Rare Tumors of the Thyroid Gland

Diagnosis and WHO Classification

José Manuel Cameselle-Teijeiro
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To my wife Soledad and my daughter Sole, the two "suns" that illuminate my life.

JMC-T

To my daughters Victória and Valentina.

CE

To my six grandchildren Mariana, Joana, Mafalda, Ricardo, Luísa and Manuel who are helping me to approach my seventies cheerfully.

MSS

Foreword

The Webster Dictionary equates "rare" to "unusual" and "seldom occurring," a practice that has been widely applied to medicine in general and pathology in particular, while acknowledging the fact that the two terms are not strictly synonymous.

At present, the term "rare" is generally preferred, as evidenced, for example, by the existence of several active national and international "rare tumors networks."

Alas, it is very difficult to define what a "rare" tumor is. To wit: Is carcinoid tumor of the lung a rare tumor? What about a chondrosarcoma of bone in a 12-year-old boy? Or a histologically typical primary melanoma of gallbladder?

In order to be consistent with this approach, a proposal has been made of reverting these queries by establishing strict criteria in order to determine if the tumor being evaluated fulfills all those criteria or not.

The content and structure of the present book, written by well-recognized experts in the field, provides an authoritative view of the issue and of the evolution that has occurred in the identification and nomenclature of rare thyroid tumors during the past 20 years, as a result of the increased recognition of variants (and of variants of variants) of well-recognized entities, our changing views of their histogenesis, and the impact that sophisticated technologies have had in our understanding.

The present monograph by José Manuel Cameselle-Teijeiro and coworkers can be viewed as complementary to the fourth edition of the WHO "blue book" on thyroid tumors, in the sense of expanding considerably on all those aspects of thyroid tumor pathology. In a way, it can be seen as a collection of extremely useful additions that for theoretical and practical reasons could not be dealt with enough detail into the "mother" publication, i.e., the WHO series on the subject.

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Preface

This book is primarily addressed to histopathologists and cytopathologists, as well as to pathology residents and clinicians (endocrinologists and surgeons, mainly) who have to deal with thyroid tumours and feel challenged by difficult cases.

Following the classic organization of thyroid tumour books, we describe and illustrate the pathology of rare or, at least, unusual thyroid tumours and tumour-like lesions, both benign and malignant, mostly epithelial and primary but also nonepithelial and secondary.

For the sake of simplicity, we start by the rare variants of papillary carcinoma and related tumours including, whenever appropriate, difficult differential diagnostic problems. Afterwards, we continue with the rare variants of the major histotypes of thyroid carcinomas before addressing hereditary tumours and, finally, the abundant group of rare, and frequently peculiar, tumours and tumour-like lesions of the thyroid.

Besides discussing briefly, in a separate chapter, the therapeutic problems raised by such rare tumours, we emphasize the immunohistochemical features and the genetic data that should be used to identify each clinicopathological entity and thus contribute to improve the differential diagnosis from an anatomic pathology standpoint.

In selected cases, we also use the aforementioned molecular biomarkers to progress in the understanding of thyroid tumour pathogenesis, profiting from the fact that rare tumours, sporadic or familial, may be considered as a sort of experiments of nature that can provide interesting insights if appropriately studied. This scientific approach is however an exception since the book was conceived and produced to be as practical as possible for diagnostic purposes.

In order to achieve the maximum diagnostic usefulness, we did our best to illustrate the most important morphological features of the rare entities we have experience on and to organize, besides the general index, a separate index of the 64 entities (and variants) documented by 115 plates with 425 photographs.

We expect the book will be useful to the large spectrum of professionals and trainees we identified in the first paragraph of this Preface, as well as to the researchers interested in the area of thyroid oncology who feel challenged by the learning opportunities created through the study of the extraordinary set of rare "animals" herein presented.

Santiago de Compostela, Spain — José Manuel Cameselle-Teijeiro

Porto, Portugal — Catarina Eloy

Porto, Portugal — Manuel Sobrinho-Simões

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The expert assistance of Mrs F. Magalhães in preparing reference lists, as well as organizing the text into a publishable format and typing it, is gratefully acknowledged. Twenty-five of the 87 tumoural cases illustrated in this book come from our consultancy practice. The names of the colleagues to whom we are indebted are referred along the text. The task of producing this work has been greatly facilitated by the skill and knowledge of the editorial staff of Springer.

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Contents

Introduction

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Manuel Sobrinho-Simões, Catarina Eloy, Isabel Amendoeira, Paula Soares, Javier Caneiro-Gómez, Miguel Melo, and José M. Cameselle-Teijeiro

We think this is the right time to publish a book on rare tumours of the thyroid gland for a number of reasons.

The fourth edition of the WHO classification of thyroid tumours is scheduled to appear still in 2017 [1], 13 years after the third edition. During this period, it was possible to evaluate the relative frequency of the so-called rare tumours of the thyroid, to identify some new ones and to incorporate in the description of most of them, addi-

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tional molecular data at both the immunohistochemical and the genetic level.

Next-generation sequencing (NGS) methods have expanded enormously the latter field (genetic alterations) and are forcing us to rethink the classification of tumours in the thyroid, as well as elsewhere. The most impressive alteration in the evaluation of thyroid tumours after NGS regards the acknowledgement that the encapsulated follicular variant of papillary carcinoma should be put together, follicular adenoma and follicular carcinoma—the group of RAS-like tumours—rather than with the other subtypes of papillary carcinoma that fit into the group of BRAF-like tumours [2, 3]. Besides demonstrating the importance of "old" morphologic features (architecture, desmoplasia, infiltrative or expanding growth pattern, encapsulation), the aforementioned findings raise one of the most interesting problems of today's onco-pathology: How to incorporate into the classic morphologic classifications of tumours the molecular data? Such classifications predate the knowledge about the crucial role played by somatic mutations and other genetic alterations in tumour development. This new knowledge is changing tumour nosology and should be reflected in tumour classification whenever the molecular alterations provide meaningful information for diagnosis, prognosis and/or therapy selection purposes.

We have evolved from the sheer phenotype (e.g. oncocytic, oxyphilic or Hürthle cells) to the fine description (mitochondrion-rich cells) and from there to the present times in which we know the mutations of the nuclear genes encoding the mitochondrial proteins and the mutations of the mitochondrial OXPHOS genes that cause the oncocytic phenotype [4]. Furthermore, we know that the large majority of the oncocytic adenomas and carcinomas of the thyroid—which are not rare at all—are sporadic and may be linked to mutations of mitochondrial complex I genes and to large deletions of the mitochondrial DNA [5], whereas a limited number of oncocytic tumours are hereditary and are caused by germline mutations of nuclear genes [6]. The latter are associated with familial clustering of benign and/or malignant oncocytic tumours and are, indeed, rare tumours but will not be specifically addressed in this book because their phenotypes are similar to the common (and frequent) oncocytic tumours of the thyroid.

Many hereditary thyroid carcinomas, namely, those of C-cell origin (medullary thyroid carcinomas—MTC) will not also be addressed because they usually present a quite variable but identifiable phenotype that is easily confirmed by calcitonin immunoreactivity (and are not that rare). The same does not hold true, however, for some peculiar and rare morphologic and/or immunohistochemical variants of medullary carcinoma (e.g. calcitonin-negative MTCs), nor to some hereditary, well-differentiated carcinomas occurring in syndromic contexts (e.g. cribriform-morular variant of papillary carcinoma).

The field of hereditary well-differentiated carcinomas other than MTC is very interesting both diagnostically and pathogenically. Besides the cases with a peculiar morphology—the cribriform-morular carcinoma is a paradigm of this group—there are a number of cases of benign and malignant well-differentiated epithelial tumours that do not have a peculiar morphology but are extremely important for understanding thyroid carcinogenesis. This holds true, for example, for tumours arising in the context of Cowden and DICER syndromes. Curiously, most if not all of such hereditary well-differentiated carcinomas lack typical nuclear characteristics of papillary or follicular carcinoma, and they do not also display the typical genetic alterations of any of the two major types of carcinoma. This leads to the diagnosis of "Well differentiated carcinoma, not otherwise specified" concurring with the recently published results of Yoo et al. [7] that highlight the existence of a third molecular group of well-differentiated carcinoma—tumours that are not BRAF-like nor RAS-like.

Another issue we will try to address regards the peculiar morphology that some thyroid tumours display, not because of the neoplastic cells themselves, nor of their structural organization, but for the prominence of stromal elements, lymphocytes, macrophages and vessels. The exuberance and pattern of such host responses frequently give rise to rare morphologic entities that should be identified because they may be the consequence of a singular etiopathogenesis or many carry a special prognosis/therapy response. Like in the other his-

totypes of thyroid tumours, the search for genetic and/or epigenetic alterations in these settings is a must, and we will try to do it along the book.

Summing up, besides illustrating the rare morphology of tumours of the thyroid, we will also try to link their clinico-pathologic characteristics to molecular features (immunohistochemical and genetic alterations) in order to progress in the understanding of thyroid carcinogenesis.

For the sake of keeping the book as simple to use as possible, we decided to organize the chapters following the major chapters of the WHO books.

The second chapter will focus on rare variants of papillary thyroid carcinoma (PTC) starting by the hobnail (micropapillary) variant of PTC, a recently described variant that combines a peculiar morphology with quite specific molecular features and carries a guarded prognosis. Besides other rare (morphologic) variants, the chapter also includes some primary or metastatic tumours that raise difficult diagnostic problems either due to their awkward morphology or unexpected immunohistochemical features (e.g. mixed medullary-papillary carcinoma).

The third chapter is devoted to rare variants of follicular thyroid carcinoma (FTC) using, as a starting point, cases of Hürthle (oncocytic cell) carcinoma composed of clear cells and cases that do not display immunoreactivity for TG or TTF1. In the new WHO book (2017), the category of Hürthle cell (oncocytic) carcinoma, NOS, has been "rediscovered" paying a tribute to the unique clinical, macroscopic, histologic, ultrastructural and molecular features of such tumours [1]. Besides other rare morphologic and/or molecular variants of FTC, the chapter includes also a number of diagnostically difficult follicular adenoma subtypes.

The fourth chapter uses a case of poorly differentiated carcinoma (PDTC) to introduce the rare (and heterogeneous) group of small cell tumours of the thyroid, with an emphasis on the recently described CEFTE (carcinoma with Ewing family tumour elements) together with other rare histotypes that, at least superficially, fit into the area of poorly differentiated/undifferentiated carcinomas. This heterogeneous group of tumours is used to highlight the crucial importance of immunohistochemistry in the differential diagnosis of tumours depicting a small cell phenotype, as well as in the precise diagnosis of thyroid lymphomas and rare flowers such as the atypical (calcitonin-negative) MTC.

The fifth chapter is headed by a case cribriform-morular variant of PTC as an example of a rare form of PTC that is usually hereditary but may also be sporadic. This case is used to discuss the differential diagnosis with other thyroid tumours and to present a number of other rare, hereditary, non-medullary tumours occurring either isolated or in a syndromic context.

The sixth chapter is entitled "Other rare tumours and tumour-like lesions" and includes a heterogeneous group of rare thyroid tumours (thymic origin, mesenchymal, etc.) and tumour-like conditions. The chapter is headed by a series of tumour-like lesions that fit into the umbrella descriptive term of lesions originated from solid cell nests (SNC). Besides raising diagnostic problems, namely, when displaying a tumoural phenotype, such SCN lesions provide important clues for understanding the pathogenesis of some thyroid tumours.

In the last chapter, we briefly address the therapeutic problems raised by some of the aforementioned rare tumours.

References

1. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World health organization classification of tumours. pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
2. Castro P, Rebocho AP, Soares RJ, Magalhães J, Roque L, Trovisco V, Vieira de Castro I, Cardoso-de-Oliveira M, Fonseca E, Soares P, Sobrinho-Simões M. PAX8-PPARgamma rearrangement is frequently detected in the follicular variant of papillary thyroid carcinoma. J Clin Endocrinol Metab. 2006;91(1):213–20.
3. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159:676–90. 49
4. Máximo V, Lima J, Prazeres H, Soares P, Sobrinho-Simões M. The biology and the genetics of Hurthle cell tumors of the thyroid. Endocr Relat Cancer. 2012;19(4):R131–47. doi:10.1530/ERC-11-0354.

