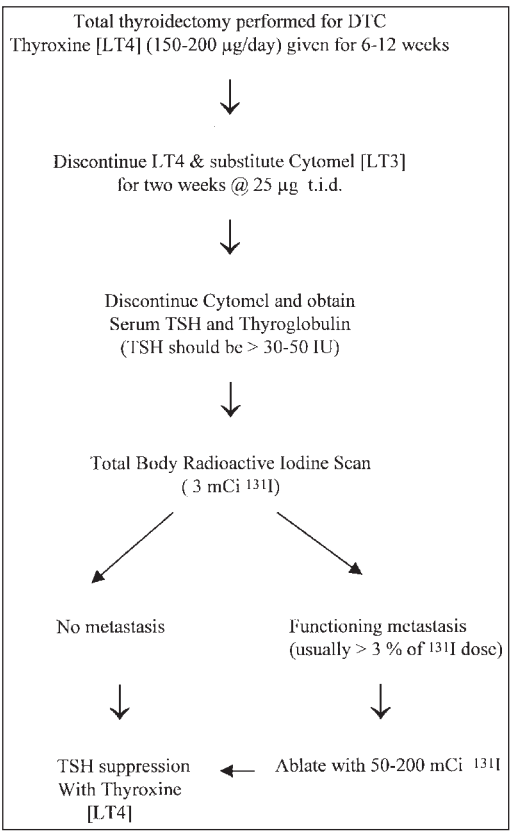

Fig. 6.1. Total thyroidectomy performed for DTC.

Recurrent Thyroid Carcinoma

The presence of a new cervical mass or cervical lymphadenopathy after thyroidectomy is usually the first sign of recurrence of differentiated thyroid carcinoma. A conventional radiologic imaging study such as cervical ultrasonography often begins the investigation. Fine needle aspiration biopsy with or without ultrasonographic guidance is useful to establish a cytologic diagnosis of recurrent thyroid carcinoma. Computerized tomography of the neck with contrast is usually avoided unless extensive local, tracheal, or mediastinal invasion is suspected. The large dose of iodinated oral and intravenous contrast necessary to complete this study may make diagnostic and therapeutic radioactive iodine ablation problematic. Surgical resection of any palpable cervical disease is advisable if safe performance can be accomplished.[1] This may include a modified radical neck dissection and/or completion thyroidectomy depending on the site and extent of recurrent disease. Palliative endoscopic procedures and extensive resections involving neurovascular structures, larynx, trachea, esophagus, and the upper mediastinum have been described, but must be individualized considering the patient's other medical risk factors. A wide variety of reconstructive procedures are available to replace or reconstruct these vital structures in the neck. External beam radiotherapy and/or chemotherapy can be used for recurrent unresectable thyroid carcinomas that do not concentrate radioactive iodine, but the response is usually transient.

Postoperative Surveillance

The goal of following patients with DTC is to detect recurrence or distant metastasis at an early and treatable stage. Thyroid hormone supplementation should be given to all patients with thyroid carcinoma to achieve complete suppression of their serum TSH. Physical examination of the neck, serum TSH, thyroglobulin and free thyroid hormone levels are usually evaluated every 3-4 months for the first 2 years after thyroidectomy and every 6-12 months thereafter.[1] Adjustments in the dose of thyroid hormone may be necessary on a periodic basis. Any abnormal physical findings can be evaluated with cervical ultrasonography and patients at high risk for recurrent thyroid carcinoma usually undergo periodic cervical ultrasonography as an additional tool for surveillance and early detection of recurrent disease. The use of chest radiography on a routine basis for these patients has become somewhat controversial. The yield of positive studies is understandably low in patients with no detectable serum thyroglobulin values. A baseline chest radiograph is often performed and repeated every 2 or 3 years in patients with aggressive tumors.

Patients with physical findings, laboratory values, or imaging studies suggestive of recurrent, persistent or metastatic thyroid carcinoma should undergo total body radioactive iodine scanning and treatment if possible. A negative radioactive iodine scan does not always exclude the presence of recurrence, but does eliminate radioiodine as a treatment modality. Clearly, patients with positive conventional imaging studies and elevated serum thyroglobulin levels should be presumed to have recurrent disease, despite a negative radioactive iodine scan. Surgical resection of these

recurrences, or occasionally the solitary pulmonary or osseous metastasis, is usually warranted to achieve the most acceptable long-term survival rates.

Summary

The vast majority of patients with differentiated thyroid carcinoma are cured with surgical excision of the thyroid tumor. Local, regional, and distant spread is possible along with early and late recurrence of thyroid carcinoma manifested by large, undifferentiated, metastatic and invasive tumors. Appropriate surgical resection based on the expected tumor behavior and prognosis is advisable in most patients with DTC. Careful long-term surveillance includes physical examination, thyroid hormone medication, periodic laboratory and imaging studies, and the use of diagnostic and therapeutic radioactive iodine. Conventional chemotherapy and external beam radiotherapy play a limited role in the treatment of differentiated thyroid carcinoma.

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CHAPTER 7

Medullary Thyroid Carcinoma

Jeffrey F. Moley

Introduction

Medullary thyroid carcinoma (MTC) is a tumor of the thyroid C-cells, which are neuroendocrine cells, also known as the parafollicular cells. C-cells are found in small groups of two or more, adjacent to the thyroid follicles. C-cells secrete a number of substances, the most important of which is calcitonin, which is an excellent marker for the presence of MTC. Measurement of calcitonin levels following the administration of the secretagogues calcium and pentagastrin has been extremely useful in the screening of individuals predisposed to the hereditary forms of the disease, and in the follow-up of patients who have been treated. MTC cells may also secrete carcinoembryonic antigen (CEA), and a number of other substances, including neuron-specific enolase, somatostatin, adrenocortical stimulating hormone, serotonin, chromogranin, and substance P.

Medullary thyroid carcinoma may be unilateral or bilateral and is often associated with a proliferative lesion, C-cell hyperplasia, particularly in hereditary settings. The tumor frequently spreads to regional lymphatics, including paratracheal lymph nodes, nodes of the jugular chain, and upper mediastinal nodes. Histologic features of aggressiveness include vascular, lymphatic, and capsular invasion. Aggressive primary tumors and nodal metastases may invade adjacent structures including trachea, strap muscles, esophagus and recurrent nerve. Distant metastatic spread may occur to liver, lungs, and bone. MTC causes death by either local complications, such as invasion of vital structures in the neck and upper mediastinum, or by complications of distant metastases.

Medullary thyroid carcinoma may be sporadic or hereditary (Table 7.1). The majority of cases of MTC are sporadic (75-80%). These cases are usually unilateral in early stages, and there is no family history of MTC or other endocrine tumors. Sporadic MTC almost always presents as a mass in the neck, and metastases to lymph nodes in the neck are frequently present at the time of diagnosis. Diagnosis is made by fine needle aspiration cytology, and measurement of stimulated calcitonin levels. The familial forms of MTC are characterized by multifocal, bilateral MTC, associated with other endocrinopathies, depending on the particular syndrome. These syndromes, which include multiple endocrine neoplasia (MEN) types 2A and 2B, and the related disorder, familial, non-MEN medullary thyroid cancer (FMTC), are inherited in an autosomal dominant fashion. In MEN 2A, all patients develop MTC, while approximately 50% have pheochromocytomas and 30% have parathyroid hyperplasia. In patients with MEN 2B, MTC also occurs in all patients, but develops at an earlier age (infancy), and is more aggressive than MTC in MEN 2A. MTC

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Table 7.1. Features of medullary thyroid carcinoma

Clinical Setting	Features of MTC	Inheritance Pattern	Associated Abnormalities	Genetic Defect
Sporadic MTC	unifocal	none	none	Somatic RET mutations in > 20% of tumors
MEN 2A	multifocal, bilateral	autosomal dominant	pheochromocytomas, hyperparathyroidism	Germ-line missense mutations in extracellular cysteine codons of RET
MEN 2B	multifocal, bilateral	autosomal dominant	pheochromocytomas, mucosal neuromas, megacolon, skeletal abnormalities	Germ-line missense mutation in tyrosine kinase domain of RET
FMTC	multifocal, bilateral	autosomal dominant	none	Germ-line missense mutations in extracellular or intracellular cysteine codons of RET

is almost never cured in patients with MEN 2B. About 40% of MEN 2B patients also develop pheochromocytomas, but they do not have parathyroid hyperplasia. They have multiple mucosal neuromas (Fig. 7.1), ganglioneuromas of the GI tract with megacolon, and a characteristic "marfanoid" phenotype with skeletal abnormalities. FMTC is the most indolent form of MTC. These patients develop only MTC, at a later age than MEN 2A or 2B.

Patients with MEN 2A and FMTC have a better long term outcome than patients with MEN 2B or sporadic tumors. In MEN 2B, MTC develops at an extremely early age, and is often metastatic by the time the patient is five or six years old. In MEN 2A, MTC develops slightly later, in the early teen years, and in FMTC, the MTC may not develop until the third or fourth decade. The pattern of spread and metastasis is similar in hereditary and sporadic forms of MTC. Within these clinical settings, however, there is variation. Particularly in the sporadic cases, the disease is unpredictable and patients may survive many decades or die within several years after presentation.

In MEN 2A and FMTC the outward phenotype is normal, and the diagnosis is either made by genetic testing, or by detecting the presence of endocrine neoplasia. In MEN 2B, the presence of mucosal neuromas, the characteristic tongue nodules (Fig. 7.1), or problems with colon function (megacolon), may suggest the diagnosis to an astute clinician. Relatives of patients with known MEN 2A, 2B, or FMTC, may be screened for MTC by measurement of stimulated calcitonin levels and by genetic testing, which will be discussed later. The most sensitive way to test for plasma calcitonin is after the administration of the provocative agents calcium and pentagastrin. After obtaining basal levels, intravenous calcium (2mg/kg/1 min),

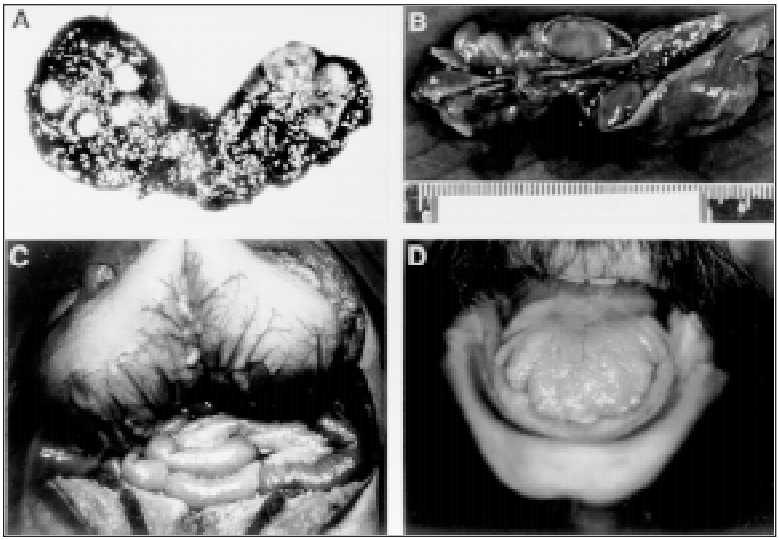

Fig. 7.1. Features of patients with hereditary medullary thyroid carcinoma (MTC). A, bisected gland from patient with MEN 2A showing multicentric, bilateral foci of MTC. B, Adrenalectomy specimen from patient with MEN 2b demonstrating pheochromocytoma. C, Megacolon in patient with MEN 2B. D, midface and tongue of patient with MEN 2B showing characteristic tongue nodules secondary to neuromas. Reprinted with permission from Moley JF. Medullary Thyroid Carcinoma, Textbook of Endocrine Surgery, Edited by O.H. Clark and Q-Y Duh, W.B. Saunders, Philadelphia, 1997.

followed immediately by pentagastrin (0.5 ug/kg/5 sec), is infused, and blood is drawn for measurement of calcitonin levels at 1, 3 ,and 5 minutes.[1] Pheochromocytomas may be detected by measurement of urinary catecholamines, including metanephrines and vanillymandelic acid (VMA). Hyperparathyroidism is detected by measurement of serum calcium levels.

Primary Surgical Treatment

Surgical treatment of medullary thyroid carcinoma is influenced by several factors. First of all, MTC cells do not take up iodine and radioactive iodine treatment is ineffective. Second, MTC is multicentric in 90% of patients with the hereditary forms of the disease, and in 20% of patients with the sporadic form. Third, with the exception of children whose MTC is discovered as part of a genetic or biochemical screening program, over 50% of patients who present with MTC have nodal metastases. Last, the ability to measure postoperative stimulated calcitonin levels has allowed assessment of the adequacy of surgical extirpation. Total thyroidectomy is therefore widely accepted as appropriate treatment of the primary tumor, accompanied by a central node dissection. This operation entails complete extirpation of the

tumor, with removal of all thyroid tissue and all nodal tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly is removed. After the parathyroid glands are identified, central nodal tissue on the anterior surface of the trachea is removed, exposing the superior surface of the innominate vein behind the sternal notch. Fatty and nodal tissue between the carotid sheaths and the trachea is removed, including paratracheal nodes along the recurrent nerves. On the right, the junction of the innominate and right carotid arteries is exposed, and on the left, nodal tissue is removed to a comparable level behind the head of the left clavicle. A systematic approach to the removal of all nodal tissue in the central neck has been reported to improve recurrence and survival rates when compared retrospectively to procedures where only grossly involved nodes were removed.[2]

At our institution, total parathyroidectomy with autotransplantation is done as part of this operation for MTC. We prefer this approach to routine preservation of parathyroids because the parathyroid glands are closely associated with perithyroidal lymph nodes and preservation of these glands risks leaving nodal metastases. Also, the vascular supply to a parathyroid gland may be interrupted by dissection and excision of perithyroidal and central nodes. Parathyroid glands are therefore removed and preserved in cold saline at the time of thyroidectomy for MTC. At the end of the procedure, one or two glands are sliced into twenty 1 x 3 millimeter pieces and autotransplanted into the muscle of the non-dominant forearm (in patients with MEN 2A), or sternocleidomastoid muscle (in patients with sporadic MTC, FMTC, and MEN 2B). Remaining parathyroid tissue is viably frozen and stored. The autografts generally function well within four to six weeks, at which time patients can be taken off of calcium supplementation. In a recent series of thyroidectomies performed in thirteen patients with hereditary MTC identified by genetic screening, total thyroidectomy and central node dissection with parathyroidectomy and parathyroid autografting was performed in all patients. All patients were normocalcemic after stopping calcium supplementation eight weeks postoperatively.[1] In other series, the percentage of patients requiring calcium supplementation following parathyroidectomy with parathyroid autografting has ranged from 0-20%. Other experts in this field attempt to preserve the glands with vascular supply intact during thyroidectomy for MTC.[3,2]

Ipsilateral or contralateral modified neck dissection node is done in patients in whom there is clinical suspicion that the jugular nodes may be involved with tumor. Patients with palpable adenopathy in the anterior or posterior jugular chain should undergo ipsilateral functional or modified radical neck dissection. In patients without such gross evidence of nodal involvement, the indications for removal of lateral nodes is less clear. Some authors have recommended sampling of the midjugular nodes, with performance of formal neck dissection reserved for patients in whom metastatic tumor is demonstrated. Our approach is to perform ipsilateral neck dissection in patients who have palpable adenopathy in central, paratracheal, or jugular nodes, and in patients with large (> 2 cm) primary tumors. This operation entails removal of nodes anterior to and posterolateral to the jugular vein, from the level of the facial vein to the subclavian vessels, and laterally to the accessory nerve. Unless invaded by tumor, the jugular vein and sternocleidomastoid muscle are left intact.

Current Research: Genetic Testing for MEN 2A, MEN 2B, and FMTC

The development of genetic testing for MEN 2A, MEN 2B, and FMTC has simplified and improved screening of at-risk patients in affected families. Reliance on calcium-pentagastrin stimulated calcitonin testing for clinical screening has several drawbacks. First of all, a positive test usually indicates that cancer has already developed, and there are a few patients who will develop distant metastatic disease, even after thyroidectomy with removal of small primary tumors. These patients would benefit from earlier thyroidectomy. Second, because the disease is inherited in an autosomal dominant fashion, 50% of those tested will never develop disease and would be spared the expense and inconvenience of routine scheduled testing if a definitive genetic test were applied. Third, the provocative calcitonin test is unpleasant and uncomfortable and patients do not like it. Some patients have refused to return for subsequent testing because of fear of the test. Genetic testing obviates the need for calcitonin testing in the screening of at-risk individuals in families known to harbor a mutation in RET. Stimulated calcitonin testing remains an important modality in following patients for recurrent or residual disease after thyroidectomy.

In 1987 the gene for MEN 2A was localized to the pericentromeric region of chromosome 10 (10q11.2). Subsequent studies demonstrated that MEN 2B and FMTC mapped to the same region. The critical region for MEN 2A was further narrowed to a 480 kb segment near the centromere of human chromosome 10. The RET protooncogene is included within this critical region, making this an obvious candidate gene for the MEN 2 diseases. The RET protooncogene is a member of the receptor tyrosine kinase gene family and was originally found to be a dominant transforming gene activated by the replacement of the 5' region with a portion of a zinc finger-like gene in T cell leukemia cell lines. This transmembrane oncogene basically consists of three domains: a cysteine-rich extracellular receptor domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain. RET consists of at least 20 exons, and is expressed as five major mRNA species. Mutations in the RET proto-oncogene were found to be responsible for multiple endocrine neoplasia type 2A, MEN 2B, and FMTC.[4,5] In MEN 2A and FMTC, nonconservative point mutations within codons specifying cysteine residues in the extracellular domain of the RET gene product are found (Table 7.2). In MEN 2B, a mutation is found in the intracellular tyrosine kinase domain. Mutations causing FMTC have also been found in intracellular cysteine residue.[6]

The ability to detect germline RET gene mutations in at-risk individuals from kindreds affected by MEN 2A and FMTC allows gene carriers to be identified before they develop overt neoplasms. Preventative thyroidectomy should be performed before these patients develop medullary thyroid carcinoma. Family members who are found not to have inherited the mutation will not develop MTC and therefore need not undergo further stimulated calcitonin testing. Genetic testing is the standard of care in patients with familial forms of medullary thyroid carcinoma.

Table 7.2. RET mutations in hereditary MTC

Syndrome	Missense Germ-line mutations in the RET proto-oncogene	
	Exon	Codon
MEN 2A, FMTC	10	609
		611
		618
		620
	11	634
FMTC	13	768
	14	804
	15	891
MEN 2B	16	918
		883

Thyroidectomy in Carriers of RET Gene Mutations

Several series have reported the performance of preventative thyroidectomy on members of at-risk MEN 2A and FMTC kindreds who are found to be carriers of RET gene mutations by genetic testing. The first two such reports were from S. A. Wells et al in the Department of Surgery at Washington University in St. Louis and K. Lips et al from the Netherlands.[1,3] In the series from Washington University, one hundred thirty-two individuals from seven different kindreds affected by MEN 2A were evaluated.[1] Of the 132 individuals, 48 had an established diagnosis of MEN 2A and 58 were at 50% risk for inheriting the disease but had no clinical evidence of endocrine neoplasia. Twenty-six unaffected spouses of MEN 2A kindred members served as controls. All individuals were evaluated by both direct and indirect genetic testing for the presence of RET gene mutations. In patients at 50% risk for disease (having an affected parent or sibling), stimulated calcitonin levels were also determined. In 21 at-risk individuals, a germ-line RET mutation was identified. The other thirty-seven family members had two normal RET alleles. All 26 unaffected control individuals had normal RET alleles.

Preventative thyroidectomy was performed in patients who were found to have inherited an RET mutation. In these patients, total thyroidectomy, central lymph node dissection and parathyroid autotransplantation to the nondominant forearm was performed. Following thyroidectomy and parathyroid autotransplantation, patients were placed on thyroid, calcium, and vitamin D supplementation. Approximately eight weeks after the operation, the oral calcium and vitamin D were stopped. Two weeks after the oral calcium and vitamin D replacement was stopped, the serum calcium concentration was within the normal range in each patient. There were no complications in this series. On histologic examination, 14.5 nodes were removed per patient, and none contained metastases. In all patients, the stimulated plasma calcitonin levels were normal after total thyroidectomy. Seven patients had elevated

preoperative plasma calcitonin levels, and each had microscopic evidence of MTC on histologic examination. Two of the seven had macroscopic disease. The patients with normal preoperative plasma calcitonin levels had either macroscopic MTC, microscopic MTC, or C-cell hyperplasia only.

Lips et al identified fourteen young members of families affected by MEN 2A who had normal calcitonin testing, but who were found to be MEN 2A gene carriers by DNA testing.[3] Thyroidectomy with parathyroid preservation was done on eight of these fourteen, and foci of MTC were identified in all eight.

To date, our group at Washington University has performed 62 prophylactic thyroidectomies in at-risk kindred members found to have RET gene mutations. Lymph node metastases were identified in three patients. Postoperative calcitonin levels were normal in all patients except for one six year old girl with MEN 2B.

Total thyroidectomy can be a difficult procedure, and in an elective preventative setting, in a child or infant, this operation must be performed meticulously and carefully in order to prevent the occurrence of medullary thyroid carcinoma without complications of recurrent nerve injury or hypoparathyroidism. It is recommended that only surgeons experienced in this procedure perform these operations. In the series just described, the likelihood of MTC recurrence is low, but patient followup over the next decades will need to be continued.

Management of Persistent or Recurrent Medullary Thyroid Carcinoma

When medullary thyroid carcinoma presents as a neck mass, as in patients with sporadic disease, and those hereditary cases which did not have the benefit of screening, over 50% will have persistent or recurrent elevation of calcitonin levels following primary surgery, indicating the presence of persistent tumor. In one study of patients who presented with palpable tumors, 15/18 (83%) of patients with hereditary disease and 11/20 (55%) patients with sporadic tumors had persistent disease as indicated by elevated calcitonin levels postoperatively. Patients with persistently high levels of calcitonin following thyroidectomy may do well and remain asymptomatic for many years.[7] Other patients develop local or distant recurrences which may cause symptoms and death. A Norwegian study of 84 cases of MTC found that over 50% of patients who presented with cervical node metastases eventually died of disease. Medullary thyroid carcinoma cells do not take up radioactive iodine, and this form of therapy has not been found to be helpful in the treatment of patients with metastatic tumor. The use of external beam radiation therapy has not been show to be consistently effective, and in most studies, pre- and postradiation calcitonin levels were not reported. In a report by Samaan et al,[8] 202 patients were studied retrospectively. The authors felt that the characteristics of treated and untreated patient groups were comparable, and it was found that the patients who received external beam radiation therapy had a worse outcome than patients who did not. Further studies are needed to define the role of radiation therapy in this disease.

Systemic chemotherapy has been reported to have a poor response rate, and has not been found to be consistently effective in patients with MTC. Adriamycin alone results in partial responses in approximately 30% of patients. These studies also are

difficult to interpret due to lack of consistent pre- and posttreatment stimulated calcitonin measurements.

Reoperation for persistent or recurrent MTC in the neck has been reported by our group and others, and at present appears to offer the most consistent improvement in calcitonin levels, compared to other treatments.[9] A significant reduction in stimulated calcitonin levels following reoperation has been reported in most patients. In our two series of patients, from 1990-1992, and from 1992-1996, all patients had persistent or recurrent elevation of stimulated calcitonin levels following primary surgery for MTC. Localization studies, including selected venous catheterization, CT scanning, and physical examination were successful in localizing tumor in half the cases. Diagnostic laparoscopy with careful examination of the liver must be performed prior to neck reoperation with curative intent. We found that diagnostic laparoscopy identified liver metastases in ten of 44 patients, despite negative liver imaging studies (computed tomography, nuclear scanning) in 90% of these patients (Fig. 7.2).[10]

In the surgical approach used at our institution, the central zone of the neck, including the thyroid bed, is explored and all residual soft tissue and lymph nodes are removed (Fig. 7.3). Unilateral or bilateral functional neck dissections are also done, and median sternotomy with mediastinal node dissection is done in patients with evidence of localized upper mediastinal metastases that are not accessible through

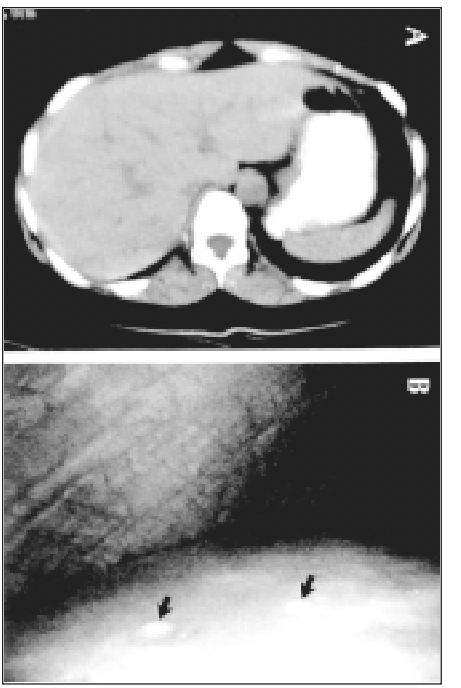

Fig. 7.2. A) Computed Tomography (CT) of liver from patient with MEN 2A, recurrent MTC and elevated calcitonin levels- there is no evidence of liver metastases on the scan. B) Laparoscopic view of liver from the same patient showing multiple small raised whitish lesions on and just beneath the surface of the liver, confirmed to be metastatic MTC by biopsy. These small, multiple metastases are often not seen on routine CT scanning or other imaging modalities, including nuclear scanning. Reprinted with permission from Tung WS, Vesely TM, and Moley JF. Surgery 1995; 118:1024.

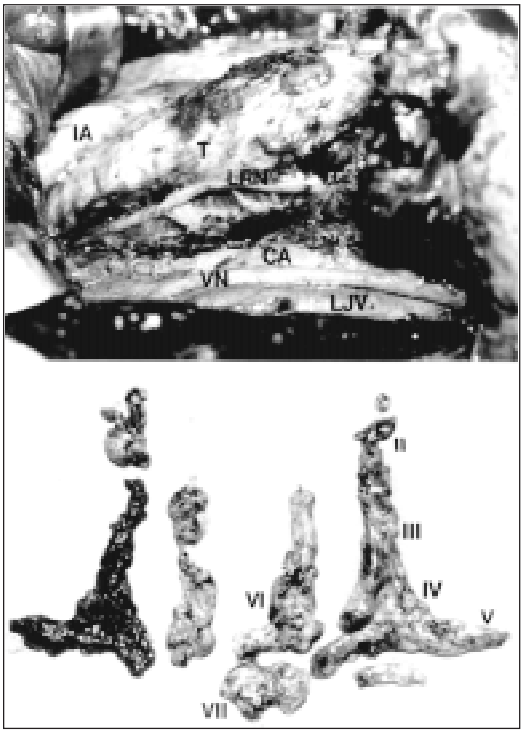

Fig. 7.3. Intraoperative photograph of neck following central node dissection (top), and specimen from the same patient following central and bilateral neck dissection (bottom). Top: IA-innominate artery, T-trachea, LRN-left recurrent nerve, CA-left carotid artery, VN-left vagus nerve, LVJ-left jugular vein. Bottom: II, III, IV, V, VI, VII-lymph node levels in resected specimens. Level II-high jugular nodes, Level III-mid jugular nodes, Level IV-low jugular nodes, Level V-posterior triangle nodes (partial resection), Level IV-paratracheal nodes, Level VII-superior mediastinal nodes. Reprinted with permission from Moley, J.F. Medullary thyroid cancer. In: Orlo Clark et al. Textbook of Endocrine Surgery. Philadelphia: W.B.Saunders, 1997.

the neck. In our most recent series, calcitonin levels were normalized postoperatively in 17/45 patients undergoing resection with curative intent. In an additional 22 patients, levels were reduced by one third or more (Fig. 7.4).[9] Complications were minimal. No transfusions were required and there were no deaths.

These reports support the use of reoperation in patients with persistently elevated stimulated calcitonin levels with disease felt to be confined to the neck. These operations can be done safely in the majority of cases, and may result in long-term survival benefit or prevention of local tumor recurrence complications in the neck. Long term followup of these patients will be needed to confirm the presumed benefit derived from these operations.

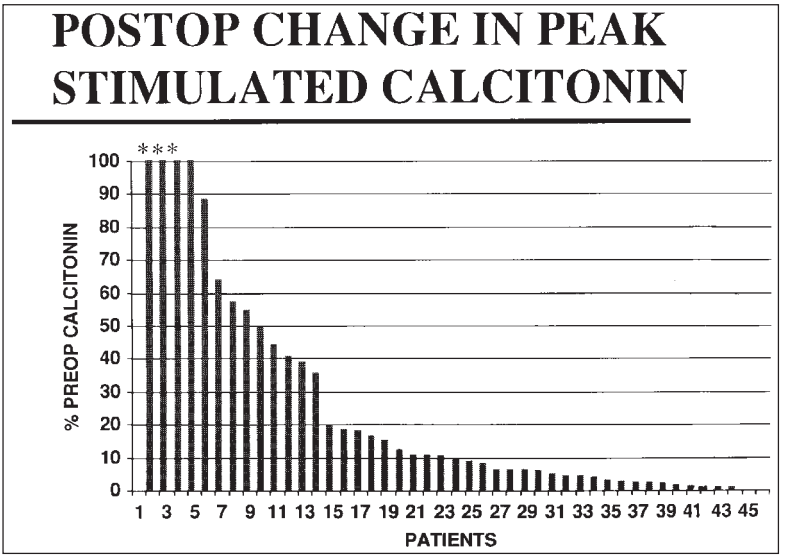

Fig. 7.4. Postoperative change in peak stimulated calcitonin levels. The shaded bars indicate the postoperative stimulated calcitonin levels of the 45 patients who underwent the curative cervical re-exploration and dissection. The postoperative calcitonin level is expressed as a percentage of the preoperative calcitonin level. One hundred percent indicates no change in calcitonin level, 10% indicates that the stimulated calcitonin level fell by 90%. *Postoperative levels were higher than preoperative levels. Reprinted with permission from Moley JF et al. Ann Surg 225:734-743.

Conclusions

Medullary thyroid carcinoma is one of the most interesting human cancers. It occurs in sporadic and familial clinical settings and is the first human cancer in which routine genetic testing has become the standard of care. Surgical management is the core therapy for this disease, as no other treatment modalities offer any hope at present. With the identification of familial colorectal and breast cancer genes, prophylactic surgery has become a very controversial issue in clinical management of cancer-prone individuals. Surgery for breast and colon cancer has a higher long term physical and psychological morbidity than thyroidectomy, and decisions in those patients will be challenging. A new era of surgical intervention for malignant disease is upon us. Surgical oncologists, who established the benefit of a multidisciplinary approach to patients with cancer, must approach the patient with a hereditary predisposition to cancer in a similar way, with the involvement of genetic counselors, pediatricians, and basic scientists. The next decades will hold many exciting developments in this field.

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CHAPTER 8

Anaplastic Thyroid Carcinoma

Ashok R. Shaha

Introduction

Approximately 16,000 new patients with thyroid cancer are expected to be seen in the United States in 2000. There appears to be a steady increase in the incidence of thyroid cancer in the United States, but the mortality from thyroid cancer (1,200) has essentially remained unchanged in the past twenty years. The overall incidence of anaplastic thyroid cancer in various series ranges between 4-6%.[1-3] It appears that there is a decrease in the incidence of anaplastic thyroid cancer in the United States, however there appears to be a higher incidence in areas of iodine-deficiency and regions of endemic goiters. Anaplastic thyroid cancer forms one of the most deadly tumors among all human neoplasms. It is interesting that in the same human organ there exists one of the best cancers (papillary) and one of the worst cancers (anaplastic thyroid). The average survival in anaplastic thyroid cancer is approximately 6-12 months. The majority of patients die of advanced local disease, distant metastases, airway problems or cachexia. In approximately half of the patients with anaplastic thyroid cancer, the presence of pre-existent papillary or follicular cancer is noted pathologically. This leads to the belief that early diagnosis and treatment of malignant thyroid tumors is essential to decrease the overall incidence of anaplastic thyroid cancer. It is also extremely important to make a definitive diagnosis of anaplastic thyroid cancer and not to confuse poorly-differentiated, medullary or small-cell anaplastic thyroid cancer with giant and spindle cell thyroid cancer. The small cell anaplastic thyroid cancer needs to be distinguished further from thyroid lymphoma, where the outcome is much better and definitive treatment is available. Recent review of the National Cancer Data Base, published by Hundahl et al, reported 893 patients with anaplastic thyroid cancer in a series of 53,856 thyroid cancer patients (2%).[4]

Clinical Presentation

Anaplastic thyroid cancer is generally seen in elderly patients. There is a higher incidence in women, probably related to overall higher incidence of thyroid cancer and nodular goiter in females. It accounts for 2% of all thyroid cancers in Japan.[5] The incidence varies between 5-14% in Europe and the United States. It is commonly a disease of sixth-decades onwards, but a small number of patients below the age of 40 are also seen with anaplastic thyroid cancer.[4] The most common clinical presentation is a rapidly growing thyroid mass in the central compartment of the neck. The history is generally of short duration, extending between 3-4 months. The other associated symptoms are hoarseness, dysphagia, pain in the cervical region,

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and sometimes dyspnea. A patient may occasionally give a history of pre-existent nodular goiter for a long period of time that shows a sudden change in size and rapid growth. A patient may also present with wide-spread metastatic disease to the neck nodes and lungs. The systemic metastases generally involve the lungs (75%), brain (15%), and adrenal glands (33%). The clinical examination usually reveals a firm mass in the thyroid region that appears to be fixed to the central compartment and cannot be separated from the trachea. Vocal cord paralysis, due to direct extension of the disease in the recurrent laryngeal nerve, is a common finding and lymph node enlargement is also quite frequent (about 80%).

Diagnosis

Early diagnosis may be made by strong clinical suspicion. A fixed mass in the central compartment with vocal cord paralysis should wave a red flag for the clinician. The diagnostic work-up includes a fine needle aspiration. While the FNA may not make a final diagnosis of anaplastic thyroid carcinoma, the presence of giant and spindle cells should trigger the diagnosis. Confirmation may be obtained by core or open biopsy, although open biopsy is best avoided as the tumor may fungate through the skin in the area of biopsy. The patient may occasionally present with severe airway distress due to airway compression or bilateral vocal cord palsy. The management of airway in such individuals poses a major clinical challenge to the treating physician. The CT scan is very helpful in evaluating the extent of the disease in the central compartment, lymph node metastasis and the position of the trachea (Fig. 8.1). The chest X-ray is routinely performed to rule out gross metastasis. It is important to make a definitive histopathological diagnosis of anaplastic thyroid cancer (giant and spindle cell tumor) and to rule-out poorly-differentiated thyroid cancer or lymphoma. This may require, in select cases, appropriate immunohistochemistry.

Pathology

These tumors grow in solid fashion, with the presence of giant and spindle cells often with multiple hyperchromatic nuclei. (Figs. 8.2 and 8.3) The squamoid variant resembles squamous carcinoma, while spindle cell anaplastic carcinoma resembles sarcoma. Reactive osteoclast-giant cells may also be present. Immunohistochemistry reveals a positive reaction to cytokeratin, vimentin and epithelial membrane antigen. Carcino-embryonic antigen may be localized in certain areas of the tumor.[2,6] Most of the anaplastic thyroid cancers show a high index of P53 mutation.[7] There appears to be a step-wise progression from benign follicular cells to anaplastic thyroid cancer with expression of oncogene activation and loss of tumor-suppressor gene activity. The expression of *ras* mutation in well-differentiated thyroid carcinoma reflects an early event of oncogene activation, while the high expression of P53 in anaplastic carcinoma suggests a late event. The sequencing analysis showed the presence of mutations at codons 135, 141, 178, 213, 248 and 273. Ito showed the mutations in the P53 gene by PCR technique.[7] No mutations were detected in papillary carcinoma in exons 5 to 8, while 6 out of 7 anaplastic carcinomas revealed mutations. These studies suggest that P53 mutations play an important role in the progression of differentiated thyroid cancer to anaplastic thyroid cancer.[8]

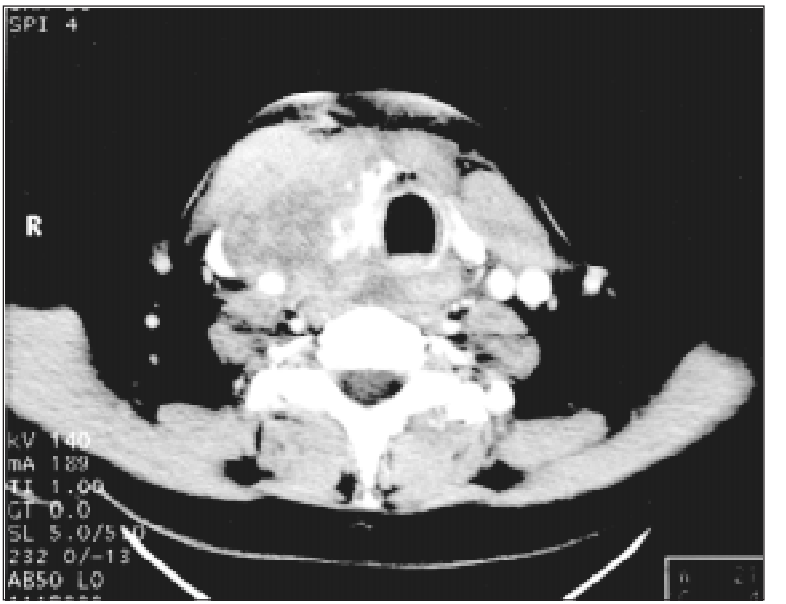

Fig. 8.1. This CT scan shows a large heterogenous thyroid tumor with tracheal and esophageal displacement.

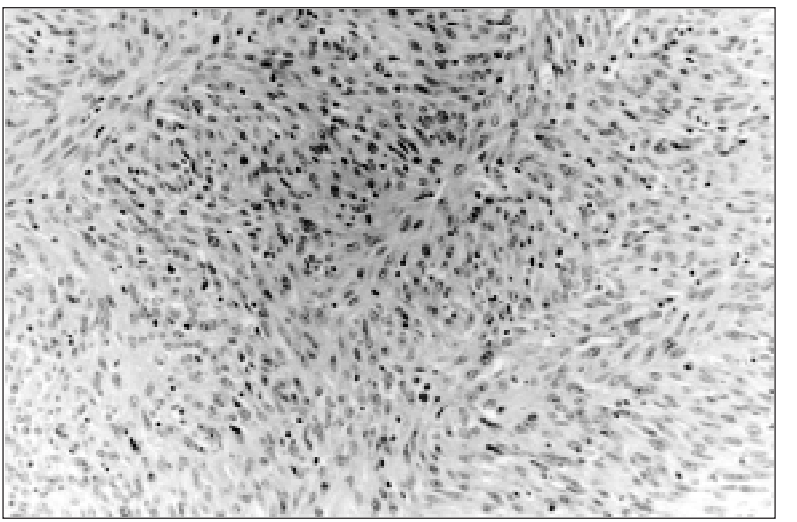

Fig. 8.2. Anaplastic thyroid cancer (low power).

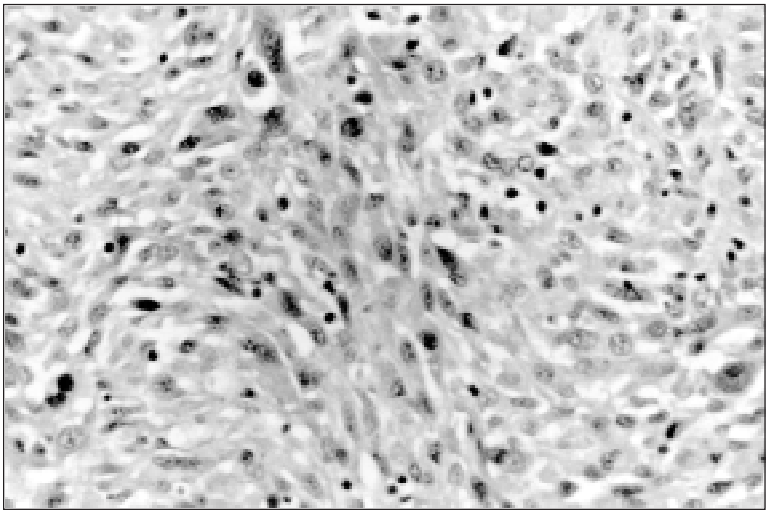

Fig. 8.3. Anaplastic thyroid cancer (high power).

Treatment

Since the average life expectancy of these patients is counted in months, the role of initial aggressive surgery is always questioned. The majority of patients recur promptly after a radical surgical intervention and, in most of the patients, all gross disease can rarely be removed. Kim and Leeper showed promising results in the mid-1980s with the use of Adriamycin-based chemotherapy and external radiation therapy.[10] Doxorubicin has since been routinely used and become an integral part of the management of patients with anaplastic thyroid cancer. In spite of the aggressive treatment approach of chemotherapy, radiation therapy in various forms, and salvage surgery, the overall outcome has essentially remained unchanged (Fig. 8.4). Most of the studies have shown, however, that when a curative resection could be performed, the survival was much better. Obara et al from Japan performed radical resection in 14 of 24 patients.[5] Postoperatively, external radiation therapy and chemotherapy was utilized. Overall one-year survival in their studies was 20% for the surgical group and 12% for the entire study group. None of the patients survived for more than 30 months. Securing airway in patients who present with bilateral vocal cord paralysis is quite difficult. If the patient or the family is not prepared for anticipated short-term life, a due consideration should be given to tracheostomy. A tracheostomy in such individuals may be very difficult and securing an airway prior to tracheostomy requires close cooperation with an anesthesiologist and expertise in fiberoptic intubation. A preoperative CT scan is helpful to evaluate the extent of the central compartment disease, position of the trachea, and airway compression. Schlumbeger et al[9] from France reported their experience of 20 patients with two types of chemotherapy, including a combination of Doxorubicin 60 mg and Cisplatin

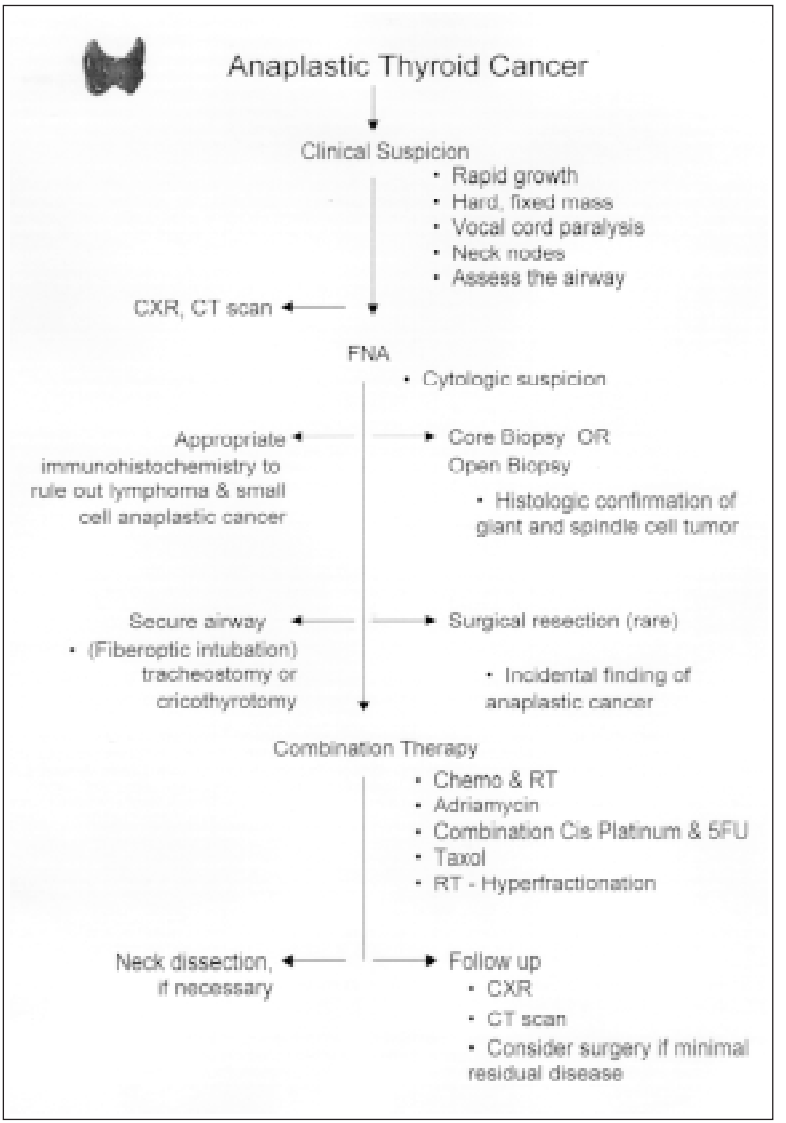

Fig. 8.4. Management flow chart for anaplastic thyroid carcinoma.

90 mg per square meter. Hyperfractionated, accelerated radiation therapy was used. Survival exceeding 20 months was observed in 3 patients. The cause of death in 14 patients was distant metastases. They suggested that gross tumor resection should be performed whenever possible. Kim and Leeper described their experience with 41 patients with locally advanced thyroid cancer according to a combination regimen of low-dose Adriamycin and external radiation therapy, The second group of patients with anaplastic thyroid cancer received a combination regimen consisting of once weekly Adriamycin 10 mg per square meter before hyperfractionated radiation therapy.[10,11] They used 160 cGy per treatment, twice daily, for three days per week, for a total dose of 5,760 cGy in 40 days. Their local tumor response rate was 84% and two-year local control rate was 68%. The median survival, however, was only one year. Venkatesh et al from MD Anderson reported a large study of 121 cases of anaplastic thyroid cancer.[12] The mean survival for the entire group was 7.2 months. A significant percentage of their patients (25%) had areas of well-differentiated thyroid carcinoma. Their experience showed that the younger patients lived longer than the older patients and the patient who presented at an earlier stage responded better than a patient with metastases at the time of presentation. They recommended multimodality treatment and further evaluation. Tennvall[13] and the Swedish Anaplastic thyroid cancer Study Group reported their experience of combining Doxorubicin and hyperfractionated radiotherapy and surgery in 1994. Their treatment regimen included hyperfractionated radiotherapy, Doxorubicin and debulking surgery. Twenty mg of Adriamycin was used intravenously per week. Debulking surgery was possible in 23 patients (70%). The study showed a local control of 48%, while death was attributed to only 8 patients (24%) due to local failure. This appears to be a major advance in this mutilating disease. Kobayashi[14] from Japan reported an experience of 37 patients treated between 1971 and 1993 with a combination therapy. Thirty-four patients died within one year of diagnosis. They concluded that patients with primary lesions less than 5 cm who had a complete resection and radiotherapy survived significantly longer than other patients. Hyperfractionated radiotherapy was effective for local control. Tan[15] and his colleagues from Roswell Park Cancer Institute in Buffalo reported a 24-year experience of 21 patients with anaplastic carcinoma of the thyroid. Estimated five-year survival was 10%. Tumor size less than 6 cm and female gender were significant prognostic factors. Five patients who underwent complete resection had a better survival. Junor et al[16] treated 91 patients with anaplastic thyroid cancers between 1961 and 1986. Their results showed dyspnea to be the only symptom strongly influencing survival. They also showed increased survival with thyroidectomy. Nilsson et al[17] reviewed their experience over a 25-year period, with various combinations in the treatment of anaplastic thyroid cancer. Their most recent approach is to treat patients with Doxorubicin, preoperative accelerated hyperfractionated radiotherapy and surgery. Tallroth et al[18] have used a combination of chemotherapy, including Bleomycin, Cyclophosphamide and 5 FU. All survivals in their study had undergone surgery, but they noticed more complications related to combination chemotherapy and it was replaced by Adriamycin.

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CHAPTER 9

Complications of Thyroid Surgery

Richard A. Prinz

Thyroid surgery has progressed dramatically since the mid-1850s when half or more of the patients undergoing this operation would die from the procedure. Currently, thyroidectomy is a very safe operation which has an associate mortality rate that approaches zero. In other words, the mortality of a thyroidectomy is really the mortality of a general anesthetic. The morbidity associated with thyroid surgery is also very low. Nevertheless, the complications of thyroidectomy remain a matter of concern especially since thyroid disease often occurs in younger patients who have long life expectancy. Most complications associated with thyroidectomy can be minimized or even avoided by an experienced thyroid surgeon who has in depth knowledge of the anatomy of the central neck compartment and who employs meticulous surgical technique to protect the vital structures within it.

As with most operations, the complications associated with thyroidectomy can be listed as general and local. General complications include cardiac and pulmonary problems, gastrointestinal dysfunction such as nausea, vomiting and ileus, and renal and urinary tract problems. Local problems include those common to all operations such as bleeding, infection and seroma formation and those specific to thyroidectomy such as injury to the recurrent laryngeal nerve and/or the superior laryngeal nerve, hypoparathyroidism and airway obstruction. Other local complications such as injury to the esophagus, trachea, thoracic duct, jugular vein, carotid artery and spinal accessory nerve are extremely rare following thyroidectomy but still must be kept in mind especially when dealing with large invasive tumors or performing a combined neck dissection.

The general problems that occur with thyroidectomy are related to the underlying thyroid disease, the patient's associated medical condition and to the general anesthetic rather than to the procedure itself. These non procedure related problems are all relatively rare and occur in less than 1-2% of patients in large reported series of thyroidectomy. Of the cardiac complications, arrhythmias are the most common and occur in patients with hyperthyroidism or underlying cardiac disease. Pulmonary problems are surprisingly infrequent considering the amount of airway manipulation that is done during thyroidectomy. Atelectasis, bronchitis or pneumonia occur in less than 1% of patients. Urinary tract problems are extremely unusual. Postoperative nausea and/or vomiting can occur in as many as 10-15% of patients but is not due to ileus or other gastrointestinal dysfunction. This troublesome problem is anesthesia related and can be substantially lessened by modern antiemetic prophylaxis.

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Bleeding after thyroidectomy is quite unusual if meticulous attention to hemostasis has been employed. Nevertheless, it can be life threatening if tracheal compression or laryngeal edema cause respiratory compromise. The thyroid gland is extremely vascular and bleeding can occur anywhere in the operative field. Sites of potential hemorrhage include the superficial arteries and veins in the neck and any of the vessels that directly supply the thyroid. Ligatures may come loose or vessels that went in spasm and did not bleed during the dissection may be the source of hemorrhage. Bleeding from these sources can start when the patient is extubated if severe coughing or straining that increases intrathoracic pressure and thereby raises the pressure in the neck veins occurs. To avoid this problem all potential sources of bleeding must be securely ligated during the course of the operation. Special care must be taken with the vessels to the superior pole of the thyroid. These can retract out of view and be especially difficult to control if care is not taken to securely ligate them before they are transected. Before closing the incision, the operative field should be bone dry. It is prudent to check for bleeding by placing the patient in Trendelenburg position and having the anesthesiologist hyperinflate the lungs. Both of these maneuvers will increase venous pressure and hopefully allow the identification of bleeding sources.

After thyroidectomy, patients should be kept in a semi-Fowler position with the head elevated sufficiently to lower venous pressure in the neck. Drains will not prevent hemorrhage and are unlikely to prevent tracheal compression or laryngeal edema if bleeding occurs since clot formation usually causes them to malfunction. The majority of life threatening hemorrhages occur within the first few hours after the operation. Patients should be closely observed in a recovery room setting. The neck contour will be distorted if bleeding occurs and the depression of the supraclavicular fossa will be obliterated. The neck should be inspected before the patient leaves the recovery room to make sure that this has not occurred. Large bulky dressings will mask this finding and should be avoided. When symptomatic bleeding occurs prompt management is required. If there is any respiratory distress, the wound should be opened immediately to release and drain the hematoma. A tracheostomy should be performed to secure the airway if respiratory distress is not relieved by draining the hematoma. An alternative approach is to insert an endotracheal tube to secure the airway and then return the patient to the operating room to drain the hematoma and gain hemostasis. One must remember that this is a life threatening situation and there should be no delay in insuring the patient has a patent airway.

Small hematomas and/or seromas that do not pose any respiratory problem are common after thyroidectomy. This is especially true when dealing with large glands that leave a sizeable dead space or when dealing with reoperations because of the associated scar tissue. Most of these small hematomas or seromas will resolve spontaneously or can be treated by aspiration with a needle and syringe.

Respiratory compromise can also occur with tracheal collapse from chondromalacia or kinking of a soft tortuous trachea. These problems are quite rare and usually occur with long standing large multinodular goiters that have compressed the trachea and have often recurred after prior operations. When the thyroid is removed, the trachea can collapse or kink because the integrity of the cartilaginous rings has

been lost. In this situation, the thyroid gland was acting as an external support of the trachea even though the gland had compressed and compromised the cartilaginous integrity of the rings. Tracheostomy is the standard treatment if a soft trachea is encountered although prolonged endotracheal intubation and external splinting of the trachea by custom made rings or marlex mesh has been tried.

The nerves supplying the larynx and the pharyngeal constrictors arise from the nucleus ambiguous and course through the vagus nerve. The recurrent laryngeal nerves and the superior laryngeal nerves are branches of the ipsilateral vagus nerves. Each recurrent laryngeal nerve supplies all of the ipsilateral intrinsic muscles of the larynx, the cricopharyngeal muscle and sensation to the laryngeal mucosa below the vocal cords. The superior laryngeal nerve has two branches: the internal laryngeal nerve which supplies ipsilateral laryngeal sensation above the true vocal cords and the external laryngeal nerve which gives motor supply to the ipsilateral external cricothyroid muscles. The recurrent laryngeal nerve usually tracks upward in the neck in the tracheoesophageal groove medial to the carotid artery. Its course is often more oblique on the right and more vertical on the left. The recurrent nerves cross the lower lateral border of the thyroid at the level where the inferior thyroid artery enters the gland. Most commonly they pass behind this artery but they can course anterior to it. The nerves then course behind the lobe and pass through or behind Berry's ligament before penetrating the cricothyroid muscle to enter the larynx. There can be a great deal of individual anatomic variation in the location and course of the recurrent laryngeal nerve. In approximately 1% of the population, the right recurrent laryngeal nerve is non recurrent and enters the larynx from a superior or lateral position. Likewise it is not always a single strand and it can be quite variable in its pattern of branching. The normal location of the recurrent laryngeal nerves and their common anatomic variations must be understood and kept in mind when performing thyroidectomy if injury to them is to be avoided.

Complications involving the recurrent laryngeal nerves cause considerable morbidity. Although injury to a single nerve can remain asymptomatic, patients are more likely to have temporary or permanent hoarseness. Recurrent laryngeal nerve injury associated with thyroidectomy has progressively decreased but still occurs in 0.1-5% of patients. The main reason for the improved results is that the current recommended surgical approach identifies the nerve and protects it throughout the course of the dissection. If the recurrent laryngeal nerve has been stretched or roughly handled, neurapraxia may occur which can last for up to six months as the nerve regenerates along the intact axon sheath. If the nerve is inadvertently transected, permanent hoarseness will occur. If this complication is recognized intraoperatively, the nerve should be re-anastomosed using the operating microscope. If the patient is hoarse and the recurrent laryngeal nerve is not functioning in the postoperative period, it is likely that this will be temporary if the nerve was identified and noted to be intact during the operation. The chance of recovery is high and the patient should be observed for at least six months to allow for this possibility. When impaired recurrent laryngeal nerve function persists for more than a year, the injury is permanent and a number of measures can help lessen hoarseness. These include speech therapy, Teflon injection into the vocal cord, nerve anastomoses and other more

involved surgical procedures. Bilateral recurrent laryngeal nerve injury will cause respiratory distress and stridor since both vocal cords will assume a midline position. Patients will require reintubation or tracheostomy to secure an airway. Again it is important to delay any definitive procedure until one is certain that the injuries are permanent and that all chance of recovery is exhausted. A vocal cord lateralization procedure can be performed if the injury has been present for over a year.

The superior laryngeal nerve can be injured when taking down the superior pole of the ipsilateral thyroid lobe. This will lead to subtle loss of voice pitch, and voice volume. The patient will complain of voice weakness and sounding different. This is a serious matter for professional singers and other individuals who earn their livelihood from their public speaking. When bilateral injury occurs patients can experience swallowing disorders and be susceptible to aspiration. Damage to the superior laryngeal nerve occurs in 0.3-2% of patients undergoing thyroidectomy. This is likely to be a low estimate since the complication is probably under reported because of the subtlety of its symptoms.

Rarely the cervical sympathetic trunk may be damaged during thyroidectomy. This will result in Horner's syndrome. This is quite an unusual complication but can occur with very large glands, invasive tumors or with reoperations when scar tissue has obliterated normal tissue planes. Injury to the spinal accessory nerve can occur with neck dissections when combined with thyroidectomy but should not occur with thyroidectomy alone. Other local injuries to the carotid arteries, jugular veins and thoracic duct are also rare and usually occur when dealing with invasive tumors, reoperations or performing associated neck dissection.

Transient asymptomatic hypocalcemia occurs in most patients undergoing thyroidectomy. Acute symptomatic hypocalcemia and/or permanent hypocalcemia were once quite common with thyroid surgery especially in patients having total thyroidectomy. Rates of these problems have decreased dramatically as the understanding of the anatomy and physiology of the parathyroid glands has increased. Large series of thyroid operations have been reported in which the rates of permanent hypocalcemia due to hypoparathyroidism is less than 1-2%.

Permanent hypoparathyroidism will occur if all the parathyroid glands are removed or rendered ischemic during thyroidectomy. This is a serious problem with acute and long term sequelae. Symptoms of acute postoperative hypocalcemia usually develop from 1-7 days postoperatively. Numbness and tingling starts around the mouth and then progresses to the hands and fingers and feet and toes. A positive Chvostek's sign (twitching of the ipsilateral lip when tapping over the facial nerve) and a positive Trousseau's sign (carpal spasm when a tourniquet is placed on the arm for 5 minutes) are often present. If untreated, carpal pedal spasm, tetany and life threatening cardiac arrhythmias may occur. Symptom occurrence is variable and depends on the rate and decrement of the drop in ionized calcium. For symptomatic patients, treatment consists of intravenous administration of calcium gluconate. Calcium chloride should be avoided if possible since it will cause tissue necrosis if it is extravasated. Asymptomatic patients with mild hypocalcemia should be treated with oral calcium supplements. If the total serum calcium is less than 8 mg/dl, vitamin D replacement therapy should be initiated with 1 alpha-hydroxy

cholecalciferol. It is important to measure serum phosphorous in addition to serum calcium when evaluating these patients. If the serum phosphorous is low, the cause of hypocalcemia may be the "bone hunger" syndrome but if the serum phosphorous is high the cause of hypocalcemia is hypoparathyroidism. Hypoparathyroidism can be temporary or long term. If hypocalcemia and hyperphosphatemia remain after a year, permanent hyperparathyroidism is present and the patient will require long term therapy with oral calcium and vitamin D. Permanent hypoparathyroidism is a serious life long disability that requires regular monitoring of serum calcium levels and adjustments in replacement therapy. Fatigue, paresthesis, irritability and cataract formation are common continuing problems.

Permanent hypoparathyroidism is almost always preventable. Special attention must be given to identifying the parathyroid glands and preserving their blood supply during thyroidectomy. The branches of the inferior thyroid artery should be individually ligated in a manner that will preserve the vascular supply to each parathyroid gland. If a gland cannot be left in situ with an intact vascular pedicle, it should be removed and autotransplanted into the ipsilateral sternocleidomastoid muscle after it has been confirmed by frozen section. Any gland that appears ischemic without a good vascular supply should be autotransplanted because there is no reason to hope it will recover function and autotransplantation is a much more reliable technique for preserving its viability. After removing the thyroid, the specimen should be inspected before it is sent for pathologic evaluation. If a parathyroid gland has been inadvertently removed it should be separated from the thyroid and autotransplanted. Using meticulous technique to preserve well vascularized parathyroid glands in the neck and liberal use of parathyroid autotransplantation will effectively limit the rate of permanent hypoparathyroidism with thyroid surgery including total thyroidectomy.

Thyroidectomy has become a safe operation with little risk of mortality and long term morbidity. This is clearly attributable to the increased understanding of the anatomy and physiology of the thyroid gland and its associated structures. With meticulous operative technique and careful attention to detail, injury to the recurrent laryngeal nerves and superior laryngeal nerves and permanent hypoparathyroidism can be minimized. This is even true in settings such as reoperations where the risks of injury to these structures are greater from scarring and distorted anatomy.

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CHAPTER 10

Embryology, Anatomy and Physiology of the Parathyroid Glands

Heather Rossi, Richard A. Prinz, Edgar Staren

Historical Aspects

In 1880, Ivar Sandstrom a Swedish medical student, discovered the human parathyroid glands. This finding attracted little attention at first and an understanding of their function was slow in developing. The importance of the glands became evident when Vassale and Generali observed the occurrence of tetany following parathyroidectomy and the reversal following the administration of calcium. In 1891, von Recklinghausen reported the bone disease he named "osteitis fibrosa cystica". An association between hyperparathyroidism and bone disease was made in 1904 when Askanazy reported the bony changes described by von Recklinghausen in a patient with a parathyroid tumor. Initially, parathyroid tumors were thought to be the compensatory result of bone disease rather than its cause. In 1915 Friedrich Schlaugenhaufer proposed that a single enlarged gland might be the cause of bone disease and not the result. The Viennese surgeon, Felix Mandl performed the first parathyroidectomy for Von Recklinghausen's disease in 1925. This began the era of surgical treatment for hyperparathyroidism.

Embryology and Anatomy

During the 4th and 5th weeks of life, brachial arches begin to develop as neural crest cells migrate into the future head and neck region of the embryo. Each arch consists of a core of mesenchyme covered externally by surface ectoderm and internally by endoderm. Externally the arches are separated by branchial groves and internally by extensions of the pharynx called branchial pouches. The superior parathyroid glands arise from the fourth branchial pouch. The ventral portion of the fourth pouch fuses with the thyroid gland (Fig. 10.1). It gives rise to the parafollicular cells or C-cells of the thyroid gland which migrate from the neural crest cells of the ultimobranchial bodies of the fourth and fifth branchial pouches. Embryologically, it makes sense that both the parafollicular cells and the parathyroid glands produce substances that are involved in calcium regulation. The superior parathyroid glands tend to be located near the point of intersection of the middle thyroid artery and the recurrent laryngeal nerve. The glands are often attached to the thyroid capsule posteriorly. Rarely they may be embedded within the thyroid gland itself. Alternative locations include the tracheoesophageal groove and the retroesophageal space (Fig. 10.2). The primary blood supply to the glands originates from the inferior

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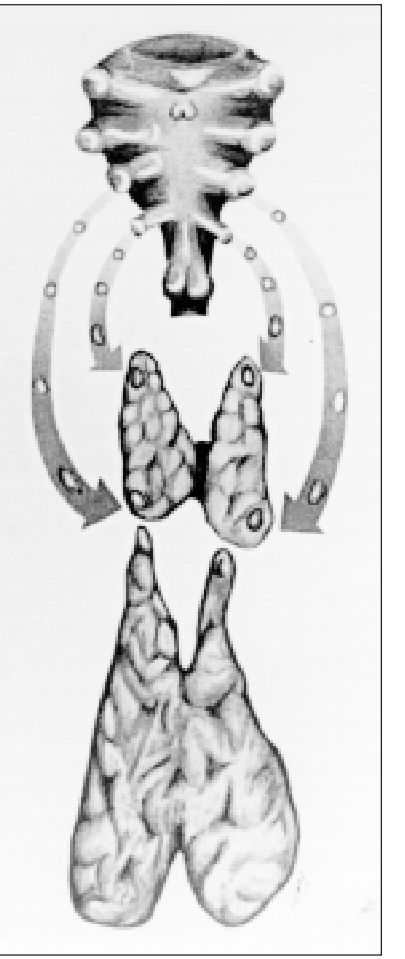

Fig. 10.1. Descent of the parathyroid glands from the third and fourth branchial pouches.

thyroid artery. The superior thyroid artery or the thyroid ima artery may also rarely supply these glands.

The inferior parathyroid glands as well as the thymus, develop from the third branchial pouch. They descend with the thymus and frequently lie beneath the thymic capsule (Fig. 10.1). They are often found in a plane ventral-medial to the recurrent laryngeal nerve typically near the lower pole of the thyroid gland lateral to the trachea. The location of the inferior glands tends to be more variable than that of the superior glands. When there are ectopic glands, they are often found with thymic remnants. A common site for ectopic tissue is the anterior mediastinum. Less common locations include within the aorto-pulmonary window, pericardium,

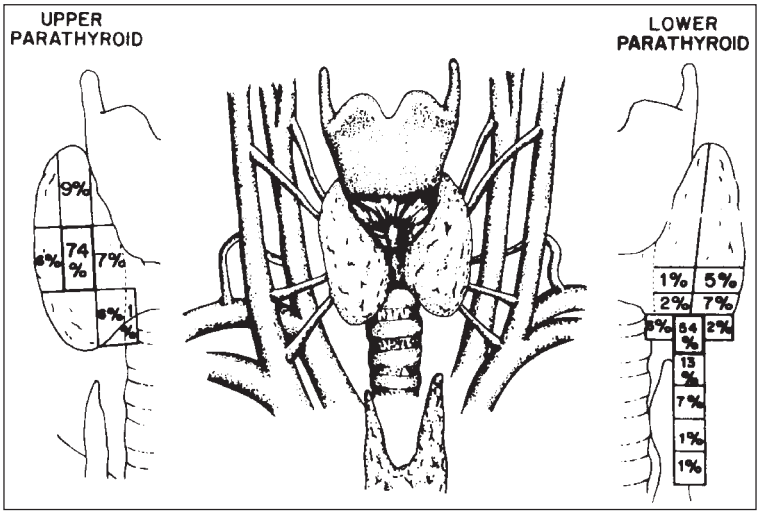

Fig. 10.2. Anatomic location and their described percentage of occurrence of the upper and lower parathyroid glands.

carotid sheath, and pharyngeal submucosa. The blood supply to the inferior glands originates from the inferior thyroid arteries.

There is substantial variability in the number and location of the parathyroid glands. The usual number of glands an individual has is four. Less commonly, greater than five and less than three have been reported. Size and weight generally are regarded as the most important determinants for normal tissue. The average normal gland has a dimension of 5-6 x 2-3 x 1-2 mm. Glands greater than 6 x 3 x 2 mm are generally suggestive of hyperplasia. The weight of a gland is less variable with the average ranging from 30-75 mg.

The color of a normal parathyroid tends to be yellow-brown. However, this is dependent on the amount of adipose tissue that it contains and its degree of vascularity. The yellow-brown is distinct from the brighter yellow of fat. A normal gland in the presence of a parathyroid neoplasm or adenoma often appears yellowish-tan in color as a result of atrophy. In hyperplasia, the gland may appear reddish in color secondary to the associated hyperemia.

Histology

Parathyroid glands are composed of two different cell types: chief cells and oxyphil cells. Chief cells are thought to produce parathyroid hormone (PTH). Oxyphil cells appear in the parathyroid glands after puberty and their number increases with age. The function of the oxyphil cell is unknown. Cells with structural characteristics between the two are also seen. This suggests that both cell types arise from a single cell of origin. Secretory cells are replaced with fat with increasing age. Adipose tissue constitutes greater than 50% of a gland in older individuals.

Physiology

The parathyroid glands play a key role in the metabolism of calcium and phosphate. There is an extensive number of interactions and feedback loops. The following discussion will highlight the major events.

Calcium

Approximately 99% of total body calcium is found in the skeleton and teeth and only a small fraction is present in the extracellular fluids. Calcium exists primarily in two forms: ionized and protein-bound. Approximately half is protein-bound and the other half is ionized. Normal serum calcium ranges from 9-10.5 mg/dl. It is the ionized fraction that is involved in physiologic functions such as blood coagulation, muscle contraction, nerve transmission, enzymatic reactions, and hormone metabolism.

Phosphate

Phosphate, like calcium, is a crucial ion for most biological systems. Phosphate is important as a high energy transfer component (i.e., ATP) and is crucial in the pathways of glycolysis. Normal serum plasma levels range form 2.5-4.5 mg/dl. These levels vary inversely with serum calcium levels.

Regulation of Calcium and Phosphate Metabolism

Three main organ systems are involved in the regulation of serum calcium. These are the gastrointestinal tract, the skeleton and the kidneys. The primary hormonal regulators are parathyroid hormone (PTH), Vitamin D and calcitonin. Their effects at the target organs are outlined in Table 10.1.

Parathyroid Hormone

Parathyroid hormone appears to be the most important regulator of calcium-phosphate homeostasis. PTH is produced in the parathyroid glands as a 115-amino-acid precursor molecule (preproPTH). This is then successively cleaved within the cell to form the 84-amino-acid peptide that is termed PTH. It is this form of the hormone that is packaged and released into the circulatory system. It binds to PTH receptors on target cells and activates the adenylate cyclase system to produce the second messenger cAMP. It is this activation of signal transduction that induces intracellular calcium mobilization and protein kinase C activation in PTH responsive cells.

The serum ionized calcium and phosphate concentrations reflect the net transfer of ions from the gastrointestinal tract, bone and kidney. When serum calcium levels fall, PTH is released to promote calcium reabsorption at the proximal tubule and loop of Henle in the kidney. PTH also stimulates the release of calcium from the exchangeable bone pool.

The effects of PTH on the kidney occur within minutes of its release from the parathyroid glands. The overall effect, however, depends on several factors. Chronic elevation of PTH increases renal production of 1,25-dihydroxyvitamin D [1,25-$(OH)_2D$]. This steroid hormone promotes the absorption of both calcium and

Table 10.1. Effect of hormonal regulators at target organs

	GI Tract	Skeleton	Kidneys
PTH	no effect	increases bone resorption	stimulates Ca resorption
Vitamin D	increases Ca-Phos absorption	increases bone resorption	no effect
Calcitonin	no effect	inhibits bone resorption	inhibits Ca and Phos resorption

phosphate from the gut. The time frame requires at least 24 hours to achieve eucalcemia. The increase in the active form of vitamin D serves as a negative feedback inhibitor of PTH. When PTH levels are increased as in hyperparathyroidism, hypercalcemia results from increased bone mobilization, increased intestinal absorption and decreased urinary excretion.

Parathyroid hormone affects phosphate levels primarily by promoting phosphate excretion at the proximal and distal tubules of the kidney. Serum phosphate levels do not alter PTH levels directly. Hypophosphatemia enhances the conversion of vitamin D to 1,25-$(OH)_2D$ in the kidney and promotes phosphate retention through its intestinal and renal effects. Hyperphosphatemia inhibits the conversion of vitamin D to its active form and lowers serum calcium by complexing with it. This lowers serum calcium levels and indirectly stimulates PTH secretion.

Parathyroid hormone acts on bone in two ways. The first is through rapid mobilization of calcium and phosphate from the exchangeable bone pool. The second results from the dissolution of bone matrix and bone remodeling. In its initial action on bone, PTH enhances osteoclastic activity and thus bone resorption. Through the act of bone resorption, PTH stimulates osteoblastic activity and thus bone formation since these are coupled reactions.

Calcitonin is a 32-amino-acid peptide hormone that plays a lesser role in calcium metabolism. Calcitonin is produced by the parafollicular cells of the thyroid gland and its release is stimulated by hypercalcemia. Calcitonin's main function is to lower serum calcium levels. It inhibits bone resorption by binding to osteoclast receptors and blocks the release of calcium and phosphate from bone. In the kidney, calcitonin inhibits the reabsorption of calcium and phosphate at the ascending loop of Henle and therefore promotes calcium excretion in the urine. The role and importance of calcitonin in calcium homeostasis must be relatively minor since patients after total thyroidectomy with absent levels and patients with medullary thyroid carcinoma and very high levels do not have problems maintaining normal serum calcium levels.

Disorders of the Parathyroid Glands

Hyperparathyroidism

The etiology of hyperparathyroidism is unknown. Gland overactivity is manifested through the peripheral effects of excess hormone. Primary hyperparathyroidism occurs when the normal negative feedback control of serum calcium is disrupted. There is an inappropriate excess of PTH production relative to the level of serum calcium. Secondary hyperparathyroidism occurs primarily in patients with renal disease. Dysfunctional mineral homeostasis leads to a compensatory increase in parathyroid gland function and size. Tertiary hyperparathyroidism develops when a hyperplastic gland develops autonomous function secondary to prolonged compensatory stimulation.

Primary Hyperparathyroidism

As stated above, primary hyperparathyroidism is due to excessive production and release of PTH. The incidence is approximately 1:1000 or greater in the general population and approximately 50,000 new cases are diagnosed each year in the United States. The incidence of the disease increases with age and is more common in females. The etiology in most patients is unknown. There has been a higher than expected incidence in people with a history of prior neck irradiation.

Primary hyperparathyroidism may be associated with any of the following: adenoma, hyperplasia or carcinoma. Single chief cell adenomas are the most common and account for the majority of cases (80-85%). Most adenomas occur sporadically and affect only a single gland. However double adenomas account for approximately 3-8% of the cases.

Recent molecular studies have begun to identify genetic factors associated with the development of hyperparathyroidism and parathyroid neoplasms. The proto-oncogene, parathyroid adenoma-1 (PRAD-1) found on chromosome 11, is activated in some parathyroid adenomas. Adenomas in which PRAD-1 is activated have undergone tumor-specific DNA rearrangements in the regulatory region. This leads to unregulated expression of PRAD-1 in the adenoma cell. Also, deletion or loss of function of tumor-suppressor genes have been implicated.

Parathyroid hyperplasia typically refers to the enlargement of all four glands. Hyperplasia is often associated with the autosomal dominant multiple endocrine neoplasia (MEN) syndromes (Table 10.2). In patients with MEN 1, there is a high penetrance of hyperparathyroidism. Hyperparathyroidism also occurs in MEN 2a, but with much less frequency. It almost never occurs in MEN 2b. In MEN 2 syndromes, mutations have been identified in the receptor tyrosine kinase (RET) gene on chromosome 10. It has been postulated that these mutations may be responsible for the various phenotypes seen in MEN 2a and 2b.

Parathyroid carcinoma is rare and probably accounts for less than 1% of all parathyroid hormone dependent hypercalcemia. Carcinoma should be considered in patients with severe hypercalcemia and a firm palpable cervical mass. Vascular or capsular invasion is a good predictor of malignancy, however these findings are not

Table 10.2. Multiple endocrine neoplasia syndromes associated with hyperparathyroidism

MEN 1
Parathyroid hyperplasia
Pituitary tumors
e.g., growth-hormone secreting, prolactin-secreting
Pancreatic tumors
e.g., gastrinomas, insulinomas, glucagonomas and VIPomas
Others
adrenocortical, thyroid, subcutaneous or visceral lipomas
MEN 2a
Parathyroid hyperplasia
Medullary thyroid
Pheochromoctyoma
MEN 2b
Mucosal neuromas
Marfanoid habitus
Medullary carcinoma of the thyroid
Pheochromocytoma
Hyperparathyroidism (very rarely present)

always present. Local recurrence and/or distant metastases to lung, liver, or bone are diagnostic of malignancy.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism implies parathyroid gland overactivity that is secondary to an exogenous defect. This disorder is generally seen in patients with chronic renal dysfunction. However, it has also been observed in patients with severe calcium and vitamin D deficiencies.

Other mechanisms that lead to this state include reduced intestinal calcium absorption, bone resistance to PTH, reduced 1,25 $(OH)_2D$ production and renal phosphate retention. Secondary parathyroid hyperplasia usually will resolve with correction of the underlying abnormality.

Clinical Manifestations

Primary hyperparathyroidism may present in a variety of ways. Patients may be asymptomatic and the disease may be recognized through routine screening laboratory tests. Other patients may present with severe renal or bone disease. Because calcium affects nearly every organ system, calcium dysregulation may present clinically with a multitude of signs and symptoms. The most common symptoms include fatigue, weakness, depression, arthralgia and constipation. Conditions associated with hyperparathyroidism include kidney stones, chondrocalcinosis, osteitis fibrosa cystica, osteoporosis, hypertension, gout, peptic ulcer disease and pancreatitis. Patients with excess PTH production may experience progressive loss of bone mineralization. This is manifested as subperiosteal resorption, osteoporosis and pathologic fractures. Skeletal involvement is most readily demonstrated by radiographic films.

Subperiosteal resorption is usually evident in the clavicles and distal phalanges. Skull films commonly show diffuse granularity and cystic lesions. Abdominal films may show nephrocalcinosis or nephrolithiasis.

Many other diseases are associated with hypercalcemia (Table 10.3). In hospitalized patients the most likely cause of hypercalcemia is an underlying malignancy. In patients who are not hospitalized, the most likely cause of hypercalcemia is primary hyperparathyroidism. The diagnosis of primary hyperparathyroidism is confirmed by at least two measurements of serum calcium and immunoreactive PTH. If the patient has both elevated levels of serum calcium and PTH that are reproducible, the diagnosis is certain.

There are four basic goals when managing hypercalcemia. These include correcting dehydration, enhancing renal excretion of calcium, inhibiting increased bone resorption and treating the underlying disorder. Various agents have been described to reduce the serum calcium concentration (Table 10.4). However, definitive management requires correction or treatment of the underlying disorder. When hypercalcemia is due to hyperparathyroidism, operative management is generally the treatment of choice.

Hypoparathyroidism

Total serum calcium includes ionized and protein-bound fractions. A common cause of measured hypocalcemia is hypoalbuminemia. However, symptoms of hypocalcemia occur only if the ionized fraction of calcium is reduced. The differential diagnosis for hypocalcemia is large (Table 10.5). Hypocalcemia due to hypoparathyroidism is uncommon. The most common cause is inadvertent devascularization or removal of the parathyroid glands during thyroid or parathyroid surgery. Hypocalcemia can result from reduced PTH secretion secondary to hypoparathyroidism or decreased end-organ responsiveness to PTH. This second disorder is termed pseudohypoparathyroidism. In pseudohypoparathyroidism, PTH is available but its affect at target tissues is decreased. The inability to respond normally is the result of dysfunction at the target cell level. This is due to a deficiency of the G-protein to couple the PTH receptor to the adenylate cyclase enzyme.

Table 10.3. Differential diagnosis of hypercalcemia

Endocrine	External agents
hyperparathyroidism	thiazides
familial hypocalciuric hypercalcemic	vitamin A
pheochromocytoma	vitamin D
adrenal insufficiency	lithium
Malignancy	aluminum
multiple myeloma	Granulomatous disease
solid tumors with bony metastases	sarcoidosis
Immobilization	tuberculosis

Table 10.4. Treatment modalities for hypercalcemia

Hydration
- expansion of ECF, increased GFR and glomerular filtration of calcium

Loop diuretics
- block calcium reabsorption in the ascending limb of Henle

Biphosphonates (etridonate, pamidronate, clodronate)
- inhibit resorption and formation of bone crystals

Plicamycin
- inhibits osteoclastic activity

Calcitonin
- inhibits bone resorption and increases renal excretion of calcium

Gallium nitrate
- inhibits bone resorption by reducing the solubility of hydroxyapatite crystals

Glucocorticoids
- inhibits growth of neoplastic lymphoid tissue

Phosphate
- forms calcium phosphate complex

Table 10.5. Differential diagnosis of hypocalcemia

Hypoparathyroidism
- infiltrative (hemochromatosis, sarcoid, Wilson's disease)
- postsurgical
- autoimmune
- congenital (DiGeorge's, Kearns-Sayre Syndrome)

Pseudohypoparathyroidism

Vitamin D deficiency
- malabsorption
- poor nutrition
- liver disease

Drugs
- anticalcemic agents
  - gallium nitrate
  - plicamycin
  - calcitonin
- antineoplastic
  - doxorubicin
  - cisplatinum
- others
  - amphotericin B
  - ketoconazole

Parenteral nutrition

Hungry bone syndrome

Hypoparathyroidism results in mineral disturbances because the amount of PTH is inadequate to maintain normal serum calcium levels. Hyperphosphatemia occurs because of the diminished effect of PTH to promote phosphate excretion from the kidney. Since PTH is required for the renal conversion of vitamin D to its active form, levels of 1,25-$(OH)_2$D are also low. Low levels of the active form of vitamin D lead to reduced intestinal calcium absorption and decreased mobilization from bone.

Table 10.6. Signs and symptoms of hypocalcemia

General	
	confusion
	weakness
	behavioral changes
Neuromuscular	
	psychosis
	seizure
	carpopedal spasms
	cramping
Cardiac	
	T wave changes
	prolonged Q-T interval
Respiratory	
	laryngospasm
	bronchospasm
	stridor

Clinical Manifestations

The signs and symptoms of hypocalcemia are similar regardless of the underlying cause (Table 10.6). The patient may be asymptomatic or present with evidence of tetany or sustained muscle contraction. Symptomatic hypocalcemia is characterized by abnormal neurologic or neuromuscular excitability. Acute signs include numbness around the mouth and paresthesias of the distal extremities. Chvostek's and Trousseau's signs may be demonstrated. Chvostek's sign is elicited by tapping the facial nerve anterior to the ear. Twitching of the facial muscle indicates a positive test. Trousseau's sign may be demonstrated by occluding blood flow to the forearm for 3 minutes. Carpal spasm indicates hypocalcemia. If hypocalcemia is severe and remains unrecognized, generalized seizures, airway compromise and even death may occur.

Hypoparathyroidism will vary in its severity and therefore need for treatment. For some patients with decreased reserve, situations of increased stress on the glands (i.e., pregnancy or lactation) result in hypocalcemia. For others, PTH deficiency is a chronic symptomatic disorder requiring life-long treatment. The treatment for acute hypocalcemia is the intravenous infusion of calcium. Oral calcium and vitamin D are used for long-term management.

The clinical course of pseudohypoparathyroidism is variable. Some patients will require calcium supplementation while others will undergo spontaneous remission. The reason for this is as yet unclear.

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CHAPTER 11

Diagnosis and Management of Primary Hyperparathyroidism

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Introduction

Hyperparathyroidism is a condition in which there is inappropriate hypersecretion of parathyroid hormone. Its various clinical presentations are termed primary, secondary, tertiary, and ectopic hyperparathyroidism. Primary hyperparathyroidism occurs when the normal feedback control of parathyroid hormone secretion by serum calcium is disturbed and parathyroid hypersecretion becomes autonomous. Secondary hyperparathyroidism occurs most commonly with chronic renal disease but also as compensation for true hypocalcemia associated with certain gastrointestinal, bone, or endocrine diseases. When secondary hyperparathyroidism progresses to autonomous parathyroid gland hypersecretion due to loss of feedback control, the condition is called tertiary hyperparathyroidism. Hypercalcemia resulting from secretion of parathyroid hormone-like substances, i.e., parathyroid hormone-related peptide, by tumors is called ectopic hyperparathyroidism.

The incidence of primary hyperparathyroidism in the general population is about 0.025%. The condition is seen predominantly among postmenopausal females. Primary hyperparathyroidism is the commonest cause of hypercalcemia in nonhospitalized patients. It is often first suspected when a routine chemistry survey shows an elevated serum calcium level in a patient who is asymptomatic or has minimal complaints. Therefore, the classic presentation of renal stones, painful bones, abdominal groans, psychiatric moans, fatigue overtones and hypertones (hypertension) is rarely seen today.

Diagnosis

Symptoms related to nephrolithiasis, bone pain, acid-peptic disease, polyuria and polydipsia, weakness, fatigue, depression, constipation, hypertension and pancreatitis may be present. Many patients initially considered to have asymptomatic primary hyperparathyroidism would, on closer questioning, admit to one or more of the above symptoms. A positive family history of hypercalcemia or a history of irradiation to the head and neck in childhood may on occasion be elicited.

A single adenoma is the most common cause of primary hyperparathyroidism (75-85%), followed by four-gland hyperplasia (10-20%), multiple adenomas (2-7%), and carcinoma (< 1%). Even large parathyroid adenomas are usually not clinically palpable. A palpable nodule in these patients is most often a thyroid nodule. There is a higher incidence of benign and malignant thyroid disease in patients with

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hyperparathyroidism. Patients may show radiological evidence of nephrolithiasis, nephrocalcinosis, subperiosteal bone resorption especially of the phalanges, or overt osteitis fibrosa cystica. Bone densitometry and bone biopsy may show abnormalities when roentgenograms are negative.

Hypercalcemia with an elevated serum parathyroid hormone level, or a serum calcium level associated with an inappropriately high parathyroid hormone level, is the mainstay of diagnosis. Serum ionized calcium levels are more sensitive than total serum calcium levels but are not usually needed in most clinical situations. The modern two-site immunoassay for the intact parathyroid hormone is more sensitive and specific than older immunoassays and should be used routinely.

Biochemical abnormalities, in addition to increased serum calcium and parathyroid hormone levels, include decreased serum phosphate and increased serum chloride and uric acid levels. The serum chloride-to-phosphate ratio will usually be greater than 33. Both urinary calcium and phosphate excretion will be increased. Hyperparathyroidism with apparent normocalcemia may be encountered with hypoalbuminemia, vitamin deficiency, renal failure, pancreatitis, magnesium deficiency, and excess phosphate intake.

Differential Diagnosis

Other causes of hypercalcemia should be ruled out before making the diagnosis of hyperparathyroidism. The following should be kept in mind:

1. Hypercalcemia of malignancy is the commonest cause of hypercalcemia in the hospitalized patient (e.g., breast cancer with skeletal metastasis, multiple myeloma).
2. Ectopic parathyroid hormone (parathyroid hormone-related peptide) production as a paraneoplastic manifestation of malignant disease (e.g., squamous cell carcinoma of lung, renal cell carcinoma, bladder carcinoma) is another manner in which cancer can cause hypercalcemia. The radioimmunoassay for intact parathyroid hormone is very specific and does not cross-react with the ectopic form of the hormone. In addition, new radioimmunoassays can accurately detect the parathyroid hormone-related peptide that is produced by these cancers.
3. Medications and dietary supplements can cause hypercalcemia and the possibility of milk-alkali syndrome, hypervitaminosis D, and intake of thiazide diuretics or lithium should be considered.
4. Granulomatous disorders, such as sarcoidosis and tuberculosis, are known to be associated with hypercalcemia.
5. Hyperthyroidism can cause hypercalcemia which may be ameliorated by antithyroid medications.
6. Less than 5% of patients with primary hyperparathyroidism will have a Multiple Endocrine Neoplasia (MEN) Syndrome. These patients typically have hyperplasia of all their glands. MEN I (Werner's Syndrome) includes primary hyperparathyroidism, pituitary adenomas, and pancreatic islet cell neoplasms. MEN IIa (Sipple's Syndrome) consists of medullary

carcinoma of the thyroid, pheochromocytoma, and primary hyperparathyroidism. Serum calcitonin levels serve as a useful tumor marker for medullary carcinoma of the thyroid. A history of headaches, excessive sweating, tachycardia, palpitations, or hypertension should alert the clinician about the possibility of an associated pheochromocytoma. Measurement of 24-hour urinary levels of catecholamines, metanephrines, and vanillylmandelic acid is the best screening test for pheochromocytoma.

7. Benign familial hypocalciuric hypercalcemia (FHH) is a rare disorder that requires measurement of 24-hour urinary calcium excretion for exclusion. Urinary calcium will be low in FHH but will be normal or elevated in primary hyperparathyroidism. The condition is not benefited by parathyroidectomy.
8. Paget's disease of bone and prolonged immobilization are other causes of hypercalcemia.

The hypercalcemia of sarcoidosis, hypervitaminosis D, skeletal metastases, and multiple myeloma may respond to hydrocortisone administered at 150 mg/day for ten days (hydrocortisone suppression test) but no such response is seen with primary hyperparathyroidism. This is rarely used nowadays as the accuracy of parathyroid hormone measurement has improved.

Indications for Surgery

Surgery is indicated for all patients with symptomatic hyperparathyroidism, unless contraindicated due to high risk. Nephrolithiasis, bone changes and neuromuscular symptoms have the best therapeutic response to surgery, but even psychiatric problems and difficulties with strength and stamina can be benefited in some patients. Hypertension and established renal failure are usually not improved by parathyroidectomy. Although controversial, the current trend is to recommend surgery even for asymptomatic hyperparathyroidism, especially in younger patients. The National Institutes of Health Consensus Development Conference laid down certain indications for operation in patients with asymptomatic primary hyperparathyroidism which have been described as "reasonable but conservative": patients below 50 years, who request surgery, that have serum calcium levels greater than 11.5 mg%, that have age-matched creatinine clearance reduced by more than 30% or 24-hour urinary calcium greater than 400 mg%, and with measurable bone mass reduction.

Operative Surgery

Under general anesthesia with endotracheal intubation, the patient is placed in the supine position with about 15° of reversed Trendelenburg inclination to empty the neck veins. A roll is placed under the shoulders to facilitate extension of the neck; the head is stabilized on a foam ring or doughnut. A transverse incision is made in a skin crease about two-finger breadths above the sternal notch. The skin and subcutaneous tissue including platysma are divided and superior and inferior subplatysmal skin flaps are raised. The deep cervical fascia is divided vertically in the midline and the strap muscles are retracted laterally. Both sides of the neck are then explored one after the other. The ipsilateral thyroid lobe is rotated up and medially,

the middle thyroid vein is ligated and divided, and gentle dissection is performed to identify the inferior thyroid artery, the superior thyroid artery, the recurrent laryngeal nerve, and the superior laryngeal nerve.

The superior parathyroid gland is usually in a plane posterior to the recurrent laryngeal nerve, while the inferior parathyroid gland usually lies in a plane anterior to the recurrent laryngeal nerve. Most often, the superior parathyroid gland is found in relation to the posterior capsule of the thyroid gland. The location of the inferior parathyroid gland is more variable and it may lie close to the inferior thyroid artery, within the thyro-thymic ligament, the thymus gland, or the chest. Meticulous dissection must be used to identify all four parathyroid glands. If an obvious adenoma is identified on one side, the other side is still explored as more than one adenoma may be present. Sometimes supernumerary parathyroid glands may be found. Frozen section examination of a sliver of tissue from each parathyroid gland is performed intraoperatively to differentiate the organ from fat or lymph nodes if there is any uncertainty. At the end of this initial exploration, if all four parathyroid glands have not yet been found, a systematic search is made in the various possible ectopic sites including the carotid sheath, the tracheoesophageal groove, the retrotracheal plane, the retroesophageal space and the retropharyngeal space. Next, the thymic remnant is excised via the cervical route and sent for frozen section examination. If the elusive parathyroid gland is still not found, then a thyroid lobectomy is performed on the side of the missing gland to exclude an intrathyroid parathyroid gland. Median sternotomy to detect an anterior mediastinal parathyroid gland is not indicated during the first exploration. If a missing gland is not found after a thorough exploration, the operation should be terminated and the diagnosis reevaluated. If the diagnosis is confirmed, localization studies should be performed before undertaking a reexploration. If the missing gland is localized deep in the chest, video-assisted thoracoscopy or median sternotomy can be performed.

If the pathology seen at operation is a single-gland parathyroid adenoma, only the involved gland is excised. If two or three parathyroid glands are found to be enlarged, the abnormal glands are excised and the normal glands are left in situ. If four-gland hyperplasia is present, three-and-a-half glands are excised and the remaining half gland is left in situ and marked with a suture or clip. With subtotal parathyroidectomy, the surgeon must be sure the blood supply to the remaining gland has not been compromised by the dissection. For four-gland hyperplasia, some authorities prefer to perform total parathyroidectomy with heterotopic autotransplantation of parathyroid tissue into a forearm muscle. If recurrent disease develops in the autograft, further excision of parathyroid tissue from the forearm can then be performed under local anesthesia. Associated thyroid disease should be dealt with if encountered during parathyroidectomy.

Complications of Surgery

In experienced hands, morbidity associated with parathyroidectomy is impressively low (< 1%) and mortality is extremely rare. Postoperative bleeding may compromise the airway but is extremely rare in occurrence. Postoperative infection is uncommon. Recurrent laryngeal nerve injury causes hoarseness. Injury to the

superior laryngeal nerve or its external laryngeal branch affects the tone and range of the voice and is important for professional singers and dramatists. Mild postoperative hypocalcemia is treated with oral calcium replacement. Mild hypocalcemia may be detected biochemically or may manifest as perioral or digital numbness and tingling. Severe postoperative hypocalcemia is a risk especially in patients with skeletal manifestations of primary hyperparathyroidism ("hungry bone syndrome"). Carpopedal spasm, tetany, or generalized convulsions can occur. Severe hypocalcemia must be treated with intravenous calcium infusion. Intravenous infusion of calcium chloride through a peripheral line carries the danger of tissue necrosis if it extravasates. It should only be administered through a central line. Intravenous calcium gluconate is much safer. Magnesium deficiency must also be corrected. Cryopreservation of parathyroid tissue in liquid nitrogen, if available, ensures viability for at least18 months. It can play an important role in the management of postparathyroidectomy hypocalcemia and should be considered whenever the surgeon is unsure that the patient has viable normal parathyroid tissue remaining in the neck. This is especially true in reoperations.

Persistent hypercalcemia after parathyroidectomy is a consequence of residual disease resulting from inadequate surgical exploration, missed pathology, inadequate excision of diseased parathyroid tissue, or presence of a supernumerary or mediastinal parathyroid gland. Recurrent hypercalcemia, on the other hand, is defined as postoperative hypercalcemia that occurs after at least a six-month period of documented normocalcemia. It is due to a recurrence of the disease rather than due to missed pathology at the first operation. For postoperative hypercalcemia, localization studies are indicated and re-exploration is usually required. With re-exploration of the neck the risk of complications is substantially higher.

Localization Studies

Localization studies are reserved for patients requiring surgical re-exploration. Noninvasive localization studies are undertaken first and include high-resolution ultrasonography, computerized tomography (CT), magnetic resonance imaging, and technetium sestamibi scintigraphy.

Ultrasound is useful in localizing parathyroid lesions close to or within the thyroid gland, but is of limited value for deep cervical, superior cervical, retrotracheal, retroesophageal or mediastinal locations due to acoustic interference from air and bone. Ultrasonography has the advantage of being a three-dimensional investigational modality that is relatively inexpensive, but it is very operator-dependent. It has a success rate of 35-75% in previously operated patients.

Computerized tomography and magnetic resonance imaging are particularly well suited for ectopic and mediastinal parathyroid lesions. The major limitation of CT is that it does not easily differentiate thyroid tissue and lymph nodes from parathyroid tissue. Thyroid, fat and parathyroid tissue can have a similar appearance with magnetic resonance imaging. The success rate for both modalities in previously operated patients ranges from 45-80%. Computerized tomography is costlier than ultrasonography, while magnetic resonance imaging is even more expensive.

The newest radionuclide for parathyroid scanning is technetium sestamibi. It is taken up and retained by abnormal parathyroid glands. Sestamibi scans tend to be false negative in patients with small adenomas or with hyperplasia. False-positive results have occurred in patients with thyroid nodules. Successful preoperative localization of parathyroid lesions ranged from 30-85%.

If noninvasive localization studies fail to identify the hyperfunctioning gland, invasive studies that can be performed include selective venous sampling for parathyroid hormone and angiography. Selective venous sampling does not truly localize the gland but merely lateralizes the side of the pathology. The value of these invasive modalities of parathyroid localization is highly dependent on the experience of the radiologist. Parathyroid angiography carries a real risk of death or major neurologic complications and should only be done by an experienced angiographer.

A new algorithm for noninvasive preoperative localization prior to re-exploration uses sestamibi scintigraphy combined with three-dimensional SPECT imaging, followed by ultrasound-guided fine needle aspiration confirmation of parathyroid tissue. This approach combines functional, anatomic, and histologic documentation of pathology and is highly reliable.

Management of Specific Situations

Management of Hypercalcemic Crisis

Patients with primary hyperparathyroidism may develop acute life threatening hypercalcemia when serum calcium concentrations rise above 15 mg%. The clinical manifestations include muscle weakness, nausea, vomiting, lethargy, coma, and death. Treatment includes vigorous rehydration and therapeutic measures to counter hypercalcemia. This should be followed by urgent parathyroidectomy. The patient is rehydrated with intravenous saline until a urine output of 100 mL/h is obtained. Intravenous furosemide (Lasix) is given after rehydration to prevent fluid overload and encourage renal calcium excretion. Serum potassium must also be replaced. If hypercalcemia is not improved substantially with these measures, a biphosphonate such as disodium pamidronate is the best for hypercalcemia due to hyperparathyroidism. Calcitonin may be effective especially if the skeletal system has been involved, but is expensive and not long lasting in effect. Mithramycin takes 24 hours to effect a change and is more useful in the setting of hypercalcemia secondary to malignancy. Serum parathyroid concentration must be measured urgently. If a noninvasive parathyroid localization study can be obtained quickly prior to surgery it may provide helpful information, but it should not appreciably delay operative intervention. Without urgent parathyroidectomy, mortality is high.

Management of Primary Hyperparathyroidism in Pregnancy

Newborns of mothers with primary hyperparathyroidism are prone to develop neonatal tetany. To reduce the risk of morbidity and mortality in the fetus, the mother should undergo parathyroidectomy in the second trimester of pregnancy.

Neonatal Hyperparathyroidism

Neonatal hyperparathyroidism is a rare condition associated with hypotonia, poor feeding, respiratory distress, and a high mortality rate. Total parathyroidectomy with autotransplantation is indicated.

Parathyroid Carcinoma

Parathyroid carcinoma occurs in less than 1% of patients with primary hyperparathyroidism. Local invasion or distant metastases are hallmarks of the disease, and the primary lesion is palpable in 50% of patients. Markedly elevated serum parathyroid hormone, calcium, and alkaline phosphatase levels are characteristic. Surgical treatment involves radical resection of the tumor, ipsilateral thyroid lobectomy, and regional lymph node dissection. The five-year survival rate following radical surgery is 50%. Radiotherapy and chemotherapy have not been of value.

Controversies in Management

Surgery versus Observation for Asymptomatic Hyperparathyroidism

Whether or not to submit asymptomatic patients with hyperparathyroidism to surgery remains a topic of discussion. A final answer to this question can be obtained only from a prospective, randomized, controlled trial. The advantages of surgery over prolonged observation are several. The prevention of disease progression with surgery is more effective than the reversal of symptoms and signs that are already manifest. Surgery is less expensive than prolonged medical follow-up and is more convenient for many patients. In experienced hands the complication rate of surgery is low (< 1%). A substantial proportion of patients are lost to medical follow-up. The younger the patient, the greater the likelihood of progression to overt disease. A number of patients will, in retrospect, report improvement in nonspecific symptoms following surgery. The importance of adopting a uniform policy for asymptomatic hyperparathyroidism is underlined by the fact that this subgroup of patients has been steadily increasing since the advent of routine multichannel screening of serum biochemistry.

Surgical Localization versus Preoperative Localization for Initial Parathyroidectomy

Routine use of preoperative localization studies prior to initial neck exploration is often recommended and frequently debated. The main fallacy of this approach is that the patients most likely to fail surgical localization at initial exploration are those with ectopic glands or multiple gland disease. It is in this same subgroup of patients that localization studies would in all likelihood be unsuccessful. Furthermore, surgery is successful in 95-98% of patients who have not had preoperative localization studies when performed by an experienced parathyroid surgeon. As none of the preoperative localization studies approach this success rate, routine preoperative imaging cannot be justified.

Preoperative Localization Studies with Unilateral Exploration

Some authorities have suggested that if preoperative localization studies and unilateral surgical exploration identify one enlarged gland and one normal gland on the same side, then the contralateral side need not be explored. Given that preoperative imaging has a maximum sensitivity of 80%, unilateral exploration carries a clinically important risk of inadequate parathyroidectomy due to missed double adenomas or unrecognized asymmetric hyperplasia. The consensus among parathyroid surgeons is that initial bilateral surgical exploration without preoperative imaging is safe and effective and is the preferred course of management.

Parathyroid Cysts—Functional or Nonfunctional?

Parathyroid cysts were thought to be nonfunctional. However, recent reports suggest that parathyroid cysts can not only be functional and cause hypercalcemia but they can also present with hypercalcemic crisis.

Future Prospects

Performance of Concomitant Surgical Procedures

When a patient with primary hyperparathyroidism has an additional surgical condition requiring operative intervention, it has been shown that the two surgical procedures can be safely performed concomitantly. To justify concomitant surgery, both procedures should have a clear clinical indication, and postponing surgery for the associated condition would be a cause for concern. In general, the parathyroidectomy should be given priority and performed first. Even minor procedures performed in the presence of any degree of hyperparathyroidism can precipitate an acute and fatal hypercalcemic crisis.

Intraoperative Parathyroid Hormone Assay and Urinary cAMP Levels

Intraoperative methods of assessing the adequacy of parathyroid excision are being sought. Urinary cAMP levels are reduced rapidly when surgery has been adequate, but this test is time consuming and therefore not suitable in most intraoperative settings. Instead, the recently developed immunometric assays of intact parathyroid hormone are more accurate than urinary cAMP measurements and can be performed more swiftly when modified. These “quick” parathyroid hormone assays take 15-30 minutes to perform, are especially valuable in reoperations, and are gaining in popularity.

Video-Assisted Thoracoscopy for Removal of Parathyroid Glands Deep in the Chest

Abnormal parathyroid glands located in the mediastinum that are not accessible through a cervical incision have required median sternotomy or thoracotomy for their removal. With the recent advent of minimally invasive surgery, video-assisted thoracoscopic removal of mediastinal ectopic parathyroid glands has been accomplished. These ectopic parathyroid glands were first identified with technetium-thallium or sestamibi scintiscans and then precisely localized with computed

tomography prior to video-assisted thoracoscopic removal. The advantage of avoiding the morbidity of open procedures is obvious.

Calcium-Receptor Agonist for Medical Treatment of Primary Hyperparathyroidism

A preliminary communication reports that the calcimimetic drug R-568 reduces serum parathyroid hormone and ionized calcium concentrations in patients with mild primary hyperparathyroidism. This investigational drug may have the potential of becoming a nonoperative alternative for the treatment of mild primary hyperparathyroidism in postmenopausal women and asymptomatic primary hyperparathyroidism.

Genetic Testing for Multiple Endocrine Neoplasia Syndromes

Patients with primary hyperparathyroidism and relatives of patients with MEN syndromes can now undergo genetic testing to facilitate early diagnosis of MEN syndromes. A genetic defect on the long arm of chromosome 11 has been implicated in MEN I syndrome, while mutations of the centromeric region of chromosome 10 have been identified in the MEN II syndrome.

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CHAPTER 12

Parathyroid Localization Studies

Gordon Bodzin, Edgar D. Staren and Richard A. Prinz

Introduction

It has been stated, and often repeated, that the best parathyroid localization procedure is to localize an experienced parathyroid surgeon. This being said, a considerable body of literature has been devoted to studies designed to determine the best modality for localizing an abnormal parathyroid gland. The reasons for this are as follows:

1. Surgical therapy is employed almost exclusively in the treatment of hyperparathyroidism;
2. Recently, some authors have advocated unilateral neck dissection in the treatment of parathyroid adenomas;
3. Although the normal anatomic locations of the four parathyroid glands are well described, abnormal glands may be found in ectopic locations;
4. Supernumerary glands may be present;
5. Parathyroid surgery is a time consuming and technically difficult operation; and
6. Even in the most experienced hands, there is still about a 5% rate of failure to cure hyperparathyroidism with a single operation.

Due to the above factors, it has become necessary to pursue studies to localize abnormal parathyroid glands. Because of the high success rate of initial exploration, most authors do not advocate preoperative localization studies. In addition, some have cautioned that an inexperienced surgeon might be lulled into a false sense of security by a scan that shows a single adenoma. In reality, the patient might have more than one abnormal gland, which would be missed if a complete exploration were not performed. However, as mentioned above, some authors advocate unilateral neck dissection in certain cases. In these situations, it is necessary to perform some kind of localization study in order to decide which side of the neck to explore. Also, in the case of hypercalcemic crisis, where it is necessary to make sure all abnormal glands are found, most authors advocate performing some type of preoperative localization.