5. Máximo V, Soares P, Lima J, Cameselle-Teijeiro J, Sobrinho-Simões M. Mitochondrial DNA somatic mutations (point mutations and large deletions) and mitochondrial DNA variants in human thyroid pathology: a study with emphasis on Hürthle cell tumors. Am J Pathol. 2002;160(5):1857–65.
6. Máximo V, Botelho T, Capela J, Soares P, Lima J, Taveira A, Amaro T, Barbosa AP, Preto A, Harach HR, Williams D, Sobrinho-Simões M. Somatic and germline mutation in GRIM-19, a dual function gene involved in mitochondrial metabolism and cell death, is linked to mitochondrion-rich (Hurthle cell) tumours of the thyroid. Br J Cancer. 2005;92(10):1892–8.
7. Yoo SK, Lee S, Kim SJ, Jee HG, Kim BA, Cho H, Song YS, Cho SW, Won JK, Shin JY, Park do J, Kim JI, Lee KE, Park YJ, Seo JS. Comprehensive analysis of the transcriptional and mutational landscape of follicular and papillary thyroid cancers. PLoS Genet. 2016;12(8):e1006239.

Rare Papillary Thyroid Carcinomas

2

José M. Cameselle-Teijeiro, Catarina Eloy, Isabel Amendoeira, Paula Soares, Javier Caneiro-Gómez, Miguel Melo, and Manuel Sobrinho-Simões

Introduction

Papillary thyroid carcinoma (PTC) is a malignant epithelial tumour showing evidence of follicular cell differentiation and a set of distinctive nuclear features. Following the criteria of the last WHO classification, either papillae or invasion is required for a diagnosis of PTC [1]. Although the diagnosis of PTC is not usually problematic, numerous variants of PTC have been recognized,

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sometimes raising diagnostic difficulties. In the follicular-patterned tumours with PTC nuclear features, the diagnosis is based primarily on the identification of invasion signs and will not be addressed in this book [1, 2]. It is particularly important to recognize those variants of PTC that are associated with clinical aggressiveness, as is the case with tall cell variant, columnar cell variant, the recently described hobnail (micropapillary) variant of PTC and PTC displaying diffuse nuclear immunoreactivity for P53. Since the hobnail (micropapillary) variant of PTC is the rarest form of the aforementioned three morphologic variants and its diagnosis is more difficult, it will be specially addressed in this chapter, together with other (very) unusual forms of PTC.

Hobnail (Micropapillary) Variant of Papillary Thyroid Carcinoma

Hobnail (micropapillary) variant of PTC has been recently defined in the WHO classification as a rare variant requiring more than 30% of cells with hobnail features [1]. Because hobnail histology is more prevalent than micropapillary features, and the hobnail features appear to be more important for the diagnosis and prognosis of these tumours, hobnail variant (HV) of PTC is the preferred designation [3]. The prevalence of HV of PTC ranges from 0.2 to 1.2% of all PTCs [3–5].

This aggressive tumour is characterized by an advanced stage at presentation, with more than half of cases diagnosed in stages III or IV [3, 4, 6–8]. Regional lymph node metastases are present in more than 70% of cases, and distant metastases in about 30% of cases, mainly to the lung and bones [3–5, 7–10]. Extrathyroidal extension is seen in 70% and local tumour recurrence in about 25% of patients [3–8, 10]. The HV of PTC is prone to progression to undifferentiated carcinoma, thus confirming its aggressiveness [8]. For treatment, see Chap. 7.

Macroscopically, these tumours are usually large, being multifocality detected in about half of the cases [3–12]. The HV of PTC is characterized histopathologically by a combination of hobnail and micropapillary patterns [1, 4, 13] (Fig. 2.1). The hobnail cell appearance exhibits a peculiar loss of polarity in which the tumour cells lining the papillary or follicular structures display a high nuclear/cytoplasmic ratio with the nuclei located in the middle or apex of the cytoplasm. In the micropapillary areas, the neoplastic cells are loosely arranged in small clusters lacking fibrovascular cores coexisting with micropapillary structures usually lined by cuboidal, flat or hobnail cells indicating loss of polarity and cohesiveness (Fig. 2.2). HV of PTC typically shows a variable combination of papillary and follicular growth patterns and many clusters of hobnail cells that often show moderate to rarely high nuclear pleomorphism (Fig. 2.3), prominent nucleoli and

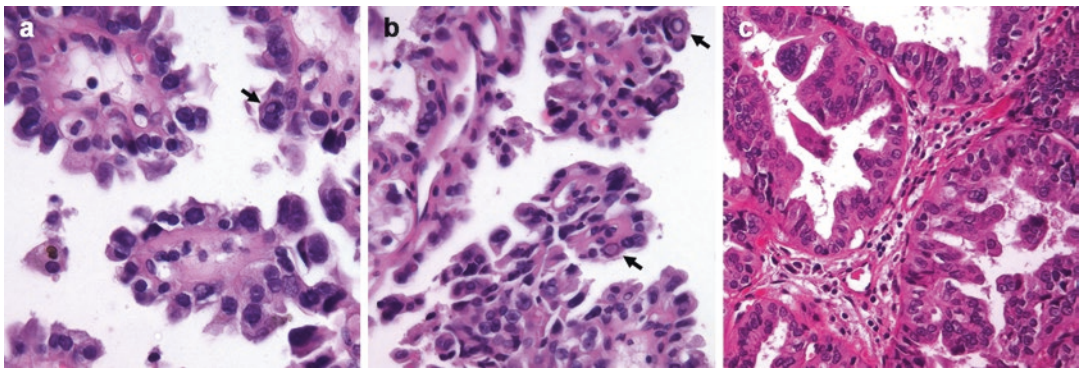


Fig. 2.1 Hobnail (micropapillary) variant of papillary thyroid carcinoma. This variant typically shows a variable combination of papillary (**a**), micropapillary (**b**) and follicular growth pattern (**c**). Both the papillae and the follicles are lined by hobnail cells with dark chromatin. Isolated nuclei with nuclear clarification and pseudoinclusions can also be seen (*arrows*). In some cases, the cytoplasm is abundant and eosinophilic (**c**)

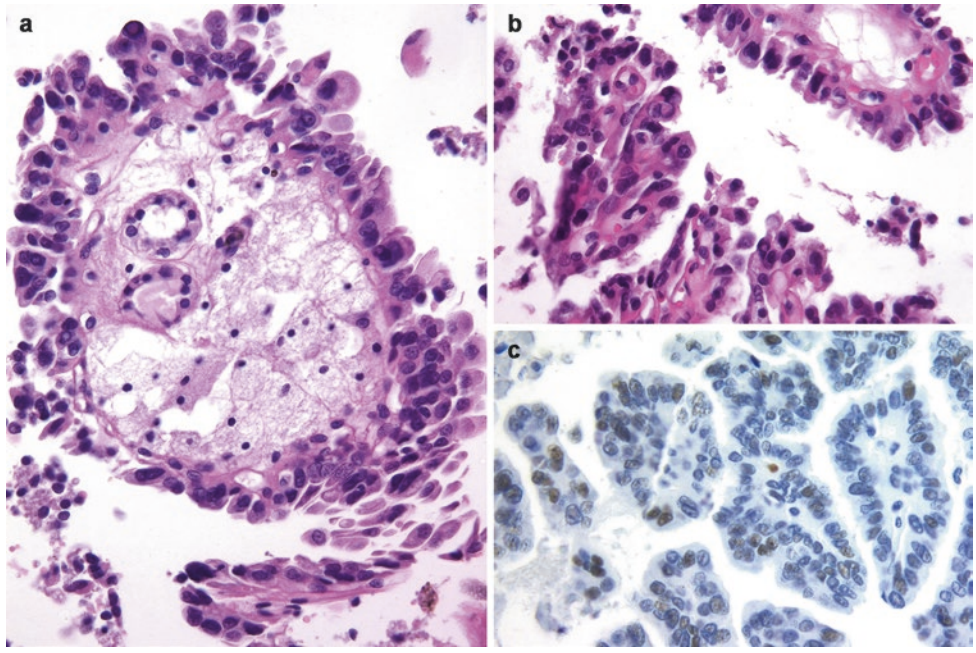


Fig. 2.2 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In this variant, hobnail cells are usually associated with a micropapillary pattern of growth evidencing a loss of polarity and cohesiveness (**a**, **b**). In contrast to what occurs in classic papillary carcinoma, nuclear p53 immunoexpression is usually found in this variant (**c**)

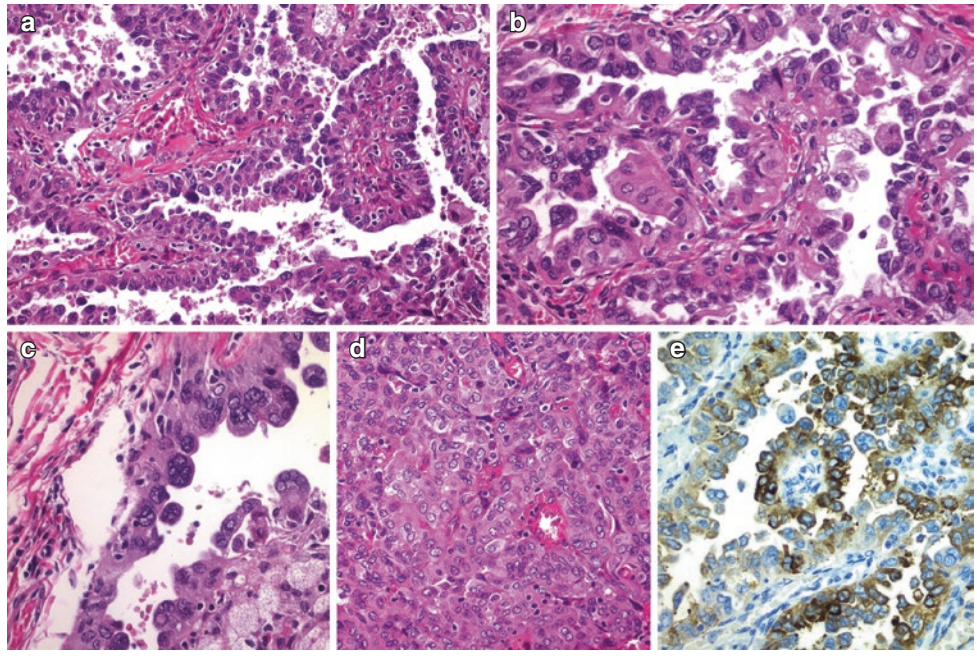


Fig. 2.3 Hobnail (micropapillary) variant of papillary thyroid carcinoma. This case showed in addition to papillary areas with typical hobnail cells (**a**, **b**), tumour cells with nuclear pleomorphism (**c**) and solid growth pattern areas (**d**). Tumour cells showed positivity for thyroglobulin (**e**) (Courtesy of Olga Prieto Gómez, Pontevedra, Spain)

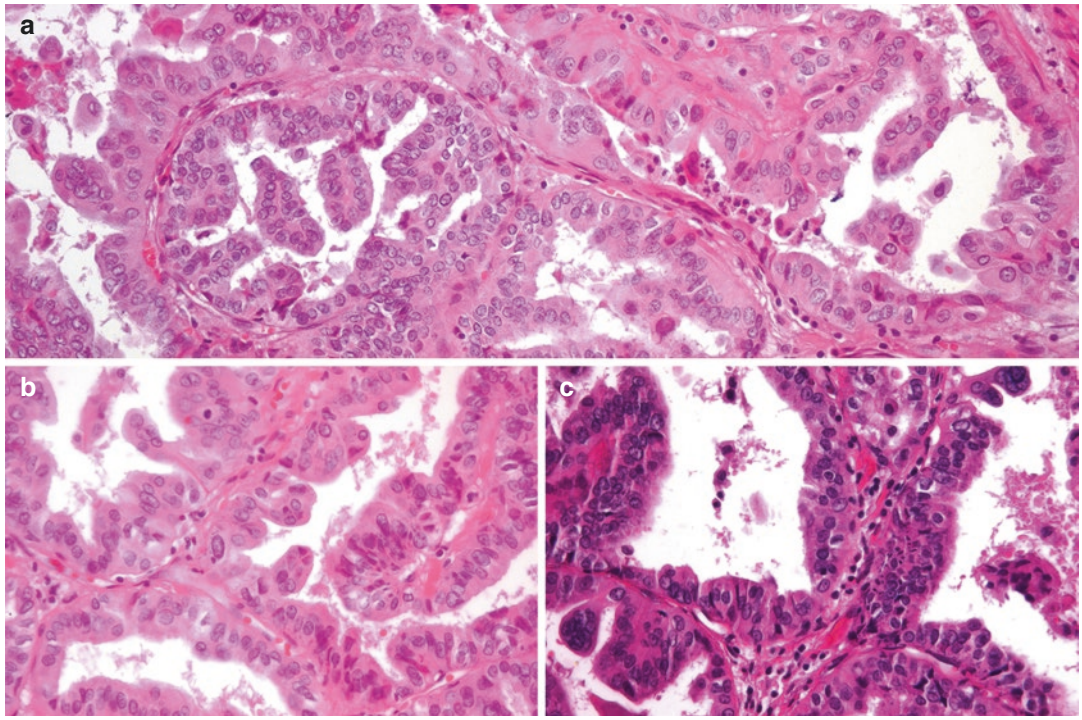


Fig. 2.4 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In the three microscopic photographs of this same case of hobnail variant of PTC, micropapillary pattern of growth coexist with tall/columnar pattern, tumour cells showing tall, dense eosinophilic (oncocytic) cytoplasm with mild (tall cell like) or prominent nuclear stratification (columnar cell like) (**a**–**c**)

dark chromatin [3, 8, 9]. Typical nuclear features of PTC are present but can be focal (Fig. 2.1). The cytoplasm is usually abundant and eosinophilic; there are cases with extensive clear cell change due to accumulation of glycogen [12] or with true Hürthle (oncocytic) cells by accumulation of abnormal mitochondria [14]. The typical areas of HV of PTC can be mixed with aggressive histologic variants such as tall cell, columnar cell and/or trabecular/solid variant in varying proportions [5, 7, 8] (Figs. 2.4 and 2.5).