For the purposes of this chapter, we will focus on noninvasive studies, although some authors have attempted localization using invasive techniques such as selective venous sampling or angiography. Although these techniques have proved advantageous in specific cases, they are not employed very often due to the morbidity and expense involved. Furthermore, they have not demonstrated significant advantages over noninvasive studies. The studies we will discuss include computed tomography

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(CT), magnetic resonance imaging (MRI), ultrasound (US), and various nuclear medicine studies.

CT

Computed tomography has been used to evaluate the parathyroid glands, and is most useful in the setting of persistent or recurrent hyperparathyroidism after initial neck exploration. This is because CT can help delineate scarred tissue planes. It is also useful for visualizing glands in the mediastinum, and in locations in the neck which are difficult to visualize using ultrasound, such as retroesophageal or juxtavascular locations. When CT is used, the protocol includes thin cuts (either 3-4 mm cuts or overlapping 6-8 mm cuts). The scanning volume should include the neck from the hyoid bone to the apices of the lungs initially. In the setting of previous operations, the mediastinum should be included as well, to reduce the chance of missing an ectopic gland. An initial noncontrast scan should be done, followed by a contrast-enhanced scan. The contrast scans can be especially helpful in the setting of glands located near the thyroid. The thyroid, because of its high affinity for iodinated contrast, enhances significantly. The parathyroid adenoma will also usually enhance on these scans. Conversely, other nearby structures that might be misidentified as adenomas, such as the longus colli muscle or a thyroid nodule, usually do not enhance. Some authors, however, assert that the contrast medium is of little or no help in differentiating thyroid structures from parathyroid abnormalities. Densitometric analysis of these structures have revealed that the parathyroid adenoma is usually less dense than the thyroid on both plain and contrast-enhanced scans. Some authors advocate omission of the mediastinum on contrast-enhanced scans if the initial nonenhanced scan is negative in that area. It is especially important that these scans be read by an experienced radiologist, as several studies have demonstrated that glands initially missed can be found retrospectively once their locations are surgically proven.

CT also has significant limitations in identifying parathyroid abnormalities. Perhaps most importantly, the resolution of most CT scanners is not sufficient to identify structures less than 5 mm. The newer spiral CT scanners may be less limited in this regard, but very few studies have examined their abilities in this particular area. The CT is also limited by the fact that the incidence of multinodular goiter and thyroid nodules is somewhat higher in patients with hyperparathyroidism. These can distort the anatomy of the neck, and may make contrast administration unadvisable in some cases. CT is not useful for identifying intrathyroidal glands. CT was originally introduced in hopes of reducing the false negative rate of ultrasound exams, and of obviating the need for more invasive arteriography or venous sampling. While it is useful for filling in gaps left by US, other noninvasive modalities, such as MRI and nuclear medicine scans are also available, removing the need for invasive studies in most cases, as mentioned above. CT is also susceptible to artifacts induced by surgical clips left during the initial cervical exploration. Given these limitations, CT has been found to have a sensitivity in the 70% range, and a specificity in the 85%

range. When combined with other studies, such as US, the sensitivity is raised to the 90% range, and specificity is increased as well.

MRI

Magnetic resonance imaging is the newest modality used for parathyroid localization. It has become an established and well accepted method for evaluating abnormalities of the parathyroid glands. Most authors recommend the acquisition of thin (3-5 mm) sections. The scan volume should extend from the hyoid bone superiorly to at least the lung apex. As mentioned above, most authors do not advocate routine preoperative scans. Therefore, most of these studies will be done in patients who have had a previous bilateral neck dissection. For this reason, electrocardiogram (ECG)-gated scans of the mediastinum from the cervico-thoracic junction to the base of the heart should be done as well to search for ectopic glands which can be found from the hyoid bone to the pericardium. Without getting too technical, T1 and T2 weighted scans, as well as gadolinium-DTPA enhanced T1-weighted images should be done. The T2-weighted images are susceptible to degradation due to swallowing or other patient motion. The contrast-enhanced scans are especially useful in situations where the T2-weighted images are of poor quality, or the initial T1-weighted images are of borderline quality. Fat suppression techniques can also be used to enhance visibility of the parathyroid (and thyroid) glands.

Since the normal parathyroid gland is small, it is difficult to detect using current MRI techniques. The most common appearance of abnormal glands is of intermediate signal on T1 (similar to thyroid or muscle), and high signal on T2 (similar to or greater than fat). However, this appearance can be altered by hemorrhage or other histologic characteristics. Hemorrhage into the adenoma can cause it to show high signal on both T1 and T2 images. Conversely in some cases, an adenoma may show low signal intensity on both T1 and T2 scans. This may occur in the case of a degenerated or fibrotic adenoma. As mentioned above, Gd-DTPA enhanced images can help to make the parathyroids more conspicuous, and are useful when the T2 images are of poor quality, or the patient is not cooperative. One major advantage of MRI over ultrasound in particular, is that it can be used to examine all of the potential ectopic locations. It has also been demonstrated in some studies to be significantly more sensitive and specific than CT and nuclear medicine scans for identifying glands in mediastinal locations.

There are some disadvantages to using MRI as well. The most significant one is that the normal cervical lymph nodes have an appearance on MRI that is the same as that of abnormal parathyroid glands. Consequently, MRI can only differentiate between these two structures on the basis of shape and location. Fortunately, this is usually fairly straightforward. Likewise, other structures in the neck, such as cervical ganglia, can also appear similar to an abnormal parathyroid gland. Because of their embryologic origins, occasionally ectopic glands may be found within the thyroid itself. This can be problematic, since up to 40% of thyroid glands can contain high T2 signal foci, even when no thyroid disease is present. Finally, the MRI scan may not identify all of the

abnormal glands in a patient with hyperplasia. This fact once again underscores the need for careful exploration at the hands of an experienced surgeon.

US

Ultrasound examination of the neck in hyperparathyroidism has many features which make it an attractive technique for parathyroid localization. It is a painless, relatively quick (about 30 minutes) exam, which does not require any contrast injection. Although some authors have advocated the use of 5 mHz transducers, most feel that a 7.5-10 mHz linear array transducer is most appropriate. As with the other modalities, it is important that the ultrasound technician be experienced in this area. The examination area should include the entire thyroid gland, to the carotid artery and jugular vein laterally, to the hyoid bone superiorly, and to the sternal notch inferiorly. The use of endoscopic ultrasound has been investigated, but has been found to be useful only in the case of glands located posteriorly near the esophagus. Parathyroid adenomas, and some larger hyperplastic glands, appear on US as oval hypoechoic or anechoic masses. They are often found posterior to the thyroid gland, usually medial to the carotid artery, and just anterior to the longus colli muscle.

Although ultrasound can identify intrathyroidal masses, it cannot differentiate thyroid lesions from intrathyroidal parathyroids based on appearance alone. Usually, these lesions can only be differentiated on the basis of needle-aspiration biopsy. This procedure is somewhat technically difficult, and insufficient biopsy specimens are common. As with the other types of exams discussed, ultrasound is not particularly sensitive for the identification of diffuse hyperplasia. Sensitivities for this condition are less than 50% in most cases. Again, although the US exam may identify a single predominant gland, this does not rule out the presence of hyperplasia or multiple adenomas. The overall sensitivity and specificity varies widely between studies. This variation is mostly due to differences in type of transducer, and as mentioned above, US is particularly dependent on operator expertise. It is also susceptible to the artifacts created by previous surgical exploration, as well as thyroid lesions which may obscure the much smaller parathyroid glands. This can be a particular problem in the setting of MEN syndromes. US cannot be used to examine the mediastinum because of a lack of appropriate windows. The high-resolution transducers are also limited in the detection of masses deeper in the neck, because of their limited range of depth. Several authors have reported on the use of ultrasound guided ablation of parathyroid glands using ethanol injection, especially in patients with secondary hyperparathyroidism. They report varying success rates, but advocate this technique in patients who are poor surgical candidates. As mentioned above, ultrasound can be useful in a combination of exams with CT, MRI, and/or nuclear medicine studies.

Nuclear Medicine Studies

Various nuclear medicine protocols have been developed for imaging of parathyroid glands. Most of these involve subtractions studies in which two different images are obtained, and then one subtracted from the other to reveal the structures in

question. In the case of parathyroid studies, this usually involves the subtraction of the thyroid gland from the images obtained. This can be done either using two different radionuclides, or a single agent with immediate and delayed images obtained. Other studies can be done without using subtraction techniques. Single photon emission computed tomography (SPECT) imaging can be used with some of the agents, in order to provide a three-dimensional image that can be used for more precise preoperative localization, especially in mediastinal locations. Nuclear medicine studies are not limited by anatomical features, which makes them useful for identifying ectopic glands. There have been reports of the use of hand-held gamma detectors intraoperatively to assist in locating the glands. Once again, as mentioned in the other studies, most authors do not advocate routine preoperative studies before neck exploration for primary hyperparathyroidism.

Until recently, the most commonly used protocol was a $^{201}Tl/^{99m}Tc$ subtraction study. This protocol revealed about an 80% sensitivity for adenomas, and somewhat less for hyperplasia. The major disadvantage of this protocol was that it was very sensitive to patient movement. Also, because the ^{201}Tl and ^{99m}Tc images are not exactly superimposable, small juxtathyroidal lesions can be missed. Studies using ^{123}I as the thyroid agent revealed similar results and disadvantages. More recently, a new technetium derivative, ^{99m}Tc -hexakis,2-methoxy-isobutyl-isonitrile (sestamibi or MIBI), has been shown to hold significant advantages over $^{201}Tl/^{99m}Tc$ subtraction. This isonitrile derivative was originally developed for cardiac imaging, and can be used in subtraction protocols with ^{99m}Tc or ^{123}I like thallium, and can also be used as a single agent in delayed-imaging protocols. Unlike the above-mentioned problem with thallium, the sestamibi images can be more directly subtracted from ^{99m}Tc, without losing sensitivity in juxtathyroidal lesions. The dosage characteristics of sestamibi also allow for a significantly smaller dose of radiation to the patient.

The availability of single agent (nonsubtraction) studies removes the error that is commonly introduced by patient movement in subtraction studies. Many authors also point out that if a single agent study does not reveal the offending gland, the second agent can then be injected immediately, so nothing is lost by attempting a single-agent study. Special protocols can make the sestamibi study as sensitive as a dual-agent study in some cases. One of these protocols, FADS (Factor analysis of dynamic structures) uses sophisticated computer analysis to identify the differential washout of sestamibi from the thyroid and parathyroids. Using this technique, sensitivity as high as 85%, and specificity of 95% have been reported for adenoma. This technique is not available in all institutions, however. As mentioned above, SPECT imaging can be used with sestamibi, allowing both greater sensitivity than planar images alone, and three dimensional localization of abnormalities. The sensitivity of sestamibi studies for multigland hyperplasia is somewhat better than other imaging modalities.

An ideal protocol has yet to be developed for MIBI imaging. This has led to wide variability in both sensitivity and specificity of these scans. In general, the subtraction studies tend to have slightly greater sensitivity, but less specificity than single agent scans. In addition, several thyroid lesions, such as adenomas, may show uptake

on subtraction studies in particular. This may be due to differential kinetics in these thyroid lesions as compared to normal thyroid tissue. In situations where SPECT is not used, planar images have a much lower anatomical resolution than CT or MRI. Again, although sensitivity and specificity are in the 80-90% range, these are still lower than the success rate of initial neck exploration, and consequently should not be used as a routine preoperative study in patients with primary hyperparathyroidism.

Discussion

Future directions for research include increased resolution of CT and MRI scans. These would improve detection of small adenomas and possibly hyperplasia. Nuclear medicine scans using newer radionuclides such as technetium tetrafosmin are under investigation, and may increase sensitivity and/or specificity. FDG-PET scans have also shown some promise, but are only available in certain large centers.

The localization of parathyroid glands in recurrent or persistent hyperparathyroidism is an important, but difficult issue preoperatively. It is essential that the study done be able to identify remaining parathyroid glands with high sensitivity and specificity. The study should also be able to examine all potential sites for ectopic glands, and should be minimally invasive. Given these caveats, no single study is able to satisfy all of these conditions. Most authors, including this one, therefore recommend a combination of complimentary studies for parathyroid localization. Consider a protocol as follows: Given a patient with biochemically proven hyperparathyroidism, and previous neck dissection, perform ultrasound as described above. Following ultrasound, perform sestamibi scan initially with single agent. Follow with subtraction scan if single agent scan negative. If sestamibi and ultrasound positive in the same location, take patient to OR. If not, follow with MRI scan. Using similar protocols, many investigators have found sensitivities in the 95% range, and specificities approaching 100%.

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CHAPTER 13

Secondary and Tertiary Hyperparathyroidism

P. Anthony Decker, Eric Cohen and Michael J. Demeure

Hyperparathyroidism is classified into primary, secondary and tertiary forms. Primary hyperparathyroidism refers to autonomous oversecretion by an adenoma or hyperplastic glands. Secondary hyperparathyroidism refers to an increased secretion of PTH in response to the mineral derangements seen with chronic renal failure, rickets, osteomalacia or malabsorption. Tertiary hyperparathyroidism is the persistent, autonomous oversecretion of PTH after the cause of secondary hyperparathyroidism has been corrected, usually by renal transplant.

Historically, Sir Richard Owens first described the parathyroid glands in 1852 from an autopsy on a rhinoceros. Elucidation of parathyroid physiology and pathophysiology was difficult, and not until 1934 was the association between hyperparathyroidism and renal failure made by Albright. Nearly all patients with renal failure develop progressive elevation of parathyroid hormone (PTH) levels and become more severe as renal failure progresses. Hypersecretion of PTH can have deleterious effects. In 1960 Stanbury proposed and Nicholson undertook the first subtotal parathyroidectomy to halt progression of bone disease in renal failure.

Symptoms of secondary hyperparathyroidism include bone pain, pruritis, malaise and pathologic fractures, all related to bone remodeling and a disturbance of mineral homeostasis. Early in its course, secondary hyperparathyroidism is amenable to medical treatment with dietary phosphate restriction, phosphate binders, oral calcium and vitamin D supplements. Due to improved medical management and increased understanding of the involved pathophysiology, less than 5% of patients will come to parathyroidectomy.

Concerns have been raised regarding training in surgery for patients with secondary hyperparathyroidism. In 1995, the mean number of parathyroid operations performed by graduating general surgery residents was 6.1 ± 3.4. Few fellowships exist, and the fellows may compete with the general surgery residents for these cases. Transplant surgeons perform some of these operations, as they have established relationships with the referring nephrologists and frequently know the patients from past transplants or venous access operations. Otolaryngologists also perform parathyroidectomies. With better medical management and as fewer patients come to surgery, training future surgeons to care for the patient with secondary hyperparathyroidism may become more difficult.

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This chapter examines pathophysiology, diagnosis, indication for surgery and type of operation for secondary hyperparathyroidism, as well as providing review of management in an area where the number of operations is decreasing.

Physiology

Parathyroid hormone (PTH) is synthesized by the chief cell of the parathyroid gland as a lipid-soluble 110 amino acid precursor, pre-pro-PTH, which is packaged into secretory vesicles then immediately shortened to inactive pro-PTH, which is not lipid soluble. PTH is released as an active 84-amino-acid peptide. Circulating PTH is cleaved in the peripheral circulation into an active 34 AA amino-terminus moiety and an inactive 50 AA carboxy-terminus fragment. The carboxy-terminus is cleared by the kidney, so it will be found to be elevated in renal failure patients. Assays exist for the amino fragment, carboxy fragment and intact PTH.[1] The intact PTH molecule may be detected by a dual antibody assay.

PTH synthesis is stimulated by low levels of calcium, acidosis, high levels of phosphate and low levels of calcitriol. Conversely, high calcium and calcitriol and low phosphate inhibit its synthesis. Parathyroid sensitivity to calcium (calcium/PTH set point) is altered by acidosis and circulating vitamin D levels. PTH regulates serum calcium by its effects on the intestines, bones and kidneys. PTH works indirectly on the gut to increase absorption of dietary calcium by stimulating renal synthesis of calcitriol. PTH directly increases resorption of calcium from both the rapid and slow pools in the bones, by increasing osteoclast number and activity. In the kidney, PTH acts to increase tubular calcium and magnesium reabsorption, enhance phosphate clearance and increases urinary bicarbonate and cAMP.

Vitamin D starts as 7-dehydrocholesterol, which is photoisomerized in the skin to cholecalciferol. This compound is then hydroxylated at the 25 position in the liver, and hydroxylated again at either the 24 (inactive) or 1α(active) position in the kidney, which is the rate-limiting step. PTH increases 1α-hydroxylase activity and decreases 24-hydroxylase activity, preferentially promoting the synthesis of the active form of Vitamin D. Like most steroid hormones, 1,25 dihydroxycholecalciferol (calcitriol) exerts its effects by binding to an intracellular receptor. Calcitriol inhibits PTH gene transcription and inhibits parathyroid cell proliferation, in contrast to hyperphosphatemia which induces parathyroid proliferation. Calcitriol upregulates its own receptor on the parathyroid cell making them more sensitive to calcitriol. Vitamin D also helps PTH to increase osteoclast activity and promotes phosphate reabsorption in the kidney. Recently reported cloning of the 1α-hydroxylase gene may lead to improved understanding of secondary hyperparathyroidism.[2] See Figure 13.1 for an overview of the parathyroid hormone axis regulation.

Pathophysiology

As functional renal cell mass decreases, even prior to the need for dialysis, many aspects of mineral homeostasis are perturbed (Fig. 13.2). Decreased phosphate clearance causes hyperphosphatemia, resulting in a chronic reduction in ionized calcium which stimulates PTH production and parathyroid cell hyperplasia. There is also a decreased production of 1,25-dihydroxy-vitamin D, presumably owing to a

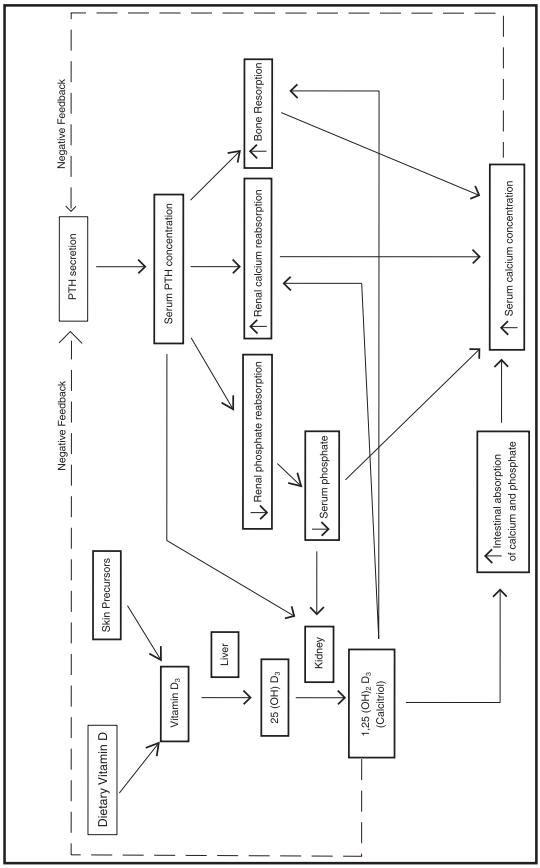

Fig. 13.1. Overview of parathyroid hormone axis regulation. Used with permission from Pharmacotherapy.

loss of 1α-hydroxylase activity. This leads to decreased intestinal absorption of calcium as well as a loss of inhibition of PTH production and parathyroid cell hyperplasia. The acidosis associated with renal failure further augments parathyroid hyperplasia. These effects may be noted with even mild renal insufficiency (GFR 40-50 cc/min). The above factors combine to result in an elevated production of PTH as a compensatory effort to restore normocalcemia, normophosphatemia and normal levels of calcitriol. As renal loss continues, the demand on the parathyroid increases, and with no renal function, PTH levels may exceed 1000 pg/ml (normal range 10-65 pg/ml). Mineral imbalances are inevitable.

CHAPTER 14

Parathyroid Cancer

Constantine V. Godellas

Introduction

Cancer of the parathyroid gland is an exceptionally rare entity. Its classic presentation and course is similar to that, as first described by de Quervain in 1909, of a patient with a large, locally invasive neck mass, that progressed to lung metastases after removal of the neck lesion.[1] Although not mentioned in his initial report, many patients also present with marked hypercalcemia. Unfortunately, it is frequently difficult to differentiate a parathyroid carcinoma from an adenoma, even on pathologic review. Many times the diagnosis is made only when there is local recurrence of the tumor or when metastases arise.

Hyperparathyroidism is reviewed in depth in another chapter of this textbook, but in order to discuss parathyroid cancer some of the same principles will be covered here. This chapter will focus on the epidemiology, diagnosis, treatment, and follow-up of the patient with documented or suspected parathyroid cancer.

Epidemiology

Parathyroid cancers make up less than 1% of all cases of hypercalcemia attributed to hyperparathyroidism. Most large series report the incidence of parathyroid cancer in patients with hyperparathyroidism as ranging from 0.14-2.3%.[1-4] Since these reports are usually from highly specialized, tertiary referral centers, it is likely that the true incidence is somewhere in the middle or lower end of this range. Therefore most references quote the incidence as being much less than 1%.

Unlike benign adenomas, where there is a marked female preponderance, there is probably only a slight increase in incidence of parathyroid cancer in females. The median age at diagnosis in most series is the late fifth decade. There is no known etiology for this malignancy, although some series have postulated a familial predisposition. There are rare isolated reports of parathyroid cancer secondary to radiation exposure.[5,6]

Diagnosis

Although the diagnosis is often difficult, parathyroid cancer can frequently be suspected by obtaining a thorough history and physical examination of the patient. Parathyroid cancers, unlike many other endocrine malignancies, are almost always functional. Typically, they secrete large amounts of parathyroid hormone which causes markedly elevated serum calcium levels. Most patients found to have parathyroid cancer have serum calcium levels above 14-15 mg/dl.[7] In fact, some of the most

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common presenting symptoms for these patients relate to the marked hypercalcemia and include renal and skeletal complaints.

Patients with parathyroid cancer present with a much higher incidence of bone pain, proximal muscle weakness, hematuria, and renal colic than patients with benign parathyroid pathology. Also, patients who present in hypercalcemic crisis, sometimes referred to as parathyroid storm, are more likely to harbor a parathyroid carcinoma than a benign adenoma as a cause for their hyperparathyroidism.[3]

On physical examination patients with parathyroid carcinoma are much more likely to have a palpable neck mass than those patients with benign parathyroid pathology. A parathyroid adenoma or hyperplastic gland is almost never palpable and Albright's Rule states that a palpable neck mass in a patient with benign hyperparathyroidism is usually a thyroid nodule. Any patient with hyperparathyroidism and palpable cervical lymphadenopathy should be suspected of having a parathyroid malignancy. Although, one must remember that malignancies other than parathyroid cancer, including lymphoma and lung cancer, can cause hypercalcemia and cervical adenopathy. Finally, if the patient has hoarseness, one should think of a parathyroid cancer invading or compressing the recurrent laryngeal nerve. This is almost never seen with benign parathyroid disease.

The laboratory evaluation is similar to that described for the patient with hypercalcemia in earlier chapters. Fluid and electrolyte status should be examined, especially in patients with marked hypercalcemia. Associated fluid and electrolyte abnormalities are likely secondary to gastrointestinal dysfunction, renal insufficiency, and abnormalities in calcium homeostasis. An intact parathyroid hormone (PTH) level assayed by radioimmunometric techniques should be measured to confirm that parathyroid gland hyperactivity is the cause of the hypercalcemia. Intact PTH levels in patients with parathyroid carcinoma are frequently several-fold greater than in patients with benign parathyroid disease.[7]

Preoperative radiologic examination should, at the minimum, include a chest x-ray to evaluate for pulmonary metastases from the primary parathyroid cancer, and to exclude primary lung cancer or metastases from another source. If a parathyroid malignancy is suspected preoperatively, a computed tomography (CT) scan of the neck and chest is useful to evaluate the extent of the cervical disease, including substernal extension, local invasion, or lymphadenopathy, and to examine for pulmonary metastases.

Other entities in the differential diagnosis of hypercalcemia are obviously considered. Many of these can be ruled out by the measurement of the serum intact PTH level. If metastases or an invasive cancer are not identified preoperatively, the diagnosis of parathyroid malignancy cannot be made with certainty, and the more common causes of hyperparathyroidism, adenoma and hyperplasia, must still be considered the most likely diagnosis. However, parathyroid cancer must be suspected in the patient with marked hypercalcemia secondary to hyperparathyroidism, and a palpable neck mass.

Treatment

Surgery is the only effective treatment for parathyroid carcinoma. Prior to any operation, however, severe underlying hypercalcemia must be corrected, as well as any metabolic abnormalities resultant from this. Once the patient is considered an acceptable surgical candidate, a high index of suspicion must be maintained in order to expect a reasonable chance for cure. In other words, preoperatively one should be very suspicious of the patient with an extremely high serum calcium level and a palpable neck mass. Likewise, any patient with clear evidence of metastases or recurrent laryngeal nerve involvement preoperatively should be approached in a similar manner. Intraoperatively, a markedly enlarged gland in association with extreme hypercalcemia, a grayish-white, firm, fibrotic gland, or a locally invasive gland, should all be considered probably malignant.

The procedure of choice for a patient with a parathyroid cancer should be radical or en bloc resection of the parathyroid gland and, at the minimum, the ipsilateral thyroid lobe, and include any associated structures which appear to be invaded. Frequently it is necessary to resect ipsilateral strap muscles either because of invasion, or to allow for better exposure. Resection of the recurrent laryngeal nerve should be considered if in so doing it will allow for complete removal of the cancer. If the nerve is involved, the patient will already have lost function of the cord or will soon do so. Thus, sacrificing the nerve in order to obtain clearance of the tumor is advisable. Rarely, the cancer will be extremely aggressive and invade into the trachea and esophagus. Usually this is identified preoperatively, either from symptoms of dysphagia or respiratory difficulties, or by CT scan or other imaging modalities. If identified preoperatively, appropriate preparations for tracheal or esophageal resection can be made. If encountered intraoperatively, resection of involved sections of trachea and esophagus should still be considered in order to obtain tumor clearance.

All patients with documented or suspected parathyroid cancer should undergo dissection of the lymph nodes in the central, or paratracheal, compartment. Ipsilateral modified radical neck dissection is performed only if there is evidence of adenopathy on the affected side. There is currently no role for elective modified radical neck dissection for parathyroid carcinoma.

Frequently the diagnosis of parathyroid cancer is not made even on pathologic examination. The histopathologic appearance of parathyroid cancer can be quite similar in cellular features to that of a benign adenoma. Criteria have been put forth to make the diagnosis pathologically, with the most common being those of Schantz and Castleman.[8] Their criteria include the presence of: 1) a fibrous capsule or trabeculae, 2) mitotic figures, 3) invasion of the capsule or surrounding vessels, 4) a cellular architecture which has a trabecular or rosette-like appearance. Cytologic criteria include nuclear polymorphism and enlargement. None of these features alone are specific for carcinoma. The gross histopathologic features of the tumor are the most important findings in making the diagnosis. If the pathologist sees invasion of thyroid tissue or muscle then the diagnosis can be made with certainty. Many times these features are better seen intraoperatively by the surgeon who should be able to make the diagnosis from these findings. In some patients with parathyroid cancer,

the conclusive diagnosis is not made until the patient develops local recurrence, or nodal or distant metastases.

Follow-Up

A very high index of suspicion should be maintained for any patient assumed to have cancer in whom a pathologic diagnosis is not made. Frequently the diagnosis of parathyroid cancer is made only when the patient develops a metastasis or a recurrent, locally invasive tumor. Serum calcium levels should be followed, as well as PTH levels. They are both sensitive markers for parathyroid cancer recurrence. Patients can usually be monitored with physical examination of the neck, although it is sometimes difficult to palpate small recurrences in the setting of scar tissue from a previous operation. Serial ultrasounds may be useful in patients whose necks are difficult to examine due either to body habitus or postoperative scarring.

Long term follow-up is necessary as parathyroid cancer is usually a slow-growing malignancy marked by late local recurrence and/or metastases to lung and bone. Five-year survival rates are approximately 50%, although, they are higher for patients who have undergone curative resection.[3,4,9,10] The major sequelae of recurrent or metastatic disease is similar to that for other endocrine cancers in that patients have symptoms related to excess hormone production and to the local effects of the tumor. Parathyroid cancer patients with recurrent or metastatic disease usually have elevated serum PTH levels leading to hypercalcemia. Tumor progression more commonly causes problems from marked hypercalcemia due to increased production of PTH, but tracheal and esophageal obstruction can also occur. There is no good evidence to suggest that chemo- or radiation therapy have a beneficial role in managing recurrent or metastatic disease. Radiation therapy is given for nonresectable local recurrence and bone metastases, but it has no effect on long term survival. Resection of recurrent and metastatic tumor is frequently useful in controlling PTH secretion and hypercalcemia.[2] Other pharmacologic means directed at controlling hypercalcemia may be necessary in the patient who is not a surgical candidate.

Summary

A patient presenting with extreme hypercalcemia secondary to markedly elevated levels of parathyroid hormone, and a palpable neck mass, should be suspected of having a parathyroid carcinoma. Surgical excision can be curative if the surgeon's index of suspicion is high and a complete resection is performed. Locally recurrent or metastatic disease are not contraindications to surgery, since an operation may be the most effective means available to control the resultant life-threatening hypercalcemia.

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CHAPTER 15

Parathyroid Autotransplantation

Andrew Saxe

Introduction

This chapter's title suggests a constraint to consider only autotransplantation of parathyroid glands. Although at present parathyroid transplants are, indeed, restricted to autotransplantation that may not be the case forever and an introductory review of terminology is warranted.

The term autotransplantation implies movement of parathyroid tissue from one location to another location in the same individual. Relocation of the resected tissue may be done at the time of parathyroidectomy (termed "immediate") with fresh tissue, or at a later time ("delayed" or "deferred") with tissue which has been stored for the interval in a frozen state (**"**cryopreserved"***)***. Tissue transplanted from one individual to another is termed an allotransplant. In the early days of parathyroid transplantation investigators had hoped that endocrine tissue in general, and parathyroid tissue in particular, was immunologically privileged and would not be rejected if transferred from one patient to another. This has proved not to be the case. The risk of immunosuppression required to tolerate another patient's parathyroid tissue is generally considered disproportionately great compared to the alternative medical management. One can treat (although not necessarily easily) the disease for which parathyroid transplants are considered, hypocalcemia, with oral administration of calcium and vitamin D. Methods are being developed to reduce the immunogenicity of human parathyroid tissue and it may soon be possible to reconsider allottransplantation without immunosuppression.

Xenotransplantation refers to transplantation with another species' tissue. Although experimented with on occasion, parathyroid xenotransplantation is not generally perceived as practical for the foreseeable future.

It is worthwhile, also, in an introduction, to consider ways in which the function of autotransplanted parathyroid tissue can be assessed. Unless all parathyroid tissue has been removed with certainty (except that transplanted) posttransplant normocalcemia cannot be taken as an absolute indication of transplant success. Normocalcemia may reflect function of either residual parathyroid tissue alone, transplanted tissue alone, or a combination of residual tissue and transplanted tissue. In fact, the disease for which parathyroid transplants are most used, parathyroid hyperplasia, is that in which one is least certain whether additional parathyroid tissue unintentionally remains in situ. Reports of autotransplant success in the setting of parathyroid hyperplasia using normocalcemia alone must be considered to overstate success. It is, however, possible to test function of transplants directly. Detection of parathyroid hormone (PTH) concentrations in blood exiting the transplant which

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are substantially greater than background concentrations of PTH can be taken as evidence of graft function. For patients who have been hypocalcemic for a period of time and undergo deferred autotransplantation with cryopreserved tissue resolution of hypocalcemia can be used as proof of function. Other methods of calculating success rates of parathyroid transplants entail imaging studies although one could argue that viability detected on the study is not synonymous with adequate release of PTH.

History

The early history of parathyroid transplantation is obscure, fascinating and controversial. Several reviews are available.[1] In this author's view the first important publications pertaining to practical, clinical surgery are those of Dr. Frank Lahey. He reported inspecting resected thyroid glands and transplanting into the sternocleidomastoid muscle parathyroid glands which had been removed unintentionally. Dr. Lahey acknowledged that he was not able to prove the success of the transplants. He acknowledged, also, the difficulty in correctly identifying parathyroid tissue and advocated frozen section analysis prior to implantation.

Indications for Autotransplantation

During Thyroid Surgery

Parathyroid tissue inadvertently removed in the course of thyroid surgery should be autotransplanted to an accessible sternocleidomastoid muscle. When operating for malignancy, it is wise, as first suggested by Lahey, to biopsy the "parathyroid" prior to autotransplantation to be certain one is not transplanting a lymph node with metastatic disease. In this author's view there is no justification in intentionally resecting normal parathyroid glands and reimplanting them in the sternocleidomastoid muscle or elsewhere. Olson et al[2] reported upon an extensive experience with parathyroid transplantation during thyroid surgery.

During Parathyroid Surgery

At Initial Surgery

Adenoma

One does not transplant adenoma tissue at initial surgery for hyperparathyroidism because additional normal parathyroid tissue is left in situ. Tissue should be cryopreserved if possible as a hedge against the unusual occurrence of hypoparathyroidism and for research .

Hyperplasia

The proper place of autotransplantation for multiple gland disease ("hyperplasia") remains controversial and two competing strategies have emerged. Champions of what is termed "subtotal parathyroidectomy" propose resection of all but the equivalent of a normal parathyroid gland, leaving the residual tissue attached to its native blood supply. The resected tissue should be cryopreserved because the incidence

Table 15.1.Comparison of strategies for managing parathyroid hyperplasia

	Advantages	Disadvantages
Subtotal parathyroidectomy	Avoids a period of profound hypoparathyroidism while graft is starting to function	Requires neck exploration to address recurrent or persistent hyperparathyroidism attributable to hyperfunction of the residual tissue with risk of recurrent nerve injury
Total parathyroidectomy with autotransplantation.	Recurrent or persistent hyperparathyroidism attributable to hyperfunction of the residual tissue can be resected under local anesthesia without placing the recurrent nerves in jeopardy Graft function can be assessed by comparing PTH concentrations in blood from grafted arm to nongrafted arm.	Patient sustains weeks of hypoparathyroidism before graft functions

of postoperative hypoparathyroidism in this setting is approximately 10% (see reference 1 and Table 15.2).

The alternative strategy (termed "total parathyroidectomy and autotransplantation") is to resect all parathyroid tissue and immediately autotransplant the equivalent of one or two (50-100 mg) normal parathyroid glands. Because the autotransplanted tissue is abnormal, hypersecretory tissue, there is a risk of recurrent hyperparathyroidism attributable to the transplanted tissue. To simplify reresecting the autograft, should that be necessary, one usually places the tissue in the forearm. Although the autotransplant is performed at the time of surgery with "fresh" tissue, not all transplanted tissue functions adequately to prevent long-term hypoparathyroidism. Even if ultimately successful the strategy of total parathyroidectomy and autotransplantation necessitates a period of hypoparathyroidism before the grafted tissue regains a blood supply and can provide adequate levels of PTH. This period lasts generally one to four months.

Secondary hyperparathyroidism is the most frequent indication for autotransplantation and there is a sufficiently large number of patients to permit comparison of the two strategies. As it turns out, the risk of hypoparathyroidism following total parathyroidectomy with autotransplantation is virtually identical to that of subtotal parathyroidectomy (See reference 1 and Table 15.2). Similarly, the risk of recurrent or persistent hyperparathyroidism attributable to parathyroid inadvertently left in situ or to hypertrophy of the graft (or residual in situ tissue in the case of subtotal parathyroidectomy) is the same in both approaches. Table 15.1 summarizes the

Table 15.2. Recent results of surgery for secondary hyperparathyroidism

	Subtotal parathyroidectomy			Total parathyroidectomy & Transplant			Total parathyroidectomy		
Author	**Patients**	**Persist/Recurr**	**Hypocal**	**Patients**	**Persist/Recurr**	**Hypocal**	**Patients**	**Persist/Recurr**	**Hypocal**
Karusseit[7]				12	1(8%)	2(17%)			
Kinnaert*[8]				36	2(6%)	NA			
Knudsen[9]				21	1(5%)	1(5%)			
Nicholson[10]	11	2(18%)	4(36%)	13	2(15%)	7(54%)	24	0	13(54%)
Rothmund[11]	20	4 (20%)	4 (20%)	20	1 (5%)	4 (20%)			
Skinner[12]				8	3(38%)	NA			
Tanaka[13]**				95	8(8.4%)	NA			
Tanaka[17]***				33	8(24%)	NA			
Walgenbach[14]				86	3 (3.5%)	1 (1.2%)			
Totals / averages	31	6/31 (19%)	8/31 (26%)	324	29/324 (9%)	13/140 (9%)			

* Autotransplanted tissue placed in subcutaneum
** Transplants with non nodular tissue
*** Transplants with nodular tissue

advantages and disadvantages of each approach. Table 15.2 updates reference 1 with citations from the 1990s.

At Reoperation for Persistent or Recurrent Hyperparathyroidism

The choice of strategy at reoperation can be even more problematic. For the surgeon reoperating for an overlooked adenoma who has confidence that normal glands remain, resection and cryopreservation of the adenoma without transplantation of resected tissue is the appropriate procedure. Even without assurance that additional normal glands are available, cryopreservation without autotransplantation of resected tissue (which is intrinsically abnormal) is this author's counsel. Should the patient become persistently and profoundly hypoparathyroid, with undetectable serum PTH, then cryopreserved tissue can be autotransplanted to the forearm under local anesthesia.

The final scenario, reoperation for multiple-gland disease, is the most controversial of all. The incidence of recurrent hyperparathyroidism in this setting is so great that total parathyroidectomy without transplantation is warranted. That residual hyperfunctioning tissue often remains even after attempted total parathyroidectomy is attested to by a 50% incidence of normocalcemia or hypercalcemia following intentional "total" parathyroidectomy at reoperation for multiple-gland disease.[3] Cryopreservation only, without immediate transplantation, is advised. The alternative, of course, is total parathyroidectomy with immediate autotransplantation of a portion of resected tissue into the forearm.

Cryopreservation of resected tissue when operating for recurrent or persistent hyperparathyroidism is important; the incidence of hypoparathyroidism is reported as high as 30% (average: 12-18%).[1]

Allo- and Xenotransplantation

A number of investigators have attempted to reduce the immunogenicity of parathyroid tissue by physical and chemical alteration. These attempts have generally pursued strategies developed in the course of studying pancreatic islet cell transplants. They have been only partially successful and not brought to clinical trials. There is, however, a new technique which appears to be the most promising yet explored. This approach, "microencapsulation," coats individual cells with an alginate which permits egress of hormone but prevents destruction by the immune system. It has been shown to be effective in animal models of both allotransplantation and xenotransplantation.[4,5]

Technique of Autotransplantation

Parathyroid tissue to be transplanted is kept in chilled isotonic fluid until used. A muscle pocket, approximately two centimeters in depth, is prepared by separating muscle fibers and packing the cavity for several minutes to assure hemostasis. Into the cavity are placed 8-10 pieces of parathyroid tissue; care is taken to keep the parathyroid from floating out of the pocket. The pocket is closed with Prolene suture left long to both secure the tissue and mark the site. An additional one or two pockets are created in a similar fashion.

There is evidence that parathyroid tissue will function if placed in the subcutaneum.

Cryopreservation

Our laboratory has adapted methods introduced by Wells and Christiansen[6] over 20 years ago, which can be summarized in this fashion:

Parathyroid tissue is transferred as promptly as possible from the patient to chilled, sterile culture media. We employ RPMI-1640 but presumably any isotonic media would be satisfactory. In the absence of media, saline is a better alternative than water.

Tissue is transported in the media to a laboratory where it can be processed in a sterile fashion. We work under a laminar flow hood. The tissue is placed in fresh sterile media in a Petri dish on ice and adherent fat is removed from parenchyma. The tissue, stiffened by chilling, is cut into cubes approximately 1-2 mm per side.

In separate test tubes (on ice) two solutions are prepared—one a 20% (by volume) solution of autologous serum in media, and the other a 20% solution of dimethylsulfoxide (DMSO) in media.

An aliquot of 0.6 ml of 20% serum solution is added to each 2 ml polypropylene cryopreservation vial (embedded in ice) prior to introducing tissue. While keeping the cryopreservation vials on ice, approximately 20 pieces of tissue are placed in each vial. Following addition of tissue, 0.6 ml of the 20% DMSO is added to each vial. The vials are gently mixed and returned to ice.

We use Mr. Frosty Cryo 1˚C Freezing Containers (Nalge, Rochester NY) to freeze the tissue. Chilled isopropyl alcohol is added to the Container reservoir and the Container is placed overnight in a –70˚C freezer. The following day the vials can be transferred to liquid or vapor phase nitrogen for long-term storage.

To thaw the tissue we prepare a tube of chilled 20% serum in media. Cryopreservation vials are removed from liquid nitrogen and placed in a 37˚C water bath until the ice within the vial has nearly melted leaving a core of frozen media. One half ml of the serum/media is added to the vial and the vial returned to the water bath until the core has melted. Then, 0.5 ml aliquots of media are aspirated and replaced by the fresh serum/media solution. This cycle of aspirating and replacing fresh solution is repeated three times keeping the vial on ice. The tissue is removed, placed in fresh media and kept on ice until used.

Transplantation with cryopreserved tissue is less successful than transplantation with fresh tissue although the explanation is not obvious.[1,2] Length of storage does not predict viability. Presumably, unpredictable amounts of tissue do not survive the freeze-thaw cycle and the amount of viable tissue being transplanted is uncertain.

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CHAPTER 16

Parathyroid Reoperations

Scott R. Schell, Robert Udelsman

Introduction

Parathyroidectomy, when performed by experienced surgeons, results in a success rate that exceeds ninety-five percent. Unfortunately, a subset of patients fail initial exploration (persistent primary hyperparathyroidism (HPT)), or develop recurrent HPT following what appeared to be successful parathyroidectomy. Depending upon the skill of the surgeon performing the initial neck exploration, between five and thirty percent of patients who undergo neck exploration for HPT can be expected to have persistent, or redevelop hypercalcemia due to elevations in PTH. The majority of these patients, approaching 80%, will subsequently be found to have a missed parathyroid adenoma, while the remaining patients will have multi-gland hyperplasia with or without associated multiple endocrine neoplasia syndromes.

Confirming the Diagnosis in Patients with Recurrent or Persistent Hypercalcemia

Patients who present with recurrent or persistent hypercalcemia should have their diagnosis confirmed prior to proceeding to imaging studies or surgical exploration. Evaluation of hypercalcemia in this setting begins with measurement of an intact serum PTH level, total and ionized calcium levels, 24 hour urinary calcium, and serum creatinine. There are many causes of hypercalcemia, however in primary HPT intact PTH and calcium are both elevated. A normal or high 24 hour urinary excretion of calcium is typical of primary HPT. Other causes of hypercalcemia, with the exception of familial hypocalciuric hypercalcemia (FHH) and secondary HPT, result in suppressed PTH levels. The rare genetic syndrome FHH is characterized by a low 24 hour calcium excretion.

It is essential to obtain and review all previous laboratory data, operative reports, and pathology findings. Prior to reoperation, it is also extremely useful to contact the initial surgeon to obtain additional details of the previous operation. Careful attention should be noted to the number and location of individual glands described at initial exploration, as well as any glands that were removed or biopsied. Generally, if three normal glands were documented at initial exploration, the recurrent symptoms are most frequently attributed to a single, missed adenoma.

Likewise, pathology reports and specimens should be reviewed. The size, weight, and number of glands excised should be reviewed, as well as determination whether the excised tissue was confirmed to be parathyroid. This approach is helpful in

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distinguishing single or double adenomas versus multi-gland hyperplasia. Any gland that was reported as "normal" and was not biopsied remains unproven.

Table 16.1 reviews the anatomic location and frequency of parathyroid disease in patients undergoing reoperation for persistent or recurrent hyperparathyroidism.[1] It is noteworthy that in approximately 70% of cases, the culprit parathyroid was located in the neck. In 1996, Jaskowiak et al[2] reviewed the National Cancer Institute/National Institute of Health series of 288 patients with recurrent hypercalcemia due to elevated PTH following surgical exploration at outside institutions. In 222 patients with presumed missed adenomas, this group achieved 97% cure of hypercalcemia through sequential preoperative imaging and systematic neck exploration. The most common site, accounting for 27% of cases, for missed adenomas in this series was in the tracheo-esophageal groove in the posterior superior mediastinum. The most common ectopic sites for parathyroid adenoma were thymus (17%), intrathyroidal (10%), undescended glands (8.6%), carotid sheath (3.6%), and retroesophageal space (3.2%).

Localization Studies in Patients with Persistent or Recurrent Hypercalcemia

Following careful review of operative history and confirmation of biochemical markers of elevated PTH, a number of studies may be employed to localize the source of PTH production. Most experts have recommended obtaining one or more concordant studies in all patients who have an indication for reoperation for recurrent or persistent HPT. Localization studies are broadly divided into 1) Noninvasive: Computed tomography, magnetic resonance imaging, radionuclide imaging, and ultrasound studies, and 2) Invasive: Arteriography and venous angiography with highly selective sampling for PTH. Percutaneous needle biopsy under ultrasound guidance is another useful technique.

Ultrasonography has been effectively employed to identify abnormal parathyroid glands within or immediately adjacent to the thyroid gland (Fig. 16.1). Libutti[3] et al have reported their experience with a series of patients in whom preoperative or intraoperative ultrasound (IOUS) was helpful in localizing intrathyroidal parathyroid glands. Although noninvasive, readily available and inexpensive, ultrasound is not useful in detecting glands located in the retrosternal, mediastinal, or retrotracheal positions. Further, accurate interpretation requires an ultrasonographer and radiologist skilled in assessing these structures. If a lesion is identified on ultrasound, these images can be used to guide percutaneous aspiration biopsy. This technique requires a skilled individual, and the sample is analyzed for PTH and cytology, including staining with an anti-PTH antibody.

Computed tomographic scanning has been largely replaced by other modalities. Occasionally, it is still useful for its capability to demonstrate distinct anatomic structures, as shown in Figure 16.2.

Magnetic resonance imaging (MRI) can be used to localize parathyroid adenomas with accuracy that has been reported to approach 70%. However, in our practice, MRI has not been nearly as useful in detecting these lesions. MRI is particularly

Table 16.1. Location and frequency of disease in patients undergoing reoperation for persistent or recurrent hyperparathyroidism

Location	Percentage
Neck	
Inferior pole	21%
Superior pole	20%
Thymic tongue	10%
Retrotracheal / retroesophageal	6%
Intrathyroidal	5%
Tracheoesophageal groove	4%
Carotid sheath	3%
Medial to upper pole	2%
Upper thyroid capsule	1%
Undescended	1%
Mediastinum	
Superoposterior	14%
Anterior	13%
Middle	1%

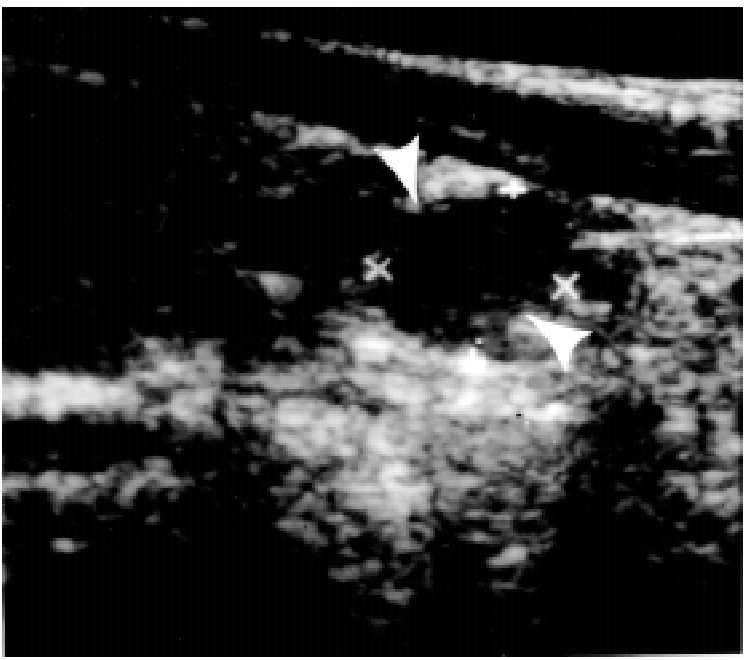

Fig.16.1. Ultrasound of the neck. Parathyroid adenoma is the echopenic lesion relative to the thyroid as indicated at white arrows.

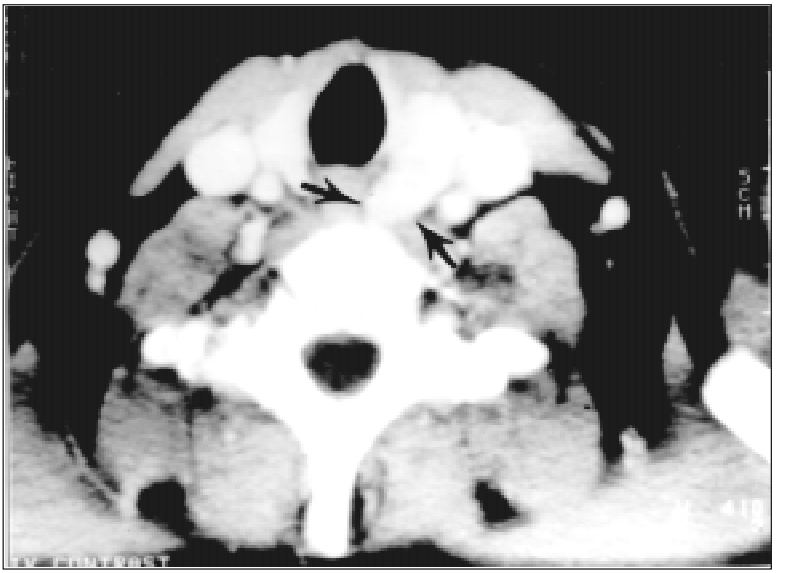

Fig.16.2. Computed tomographic (CT) scan of the neck following administration of intravenous contrast. Black arrows indicate the location of a 1.5 cm. enhancing parathyroid recurrence.

valuable for detecting lesions in the mediastinum, and positions deep within the neck. Up to two-thirds of parathyroid lesions detected with MRI imaging are visualized when examining T_2 or gadolinium-enhanced images (Fig. 16.3). Unfortunately, MRI scanning remains costly, particularly when using contrast enhancement. Some patients are unable to tolerate the small bore of the imaging gantry due to claustrophobia.

The evolution of nuclear scintigraphy and the application of single photon emission computed tomography (SPECT) image analysis have yielded dramatic improvement in the interpretation and accuracy of this imaging modality. Previously used technetium-thallium isotope scanning has been largely replaced with technetium-99m (Tc-99m) sestamibi scintigraphy for parathyroid imaging. Application of delayed SPECT image analysis has been reported by Neumann[4] et al to improve results to 91% sensitivity and 88% negative predictive value in patients undergoing reoperation for persistent elevations in PTH. It has become our imaging technique of choice.