Mitotic figures are more frequent than in conventional PTC [3–6, 9, 10]. The Ki-67 index is about 5–10% [3, 7, 8]. Foci of necrosis were detected in about 5% of cases and lymphovascular invasion is seen in more than half of the cases. Some papillae may have stalks composed of loose myxoid stroma or may contain lymphocytes or foamy macrophages (Fig. 2.2). Psammoma bodies are rarely seen. Thyroiditis and nodular hyperplasia in the remaining thyroid tissue have been described in some cases. Coexistence of small foci of undifferentiated carcinoma has been reported in two cases, and tumour progression from HV of PTC to undifferentiated carcinoma either in the tumour recurrence or in metastases can also been seen [4] (Fig. 2.6). Although hobnail features are more commonly observed in association with

Fig. 2.6 Hobnail (micropapillary) variant of papillary thyroid carcinoma. In this case with typical morphology of hobnail variant in the primary thyroid tumour (**a**), liver metastasis showed two neoplastic components: columnar cell papillary thyroid carcinoma areas (**b**), positive for thyroglobulin (**d**), merging with solid areas composed of undifferentiated round cells (**c**) with negativity for thyroglobulin but showing positivity for thyroid transcription factor (TTF-1) (**e**). See [9] for additional details

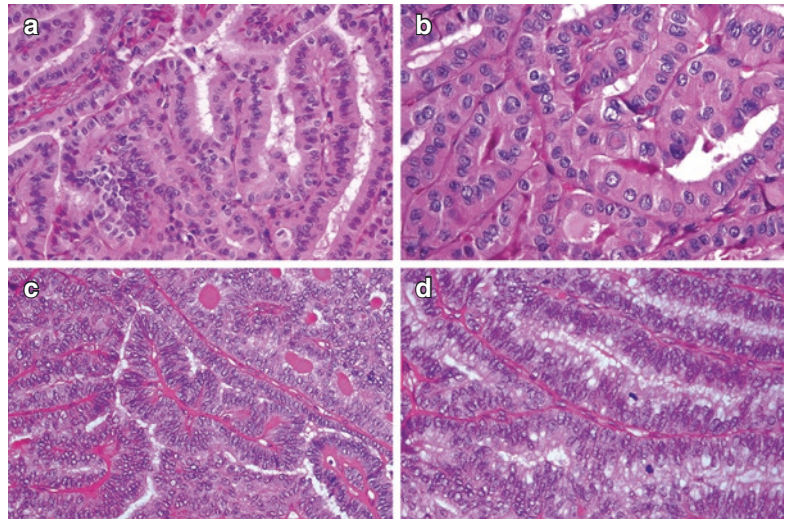
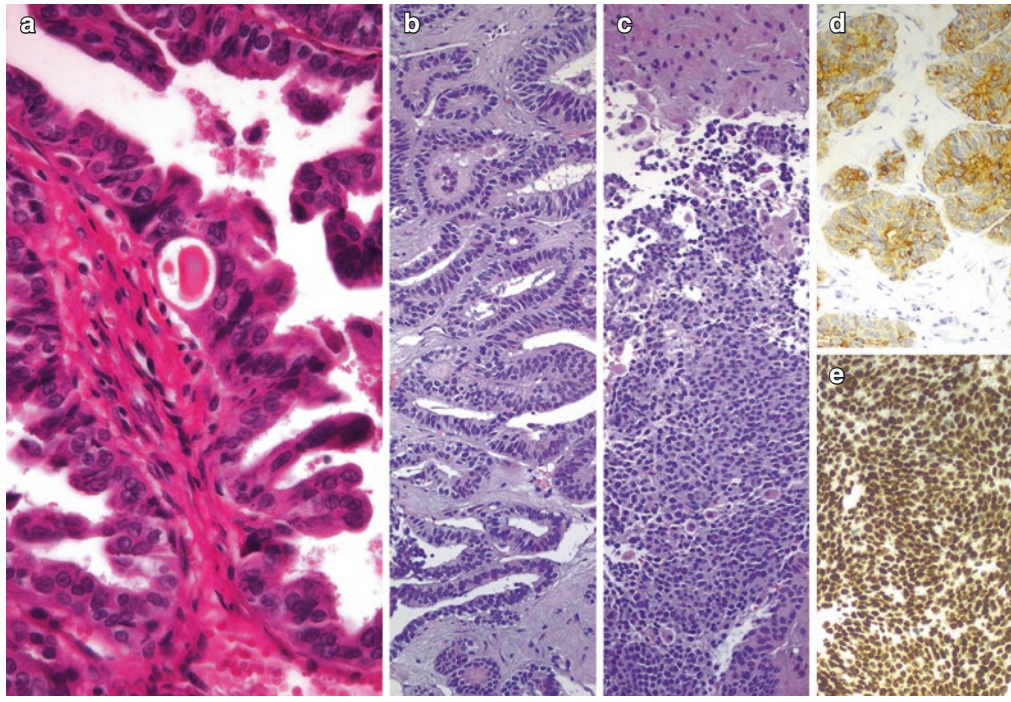


Fig. 2.5 Tall and columnar cell variants of papillary thyroid carcinoma. Hobnail variant of papillary thyroid carcinoma (PTC) can be mixed with other aggressive histologic variants such as tall cell and columnar cell variants in varying proportions. However, by definition, tall cell variant of PTC is made by cells that are two to three times taller than wide and which show abundant eosinophilic cytoplasm (oncocytic) (**a**, **b**). Typical nuclear features of papillary carcinoma are present, and nuclear pseudoinclusions are usually easily found (**b**). Since tall cell areas are frequently present in otherwise classic PTC, at least 30% of all tumour cells are reasonably required for the diagnosis of tall cell variant of PTC. Columnar cell variant of PTC is composed of columnar cells with marked pseudostratification that, at variance with the tall cell variant, lack typical nuclear features of PTC (**c**, **d**). The neoplastic cells show occasional clear cytoplasm reminiscent of an endometrioid adenocarcinoma (**d**), and coexistence of round tubular follicles with prominent nuclear pseudostratification may mimic an intestinal adenocarcinoma. Tall and columnar cell variants of PTC are both positive for thyroglobulin but lack hobnail features and micropapillary growth pattern



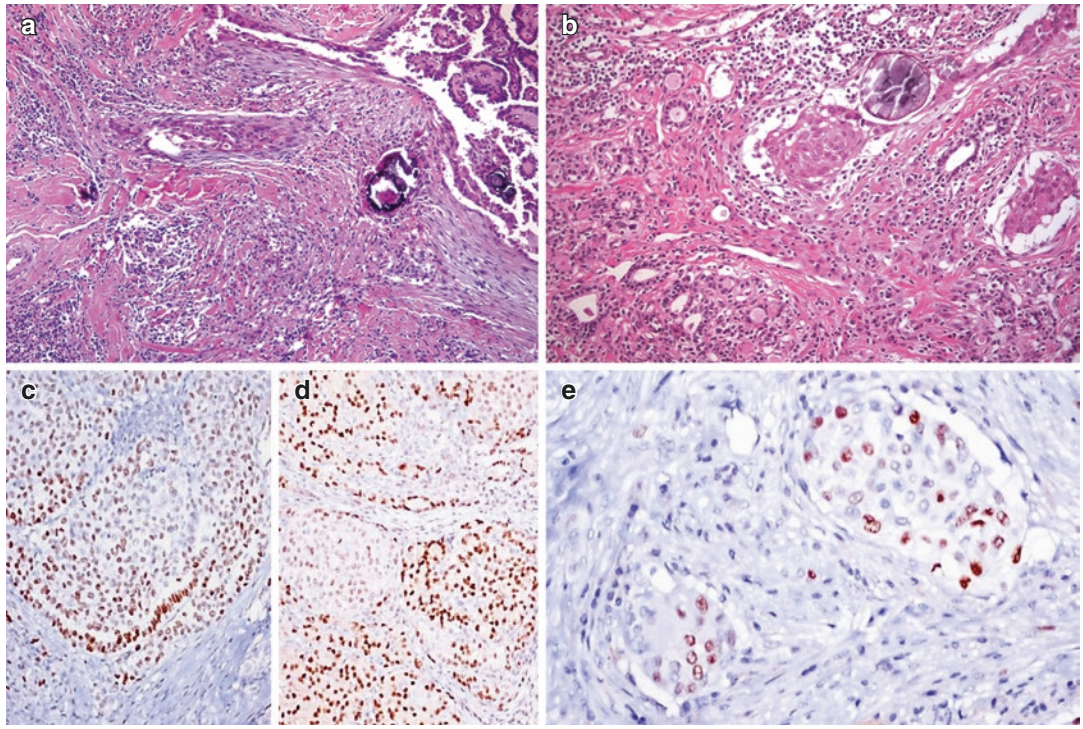


Fig. 2.7 Diffuse sclerosing variant of papillary thyroid carcinoma. In this variant there is diffuse involvement of one lobe or of the entire gland characterized by dense sclerosis, numerous psammoma bodies, papillary structures, prominent squamous metaplasia and background changes of chronic lymphocytic thyroiditis (**a**, **b**). Papillary formations partially lined by hobnail cells are typically seen (**a**). Tumour cells are positive for TTF1 (**c**), PAX8 (**d**) and p63 (**e**)

poorly differentiated thyroid carcinoma (PDTC) (22%) than with PTC [5] (1.3%), differential diagnosis between HV of PTC and PDTC should be made according to the Turin criteria [15] (see Chap. 4). Interestingly, numerous small papillary formations partially covered with hobnail cells are typically seen in the diffuse sclerosing variant of PTC, but in this variant, the papillae are located within intrathyroidal cleft-like spaces, associated with extensive squamous metaplasia, large number of psammoma bodies, lymphocytic thyroiditis and prominent fibrosis [1] (Fig. 2.7). Hobnail-like features may also occur as degenerative changes in cystic areas, but in this setting, the lesions do not display an infiltrative component and lack typical nuclear features of PTC.

Tumour cells are immunoreactive for thyroglobulin (Fig. 2.3), thyroid transcription factor-1 (TTF-1), TTF2 (FOXE1), paired box-8 (PAX8), cytokeratins (CK) (CK AE1/3, CK 7, CK 19), epithelial membrane antigen (EMA), Hector Battifora mesothelial cell-1 (HBME-1), galectin-3, cyclin D1, p27KIP1 and PTEN [3, 4, 6–10, 13]. Interestingly, in some cases, displaying positivity for thyroglobulin in the primary tumour and lymph node metastases, there may be total or partial negativity in distant metastases [3, 8, 13] (Fig. 2.6). Tumour cells are negative for CK 20, thyroperoxidase, calcitonin, chromogranin A and synaptophysin. Strikingly, intense and diffuse nuclear p53 expression is detected in most cases [3, 6–8, 10, 13, 16] (Fig. 2.2).