We routinely use delayed Tc-99m sestamibi with SPECT imaging for all cases of persistent or recurrent hypercalcemia. If this study yields images that are unequivocal, and are in agreement with our review of the prior operative data, we proceed directly to surgical re-exploration (Fig. 16.4). It is occasionally the only localization procedure required, and is extremely helpful in localizing and triangulating coordinates of adenomas deep within the mediastinum or retroesophageal positions. Following

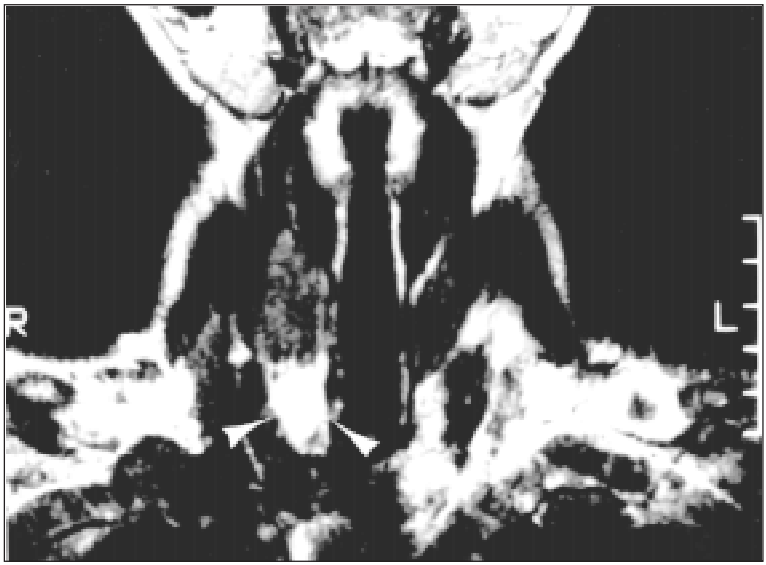

Fig.16.3. T2-weighted magnetic resonance image (MRI) of neck. White arrows indicate a 1.8 cm. parathyroid adenoma.

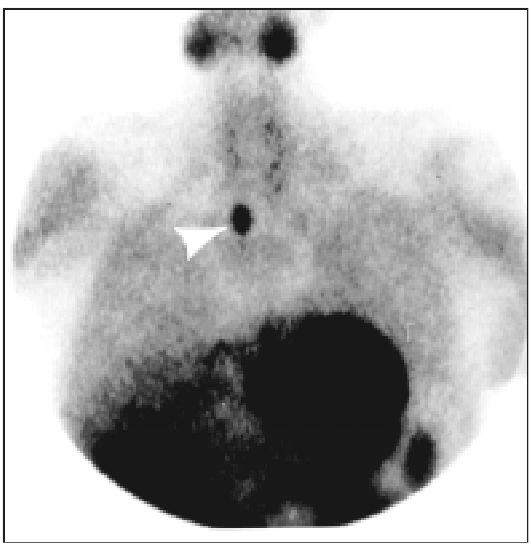

Fig.16.4. Tc-99m sestamibi imaging in a patient with hyperparathyroidism. The white arrow indicates the location of a mediastinal parathyroid gland located in the right thymic lobe.

sestamibi scanning, MRI with contrast enhancement or ultrasound is our next noninvasive study.

In situations where review of previous surgical and pathologic data combined with imaging studies have not yielded convincing localization information, or in situations where these data are discordant, we proceed to angiography and highly selective venous catheterization for PTH measurements (Fig. 16.5). This procedure is costly, invasive, time-consuming, and exposes the patient to a significant radiation dose. Accordingly, we select this procedure only after exhausting other localization methods. Occasionally, we have encountered confusing data when intact PTH levels are returned from our laboratory, often several days after venous sampling. We have recently begun using the rapid-PTH assay to quantify PTH levels during the catheterization procedure. This technique provides almost immediate hormone data during the procedure, and allows us to dynamically guide the angiographer to additional sampling if a subtle, but nondiagnostic, gradient is observed (authors, manuscript in preparation.).

Figure 16.6 provides a diagrammatic approach to preoperative localization studies in these patients.

Operative Approach in Patients with Persistent or Recurrent Hypercalcemia

After localization studies have identified the location of the tumor, careful operative planning is essential. Since the majority of patients will have a missed adenoma, we recommend a focused approach, in contrast to our standard practice of bilateral neck exploration for first-time operations. This approach minimizes the dissection required, and thus risk of injury to the recurrent laryngeal nerves. Prior to beginning each operative procedure, we prepare for cryopreservation of any resected parathyroid tissue, insuring the availability of reagents and equipment required for the procedure. In all reoperative parathyroid surgery, we consider the possibility that the parathyroid gland that we plan to resect may be the patient's only residual functioning parathyroid tissue.

The patient is positioned supine with support beneath their shoulders and neck extended. The chest is prepped and draped together with the neck, in preparation for possible partial or complete median sternotomy. If localization studies guide us to the lateral neck, we prefer to reopen the previous Kocher collar incision, through the level of the platysma muscle. Next, the lateral neck, on the side of interest, is entered in the space lateral to the strap muscles, and anterior to the sternocleidomastoid muscle. This provides excellent exposure to the lateral neck. In the vast majority of cases, this route is free of adhesions, and facilitates recurrent laryngeal nerve identification and protection. The thyroid gland is approached laterally and posteriorly.

If the suspect parathyroid gland appears in the anterior mediastinum, we reopen the Kocher incision and mobilize the left and right horns of the thymus separately. The thymic lobes can be elevated into the operative field with gentle traction, and can be delivered intact. Frequently, a large vein diving below the clavicle and sternum along the thyrothymic ligament is a sentinel to an adenoma within the thymus.

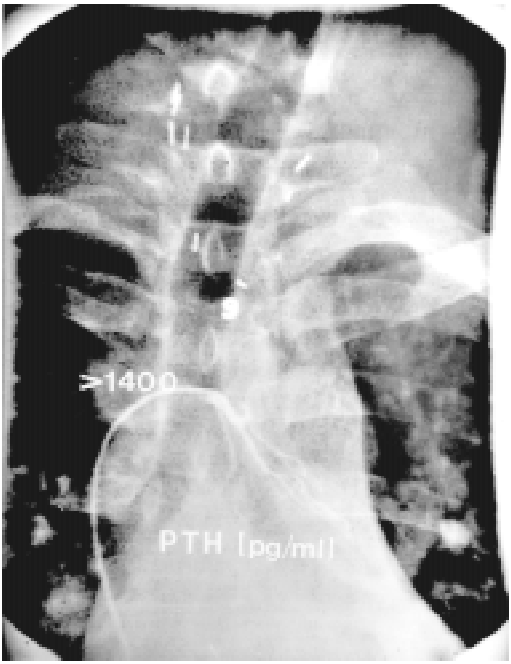

Fig.16.5. Highly selective venous sampling of the left thymic vein demonstrating a PTH level greater than 1,400 pg/ml. All other samples demonstrated PTH levels ranging from 100-150 pg/ml proving a specific gradient. Multiple surgical clips are from a previous failed exploration.

After locating and removing the parathyroid adenoma, we immediately halve the gland, and cryopreserve one portion. Cryopreservation requires reagents, technical expertise, and a liquid nitrogen storage facility. The cryopreserved tissue can subsequently be auto-transplanted into the nondominant forearm, with successful takes reported to occur in 85% of patients.[5]

Intraoperative Rapid PTH Assay

The recent development of a rapid assay for measurement of intact PTH has had a significant impact upon reoperative parathyroid surgery.[6,7] The characteristics of the assay provide for complete sample analysis and reporting in less than fifteen minutes. This assay has become a standard component of all of our reoperative cases. A large-bore peripheral I.V. inserted into the antecubital vein provides reliable access for serial venous samples obtained during surgery. Two baseline samples are obtained at the start of the operation. Following excision of the suspect parathyroid gland, additional samples are obtained ten and fifteen minutes after removal. A greater than 50% decrease in PTH below baseline levels is considered a positive result.[6,7]

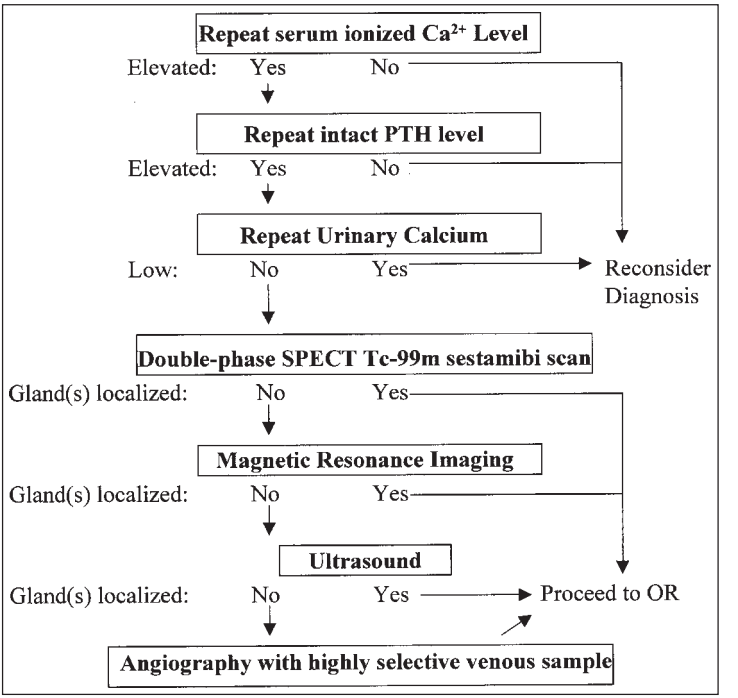

Fig.16.6. Preoperative localization studies in patients with persistent or recurrent hypercalcemia.

Postoperatively, we assess the patient for symptoms and signs of hypocalcemia. A serum ionized calcium level is obtained the following morning. The majority of patients are discharged the morning after surgery. They are carefully instructed to recontact us if they develop any symptoms or manifestations of hypocalcemia. Figure 16.7 provides a diagrammatic approach to operative exploration in these patients.

Summary

Reoperative parathyroid surgery is best avoided by performing a meticulous initial operation. Patients who present with persistent or recurrent hyperparathyroidism require a systematic, step-wise approach to confirm this diagnosis, localize the culprit gland, and extirpate the abnormal parathyroid tissue while avoiding injury to the recurrent laryngeal nerves.

It seems clear that patients benefit most from initial parathyroid exploration at the hands of experienced surgeons. Over 95% of patients who have exploration by an experienced surgeon are successfully treated at their first operation, while operation by inexperienced surgeons can decrease the success rate to 70%. When patients present with recurrent or persistent hypercalcemia due to elevated PTH levels, their

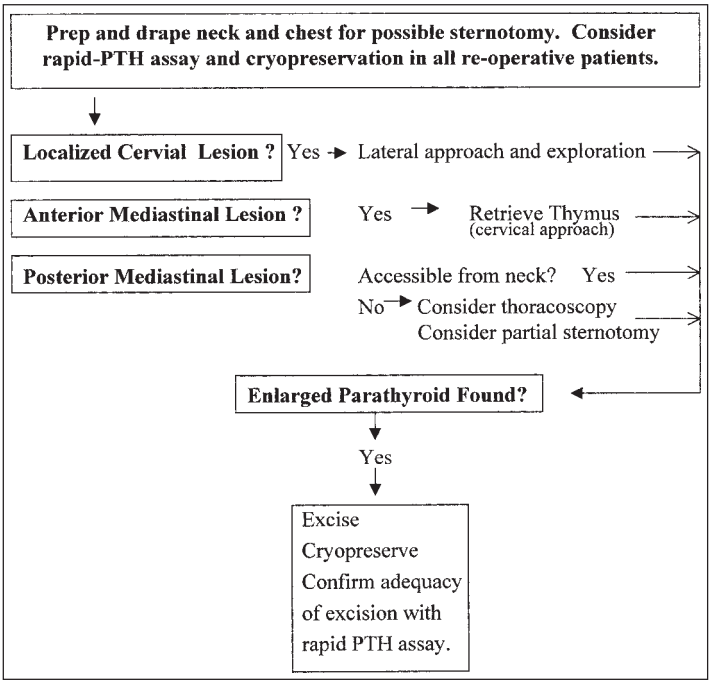

Fig.16.7. Operative approach for patients with persistent or recurrent hyperparathyroidism.

care is best undertaken by surgeons at institutions capable of providing a full range of noninvasive and invasive imaging studies.[8]

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CHAPTER 17

Adrenal Embryology, Anatomy and Physiology

Richard A. Prinz

History

Discovery of the human adrenal is credited to Eustachius who published the first accurate anatomic drawings depicting their presence and relationship to the kidneys, inferior vena cava and aorta. The function of these glands remained unknown for the next three centuries. In 1805, Cruvier described the anatomic division of the gland into an outer cortex and an inner medulla. The physiologic importance of the adrenals started to become apparent in 1855 when Addison described clinicalopathologic features of patients he studied at autopsy who had destruction of both adrenal glands. The clinical syndrome of adrenal insufficiency continues to bear the eponym Addison's disease. The following year Brown Sequard demonstrated that the adrenal glands were essential for life by performing adrenalectomy in experimental animals.

In 1886, Frankel first described a tumor which was subsequently called by the pathologist Pick in 1912 pheochromocytoma because of the dark color it turned when exposed to chromaffin salts. The presence of a substance in the adrenal medulla that raised blood pressure was described by the London physiologists Oliver and Scharpey-Schafer who named it adrenaline in 1893. Two years later Abel isolated epinephrine at Johns Hopkins. The structure of adrenocortical steroids was elucidated in the 1930s and this allowed Kendall and coworkers to synthesize cortisone.

Embryology

Within the capsule of each adrenal are two anatomically and functionally distinct endocrine glands. The adrenal cortex arises from mesoderm while the medulla arises from neuroectoderm. During the 4-6 weeks of gestation cells destined to become the adrenal cortex develop from the mesoderm between the root of the dorsal mesogastrium and the urogenital ridge. These developing cells are then penetrated by nerve fibers through which medullary cells will migrate. By the eighth week, the gland has differentiated into two distinct zones: a thin outer zone that will become the cortex in the adult and a large centrally located fetal zone. The fetal zone produces steroids during gestation but involutes during the first two weeks after birth and is completely gone by one year of age. During the second and third month of gestation, the weight of the adrenals increases from 5-80 mg and the glands are much larger than the adjacent kidneys. After the twentieth week of gestation, cortical growth and development is dependent on pituitary gland stimulation. Anencephalic fetuses

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are born with an atrophic adrenal fetal zone. After birth the three zones of the adult adrenal cortex develop as the fetal zone involutes. Nests of cells under the mesodermal capsule are the rudiment of the zona glomerulosa. The fascicular and reticular zones of the adult cortex arise from the glomerulosa after birth and are fully differentiated by about age 12.

During fetal development, primitive adrenocortical cells can migrate widely. Accessory or ectopic adrenal tissue can be found in the broad ligament, near the celiac access, adjacent to the ovarian or testicular veins and around the kidney or uterus. On rare occasions adrenocortical tissue has been found in other parts of the abdomen, thorax and central nervous system. These rests of ectopic adrenal tissue are important because they can cause persistent or recurrent hypercortisolism in patients with high levels of ACTH production.

The adrenal medulla and sympathetic nervous system develop together from the neuroectoderm. During the fourth week of gestation, the neural plate develops and then infolds to form the neural tube. A part of the neuroectoderm adjacent to the tube separates and remains between the neural tube and the ectoderm as the neural crest. In the second month of embryonic life cells from the neural crest migrate ventrally from the apex of the neural tube to the dorsal aorta. These cells aggregate and differentiate into neural blasts that form sympathetic neurons or pheochromoblasts that will form chromaffin cells. Some primitive adrenal medullary cells remain closely associated with the developing sympathetic nervous system and give rise to extra adrenal chromaffin cells and chromaffin bodies. Extra adrenal chromaffin cells regress and degenerate postnatally while those in the adrenal medulla complete their maturation. Some extra adrenal cells may persist anywhere along the embryonic path of neural crest cell migration. The persistence of extra adrenal chromaffin cells accounts for the occurrence of extra adrenal pheochromocytomas later in life.

Anatomy

The adrenal glands are bilateral retroperitoneal organs located on the superior medial aspect of the upper pole of each kidney. Each gland weighs from 3-6 gm and measures approximately 5 cm in length, 3 cm in width and 1 cm in thickness. The glands have a darker golden orange color compared to the surrounding perirenal fat.

The right adrenal is triangular or pyramidal in shape with its base resting on the kidney inferiorly. Medially, it abuts the lateral posterior aspect of the inferior vena cava while posteriorly it rests on the right crus of the diaphragm. The left adrenal is flatter and more crescent shaped. It extends more inferiorly along the medial aspect of the upper pole of the left kidney. It is found between the aorta medially, the pancreas and spleen anterior superiorly, the left renal artery inferiorly and the crus of the left diaphragm posteriorly.

The adrenals are highly vascular tissues and are supplied by multiple small branches of the inferior phrenic artery, the renal artery and the aorta. These numerous small arterioles anastomose over the surface of the gland before entering the perimeter of the capsule. The microvasculature within each gland integrates the function of the

cortex and the medulla. The medulla has a dual blood supply. Some vessels pass directly through the cortex but the majority of medullary blood flow takes an indirect route entering first through the cortical plexus and then forming cortical sinusoids which empty into the medullary sinusoids. Blood coming through this indirect route is rich in cortisol when it reaches the medulla. This cortisol rich venous affluent stimulates the synthesis and enzymatic activity of phenylethanolamine-N-methyltransferase (PNMT) which converts norepinephrine to epinephrine. Extra adrenal chromaffin tissues lack this regulatory enzyme and therefore secrete norepinephrine predominantly. Nitric oxide is an important factor regulating local blood flow to the various zones of the cortex and medulla.

The rich venous plexus in each gland usually drains through a single adrenal vein. The right adrenal vein is typically short and drains directly into the inferior vena cava at the upper medial aspect of the gland. Because of its short course, the right adrenal vein can be difficult to catheterize when performing venous sampling studies for hormone analysis and difficult to ligate during adrenalectomy which makes the risk of life threatening caval hemorrhage much greater. On the left side, the adrenal vein is longer and drains into the left renal vein.

The lymphatic drainage of each gland is through two plexuses. One deep to the capsule and one in the medulla. These drain into the adjacent periaorta, subdiaphragmatic and renal lymph nodes. Relative to its size, the adrenal has a larger autonomic supply than any other organ and this supply consists almost exclusively of sympathetic fibers. The adrenal cortex has little direct innervation but does have a vasomotor supply with sympathetic axons innervating the subcapsular arteriolar plexus. The medulla is richly supplied by preganglionic sympathetic nerve fibers from the greater splanchnic nerve, celiac ganglion and other plexuses. Sympathetic stimulation causes catecholamine release as is seen by the decrease of plasma catecholamines in normal persons after receiving clonidine, a central alpha-2 agonist, or phentolamine, a ganglionic blocking agent. Unlike the normal medulla, pheochromocytomas are not innervated so their release of catecholamines is not controlled by neural stimulation. Therefore the clonidine and phentolamine suppression tests fail to inhibit plasma catecholamine levels in patients with pheochromocytomas.

Microscopic Anatomy

Each gland consists of a thick outer cortex and a thin inner medulla. The cortex makes up 80-90% of the volume of a normal gland while the medulla accounts for 10-20%. The external cortex is rich in lipids which gives the gland its characteristic dark yellowish orange color. The cortex has a firmer consistency than the reddish brown well vascularized medulla. Histologically, the adult adrenal cortex is divided into three zones: an outer zona glomerulosa, a middle zona fasciculata and an inner zona reticularis. The outer most layer or zona glomerulosa gets its name from the arrangement of columnar epithelial cells in clusters or anastomosing cords. The aldosterone (mineralocorticoid) secreting cells of the zona glomerulosa are small, have an intermediate number of lipid inclusions and constitute about 15% of the cortex. The zona fasciculata comprises approximately 75% of the cortex. Its cells have a large amount of cytoplasm relative to the nucleus, appear foamy secondary to

many lipid inclusions and are arranged in a parallel array. Cells of the inner zona reticularis have compact cytoplasm, few lipid inclusions and are arranged in clusters. ACTH stimulation causes cells in the fasciculata and reticularis zones to enlarge due to increased lipid storage and mitochondrial and endoplasmic reticulum proliferation. The two inner zones of the cortex secrete adrenocortical steroids. The fasciculata secretes primarily cortisol while the reticularis secretes sex hormones including testosterone, estradiol and dihydroepiandrosterone.

The center of the adrenal gland, the medulla, is composed of rounded clusters or short cords of chromaffin cells that are surrounded by nerves and blood vessels. The cells from the medulla give a characteristic color reaction determined by their content of catecholamines. With dichromate salts, they give the brown "chromaffin" reaction and with silver salts they give the black "argentaffin" reaction. These cells have large numbers of catecholamine containing granules. In the normal human adrenal, epinephrine predominates in these granules because of the high activity of PNMT induced locally by high levels of glucocorticoids.

Adrenal Steroid Biochemistry and Physiology

The adrenal cortex secretes steroid hormones including cortisol, aldosterone, and sex steroids. Plasma cholesterol is the source substrate used for all steroid synthesis. Cholesterol is either extracted from plasma or manufactured locally within the adrenal cortex. The biosynthetic pathways of all adrenal steroid synthesis are shown in Figure 17.1. The pathways are compartmentalized in the cortical zones with the zona glomerulosa producing aldosterone, the zona fasciculata producing cortisol and the zona reticularis producing testosterone, estrone and estradiol. All adrenal steroids have either 19 or 21 total carbon atoms and share a common 17 carbon structure made up of three hexane rings and a single pentane ring. Congenital absence of enzymes involved in any of the pathways shunts pregnenolone derivatives through unaffected pathways and causes specific clinical syndromes.

Mineralocorticoids

Aldosterone, the major mineralocorticoid in man, is secreted from the zona glomerulosa. Approximately 40% of this hormone circulates bound to albumin, 20% to transcortin and the remainder is free. Its plasma half life is approximately 15 minutes. Aldosterone is degraded in the liver by enzymatic reduction and conjugation with glucuronic acid and then excreted by the kidney. Only minute amounts of free aldosterone are normally found in the urine. Aldosterone plays a key role in regulating extra cellular fluid volume and fluid and electrolyte balance. It stimulates sodium reabsorption and potassium and hydrogen ion secretion by the distal convoluted tubule of the kidney. It has similar effects in enhancing sodium retention by sweat glands, salivary glands and the gastrointestinal mucosa. By causing the kidney and other tissues to retain sodium aldosterone increases the extra cellular fluid volume.

Aldosterone secretion is regulated primarily by the renin-angiotensin system and plasma aldosterone levels. Plasma sodium atrial natriuretic peptide and ACTH have a less important role in its regulation. The renin angiotensin system is activated by secretion of renin from the juxtaglomerular cells of the kidney in response to a

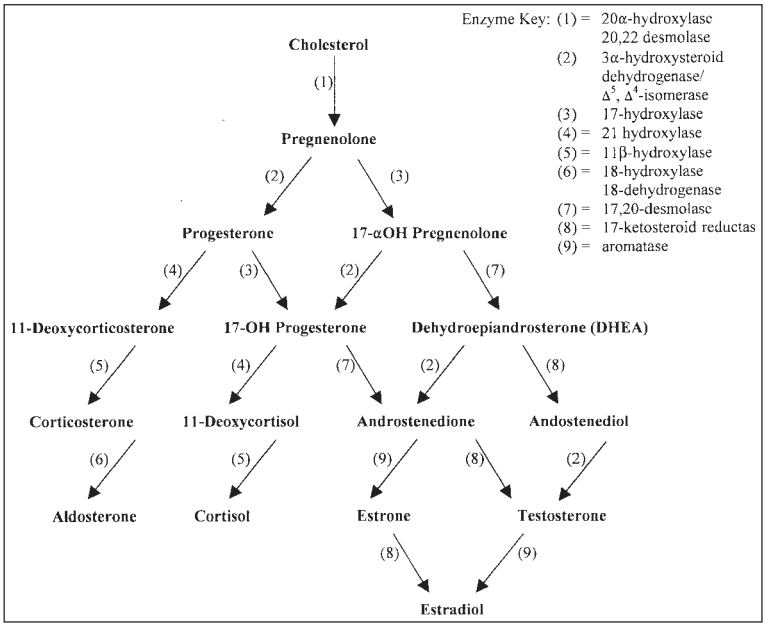

Fig. 17.1. The pathways for synthesis of steroid hormones in the adrenal cortex are depicted.

decrease in renal blood flow, sympathetic nerve stimulation or a decrease in plasma sodium. Renin then enzymatically cleaves angiotensinogen to form angiotensin I. This in turn is cleaved by angiotensin converting enzyme (ACE) in the lung to form angiotensin II. Angiotensin II is a potent vasoconstrictor that binds to membrane receptors on the zona glomerulosa cell surface. This stimulates aldosterone biosynthesis and release from the adrenal through the receptor mediated activation of phospholipase C. Factors that decrease renal artery blood flow such as hemorrhage, dehydration, upright posture or renal artery stenosis stimulate the renin angiotensin system. Restoration of blood volume and pressure as well as high levels of aldosterone inhibit the release of renin and angiotensin. In other words there is a negative feedback loop with angiotensin II and aldosterone causing reabsorption of sodium and expanding the extracellular fluid volume. This increase in sodium and in extracellular fluid volume decreases the secretion of renin and formation of angiotensin II. There is a reciprocal relationship between serum potassium and aldosterone. An increase of serum potassium will increase aldosterone secretion proportionately whereas a fall in serum potassium will decrease aldosterone secretion. ACTH plays a comparatively minor role in aldosterone regulation and unlike the zona reticularus and fasciculata, the zona glomerularosa does not atrophy after hypophysectomy.

Cortisol

Glucocorticoids are essential for human life. The principle glucocorticoid in man is cortisol which is produced in the zona fasciculata. A normal adult secretes 10-30 mg of cortisol each day. Cortisol secretion has a diurnal pattern with peak serum levels occurring in the early morning and low levels occurring at night. Serum cortisol levels are continuously regulated by a feedback loop involving the hypothalamus and the pituitary (Fig. 17.2). Release of ACTH from the pituitary is the main mediator of cortisol secretion. Several hormones can stimulate pituitary release of ACTH but the most important is corticotropin releasing factor (CRH) which is secreted by the hypothalamus. Increases in serum cortisol inhibits hypothalamic secretion of CRH and pituitary secretion of ACTH while decreases in serum cortisol will stimulate the secretion of these two hormones. ACTH binds to receptors on the adrenal cell surface. This hormone receptor complex activates the adenylate cyclase-cyclic-AMP-protein kinase A system. This increases the conversion of cholesterol to pregnenolone. Chronic ACTH stimulation increases the number and activity of enzymes involved in cortisol synthesis and causes hypertrophy of the adrenocortical cells involved in this synthesis.

Circulating cortisol is cleared primarily by the liver and has a plasma half life of approximately 90 minutes. The liver converts cortisol to inactive metabolites which are conjugated and then excreted in the urine. These conjugated metabolites can be measured as 17-hydroxycorticosteroids. Normally only a small quantity of free cortisol can be found in the urine. Approximately 75% of plasma cortisol is bound to transcortin (corticosteroid binding globulin) while 15% is bound to albumin. Only 10-15% of cortisol is present as the free active hormone.

To exert their physiologic effects, steroid hormones bind to specific intracellular cytosolic receptors. The activated steroid receptor complex enters the cell nucleus where it binds to DNA. This activates transcription of target genes. Glucocorticoids have broad physiologic actions and cortisol plays important roles in intermediary metabolism, immune modulation, wound healing and regulation of intravascular volume (Table 17.1).

Adrenal Sex Steroids

The cells of the zona reticularus convert pregnenolone to 17-hydroxypregnenolone and subsequently to dehydroepiandrosterone and androstenedione. DHEA is the major sex steroid produced by the adrenal cortex. DHEA and androstenedione are weak androgens and are converted in peripheral tissues to testosterone and estrogens. Adrenal androgen release is stimulated by ACTH and is not affected by gonadotropin stimulation. There is no diurnal variation of serum DHEA.

Normally the gonads are the principal source of sex steroids in males and females. Adrenal androgens promote development of male secondary sexual characteristics. Excessive production of adrenal sex steroids either prenatally or postnatally results in disorders of sexual development such as masculinization and feminization.

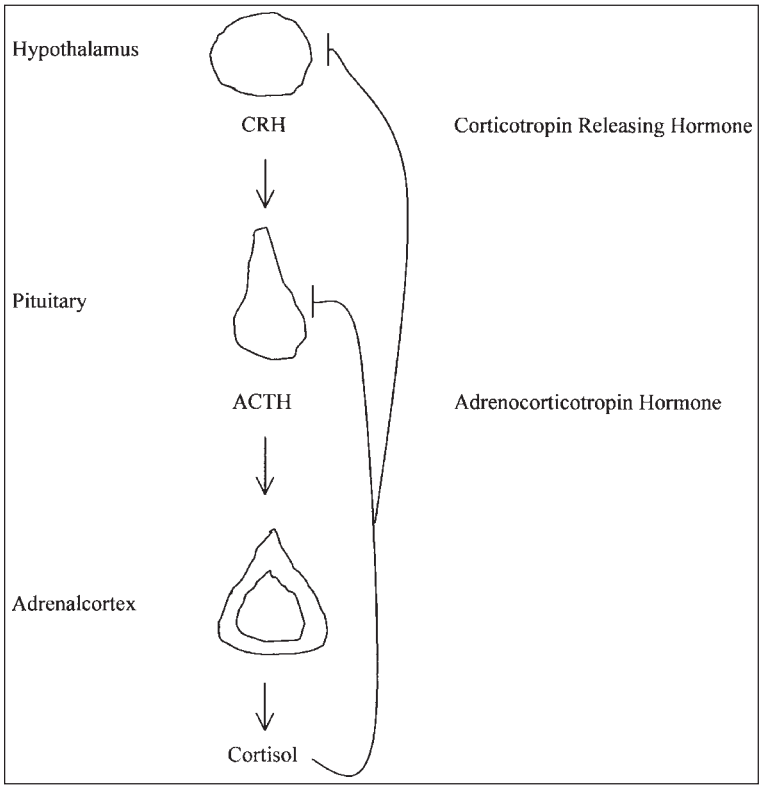

Fig. 17.2. The hypothalamic-pituitary-adrenal negative feedback loop that regulates cortisol secretion by the adrenal cortex is shown.

Catecholamines

The adrenal medulla synthesizes and secretes a number of biologically active amines including dopamine, norepinephrine and epinephrine. These catecholamines are synthesized from tyrosine. The conversion of tyrosine to dihydroxyphenylalanine (DOPA) by the cytosolic enzyme tyrosinehydroxylase is the rate limiting step in catecholamine synthesis (Fig. 17.3) Phenylethanolamine-n-methyltranspherase (PNMT) which is required for the conversion of norepinephrine to epinephrine is localized exclusively in cells in the adrenal medulla and the organ of Zuckerkandl. This explains why epinephrine secreting tumors arise only in these two tissues with few exceptions. Catecholamines are stored in the adrenal medulla in granular vesicles in which epinephrine represents approximately 80%, norepinephrine 20% and dopamine a minute fraction of the content of these chromaffin granules. These granules are discharged into the circulation by exocytosis when these cells are

Table 17.1. Effects of glucocorticoids (cortisol)

Function	Effect
Metabolism	
Carbohydrate	↑Blood glucose ↑Release of glucagon ↑Glycogenolysis and gluconeogenesis ↑Insulin resistance ↓Glucose uptake
Protein	↑Protein catabolism
Lipid	↑Mobilization of free fatty acids ↑Truncal obesity
Circulation	↑Cardiac output ↑Intravascular volume ↑Blood pressure ↓Cellular permeability
Immune System	↓Lymphocyte activation ↓Monocyte and neutrophil migration ↓Mast cell lysosomal degranulation ↓Antibody formation ↓Resistance of infection
Musculoskeletal	↑Muscle weakness ↑Osteoporosis ↓Collagen synthesis ↓Fibroblast activity ↓Wound healing
CNS	↑Psychosis ↑Euphoria
Eye	↑Cataracts ↑Corneal ulcers

stimulated. The half life of plasma epinephrine and norepinephrine is very short (1-2 minutes). There are three pathways by which catecholamines are cleared from the circulation. These include uptake by sympathetic neurons, uptake and degradation by peripheral tissues and excretion in the urine. Catecholamines are metabolized in the liver and kidney by two enzymes, monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT). The inactive metabolites that result from this enzyme degradation are vanillylmandelic acid (VMA), normetanephrine and metanephrine. These breakdown products are cleared by the kidney and can be measured in the urine either as free compounds or as conjugates of glucuronide or sulfate.

Catecholamines have wide ranging effects on almost all tissues and organs in the body. Catecholamines act by forming complexes with alpha or beta receptors on the

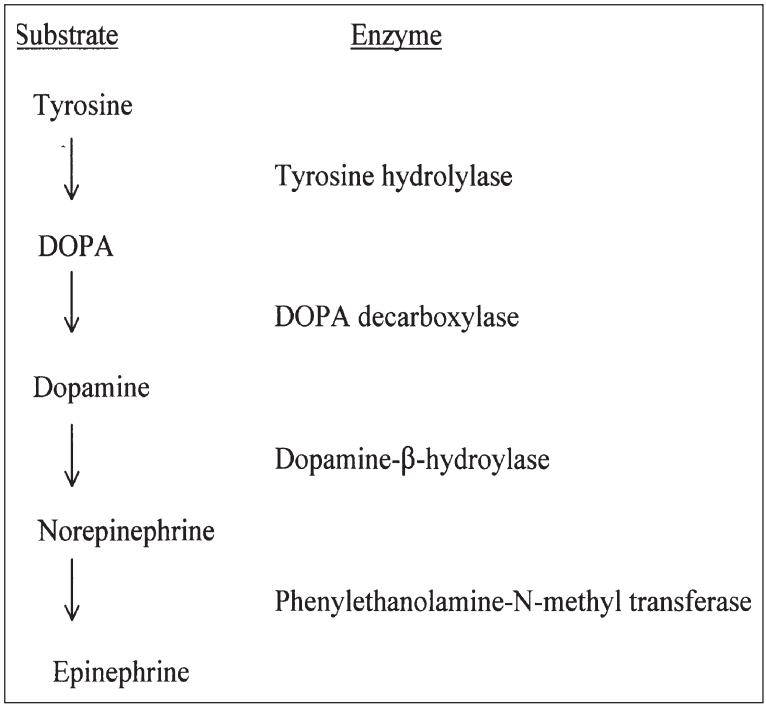

Fig. 17.3. Catecholamine synthesis.

cells of target tissues. Alpha receptors have the highest affinity for norepinephrine and less for epinephrine. Beta receptors are more responsive to epinephrine. Catecholamines have profound cardiovascular and metabolic effects and also influence the secretion of many hormones. The principal physiologic effect of alpha receptor stimulation is vasoconstriction. There are two types of beta receptors. The $beta_1$-receptor mediates inotropic and chronotropic stimulation of cardiac muscle. The $beta_2$-receptor induces relaxation of smooth muscle in noncardiac tissues including blood vessels, bronchi, uterus and adipose tissue. Catecholamines increase cellular calorigenesis by increasing oxygen consumption and heat production. In the liver and heart they stimulate glycogenolysis which increases the availability of carbohydrate for tissue use. They induce lipolysis and increase release of fatty acids and glycerol from adipose tissue. Both norepinephrine and epinephrine inhibit insulin secretion.

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CHAPTER 18

Cushing's Syndrome

David Bailey Wilson and Richard A. Prinz

Introduction

Definition

In 1932, Harvey W. Cushing defined a syndrome he called "pituitary basophilism." Muscular weakness, truncal obesity, abdominal striae, diabetes and hypertension characterized this clinical complex. Today, the condition resulting from chronic glucocorticoid excess due to any source is known as "Cushing's syndrome," as opposed to the pituitary-derived "Cushing's disease."

Statistics

Cushing's syndrome is a rare disorder, with a prevalence of 10 patients per million population per year. It can be classified into ACTH (corticotropin)-dependent and ACTH-independent disease. Eighty percent of patients have ACTH-dependent disease, with a pituitary (70%) or ectopic (10%) source of the excess ACTH. Either of these conditions results in adrenal cortical hyperplasia of the zona reticularis and fasciculata. The resulting cortisol hyperproduction leads to the clinical manifestations of the syndrome. Pituitary tumors are more common in women than men, and often occur in the second and third decades of life. Ectopic ACTH syndrome may occur with a number of different tumors, and usually is rapidly progressive. Ectopic ACTH production is more common in men than in women, and typically occurs in the fourth and fifth decades of life.

Twenty percent of patients have ACTH-independent disease. This is due to an adrenal source of excess cortisol, either an adenoma (10%), or carcinoma (10%). ACTH production is suppressed by the autonomous production of cortisol in these patients. ACTH-independent Cushing's syndrome occurs more commonly in women, who are typically aged 20-40.

Diagnosis

Clinical Suspicion

A high index of suspicion is necessary to make the diagnosis of Cushing's syndrome early in its course. A constellation of symptoms and signs are recognized. These include a characteristic round facies, proximal muscle weakness, truncal obesity, buffalo hump, thin skin, hirsutism, easy bruisability, purple striae, depression, osteoporosis, hypertension, and glucose intolerance (Table 18.1).

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Table 18.1. Clinical symptoms of Cushing's disease

Round facies
Proximal muscle weakness
Truncal obesity
Buffalo hump
Thin skin
Hirsutism
Easy bruisability
Purple abdominal striae
Depression
Osteoporosis
Hypertension
Glucose intolerance

Confirmatory Tests

A 24-hour urine collection for free cortisol is the most common screening test. Low dose dexamethasone suppression test follows (either as 1 mg po before bedtime or as 0.5 mg po q6˚ for 48 hours). An elevated 24 hour urine free cortisol level or a failure to suppress plasma cortisol by dexamethasone suggests Cushing's syndrome with 95% accuracy.

ACTH Level

The next step is to distinguish between ACTH-dependent and independent disease. Immunoradiometric assays (ACTH-IRMA) can consistently and reliably detect suppressed levels of ACTH, with an ACTH-independent adrenal source of cortisol. This is an improvement over older radioimmunoassays which could not always distinguish ACTH from nonsuppressed precursor molecules, and gave falsely elevated results.

Localizing

ACTH-Dependent

Having distinguished between ACTH-dependent and independent disease, localization of the tumor is possible. Clinically, patients with a pituitary source of ACTH tend to have a long-standing history of slowly developing symptoms and signs. In contrast, most ectopic sources of ACTH have a rapidly progressive course.

High dose dexamethasone suppression testing (HDDMS) is a noninvasive method to distinguish pituitary from ectopic sources of excess corticotropin. Dexamethasone is given as either 2 mg po q6˚ for 48 or as 8 mg po before bed. Suppression of 24 hour urine free cortisol or plasma cortisol by more than 50% is consistent with pituitary disease. This is because of the pituitary's partial sensitivity to feedback suppression by the exogenous steroid. Sensitivity and specificity of this test range from 80-90%. Because the test's accuracy is less than the pretest probability of having pituitary disease, some authors advocate stricter criteria for a positive test. Suppression of 24 hour urine free cortisol by > 90%, and 17-hydroxy-corticosteroid

secretion by > 64%, gives HDDMS 100% specificity.[1] Magnetic resonance imaging is most commonly used to identify suspected pituitary disease. Scanning before and after gadolinium enhancement allows identification of some microadenomata (< 10 mm.) as well as any local invasion or compression of the adjacent structures. If the diagnosis is still in doubt, simultaneous sampling of the inferior petrosal sinuses should be performed. Invasive and expensive, inferior petrosal sinus sampling requires specialized interventional radiology techniques. In this procedure, the left and right petrosal sinuses are individually cannulated, most commonly via a femoral vein approach. Blood samples are drawn before and after an infusion of corticotropin releasing hormone (CRH). Using CRH stimulation, IPSS can identify and lateralize a pituitary source of excess ACTH with nearly 100% accuracy.

ACTH-Independent

For ACTH-independent Cushing's syndrome, radiographic imaging is used to distinguish unilateral from bilateral adrenal pathology. Computed tomography is the standard modality for gaining anatomic information. Thin sections through the adrenals (3-5 mm) will reveal a unilateral adenoma (80%), carcinoma (10%), or bilateral symmetric or asymmetric pathology (10%). Carcinomas tend to be larger (> 5 cm), inhomogeneous, with an irregular border. Distinguishing adenoma from carcinoma in large tumors can be aided by magnetic resonance imaging. Carcinomas appear brighter than the liver on T2 weighted images.

Iodocholesterol scintiscanning with the radiolabeled cholesterol analog NP-59 is a noninvasive test of adrenal function. Taken up by active adrenal tissue, this isotope is not metabolized. Hyperfunctioning lesions as small as 1-2 cm can then be visualized because of the high concentration of isotope. Undifferentiated carcinomas do not show activity. Although NP-59 requires several days to complete and can be variable in its uptake and reliability, it is useful in distinguishing between unilateral and bilateral disease (Fig. 18.1).

Treatment

Medical Therapy

Pharmacological blockade of cortisol synthesis is possible. Metyrapone, an 11-beta hydroxylase inhibitor, can be used preoperatively in severe cases of Cushing's syndrome. It is also used along with ketoconazole and aminoglutethamide to reduce the cortisol synthesis in metastatic disease. Mitotane can be used in metastatic or unresectable disease. Its onset of action is slow, requiring several weeks to control symptoms. Remission occurs in 80% of patients, but relapse follows cessation of therapy. Octreotide, a synthetic somatostatin analogue, has been shown to reduce ACTH production and thereby cortisol levels. It can be used either preoperatively to decrease the risk of operation, or more long term with unresectable tumors in patients with ectopic ACTH syndrome.[2]

Patients with Cushing's syndrome are typically at increased risk for perioperative complications. They are obese, have glucose intolerance, and are more susceptible to infections. Perioperative antibiotics are indicated. Glucocorticoid supplementation

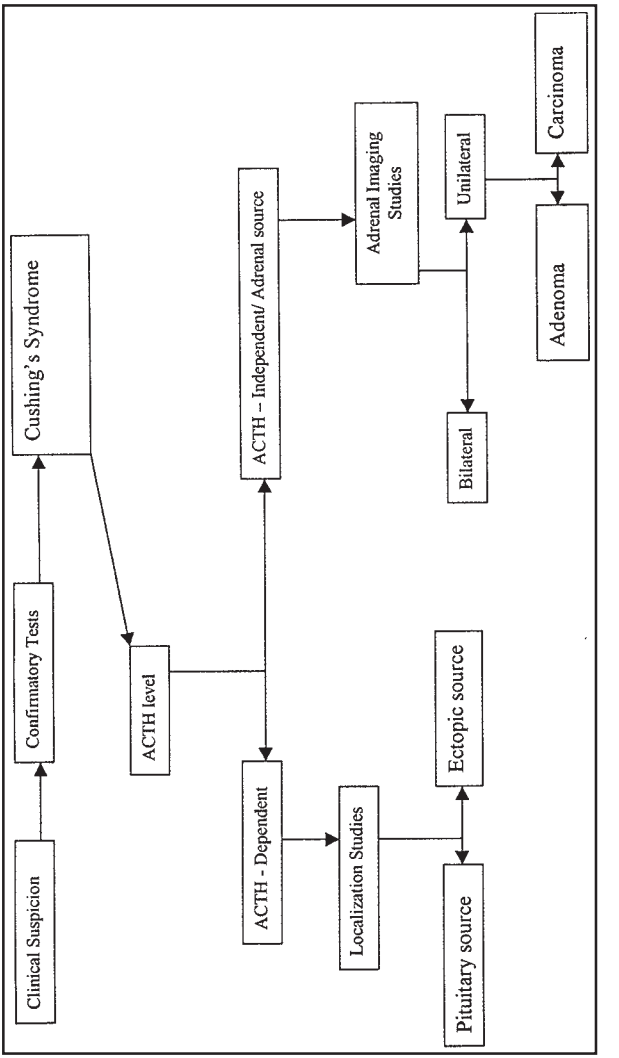

Fig. 18.1. Diagnostic workup

is necessary perioperatively as well. Usually hydrocortisone 100 mg is given IM or IV preoperatively and q6 hours postoperatively until oral supplements are tolerated. With a unilateral cortisol producing adenoma, the contralateral gland's function is usually suppressed. This varies in duration, but recovery of the hypothalamic-pituitary-adrenal axis usually requires at least two to twelve months. After bilateral adrenalectomy, glucocorticoid and adrenocorticoid supplements are required for life.

Operative Therapy

The optimal treatment of Cushing' s syndrome is surgical resection of the source. This is true for both ACTH-dependent and independent disease.

Pituitary

Corticotroph adenomas are found in approximately 80% of patients with Cushing's disease. Most are monoclonal, and surrounded by suppressed normal pituitary tissue. Some patients have separate corticotroph hyperplasia, either with or without an adenoma. No conclusive evidence has been found, however, of hypothalamic or other central nervous system source of excessive stimuli of corticotropin release. Transsphenoidal resection of an adenoma or hyperplastic corticotropic tissue is standard treatment. Patients with a microadenoma confined to the sella have the highest likelihood of cure. Up to 88% will have a long-term remission. An undetectable postoperative corticotropin level suggests a cure. Incomplete removal of a tumor, or subtotal resection of a diffusely hyperplastic gland leads to a fall in ACTH and cortisol levels to nearly normal levels, and clinical improvement Feedback regulation of the pituitary remains abnormal, though, and ACTH secretion often increases with time necessitating further treatment.

Repeat surgery on the pituitary can be performed. After successful resection of a recurrent or persistent adenoma, remission rates in the range of 70-75% can occur. Diabetes insipidus, cerebrospinal fluid rhinorrhea, low-grade meningitis, hypothyroidism, and hypogonadism are the more common complications. Radiation therapy with adjunctive adrenolytic drugs is also an important second- line therapy. Doses in the range of 45-54 Gy are used. The timing of repeat surgery or radiation therapy is usually based on symptom return, am plasma cortisol levels, 24˚ urine free cortisol, and low dose dexamethasone suppression testing.

Bilateral adrenalectomy provides definitive treatment for ACTH-dependent pituitary disease refractory to the above therapies. Beside the need for life-long glucocorticoid and mineralocorticoid supplementation, Nelson's syndrome occurs in approximately 5-25% of patients with Cushing's Disease treated with bilateral adrenalectomy. Defined by hyperpigmentation, elevated ACTH levels, and an aggressively expanding pituitary tumor, Nelson's syndrome is due to the absence of cortisol feedback inhibition on the pituitary. Prophylactic pituitary irradiation has reduced this occurrence by 50%. Controversy remains over the use of radiation therapy on glands that have been treated with surgical resection.

Ectopic ACTH Syndrome

Certain nonpituitary neoplasms may produce biologically active ACTH, among other hormones. This accounts for 10-30% of patients with Cushing's syndrome from all causes. A majority of these tumors will be found in the chest. Small cell lung carcinoma is the most common lesion, accounting for fifty percent of the patients. Another 10% are from thymic carcinomas and carcinoids. Bronchial adenomas and carcinoids cause approximately 5%. Pancreatic tumors, including carcinoids and islet cell carcinomas, are the source in 10% of cases. Pheochromocytoma, neuroblastoma, ganglioma and paraganglioma account for 5%, as does medullary carcinoma

of the thyroid. Anecdotal reports show ACTH activity in a variety of common and uncommon neoplasms. Virtually all nonmesodermal neoplasms have been reported to synthesize this hormone.[3] Although most of these tumors express a glucocorticoid receptor, transcription of the proopiomelanocortin gene and secretion of ACTH are not subject to feedback inhibition by cortisol. Bronchial carcinoids may be an exception, with some susceptibility to high-dose dexamethasone suppression. These slow growing tumors often produce Cushing's syndrome long before they can be found clinically. A relatively recent advance in making this difficult diagnosis utilizes the finding that ectopic corticotropin-producing tumors often express somatostatin receptors while pituitary and adrenal adenomas do not. This can be exploited for localization by using labeled octreotide scintigraphy (octreoscan). This modality is 80% successful in localizing these tumors.

Adrenal

For patients with an adenoma, adrenalectomy is curative. The recommended approach is based on the tumor's size and malignantcy potential, the patient's body habitus and the surgeon's experience. Tumors less than 5 cm can be resected through a flank or posterior approach. By avoiding the peritoneal cavity, paralytic ileus and the risk of future adhesions are avoided. Larger tumors should be approached transabdominally or with a thoracoabdominal approach. These approaches allow for en bloc resection of adjacent organs in the case of locally invasive carcinomas.

Worldwide, the incidence of adrenal carcinoma is 2/1,000,000. Two thirds of these tumors secrete excess steroid hormones, and Cushing's syndrome is the most common resultant clinical entity. They also can secrete multiple other hormones. One clinical finding that suggests the presence of a carcinoma is virilization or defeminization. The tumors are often large (> 6 cm) with necrosis, calcification, and local invasion. At the time of diagnosis, 33% are confined to the gland, while 38% have distant metastases. The most common targets are lungs (70%), liver (40%), lymph nodes (40-70%), and bone (30%). The remainder are locally invasive. Surgical debulking with adjuvant mitotane therapy offers the best chance for remission. Still, median survival from the onset of symptoms is only 4 years and 5 year survival is 10%.

Bilateral adrenalectomy can be performed with either an anterior or a bilateral posterior approach. For patients who have persistent or recurrent disease after transsphenoidal pituitary resections, or occult or unresectable ectopic tumors, bilateral adrenalectomy can result in substantial symptomatic improvement.[5] Primary adrenal hyperplasia is also an indication for bilateral adrenalectomy.

Five to ten percent of patients with Cushing's syndrome will have bilateral adrenal nodules on high-resolution CT scans. The nodules range in size from 0.5-7 cm. These are believed to be an end response to long-standing ACTH stimulation in which the nodules become ACTH-independent. Biochemical and radiological test results are mixed or inconsistent since there may be findings of both ACTH dependence and independence. Treatment depends upon identifying an ACTH producing tumor, either orthotopic or ectopic. Successful resection results in both clinical

cure and involution of the nodules. Bilateral adrenalectomy is necessary if the ACTH-producing tumor cannot be identified and resected.

Primary pigmented nodular adrenal dysplasia (PPNAD) is a rare ACTH-independent bilateral disease consisting of small darkly pigmented adrenal nodules. The disease can be sporadic or familial and is thought to be autoimmune in origin. Subtle adrenal enlargement and nodularity is inconsistently seen on preoperative CT scans. Bilateral adrenalectomy is curative. Twenty percent of these patients will have Carney's complex, which is an autosomal dominant disease of multiorgan tumors. The complex includes cardiac myxomas, testicular tumors, pigmented skin lesions, cutaneous myxomas, breast myxoid fibroadenomas, pituitary adenomas and other myxoid and fibrous tumors.

Advances

Laparoscopic Adrenalectomy

Tumors up to 6-8 cm in diameter can be removed laparoscopically. The technique was first reported in 1992 by Gagner et al and has since been reported widely.[5] Advantages to this approach include shorter hospital stay, shorter convalescence, and decreased postoperative narcotic requirements. In Cushing's syndrome, another potential advantage includes fewer infectious and wound complications.[6]

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CHAPTER 19

Aldosteronoma

William B. Inabnet

Introduction

Aldosteronomas, often referred to as aldosterone-producing adenomas, are the most common cause of primary aldosteronism, a surgically correctable type of hypertension that occurs in 0.5-2% of all hypertensive patients.[1,2] As first described by Conn 45 years ago, primary aldosteronism is a syndrome characterized by hypertension, depletion of potassium, retention of sodium, and suppression of plasma renin activity (PRA), all of which are caused by an elevation in plasma aldosterone. Idiopathic hyperaldosteronism is the second most common cause of primary aldosteronism and is characterized by bilateral adrenocortical hyperplasia. Since the management of aldosterone-producing adenomas and idiopathic hyperaldosteronism is markedly different (surgical resection vs. medical therapy), the accurate differentiation of these two forms of primary aldosteronism is imperative. Other less common causes of primary aldosteronism include aldosterone-producing carcinoma, glucocorticoid-remediable hyperaldosteronism, and primary adrenal glomerulosa hyperplasia, a rare disorder characterized by unilateral nodular hyperplasia of one predominant adrenal gland.[3]

Secondary hyperaldosteronism occurs in states of decreased renal arterial blood flow, leading to an increase in sodium reabsorption and blood volume. This resultant activation of the renin-angiotensin-aldosterone system leads to systemic hypertension in the setting of elevated levels of aldosterone and renin. In contrast, renin levels are low in primary aldosteronism.