Fine needle aspiration biopsy (FNAB) is an effective method for diagnosing PTC, including HV cases [4, 8, 10–12]. In HV of PTC, the FNAB samples are typically highly cellular with little colloid and a bloody background. The tumour cells are organized in papillary-like, micropapillary and/or discohesive cell clusters in variable proportions. The characteristic isolated cells are of small to medium size showing eccentric nuclei teardrop cytoplasm (hobnail appearance), the so-called comet-like cells (Fig. 2.8). Syncytial cell clusters with apically placed nuclei may also

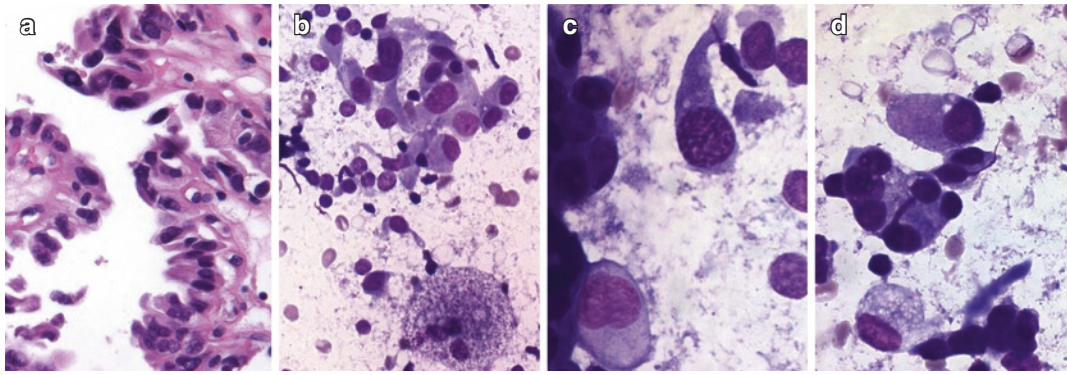


Fig. 2.8 Cytological specimens from hobnail variant of papillary thyroid carcinoma. Hobnail variant of PTC showing discohesive cells with loss of polarity and large nuclei (**a**). In this variant, samples from fine needle aspiration biopsy characteristically show isolated cells with eccentric nuclei teardrop cytoplasm (hobnail appearance), the so-called comet-like cells (**b**–**d**)

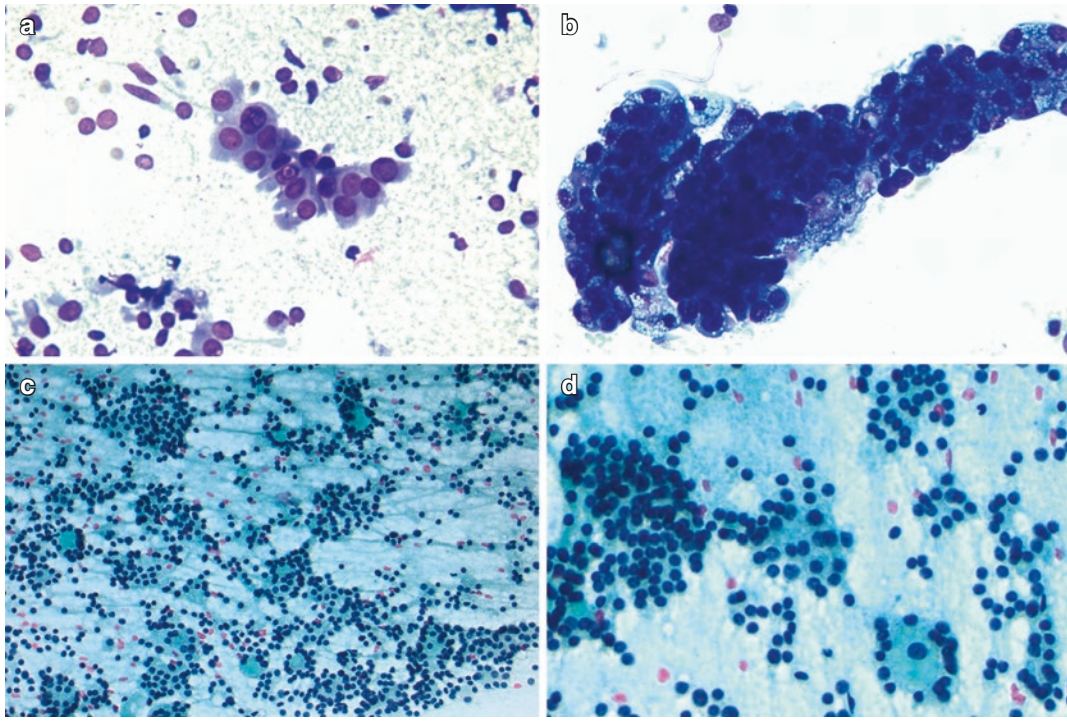


Fig. 2.9 Cytological samples from hobnail variant of papillary thyroid carcinoma. In these samples from the case showed in Fig. 2.3, columnar cells with nuclear pseudoinclusions (**a**, Diff-Quik stain) and bubbled cytoplasm (**b**, Diff-Quik stain) are seen. A poorly differentiated component, composed by aggregates of small cells with dark nuclei, is also detected ((**c**, **d**), Papanicolaou stain)

appear. Typical pseudoinclusions or multiple soap-bubble-like intranuclear inclusions are commonly detected. Variable degrees of nuclear atypia, grooves, nuclear stratification and atypical mitoses can also be seen [4, 10, 11] (Fig. 2.9). Immunohistochemical positivity for thyroglobulin, TTF-1, HBME-1, E-cadherin and p53 can be detected in cytological samples [10].

In addition to the frequent immunohistochemical positivity for p53 protein, *BRAF*^{V600E} mutation has been detected in about 70% cases of HV of PTC using both cytological or tissue samples

[4, 5, 7, 8, 10, 11, 13]. Concurrent *BRAF*^{V600E} and *TERT* promoter mutations were found in one case with undifferentiated carcinoma areas in distant metastases [8], but no *TERT* promoter mutations were identified in a series of ten cases of common HV of PTC [4]. *RET/PTC1*, but not *RET/PTC3* rearrangements, have been detected in less than 20% of HV cases [7, 8, 13].

Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

The diffuse sclerosing variant of PTC is more frequent in female, young patients [1]. It is a PTC variant that diffusely involves one or both thyroid lobes, clinically mimicking Hashimoto thyroiditis [1, 2]. This variant is characterized by dense sclerotic stroma involving nests of solid, squamoid, spindled and papillary arranged cells (Fig. 2.7). The cells express focally thyroglobulin, TTF-1, PAX8 and p63 (Fig. 2.7). Abundant psammoma bodies, lymphocytic infiltration and extensive lymph vessel invasion are also present. Lymph node and lung metastases are frequent and may be difficult to diagnose since they may be thyroglobulin (often) and TTF-1 (more rarely) negative. The disease-free survival rate is lower than that of patients with conventional PTC.

Spindle Cell Variant of Papillary Thyroid Carcinoma

Spindle cell transformation or metaplasia has been so far demonstrated in the context of epithelial benign and malignant conditions [1, 2, 17]. Rare cases of PTC show areas of spindle cell differentiation that may represent more than 80% of the tumour [1, 17]. Microscopically, spindle tumour cells are arranged in bundles, frequently showing nuclear grooves and occasional, less frequent, pseudoinclusions (Fig. 2.10). Follicular structures are usually seen in the periphery of the

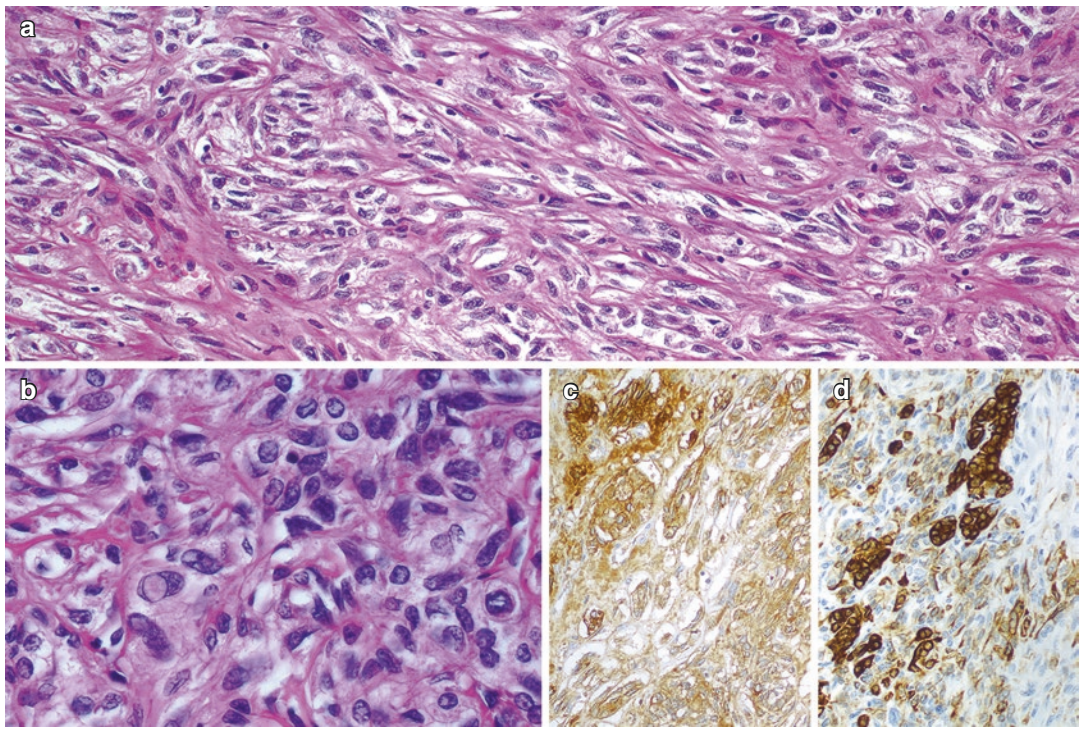


Fig. 2.10 Spindle cell variant of papillary thyroid carcinoma. This variant is mainly composed of spindle cells arranged in bundles having a mesenchymal-like appearance (**a**). The nuclei of the spindle cells are large, oval and grooved and displayed pseudoinclusions (**a**, **b**). Tumour cells are immunopositive for thyroglobulin (**c**) and keratins (clone AE1/AE3) (**d**)

tumour. The spindle cells are actually epithelial in nature and follicular cell originated, as evidenced by their positivity, sometimes focal, for pan-keratins and thyroglobulin, TTF-1 and PAX8 (Fig. 2.10). The differential diagnosis of this tumour includes reactive processes and a variety of primary thyroid tumours and metastatic neoplasms (see spindle cell tumours in Chap. 6). In contrast to reactive changes occurring post FNAB, true spindle cell foci of PTC are not associated with haemorrhage, new capillary blood vessels or hemosiderin-laden macrophages. Distinguishing features from anaplastic carcinoma include the fact that the PTC spindle cells are bland without mitotic activity, pleomorphism and necrosis. Because spindle cell variant of PTC behaves similarly to PTC lacking such features, it is important to separate this variant of PTC from aggressive spindle cell malignant neoplasms (see Chap. 6).

Spindle Cell Papillary Carcinoma with Fasciitis-Like Stroma/ Fibromatosis

In rare cases, the stroma of PTC is so abundant and cellular as to resemble nodular fasciitis, fibromatosis and other proliferative myofibroblastic processes [1, 2]. PTC with fasciitis-like stroma, also designated as PTC with fibromatosis-like stroma, is a biphasic tumour composed by a stromal benign component and PTC neoplastic foci [1]. The stromal component may predominate obscuring the presence of PTC foci. The stromal cells are spindled, bland looking and arranged in fascicles in a more or less collagen-rich background. This component, thought to be representative of a myofibroblastic population, expresses nuclear beta-catenin and cytoplasmic smooth muscle actin and does not express cytokeratins nor TTF-1 [18]. The PTC foci disclose the typical nuclear features and the respective immunohistochemical profile. The recognition of this malignant component, with the eventual aid of cytokeratins staining to highlight the epithelial cells, will allow the differential diagnosis with other stromal-rich lesions of the thyroid, namely, end-stage/fibrous variant of Hashimoto thyroiditis, IgG4-associated/Riedel thyroiditis, multifocal fibrosing thyroiditis and solitary fibrous tumour (see Chap. 6). The distinction between PTC with fasciitis-like stroma and paucicellular variant of anaplastic carcinoma is not difficult since the latter presents as (very) large tumour with atypical, often bizarre, cells throughout its extension (see Chap. 6). The overall and recurrence-free survival for patients with PTC with fasciitis-like stroma/fibromatosis may be lower than for other PTC variants.

The case illustrated in Fig. 2.11 is a PTC with fasciitis-like stroma diagnosed in a 68-year-old female patient submitted to total thyroidectomy due to nodular adenomatous goitre. The macroscopic examination disclosed a poorly circumscribed nodule in the isthmus with microscopic predominance

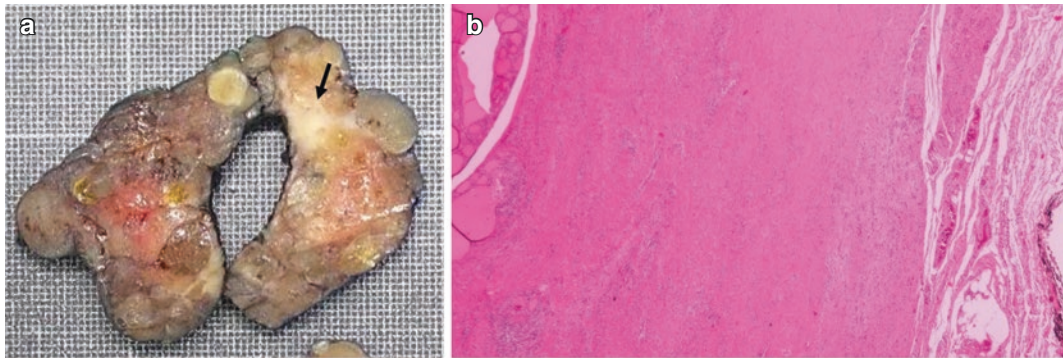
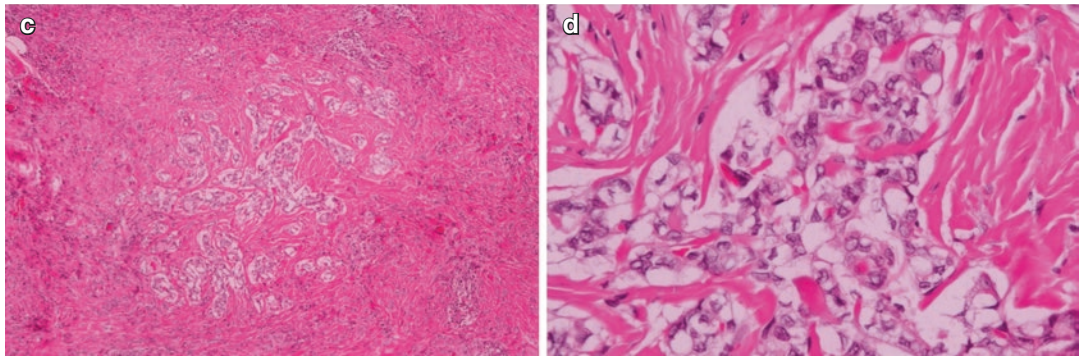


Fig. 2.11 Spindle cell papillary carcinoma with fasciitis-like stroma. Macroscopic features of the tumour (*arrow*) (**a**). There is abundant sclerotic stroma without atypical nuclei (**b**). Scattered foci of epithelial cells are arranged in trabeculae or small follicles (**c**). Papillary thyroid carcinoma nuclear features can be seen in the epithelial foci (**d**) (Courtesy of Eva Sigstad and Krystyna Kotanska-Grøholt, Oslo, Norway)



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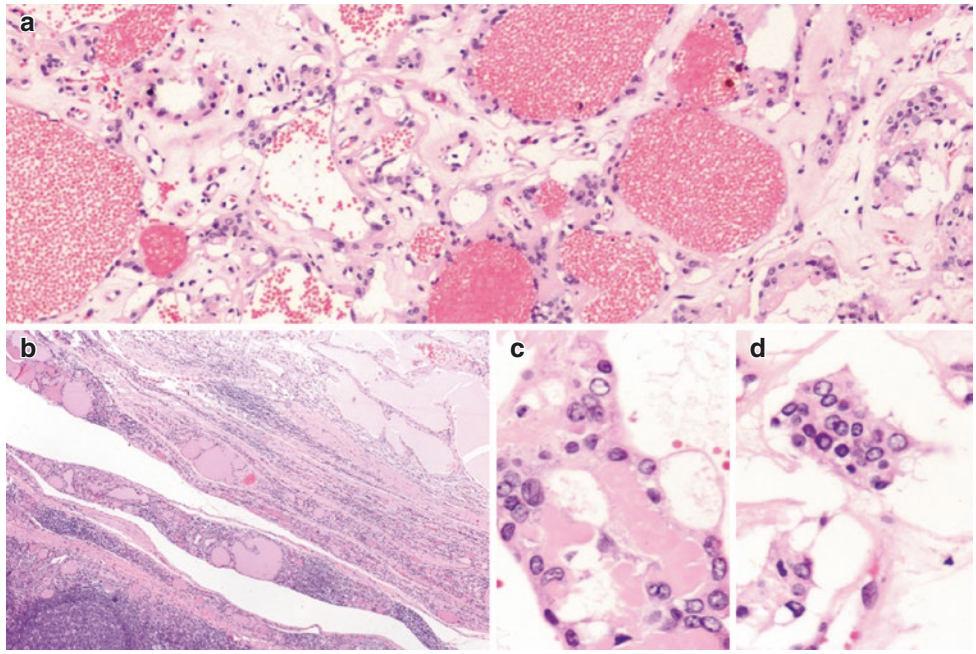


Fig. 2.12 Angiomatoid variant of papillary thyroid carcinoma. The vascular-like pattern of the tumour (**a**) in a background of Hashimoto-type thyroiditis (**b**) and the typical PTC nuclear features (**c**), including nuclear pseudoinclusions (**d**), can be seen in this angiomatous variant of PTC (Courtesy of Alexandra Betts, Malta)

of a cellular bland stroma component with occasional lymphoid aggregates and scarce PTC foci.

Angiomatoid Variant of Papillary Thyroid Carcinoma

The angiomatoid variant of PTC that develops in the context of Hashimoto thyroiditis can be confused with a vascular tumour if the characteristic nuclear features of PTC in the cells lining the vascular-like spaces are not searched at high magnification [19]. Such vascular-like spaces can display a prominent anastomosing pattern; are lined by TTF-1, PAX-8 and thyroglobulin positive; are cuboidal to flat cells; and are surrounded by a collagenous to myxoid stroma.

The case illustrated in Figs. 2.12 and 2.13 is from a 56-year-old woman with clinical and cytological diagnosis of Hashimoto thyroiditis

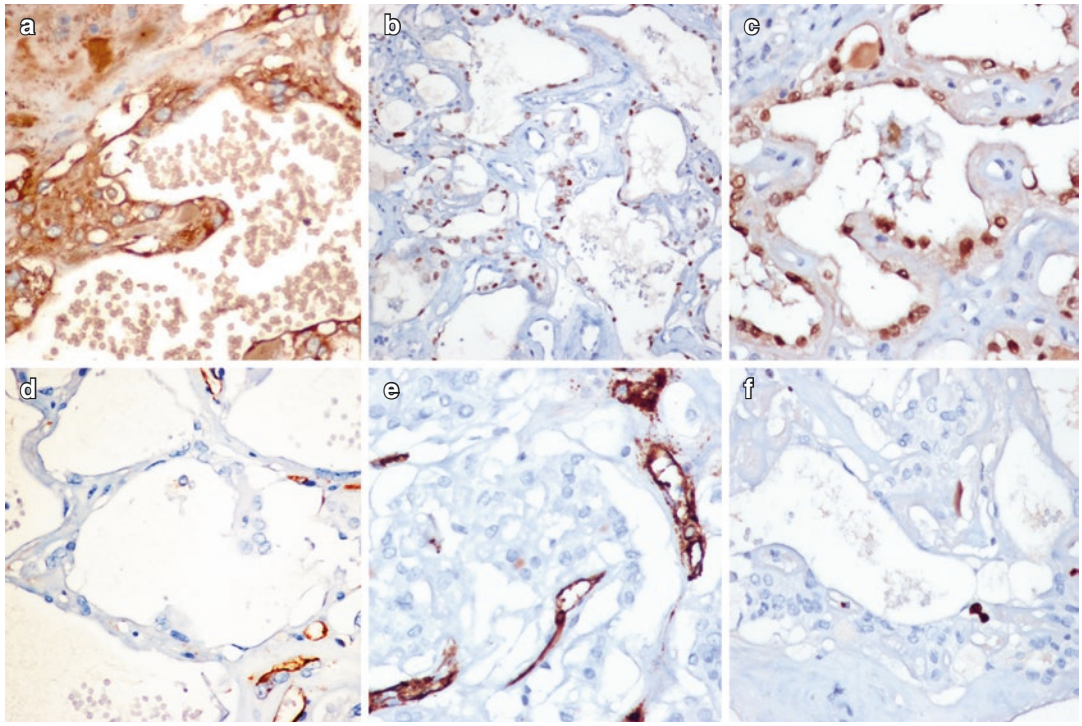


Fig. 2.13 Immunohistochemical profile of the cells that line the vascular-like spaces in the angiomatous variant of papillary carcinoma. The tumour cells express thyroglobulin (**a**), TTF-1 (**b**) and PAX8 (**c**), while the vascular markers CD31 (**d**) and CD34 (**e**) are not expressed. The Ki-67 labelling index is very low fitting with the low-grade features of the tumour (**f**)

(thyroid peroxidase antibodies >1000 IU/ml) who presented with a painless nodule in the left lobe measuring 25 mm in its largest dimension, documented in the neck ultrasound. This nodule was "cold" at scintigraphy. Macroscopically, the thyroid had a pale, vaguely nodular appearance. An encapsulated nodule measuring 25 × 25 × 17 mm was present in the upper half of the left lobe. This nodule had a solid, brownish, variegated cut surface. At histological examination, there were lesions consistent with Hashimoto-type thyroiditis and a well-circumscribed nodule surrounded by an irregular capsule (Fig. 2.12). The nodule had an angiomatoid appearance caused by irregularly shaped spaces filled with red blood cells. The lining of the spaces and some solid/trabecular areas intermingled with the spaces were composed by cells with clear and irregularly shaped nuclei, some with pseudoinclusions. There were no signs of vascular invasion. The neoplastic cells in the nodule expressed TTF-1, PAX8, thyroglobulin and cytokeratins (Fig. 2.13). Calcitonin, CD31, CD34 and D2-40 were not expressed in the neoplastic cells. CD31 and CD34 highlighted a prominent vascular network in the nodule. *BRAF* and *N-RAS* mutations were not detected.

Thyroglobulin-Negative Papillary Thyroid Carcinoma

PTC without thyroglobulin expression represents the type of tumour that is difficult to say if it is rare or if it is common but has been passed by undetected. In cases with less typical PTC cells, as occurs in the spindle cell variant, the solid variant or in the solid areas of the diffuse sclerosing variant of PTC, thyroglobulin can be expressed only focally [1, 2]. Cases of PTC that are completely negative for thyroglobulin in the setting of a normally stained remaining thyroid

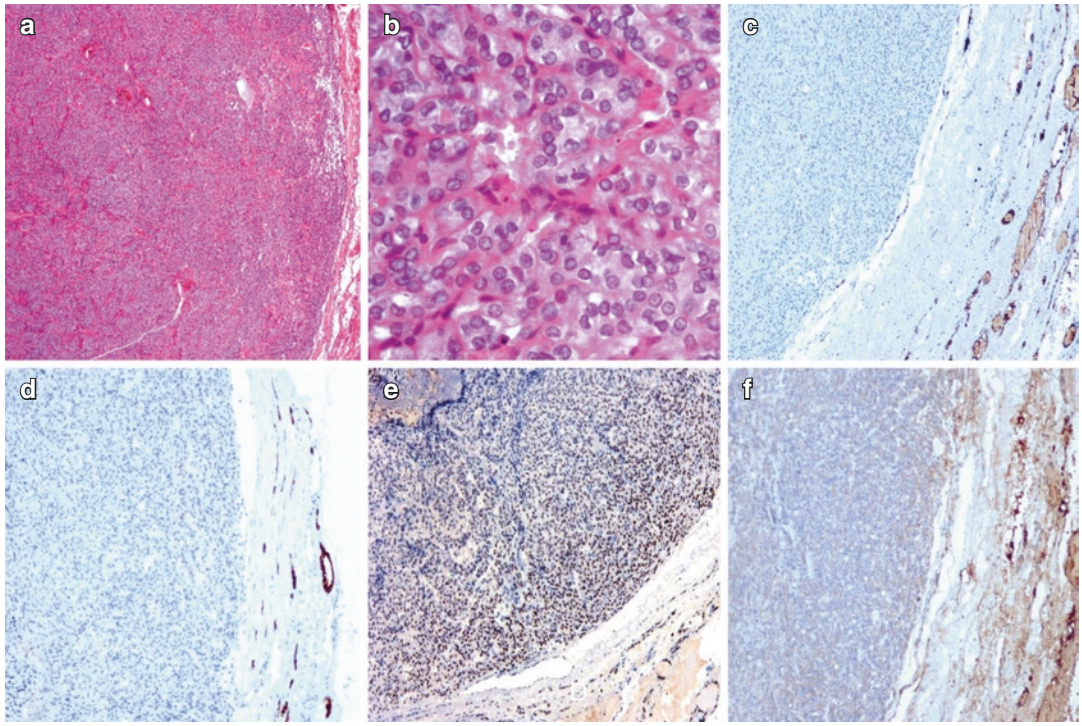


Fig. 2.14 Thyroglobulin-negative papillary thyroid carcinoma. This image shows a PTC with solid pattern (**a**) disclosing the typical nuclear features (**b**) and without reactivity for thyroglobulin (**c**) and thyroperoxidase (**d**). Tumour cells are positive for TTF-1 (**e**) and T4 (**f**)

tissue may represent situations with underlying somatic mutations of the thyroglobulin gene or other genes codifying proteins engaged in the production of thyroglobulin. The search for other products of the follicular cell metabolism, such as thyroperoxidase and T4, can help in the identification of the follicular cell differentiation, thus ruling out a C-cell differentiation. One can also search for the presence of thyroglobulin mRNA using FISH. It is very important to exclude a lack of thyroglobulin expression due to poor fixation or other pre-analytical limitations. The case of thyroglobulin-negative PTC illustrated in Fig. 2.14 is from a 2-year-old boy with a 1.5 cm nodule in the thyroid, well circumscribed, with a predominantly solid growth pattern that did not disclose infiltrative growth nor vascular invasion. The nuclei of the neoplastic cells were clear and irregularly shaped, typical of PTC. The neoplastic cells in the nodule did not express thyroglobulin nor thyroperoxidase and expressed vimentin, TTF-1 and T4 (Fig. 2.14). Calcitonin was not expressed in the neoplastic cells.