This chapter will provide a basic overview of primary aldosteronism, paying particular attention to the presentation, diagnosis, localization, and management of aldosterone-producing adenomas.

Etiology

Aldosterone-producing adenomas, which arise from the zona glomerulosa of the adrenal cortex, are benign neoplasms that account for 60-70% of patients with primary aldosteronism.[2,3] In most instances, these lesions are unilateral, single, and less than 2 cm in diameter. Gross inspection of the cut surface reveals a well-demarcated lesion that has a characteristic yellow-tan color. Microscopic examination shows large lipid-laden cells arranged in small cords separated by connective tissue.

Idiopathic hyperaldosteronism is the cause of primary aldosteronism in approximately 25-35% of cases.[2,3] In contrast to aldosterone-producing adenomas, idiopathic hyperaldosteronism is a bilateral process characterized by diffuse or focal hyperplasia of the adrenal cortex. The zones of adrenal hyperplasia may contain

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either micro or macronodules, or both. The presence of a macronodule in a hyperplastic adrenal gland is not uncommon and may resemble an aldosterone-producing adenoma, often making gross differentiation difficult. Histologically, idiopathic hyperaldosteronism is characterized by hyperplasia of the zona glomerulosa of both adrenal glands.

Several endocrine authorities have hypothesized that the pathogenesis of idiopathic hyperaldosteronism and aldosterone-producing adenomas form a continuum and may in fact be related processes.[1-3] For example, it is well known that an aldosterone-producing adenoma can coexist within a zone of hyperplasia in the same adrenal gland. Concomitantly, nonfunctioning macronodules may be seen in a hyperplastic adrenal gland or in association with an adenoma. In these circumstances, it is important to thoroughly evaluate all the clinical and diagnostic information to assure the correct diagnosis.

Glucocorticoid-remediable hyperaldosteronism is a rare, familial form of hypertension that represents 1-3% of patients with primary aldosteronism.[1,4] This disorder is caused by the dysregulation of aldosterone secretion so that aldosterone is under the control of adrenocorticotropin (ACTH) rather than the renin-angiotensin system. Glucocorticoid-remediable hyperaldosteronism is ameliorated by the administration of exogenous glucocorticoids.[4]

Adrenocortical carcinoma is an uncommon cause of primary aldosteronism, occurring in less than 1% of patients.[3] These tumors tend to be large and aggressive with an overall 5 year survival of approximately 35%. The isolated overproduction of aldosterone is uncommon occurring in 3-5% of adrenocortical carcinomas. More commonly, aldosterone is produced and released with other adrenal steroids, creating a mixed hormonal presentation.

Clinical Presentation

Hypertension and hypokalemia are the hallmark features of primary aldosteronism. Primary aldosteronism usually presents during the forth or fifth decade of life with a female to male ratio of 2:1 in most series.[2] The hypertension is typically moderate in severity, although cases of severe hypertension can occur. A moderate elevation in diastolic blood pressure is most common, typically ranging from 100-130 mm Hg. Some patients are refractory to medical management and require multiple antihypertensive medications to achieve adequate blood pressure control. Spontaneous hypokalemia to a value less than 3.4 mEq/L is common, especially following the administration of large amounts of sodium chloride. Potassium-wasting diuretics (i.e., thiazide and furosemide) are a common cause of hypokalemia; persistent hypokalemia following the cessation of diuretic therapy should raise the suspicion of primary aldosteronism.

The clinical manifestations of primary aldosteronism arise from the direct influence of aldosterone on sodium and potassium homeostasis. Aldosterone increases the reabsorption of sodium in the distal renal tubule in exchange for potassium and hydrogen ions. Normally, the reabsorption of sodium is counterbalanced by the loss of potassium and hydrogen in the urine, all of which are under the influence of the

renin-angiotensin-aldosterone system. However in states of excessive aldosterone production, renin production by the kidneys is suppressed, impairing the normal feedback mechanism. The resultant retention of sodium and water leads to hypertension and the urinary loss of potassium and hydrogen causes a hypokalemic metabolic alkalosis.

The symptoms of primary aldosteronism are a direct result of these metabolic derangements. Hypokalemia causes the majority of symptoms, including proximal muscle weakness, muscle cramps, polyuria, polydipsia, nocturia, headache, and general fatigue. Chronic hypokalemia also impairs insulin secretion and can result in glucose intolerance in up to half of the patients.[1] In advanced cases, the metabolic alkalosis can lead to muscle paralysis or tetany, a presentation that occurs more frequently in Asian patients.[2]

Diagnosis

Primary aldosteronism should be suspected in all patients with hypertension and spontaneous hypokalemia, but laboratory tests are necessary to firmly establish the diagnosis. The diagnostic strategy is divided into three parts: screening tests, confirmatory tests, and tests that differentiate between aldosterone-producing adenomas and idiopathic hyperaldosteronism.

Screening tests for suspected primary aldosteronism include the measurement of serum potassium and urinary aldosterone levels. The occurrence of spontaneous hypokalemia in a hypertensive patient should heighten the level of suspicion of aldosterone overproduction, especially when the serum potassium is less than 3.4 mEq/L. However, many patients may have a serum potassium level at the lower limits of normal (i.e., 3.5-3.6 mEq/L) leading some authorities to recommend confirmatory tests in all hypertensive patients with serum potassium levels in this range. Diuretic-induced hypokalemia that does not respond to potassium supplementation is another indication for additional testing. Twenty-four hour urine collections for aldosterone, potassium, and sodium are also useful in screening for primary aldosteronism.

Biochemical confirmation involves the demonstration of increased plasma aldosterone levels in the setting of suppressed plasma renin activity (PRA). All antihypertensive medications should be discontinued four weeks prior to testing, except for spironolactone which should be stopped six weeks in advance.[3] The continued administration of antihypertensive medication may be necessary in severe cases of hypertension; in this setting, an agent that does not affect the renin-aldosterone axis is preferred (i.e., prazosin). Due to the excessive production and release of aldosterone, plasma aldosterone levels will be elevated, typically exceeding 30 ng/dL. Plasma renin activity will usually be less than 1.0 ng/dL due to the negative feedback of aldosterone on renin production. The plasma aldosterone/PRA ratio has proven to be a very sensitive marker of primary aldosteronism with a ratio greater than 50 being highly suggestive of endogenous aldosterone over production.

If the diagnosis is still uncertain following these tests but is suspected on clinical grounds, additional studies may be helpful including sodium chloride loading or

the administration of mineralocorticoids, both of which suppress the release of aldosterone in the normal individual. Conversely, the administration of furosemide or the restriction of sodium intake will raise the PRA in normal subjects, but will have little effect in patients with primary aldosteronism. Finally, the captopril test is helpful in certain cases. The administration of captopril, an angiotensin-converting enzyme inhibitor, will decrease serum aldosterone levels in normal individuals but will have no effect on patients with autonomous aldosterone over production.[1,3]

Once the diagnosis of primary aldosteronism has been confirmed, it is necessary to differentiate between aldosterone-producing adenomas and idiopathic hyperaldosteronism. As previously mentioned, the latter disorder does not respond to adrenalectomy and is best treated medically with spironolactone. At most centers computed tomography has replaced postural studies as the study of choice for determining the etiology of primary aldosteronism, however, postural studies may be helpful in equivocal cases. Postural testing takes advantage of the fact that aldosterone-producing adenomas are unresponsive to the effects of angiotensin. The posture test involves measuring plasma aldosterone levels in the supine position at 8:00 AM and again in the upright position at 12:00 noon after four hours of standing. In the upright position, PRA and angiotensin levels increase. Therefore, plasma aldosterone levels increase in idiopathic hyperaldosteronism after standing and decrease in patients with aldosterone-producing adenomas.[2,3,5] The posture test correctly differentiates between aldosterone-producing adenomas and idiopathic hyperaldosteronism in 75-85% of patients.[1,5]

Localization

Although there are several localizing studies the clinician can choose from, computed tomography is the most widely employed and cost-effective modality for imaging the adrenal glands in primary aldosteronism. With the development of the new generation high-resolution scanners, the sensitivity of CT now approaches 90%, especially when focused on the adrenal glands.[2] Advantages of CT scanning include widespread availability, low radiation exposure, noninvasiveness, high sensitivity, and the ability to detect adenomas less than 1 cm in size. Furthermore, CT scanning can be performed in an outpatient setting. Occasionally CT scanning will identify additional nodules in either the ipsilateral or contralateral adrenal gland. Since multiple nonfunctioning nodules do occur in idiopathic hyperaldosteronism, the presence of multinodularity is an indication for additional localization studies.

Following a negative or equivocal CT scan, iodine-131-6β-iodomethyl-norcholesterol scanning (NP-59) with dexamethasone suppression is the next localizing study of choice. In patients with idiopathic hyperaldosteronism, NP-59 scanning will demonstrate diffuse bilateral uptake. However, since corticosteroids inhibit the uptake of radiolabeled cholesterol by hyperplastic adrenal glands, the administration of dexamethasone increases tracer uptake by aldosterone-producing adenomas thereby improving the sensitivity of their detection. Disadvantages of NP-59 scanning include higher radiation doses, the need to block the thyroid to prevent radioiodine uptake, and the length of the study, which can take five to seven

days to complete. This study, which can be performed as an outpatient, has a sensitivity of approximately 90%.[2]

Bilateral adrenal venous sampling remains the gold standard for determining the diagnosis of primary aldosteronism.[1-4] However, this study is technically demanding and the results vary from institution to institution. In order to have a reliable study, the angiographer must cannulate both adrenal veins which can be technically challenging, especially with the shorter right adrenal vein. The diagnostic accuracy of adrenal venous sampling is improved by determining aldosterone to cortisol ratios for each venous sample thereby minimizing dilutional effects. Bilateral adrenal venous sampling is invasive, expensive, and time consuming and should be utilized only when CT and NP-59 scanning fail to establish the diagnosis.

Treatment

The treatment of primary aldosteronism is dependent upon the etiology. Unilateral adrenalectomy is the treatment of choice for aldosterone-producing adenomas, a procedure that relieves symptoms or ameliorates hypertension in up to 80% of patients.[6] Idiopathic hyperaldosteronism, on the other hand, is best treated with antihypertensive medication. Patients with idiopathic hyperaldosteronism typically do not improve after bilateral adrenalectomy which puts them at risk of an Addisonian crisis for the rest of their lives.[2,5] Therefore, spironolactone is the preferred treatment in these patients, though the occurrence of side effects such as gynecomastia and impotence may require the use of an alternative medication such as Amiloride. Amiloride is a potassium-sparing diuretic that effectively treats hypertension while restoring potassium balance.

All patients undergoing adrenalectomy for primary aldosteronism require preoperative medical optimization. Correction of Hypokalemia and other electrolyte abnormalities is essential to decrease the risks of surgery. Spironolactone should be administered one to two weeks prior to surgery to minimize potassium wasting and to help achieve adequate control of hypertension.

Surgical approaches to the adrenal glands include the posterior, flank, and transabdominal techniques. However, since 1992, laparoscopic adrenalectomy has become the technique of choice for approaching the adrenal glands for most nonmalignant adrenal pathology. Given that most aldosterone-producing adenomas are less than 2 cm in diameter, laparoscopic adrenalectomy is particularly well-suited for this type of pathology. Laparoscopic adrenalectomy has numerous advantages over the conventional open approach, including fewer wound complications, shorter hospitalization, and quicker recovery.[5] The duration of surgery with laparoscopic adrenalectomy now approaches that of open adrenalectomy, especially in experienced hands. Excellent results have been obtained with both the transabdominal and the retroperitoneal laparoscopic approaches, however, the identification of anatomical landmarks is often more challenging in the retroperitoneal space.[6,7] In this setting, laparoscopic ultrasound can be helpful. The choice of laparoscopic approach—transabdominal or retroperitoneal—ultimately depends on the surgeon's preference and familiarity with each technique.

Summary

Aldosterone-producing adenomas are the most common cause of primary aldosteronism, a disease characterized by hypertension and hypokalemia. The diagnosis is established by demonstrating elevated plasma aldosterone levels in the setting of suppressed PRA. Differentiation of aldosterone-producing adenomas and idiopathic hyperaldosteronism is achieved by computed tomography of the adrenal glands with the addition of postural studies in equivocal cases. Aldosterone-producing adenomas are treated with adrenalectomy whereas idiopathic hyperaldosteronism is best treated with potassium sparing antihypertensive medication. Unilateral adrenalectomy offers excellent relief of symptoms in the majority of patients.

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CHAPTER 20

Adrenocortical Cancer

Constantine V. Godellas

Introduction

Adrenocortical carcinoma is an uncommon neoplasm. Even though many of these tumors are functionally active and secrete steroid hormones, they usually present in an advanced stage. Therefore the overall prognosis for adrenocortical cancer is poor. Complete surgical resection offers patients with this malignancy the only possible chance for cure. Unfortunately, because of late presentation, complete resection is often not possible. As with most other rare conditions, a high index of suspicion, as well as thorough knowledge of the disease, help in making a correct and timely diagnosis.

Many of the issues related to the diagnosis and preoperative evaluation of the adrenal gland addressed in this chapter are covered in other chapters. Several important factors, such as early diagnosis, are addressed in the chapter on adrenal incidentaloma and in the chapters on the various functional adrenal tumors. This chapter will specifically discuss the epidemiology, diagnosis and treatment of the patient with adrenocortical cancer.

Epidemiology

Cancers of the adrenal gland make up only 0.05-0.2% of all cancer deaths.[1] Adrenocortical cancer has a bimodal age distribution with the first peak prior to age 5, and the second peak between the ages of 40 and 50.[2] Those patients who present prior to 5 years of age usually do so with virilization (> 90%).[3] Most patients with adrenocortical cancer are female. In general, men tend to present at an older age. Functional cancers are found more frequently in women, and nonfunctional cancers occur more frequently in men.[4]

With the advent of high quality CT scanners, an increased number of smaller adrenal neoplasms are being discovered. The adrenal incidentaloma, as these neoplasms are known, is discussed in detail in another chapter. The risk of an adrenal incidentaloma that is less than 5 cm in size being a malignant adrenocortical carcinoma is extremely unlikely. However, when the size of the mass is 6 cm or greater, the risk of malignancy greatly increases.[5] As described in the chapter on adrenal incidentaloma, this fact is extremely important in the evaluation and management of these masses.

The exact etiology of adrenocortical cancer is unknown. There is one rare inherited disorder associated with adrenal cancer. The Li-Fraumeni syndrome is secondary to an inherited mutation in the P53 tumor suppressor gene. It consists of adrenocortical cancer, breast cancer, osteosarcoma, and/or brain tumor. While it is possible

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that the adrenal mass may be secondary to a metastasis, it is probably more likely a primary adrenal cancer, in the presence of these other tumors.

Diagnosis

As with most other endocrine malignancies, cancers of the adrenal gland are frequently functional. The adrenal cortex produces a variety of steroid hormones, so not unsurprisingly, adrenocortical cancers frequently produce a similar variety of hormonally active substances. Since they usually secrete less active precursors or several different substances, the excess hormone production is usually not recognized until the tumor has become relatively large. Likewise, the hormonal symptoms are subtle and gradual in onset which makes them more difficult to recognize. Hormonal symptoms include progressive weight gain, consistent with hypercortisolism, feminization, virilism, or menstrual irregularities, seen in patients with hypercortisolism or excess sex steroid hormone production, weakness, fatigue, and mental status changes, which can be seen with hypercortisolism and hyperaldosteronism.

Most adrenal cancers are greater than 6 cm when they are diagnosed. Those patients who do not present with hormonal symptoms, present because of tumor size or invasion. These tumors are just as likely to become symptomatic because of the large size they can attain in the confines of the relatively small retroperitoneal space or because of their invasion of adjacent structures. These tumor size related symptoms include abdominal pain or pressure, weight loss, hematuria, left varicocele, dyspnea, or altered gastrointestinal function.

Physical findings include truncal obesity with peripheral muscle wasting as in Cushing's syndrome, virilization in women or feminization in men, abdominal striae, and left varicocele. Virilization in women can include hirsutism, clitoromegaly, severe thinning of the hair, and deepening of the voice. Feminization in men is usually manifested by breast enlargement, softening of the skin, and frequent mood changes. The above physical findings are all secondary to excess sex hormone production. It is unusual to palpate an adrenocortical cancer since truncal obesity can often occur. However, a patient may present with a left varicocele from occlusion of the left spermatic vein, or even bilateral lower extremity edema secondary to obstruction of the inferior vena cava.

Laboratory findings include elevated urinary levels of dehydroepiandrosterone (DHEA) in the majority of patients. DHEA has minimal direct biologic activity, but is converted into active androgens in the periphery. Elevated plasma and urinary levels of cortisol are frequently seen. Elevated urinary levels of 17-ketosteroids, the breakdown product of both cortisol and androgens, can be found as well. It is rare to find elevated levels of aldosterone alone in adrenocortical cancers. It is more common to find a combination of increased hormone levels. Those tumors that have no hormonal activity usually present at a later, more advanced stage, are usually less differentiated, and portend a poor prognosis.

CT is the most useful radiographic test in the evaluation and diagnosis of adrenocortical cancer. Differentiation between a benign adrenal adenoma and a malignant adrenocortical neoplasm is described in the chapter on adrenal incidentaloma. In

general, the noncontrast-enhanced CT scan offers the best differentiation between benign and malignant masses. Unfortunately it is less than adequate in addressing issues of invasion or metastases. For this reason, most patients undergo contrast-enhanced CT scans. In this setting, delayed contrast-enhanced CT scans have been found to be almost as good as the nonenhanced scans.[6] In addition, invasion of surrounding structures including the ipsilateral kidney, diaphragm, liver, or major blood vessels can be identified, if present, and indicate the malignant nature of the mass as well as its potential for resection.

Staging of adrenocortical carcinoma is by the AJCC Staging System, similar to that utilized for other cancers (Table 20.1). This is important for prognosis since stage at initial operation has prognostic importance. Overall, 5 year survival rates are approximately 25-30%, and 10 year survival rates are around 10%. Approximately 70% of patients present with stage III or IV disease.[2,7]

Treatment

Once the diagnosis of adrenal cancer has been made, the only chance for cure is complete surgical resection. Unfortunately, because of the late diagnosis in many patients, many of these tumors have already metastasized, or have invaded contiguous structures, making complete resection impossible. If the patient has advanced local disease but no evidence of metastases, en bloc resection of invaded structures should still be undertaken, if it can be done safely, as resection of even advanced local disease can be curative.[7]

Prior to resection, all patients should have evaluation of the function of the opposite kidney, since resection of the ipsilateral kidney is not uncommonly required. Usually a normal serum creatinine and a good quality CT scan done with intravenous contrast is sufficient to confirm adequate contralateral kidney function. The abdominal CT scan can also demonstrate if there is direct invasion of surrounding structures and if there is tumor thrombus in the vena cava. While these are not necessarily contraindications to operation, it is important information to have preoperatively in order to make the appropriate plans for resection. Furthermore, the preoperative CT scan can show if there is metastatic disease in the liver or retroperitoneal nodes which are frequent sites of tumor spread. These findings would obviously preclude curative resection. A chest x-ray is usually adequate to evaluate the lungs, although a chest CT is clearly superior and should be done if there is any question of metastatic disease to the lungs.

Unless there is strong evidence to suggest that the adrenal mass is secondary to a metastases from another site, such as the lung, colon, or breast, needle biopsy to confirm the diagnosis of adrenocortical cancer should not be done. There is a chance that seeding of the needle tract may occur, precluding any chance at possible cure and the mass in all likelihood will require resection regardless of the biopsy result.

All patients should have some prophylaxis against thromboembolism, since patients undergoing resection of an adrenal cancer are at increased risk for pulmonary embolism. Preoperative preparation and perioperative management should include administration of hydrocortisone if the patient has any evidence of hyper-

Table 20.1. AJCC Staging for adrenocortical cancer

T1- < 5 cm, no local invasion
T2 - > 5 cm, no local invasion
T3 - Any size, local invasion into periadrenal fat
T4 - Any size, local invasion of adjacent organ or organs
N0 - No positive lymph nodes
N1 - Positive lymph nodes
M0 - No distant metastasis
M1 - Distant metastasis

STAGE
I - T1, N0, M0
II - T2, N0, M0
III - T1-2, N1, M0 or T3, N0, M0
IV - T3, N1, M0 or M1 or T4

cortisolism, as the remaining gland may be functionally suppressed. A mechanical bowel prep should be performed since the tumor may involve or invade the colon.

There are several approaches by which the adrenal gland can be removed. The appropriate approach for each individual patient should be based on a number of factors.[8] Foremost among these is that if an adrenal cancer is suspected either by the size of the tumor, evidence of direct local invasion, multiple hormone secretion, or radiographic characteristics, this gland should not be removed laparoscopically. While in the past, lesion size may have technically precluded laparoscopic resection of an adrenal cancer, size is no longer a limiting factor with newer laparoscopic techniques and more extensive experience. However, laparoscopy does not allow the adequacy of exposure, the completeness of lymph node dissection, and the necessary enbloc resection that make complete surgical excision possible. Since complete surgical resection is the best prognostic factor predicting long term survival and provides the only chance for cure, nothing should compromise its possibility.[2,7] Likewise, the question of port site recurrence remains real with laparoscopic adrenalectomy.

For much the same reasons that laparoscopic resection is not advocated, the posterior approach is also not a good alternative for the patient with a suspected adrenocortical cancer. The abdomen can not be adequately evaluated, resection of contiguous structures is difficult if not impossible, and complete surgical excision is usually not attainable. This approach has limited exposure and makes removal of lesions larger than 5-6 cm technically difficult if not impossible.

Transabdominal, flank, and thoracoabdominal approaches are all potentially acceptable methods based on location and size of the tumor, invasion of surrounding structures, the patient's body habitus, and finally surgeon preference. For small tumors on either side, a midline, flank, or subcostal incision can be used. The midline incision gives the surgeon more flexibility if unexpected findings are uncovered at the time of exploration. A thoracoabdominal approach is utilized on either side for extremely large tumors, or for tumors that have direct invasion into other struc-

tures, especially the diaphragm. The abdominal incision is usually made first in these patients in order to determine the necessity for extension into the chest.

If there is direct extension into the kidney, pancreas, spleen, liver or diaphragm, enbloc resection should still be undertaken, if possible, with either partial or total removal of the involved structure. In those patients who have tumor thrombus into the inferior vena cava, thrombectomy is necessary, often necessitating cardiopulmonary bypass.

There is no conclusive data to suggest that adjuvant chemo-or radiation therapy after complete resection is necessary. Some investigators have used mitotane (o,p'-DDD) preoperatively and feel there is some benefit, but this is far from proven. The role of chemo- and/or radiation therapy are unclear even in the incompletely resected patient. The main thrust of postoperative management is close follow-up. Common sites of recurrence include the lungs, liver, and adrenal bed. Annual chest x-ray, abdominal CT scan, and urinary steroid hormone measurement should be performed since complete resection of isolated recurrences may lead to long term survival. Patients who become symptomatic should have all of the above tests performed. If persistent or recurrent disease is not identified by then, positron emission tomography (PET) scanning may be helpful in identifying or ruling out adrenocortical cancer.

Palliative treatment of the patient with unresectable/metastatic disease is frequently directed at symptom control. Mitotane is one of the few effective chemotherapeutic agents for patients with adrenocortical cancer.[9] It can palliate the endocrine effects of the cancer and can provide great symptomatic relief for these patients because of its adrenolytic activity. It is commonly associated with gastrointestinal and neuromuscular side effects, which often limit its usefulness. Doxorubicin and newer agents such as suramin have been used with variable success. There is some evidence to suggest that tumor debulking may be beneficial in the patient with severe symptoms in order to make them more responsive to subsequent medical therapy.[10] Caution is warranted with this approach since the benefits are unproven and the risks or major morbidity with extensive resection are high.

The main role of radiation therapy is symptomatic relief of bone metastases. Some surgeons will use postoperative radiation of the adrenal bed after tumor resection, but the benefit of this is again unproven. There is an occasional role for radiation to the adrenal bed where a cancer has recurred and is unresectable. Unfortunately the use of radiation has not prolonged survival in these patients.

Summary

Adrenocortical carcinoma is a rare endocrine malignancy which presents with either symptoms of hormonal excess or abdominal discomfort. Evaluation is directed at both diagnosis and identification of the extent of disease both locally and distally. Hormonal studies are used to rule out pheochromocytoma and to identify excess steroid production which is important in the preoperative preparation of the patient. The only chance for cure is complete surgical resection. There is no good treatment

for unresectable or widely metastatic disease. Recurrent disease should be treated by resection, if all disease can be resected.

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CHAPTER 21

Adrenal Incidentaloma

Constantine V. Godellas

Introduction

Computerized tomography (CT) is frequently used to evaluate patients with abdominal complaints. With the high quality of current CT scanners, many unsuspected adrenal masses are identified during this process. These masses are commonly called adrenal incidentalomas. They have a prevalence of 0.3-5% in patients having CT scans for reasons other than adrenal pathology or metastatic work-up.[1-4] In patients undergoing CT scanning who do not have a history of malignancy and who do not have signs or symptoms to suggest adrenal hormone excess, the overwhelming majority of these incidentalomas will be benign, nonsecretory adrenal cortical adenomas.[1,2] There are some patients however who will have an unsuspected adrenocortical carcinoma.

The main dilemma posed by an adrenal incidentaloma is how to manage the patient with an identified mass but no history of malignancy, a normal physical examination, and no evidence of a biologically active tumor. While missing the diagnosis of a benign functional adrenal tumor can often be remedied at a later date with no untoward sequelae, missing an adrenocortical carcinoma may be deadly.

Diagnosis

Obtaining a thorough history and physical examination should be the first step in evaluating the patient found to have an adrenal incidentaloma. Functional tumors, primary adrenocortical cancers, or metastases to the adrenal gland can often be diagnosed on the basis of a detailed history and physical examination alone. Questions should therefore be directed to rule out these entities. The patients should be asked about excessive weakness, extremes of mood, or recent unexplained weight changes. Females should be asked about a deepening of their voice, recent growth of hair on their face, chest, or arms, or changes in menstruation. Likewise, males should be questioned about breast enlargement or impotence. All of these questions are directed at identifying benign or malignant functioning adrenocortical tumors that can secrete steroid hormones such as cortisone, aldosterone, or sex hormones. In addition, the presence of symptoms associated with a pheochromocytoma, such as hypertension, headache, diaphoresis, flushing, and palpitations should be sought.

Patients should also be questioned in depth about a history of prior malignancy, change in bowel habits, blood in the stool or urine, previous mole removal, and tobacco use. Positive answers to these questions might suggest that the mass may be secondary to a metastases, especially from a breast, lung, colon, melanoma, or renal

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cancer, and lead to further studies to determine the presence of a primary tumor or other metastatic disease.

On physical examination patients should be evaluated for hypertension, hirsutism, feminization, or evidence of Cushing's disease which would all point to a functioning adrenal tumor. Physical findings of a breast mass, adenopathy, or guaiac-positive stools might lead one to suspect a metastasis as the cause for the adrenal mass.

Laboratory studies are directed at ruling out a functional tumor and should include, at the minimum, a serum potassium level, a serum cortisol level, a 24 hour urine for 17-hydroxycorticosteroids and 17-ketosteroids, and a 24 hour urine for vanillylmandelic acid (VMA), catecholamines, and metanephrines. A low serum potassium level, especially in association with hypertension, in a patient not taking diuretics should lead to further specific studies to exclude or diagnose an aldosteronoma. Cushing's syndrome should be suspected with an increased serum cortisol level or an increased 24 hour urinary 17-hydroxycorticosteroid level. These findings should prompt use of low-dose and high-dose dexamethasone suppression tests to determine the presence of Cushing's syndrome and if Cushing's disease is the source. Elevated urinary levels of 17-ketosteroids suggest an adrenocortical malignancy. Increased urinary levels of VMA, catecholamines, and/or metanephrines, especially in the face of symptoms like hypertension, clearly indicate pheochromocytoma as the reason for the mass. Diagnosis and management of functional adrenal tumors and adrenocortical cancer are all reviewed in detail in other chapters and will not be further discussed here.

Additional radiographs should include a chest x-ray to rule out pulmonary pathology. The chest x-ray may demonstrate a primary lung cancer, which may have metastasized to the adrenal gland, or may demonstrate multiple metastases from another source (breast, colon, renal) which may also have metastasized to the adrenal gland. There is also the possibility that the chest x-ray may demonstrate a metastases from a primary adrenal gland carcinoma. In females, a mammogram may be necessary to rule out a primary breast cancer. Air contrast barium enema or colonoscopy may also be utilized in patients with guaiac positive stool to rule out a primary colon cancer.

Another diagnostic tool is CT- or ultrasound-guided fine needle aspiration (FNA). This is used in the patient with a presumed metastasis to the adrenal gland to confirm the diagnosis if there is any uncertainty. It is important that FNA be used selectively, however, since there are rare patients in whom an isolated adrenal metastasis should be treated with resection for possible cure. In this instance, needle biopsy is avoided because of the potential for seeding the needle tract with tumor. These patients should undergo an extensive work-up for other sites of metastases. Positron emission tomography (PET) scanning may be useful in this situation. There are reports of long-term survivors from resected solitary metastases to the adrenal gland in patients with colon and lung primaries. The most important first step in any patient scheduled for percutaneous needle aspiration is to biochemically rule out the presence of a pheochromocytoma. Disastrous complications, including death,

have occurred in patients with pheochromocytomas who underwent needle biopsy without appropriate prior alpha blockade.

Management

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The patient with an adrenal incidentaloma has presumably already had an abdominal CT scan. Many of these are performed with intravenous contrast. Several studies demonstrate, however, that an unenhanced CT scan is the best routine imaging modality to differentiate a benign adrenal mass from a malignant one. A benign adrenal mass on an unenhanced CT scan has a low attenuation reading (10 HU or <) whereas a malignant adrenal mass usually has a higher attenuation reading (> 30 HU).[5,6] Cystic lesions are sometimes difficult to interpret by CT alone and further studies, including needle aspiration may be useful. Aspiration of simple adrenal cysts may not only be diagnostic, but also therapeutic.

Over the past several years, magnetic resonance imaging (MRI) has been helpful in evaluating tumors smaller than 6 cm that are biochemically inactive. A T2-weighted image of an adrenal mass which is less in intensity than that of the liver or spleen is indicative of a benign adenoma. Unfortunately, the sensitivity and specificity of T2-weighted MRI in identifying a primary adrenal cancer or a metastasis are not high, and T2-weighted MRI has not lived up to its initial promise of delineating a benign tumor from a malignant one. Chemical-shift MRI has proved to be slightly more accurate with sensitivities and specificities in the 95-100% range.[7] Currently chemical-shift MRI appears to be the most sensitive and specific imaging modality for the differentiation of a benign from malignant adrenal mass, with the unenhanced CT scan being a close second.

Meta-iodobenzylguanidine (MIBG) scanning is useful in identifying the sites of primary or metastatic pheochromocytomas, but it has no role in differentiating a benign adrenocortical mass from a malignant one. Positron emission tomography (PET) scanning may be useful in ruling out metastasis as the cause of the adrenal mass, but its role in differentiating a benign adenoma from a primary malignancy is, as yet, unclear.

Treatment

Once a patient is truly deemed to have a nonfunctioning, adrenal incidentaloma, the size of the adrenal mass becomes the most important factor in determining whether surgery should be considered. In the past, most authors recommended 6 cm as the cutoff for observing adrenal incidentalomas. This size was chosen because several studies indicate that most adrenocortical cancers are greater than 6 cm.[8,9] The problem is that most patients cured of their adrenocortical cancer have tumors that are less than 6 cm. This makes sense since complete resection affords patients the best chance at long term cure, therefore the patient with a T1 lesion (< 5 cm) has the best chance for a five-year survival.[10]

It is known that benign adrenal adenomas increase in incidence with increasing age. While rare, adrenocortical cancer has a bimodal age distribution with the first peak prior to age 5, and the second peak between the ages of 40 and 50.[2,10] Those patients who present prior to 5 years of age usually present with virilization (> 90%)

while those patients in the second peak usually (about 70%) present with evidence of a functioning tumor. While most patients with adrenocortical cancer have some evidence of excess hormone secretion which would seem to aid in diagnosis, approximately 70% of these patients have advanced disease (stage III or IV) on presentation. Since benign tumors increase with age and cancers have a bimodal distribution, it can be assumed that a nonfunctioning adrenal mass, < 6 cm in a 70 year old patient is more likely to be a benign adenoma than an adrenocortical carcinoma. By the same token, a 4 cm, nonfunctioning mass in a 45 year old patient would be suspicious for carcinoma.

Until there is one test or series of tests which can truly delineate a benign adrenal adenoma from a carcinoma, there will always be variability in how physicians approach adrenal incidentalomas. It is generally agreed that the patient with a functioning adrenal neoplasm of any size should undergo resection. It is also fairly standard for the patient with an adrenal mass of greater than or equal to 6 cm to have that mass resected. The main controversy is in how to manage the patient who presents with an incidentaloma between 3-6 cm in size. There is still a fair amount of literature that suggests that patients with nonfunctioning tumors of less than 6 cm should be observed. While this is, in theory, a valid concept, most physicians currently use some modification of this approach. Additional imaging studies may be performed, including chemical-shift MRI, to better delineate the nature of the mass. For instance, younger patients with a 3 to 5 cm tumor and an unfavorable MRI should probably undergo an early operation. While the vast majority of these tumors will be benign, adrenalectomy can usually be performed safely, and in the long run the patient is spared the worry, expense, and time lost from repeated physician visits and imaging studies. More important, the patient discovered to have an early adrenocortical cancer can potentially be cured (Fig. 21.1)!

In those patients thought to have benign adenomas that are not resected, or in those patients who elect not to have surgery at an early date, unenhanced CT scans should be repeated at frequent intervals to check for enlargement of the mass. The first CT scan should be performed approximately 3 months after the initial scan, and subsequent scans should be performed at 3-6 month intervals for 18 months. At this point scans should be performed on a yearly basis. The patient should also be questioned thoroughly at each visit about any changes that might suggest that the incidentaloma is becoming functional. The patient should also undergo routine biochemical screening at least annually to include measurements of serum potassium and cortisol levels, and urine for 17-hydroxycorticosteroids and 17-ketosteroids, VMA, catecholamines, and metanephrines. If there is any change in the size and/or attenuation reading, or if the patient begins to have signs, symptoms, or biochemical evidence of a functioning tumor, adrenalectomy should be strongly considered.

The method of adrenalectomy is also somewhat controversial. Although not the focus of this chapter, the method of adrenalectomy is an important consideration in the patient with an adrenal incidentaloma. The ability of the surgeon to perform laparoscopic adrenalectomy should not lower the threshold for removing what is

truly considered a benign asymptomatic lesion. All patients are evaluated for operation in a similar manner, and the indications for surgery are as previously stated. It is at this point that the type of operation should be considered. Most masses less than 6 cm can be considered for laparoscopic adrenalectomy. As with all laparoscopic procedures, the need to convert to an open operation must always be taken into account. For patients with larger masses, the technical aspects and increased risk of malignancy make the laparoscopic approach less desirable, and these patients should be explored via a transabdominal approach.[11]

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CHAPTER 22

Pheochromocytoma

Michael J. Demeure

Introduction

Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from the adrenal medulla or extra-adrenal sympathetic ganglia (paragangliomas). Pheochromocytomas occur with a prevalence of approximately 1-2 per 100,000 adults.[1] They account for 0.1-1% of cases of hypertension.[2] The first report of a pheochromocytoma discovered at autopsy was by Fränkel in 1886.[3] The first successful removal of a pheochromocytoma was in 1926 by Cesar Roux in Lausanne, Switzerland.[4] Later the same year, C.H. Mayo performed the first successful excision of a pheochromocytoma in the United States.[5] In neither case was the diagnosis established before the operation. Kvale and colleagues established the modern standard for preoperative preparation of patients with pheochromocytomas allowing for safe surgical extirpation when they reported removal of 61 tumors from 51 patients without a death.[6]

In recent years, considerable progress has been made in the understanding and treatment of these tumors. While pheochromocytoma is ultimately a surgical disease, given the relative rarity of the condition and the fact that the median operative experience reported by graduating surgical chief residents in the United States each year is about one adrenalectomy,[7,8] a surgeon treating patients with pheochromocytomas face a particular challenge. The surgeon treating a patient with a pheochromocytoma must have a thorough understanding of the clinical syndrome and associated conditions, the diagnostic and radiological tests utilized and effective preoperative preparation before undertaking the operation to remove the tumor. In recent years, the repertoire of adrenalectomy operations has grown with the addition of laparoscopic techniques to the surgeons' armamentarium.

Genetics and Associated Conditions

Between 80-90% of pheochromocytomas are sporadic in origin. The remaining tumors occur as part of several clinical syndromes. Pheochromocytomas are a feature of the Multiple Endocrine Neoplasia (MEN) type 2 syndromes. MEN type 2a is an autosomal dominant hereditary syndrome composed of medullary thyroid cancer and pheochromocytoma. MEN type 2b adds the additional features of mucosal neuromas, intestinal ganglioneuromas, parathyroid hyperplasia and a characteristic Marfanoid habitus. While nearly all patients who inherit a MEN type 2 genetic mutation will develop medullary thyroid cancer, penetrance relative to pheochromocytoma is variable, ranging from about 10% to nearly all, dependent on the particular kindred. The overall prevalence is approximately 40%.[9] Genetic linkage

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studies have located the gene loci for MEN types 2a and 2b to chromosome 10. Subsequent studies have characterized genetic mutations in the *ret* protooncogene, part of the tyrosine kinase gene family.[10] For MEN type 2a, germline missense mutations have been found in one of eight codons within exons 10, 11, 13, 14, and 16 but within each kindred the mutation is the same allowing for relatively simple and reliable genetic screening once the index mutation is identified.[11] A mutation in exon 16 has been described among patients of the MEN type 2b kindreds.[12]

Other syndromes include pheochromocytomas in their constellations. Approximately 1% of patients with von Recklinghausen's neurofibromatosis has a pheochromocytoma whereas approximately 5% of patients with pheochromocytomas have neurofibromatosis.[13] Von Hippel-Lindau disease (retinal hemangiomatosis, cerebellar hemangioblastomas and renal abnormalities including hypernephromas) is caused by germline mutations of a tumor suppressor gene located on chromosome 3p25.[14] The incidence of pheochromocytomas is between 10-19% among patients with von Hippel-Lindau disease, but may vary greatly with the particular family transmission pattern so that pheochromocytomas may be expressed from not at all to greater than 90% of affected individuals.[15] Carney and colleagues reported a rare triad of extra-adrenal pheochromocytoma, gastric leiomyosarcoma and pulmonary chondroma.[16] Pheochromocytomas are also associated with tuberous sclerosis and the Sturge-Weber syndrome.

Clinical Presentation

Pheochromocytomas account for approximately 0.1-1% of hypertensive patients. While hypertension is the most common clinical feature of a pheochromocytoma, hypertension may be episodic in one third of patients and absent in one fifth.[17] In a hypertensive patient, the triad of paroxysms of headache, palpitations and sweating is classic but not diagnostic because the prevalence in this group of patients is only 5.9%.[18] The clinical picture, however, may be obscure. A significant proportion of patients may present with atypical symptoms including anxiety, tremulousness, abdominal pain and vomiting, weight loss, visual disturbances, shortness of breath or cardiac failure. The initial finding may be the consequence of hypertension such as a myocardial infarction or stroke.[19,20] For some patients with pure epinephrine-producing tumors the initial presentation may be hypotension or shock due to epinephrine-mediated peripheral vascular dilation.[21] Death from unsuspected pheochromocytomas is not uncommon. In a postmortem study of 62 patients who died of pheochromomcytomas from 1981-1989, 16 died during the perioperative period of unrelated procedures.[22] This series included 48 patients with benign pheochromocytomas and 14 who had malignant tumors.

Diagnosis

A pheochromocytoma should be considered when a patient's symptoms are suggestive and in particular when hypertension is episodic or difficult to control with medication. The differential diagnosis includes thyrotoxicosis, drug use, acute clonidine withdrawal, hypoglycemia, anxiety or panic attacks and cardiovascular deconditioning.[2] The diagnosis of pheochromocytoma is a biochemical one, based

on the demonstration of elevated levels of catecholamines or products of catecholamine metabolism. While the hypertension associated with pheochromocytomas is attributable to excess levels of circulating catecholamines and a resultant increase in peripheral vascular resistance, there is a poor correlation of the height of arterial pressures with plasma catecholamine concentrations.[23,24] This observation may be due to varying responses of the vascular system to secreted catecholamines owing to differences in the rate of catecholamine inactivation and metabolism, the extent and rate of catecholamine diffusion into target tissues or the reactivity of vascular smooth muscle.[25] Furthermore, pheochromocytomas may produce a wide repertoire of vasoactive hormones including dopa, vasoactive intestinal peptide, atrial natriuretic peptide, vasopressin and other peptides.[17,26]

The traditional diagnostic standard is a 24-hour collection of urine for determination of catecholamines, vanillylmandelic acid and metaphrine levels. Determination of urinary metanephrines is the single most sensitive assay[27] but combining the three studies raises the diagnostic accuracy to approximately 99%. Rarely are tumors missed by a combination of these measurements.[28] The tests may be rendered inaccurate by interfering substances including methylglucamine, a component of many iodine-base contrast mediums[1] or poor patient compliance. Overnight urinary measurement may simplify collection and enhance diagnostic accuracy. When compared to 24 h results in one study, overnight urinary norepinephrine levels provided a better diagnostic sensitivity and specificity (100% sensitivity and 98% specificity compared with 88% and 82%).[29] The authors claimed sleep urine samples simplify the collection protocol while avoiding the effects of stress and exercise. A single lab draw for measurement of plasma catecholamines offers convenience and may avoid the problems associated with urinary collections when screening patients for pheochromocytomas but these patients may have isolated plasma catecholamine concentrations that fall into the range seen for patients with essential hypertension yielding false-negative results.[23] The measurement of plasma levels of metanephrines has been suggested as a screening test citing enhanced sensitivity with a single determination.[30] In this study of 52 patients with pheochromocytomas, 67 normotensive patients and 51 patients with essential hypertension, no patient with a pheochromocytoma had normal plasma concentrations of both normetanephrine and metaphrine. In comparison, measurement of plasma catecholamines yielded false-negative results for eight patients (15%). Tests for urinary catecholamines alone had a sensitivity of 89%, or 5 false-negatives among the 52 patients. False positive elevations in serum and urinary catecholamine levels may be seen in acute alcohol or clonidine withdrawal, cocaine abuse, hypoglycemia, myocardial ischemia, stroke, severe congestive heart failure or treatment with certain vasoactive drugs such as hydralazine, minoxidil or dopamine.[17]

In some unusual cases, provocative testing may be necessary. Because provocative tests are considered dangerous, the use of agents such as histamine and tyramine has been abandoned in favor of glucagon.[23] A clonidine suppression test may be useful to distinguish the patient with a pheochromocytoma from the patient with essential hypertension and elevated catecholamine levels.[41] Two to three hours after clonidine administration, patients with essential hypertension should have a decrease

in resting catecholamine levels to less than 500 pg/ml. This test is based on the central α-agonist action of clonidine that normally decreases plasma catecholamines by reducing sympathetic tone.[32] Pheochromocytomas do not respond to a single dose of clonidine because they are not innervated and secrete catecholamines in an autonomous manner.

Chromogranin A is an acidic, monomeric protein that is stored and released with catecholamines from storage vesicles in the adrenal medulla. A serum chromogranin A level has been proposed as a diagnostic marker in the differential diagnosis of pheochromocytoma because it is not subject to drugs commonly used to treat hypertension including phentolamine and clonidine.[33] Hsiao and associates studied a series of 37 patients with pheochromocytoma, 67 normotensive healthy controls, 50 with essential hypertension, 24 with secondary hypertension and 5 with hypertension in whom a pheochromocytoma was excluded.[34] Measurement of supine serum chromogranin A level had a diagnostic sensitivity of 83% and a specificity of 96%. A major limitation of serum chromogranin A as a diagnostic test is that mild renal impairment (creatinine clearance rate less than 80 ml/min) may significantly increase levels of chromogranin A.[35]

Localization of Tumors

Once the diagnosis is established by clinical and biochemical means, the pheochromocytoma may be located by magnetic resonance imaging (MRI), computerized tomography (CT) or radionuclide scanning with ^{123}I-metaiodobenzylguanidine (MIBG). In Sweden where the reporting of all tumors has been compulsory since 1958, 22% of pheochromocytomas occur outside the adrenal medulla.[36] Reported extra-adrenal sites include the para-aortic region from the diaphragm to the inferior renal poles (organs of Zückerkandl), sympathetic ganglia, heart, bladder, distal ureter, ovary, broad ligament, vagina, prostate, spermatic cord, and anus.[37] At least 85% of extra-adrenal and 98% of all pheochromocytomas occur below the diaphragm.[38] The catecholamine profile may suggest the anatomic location. The adrenal medulla and organs of Zückerkandl possess phenyl-ethanolamine-N-methyl transferase, the enzyme that converts norepinephrine to epinephrine, but other extra-adrenal tissues lack the enzyme.[38] A urinary profile indicating high levels of epinephrine suggest, therefore, an adrenal pheochromocytoma but exceptions have been reported. Noreepinephrine secreting tumors may be either in the adrenal gland or in an extra-adrenal location.

MRI offers distinct advantages over CT in the imaging of pheochromocytomas. Like CT, MRI defines anatomic detail and assesses the liver and retroperitoneum for possible metastatic disease but unlike CT, MRI also provides functional confirmation. On T2 weighted imaging, pheochromocytomas characteristically show bright enhancement (Fig. 22.1). Due to this particular feature, MRI is highly accurate in differentiating pheochromocytomas among adrenal masses.[39,27] It is the author's belief, that MRI is more sensitive than CT for the detection of extra-adrenal pheochromocytomas, or paragangliomas, although perhaps radionuclide imaging is better suited for these tumors. MRI also offers the advantage over CT in that no iodine-containing contrast is administered which could provoke hypertension. Conversely,

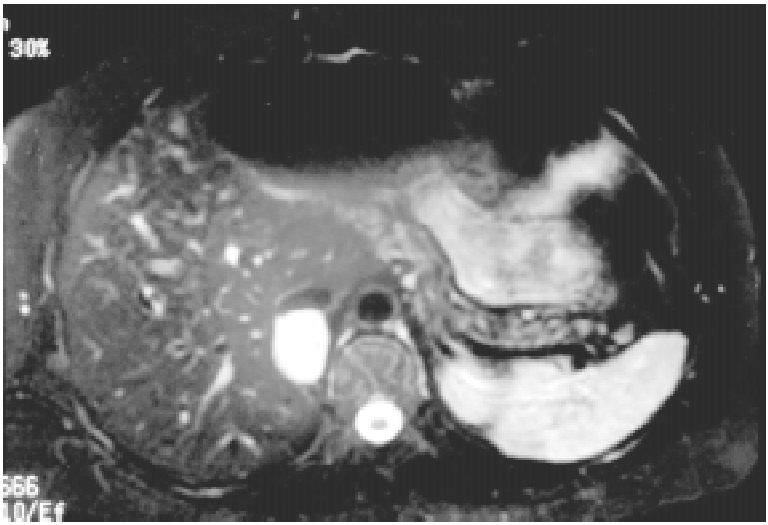

Fig. 22.1. This MRI shows a pheochromocytoma of the right adrenal gland with typical enhancement on T2 weighted imaging.

MRI may require sedation to manage claustrophobia caused by closed tube systems and tends to be more expensive.

Imaging with radionuclide analogues of catecholamine precursors such as ^{123}I-MIBG, provide functional as well as regional anatomic localization. As such radionuclide imaging is complimentary to CT or MRI. MIBG is taken up and concentrated in the pheochromocytomas, paragangliomas and their potential metastases, with 80-90% sensitivity.[32] Scanning may also be accomplished with ^{111}indium-labeled pentetreotide (Octreoscan™) which appears to have similar sensitivity to MIBG. The advantages of MIBG over Octreoscan™ include increased sensitivity for neuroblastoma (92% vs. 77%) and ganglioneuroma (100%), lack of renal accumulation which may obfuscate interpretation, and evaluation of MIBG avidity for potential subsequent therapeutic ablation of malignant disease.[40] One clinical setting for which radionuclide imaging with MIBG is particularly useful is when a pheochromocytoma cannot be located by CT or MRI. If a malignant pheochromocytoma is suspected, whole body imaging with MIBG may demonstrate metastatic disease in the lungs or bones. MIBG is also particularly useful if one is considering unilateral adrenalectomy in a patient with MEN type 2, to establish the lack of contralateral or extra-adrenal involvement. Arteriography and selective venous catheterization are rarely needed and should be done only after adequate adrenergic blockade. Selective venous catheterization for catecholamines may be useful to locate some extra-adrenal tumors.[41] Rare bladder pheochromocytomas may be seen by cystoscopy in 80% of such cases.[42]

Preoperative Management

In order to minimize the risk of a hypertensive crisis during an operation for pheochromocytoma, preoperative control of hypertension is essential. The author's preferred method to control blood pressure has been to administer an alpha-adrenergic blocking drug such as phenoxybenzamine or prazosin for 10-14 days before operation. Preparation generally begins with 10 milligrams of phenoxybenzamine twice daily. The dose is gradually increased to a target of 20 milligrams three times daily. Increasing the dose gradually helps minimize orthostatic hypotension and allows time for resolution of the contracted fluid state typical of these patients. The use of selective α_1 blocking agents such as prazosin, terazin or doxazosin instead of phenoxybenzamine for preoperative preparation has been reported with apparently good results.[17] Propranolol is added to the regimen if the patients have tachycardia only after adequate alpha-adrenergic blockade. Administration of beta-blocking agents without prior adequate alpha-blockade may precipitate pulmonary edema and shock.[43] Other preparative regimens have been reported based on metyrosine which is a synthetic blocking agent of tyrosine hydroxylase, the rate-controlling enzyme in the norepinephrine synthetic pathway. Criticisms of this regimen are that control of hypertension may not be adequate and hypertensive crisis during operation has been reported.

All patients should have a chest radiograph. The most common sites for metastases in malignant pheochromocytoma are the liver and lung. An electrocardiogram and an echocardiogram are necessary, as chronic catecholamine excess may have had deleterious effects on the heart resulting in a dilated cardiomyopathy. Preoperative complete blood count and assessment of electrolytes and clotting factors are routinely done.

Patients with pheochromocytomas are at risk for drastic fluctuations in blood pressure during induction of anesthesia, intubation or operative dissection of the tumor. Nitroprusside or phentolamine should also be readily available and administered as necessary to control hypertension. A short acting beta-blocker such as esmolol should be used to control tachycardia. Enflurane or isoflurane are considered the inhalational agents of choice because they do not sensitize the myocardium to catecholamines and may, therefore, reduce the risk of induced arrhythmia. Halothane, on the other hand, may sensitize the heart and increase the potential for arrhythmia.