Taking into consideration that the follow-up of patients with PTC is mainly based on serum thyroglobulin measurements, this variant raises important questions from the clinical standpoint. The identification of this variant in the original pathology report should prompt physicians to perform more frequent imaging procedures, because serum thyroglobulin may not be a reliable tumour marker in this setting. On the other hand, if during the follow-up of patients with differentiated thyroid carcinomas physicians face the rare occurrence of disease persistence/recurrence with undetectable serum thyroglobulin levels, the hypothesis of a thyroglobulin-negative variant should be sought.

Papillary Thyroid Carcinomas with Unusual Immunohistochemical Reactivity

Rare cases of PTC, particularly its columnar cell variant, as well as the morular structures of the cribriform-morular variant of PTC (see Chap. 5),

can show aberrant nuclear CDX2 expression, an intestine-specific homeobox gene transcription factor [20–23]. Besides, there are rare cases of PTC with positivity for CA19.9 in the primary and/or metastatic foci, as well as cases of PTC with anaplastic transformation also reported as having CA 19.9 positivity [24, 25]. In Fig. 2.15, we illustrate a case of PTC with marked nuclear stratification (columnar cell variant) and positivity for both CDX2 and CA19.9.

Another interesting finding regards the co-expression of thyroglobulin and p53 in some cases (less than 3%) of PTC that usually display dark pseudostratified nuclei and are thought to carry a guarded prognosis [26–28]. Some aggressive forms of PTC such as tall cell, columnar cell and hobnail variant of PTC, as well as rare cases of mixed columnar cell and tall cell variant of PTC, (poorly differentiated) cribriform-morular variant of PTC and squamous cell carcinoma associated with tall cell variant of PTC, exhibit a higher rate of p53 immunopositivity than common PTC [3, 8, 13, 20, 23, 29–31]. The case illustrated in Fig. 2.16 (courtesy of Abir Al Ghuzlan, Villejuif, France) is a partially encapsulated classic PTC occurring in a 22-year-old

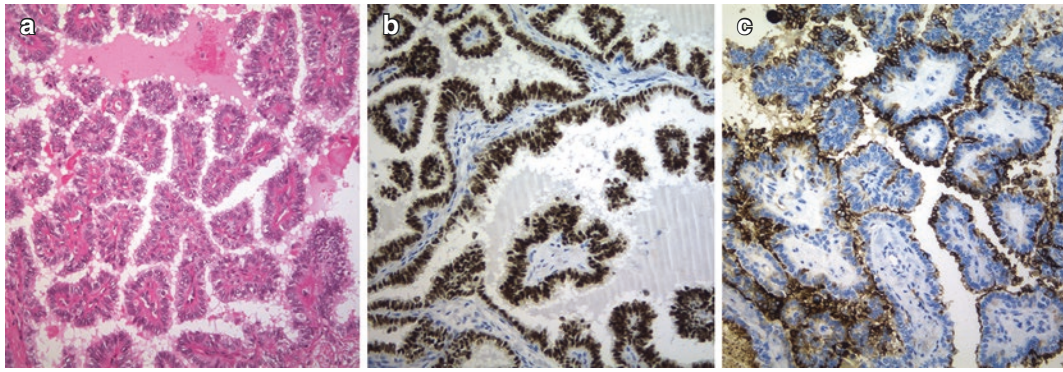


Fig. 2.15 Papillary thyroid carcinoma with unusual immunohistochemical features. This case of columnar cell variant of PTC (**a**) showed diffuse positivity for CDX2 (**b**) and CA19.9 (**c**)

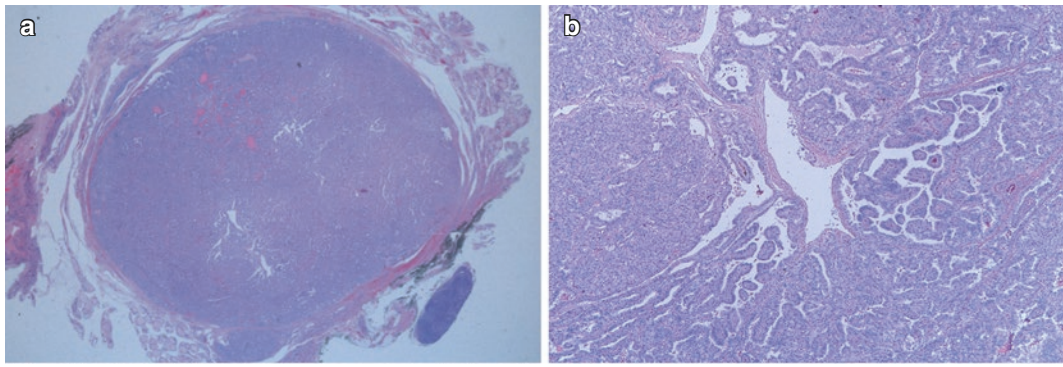
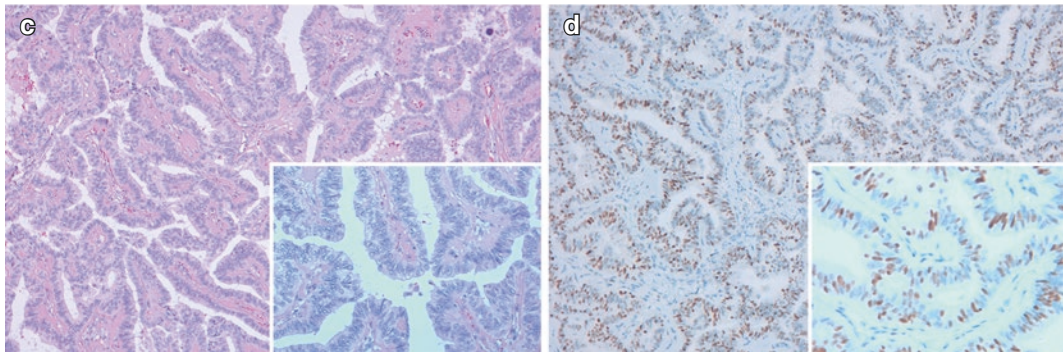


Fig. 2.16 p53 positivity in classic papillary thyroid carcinoma (PTC) with columnar cell carcinoma features**.** Partially encapsulated classic PTC (**a**) with papillary architecture (**b**, **c**) and columnar cell features (**c**). Intense, diffuse immunoexpression for p53 was encountered (**d**)



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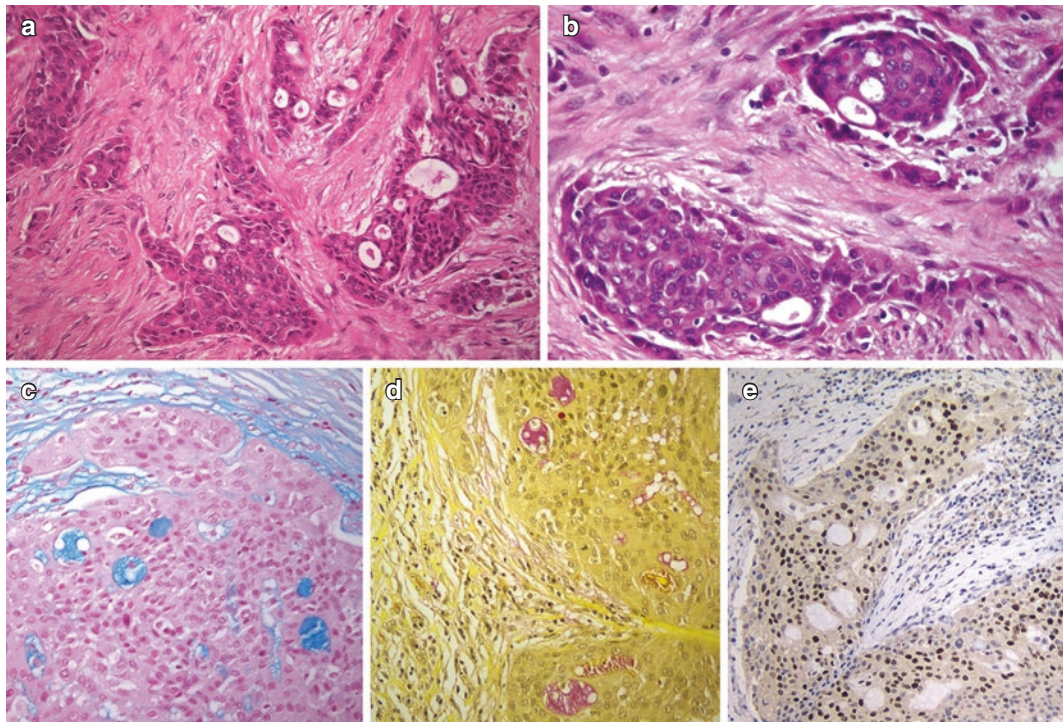

Fig. 2.17 Mucoepidermoid carcinoma of the thyroid. The tumour is composed of epithelial nests showing epidermoid and mucinous components surrounded by a fibrotic stroma (**a**, **b**). Mucinous material positive for Alcian blue stain (**c**) and Mayer's mucicarmine (**d**) can be seen in the glandular lumina. Positivity for p63 can also be seen in epidermoid and ductal cells (**e**)

woman that displayed foci with columnar cell carcinoma features (pseudostratification of the neoplastic cells and crowding of the nuclei) and intense nuclear immunoexpression for p53. Staging, including the presence of capsular and, mainly, vascular invasion, remains, nevertheless, the most important prognostic factor [16].

Mucoepidermoid Carcinoma (MEC) of the Thyroid

MEC is a malignant epithelial neoplasm characterized by a combination of squamous and mucinous components [1, 2]. Figure 2.17 shows the typical features of MEC, demonstrating inter-

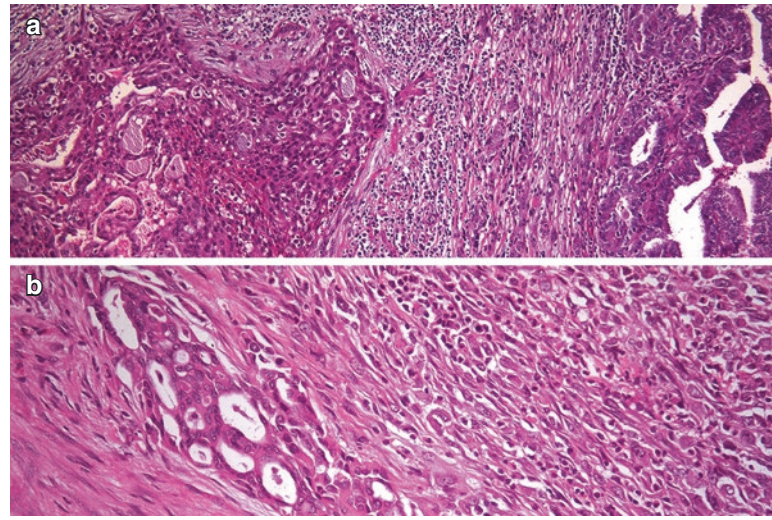

Fig. 2.18 Mucoepidermoid carcinoma of the thyroid. In this case, mucoepidermoid carcinoma (at *left*) is associated with PTC (at *right*) (**a**). In the picture below, mucoepidermoid carcinomas (at *left*) with anaplastic transformation (at *right*) is seen (**b**)

twined nests of epidermoid cells and mucinous components in a fibrotic stroma. The epidermoid component is arranged in sheets usually with keratin pearl formation, whereas the cuboidal, goblet-like mucous cells line ducts or glandular spaces. Hyaline bodies (PAS-positive droplets) resembling colloid may appear in the mucocyte cytoplasm. A cribriform-like pattern with elongated lumina containing colloid-like material and papillary infoldings can be seen. Ciliated cells are sometimes present. Mucin can be intra- and/or extracellular. The tumour cells have medium-sized nuclei with rather pale chromatin resembling PTC nuclei. Nuclear grooves and pseudoinclusions can be seen, and psammoma bodies occasionally occur. Mitotic figures are rare as are foci of necrosis. PTC (classic, follicular variant or tall cell variant) has been found associated with MEC (Fig. 2.18). In some rare cases of MEC (with or without PTC), there is merging with undifferentiated (anaplastic) areas (Fig. 2.18) or coexisting poorly differentiated (insular) transformation. Areas with follicular carcinoma or Hürthle cell carcinoma are much less common. Lymphocytic (Hashimoto) thyroiditis is frequently associated. Most MECs are focally positive for thyroglobulin, PAX8 and TTF-1, with positivity for p63 in epidermoid foci and ductal basal cells (Fig. 2.17). The main differences between MEC and sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) are summarized in Table 2.1.

Table 2.1 Main clinical, pathological and immunohistochemical features of mucoepidermoid carcinoma (MEC) and sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)

	MEC	SMECE
Age (years)	Median 47 (range: 10–91)	Median 55 (range: 32–89)
Gender distribution (F:M)	2:1	7:1
Extrathyroidal extension	≈25%	≈40%
Cervical lymph node metastases	≈40%	≈35%
Distant metastases	<10%	≈22%
Perineural invasion	Rare	Common
Lymphocytic thyroiditis or Hashimoto thyroiditis	≈40%	Common
Association with PTC	≈50%	Rare
Thyroglobulin positivity	Usually positive	Usually negative
TTF-1 positivity	Usually positive	≈50%

Sclerosing Mucoepidermoid Carcinoma with Eosinophilia (SMECE)

A case of SMECE from a 13-year-old female with no history of radiation exposure and a painless cervical nodule with 4 months of evolution is illustrated in Fig. 2.19. The thyroid function tests were normal and anti-thyroglobulin and anti-microsomal antibodies were detected in the serum. The ultrasound showed a solid, hypoechogenic nodule, with microcalcifications in the left lobe. The patient underwent FNAB of the nodule and a diagnosis of follicular tumour was made. The total thyroidectomy specimen disclosed a 2.5 cm well-circumscribed, whitish and firm nodule that by light microscopy was a nonencapsulated tumour composed by anastomosing clusters of squamoid cells mixed in a sclerotic background with abundant lymphocytic infiltration and eosinophils (Fig. 2.19). The tumour cells

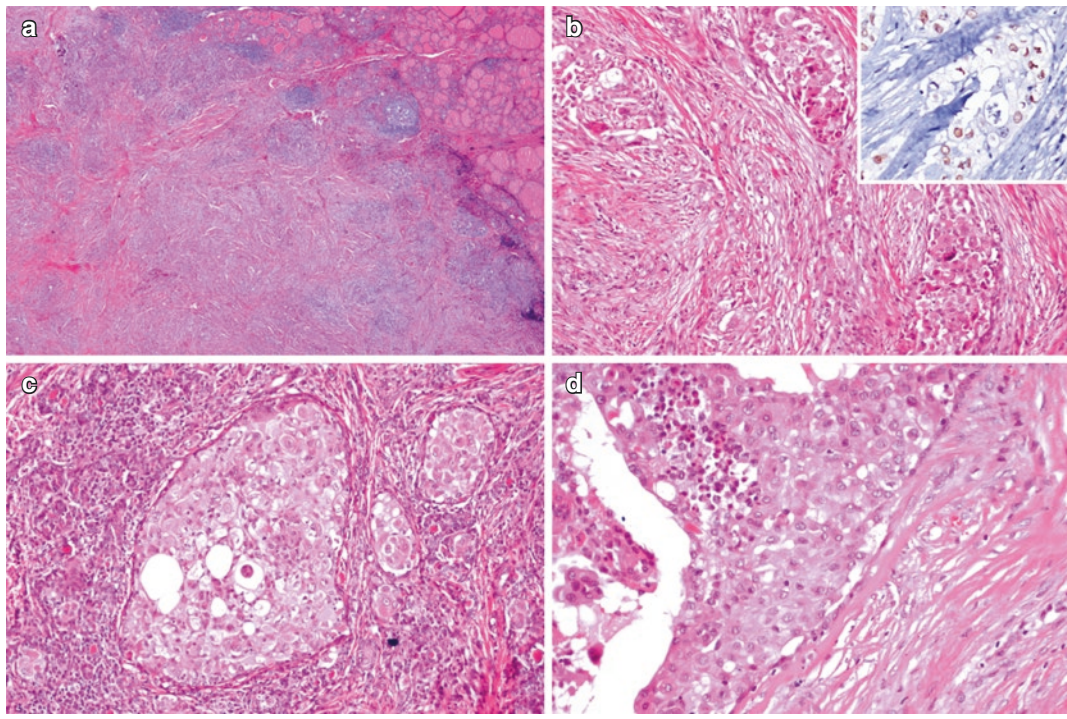

Fig. 2.19 Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE). This is a case of SMECE coexisting with exuberant lymphocytic Hashimoto-type thyroiditis (**a**). The tumour discloses nests of squamoid cells (**b**, **c**) that express p63 (**b**, *inset*) that are surrounded by a prominent collagenous stroma rich in lymphocytes and eosinophils (**d**)

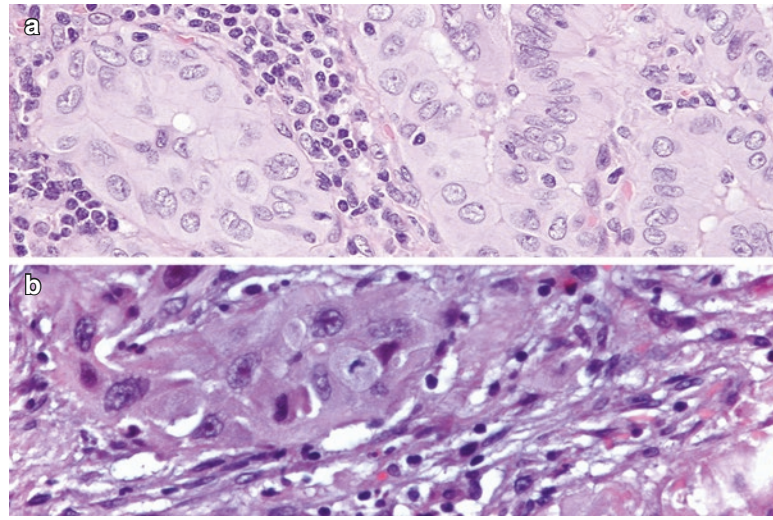

Fig. 2.20 Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE). SMECE is a low-grade tumour that may coexist with PTC and must be distinguished from both PTC with squamous cell metaplasia (**a**) and from the highly aggressive primary or metastatic squamous cell carcinoma (**b**)

showed squamoid differentiation and occasional intracellular accumulation of mucin. Thyroglobulin was not detected in the neoplastic cells as it often occurs (see Table 2.1). Vascular invasion and foci of necrosis were present. No mutations were detected in *BRAF* or (*K*-, *N*-, *H*-) *RAS* genes nor *RET/PTC* or *PAX8/PPAR*gamma rearrangements. SMECE is a low-grade tumour that may coexist with PTC and must be distinguished from PTC with squamous cell metaplasia [1, 2, 32] (Fig. 2.20).

Tumour-in-Tumour of the Thyroid with Neoplastic Solid Cell Nest Features

Tumour-in-tumour phenomena can occur in the thyroid mainly reflecting the occurrence of metastases into follicular adenoma and/or into follicular variant of PTC [33]. In other situations, the different components of the tumour that assumes a biphasic or multiphasic growth pattern originate from the thyroid [34]. This is the case of a singular tumour-in-tumour of the thyroid with neoplastic solid cell nest features illustrated in Figs. 2.21 and 2.22. It is a tumour in a 70-year-old male submitted to surgery due to non-toxic nodular goitre and normal thyroid function tests. Extensive investigation of primary tumours located in other organs was performed and nothing was found. The surgical specimen presented an encapsulated nodule in the upper pole of the right lobe with a tumour-in-tumour features and without signs of capsular or vascular invasion. There was an adenoma at the periphery of the tumour beneath the capsule. The second layer had the appearance of follicular variant of PTC and the central lesion, which constituted the core of the nodule, presented a solid pattern of growth (Fig. 2.19). This central lesion was composed of monotonous epithelioid cells with oval nuclei and eosinophilic cytoplasm that exhibited a palisade organization at the periphery, as it is frequently observed in solid cell nest component (Fig. 2.21). The central lesion did not express TTF-1, calcitonin or thyroglobulin and expressed p63, as also did the main cells of the solid cell nests (Fig. 2.22). Mutations of *BRAF* and *N-RAS* were searched, and a Q61R *N-RAS* mutation in exon 2 was detected both in the follicular variant of PTC and in the central lesion, supporting the assumption that both represent the same clonal proliferation. No mutations were identified in the *BRAF* gene.

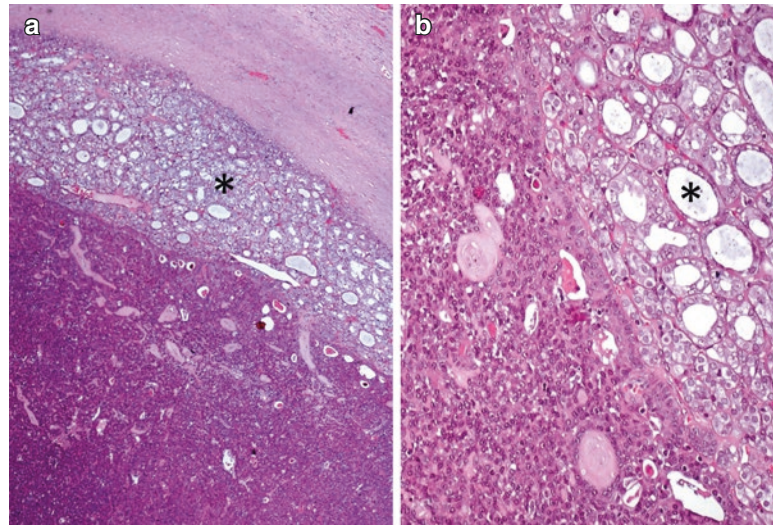

Fig. 2.21 Tumour-in-tumour of the thyroid with neoplastic solid cell nest features. The biphasic pattern of growth of a tumour-in-tumour composed by an external layer beneath the capsule with features of follicular variant of PTC (*asterisk*) and an inner core with basaloid features resembling a solid cell nest: tumour-in-tumour of the thyroid with neoplastic solid cell nest features (**a**, **b**) (See the text for details)

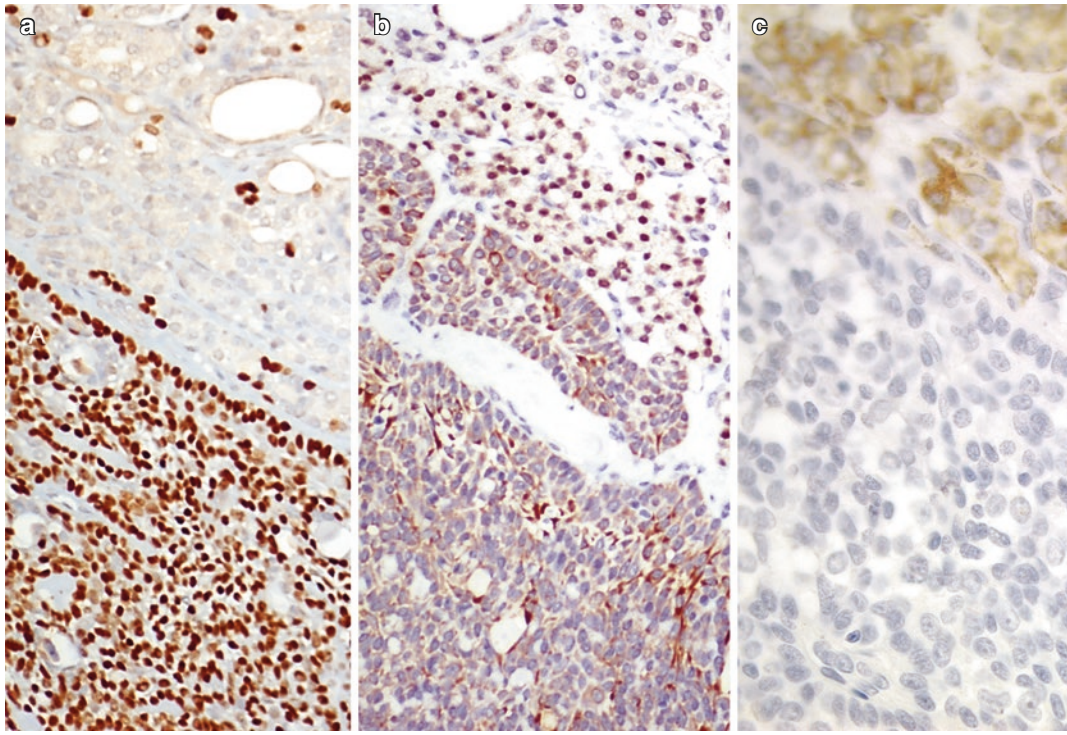

Fig. 2.22 Tumour-in-tumour of the thyroid with neoplastic solid cell nest features. This is the same case as Fig. 2.21. The nuclei of the basaloid cells of the inner core component expressed p63 (**a**) and did not express TTF-1 (**b**), at variance with the PTC external component. Thyroglobulin was not detected in the basaloid cells of the inner core component even using an in situ hybridization technique (**c**) (See the text for details)