Operations for Pheochromocytoma

The optimum route of operative approach for removal of a pheochromocytoma of the adrenal gland has been controversial. Standard textbooks in the past have favored a transabdominal approach citing as justification both an ectopic tumor rate of 10% and a rate of bilateral tumors of 10%. Most endocrine surgeons no longer subscribe to this philosophy. A better understanding of the disease process and the advent of improved localizing tests and operative techniques have lead to different approaches. For a patient who is not in a familial risk group, i.e., a patient with sporadic pheochromocytoma and a tumor localized to a single adrenal gland by MRI and radionuclide scanning, a unilateral approach is favored.[44] Unless a malignant tumor is suspected, given the advances in minimally invasive surgery, a

laparoscopic adrenalectomy is now recommended.[45-49] For patients with MEN2a or other familial syndromes, the matter is much more controversial and the decision must be based on factors including the individual patient's age, clinical presentation, family history, reliability and preferences. Because MRI and CT are useful but not infallible in the detection of liver and other metastases, the transabdominal approach is still favored for large adrenal or extra-adrenal pheochromocytomas that may be malignant (Fig. 22.2). Because about 10% of pheochromocytomas reside in an ectopic location, a thorough appreciation of potential anatomic variations is important. The adrenal glands reside in close proximity to the superior pole of each kidney. Each gland typically weighs about 4 grams. It has a golden yellow-brown appearance that is easily distinguishable from its enveloping fat. The right adrenal gland typically has a single short draining vein into the vena cava whereas the left adrenal vein enters the left renal vein. An accessory vein is not uncommon, particularly on the left side. The arterial supply is variable but generally composed of small vessels arising from the aorta, inferior phrenic arteries and the renal arteries. Common extra-adrenal sites for extra-adrenal pheochromocytomas include the organ of Zückerkandl, sympathetic ganglia, bronchi, renal hilum and urinary bladder.

Postoperative Care

Because patients may suffer hypotension after successful removal of a pheochromocytoma, blood pressure and urine output should be closely monitored. Hypotension should be treated initially with aggressive isotonic fluid administration rather than pressor agents. If hypotension persists, one should be sure there is no postoperative hemorrhage. Transient support with pressor agents is occasionally needed. Hypoglycemia may occur due to rebound hyperinsulinism after removal of the pheochromocytoma. Oral alimentation is resumed as soon as postoperative nausea has resolved, usually on the following day. Parental or oral pain medications are used as needed.

Pathology

The average weight of a pheochromocytoma is 100 grams but may range from 1 g to several kilograms.[50] The tumors may be encapsulated with fibrous septa, are highly vascular and feature a lobular pattern. A remnant of normal adrenal may be seen splayed over the adrenal tumor. The cut surface is light brown or gray with areas of necrosis, hemorrhage or cystic degeneration as typical features (Fig. 22.3). Microscopic examination shows chromaffin cells with basophilic cytoplasm and abundant secretory granules. Cellular and nuclear pleomorphism are commonly seen.[51] Histologic features such as the presence of mitotic figures or giant cells are not specific for malignancy.[52] Even apparent vascular invasion is not a criterion of malignancy due to the particular nature of the adrenal veins, the walls of which lack a continuous muscularis layer.[53,54] The diagnosis of malignancy can not be made on the basis of microscopic appearance alone.[50]

The utility of DNA ploidy analysis as a diagnostic aid is debated. A report from Native and associates showed that of 184 patients with pheochromocytomas, those with diploid DNA patterns inevitably were cured by adrenalectomy.[55] Both increased

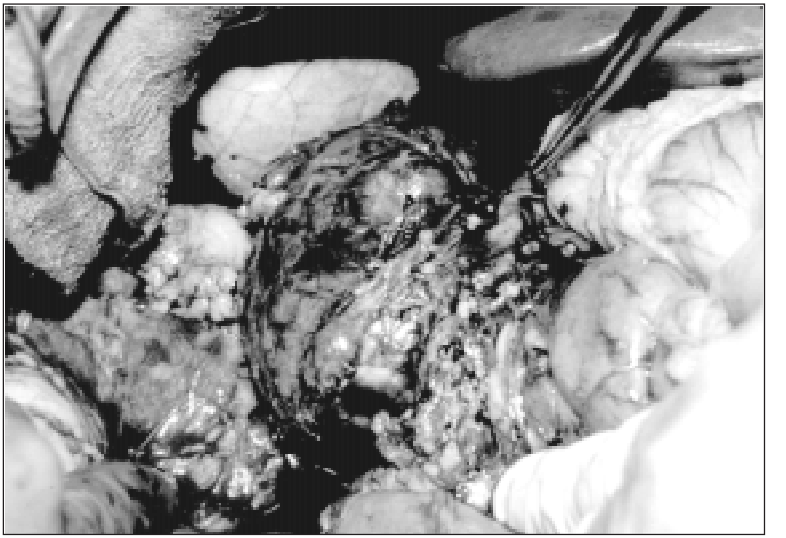

Fig. 22.2. A large malignant extra-adrenal pheochromocytoma in the preaortic region behind the head of the pancreas is depicted. It was invading the portal vein. A solitary metastasis was resected from the liver.

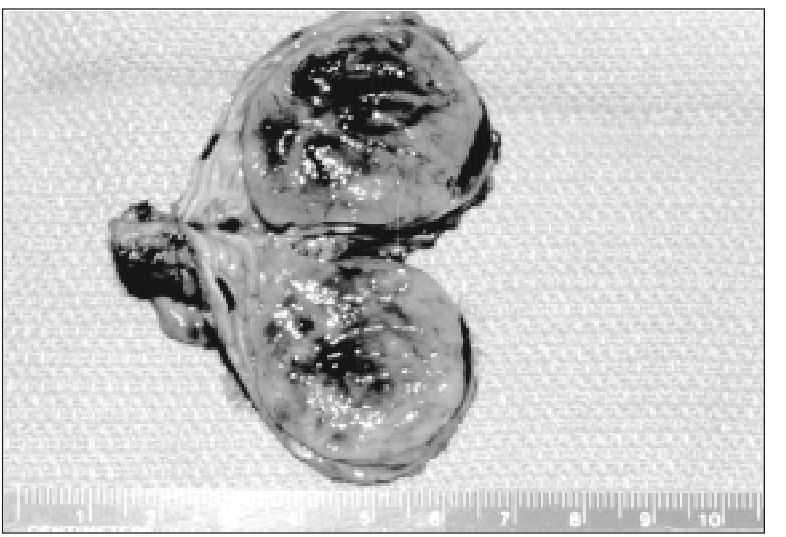

Fig. 22.3. Typical cut surface of an adrenal pheochromocytoma shows areas of necrosis, hemorrhage and cystic degeneration.

recurrence and death rates were observed for patients with nondiploid DNA patterns. Other have found discordant results citing patients whose tumors have had diploid DNA patterns yet have died as a result of recurrent malignant pheochromocytoma.[56] Review of the Medical College of Wisconsin experience with over 40 benign and malignant pheochromocytoma has found that although survival rates tend to be better for patients with diploid DNA, we too have had patients who died of malignant pheochromocytomas with diploid DNA patterns (unpublished data).

Postoperative and Long-Term Surveillance

Among those with preoperative hypertension, removal of a pheochromocytoma results in a normotensive state in 90% of patients with only 20% of these requiring medication.[57] Given the difficulty associated with distinguishing malignant from benign pheochromocytomas, long-term follow-up for all pheochromocytoma patients is recommended. A 24-hour urine collection for catecholamine assay should be done about 4-6 weeks after surgery and, if normal, yearly thereafter for at least five years. If malignancy is established based on operative or radiological findings, a MIBG scan serves to attest to the completeness of resection efforts.[58] Some have recommended life long monitoring because recurrences have been reported after twenty or more years.[52,59]

Malignant Pheochromocytomas

As previously stated the diagnosis of malignant pheochromocytoma may be difficult if not impossible on purely a clinical or histopathologic basis. There is no correlation between malignancy and histologic features including nuclear pleomorphism and the presence of giant cells or mitotic figures. Size is also not an absolute indicator of malignancy as malignant tumors may be less than the 6 cms or 100 milligram weight criteria cited by some authors.[52,60] It has been suggested that an increased proportion of extra-adrenal pheochromocytomas are malignant when compared to adrenal tumors (34.5 vs. 7.4%).[52] Regardless of the histologic criteria suggestive of malignancy, the diagnosis is only established based on the demonstration of metastatic disease in sites devoid of embryonic chromaffin tissue. The most common sites of metastases are the liver, lungs, lymph nodes, bone and brain. Some patients may have apparent clinical and biochemical cures for many years before recurrence.[60] Survival after the documentation of metastatic pheochromocytoma is typically less than 3 years.[61-63] The overall five-year survival rate is approximately 44%, but some patients may live for more than 20 years.[64]

Although no there are no randomized studies that demonstrate an improved survival from resection of metastatic disease, anecdotal evidence would suggest resection of limited metastatic disease in surgically accessible regions is warranted.[65] Surgical debulking of limited malignant disease can provide useful albeit temporary palliation, facilitate blood pressure control and perhaps an improvement of survival times.

The therapeutic use of radioactive MIBG therapy is conceptually attractive. The results, however, are difficult to evaluate because individual series with this relatively rare disease are inevitably small. A collected review of the literature cited 116 treated

cases selected on the basis of tracer uptake.[66] Initial symptomatic improvement was achieved in 76% of patients, tumor responses in 30% and hormonal responses in 45%. Five patients had complete tumor and hormonal responses, ranging from 16-58 months. Among 89 patients with follow-up data, 45% of the responders had relapsed with recurrent or progressive disease after a mean interval of 29.3 ± 31.1 months. Generally mild adverse effects were reported in 41% of the treated patients but one patient died from bone marrow aplasia. Although not a prospective randomized trial, this data suggests treatment with ^{131}I-MIBG may prolong survival for some patients and provide useful palliation for others. External beam irradiation may be useful to treat isolated bony metastases that tend not to respond to ^{131}I-MIBG. Results with chemotherapy are generally discouraging. At present the most favorable results are from a combination of cyclophosphamide, vincristine and dacarbazine, however experience is limited. [60,67] In a series of 14 patients, a complete response was seen in 14% and a partial response was seen in 43% for a mean duration of 21 months.[68] A biochemical response was seen in 79% of the patients. The regimen was associated with bone marrow toxicity and hypotension. Clinical relapses were not responsive to chemotherapy and ultimately resulted in the patients' demise.

Pregnancy

These catecholamine producing tumors are a rare cause of hypertension during pregnancy, with less than 200 cases reported in the literature. An unrecognized or untreated pheochromocytoma poses serious risks with maternal mortality in 17-48% and fetal demise in 26-54% of cases.[69,70] Mortality rates for both mother and fetus are markedly improved with early detection, pharmacological adrenergic blockade and elective removal of the adrenal tumors.[71,72]

Successful treatment of these patients requires the coordinated care of physicians of different specialties including obstetrics, endocrinology and surgery. The diagnosis can be made using measurement of urine catecholamine levels, as levels in pregnancy are the same as in the nonpregnant state. Pheochromocytomas are distinguishable from preeclampsia by a lack of proteinuria, lack of oliguria, and the absence of thrombocytopenia.[73] Once the diagnosis is established, pharmacological control of catecholamine effects should be immediately initiated until the tumor can be surgically removed. Phenoxybenzamine can be used safely during pregnancy for α-adrenergic blockade.[5] The drug should be started in low doses to prevent postural hypotension and doses gradually increased. Tumor localization can be accomplished with ultrasound and magnetic resonance imaging thereby avoiding the risks associated with radiation used for computerized tomography.[74] The use of MIBG imaging has not been tested in pregnancy but the molecule is small and, therefore, likely to cross the placental barrier so its use cannot be recommended during pregnancy.[75] The timing of surgical removal depends on the stage of pregnancy. If diagnosed late in the course of the pregnancy, removal of the tumor is delayed until immediately after delivery by Cesarean section, during the same anesthetic. Vaginal delivery is contraindicated. The ideal time to remove a pheochromocytoma diagnosed early in the pregnancy is during the beginning of the second trimester. Spontaneous abortion is less likely to occur and the gravid uterus is not yet large enough to impede

conduct of the adrenalectomy. Placement of the patient in the decubitus position favors venous return, as the uterus does not compress the vena cava as it would with the patient in the supine position. Some have debated the wisdom of adrenalectomy during pregnancy arguing that fetal mortality would be reduced if patients are managed with medications and close ambulatory monitoring with adrenalectomy being deferred until after delivery.[76]

Some have previously regarded pregnancy as a relative contraindication to laparoscopy due to possible deleterious effects of carbon dioxide peritoneal insufflation on the fetus. Limited animal studies using pregnant ewes suggest that although carbon dioxide pneumoperitoneum causes increased intrauterine pressure, decreased uterine blood flow and induces mild maternal and fetal acidosis, fetal blood gas tensions[77] and long-term fetal well being are not affected.[78] Reports now exist of successful laparoscopic cholecystectomy in pregnant women.[79] Gasless procedures using abdominal wall retractors may obviate concerns regarding the use of carbon dioxide pneumoperitoneum.[80] We recently reported what we believe to be the first laparoscopic removal of a pheochromocytoma in a pregnant woman.[81] The mother and infant are now doing well. A randomized study comparing the fetal risks of a traditional laparotomy to laparoscopic surgery has not been done and because of the rarity of the condition, is unlikely to be done.

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CHAPTER 23

Laparoscopic Adrenalectomy

Peter Y. Wong, Richard A. Prinz

Introduction

Laparoscopic adrenalectomy is a relatively new addition to the growing list of minimally invasive surgical procedures. This chapter will discuss the merits of open versus laparoscopic adrenalectomy, the indications for laparoscopic adrenalectomy, and three different techniques of laparoscopic adrenalectomy and their complications.

Open versus Laparoscopic Adrenalectomy

The adrenal glands are deep retroperitoneal organs. The choice among conventional open methods for adrenalectomy depends on the size, location, and etiology of the adrenal mass and the patient's body habitus and medical condition. The flank or posterior approach through the bed of the twelfth rib avoids transgression of the thoracic and peritoneal cavities. This minimizes postoperative pulmonary problems and paralytic ileus. It is suitable for removing normal sized or hyperplastic glands and tumors up to 5 cm in size.[1] However, exposure with the posterior approach is limited and intraabdominal exploration is precluded. Two separate incisions are required for bilateral adrenalectomy.

The anterior or transabdominal approach through a midline or upper abdominal transverse incision allows access to the entire peritoneal cavity. It is often used to perform bilateral adrenalectomy or to remove malignant pheochromocytomas. The anterior approach is associated with all the morbidity of a major laparotomy.

The lateral or transthoracic approach through the bed of the tenth or eleventh rib provides the best exposure and is well suited for tumors larger than 12 cm. The transthoracic approach carries the morbidity of a thoracotomy, allows for only limited abdominal exploration and only one adrenal gland can be removed unless the patient is repositioned for a second incision.[2]

With the advent of laparoscopic instruments and minimally invasive techniques, laparoscopic adrenalectomy has become possible. Gagner et al in 1992 published their method of laparoscopic adrenalectomy. It was quickly adopted by many surgeons and has proven useful for extirpating most benign adrenal lesions. Laparoscopic adrenalectomy is a relatively safe procedure. It has definite clinical advantages over open adrenalectomy. Laparoscopic and open adrenalectomy have been compared by our group and by other investigators (Table 23.1). The data clearly demonstrate that laparoscopic adrenalectomy decreases both postoperative length of hospital stay and requirements for parenteral pain relieving medications. Patients were discharged within 1-2 days after operation and returned to work and other normal activities earlier.[3] There is a learning curve for laparoscopic adrenalectomy, so the initial

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Table 23.1. Comparison of laparoscopic versus open adrenalectomy in terms of operative time, blood loss, length of hospital stay and pain relieving medication used.[3]

Type of Adrenalectomy	Operative Time (mins)	Blood Loss (ml)	Hospital Stay (days)	Demerol Used (mg)
Laparoscopic	212 ± 77	228 ± 66	2.1 ± 0.9	93 ± 74
Anterior open	174 ± 41	391 ± 88	6.4 ±1.5	1002 ± 540
Posterior open	139 ± 36	288 ± 118	5.5 ± 2.9	801 ± 588

* all data mean ± SEM

operating times are long but improve with experience. The mean operative time (Table 23.1) for laparoscopic adrenalectomy in our early reports was 212 ± 77 mins. More recent experience suggests that left and right laparoscopic adrenalectomy should take approximately 90-150 minutes. Laparoscopic adrenalectomy provides limited exploration of the abdomen compared to open transabdominal approaches. However, current preoperative adrenal imaging may be sufficiently accurate to eliminate the need for extensive exploration in most patients.[4]

Indications for Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy is well suited for removing benign disease of the adrenals such as cortical adenomas, pheochromocytomas, aldosteronomas, Cushing's disease and angiomyolipomas. We do not recommend laparoscopic adrenalectomy for adrenal masses greater than 6 cm in size because 80-90% of adrenocortical carcinomas are larger than this size.[5] Because of the possibility of port site seeding, laparoscopic adrenalectomy is inappropriate for any malignant lesion or any adrenal mass that appears to be malignant on CT or other imaging modalities. Lesions that are inhomogeneous with poorly defined margins and with degenerative signs such as necrosis or calcifications, or that have evidence of local or distant spread should not be removed laparoscopically (Fig. 23.1). Availability of laparoscopic adrenalectomy should not lower the threshold for removing an incidentally identified adrenal mass. The majority of these lesions are cortical adenomas that are small, benign and nonfunctional. They pose almost no harm to the patient, while general anesthesia and laparoscopic and possible open procedures do.

Techniques of Laparoscopic Adrenalectomy

Currently, there are three different approaches for laparoscopic adrenalectomy: the lateral or flank approach, the anterior approach, and the posterior retroperitoneal approach.

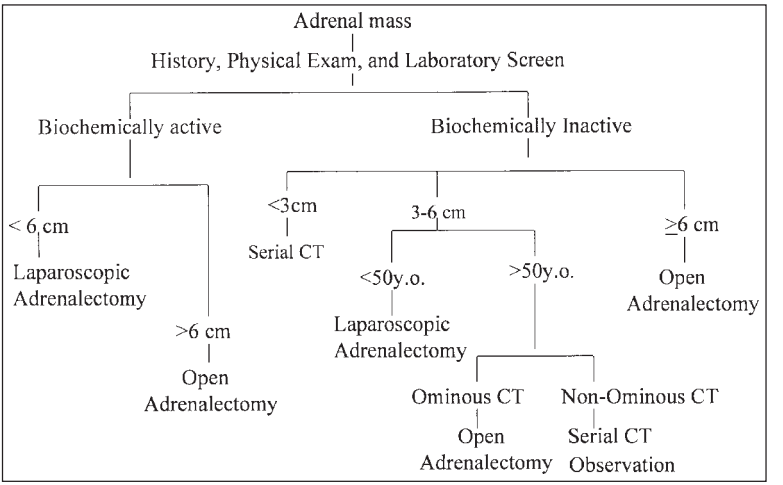

Fig. 23.1. An algorithmic approach to incidental discovered adrenal mass is shown based on function and size of the lesion.

The Lateral or Flank Approach

Left Lateral Transperitoneal Laparoscopic Adrenalectomy

As described by Gagner et al[6] (Fig. 23.2), the patient is positioned with the left side up in a lateral decubitus position for a left laparoscopic adrenalectomy. A Veress needle is inserted in the left subcostal area and the abdomen is inflated to 15 mmHg of pressure. A 10/11 mm trocar is introduced in the left subcostal area at the left anterior axillary line. A 10 mm, zero or 30˚ angle telescope is inserted into the port to visualize the insertion of other trocars. Three 10/11 mm trocars are inserted in the flank under direct vision via the telescope along a line under the twelfth rib. The patient should be in Fowler's position so that the bowel will migrate downward towards the pelvis and stay out of the area of dissection. The splenic flexure of the colon is mobilized by taking down the splenocolic ligament. The retroperitoneal space is opened between the spleen and the lateral abdominal wall. The spleen is then mobilized by dissecting its posterior attachments off the diaphragm. When the spleen is retracted medially the upper pole of the kidney is exposed and the left adrenal gland should be visible. The superior pole of the adrenal gland is mobilized and the inferior phrenic arterial branches are controlled with cautery or clips. The adrenal gland should be free once the inferior pole of the gland is dissected out and the left adrenal vein is ligated. Hemostasis is obtained and the adrenal gland is put into a plastic bag. The bag is removed from the most anterior trocar site since the abdominal wall is usually thinner there. The fascial defects at the port sites are closed with sutures, the skin incisions are closed and steri-strips are applied to the wounds.

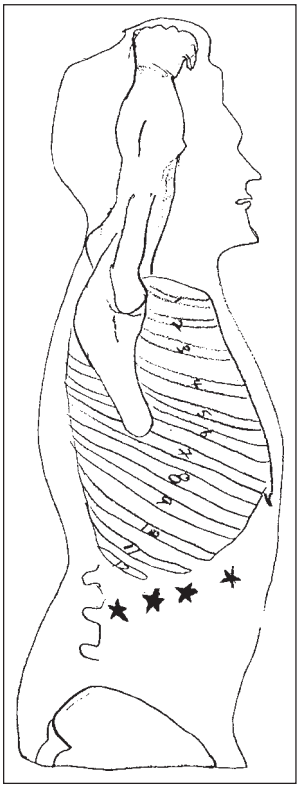

Fig. 23.2. Patient positioning and placement of laparoscopic trocar sites for the right lateral transperitoneal laparoscopic adrenalectomy approach are shown. Trocars are placed below the costal margin in the midclavicular and the anterior, mid- and posterior axillary lines.

The Right Lateral Transperitoneal Laparoscopic Adrenalectomy

As described by Gagner et al, the patient is placed in a lateral decubitus position with the right side up (Fig. 23.2). Pneumoperitoneum is obtained by inserting a Veress needle 2 cm below the right costal margin in the mid-clavicular line. Care is taken to avoid insufflating air into the liver by checking the Veress needle placement with standard laparoscopic techniques. Pneumoperitoneum to 15 mmHg is achieved. A 10/11 mm trocar is inserted in the right subcostal area at the right anterior axillary line. A 10 mm, zero or 30˚ telescope is again used to perform a diagnostic laparoscopy and to insert the other trocars under direct vision. Two more 11 mm trocars are inserted in the right flank area. The third trocar should not be placed until the retroperitoneal space is entered. The patient is then put into Fowler's position to cause the bowel to migrate downwards and away from the dissection. The right liver lobe is retracted superio-medially by using a fan or inflatable laparoscopic retractor. The hepatorenal ligament is incised to mobilize the superior pole of the right adrenal gland. The inferior vena cava must be identified early in the dissection and its position must always be kept in mind. The right adrenal vein empties directly into the cava. It is usually located at the superior medial aspect of the gland. It must be

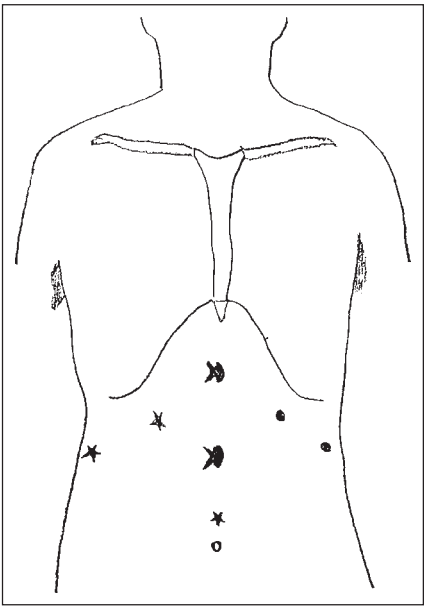

Fig. 23.3. Patient positioning and placement of laparoscopic trocar sites for the anterior laparoscopic adrenalectomy approach are shown. Trocars are placed above the naval, below the costal margin in the midclavicular and the anterior axillary line.

carefully ligated usually with clips so it can be safely transected, after it has been divided the remaining attachments are taken down to complete the dissection. The specimen is put into a plastic bag and removed through the anterior trocar site. The fascial defects and skin incisions are closed and steri-strips are applied to the wounds.

The Anterior Laparoscopic Approach

Under general endotracheal anesthesia, a urethral catheter and a nasogastric tube are inserted to decompress the bladder and stomach, respectively. The patient is placed in a semilateral position with the side of the diseased gland up (Fig. 23.3). A Veress needle is introduced above the umbilicus, and pneumoperitoneum is obtained up to 12-15 mmHg of pressure. A 10/11 mm trocar is introduced above the navel and a 10mm telescope is inserted into the peritoneal cavity. Under direct vision, two trocars are inserted subcostally, one at the anterior axillary line, and another at the midclavicular line. A fourth trocar can be used if necessary for retraction of other organs.

For a right anterior laparoscopic adrenalectomy, the liver is retracted upwards with a fan retractor, and the hepatocolic ligament is taken down. The duodenum is mobilized medially and Gerota's fascia is entered. Dissection is carried out at the upper pole of the right kidney to expose the adrenal gland. The inferior vena cava is dissected out and branches to the adrenal are clipped. The specimen is put into a plastic bag and removed through the umbilical incision.

For a left anterior laparoscopic adrenalectomy, the left colon is taken down and retracted medially by dividing the splenocolic ligament. Gerota's fascia is opened and the dissection is carried out at the upper pole of the left kidney. The adrenal

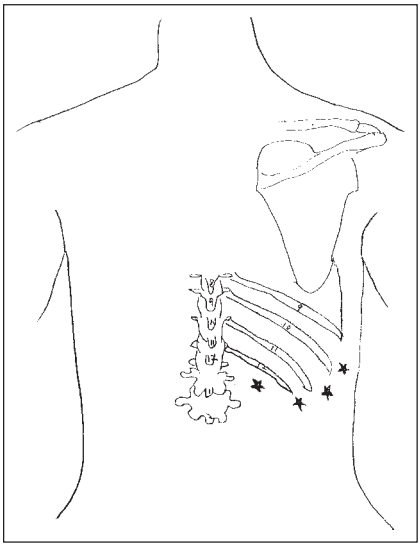

Fig. 23.4. Patient positioning and placement of laparoscopic trocar sites for the retroperitoneal laparoscopic adrenalectomy approach are shown. Trocars are placed in the back of the patient into the retroperitoneal space, lateral to the twelfth rib, between the ninth and tenth ribs, lateral to the eleventh rib and below the twelfth rib.

gland can be recognized by its orange yellow color. The left adrenal vein is located at the inferior aspect of the gland and must be securely clipped before being transected. The adrenal gland is removed within a plastic bag, which is then brought out through the umbilical port.

The Retroperitoneal Laparoscopic Approach

The patient is placed in a semi-jackknife prone position[8] (Fig. 23.4). The procedure is similar for both left and right retroperitoneal laparoscopic adrenalectomy. The surgeon stands on the right side for a right adrenalectomy and on the left for a left adrenalectomy. A balloon trocar is introduced into the retroperitoneal space 2.5 cm lateral to the twelfth rib. Using a pump, the balloon is insufflated 25-30 times. A laparoscope is inserted into the balloon trocar to examine the retroperitoneal space. The kidney, inferior vena cava, spleen or liver may be visible at this point. The balloon trocar is replaced by a standard 10mm trocar. The retroperitoneal space then is filled with carbon dioxide up to 12-15 mmHg of pressure, and the laparoscope is inserted through the trocar. Three more trocars are introduced into the retroperitoneal space under direct vision: one between the ninth and tenth ribs, a second 1 cm lateral to the eleventh rib, and a third just below the twelfth rib. The kidney is retracted downward with an atraumatic retractor placed through the port under the twelfth rib. The adrenal gland is mobilized using electrocautery and endoclips as necessary. The superior pole and anterior aspects are first dissected out for both left and right adrenalectomy. The inferior phrenic arterial branches are divided. Care should be taken during right adrenalectomy because the right adrenal vein empties directly into the inferior vena cava. The gland should be free after the main adrenal vein is ligated. The specimen is put into a plastic bag and removed

from one of the port sites. The fascial defects and skin incisions are closed and steristrips are applied over the wounds.

The flank, anterior and retroperitoneal laparoscopic approaches have all been used to successfully take out adrenal masses up to 6 cm in diameter. The choice of each laparoscopic approach is determined by the size of the adrenal mass, the patient's body habitus, history of previous abdominal surgeries and the preference and experience of the surgeon. The anterior transperitoneal approach allows one to inspect most of the abdominal cavity and provides wider exposure for removing relatively bigger glands, especially if the patient has a smaller body habitus. However, it requires more dissection and retraction when compared to the other two approaches. As in the flank approach, injury to the liver, spleen, pancreas, colon and vena cava are possible due to retraction and dissection mishaps. The posterior retroperitoneal approach allows one to perform a bilateral adrenalectomy without repositioning the patient. This method avoids adhesions from previous operations and other intraabdominal problems. However its working space is limited and may not provide the best exposure of the inferior vena cava for right adrenalectomy. Subcutaneous emphysema has been reported as a complication of retroperitoneal laparoscopic adrenalectomy.

Currently, we recommend the lateral or flank laparoscopic approach for these reasons:

a. The anatomy is more familiar,
b. It allows inspection of much of the abdominal cavity,
c. It provides wider exposure for removal of larger glands,
d. It involves less dissection and retraction than the anterior laparoscopic approach.

More study is needed to see whether the retroperitoneal approach has any clinically important advantages over the flank approach for laparoscopic adrenalectomy. Both methods will probably be used to manage particular problems posed by individual patients.

Summary

Since 1992, laparoscopic adrenalectomy has become the operation of choice for most benign functional and nonfunctional adrenal masses less than 6 cm in diameter. The advantages of laparoscopic adrenalectomy are better cosmesis; reduced operative blood loss; less postoperative pain; decreased length of hospital stay; and earlier return to work and normal activities. Due to the possibility of port site seeding and impaired likelihood of complete tumor removal, laparoscopic adrenalectomy should not be utilized for adrenal malignancies.

We recommend the lateral transperitoneal laparoscopic approach over the anterior and the retroperitoneal approaches because its anatomy is more familiar to most surgeons, intraabdominal inspection is possible, and wider exposure and less dissection is needed. Care must be taken when dissecting the right adrenal gland to avoid injury to the inferior vena cava. The adrenal gland should be removed completely

without violating its capsule and the specimen should always be placed in an endobag before extraction.

In conclusion, laparoscopic adrenalectomy is a safe and efficacious method for removing benign adrenal masses. Surgeons who perform adrenalectomy should be experienced both in open and laparoscopic approaches in order to provide the most appropriate procedure to deal with the particular problems of their individual patients.

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CHAPTER 24

Embryology, Anatomy and Physiology of Pancreas

Jacqueline L. Harrison, Edgar D. Staren, Richard A. Prinz

The pancreas is a complex organ with important endocrine and exocrine functions. Given the high prevalence of diabetes mellitus, virtually every physician will encounter patients who suffer from dysfunction of this gland. This chapter outlines the normal development, anatomy, and physiology of the pancreas so that its pathology may be better understood.

Embryology

The pancreas begins development at 5 weeks postfertilization as two endodermal growths arising from the distal part of the primitive foregut. The larger of these two growths, the dorsal pancreatic bud, eventually forms the majority of the pancreas. The ventral pancreatic bud arises close to the junction of the common bile duct with the duodenum. The mesentery at this point is still oriented in a sagittal plane, and the gut has not undergone rotation. As the duodenum rotates, the smaller ventral pancreatic bud is carried along dorsally and comes to rest posterior to the dorsal pancreatic bud. It eventually fuses with the dorsal bud to form the uncinate process and the caudal portion of the head of the pancreas (Fig. 24.1). When the two buds fuse, usually their ducts join as well. In 9% of the population, the fusion of the two ductal systems does not occur.

Annular pancreas is a rare anomaly in which a band of pancreatic tissue surrounds the second part of the duodenum. This can lead to intestinal obstruction in the newborn, or may go undetected unless inflammation or a neoplasm develops in this ring, and causes obstruction in the adult. Forty percent of infants with annular pancreas also have duodenal stenosis or atresia. The most commonly accepted explanation of this anomaly is growth of a bifid ventral pancreatic bud around the C-loop of the duodenum and fusion of this ventral bud with the dorsal bud, forming a thin ring of pancreatic tissue around the C-loop of the duodenum.

Anatomy

The pancreas is a retroperitoneal gland extending from the C-loop of the duodenum to the hilum of the spleen. It is usually 12-20 cm in length and weighs 75-125 g. The healthy pancreas is pinkish-tan and lobulated. It is divided into four parts, the head, neck, body, and tail. The head lies within the C-loop of the duodenum and overlies the common bile duct, inferior vena cava, right renal vessels, and left renal vein. A hook-like extension of the head called the uncinate process curves medially

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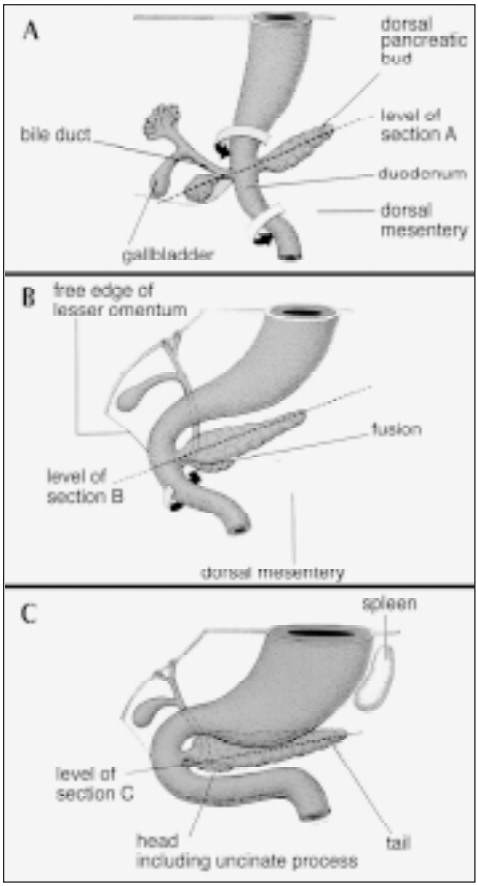

Fig. 24.1A-C. Depiction of the development of the pancreas during the fifth to eighth weeks. Reprinted with permission from Moore KL. The developing human clinically oriented embryology. Philadelphia: W.B. Saunders Company, 1988; 226.

to lie posterior to the superior mesenteric vessels. The neck is that portion overlying the superior mesenteric vessels. The superior mesenteric vein joins with the splenic vein posterior to the neck to form the portal vein. The posterior surface of the pancreatic body overlies the aorta and upper lumbar vertebrae, superior mesenteric artery, splenic vein, left adrenal gland, left kidney, and left renal vessels. The posterior wall of the stomach lies anterior to the pancreas. The vertebral column is located immediately posterior to the pancreas. This position makes the gland vulnerable to injury in cases of blunt epigastric trauma, when it can be compressed against the spine. The parenchyma and the duct may be interrupted as a result. The tail of the pancreas passes between the two layers of the lienorenal ligament along with the splenic artery and vein.

Beginning in the tail of the gland, the main pancreatic duct (duct of Wirsung) courses along near the posterior surface of the pancreas. In about 90% of the

population, it joins the duct draining the pancreatic head (duct of Santorini), and then empties into the medial side of the second portion of the duodenum (Fig. 24.2A-C). Usually the main pancreatic duct unites with the common bile duct in the duodenal wall to form a common channel which is called the ampulla of Vater. The ampulla empties into the duodenum at the major duodenal papilla. In about 9% of the population, the accessory pancreatic duct (duct of Santorini), which drains the head of the pancreas, empties separately into the duodenum via the minor duodenal papilla. It is located about 2 cm superior to the major duodenal papilla. The main duct diameter is normally 3-4 millimeters in the head, 2-3 millimeters in the body, and tapers to 1-2 millimeters in the tail. This diameter increases with aging, and may be up to 6 millimeters in the normal elderly patient.

Arterial Supply

The head of the pancreas is supplied from branches of both the celiac and superior mesenteric arteries. The gastroduodenal artery, which is the first major branch of the common hepatic artery, which in turn arises from the celiac axis, gives off a posterior and anterior superior pancreaticoduodenal artery. The anterior and posterior inferior pancreaticoduodenal arteries can arise separately or as a common channel from the superior mesenteric artery. The anterior and posterior superior pancreaticoduodenal arteries course along the anterior and posterior surfaces of the head of the pancreas and anastomose with the anterior and posterior inferior pancreaticoduodenal arteries to form the anterior and posterior pancreatic arcades (Fig. 24.3). The pancreatic head is supplied jointly with the C-loop of the duodenum by these vessels. Thus when the pancreatic head must be resected, the second portion of the duodenum must also be resected (pancreaticoduodenectomy or Whipple procedure).

The blood supply to the neck and body of the gland is provided by the dorsal pancreatic artery, which most often arises from the splenic artery, but may originate from the celiac, superior mesenteric, or common hepatic arteries. The dorsal pancreatic artery courses inferiorly along the dorsal surface of the gland to the lower pancreatic border, where it splits into left and right branches. The left branch is the transverse pancreatic artery, which runs along the inferior pancreas to anastomose with the pancreatica magna and caudal pancreatic arteries. The right division helps supply the head and uncinate process and its branches may anastomose with the superior pancreaticoduodenal or gastroduodenal arteries. The body and tail are supplied from primary branches off the splenic artery, which courses just cephalad to the gland. The largest of these branches is the pancreatica magna (great pancreatic) artery, which originates at the border of the body and tail of the gland. It divides into left and right branches which anastomose with the dorsal, caudal, and transverse pancreatic arteries.

Venous Drainage

Venous drainage is via the portal, splenic, superior mesenteric, and inferior mesenteric veins, but flow is predominantly through the splenic vein.

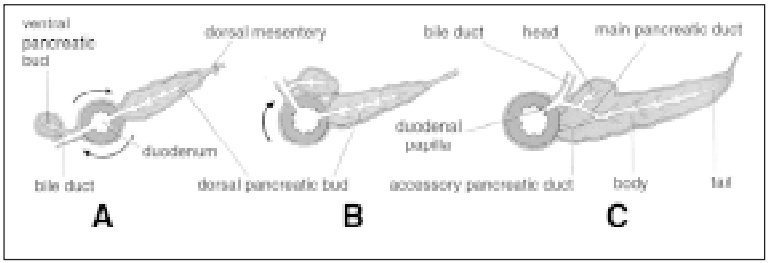

Fig. 24.2. A-C. Transverse sections through the duodenum and pancreatic buds. Rotation of the duodenum brings the ventral pancreatic bud toward the dorsal bud and they fuse. The duct of Wirsung is formed by the fusion of the distal dorsal pancreatic duct and the ventral pancreatic duct. An accessory duct is present if the proximal dorsal pancreatic duct does not degenerate. Reprinted with permission from Moore KL. The developing human clinically oriented embryology. Philadelphia: W.B. Saunders Company, 1988; 226.

Lymphatic Drainage

The lymphatics of the pancreas empty into the regional lymph nodes. The lymphatic drainage of the pancreatic head is primarily to the anterior and posterior pancreaticoduodenal nodes, with these nodes then draining predominantly to para-aortic nodes. There is some drainage to the thoracic duct, cisterna chyli, and lumbar lymphatic trunks. Lymphatics from the body and tail mainly drain to retroperitoneal nodes at the splenic hilum and superior body lymph nodes. Inferior head, inferior body, and para-aortic nodes also receive drainage from the body and tail of the gland (Fig. 24.3).

Innervation

The nerve supply to the pancreas is provided by the vagus and splanchnic nerves, extending from the celiac and superior mesenteric plexi. Sympathetic innervation arises from the greater, lesser, and lowest splanchnic nerves (preganglionic) that synapse at the celiac ganglion. Postganglionic branches then travel to the pancreas. These nerves are involved in pancreatic pain. Parasympathetic innervation is via the vagus and is exclusively efferent, and not involved with pancreatic pain.

Histology

Microscopically, the pancreas is made up of acini (Latin-clusters of grapes). Acini consist of clusters of pyramidal cells whose apices face a ductal lumen. Each acinus has 20-40 acinar cells. The acinar cells contain zymogen granules in their apical portions and are responsible for pancreatic enzyme secretion. The centroacinar cell is responsible for fluid and electrolyte secretion by the pancreas and is rich in carbonic anhydrase, an enzyme which catalyzes the production of bicarbonate from carbon dioxide and water. The ductal epithelial cells also contribute to bicarbonate and fluid secretion. The endocrine component of the pancreas, the islets of Langerhans,

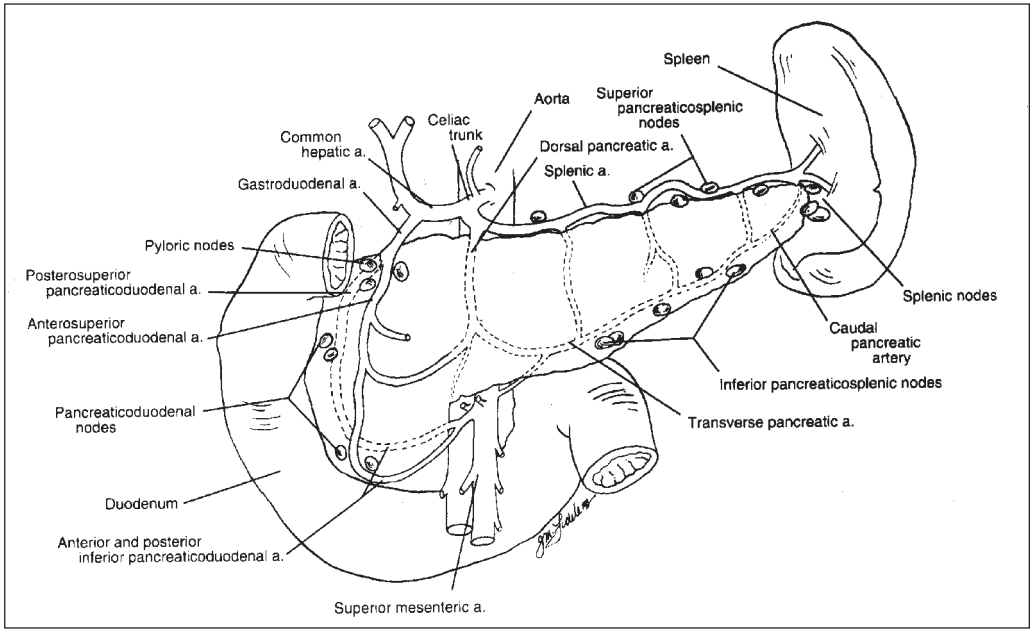

Fig. 24.3. Arterial supply and lymphatic drainage of the pancreas. Reprinted with permission from McHenry CR, Strain JW. Anatomy and embryology of the pancreas. In: Clark O, Duh Q, eds. Textbook of endocrine surgery. Philadelphia: W.B. Saunders Company, 1977; 552.

constitute only about 2% of the pancreatic mass. These islets consist of clusters of approximately 3,000 cells. Four cell types (A, B, D, and F or PP) constitute the islets. B cells are centrally located and make up about 70% of the islet cell mass. PP, A, and D cells make up approximately 15, 10, and 5% of the islet cell mass, respectively. B and D cells are scattered evenly throughout the pancreas, whereas A cells are predominantly found in the body and tail, and PP cells are concentrated in the uncinate process.

Small numbers of other cells secrete a variety of hormones such as vasoactive intestinal polypeptide, serotonin, and pancreastatin. Neural peptides such as neuropeptide Y and bombesin are also secreted by the pancreas.

Although only 2% of the pancreatic mass is endocrine tissue, 20-30% of the pancreatic blood supply perfuses these islets. Arterial blood flow perfuses the center of the islet first, where the B cells are located, and then flows to the periphery of the islet. In this way, the insulin concentration affects the release of hormones from the rest of the islet cells. The blood then continues on to perfuse the acinar cells. This islet acinar portal system is probably responsible for some endocrine regulation of exocrine activity and the local influence of insulin on glucagon secretion (Fig. 24.4).

Physiology

Exocrine

The pancreas secretes approximately 500-800 cc of exocrine fluid per day. Pancreatic juice is an iso-osmotic alkaline fluid (pH 7.6 to 9.0) containing a high concentration of bicarbonate and digestive enzymes. The major anions in this fluid are bicarbonate and chloride. Its cationic composition is close to plasma, with sodium and potassium concentrations totaling about 160 mmol/L. The bicarbonate and chloride concentrations vary inversely with each other, with chloride being the predominant anion in the basal secretory state (approximately 110 mmol/L), and bicarbonate becoming greater at higher flow rates (140 mmol/L at the maximal secretory rate). Intraductal bicarbonate undergoes passive exchange for interstitial chloride. At higher flow rates, there is less time for this exchange. Thus the intraductal bicarbonate concentration is higher at high flow rates. Bicarbonate secretion is stimulated by secretin, which is released when duodenal pH falls below 4.5. Cholecystokinin (CCK) is a weak stimulus of bicarbonate secretion, but potentiates secretin's stimulatory effect. Acetylcholine and gastrin are also weak stimuli for bicarbonate secretion.

Enzyme Secretion

Acinar cells secrete three major classes of enzymes: proteases, amylases, and lipases. The ratio of these enzymes within the pancreatic juice is variable and may change in response to nutrient intake. The major stimulant to enzyme secretion is cholecystokinin. Acetylcholine (i.e., vagal tone) is also a strong stimulus and potentiates CCK's effect. Secretin and vasoactive intestinal polypeptide (VIP) weakly provoke pancreatic enzyme secretion, but both potentiate the effect of cholecystokinin.

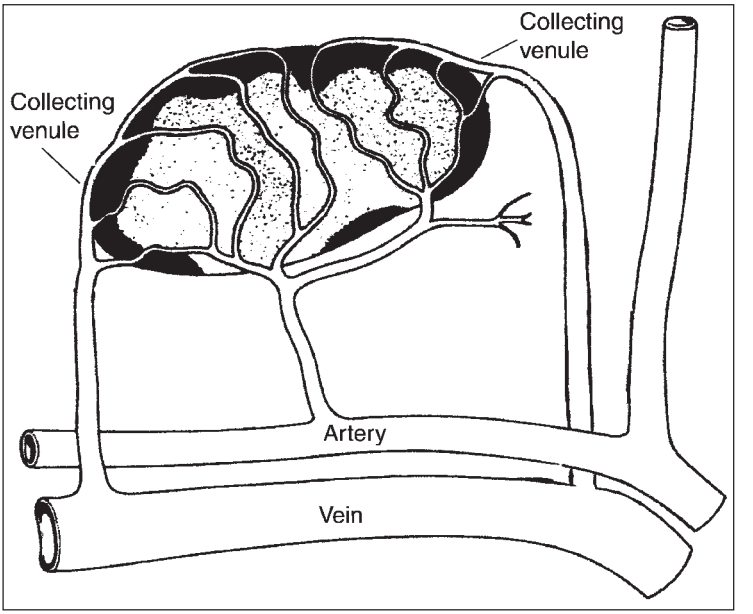

Fig. 24.4. The insulo-acinar portal system. The arteriole primarily supplies the centrally located beta cells. The nonbeta cells (black in this diagram) are then exposed to this blood via the collecting venules. In this way, insulin levels influence the secretion of the other pancreatic hormones.

Amylase is the only pancreatic enzyme that is secreted in its active form. The remaining enzymes are released as zymogens, many of which require enzymatic activation by trypsin. Trypsinogen is converted to trypsin, its active form, by a duodenal protease called enterokinase. It can also be activated by an acidic pH. Before release into the intestine, activation of trypsinogen is inhibited by an antiproteolytic enzyme secreted by acinar cells that specifically binds to trypsin. Activated trypsin in turn activates chymotrypsinogen, elastase, carboxypeptidase, and phospholipase. Many of the pancreatic enzymes require a neutral to alkaline pH for optimal function. In gastric hypersecretory states such as the Zollinger-Ellison syndrome, the resulting duodenal hyperacidity can lead to malabsorption because of inactivation of these enzymes.

Endocrine Function

Insulin

The pancreatic islets consist of 4 cell types, of which the majority (70%) are B cells (Table 24.1). B or beta cells secrete insulin. Insulin is a polypeptide synthesized in the endoplasmic reticulum as a single chain peptide called proinsulin. Cleavage of a connecting peptide, C-peptide, in the Golgi apparatus forms insulin, a peptide

Table 24.1. Islet cell hormones

Hormone	Islet Cell of Origin	Regulators of Secretion	Actions
Glucagon	A (Alpha)	Stimulated by catecholamines, hypoglycemia, arginine and alanine, cholecystokinin. Inhibited by hyperglycemia, insulin.	Increases blood glucose by stimulating hepatic glycogenolysis and gluconeogenesis. Relaxes smooth muscle of the stomach, duodenum, and sphincter of Oddi.
Insulin	B (Beta)	Stimulated by increases in blood glucose. Weakly stimulated by amino acids and fatty acids. Anabolic.	Acts on liver, muscle, and fat cells. Stimulates glucose uptake into cells. Stimulates glycogenesis, lipogenesis, and protein synthesis. Inhibits lipolysis.
Somatostatin	D (Delta)	Inhibited by insulin. Multiple inhibitory effects on other hormones. Suppresses release of gastrin, secretin, VIP, PP, gastric acid, pepsin, glucagon, and pancreatic enzymes.	Decreases gastric, intestinal, and biliary motility.
Pancreatic Polypeptide		PP or F Stimulated by oral protein ingestion, vagal tone, and hypoglycemia.	Inhibits pancreatic exocrine activity.

with a molecular weight of 5800 daltons consisting of A and B chains joined by two disulfide bonds. Rarely, synthesis and cleavage of insulin is defective, resulting in rare forms of diabetes mellitus. Secretion of insulin is stimulated predominantly by increases in blood glucose, and oral glucose stimulates insulin release to a greater extent than intravenously administered glucose. This phenomenon is due to enteric hormone secretion that potentiates the release of insulin. Glucagon and gastric inhibitory peptide appear to be the major regulators of this “enteroinsular axis”. Amino acids and fatty acids also stimulate insulin secretion, but to a lesser extent than hyperglycemia.

Insulin is released in a biphasic fashion. The first phase consists of secretion of stored insulin and lasts 4-6 minutes. The second phase is prolonged and consists of the release of insulin as it is synthesized. The plasma half life of insulin is 7-10 minutes and the hormone is primarily metabolized by the liver. In fact, 40-70% of

insulin secreted into the portal vein circulation is taken up by the liver in its first pass through that organ. Maximal insulin secretion is reached at glucose levels of 400-500 mg/dl.

The physiologic effect of insulin secretion by B cells is to reduce blood glucose concentration. Insulin causes glucose to be taken up in all cells except islet B cells, erythrocytes, hepatocytes, and cells in the central nervous system. In addition, insulin stimulates the production of glycogen, lipogenesis, and protein synthesis, and inhibits gluconeogenesis and lipolysis, all of which are anabolic effects.

Glucagon

Glucagon is a polypeptide hormone secreted by the A cells of the pancreas in response to hypoglycemia and increased circulating levels of catecholamines, amino acids such as alanine and arginine, and cholecystokinin. Its release is strongly inhibited by an increased blood glucose and by insulin. Glucagon is a counterregulatory hormone to insulin and many of its effects oppose those of insulin. It causes an increase in serum glucose by stimulating hepatic glycogenolysis and gluconeogenesis. In addition, it relaxes smooth muscle in the stomach, duodenum, and sphincter of Oddi. Along with cortisol, epinephrine, and growth hormone, it is a stress hormone, released in response to heightened physical demands on the body, as encountered with trauma, illness, or surgery. Overall, it has catabolic effects.

Somatostatin

Somatostatin is released by the D cells of the pancreas. Its secretion is inhibited by insulin. Its own effects are largely inhibitory. Secretion of somatostatin inhibits several other hormones and enzymes, including gastrin, secretin, VIP, pancreatic polypeptide, and pancreatic enzymes. In addition, it inhibits gastric, intestinal, and biliary motility. Clinical applications for these inhibitory effects are becoming more numerous, as somatostatin is used to treat or ameliorate the symptoms of pancreatic fistulae, dumping syndrome, and chronic pancreatitis.

Pancreatic Polypeptide

Synthesized and secreted by the PP or F cells of the pancreatic islets, its physiologic importance is unclear. Acetylcholine (vagal tone) is a major stimulus to its secretion, and it acts to decrease pancreatic exocrine secretion and gallbladder emptying. PP may play a part in glucose homeostasis, but how important this role is in the healthy individual is unclear.

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CHAPTER 25

Insulinoma

Geoffrey B. Thompson

Background

The first confirmation of insulin excess as a cause of hypoglycemia was made by Wilder et al in 1927 at the Mayo Clinic in a patient with a metastatic islet cell tumor. The tissue had been removed from the liver of a surgeon with metastatic islet cell cancer by Dr. W. J. Mayo. In 1929, Graham, in Toronto, successfully removed a benign insulinoma from the pancreas, resulting in cure.

Although insulinomas are the most common of the islet cell tumors, they remain a rarity, having an incidence in persons of northern European descent of four cases per 1 million patient-years. Sixty percent of patients are women with a median age at presentation of 47 years (range: 8-82 years). Virtually all tumors are intrapancreatic. Approximately 90% are solitary, 10% multiple, 6% malignant, and 8% belong to the Multiple Endocrine Neoplasia type I syndrome (MEN I). Eighty-eight percent are cured with initial surgery with normal long-term survival. Recurrence rates of 7% (sporadic) and 21% (MEN I) have been reported.[1]

Clinical Presentation[1]

Symptoms of hypoglycemia begin at plasma glucose levels of approximately 55 mg/dL and impairment of central nervous system (CNS) function at 50 mg/dL. The symptoms of hypoglycemia can be divided into two overlapping groups:

1. **autonomic** (sweating, trembling, anxiety, nausea, palpitations, hunger, and tingling) and, more specifically,
2. **neuroglycopenic** (confusion, dizziness, tiredness, headache, difficulty speaking and thinking, inability to concentrate, and weakness) (Table 25.1).

In a retrospective analysis of 60 insulinoma patients, 85% had various combinations of diplopia, blurred vision, sweating, palpitations, and weakness; 80% had confusion or abnormal behavior; 53% had amnesia or coma; and 12% had generalized seizures.

Although classically associated with fasting and exercise, symptoms can and do occur postprandially. Symptoms of hypoglycemia are nonspecific. Thus, a normal plasma glucose level obtained during symptoms helps to eliminate the possibility of a hypoglycemic disorder. Symptoms of hypoglycemia associated with plasma glucose levels less than 50 mg/dL, relieved by the correction of low glucose levels ("Whipple's triad"), prompts the need for further evaluation.

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Table 25.1. Insulinoma—signs and symptoms

Neuroglycopenic	Autonomic
confusion	sweating
abnormal behavior	trembling
dizziness	anxiety
headache	nausea
difficulty speaking	palpitations
inability to concentrate	hunger
weakness	tingling

Clinical Evaluation

Localizing studies should never be performed to establish the diagnosis of endogenous hyperinsulinism, as false positive and false negative studies occur not infrequently. Hyperinsulinism must be confirmed biochemically and factitious hypoglycemia (most often seen in female health care workers and patients with diabetic relatives) must be ruled out.

The supervised 72 hour fast is the basis for diagnosis.[1] Thirty-five percent of patients will have a positive fast within 12 hours, 75% within 24 hours, 92% within 48 hours, and 99% at 72 hours. A positive fast consists of: fasting hypoglycemia (plasma glucose ≤45 mg/dL), concomitant hyperinsulinemia (plasma insulin ≥ 6 μU/ml by RIA). Plasma C-peptide levels, measured by immunochemiluminometric (ICMA) assay, of ≥ 200 pmol/L and plasma proinsulin levels (ICMA) of ≥ 5 pmol/L, confirm the endogenous (versus factitious) nature of the hyperinsulinemia. Assays for both first and second generation sulfonylureas must be run on plasma obtained at the completion of the fast, thus ruling out a factitious cause in patients with elevations in both plasma insulin and C-peptide levels (Table 25.2).

Other useful measurements are the so-called "insulin surrogates" which can be measured quickly at the end of the fast and if positive, strongly suggest a hyperinsulinemic state. Plasma βOH butyrate levels tend to be especially low in insulinoma patients because of the antiketogenic effect of insulin (< 2.7 mmol/L). Likewise, the administration of 1 mg of intravenous glucagon will raise the plasma peak glucose level within 30 minutes at the end of the fast by ≥ 25 mg/dL. This is due to the glycogenic and antiglycogenolytic effects of insulin.

Occasionally, a witnessed hypoglycemic event may occur. If so, these end-of-fast (EOF) laboratory studies can be drawn immediately, and if confirmatory, the prolonged supervised fast can thus be avoided.

Localization[2-5]

Once the diagnosis is confirmed, reasonable attempts at preoperative localization should be undertaken, as it helps in planning surgery, educating the patient, and relieving anxiety. All insulinomas are intrapancreatic, 90% are solitary, and nearly all are demonstrable intraoperatively by an experienced surgeon aided by real-time ultrasonography. Eighty percent of insulinomas are less than 2 cm in diameter. Be

Table 25.2. Insulinoma—diagnostic criteria*

72-Hour Fast	
Neuroglycopenia	
Plasma glucose:	≤ 45 mg/dL
Plasma insulin (RIA):	≥ 6 μu/mL
Plasma C-peptide (ICMA):	≥ 200 pmole/L
Plasma proinsulin (ICMA):	≥ 5 pmole/L
Plasma sulfonylureas (1st and 2nd generation)	Negative
β-hydroxybutyrate:	< 2.7 mmole/L
Δ glucose with 1 mg IV glucagon:	≥ 25 mg/dL @ 30 minutes

*End of fast results

that as it may, insulinomas are equally distributed throughout the gland. The success rates of various localizing modalities are listed in Table 25.3.

Our preference at Mayo Clinic has been to obtain transabdominal real-time (7.5 and 10 MHz) ultrasonography in all patients with a confirmed diagnosis. When negative (40% of the time), helical computed tomography (CT) with triple-phase contrast enhancement is performed. Regardless of the results (positive or negative), surgical exploration follows in most instances. Other centers have gone exclusively to endoscopic ultrasonography with good reported results. Selective arterial calcium injection (SACI) with hepatic vein sampling (HVS) for insulin is highly accurate at regionalizing insulinomas (94%), documenting nesidioblastosis, and, on occasion, demonstrating an actual tumor blush (60-70%). The procedure is costly, invasive, and few radiologists do it well. It is probably best reserved for reoperations and in patients suspected of having nesidioblastosis.

Surgery[4]

Surgical removal of insulinoma(s) is the only curative form of treatment. Frequent meals, diazoxide, and calcium channel blockers offer limited palliation and are not without side effects and ongoing hypoglycemic episodes.

Laparotomy is performed via a transverse epigastric or upper midline incision. After thorough exploration for metastatic disease, the gastrocolic ligament is divided just outside the gastroepiploic arcade, entering the lesser sac. The duodenum is widely kocherized out to the ligament of Treitz. Mobilization of the hepatic flexure is also useful in exposing the uncinate process. The right gastroepiploic vessels are divided to facilitate complete exposure of the pancreatic head. The avascular plane, along the inferior border of the pancreatic body, is incised, allowing for bimanual and bidigital palpation of the body, proximal tail, neck, uncinate, and head of pancreas. If the insulinoma is not readily apparent, the spleen should be mobilized from its lateral attachments allowing for complete delivery of the body and tail for inspection and palpation. Exposure of the superior mesenteric vein and gastroduodenal artery serve as useful landmarks and reference points for intraoperative ultrasonography (IOUS). Whether the tumor is readily apparent or not, IOUS is performed to look for additional tumors or suspicious adenopathy, to assess the proximity of the

Table 25.3. Insulinoma—localizing studies

Localizing Study	Sensitivity
Transabdominal ultrasound	60%
Helical computed tomography (triple phase)	?
Endoscopic ultrasonography	57%
Selective arterial calcium injection with hepatic vein sampling for insulin	94%
Angiography	50%
Intraoperative real-time ultrasonography	90%
Somatostatin receptor scintigraphy	60%

insulinoma to the pancreatic and bile ducts and to examine the liver for possible metastases.[3] IOUS can also be utilized to needle localize and biopsy (FNA) suspicious pancreatic and liver lesions.

Enucleations can be safely performed in most instances and are the preferred operation for insulinomas located to the right of the superior mesenteric vein. Whipple operations are rarely necessary but can be carried out safely when necessary to avoid or treat major ductal injury. Tumors in the body, tail, and neck of the gland not amenable to enucleation or with resultant major ductal injury following enucleation can be treated by splenic-preserving distal pancreatectomy. Intravenous injection of 70-140 units of secretin will visibly demonstrate major ductal disruption following enucleation. Secretin will cause the pancreatic duct to dilate which will facilitate viewing its entire course with IOUS postenucleation. Major ductal injury can be treated with a tiny silastic stent, fine absorbable sutures, and external drainage, or more practically by internal drainage via a defunctionalized 45 cm Roux limb. Laparoscopic surgery for insulinoma has been carried out successfully in selected cases with the aid of laparoscopic ultrasound instrumentation.[6]

When no tumor is found, the operation should be terminated. There is no indication for "blind distal resection." Insulinomas are equally distributed throughout the gland, and most missed islet cell tumors are ultimately found in the head or uncinate. Reoperations following unsuccessful blind distal resections increase the risk of subsequent operative morbidity (fistulae, abscess, pseudocyst formation) and the risk of development of diabetes mellitus.[7] If completion pancreatectomy becomes necessary, cure will be insured, but premature deaths from the apancreatic state will also occur; thus the treatment becomes worse than the disease (Fig. 25.1).

Intraoperative Glucose Monitoring

We bring patients to the operating room fasting, off all glucose-containing fluids. During surgery, glucose levels are monitored continuously. Adequate levels are maintained with incremental intravenous doses of 50% dextrose. Typically, one sees a glucose rebound of ≥ 20 mg during the first 20 minutes following successful tumor removal. This result, however, may be delayed for up to several hours. False positive results can occur. Rebound hyperglycemia is expected and may last for several days.

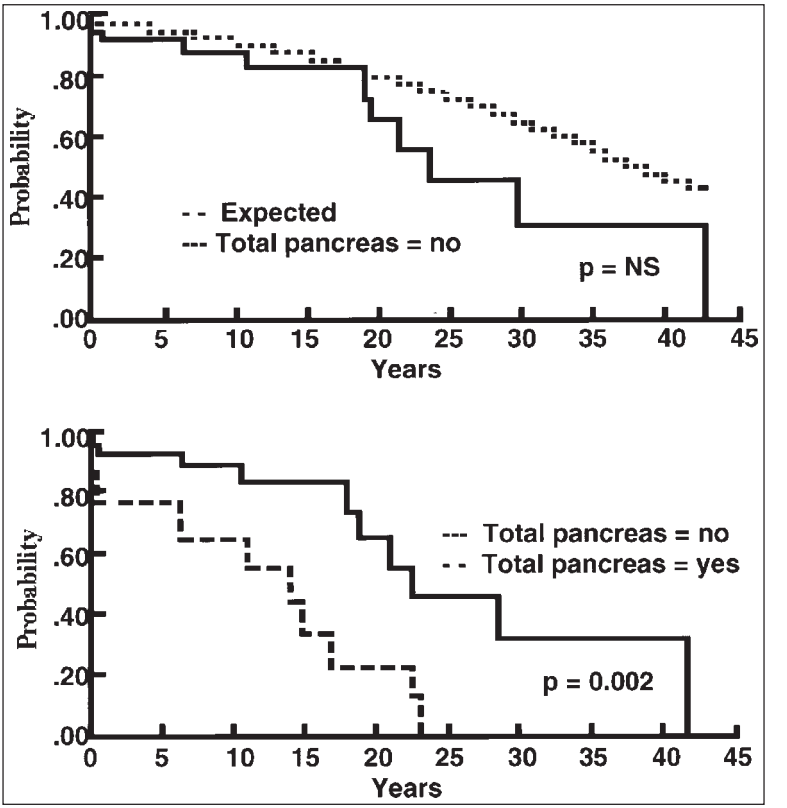

Fig. 25.1. A. Observed survival after reoperation among 30 patients not undergoing completion or total pancreatectomy was statistically similar to expected survival. B. Survival was statistically worse among those patients (n=9) undergoing completion or total pancreatectomy. (Thompson et al[7])

Insulin should not be administered unless plasma glucose levels exceed 250 mg/dL. One in seven patients will develop diabetes mellitus long term.

Results

Over 330 patients with insulinoma have been treated at Mayo Clinic since 1927. In a recent series of 119 patients treated surgically since the introduction of IOUS, only 3 failures have occurred.(CS Grant, unpublished data) In only one patient was no tumor found; the other two patients had diffuse disease associated with the MEN I syndrome and adult nesidioblastosis. These results do not justify routine use of hepatic vein insulin sampling. Overall operative morbidity was 21% with pancreatic

complications (fistulae, abscess, pseudocysts) occurring in 12%. Most complications are successfully managed nonoperatively with drainage.

MEN I Patients with Hyperinsulinism

Hyperinsulinism is second in frequency to Zollinger-Ellison syndrome in terms of functioning pancreatic islet cell syndromes in MEN I patients. Hyperinsulinism occurs in about 20% of MEN I patients. Because of the diffuse nature of the islet cell process in these patients (adenomatosis, dysplastic islets, nesidioblastosis), helical CT scanning is probably all that is needed to rule out obviously malignant tumors or metastases. An 80-85% distal subtotal pancreatectomy, with enucleation of additional remnant adenomas, is what is required to achieve long-term euglycemia in these patients.[8] The MEN I gene, termed MENIN, was identified by Chandrasekharappa et al at the National Institute of Health in 1997, utilizing positional cloning. Loss of heterozygosity at 11q13 is thought to be responsible for the loss of function leading to multiple endocrine tumors.[9] Routine genetic testing is not yet available since no major therapeutic implication exists for genetic screening in MEN I children. Ethical considerations must be considered before widespread testing is available.

Nesidioblastosis

Although rare and not infrequently found in the glands of asymptomatic patients, β-cell budding from exocrine ducts can be a cause of endogenous hyperinsulinism in adults. Confirmation may be provided by selective arterial calcium injection with hepatic vein sampling for insulin which will show an increase in insulin secretion with calcium administration in all of the arteries feeding the pancreas. Treatment consists of gradient-guided resection in selected individuals.

Malignant Insulinoma[10]

Insulin-producing islet cell carcinomas account for less than 10% of insulinomas. Prognosis is dependent on the stage of the disease. Patients with hepatic metastases fare worse than those with localized disease or regional lymphadenopathy. Formal pancreatic resection (distal pancreatectomy or Whipple procedures) along with extended regional lymphadenectomies are the procedures of choice for localized disease, and in some cases of advanced disease with uncontrolled hormonal sequelae. Solitary liver metastases should be treated with hepatic resection. Multiple liver metastases can be treated with surgical debulking, hepatic artery embolization, chemoembolization, cryotherapy, and thermal ablation techniques providing prolonged symptom relief and long-term survival in select patients. Many of these techniques can be performed percutaneously with minimal access techniques. Diazoxide has limited usefulness because of side effects, but the soon to be available longer-acting Sandostatin® analogue may provide more convenient symptom relief, without the need for multiple daily injections.

The Future

Triple-phase helical CT and endoscopic ultrasonography need to be evaluated at a multicenter level. These tests may prove to be the most sensitive preoperative

localizing studies available to date. Further understanding of the MEN I gene may better predict those patients at risk for islet cell neoplasia and carcinoma, justifying earlier screening and closer monitoring of those MEN I patients at risk. Reclassification of hyperinsulinemic hypoglycemic disorders has brought to our attention a subgroup of patients with postprandial symptomatology. It may be that some patients previously deemed "reactive" will benefit from HVS gradient-guided surgery. Further clarification is pending.

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CHAPTER 26

Gastrinoma

Craig A. Miller, E. Christopher Ellison

Introduction

The syndrome of gastrointestinal ulceration, gastric hypersecretion and diarrhea arising in the presence of a nonbeta islet cell tumor of the pancreas was first described by Zollinger and Ellison in 1955. In the years that followed, the cause of the syndrome was found to be hypersecretion of the peptide hormone gastrin from a neuroendocrine tumor. Over the past four decades the diagnosis and treatment of gastrinomas and the Zollinger-Ellison syndrome have evolved considerably, and study of the pathophysiology of hypersecreting gastrointestinal neuroendocrine tumors has contributed mightily to our understanding of the basic physiology of neuroendocrine control of gastrointestinal function.

Demographic and Pathologic Characteristics

Gastrinomas, the third most common of the gastrointestinal neuroendocrine tumors (after carcinoids and insulinomas), arise from pleuripotential cells of the APUD variety. Estimated annual incidence is 2 per million population. These tumors may appear at any age, but their incidence is greatest in those between 40 and 60 years old. The male:female ratio is 3:2. Gastrinomas occur predominantly in the pancreas and duodenum, and may appear sporadically (75%) or as part of the type I multiple endocrine neoplasia (MEN) syndrome (25%). Sporadic tumors are typically single, while those associated with MEN I are frequently multiple. One-half of gastrinomas are malignant, and early sites of metastasis include peripancreatic lymph nodes and the liver.

Clinical Presentation and Diagnosis

Signs and Symptoms

The early course of gastrinoma clinically resembles ordinary peptic ulcer disease. Abdominal pain is a common complaint. Diarrhea or steatorrhea may be present, owing primarily to gastric hypersecretion combined with inactivation of pancreatic enzymes by hydrochloric acid. Malnutrition and/or dehydration may be apparent on presentation secondary to gastrointestinal fluid losses and diarrhea. Occasionally, patients may present with serious complications of their ulcer diathesis such as bleeding or perforation.

Diagnosis

Several clinical scenarios should arouse suspicion of gastrinoma:

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1. ulcer recurrence or failure to heal despite appropriate medical and/or surgical therapy,
2. ulcer disease associated with diarrhea,
3. ulcer disease associated with hyperparathyroidism,
4. ulcers in atypical locations such as the jejunum and distal duodenum,
5. ulcer disease or unexplained refractory diarrhea in the pediatric or geriatric patient.

In these instances, fasting serum gastrin levels should be obtained initially. Typical levels on diagnosis are in excess of 1000 pg/ml (normal: < 150 pg/ml). However, normal or near-normal values do not exclude the diagnosis and, conversely, hypergastrinemia is not unequivocally diagnostic of gastrinoma. Several clinical situations may give rise to hypergastrinemia in the absence of gastrinoma, including renal failure, omeprazole therapy, atrophic gastritis with or without pernicious anemia and G-cell hyperplasia.

Gastric analysis may be of value. Basal acid output in gastrinoma is typically greater than 15meq/hr, while the ratio of basal to maximal output rarely exceeds 0.6, due to intense baseline stimulation of the parietal cells by high levels of circulating gastrin. The achlorhydria of atrophic gastritis may also be identified.

A secretin provocative test will distinguish patients with gastrinoma from those with other causes of hypergastrinemia. Two units per kilogram of secretin are administered intravenously, and serum gastrin levels obtained at baseline and at 2, 5, 10 15 and 30 minutes thereafter. An increase in gastrin concentration greater than 200 pg/ml is diagnostic of gastrinoma, since this is not seen in the other aforementioned causes of hypergastrinemia in the fasting state. All patients diagnosed with gastrinoma should subsequently undergo yearly evaluation for hyperparathyroidism to identify the presence of MEN.

Tumor Localization

After laboratory testing has established the diagnosis of gastrinoma, efforts should be made to localize the lesion(s) and detect the presence of metastatic disease. Hepatic metastases present at diagnosis portend a poor prognosis, and surgical exploration is unlikely to be of benefit in these patients. In the absence of metastatic disease, surgical resection for cure is possible.

At present, somatostatin receptor scintigraphy and abdominal computed tomography are effective and complementary methods for preoperative localization of gastrinoma and its metastases. Somatostatin receptor scanning, performed with an indium^{111}-labeled somatostatin analogue such as octreotide, accurately locates the primary tumor in 60-85% of cases, but is less helpful in identifying hepatic metastases (Fig. 26.1). CT scanning, however, provides an effective means of identifying metastatic disease in the liver. Recent experience suggests that magnetic resonance imaging may be even more sensitive than CT for detection of liver metastases, and it is reserved for situations in which the other imaging studies are unrevealing. In more difficult cases, selective visceral arterial secretin injection and peripheral or portal venous sampling for gastrin levels may help localize tumors. Endoscopic ultrasound has also been utilized with success.

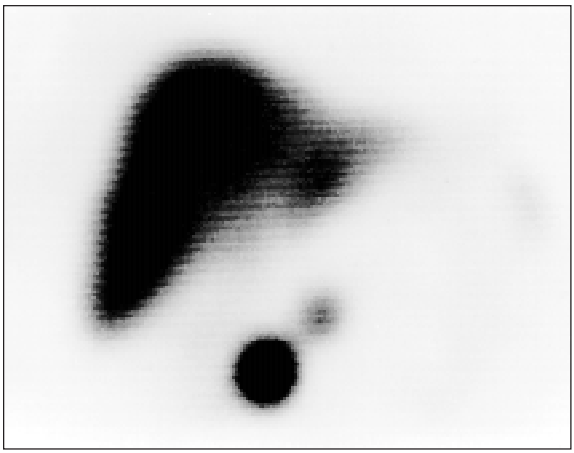

Fig. 26.1. Octreotide scan demonstrating hepatic metastases of a gastrinoma.

Treatment

The goals of treatment in the gastrinoma syndrome include:

1. control of gastric hypersecretion,
2. resection of the primary tumor and
3. management of metastatic disease. In recent years, the means of achieving each of these goals has undergone considerable evolution.

Control of Acid Secretion

Total gastrectomy was initially advocated by Zollinger and Ellison for control of the hypersecretion-associated peptic ulcer disease. This was effective, but the advent of histamine type 2 receptor blockers in the late 1970s called the necessity for this procedure into question. Currently, the proton pump inhibitor omeprazole is the pharmacologic agent of choice, with initial dosages in the range of 40-60 mg/day. Control of acid secretion is achieved in 90-95% of patients. Cost analysis studies have suggested that an antiulcer surgical procedure such as vagotomy may significantly reduce the dose of medication necessary for control of acid secretion and thus reduce expense, but this conclusion has not been universally accepted.

Management of Primary Tumor

In the absence of metastatic disease, all gastrinoma patients should undergo exploratory laparotomy even if preoperative localization studies are negative. The goal is resection of the primary tumor, which provides the best chance for cure. An exception is made in the case of MEN I, in which resectable gastrinoma disease is unusual and the results of surgery discouraging. In these cases surgery should be reserved for those with isolated lesions identified preoperatively.

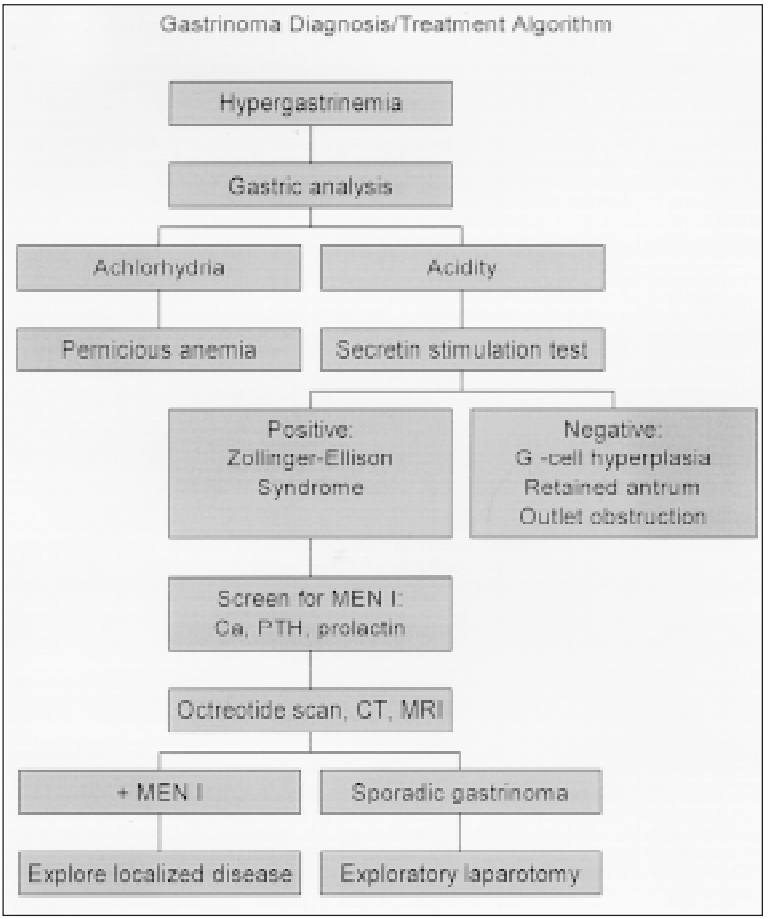

Fig. 26.2. An algorithm for the diagnosis and management of gastrinoma.

General exploration of the abdomen is performed, with special attention directed at inspection and palpation of the liver, pancreas, peripancreatic lymph nodes, splenic hilum and duodenum. Intraoperative endoscopy and duodenal transillumination may be useful in identifying small duodenal lesions. Intraoperative ultrasound may also be of value. Eighty per cent of identifiable gastrinomas will be found in the "gastrinoma triangle" (Fig. 26.2).

Identified tumors should be locally excised. Those found in the tail of the pancreas may be most expeditiously resected by means of distal pancreatectomy. Occasionally, gastrinomas in the head of the pancreas may require a Whipple resection for extirpation, although if gastric hypersecretion persists these patients are at considerable risk

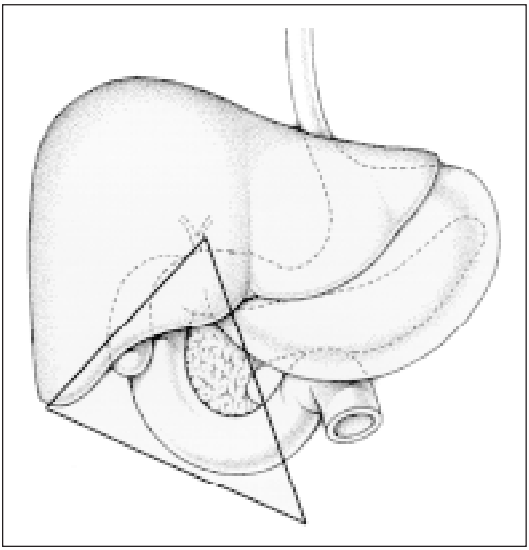

Fig. 26.3. The gastrinoma triangle.

for marginal ulceration. When no tumor is located an antiulcer procedure such as vagotomy and pyloroplasty or highly selective vagotomy is recommended, as this will reduce the medication requirements of these patients.

Although gastrinoma resection has resulted in eugastrinemia in only about 20% of patients treated at the Ohio State University, 10-year survival in patients with stage I disease improved from 78-96%, while that in stage II patients improved from 40-86%. Moreover, gastrinoma patients treated by medical means alone have been found to have a seven-fold increased risk of developing liver metastases when compared to those whose primary tumor was excised. These observations indicate routine exploratory laparotomy in surgically fit patients.

Management of Metastatic Disease

The treatment of gastrinoma which cannot be resected for cure is controversial, but there is agreement that two goals must be addressed: 1) the control of symptoms related to gastrin hypersecretion and 2) the prolongation of survival by destruction of tumor or the limitation of its growth. Surgical options in the face of metastatic disease include resection of hepatic metastases and cryoablation. Medical therapy includes both control of gastric hypersecretion by means detailed above and systemic chemotherapeutic and immunomodulatory regimens. Hepatic artery chemoembolization has also been utilized in the treatment of hepatic metastases of gastrinoma. The relative efficacy and propriety of these approaches is currently being evaluated.

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CHAPTER 27

Glucagonoma

Michael S. Sabel and Richard A. Prinz

While much less common than insulinomas or gastrinomas, glucagonomas are also neuroendocrine tumors that are associated with an extremely distinctive clinical syndrome. Glucagonomas are tumors that originate from the alpha cells of the pancreatic islets, which produce and secrete glucagon. The excess production of glucagon results in the characteristic glucagonoma syndrome, which includes diabetes, a unique rash, weight loss, anemia and thromboembolic problems. This distinctive syndrome was first described in 1942 by Becker et al, in a patient with a widespread rash, an 8-kg weight loss, an abnormal glucose tolerance test, and a large pancreatic islet cell tumor on autopsy.[1] It was not until 1959 however, when an assay that could measure circulating and tumor levels of glucagon was developed, that the connection between elevated glucagon levels and the clinical syndrome was made.

Despite important advances in biochemistry and molecular biology, many glucagonomas go undiagnosed. This is because the symptoms that make up the glucagonoma syndrome are relatively common and may easily be attributed to other causes. Glucagonomas themselves are very rare, with an incidence estimated to be between one in 20 million to one in 30 million. The peak incidence for development of the glucagonoma syndrome is between the 4th and 6th decade, with a mean age at diagnosis of approximately 55 years old. These tumors have been described in patients as young as 19 and as old as 84, but have not been reported in children. They are equally distributed between genders, with a possible slight predilection towards women.

Glucagonomas are usually slow-growing solitary tumors. Because alpha cells are more heavily concentrated in the islet cells of the body and tail of the pancreas, the majority of glucagonomas are located in these areas. They are found almost exclusively in the pancreas, although isolated reports describe neuroendocrine tumors in the kidney and duodenum that have produced the glucagonoma syndrome. Unlike insulinomas and gastrinomas, which are typically small tumors, glucagonomas are usually more than 3 cm in diameter at presentation and often much larger. Mean size at presentation is around 5-10 cm. As with most neuroendocrine tumors, glucagonomas show a wide variety of growth patterns. Thus, cellular and other histologic features may be worrisome, but are not sufficient to denote malignancy. Malignancy can only be diagnosed by the presence of local invasion or distant metastases. Approximately 70% of glucagonomas are malignant. The most common site of metastases is to the liver (50%), with the second most common site being the peripancreatic lymph nodes. Less commonly glucagonomas can spread to

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bone or the adrenal glands. They may also directly invade peripancreatic vessels or contiguous structures such as the spleen, stomach or transverse colon.

Presentation

To understand the symptoms of the glucagonoma syndrome (Table 27.1), it is crucial to understand the actions of glucagon. The excess of circulating glucagon directly or indirectly causes the symptoms associated with the glucagonoma syndrome. Glucagon is secreted from the alpha cells in the periphery of the islets of Langerhans primarily as a response to low glucose concentration. Other factors that can lead to the secretion of glucagon include stress, infection, surgery or exercise. The most important action of glucagon is to promote and sustain hepatic glucose output. After secretion from the pancreas it travels through the portal circulation to the liver where it is a potent activator of glycogenolysis and gluconeogenesis. Glucagon enhances postabsorptive glucose production, thereby increasing the plasma glucose concentration. Another intrahepatic action of glucagon is to direct incoming free fatty acids away from triglyceride synthesis and toward β-oxidation. Another function is to activate adipose tissue lipase, thereby increasing lipolysis, the delivery of free fatty acids to the liver, and ketogenesis. Glucagon plays an important counterregulatory role by promoting recovery from hypoglycemia. Other actions of glucagon include stimulation of insulin secretion, inhibition of gastric acid and pancreatic exocrine secretion, relaxation of the smooth muscle of the stomach and duodenum, induction of rapid transit through the small bowel and increased heart rate and contractility.

Diabetes

Since the primary function of glucagon is to increase blood sugar, it is not surprising that diabetes is an almost universal feature of the glucagonoma syndrome. Almost all patients with glucagonomas have either an elevated fasting blood sugar level or an abnormal glucose tolerance test. The diabetes associated with a glucagonoma appears to differ from the usual insulin dependent disease. It is generally milder, and patients are less prone to ketoacidosis or microvascular complications. The mildness is surprising given the high levels of glucagon found in these patients. There is little correlation between the severity of the diabetes and the level of circulating glucagon or the extent of the tumor.

Insulin levels may also be elevated. Because glucagonomas are slow-growing tumors, they usually cause a gradual increase in circulating glucagon levels. Augmented insulin production may be a counterregulating response to the elevated blood sugar caused by high glucagon levels.

Necrolytic Migratory Erythema

The most striking feature of the glucagonoma syndrome is its characteristic rash, known as necrolytic migratory erythema (NME). This is often the most troubling aspect of the syndrome for patients, and what prompts them to seek medical attention. NME in association with an elevated serum glucagon level is pathognomonic of the syndrome, and is seen in almost 3/4 of patients. The name accurately describes

Table 27.1. Features of the glucagonoma syndrome

Symptoms and Signs
NME (dermatitis, stomatitis, glossitis, nail dystrophy, vulvovaginitis)
Weight loss
Thromboembolic complications (DVT, PE)
Gastrointestinal complaints (diarrhea, constipation, abdominal pain)
Psychiatric disorders (depression, disorientation, nervousness)
Laboratory Findings
Diabetes or Glucose Intolerance
Anemia
Increased sedimentation rate
Panhypoaminoacidemia
Hyperglucagonemia

both the marked destruction of the epidermis and the tendency of the rash to heal in one area while developing in others. Lesions may occur anywhere, but the perineum, buttocks, groin, thighs, distal extremities, and perioral regions are most frequent. The rash also has a predilection for sites of friction, such as the intertriginous areas and sites of cutaneous trauma such as tight fitting garments and shoes. The rash characteristically waxes and wanes and is extremely pruritic. Secondary infections at the sites of excoriation can also occur.

Multiple factors have been implicated as the cause of NME, such as prostaglandins, low zinc levels and hypoaminoacidemia. While the exact cause of NME remains unclear, it is apparent that glucagon plays a key role. Treatment of the high glucagon levels either by surgical debulking or somatostatin therapy usually results in marked improvement in the rash by 48 hours and complete resolution within 7-10 days. Glucagon alone may not be the only cause of NME, since resolution of the rash does not always correlate with decreased plasma glucagon levels. In some patients, the rash clears with somatostatin therapy despite minor changes in the glucagon level. Regardless, the best therapy for the skin lesions is successful treatment of the tumor.

Other Symptoms

Weight loss without anorexia occurs in most patients with the glucagonoma syndrome. While the weight loss can occur from widespread tumor dissemination or from chronic illness, this is the cause in only a minority of patients. The weight loss is often prominent in patients with small tumors. Glucagon is extremely catabolic and weight loss may reflect a hormonal effect on carbohydrate, protein and fat metabolism.

An increased frequency of thromboembolic disease may occur in 30-50% of patients.[2] Although factor X is mainly produced by the liver, some is also synthesized by the alpha cells of the pancreas. It is elevated in the glucagonoma syndrome leading to hypercoagulability. Hence deep venous thromboses and pulmonary emboli are more common in patients with glucagonomas than in patients with other islet

cell tumors. Blood clots should be treated aggressively and DVT prophylaxis should be seriously considered prior to surgery. The bleeding times and coagulation studies are usually normal and cannot rule out a hypercoagulable state.

A normocytic, normochromic anemia is a common finding, with hemoglobin values between 8.5 and 10.5. Alterations in mental status, particularly depression, but also disorientation, insomnia and nervousness may be present. Various GI complaints have been described, the most common being diarrhea. This occurs in 15% of patients and may be due to the effect of glucagon on the small bowel mucosa. Early satiety and constipation are also sometimes seen, while abdominal pain, nausea and vomiting are less common.

Diagnosis

A glucagonoma should be suspected in patients with evidence of a pancreatic mass and a rash. It should also be considered in patients with a chronic unexplained dermatitis that is resistant to therapy. This is especially true if accompanied by glucose intolerance and/or thromboembolic phenomena. The various diagnostic tests for glucagonoma are listed in Table 27.2. The key to the diagnosis is the demonstration of an inappropriately elevated plasma glucagon level. Almost all patients will have basal concentrations well over the normal range of 25-250 pg/mL. Circulating levels can range from 300-96,000 pg/mL. A concentration above 1000 pg/mL can be considered solid biochemical evidence for a glucagonoma. The majority of patients will have levels this high at the time of diagnosis. Most of the remaining patients have levels of glucagon greater than 500 pg/ml. Glucagon can also be elevated in other disease processes, such as hepatic or renal insufficiency, pancreatitis, prolonged fasting, excessive exercise or stress, diabetic ketoacidosis, septicemia, or the use of danazol or oral contraceptives. In these conditions, the plasma glucagon level rarely rises above 500 pg/ml, and they can usually be excluded by a careful history.

In the rare situation that the glucagon level is not elevated to the levels greater than 500 pg/ml, but the patient's presentation is suggestive of glucagonoma, several other tests may provide additional information. In healthy people, an oral carbohydrate load increases serum glucose and suppresses plasma glucagon. A paradoxical rise in plasma glucagon is seen in many glucagonoma patients. Intravenous infusion of glucose has similar results. There are several agents that can be used for stimulation tests that may prove useful, although there is no standard. Intravenous secretin can produce a rise in plasma glucagon with a glucagonoma that normally does not occur. Intravenous arginine causes a small rise in glucagon levels in healthy people, but a large rise in patients with a glucagonoma. Intravenous tolbutamide normally suppresses glucagon but induces a rapid rise when given to a glucagonoma patient.

Localization

Once the diagnosis of glucagonoma is confirmed, the next step is to localize the tumor. Due to the larger size of the tumors at presentation, most are seen on standard radiologic studies. CT scan is the technique of choice both to localize the primary tumor and to demonstrate metastatic disease. Glucagonomas as small as 1 cm in diameter can be detected. It is rare that further studies will be necessary,

Table 27.2. Diagnostic tests for suspected glucagonoma

Laboratory Tests
CBC
Sedimentation rate
Protein, amino acid levels
Glucose tolerance test
Plasma glucagon level

Stimulation Tests (if glucagon level is not diagnostic)
Oral carbohydrate load
IV glucose, arginine, tolbutamide, or secretin

Localization Studies
CT
Somatostatin receptor scintigraphy
Endoscopic ultrasound
Selective angiography
Positron-emission tomography

however selective angiography has been successful in the rare case that the tumor has been missed by CT. Like other islet cell tumors, they are highly vascular and show up with a pronounced tumor blush. As the technology and widespread use of CT scanning has improved, the importance of angiography has been decreasing. Selective venous sampling can also localize tumors by identifying gradients of circulating glucagon levels. This procedure is invasive, expensive, requires special expertise and has morbidity associated with it, so its use is extremely limited.

Several newer methods for identifying neuroendocrine tumors may be employed in those rare cases where CT scan did not identify the tumor. Endoscopic ultrasound (EUS) of the pancreas allows detailed visualization of the entire gland, and can pick up abnormalities as small as 2-3mm.[3] Somatostatin receptor scintigraphy uses an indium labeled somatostatin analogue to identify glucagonomas, with a sensitivity of 100%.[4] Positron emission tomography (PET scan) is a noninvasive radiologic technique that uses bioactive substances labeled with short-lived positron emitting radionuclides. Preliminary results have been promising. SRS and PET scan may prove beneficial, but both are expensive and require further study.

Treatment

Surgery offers the only chance for cure, but it achieves this goal in only a minority of glucagonoma patients. The prognosis for patients with a glucagonoma is highly variable and depends on the size and spread of the tumor at the time of diagnosis, as well as the response to treatment which is not always uniform. Cure is sometimes possible in the presence of metastatic disease. There is a dramatic reversal of all clinical features after a curative intervention. Glucagon levels plummet and improvement in the rash can be seen within 24-48 hours. The rash resolves within 5-7 days, weight gain begins and the diabetes, anemia and hypoproteinemia reverses.[5]

Unfortunately 50-60% of patients will have metastatic disease at the time of diagnosis. Even if a cure is not feasible, aggressive surgical resection is indicated because of the debilitating effects of hyperglucagonemia. Glucagon-producing tumors are slow growing and hormonal effects may pose a greater danger than the tumor itself.

Perioperative management is particularly important in glucagonoma patients. Treatment begins with adequate preoperative preparation to control hyperglycemia and improve nutritional status. Oral protein supplementation may be beneficial, but must be used cautiously at first because they may act as a glucagon secretagogue. With severe weight loss, a period of intravenous hyperalimentation may reverse some of the tumor effects. These patients should have maximum DVT prophylaxis for any surgery. This includes subcutaneous heparin and sequential compression devises. Any postoperative thromboembolic complication should be aggressively treated with anticoagulation.

During surgery, a formal pancreatic resection consisting of a distal subtotal pancreatectomy is usually sufficient., since most tumors are in the body or tail. Enucleation is only acceptable if the tumor is clearly benign, which is unusual. As much tumor as safely possible should be removed, including nodal and hepatic metastases. This can be accomplished by wedge resection or formal hepatic resection if all gross tumor can be excised.

Chemotherapy

Because glucagonomas are frequently malignant and cannot be completely resected, many patients require chemotherapy. The two main chemotherapeutic agents used for glucagonoma include streptozotocin (STZ) and dacarbazine (DTIC). STZ has historically been the most commonly used agent. Because it has a glucose moiety, it is rapidly picked up by pancreatic islet cells. STZ however is nephrotoxic and hepatotoxic, and has severe nausea and vomiting. It may be used alone but is usually combined with 5-FU. DTIC has been reported to be the most effective therapy for advanced disease, and some consider it the drug of choice for malignant glucagonoma.[6] Its GI side effects are less severe than STZ, but it's bone marrow suppression is more common. With both drugs, one must be aware that patients may not respond and relapses may occur.

Interferon alpha has been used with some success in treating neuroendocrine tumors including glucagonoma. It acts by stimulating natural killer cell function and increasing expression of class I antigens on tumor cells. As tumor cells die, they are replaced by fibroblasts. This does not cause any change in tumor size, and thus is not recognized on CT scan. It is demonstrated on PET scanning, making this imaging technique more important in following patients on interferon therapy. While not curative, interferon alpha can be used alone or in combination with chemotherapeutic agents to control the disease for extended periods and prolong survival. It can also lead to a reduction in hormone synthesis and release within days to weeks of beginning treatment.

Somatostatin

Somatostatin is a naturally occurring hormone produced by the D cells of the islets of Langerhans and mucosa of the GI tract. It is a potent inhibitor of peptide release, and has been successfully used to control hormone secretion and clinical symptoms of glucagonomas, gastrinomas, vipomas, insulinomas, carcinoid and other neuroendocrine tumors. Octreotide is a long-acting analogue of somatostatin that can be self-administered subcutaneously. Octreotide has no reliable effect on tumor growth, but often induces a long-lasting remission of clinical symptoms. The most dramatic improvement is the rapid resolution of NME. The insulin requirements to control blood glucose may be reduced, but diabetes only rarely improves with somatostatin therapy. The hemoglobin concentration can also normalize with somatostatin analogue therapy. Side effects, including occasional abdominal pain, distension and diarrhea are uncommon and usually mild. Chronic administration of octreotide increases the incidence of gallstones. Surgeons should be cognizant of this side effect and consider removing the gallbladder when operating on patients who are likely to require long-term somatostatin analogue therapy.

Other Possibilities

Because of the frequency of hepatic metastases, the liver is an important target for locoregional intervention, especially when systemic therapy proves ineffective. Because liver metastases have a high degree of hypervascularity, various techniques have been used to interrupt their blood supply. These include surgical ligation and radiologic embolization of the hepatic arteries. The latter technique has been the most effective. The branches of the hepatic artery are selectively catheterized to gain proximity to the vessels supplying the tumor, which are then embolized. A 50% rate of partial response can be anticipated with the use of vascular occlusion therapy.[7] Improved results can be seen by combining hepatic artery occlusion with the intra-arterial infusion of chemotherapeutic agents. Chemoembolization is performed after intra-arterial infusions of a chemotherapeutic agent such as 5-FU.

Other therapeutic possibilities are being explored. Scintigraphy with radiolabeled octreotide has demonstrated the expression of a high number of somatostatin receptors on islet cell tumors. The therapeutic potential of radiolabeled Octreotide is currently being investigated. Other options for treating liver metastases include cryosurgery or percutaneous injection of ethanol. Orthotopic liver transplant has also been used to treat glucagonoma.[8]

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CHAPTER 28

VIPoma

Daniel J. Deziel

Introduction

The term VIPoma refers to a neuroendocrine tumor that secretes vasoactive intestinal polypeptide (VIP)—a neurotransmitter with a variety of target sites.[1] VIP secreting cells presumably originate from the neural crest and are found in the pancreatic islets, the adrenal medulla, peripheral and central neurons, and at other sites. Most VIPomas (90%) are pancreatic islet cell tumors. Extra pancreatic VIPomas occur predominately in the pediatric population. These tumors are often located in the mediastinum or retroperitoneum and are most frequently ganglioneuroblastomas or benign ganglioneuromas.

The term VIPoma syndrome designates a constellation of clinical symptoms and findings attributed primarily to over production of VIP.[2] This neoplastic syndrome has synonymously been known as the Verner-Morrison syndrome, the WDHA syndrome (watery diarrhea, hypokalemia, achlorhydria) and as pancreatic cholera. The VIPoma syndrome constitutes one of the four readily recognizable clinical syndromes associated with functioning islet cell tumors—the others being insulinoma, gastrinoma, and glucagonoma.[3,4] The clinical symptoms associated with somatostatinomas are more vague and less commonly appreciated as a distinct syndrome.

The term pseudo-VIPoma syndrome has been used to describe a clinical syndrome of chronic secretory diarrhea of unknown etiology. By definition these patients do not have elevated levels of VIP or other peptides. This situation is actually more common than the true VIPoma syndrome.

Current Concepts

VIP is a 28 amino acid peptide cleaved from a larger precursor molecule that is also parent to peptide histadine isoleucine (PHI) and peptide histadine methionine (PHM-27). The amino acid sequence of VIP is similar to that of a number of peptides including glucagon, secretin, PHI, PHM-27, growth hormone releasing factor, gastric inhibitory peptide, and others.

VIP is distributed widely throughout the central and peripheral nervous system and can be found in the nerves of many organ systems.[5,6] Under normal circumstances circulating levels of VIP are very low. VIP is not produced by pancreatic or gut mucosal cells. Therefore, it has been suggested that VIPomas are in fact paraneural neoplasms of neuroectodermal derivation.

VIP has a wide spectrum of actions (Table 28.1) that can influence the cardiovascular, respiratory, digestive, endocrine, neurologic, and immune systems. Targets

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Table 28.1. Actions of vasoactive intestinal polypeptide

Cardiovascular
*Vasodilation (peripheral, splanchnic, coronary, cerebral)
Hypotension
Inotropic

Respiratory
Bronchodilation
Augment ventilation
Pulmonary vasodilation
Stimulate bronchial secretion

Esophagus
Relax lower esophageal sphincter

Stomach
*Inhibit acid secretion
Relax fundic smooth muscle

Pancreas
*Stimulate water and bicarbonate secretion

Liver
Increase bile flow
Stimulate glycogenolysis

Gallbladder
Inhibit CCK contraction
Relax smooth muscle

Small Intestine and Colon
*Inhibit absorption
*Stimulate water and chloride secretion
Relax colonic smooth muscle

Kidney
Stimulate steriodogenesis

Endocrine
Pancreas:
release insulin, glucagon, somatostatin
Pituitary/Hypothalamus:
release prolactin, growth hormone, luteinizing hormone, inhibit somatostatin release
Adrenal:
stimulate steroidogenesis

Skeletal
Stimulate bone resorption

CNS
Excite cortical and spinal neurons
Hyperthermia
Stimulate glycogenolysis and glucose use
Hypnogenic
Antidiposgenic

Immune System
Inhibit mitogen induced T-lymphocyte transformation
Inhibit mast cell histamine release
Inhibit platelet aggregation and secretion
Stimulate immunoglobulin synthesis

*Actions responsible for primary clinical manifestations of VIPoma Syndrome.
Adapted from Roczen RL, Anderson DK. Gastrointestinal hormones in disease. Probl Gen Surg 1994; 11(1):36.

of VIP include smooth muscle, epithelial cells, exocrine and endocrine cells, osteoclasts, myocardium, T-lymphocytes, and neurons. The primary clinical manifestations of VIPoma are related to the effects of VIP on gastrointestinal fluid and electrolyte transport; namely:

1. stimulation of intestinal, pancreatic, and biliary water and electrolyte secretion,
2. inhibition of intestinal water and electrolyte absorption and
3. inhibition of gastric acid secretion.

Although overproduction of VIP is considered the primary cause of the VIPoma syndrome, other peptides are also produced by these tumors as demonstrated by biochemical and immunohistochemical studies.

Clinical Presentation

The characteristic clinical feature of VIPoma syndrome is profuse watery diarrhea caused by the intestinal effects of excess VIP.[1,5] This is a secretory diarrhea that persists despite fasting or nasogastric drainage. It is a large volume diarrhea typically in excess of 3 L/day. The diagnosis can essentially be excluded if stool volumes are less than 750 c.c./day. Malabsorption, steatorrhea, or hypermotility are not characteristics of this syndrome.

VIP stimulates secretion of potassium and bicarbonate and inhibits their absorption. As a consequence of these actions, large amounts of potassium (300-400 meq per day) and bicarbonate (stool pH 8.0) are lost in the stool leading to hypokalemia and acidosis. The large volume loss leads to dehydration and secondary hyperaldosteronism which further aggravates the potassium loss. The clinical manifestations of hypokalemia include muscle weakness, lethargy, and nausea. In the distal gut, chloride is absorbed in exchange for bicarbonate. Thus, patients develop a hyperchloremic, hypokalemic metabolic acidosis. The dehydration and electrolyte disturbances can be severe and life threatening.

Since VIP inhibits gastric acid secretion, most patients (70%) are hypochlorhydric and some may be achlorhydric. Hypercalcemia is seen in about one half of patients due to the osteolytic effects of VIP or due to hyperparathyroidism in patients with MEN-I syndrome. Glucose intolerance and hyperglycemia can occur as VIP promotes hepatic glycogenolysis. Tetany has also been observed and attributed to hypomagnesemia. About 20% of patients may have cutaneous flushing or a rash caused by VIP induced vasodilation. Episodic hypotension may occur in some patients. In children with neurogenic tumors, an abdominal mass may be present.

As previously noted, pancreatic VIPomas predominate in adults while extra pancreatic sites (adrenal, retroperitoneum, mediastinum) are typical in children. The mean age of diagnosed patients is 47 years and nearly two-thirds of these tumors occur in women. About 5% of VIPomas are associated with the MEN-I syndrome.

Diagnosis

The diagnostic strategy in a patient with VIPoma syndrome is to :

1. confirm the secretory nature of the diarrhea,
2. eliminate other causes of secretory diarrhea and
3. document elevated levels of VIP or other mediators. Once a biochemical diagnosis is established, imaging studies are obtained to localize the tumor.

Secretory diarrhea can be diagnosed by its persistence during a 48-72 hour trial of fasting. Measurement of fecal electrolytes should demonstrate isotonicity (i.e., 2 $[Na^+]+ [K^+]$). Exclusion of infectious causes requires stool examination for white cells, enteric bacterial pathogens, ova and parasites, and assay for *Clostridium difficile* toxin. Tests to identify other causes of secretory diarrhea are outlined in Table 28.2.

Table 28.2. Differential diagnosis of secretory diarrhea

- **Infectious Disease**
  stool culture and WBC
  stool ova and parasites
  Clostridium difficile toxin
- **Inflammatory bowel disease**
  LGI endoscopy
  UGI and SBFT
- **Celiac Disease**
  fecal fat measurement
  D-xylose tolerance test
  small bowel biopsy
- **Laxative Abuse**
  stool exam for phenolphthalein
- **Collagen Vascular Disease**
  serologic studies
  endoscopy and biopsy
- **Villous Adenoma**
  LGI endoscopy
  LGI contrast x-ray
- **Intestinal Lymphoma**
  CT scan
  UGI and SBFT
- **Carcinoid Syndrome**
  urinary 5'HIAA
  serum serotonin
  CT scan
  UGI and SBFT
- **Gastrinoma**
  serum gastrin
  secretin stimulation test
  gastric acid analysis
- **Medullary thyroid cancer**
  serum calcitonin
- **VIPoma**
  serum VIP
- **Pseudo-VIPoma**

Once secretory diarrhea is diagnosed and infectious causes are excluded, serum levels of various peptides are determined by radioimmunoassay. VIPomas are characterized primarily by elevations of VIP but multiple measurable peptides may be produced. Since VIP elevations may be intermittent, it may be necessary to obtain multiple fasting levels. VIP levels typically exceed 200 pg/mL. Pancreatic polypeptide, a nonspecific marker for islet cell tumors, may be elevated in about one half of patients. Normal levels of gastrin, secretin, and urinary 5'-HIAA are useful in excluding other neuroendocrine neoplasms (Table 28.2). Provocative tests with pentagastrin or secretin infusion may stimulate release of VIP.[7]

Localization of VIPomas is usually accomplished with intravenous and oral contrast enhanced CT scan of the abdomen and chest. The majority of pancreatic VIPomas have been single, averaging 3 cm. in size, and located in the body or tail of the gland (75%). As previously mentioned, pediatric VIPomas are usually neurogenic tumors located in the posterior mediastinum, retroperitoneum, or adrenal glands.

Other imaging studies may be necessary if CT localization is unsuccessful. Endoscopic ultrasonography is valuable for identification of smaller neuroendocrine tumors of the pancreas. Since islet cell tumors are hypervascular, magnetic resonance imaging (MRI) and visceral angiography may also be useful for detection. MRI may be more helpful than CT for the diagnosis of metastatic disease. Occasionally,

elusive tumors have been sought by transhepatic venous sampling of selected splanchnic vessels (portal vein, mesenteric vein, splenic vein) for VIP. Techniques of nuclear imaging using somatostatin receptor scans (indium labeled pentetreotide) or VIP receptor scans (iodine labeled VIP) have also been capable of identifying these tumors.[8] The ultimate localization of neuroendocrine neoplasms occurs at the time of surgical exploration. Intraoperative ultrasound can be a valuable diagnostic adjunct in this setting. To reiterate however, most VIPomas can be localized by preoperative contrast enhanced CT scan.

Treatment

Surgical excision is the only curative treatment. Prior to operation, the patient's metabolic derangements must be corrected. Restoration of hydration, electrolytes, and acid base status must be accomplished carefully and incrementally. The metabolic imbalances that these patients incur can be chronic, severe, and life threatening. The patient's cardiovascular and renal status must be monitored. Octreotide, a long acting somatostatin analog, is administered subcutaneously to control the ongoing intestinal losses. This facilitates resuscitation and permits the necessary imaging work-up prior to elective intervention. Perioperative H_2 blockers have been suggested because of rebound gastric acid secretion that may occur following tumor removal. Rebound hypertension is also a possibility.

The majority of VIPomas are located in the body or tail of the pancreas. Distal pancreatectomy has therefore been the most common resective procedure. Cephalo pancreaticoduodenectomy (Whipple resection) is performed for lesions in the head of the gland or uncinate process. Small tumors may be enucleated.

Approximately one half of VIPomas are malignant and 75% of malignant lesions are metastatic to lymph nodes or liver. Metastatic disease should be resected to the extent possible because of the symptomatic relief that tumor "debulking" can provide. Likewise, recurrent disease should be resected whenever tumor and patient characteristics permit.

Inability to localize the tumor at the time of surgery poses a difficult challenge. The retroperitoneum and both adrenal glands should be explored as potential extra pancreatic sites. Intraoperative ultrasound may detect occult pancreatic or hepatic lesions. I^{125} labeled somatostatin analogs have been injected intravenously and activity detected in the operating room with hand-held gamma counters. If the biochemical diagnosis is secure and all efforts at tumor identification have failed, subtotal distal pancreatectomy can be considered. Some patients will be found to have diffuse islet cell hyperplasia rather than a distinct tumor.

Treatment of unresectable VIPomas includes the use of antisecretory and cytotoxic drugs to control symptoms.[9] Octreotide has been the most useful agent and has replaced glucocorticoids and a host of other drugs that were formerly used. Octreotide inhibits VIP release and VIP stimulated intestinal secretion. Dose titration is required to achieve symptom control for individual patients. Octreotide may also have antitumor effects and in some patients regression of metastatic disease has been reported with octreotide therapy. Other peptides that have been investigated as VIP antagonists include calcitonin, sorbin, and peptide YY.

Cytotoxic chemotherapy has been used for patients with unresectable malignant VIPomas. Obviously there are no large prospective studies considering the scarcity of these tumors. Responses in the 50-70% range have been reported for small numbers of patients treated with streptozotocin and 5-Fluorouracil, chlorozotocin, DTIC, adriamycin, human leucocyte interferon, and interferon-α or combinations. Octreotide has also been combined with some of these cytotoxic agents with some success. Responses to chemotherapy, when they do occur, are usually partial.

Very limited experience with immunotherapy using monoclonal antitumor antibodies has been reported for malignant islet cell tumors. Hepatic arterial infusion of antibody was associated with improvement in one patient with VIPoma syndrome. Radiation therapy has little effect on endocrine tumors of the pancreas.

Outcome

Complete surgical resection eliminates symptoms and incomplete resection yields substantial palliation. VIPomas are benign in 50-60% of patients and are generally cured by resection, although recurrences have been described. Serum VIP is a useful tumor marker for surveillance. Long term survival of patients with malignant VIPomas is poor; mean survival is about one year. Survival of pediatric patients with VIP secreting ganglioneuroblastomas is in the 90% range. Overall 5 year survival of patients with malignant islet cell tumors is about 50%.

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CHAPTER 29

Somatostatinoma

Edgar D. Staren

Introduction

Somatostatin is a cyclic tetradecapeptide produced by the delta cells of the dispersed neuroendocrine cell system. Delta cells are predominantly found in the fundal and antral regions of the stomach as well as in the pancreatic islets. Lesser numbers of these cells can be found in the gastrointestinal tract.

Somatostatin inhibits the secretion of most of the gut hormones including cholecystokinin, gastric inhibitory peptide, gastrin, motilin, pancreatic polypeptide, secretin, and vasoactive intestinal peptide.[1] It therefore plays an important function as a regulator of hormone-mediated processes in digestion and metabolism. In addition, it directly inhibits gallbladder and gastrointestinal motility, gastric acid and pancreatic exocrine secretion, and intestinal absorption.

Tumors demonstrated to produce and/or stain primarily with somatostatin, or somatostatinomas, are extremely rare. In a recent review of the literature only 85 cases were reported including the first reported case in 1977.[2-4] These patients had an average age of presentation in the mid-sixth decade and ranged from 24-84 years of age. Somatostatinomas occurred equally in males and females regardless of whether the tumor was located within or outside of the pancreas.

Clinical Presentation

The classic "somatostatinoma syndrome" is characterized by the triad of mild diabetes, diarrhea/steatorrhea, and gallstones.[5] Other symptoms of patients with a somatostatinoma include most commonly, weight loss identified in 39% of patients, abdominal pain in 28% of patients, nausea/vomiting in 26% of patients, and jaundice in 20% of patients (Table 29.1). Diarrhea and/or steatorrhea occurred in only slightly more than one-third of patients. While diarrhea results from an increase in the stool osmolarity secondary to malabsorption, steatorrhea results from decreased pancreatic secretion and resultant impairment of fat absorption. Cholelithiasis also appeared in approximately one-third of patients. It is related both to the direct inhibition of gallbladder contractility by somatostatin as well as to the somatostatin-mediated inhibition of cholecystokinin release. While cholelithiasis led to jaundice from common duct involvement in some patients, jaundice was more often secondary to the tumor directly obstructing normal bile flow. Diabetes occurred in approximately one-quarter of patients with a somatostatinoma. Diabetes may occur secondary to direct suppression of insulin release by somatostatin as well as indirectly from suppressed gastric inhibitory peptide release which functions as an insulinotropic peptide. The diabetes tends to be relatively mild; this may be related to the concomitant

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Table 29.1. Symptoms of patients with a somatostatinoma

Symptom	Number of Patients (N=85)	Percent
Weight Loss	33	39
Diarrhea/Steatorrhea	31	36
Cholelithiasis	30	35
Abdominal pain	24	28
Nausea/vomiting	22	26
Diabetes	21	25
Jaundice	17	20

inhibition of glucagon release in addition to insulin suppression. Another factor may be the predominance of a somatostatin form which is relatively less inhibitory of insulin release (i.e., somatostatin 14). Other less commonly occurring symptoms included anorexia and fatigue in approximately 10% of patients. Of note, 11% of patients with somatostatinomas were found to have associated neurofibromatosis; it has been suggested that this association may be an unusual form of a multiple endocrine neoplasia syndrome since it seems to have a familial relationship.

Diagnosis

Most patients with somatostatinomas describe a variable complex of symptoms which are generally vague. The astute physician may confirm the diagnosis biochemically by demonstrating elevated plasma levels of somatostatin (normal < 100 picograms/ml). Such a measurement can certainly facilitate interpretation of otherwise ambiguous symptoms. Unfortunately, while somatostatin levels are substantially elevated in most patients with pancreatic somatostatinomas they may be normal or only slightly elevated in patients with extra pancreatic tumors. Therefore, in the patient in whom a somatostatinoma is suspected, provocative testing utilizing tolbutamide infusion or calcium/pentagastrin stimulation may be required to confirm the diagnosis.

Because of their nonspecific presentation, somatostatinomas can become relatively large tumors at the time of presentation. As such, imaging studies have been shown to be associated with an extremely high degree of accuracy.[2] In fact, computed tomography (CT) scanning, external abdominal ultrasound, angiography, and even flexible upper endoscopy were positive in nearly 90% of cases. Because of its ready availability and high accuracy, CT scanning is recommended as the first imaging study to be utilized.

Nearly half of the 85 reported somatostatinomas were found within the pancreas and then most commonly within the pancreatic head. The location of three somatostatinomas was either unknown or was unspecified. Of the 42 extrapancreatic somatostatinomas, 26 were found in the duodenum, 13 were found in the ampulla,

and the remainder were found in the cystic duct, jejunum, or rectum. The extrapancreatic somatostatinomas were generally smaller than their pancreatic counterparts and were diagnosed earlier secondary to symptoms of bleeding, jaundice, and/or abdominal pain resulting from gastrointestinal tract erosion and/or obstruction of the bile duct. The somatostatinoma syndrome occurred less commonly with extrapancreatic tumors; this may be related simply to tumor volume since extrapancreatic tumors tended to be removed before sufficiently high levels of circulating somatostatin were attained.

Pathology

Somatostatinomas were shown to most often be single, moderate-sized tumors with an exophytic character. On histopathologic examination they generally contained solid sheets, cords, or nests of well-differentiated neuroendocrine cells. On occasion, however, they appeared as quite undifferentiated tumors. In fact, rarely they demonstrated a glandular pattern which could result in a misdiagnosis of such a tumor as an adenocarcinoma. Immunohistochemical staining for somatostatin was quite reliable; it was positive in all 40 tumors in which it was evaluated. A variety of other hormones including insulin, gastrin, VIP and others may be detected as well.

Thirty (35%) patients had no evidence of metastases at the time of diagnosis. Twenty-five (29%) patients had regional lymph node metastases while 28 (33%) patients had liver metastases. In seven (8%) patients the presence or absence of metastases was not indicated. Whether the somatostatinoma originated in the pancreas or in extrapancreatic location did not seem to be related to the likelihood of metastatic development nor to the predilection for one metastatic site over another.

Surgical Treatment

As with most islet cell tumors, somatostatinomas may have a rather indolent course. Nevertheless, because of the high potential for malignant behavior an aggressive approach is warranted.

The preferred treatment for patients with somatostatinomas is surgical resection. Despite this, the frequent finding of metastases at the time of presentation precluded curative resection for the majority of patients. Data regarding debulking of tumor is quite limited.

Surgery was performed in 77 of the 85 patients (91%). The most common procedure performed was a Whipple type pancreaticoduodenectomy consistent with the most frequent tumor location in the head of the pancreas. Other types of pancreatic resections including distal, subtotal, and total pancreatectomies were performed in 20% of patients. Duodenal resections were performed in 13% of patients. Concomitant cholecystectomies were performed at the time of treatment for the somatostatinoma in 15% of patients.

Systemic Therapy

Systemic chemotherapy was administered to 25% of patients with either metastatic and/or locally aggressive tumors. Streptozotocin and/or 5 Fluorouracil were

the chemotherapeutic agents most commonly used, alone or in combination in 17 patients. Of the patients with metastatic and/or locally advanced disease, 10 of the 21 were dead from 9 months to 31/2 years after treatment. While the impact of chemotherapy on survival is difficult to evaluate, given the small numbers, chemotherapy did result in regression and symptomatic remission in some patients. It is therefore considered a reasonable approach in the symptomatic patient with recurrent and/or metastatic disease.

Summary

The somatostatinoma syndrome is characterized by mild diabetes, gallstones, and diarrhea/steatorrhea. Somatostatinomas occur most often in the mid-sixth decade and equally in men and women. The diagnosis can be confirmed by an elevated plasma somatostatin level. Computed tomography scanning is recommended as the first line imaging study. The incidence of pancreatic and extrapancreatic tumors is nearly equal; the single most frequent location is within the pancreatic head. The preferred treatment for somatostatinoma is surgical excision; despite this, the majority of patients have metastases precluding curative resection. While its effect on survival is unknown systemic chemotherapy is advised for advanced disease in an attempt to cause regression and/or symptomatic remission.

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CHAPTER 30

Carcinoid Tumors

Keith W. Millikan

Introduction

The term "karzinoid" was originally introduced by Oberndorfer in 1907 to describe small intestinal tumors that behave in a less aggressive manner than the more common adenocarcinomas.[1] Since then carcinoids have been described as benign or malignant, clinically functioning or nonfunctioning, and endocrine or nonendocrine tumors which arise from Kulschitzsky or enterochromaffin cells. These cells have characteristic light microscopy and histochemical features such as argentaffin and argyrophilic reactions. They also have the capacity for amine precursor uptake and decarboxylation therefore placing them as a subset of APUDoma tumors.

Lembeck in 1953 was the first to demonstrate the presence of serotonin in carcinoid tumors.[2] Shortly thereafter, Thorson reported a series of patients with ileal carcinoids and hepatic metastases having symptoms of diarrhea, flushing, asthma, cyanosis and right-sided valvular heart disease.[3] The "carcinoid syndrome" was thus established. Since then, immunohistochemical studies have allowed investigators to detect multiple hormonal substances associated with carcinoid tumors, although most tumors remain clinically silent. For this reason classification has been dependent on morphologic, histochemical and biochemical features of the tumors.

Current Research and Therapy

Classification and Site of Origin

Williams and Sandler have classified carcinoid tumors according to their site of origin as foregut, midgut or hindgut.[4] Foregut carcinoid tumors (bronchus, stomach, duodenum and pancreas) are argentaffin negative, have a low serotonin content and may secrete 5-hydroxytryptophan (5-HTP) or adrenocorticotrophic hormone (ACTH). Midgut carcinoid tumors (jejunum, ileum and right colon) are argentaffin positive, have a high serotonin content and rarely secrete 5-HTP or ACTH. Hindgut carcinoids are argentaffin negative, rarely contain serotonin or secrete 5-HTP or ACTH.

Immunohistochemistry has revealed that foregut carcinoids are often multihormonal. Carcinoid and Cushing syndrome, gastric hypersecretion, diarrhea, and diabetes can all be related to hormones or neuropeptides which originate from the respiratory system, duodenum or pancreas. Gastric carcinoids are usually asymptomatic and rarely contain serotonin. Midgut carcinoids produce mainly serotonin and tachykinins. Hindgut carcinoids, although usually small and benign, produce a multitude of peptides such as somatostatin, glicentin, enkephalin, substance P and insulin.

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The gastrointestinal tract accounts for 85% of all carcinoid tumors with bronchial carcinoids compromising approximately 10% and the remaining 5% are scattered among organs such as the larynx, thymus, kidney, ovary, prostate and skin. The most common site is the appendix (45%) followed by the rectum (15%) and ileum (11%). Classic pancreatic endocrine tumors such as insulinomas and glucagonomas have been excluded from the carcinoid tumors because they arise from a specific endocrine cell line such as islets of Langerhans rather than the diffuse endocrine system. Likewise, medullary carcinoma of the thyroid, pituitary adenomas, and pheochromocytomas are excluded from being a subset of carcinoid tumors.

Bronchial Carcinoids

Bronchial carcinoids comprise approximately 85% of benign lung tumors, but account for only 1-2% of all lung tumors. They may occur at any age from childhood on. Mean age is approximately 50 years with a male to female ratio which differs from reported series. The tumors may be central or peripheral. The most common presenting symptoms are pneumonia, hemoptysis and cough. It is unclear whether smoking is a contributing risk factor. Endocrine manifestations including the carcinoid syndrome are uncommon in the absence of metastases.

Bronchial carcinoids are classified as either typical or atypical. The difference is based on features of necrosis, lymphatic or vascular permeation, mitosis, nuclear pleomorphism, and an undifferentiated growth pattern. Well differentiated neuroendocrine carcinoma is another name for atypical bronchial carcinoid. Diagnosis is usually made by routine chest radiograph which demonstrates a mass with or without distal obstruction in over 90% of cases. Computed tomography (CT) is used to evaluate the extent of the mass and possible lymph node and/or liver metastases. Histologic diagnosis is made with bronchoscopic appearance and biopsy. These lesions have a strawberry appearance and bleed easily. The endoscopist should have rigid bronchoscopy available to control hemostasis if necessary. Atypical carcinoids can be misdiagnosed as small cell carcinomas. Bronchial washings and brush cytology are of no use in making the diagnosis of bronchial carcinoid.

Complete surgical resection is the treatment of choice for primary lesions. Peripheral lesions commonly require a lobectomy to remove all the regional lymph nodes. Traditionally pneumonectomy was performed for lesions near the mainstem bronchus or centrally located. More recently, bronchoplastic procedures such as a sleeve resection have been performed to preserve ventilatory function. Surgeons must be careful to attain negative surgical margins when performing lung preserving procedures. Endoluminal treatment of the primary tumor using the YAG laser, cryotherapy or brachytherapy is reserved for patients with low performance status and impaired respiratory function.

Five-year survival after resection is approximately 90% with 10-year survival remaining between 80-90%. Tumor size > 2 cm, lymph node metastases, atypical histology and symptomatic presentation have been identified as independent predictors of survival.[5] No further adjuvant therapy is needed for early stage bronchial carcinoids. Most medical oncologists will treat aggressive atypical carcinoids with

adjuvant chemotherapy and radiation therapy similar to protocols for small cell carcinoma of the lung.

Gastric Carcinoids

Proliferation of enterochromaffin-like cells (ECL) of the mucosa of the stomach can be initiated and maintained by elevated levels of plasma gastrin. The hypergastrinemia can be generated by a low acid state (atrophic gastritis or pernicious anemia) or a neoplasm (gastrinoma). Sporadic tumors can also occur. Sporadic tumors are usually solitary, large (> 1 cm), do not secrete gastrin, and exhibit a relatively aggressive growth pattern with metastases to regional nodes (55%) and liver (24%). The tumors which are associated with hypergastrinemia are generally small, multiple and exhibit benign behavior. Gastrinoma tumors can be associated with MEN type I syndrome and may metastasize more often than chronic atrophic gastritis associated tumors.

Gastric carcinoids can either be incidentally found or present with symptoms of ulcer, polyps, or carcinomas. They can bleed or cause gastric outlet obstruction. Gastric carcinoids rarely produce the classic carcinoid syndrome since they release histamine and bradykinin related peptides rather than serotonin. These hormones produce an atypical syndrome which consists of patchy bright red flushing, facial edema, lacrimation, headache and bronchoconstriction. Gastroscopy with biopsy is the most accurate diagnostic tool. The tumors most often appear as multiple polyps usually yellow in color. CT usually will not reveal the primary lesion but is important in identifying lymph node and liver metastases.

Carcinoids up to 1 cm in diameter associated with chronic atrophic gastritis are more or less invariably benign and removal by endoscopy is recommended. Lesions 1-2 cm in size have a low malignant behavior, therefore should be surgically excised and regional lymph nodes examined intraoperatively. Tumors > 2 cm should always be surgically excised with gastrectomy reserved for invasive or multifocal larger lesions. Gastric resection including the antrum, juxtapyloric duodenum cup and distal body of stomach is preferred to simple antrectomy for efficient removal of gastrin producing cells.

Duodenal and Pancreatic Carcinoids

Duodenal carcinoids are rare accounting for less than 2% of all gastrointestinal neuroendocrine tumors. Gastrinomas are the most common (60%) and usually are found in the first and second portions of the duodenum. They are usually small (< 1 cm) but tend to metastasize to regional lymph nodes (30-70%) yet only a few metastasize to the liver. Approximately one third of duodenal gastrinomas are associated with the Zollinger Ellison Syndrome (ZES). The tumors are classically embedded in the submucosa and are multiple when associated with ZES/MEN type I syndrome. Resection is the treatment of choice with 85% survival at 10 years. Endoscopy rarely finds these tumors therefore a longitudinal duodenotomy is the most efficient method to expose and resect these tumors.

Somatostatin-rich staining duodenal carcinoids (15-20%) are usually nonfunctioning and occur exclusively at the ampulla of Vater. They can present

with bleeding or obstructive jaundice and approximately 50% have lymph node metastases. Treatment is by local excision or pancreaticoduodenectomy. Gangliocytic paragangliomas are very rare and occur in the second portion of the duodenum. They occasionally bleed or are recognized incidentally. These tumors are generally benign and have an excellent prognosis after local excision.

There are well differentiated duodenal tumors that may stain for hormones such as calcitonin, pancreatic polypeptide, and serotonin. These tumors are found in the proximal duodenum and are usually less than 2 cm in size. Local excision is sufficient unless they have grown to be large in size. Poorly differentiated neuroendocrine carcinoma does occur rarely at the ampulla of the Vater. These are very aggressive tumors with a very poor prognosis.

Pancreatic islet cell tumors are not included among the carcinoid tumors as previously mentioned and they are classified according to their predominant hormone. There are tumors of the pancreas which stain intensively for serotonin and are histologically classic carcinoids. These tumors do not usually present with carcinoid syndrome. Excision is the treatment of choice if carcinoid syndrome and hepatic metastases are not present.

Midgut Carcinoids

Midgut tumors commonly produce serotonin and tachykinins but cause systemic symptoms only after they metastasize to the liver. The secretion of tryptamines from the primary midgut carcinoids and mesenteric lymph node metastases are generally inactivated after one hepatic passage due to monoamine oxidase activity. These tumors can present with gastrointestinal bleeding if they ulcerate the mucosa and submucosa of the small bowel. They rarely obstruct the liquid contents of the small intestine.

Midgut carcinoids are usually advanced at presentation unless found incidentally. They are the most common of carcinoids to present with the classic syndrome (diarrhea, flushing, right-sided heart disease, and wheezing). The tumors are commonly associated with synchronous or metachronous gastrointestinal tract tumors. Adenocarcinoma of the colon is the most common second primary tumor.

Anatomic localization of midgut carcinoids can be quite difficult. Enteroclysis and CT scans are the most common tests utilized. Enteroscopy is also an option. When attempts at localization fail, isotopically labeled somatostatin analogue (^{123} iodinated octreotide) can be used with nuclear medicine scanning. Finally, if all attempts at localization fail, then exploratory laparotomy is performed.

Biochemical characterization of midgut carcinoids involves 24 hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA). Normal range is 2-8 mg/24 hours. This test is moderately sensitive (73%) and very specific (100%). In patients where biochemical testing is negative, stimulation testing with pentagastrin has been tried. Pentagastrin acts as a secondary catecholamine stimulating test by liberating epinephrine, norepinephrine and dopamine from these tumor cells.

Tumors that have no evidence of hepatic metastases should be resected with their regional mesenteric lymph node drainage. The 5-year survival of patients with midgut carcinoids is approximately 20%. Some patients (10-15%) may be cured

with hepatic metastases if resection is possible. Liver resection will also result in palliation of symptoms if more than 90% of the tumor burden is removed. Before contemplating surgical resection, octreotide blockage (100-200 micrograms subcutaneously bid) should be initiated to prevent carcinoid crisis. Cholecystectomy should also be performed at the time of resection if hepatic embolization is required for future treatment of symptoms. All patients deemed to be tumor free should have 5-HIAA urinary levels measured every 3 months. CT scans of the abdomen are recommended every 6 months for screening recurrence. Pentagastrin stimulation tests can be performed to detect suspected tumor recurrence.

Patients with superficial liver lesions should undergo wedge resection at the time of intestinal surgery. Those patients with unilobar hepatic disease should undergo hepatic lobectomy under octreotide blockade 3-6 months after intestinal surgery. Patients with bilobar hepatic disease should undergo hepatic artery embolization after octreotide blockade is instituted.

Appendiceal Carcinoids

Carcinoid is the most frequently encountered appendiceal neoplasm (50-75%) with the appendix (45%) also being the most common site for gastrointestinal tract carcinoid tumors. The incidence of appendiceal carcinoid is approximately 5 in every 1000 appendectomy specimens with a female to male ratio of 3:1. Due to lack of symptoms, appendiceal carcinoids are usually found during surgery for appendicitis or incidentally during exploration for other reasons.

Most appendiceal carcinoids are less than 1 cm in size (70-80%) and a smaller number are between 1-2 cm (20%) with very few being larger than 2 cm. The carcinoid syndrome is rarely encountered with tumors of the appendix. Carcinoid tumors of less than 1 cm in size have an excellent prognosis and are treated by appendectomy alone. Controversy does remain concerning tumors between 1-2 cm. Although Thirlby found 5 patients out of 46 with synchronous metastases and primary tumor size between 1-2 cm, there is no evidence of tumor recurrence developing or deaths occurring when appendectomy has been performed for tumors less than 2 cm without synchronous metastases.[6] Moertel has also reported 14 patients treated by appendectomy alone for 1-2 cm tumors with no tumor recurrence over a 25 year follow-up period.[7] Carcinoid tumors greater than 2 cm have a 30-60% chance of metastasizing to regional lymph nodes. Right hemicolectomy should be performed for these patients.

Carcinoid tumors located at the base of the appendix have had right hemicolectomy advocated as their treatment of choice. There are many reports of long term survival with partial cecectomy or appendectomy with a clear margin. Patients with no signs of regional lymph node metastases are probably adequately treated by appendectomy alone. It is probably fair to offer right hemicolectomy only to younger patients with tumors at the base. In summary, for tumors <2 cm in size, an appendectomy should be all that is needed unless regional lymph nodes are palpated at exploration then right hemicolectomy should be performed. Radical right hemicolectomy should be performed for all tumors greater than 2 cm in size.

Colorectal Carcinoids

Carcinoids of the rectum constitute about 20% of all GI tract carcinoids yet only 1% of rectal tumors in general. They usually occur singly (> 95%), have an equal male to female ratio, and present in the fifth to seventh decade. Metastatic potential ranges from 5-40%. Rectal carcinoids rarely exhibit the carcinoid syndrome. In general there are two groups of carcinoids of the rectum: small solitary tumors (< 1 cm) and larger tumors which have the potential to metastasize. Seventy percent of rectal carcinoids are argyrophilic while only 10% are argentaffin positive. Most carcinoids of the colon and rectum exhibit multihormonal expression (glucagon serotonin, glicentin, somatostatin, pancreatic polypeptide-like, substance P, enkephalin and β-endorphin).

Tumor size and histologic invasion of the muscularis propria are the two most important prognostic factors. Tumors > 2.0 cm have a 60-80% chance of metastasizing , tumors 1-2 cm have a 10-15% chance of metastasizing, and tumors < 1 cm have a 2% chance of metastasizing. The principal management of rectal carcinoids is surgical excision. Tumors > 2 cm or those having evidence of muscularis invasion should be considered as adenocarcinomas and a cancer type procedure performed. Tumors < 2 cm can be resected locally but total removal with clear margins is essential to limit local recurrence or persistence with later metastatic spread. If muscularis propria invasion is documented after local excision then a cancer resection should be performed (colectomy, low anterior resection or abdominal perineal resection).

Somatostatin Receptor Scintigraphy (SRS)

Large numbers of high affinity somatostatin binding sites have been found on carcinoid tumors. In vivo visualization of carcinoids can be done using a radiolabeled somatostatin analog (^{111} In-DTPA-D-Phe ^{1})-octreotide. Although ultrasound, computed tomography and magnetic resonance imaging are fairly accurate in showing liver metastases, they do not always reveal extent of disease (small liver lesions and extra abdominal metastases) which will impact on the possibility of surgical cure. As long as the tumor has somatostatin receptors, scintigraphy can localize tumors as small as 1 cm and also negative receptor tumors in the liver. The disadvantages of SRS are that it is unable to detect tumors < 1 cm and those that are receptor negative outside the liver. The usefulness of SRS is fourfold: it may select resectable tumors that would be unrecognized with conventional imaging techniques; it may prevent surgery in patients who have metastasized to a greater extent than can be detected with conventional imaging; it may direct the choice of radiotherapy or medical therapy in patients with inoperable lesions, and finally it may be used as a screening tool to detect posttreatment recurrences.

Carcinoid Syndrome

Some patients that have carcinoid tumors develop flushing, diarrhea, wheezing and right sided cardiac valvular disease, a constellation of symptoms called the carcinoid syndrome. Most patients with these symptoms have widespread metastatic disease. Episodic or permanent flushing (94%) is the typical hallmark of the syndrome. Second to flushing in frequency is recurrent episodes of mild to explosive

diarrhea (78%). Cardiac manifestations develop late in the disease due to fibrous tissue forming on the heart valves.

Characteristically, patients with carcinoid syndrome have expansion of the serotonin pool size, an increase in blood and platelet concentrations of serotonin and elevation of 5-HIAA levels in the urine. Diagnosis of carcinoid syndrome is confirmed if 5-HIAA excretion in urine exceeds 10 mg/24 hour. Carcinoid syndrome can only in part be related to serotonin overproduction. Serotonin seems to be responsible for the diarrhea. Diarrhea can be successfully treated with serotonin antagonists such as methylsergide, cyproheptadine, ketanserin and ondansetron. Bradykinin and histamine are thought to be the principal neurohormones responsible for flushing. Bradykinin and substance P also play a minor role in diarrhea.

Medical Therapy

Gastrinomas once required total gastrectomy for control of ZES. Since the introduction of H_2 receptor antagonists and recent proton pump inhibitors, gastric acid secretion has been controlled medically. H_2 blockers are limited for long term use as they frequently require increase in dosage and frequency to control acid secretion. Somatostatin and its long-acting analog octreotide or lanreotide inhibit acid secretion and also lower serum gastrin levels. Because subcutaneous injection of somatostatin is required, proton pump inhibitors remain the treatment of choice to control acid secretion if the primary tumor or its metastases can not be controlled.

For carcinoid syndrome, somatostatin analogs have replaced most pharmacologic agents previously mentioned for the relief of hormone-mediated symptoms. Octreotide can improve or normalize diarrhea and flushing at a dose of 50-200 micrograms SC tid. Administration of octreotide in patients with carcinoid syndrome is necessary at laparotomy and preoperatively to prevent carcinoid crisis including life threatening bronchial obstruction. Side effects of long term somatostatin are rare. The one side effect worth mentioning is the formation of gallstones. Cholecystectomy should be performed at laparotomy if a patient will require long term somatostatin analog treatment.

Control of tumor growth strategies can include various options ranging from tumor debulking, hepatic artery embolization, somatostatin analogs, interferon α, combination therapy, systemic chemotherapy and liver transplantation. Somatostatin analogs have an antiproliferative potency in vitro which can have a tumor stabilization effect in humans up to 36 months. Interferon α also has a stabilization response in pancreatic and intestinal tumors. Combination therapy (octreotide and interferon) seems to be superior to either monotherapy. There are no prospective studies which address the benefit of chemotherapy on malignant carcinoids of the midgut. Anaplastic neuroendocrine carcinoma does respond to etoposide and cisplatin with a median duration of regression lasting 8 months. Chemotherapy is not justified as an antiproliferative measure for well differentiated metastatic carcinoids and should only be recommended for patients with poorly differentiated neuroendocrine carcinoma.

Hepatic Metastases

Liver metastases imply advanced disease and a major symptomatic problem in patients with carcinoid tumors. Patients with localized hepatic disease should always undergo resection for cure after preoperative octreotide blockade. Patients with distant metastatic disease and hepatic metastases may also benefit from resection for palliation of symptoms. In patients with carcinoid syndrome and bilobar hepatic disease, resection of the primary tumor should be performed first, then followed by hepatic embolization or cryotherapy of liver lesions after a trial of octreotide blockade to control symptoms. All patients with residual tumor burden should be continued on octreotide therapy postoperatively.

Secondary to their slow growth rate neuroendocrine tumors are still considered an acceptable indication for liver transplantation. In 1989 Starzl's group reported 5 patients with neuroendocrine tumors.[8] Three patients had long term survival. Several factors must be considered when selecting transplant candidates. The expected results of transplantation must be weighed against the results of other treatment modalities. The existence of extrahepatic metastases must be searched for since residual tumor growth may accelerate during immunosuppression. At present the limiting factor is access to compatible donor organs for strictly selected tumor patients when there are large numbers of patients with benign liver disease who need transplantation.

Contraindications to hepatic embolization therapy are a tumor burden exceeding 50% of liver volume, occlusion of the portal vein, hyperbilirubinemia, or persistently elevated liver enzyme levels. Relative contraindications are contrast allergy, coagulopathy, extrahepatic tumor dominance, or poor performance status. An alternative to embolization or resection especially in elderly patients is alcohol injection. The volumes of individual metastases are estimated ultrasonographically and injected with equal volumes of 70% alcohol.

Future Applications and Summary

Immunohistochemistry has identified many peptides which are secreted by carcinoid tumors. Future research will hopefully identify receptors which can be used to treat these tumors. Radiolabeled peptide receptor therapy may be used to treat inoperable metastatic disease. Radioisotope intraoperative scanning may provide the surgeon with information necessary to determine the extent of resection necessary for each tumor.

Carcinoid tumors are uncommon but not rare. They can originate from embryologic foregut, midgut or hindgut structures. Their production of different hormones is usually dependent on their site of origin. When hormonally symptomatic, hepatic metastases are usually present. Small < 1 cm carcinoids are usually benign, 1-2 cm tumors have low malignant potential and larger tumors > 2 cm can exhibit very aggressive behavior. Surgical resection when possible remains the mainstay of treatment both for cure and palliation. Octreotide therapy has been used effectively to control symptoms for inoperable patients and it is also used to prevent carcinoid crisis when these tumors are manipulated surgically or with other invasive modalities.

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CHAPTER 31

Multiple Endocrine Neoplasia Syndrome

Fumio Sato and Quan-Yang Duh

Introduction

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominantly inherited syndromes. Patients with MEN syndromes have a propensity to develop tumors of various endocrine glands, such as the parathyroid, pituitary, pancreas, adrenal and thyroid glands.

There are three well-defined types of MEN syndromes (Table 31.1). The individual endocrine tumors developed in patients with MEN are similar to those that occur sporadically. There is, however, a tendency for hyperplasia and multiple tumors. Thus the treatment of these patients may be more complicated. In addition, treatment decisions are also influenced by the possible presence of other tumors (such as pheochromocytomas in patients with medullary thyroid cancer or hyperparathyroidism in patients with gastrinoma) and the consideration for genetic screening and prophylactic operations.

Review of Current Research

MEN 1

The gene responsible for MEN 1 has recently been identified and named "*menin*".[1] It is located on chromosome 11q13. *Menin* gene appears to be a tumor suppressor gene, i.e., both alleles are inactivated in the tumor, either by complete deletion of the gene or by mutations of the active component of the gene. *Menin* mRNA is expressed ubiquitously in adult tissues including the pancreas, adrenal cortex, thyroid, testis and leukocytes. Germline mutations of the *menin* gene are found in the affected members of families with MEN 1. They are also found in some patients with sporadic MEN 1 who probably have de novo germline mutations of the *menin* gene. Overall, more than 90% of MEN 1 patients have germline *menin* gene mutations and most MEN 1 families have their own unique mutation. This heterogeneity in *menin* gene mutation may hinder the development of a rapid molecular genetic screening test for MEN 1. RFLP (restriction fragment length polymorphism) or microsatellite DNA analysis can identify the mutant gene carriers among members of a MEN 1 family. These techniques, however, may not be informative for small kindreds or sporadic cases of MEN 1. Somatic mutation of the *menin* gene may also cause endocrine tumors. For example, 20% of sporadic parathyroid adenomas have a point mutation in one allele of the *menin* gene and deletion of the other allele.

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Table 31.1. Classification of multiple endocrine neoplasia (MEN) syndromes

	Genetic defect	Clinical syndrome
MEN 1	*Menin* (chromosome 11q13)	primary hyperparathyroidism pancreatic endocrine tumors pituitary adenomas
MEN 2A	*ret* (chromosome 10q11.2, exon 10 –11; cysteine-rich region)	medullary thyroid carcinoma pheochromocytoma primary hyperparathyroidism
MEN 2B	*ret* (chromosome 10q11.2, exon 16; tyrosine kinase domain)	medullary thyroid carcinoma pheochromocytoma multiple mucosal neuromas marfanoid habitus

MEN 2

Germline mutations of the *ret* proto-oncogene cause MEN 2A and MEN 2B.[2] *Ret* is on chromosome 10 and encodes a cell membrane receptor tyrosine kinase. Point mutations of *ret* in the intracellular tyrosine kinase domain causes MEN 2B; point mutations of specific extracellular cysteine residues cause MEN 2A. Other activating *ret* mutations cause familial medullary thyroid cancer not associated with other endocrine neoplasms.

MEN 1

Manifestations

Hyperparathyroidism

Most patients with MEN 1 will develop hyperparathyroidism (Table 31.2). Two-thirds of the time hyperparathyroidism is the first manifestation of MEN 1. Patients with MEN 1 usually develop hyperparathyroidism at a younger age (< 40 years) than those with sporadic disease (> 50), and they usually develop parathyroid tumors in multiple glands (hyperplasia or multiple adenomas) instead of a solitary adenoma.[3]

Because young patients with multiple abnormal parathyroid tumors are more likely to have MEN 1, they need to be screened for coexisting pituitary or pancreas endocrine tumors.

Pancreatic Endocrine Tumors

Approximately 40-70% of patients with MEN 1 develop pancreatic endocrine tumors. These tumors are usually multiple and distributed throughout the pancreas. Most of the tumors are benign but some can be malignant. Gastrinomas cause severe peptic ulcer disease and diarrhea (Zollinger-Ellison syndrome). They are small tumors found within the pancreas, the peripancreatic tissue, and in the duodenal wall.[4] Insulinomas are the next most common pancreatic endocrine tumors found

Table 31.2. Characteristics of multiple endocrine neoplasia (MEN) 1 syndrome

		Frequency in Patients
Parathyroid	Hyperparathyroidism due to hyperplasia	100%
Pancreas	Gastrinoma, insulinoma, VIPoma, glucagonoma, somatostatinoma, PPoma	70%
Pituitary	Prolactinoma, growth hormone secreting adenoma	40%
Adrenal	Nonfunctioning cortical adenoma	10%
Others	Carcinoid tumor, thyroid, ovarian and testicular tumors, lipomatosis	Rare

in patients with MEN 1. These are usually multiple throughout the pancreas, and are associated with nesidioblastosis.[5] In contrast, sporadic insulinomas are usually solitary. Some pancreatic endocrine tumors in MEN 1 patients may secrete other hormones, such as vasoactive intestinal polypeptide (VIP), pancreatic polypeptide (PP), somatostatin, ACTH and calcitonin. Other pancreatic endocrine tumors may not secrete any hormone.

Pituitary Adenomas

Symptomatic pituitary adenomas occur in about 30% of MEN 1 patients. Prolactinomas are the most common and account for 60% of pituitary tumors in MEN 1 patients. Symptoms are usually subtle but may include amenorrhea and galactorrhea. Twenty percent of pituitary tumors in MEN 1 patients secrete growth hormone (GH). A few unusual patients, however, may develop acromegaly from ectopic production of GH releasing factor (GHRF) from pancreatic, adrenal or carcinoid tumors, thus confusing the diagnosis. Other pituitary tumors in MEN 1 patients may secrete ACTH or somatostatin.

Adrenal Tumors

Approximately 10% of patients with MEN 1 develop adrenal cortical adenomas. These generally do not secrete hormone and are usually found incidentally by imaging studies done for other reasons. Nonetheless, hyperaldosteronism, hypercortisolism, and pheochromocytomas should be ruled out when adrenal tumors are found.

Uncommon Lesions

Patients with MEN 1 can develop carcinoid tumors of the foregut, particularly of the bronchus, which is usually benign, and of the mediastinum, which is usually malignant. They may also develop lipomatosis, gastric polyps, and tumors of the testis, ovary or thyroid.

Diagnostic Evaluation and Family Screening

MEN 1 rarely becomes apparent before age 10, but can develop at any age during life, peaking between the second and fourth decades. The possibility of MEN 1 should be considered in the following situations (Fig. 31.1):

1. Hyperparathyroidism due to multiple parathyroid tumors or hyperplasia.
2. Hyperparathyroidism in young patients.
3. Patients with an endocrine tumor and a family history of primary hyperparathyroidism or Zollinger-Ellison syndrome.

In patients with known MEN 1 syndrome, a family history of MEN 1, or clinical suspicion of MEN 1, the following tests are indicated:

1. serum calcium level to rule out hyperparathyroidism
2. serum gastrin and pancreatic polypeptide levels to rule out gastrinoma
3. fasting blood glucose level to rule out insulinoma
4. serum prolactin level to rule out pituitary prolactinoma
5. head MRI or CT and visual field exam to rule out a pituitary tumor.

Treatment

Hyperparathyroidism

Because of the predisposition to develop tumors in all parathyroid glands, total parathyroidectomy with autotransplantation is recommended. Autotransplanting parathyroid tissue to the forearm avoids hypoparathyroidism and makes it easier to diagnose and treat recurrent hyperparathyroidism. Thymectomy is necessary, to remove possible ectopic parathyroid tissue, which occurs in 10% of patients. Very rarely, however, MEN 1 patients with primary hyperparathyroidism may remain eucalcemic for many years after resection of only single or double tumors. In general, hyperparathyroidism should be treated before pancreatic endocrine tumors, because hypercalcemia can aggravate their manifestation.

Pancreatic Endocrine Tumors

Patients with gastrinomas can be treated by H2 receptor blockers (e.g., cimetidine, ranitidine) or proton pump inhibitors (e.g., omeprazole). VIPomas and insulinomas, however, are usually not well controlled by medical therapy. Palliative resection is frequently necessary for MEN 1 patients with pancreatic endocrine tumors, although curative resection is difficult because the tumors are multicentric. Resecting the distal pancreas and enucleating tumors in the head of the pancreas or duodenum (for gastrinomas) is usually recommended. Pancreaticoduodenectomy may occasionally be necessary. Palliative liver resection or other cytoreductive treatment, such as cryosurgery or radio-frequency ablation for liver metastases, can prolong survival and improve the quality of life in some patients.

Pituitary Adenomas

Treatment with bromocriptin lowers the level of prolactin to normal and ameliorates symptoms in almost all patients. For tumors causing local mass effect or those secreting growth hormone, transsphenoidal hypophysectomy is indicated. Very large tumors may require radiotherapy or resection via craniotomy.

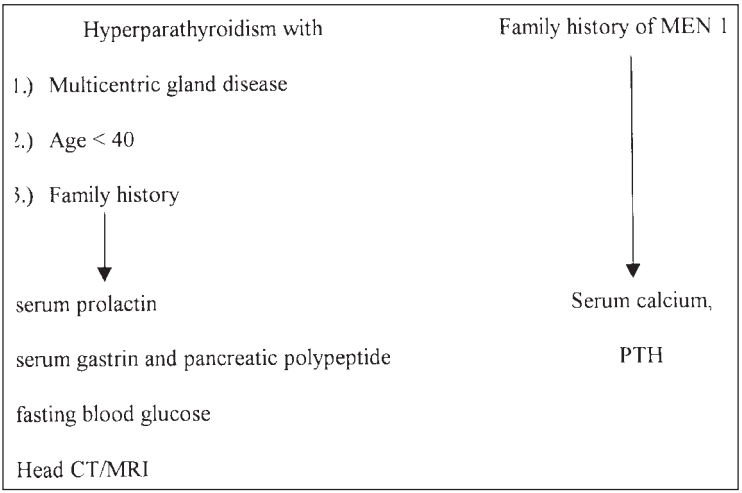

Fig. 31.1. Screening for multiple endocrine neoplasia (MEN) 1.

MEN 2A

Manifestations

Medullary Thyroid Carcinoma

Almost all patients with MEN 2A develop medullary thyroid carcinoma (MTC) (Table 31.3). These tumors are usually multicentric and preceded by C-cell hyperplasia, and they occur at a younger age than the sporadic MTC. They produce calcitonin and sometimes carcinoembryonic antigen (CEA), which are useful tumor markers used to follow the course of disease. MTC can also produce other hormones, such as ACTH and serotonin. The aggressiveness of MTC differs among the various MEN 2A kindreds and appears to depend on the specific *ret* germline mutation.

Pheochromocytoma

Over 70% of patients with MEN 2A develop pheochromocytoma. These are frequently bilateral, or are multiple and extraadrenal, but rarely malignant.[6] They usually develop in the third to fourth decade of life.

Hyperparathyroidism

Hyperparathyroidism develops in about 50% of patients and may involve multiple parathyroid glands. It occurs independently of medullary thyroid carcinoma.

Diagnostic Evaluation and Family Screening

The best screening test to determine whether a family member has inherited MEN 2 is a test for germline *ret* proto-oncogene mutation (Fig. 31.2). The genetic

Table 31.3. Characteristics of multiple endocrine neoplasia (MEN) 2A syndrome

	Frequency in Patients
Medullary thyroid carcinoma	95%
Pheochromocytoma	70%
Hyperparathyroidism	50%

screening test is more than 95% sensitive. Basal or pentagastrin-stimulated plasma calcitonin level is less sensitive and specific as a screening test, but is useful for follow-up of patients with medullary thyroid carcinoma. Metaiodobenzoguanidine (MIBG) is a useful localization study if the patient has biochemical evidence of pheochromocytoma by urinary or plasma levels of catecholamines and metabolites. MIBG can identify multiple and extraadrenal pheochromocytomas.[7-9]

Treatment

Medullary Thyroid Carcinoma (MTC)

Because these tumors are multicentric, a total thyroidectomy is indicated. A central neck and ipsilateral neck lymph node dissection is also indicated if lymph node metastasis is likely (the tumor is palpable or larger than 1 cm), because MTC is not responsive to postoperative radioiodine treatment or TSH suppression. For MEN 2A family members diagnosed genetically with no palpable thyroid tumor or elevated serum calcitonin, a prophylactic total thyroidectomy alone without lymph node dissection may not be sufficient, since 5-10% of these patients will already have central neck node metastases.

Pheochromocytoma

Bilateral adrenalectomy is recommended if the patient has bilateral pheochromocytomas. Unilateral adrenalectomy with careful follow up is an acceptable option for patients with only a unilateral lesion by imaging studies. The risk of Addisonian crisis after a bilateral adrenalectomy needs to be weighted against the risk of developing pheochromocytoma in the contralateral adrenal gland. Some surgeons perform subtotal adrenalectomy, leaving sufficiently functioning adrenal cortical tissue in one gland and complete resection of the other gland, to avoid postoperative Addisonianism. The risk of recurrence may be higher after subtotal adrenalectomy. Laparoscopic adrenalectomy is the procedure of choice if pheochromocytomas are limited to one or both adrenal glands. Laparotomy allows for a more complete exploration of the abdomen if the patient has multiple extraadrenal tumors. In patients with other synchronous tumors, pheochromocytoma should be resected first to avoid hypertensive crisis when treating other tumors.

Hyperparathyroidism

Some endocrine surgeons advocate total parathyroidectomy and autotransplantation for patients with MEN 2A at the time of thyroidectomy. The parathyroids are moved from the neck, where reoperations may be necessary. Others resect only

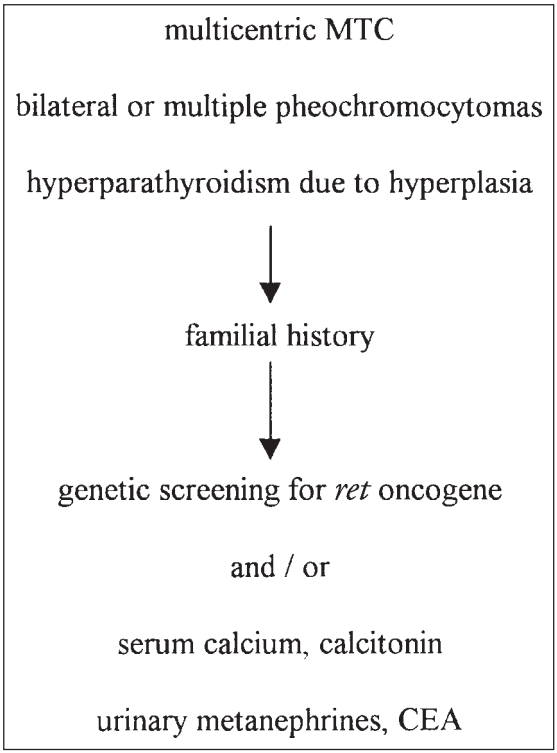

Fig. 31.2. Screening for multiple endocrine neoplasia (MEN) 2A.

obviously enlarged parathyroid tumors, arguing that recurrent hyperparathyroidism is rare and the risk of hypoparathyroidism is high in MEN 2A patients.

MEN 2B

Manifestations (Table 3.4)

Neuromas and Habitus

Patients with MEN 2B have unique physical characteristics. Almost all have marfanoid habitus and multiple neuromas. The neuromas are especially common on the lips, eyelids, and tongue, producing the "lumpy lips" appearance. The corneal nerves are thickened. These physical characteristics may be recognizable even in infancy, before the development of MTC or pheochromocytoma.

Table 31.4. Characteristics of multiple endocrine neoplasia (MEN) 2B syndrome

	Frequency in Patients
Medullary thyroid carcinoma	95%
pheochromocytoma	50%
Multiple neuromas	100%
Marfanoid habitus	70%

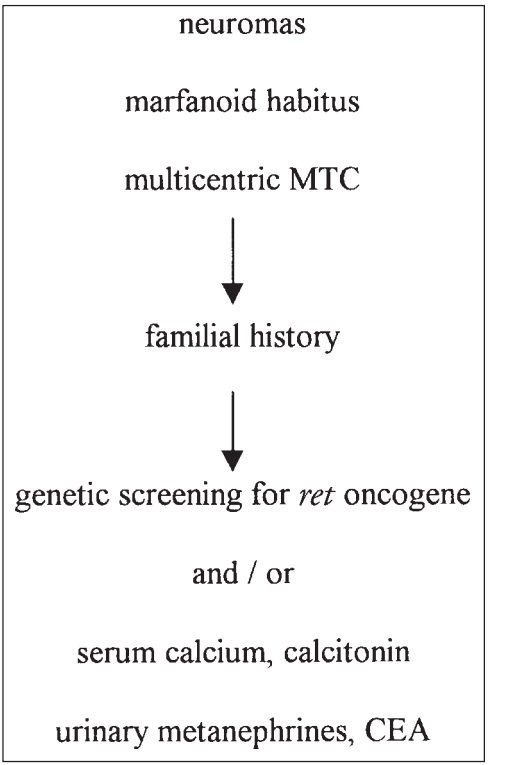

Fig. 31.3. Screening for multiple endocrine neoplasia (MEN) 2B.

Medullary Thyroid Carcinoma (MTC)

If early diagnosis is not made based on phenotype, MTC is usually the first endocrine tumor discovered. MTC develops at a significantly younger age in patients with MEN 2B, 15 years earlier than patients with MEN 2A or sporadic MTC. The clinical course of MTC in patients with MEN 2B is also more virulent than in patients with MEN 2A or sporadic MTC. Metastases are usually present at the time of initial diagnosis.

Pheochromocytoma

Pheochromocytomas develop in about 50% of patients with MEN 2B. They are similar to those found in patients with MEN 2A.

Diagnostic Evaluation and Family Screening

The characteristic features of patients with MEN 2B can usually be recognized on physical exam. Genetic diagnosis for *ret* oncogene mutation should be made as for MEN 2A (Fig. 31.3).

Treatment

Surgical treatment for MTC and pheochromocytoma is the same as for patients with MEN 2A. Because MEN 2B is more virulent, prophylactic total thyroidectomy is indicated as soon as the diagnosis is made even in young children.

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