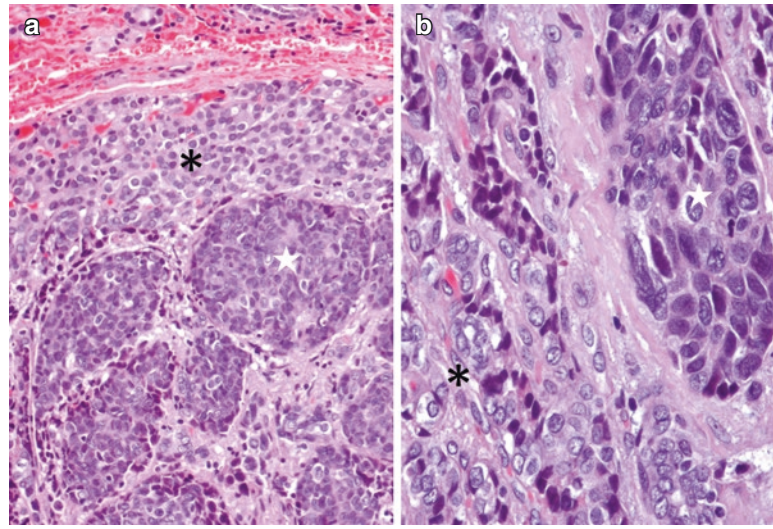

Fig. 2.23 Tumour-in-tumour phenomenon due to metastatic disease. Metastasis of invasive breast carcinoma (*white star*) into a follicular variant of PTC (*black asterisk*) (**a**, **b**)

Tumour-in-Tumour Phenomenon Due to Metastatic Disease

To illustrate the tumour-in-tumour phenomenon due to metastatic disease, we selected the case of a 51-year-old female with the diagnosis of invasive breast carcinoma with no special type, diagnosed 3 years before. The present thyroidectomy was due to a thyroid nodule (Fig. 2.23). A diagnosis of metastasis of invasive breast carcinoma into a follicular variant of PTC was made. The identification of the breast carcinoma metastatic area was not difficult as the metastatic nests were clearly demarcated from the pre-existing tumour and the clinical context was known. In other cases, the metastasis may be interpreted just as a peculiar clone of the pre-existent tumour/lesion and pass by unnoticed. In cases of biphasic or multiphasic thyroid nodules occurring in patients with previous history of cancer elsewhere, immunohistochemical testing for thyroglobulin is mandatory [33].

Mixed Medullary-Papillary Carcinoma

Figure 2.24 illustrates a case of mixed medullary-papillary carcinoma. Mixed medullary and follicular cell carcinoma is a primary malignant epithelial neoplasm of the thyroid showing morphological and immunophenotypical evidence of the coexistence of follicular and parafollicular cell-derived tumour populations within the same lesion [1, 2]. Immunohistochemistry is mandatory to prove the dual parafollicular (calcitonin positive) and follicular (thyroglobulin positive) cell differentiation. Thyroglobulin staining should be interpreted with caution due to the easy local diffusion and/or potential adsorption by medullary carcinoma cells.

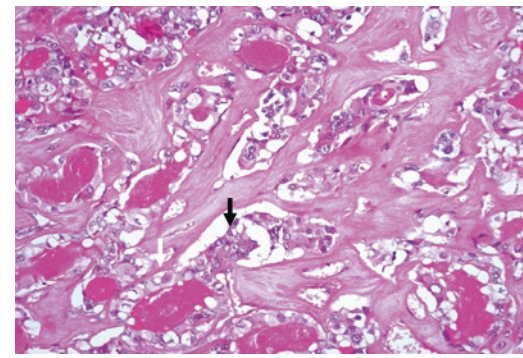

Fig. 2.24 Mixed medullary-papillary carcinoma. This tumour disclosed follicular structures that expressed thyroglobulin (*white arrow*) contiguous to solid nests of cells that expressed calcitonin (*black arrow*)

References

1. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization classification of tumours. pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
2. Rosai J, DeLellis RA, Carcangiu ML, Frable WJ, Tallini G. Tumors of the thyroid and parathyroid glands, AFIP Atlas of Tumor Pathology. Series 4. Fascicle 21. Silver Spring, MD: American Registry of Pathology; 2014.
3. Asioli S, Erickson LA, Righi A, Lloyd RV. Papillary thyroid carcinoma with hobnail features: histopathologic criteria to predict aggressive behavior. Hum Pathol. 2013;44:320–8.
4. Lee YS, Kim Y, Jeon S, Bae JS, Jung SL, Jung CK. Cytologic, clinicopathologic, and molecular features of papillary thyroid carcinoma with prominent hobnail features: 10 case reports and systematic literature review. Int J Clin Exp Pathol. 2015;8:7988–97.
5. Amacher AM, Goyal B, Lewis JS Jr, El-Mofty SK, Chernock RD. Prevalence of a hobnail pattern in papillary, poorly differentiated, and anaplastic thyroid carcinoma: a possible manifestation of high-grade transformation. Am J Surg Pathol. 2015;39:260–5.
6. Motosugi U, Murata S, Nagata K, Yasuda M, Shimizu M. Thyroid papillary carcinoma with micropapillary and hobnail growth pattern: a histological variant with intermediate malignancy? Thyroid. 2009;19:535–7.
7. Lubitz CC, Economopoulos KP, Pawlak AC, Lynch K, Dias-Santagata D, Faquin WC, Sadow PM. Hobnail variant of papillary thyroid carcinoma: an institutional case series and molecular profile. Thyroid. 2014;24:958–65.
8. Cameselle-Teijeiro JM, Rodríguez-Pérez I, Celestino R, Eloy C, Piso-Neira M, Abdulkader-Nallib I, Soares P, Sobrinho-Simões M. Hobnail variant of papillary thyroid carcinoma: clinicopathologic and molecular evidence of progression to undifferentiated carcinoma in 2 cases. Am J Surg Pathol. 2017;41(6):854–60.
9. Lino-Silva LS, Domínguez-Malagón HR, Caro-Sánchez CH, Salcedo-Hernández RA. Thyroid gland papillary carcinomas with micropapillary pattern, a recently recognized poor prognostic finding: clinicopathologic and survival analysis of 7 cases. Hum Pathol. 2012;43:1596–600.
10. Asioli S, Maletta F, Pagni F, Pacchioni D, Vanzati A, Mariani S, Palestini N, Lloyd RV, Sapino A. Cytomorphologic and molecular features of hobnail variant of papillary thyroid carcinoma: case series and literature review. Diagn Cytopathol. 2014;42:78–84.
11. Bellevicine C, Cozzolino I, Malapelle U, Zeppa P, Troncone G. Cytological and molecular features of papillary thyroid carcinoma with prominent hobnail features: a case report. Acta Cytol. 2012;56:560–4.
12. Yang GC, Fried K, Scognamiglio T. Cytological features of clear cell thyroid tumors, including a papillary thyroid carcinoma with prominent hobnail features. Diagn Cytopathol. 2013;41:757–61.
13. Asioli S, Erickson LA, Sebo TJ, Zhang J, Jin L, Thompson GB, Lloyd RV. Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases. Am J Surg Pathol. 2010;34:44–52.
14. Albores-Saavedra J. Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of 8 cases. Am J Surg Pathol. 2010;34:913.
15. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, Lloyd RV, LiVolsi VA, Papotti M, Sobrinho-Simoes M, Bussolati G, Rosai J. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 2007;31:1256–64.
16. Tavares C, Melo M, Cameselle-Teijeiro JM, Soares P, Sobrinho-Simões M. ENDOCRINE TUMOURS: Genetic predictors of thyroid cancer outcome. Eur J Endocrinol. 2016;174:R117–26.
17. Woenckhaus C, Cameselle-Teijeiro J, Ruiz-Ponte C, Abdulkader I, Reyes-Santías R, Sobrinho-Simões M. Spindle cell variant of papillary thyroid carcinoma. Histopathology. 2004;45:424–7.
18. Rebecchini C, Nobile A, Piana S, Sarro R, Bisig B, Gerasimos SP, Saglietti C, Matter M, Marino L, Bongiovanni M. Papillary thyroid carcinoma with nodular fasciitis-like stroma and β-catenin mutations should be renamed papillary thyroid carcinoma with desmoid-type fibromatosis. Mod Pathol. 2017;30(2):236–45.
19. Vigliar E, Bellevicine C, Cozzolino I, Zeppa P. Histological and fine needle aspiration cytological features of Hashimoto thyroiditis-associated 'angiomatoid' papillary thyroid carcinoma. Cytopathology. 2012;23(6):415–7.
20. Chen JH, Faquin WC, Lloyd RV, Nosé V. Clinicopathological and molecular characterization of nine cases of columnar cell variant of papillary thyroid carcinoma. Mod Pathol. 2011;24(5):739–49.
21. Cameselle-Teijeiro J, Alberte-Lista L, Peteiro-González D, Abdulkader-Nallib I, Reyes-Santías R, Soares P, Sobrinho-Simões M. CDX2 expression in some variants of papillary thyroid carcinoma. Am J Clin Pathol. 2012;138:907–9.
22. Cameselle-Teijeiro J, Menasce LP, Yap BK, Colaco RJ, Castro P, Celestino R, Ruíz-Ponte C, Soares P, Sobrinho-Simões M. Cribriform-morular variant of papillary thyroid carcinoma: molecular characterization of a case with neuroendocrine differentiation and aggressive behavior. Am J Clin Pathol. 2009;131(1):134–42.
23. Nakazawa T, Celestino R, Machado JC, Cameselle-Teijeiro JM, Vinagre J, Eloy C, Benserai F, Lameche S, Soares P, Sobrinho-Simões M. Cribriform-morular

variant of papillary thyroid carcinoma displaying poorly differentiated features. Int J Surg Pathol. 2013;21(4):379–89.
24. Yamaguchi E, Makino Y, Sato T, Uchida M, Harada Y, Maruyama R. CA19-9-producing lung metastasis after surgery for papillary thyroid carcinoma: report of a case. Surg Today. 2014;44:2157–61.
25. Ogawa M, Hori H, Hirayama M, Kobayashi M, Shiraishi T, Watanabe Y, Komada Y. Anaplastic transformation from papillary thyroid carcinoma with increased serum CA19-9. Pediatr Blood Cancer. 2005;45:64–7.
26. Nikiforov YE, Nikiforova MN, Gnepp DR, Fagin JA. Prevalence of mutations of ras and p53 in benign and malignant thyroid tumors from children exposed to radiation after the Chernobyl nuclear accident. Oncogene. 1996;13(4):687–93.
27. Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab. 2013;98(11):E1852–60.
28. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159:676–90. 49
29. Rüter A, Dreifus J, Jones M, Nishiyama R, Lennquist S. Overexpression of p53 in tall cell variants of papillary thyroid carcinoma. Surgery. 1996;120(6):1046–50.
30. Putti TC, Bhuiya TA. Mixed columnar cell and tall cell variant of papillary carcinoma of thyroid: a case report and review of the literature. Pathology. 2000;32(4):286–9.
31. Kleer CG, Giordano TJ, Merino MJ. Squamous cell carcinoma of the thyroid: an aggressive tumor associated with tall cell variant of papillary thyroid carcinoma. Mod Pathol. 2000;13(7):742–6.
32. Shah AA, La Fortune K, Miller C, Mills SE, Baloch Z, LiVolsi V, Dacic S, Mahaffey AL, Nikiforova M, Nikiforov YE, Seethala RR. Thyroid sclerosing mucoepidermoid carcinoma with eosinophilia: a clinicopathologic and molecular analysis of a distinct entity. Mod Pathol. 2017;30(3):329–39.
33. Yu J, Nikiforova M, Hodak S, et al. Tumor-to-tumor metastases to follicular variant of papillary thyroid carcinoma: histologic, immunohistochemical, and molecular studies of two unusual cases. Endocr Pathol. 2009;20:235–42.
34. Eloy C, Vinagre J, Cameselle-Teijeiro J, Paiva ME, Soares P, Sobrinho-Simões M. Tumor-in-tumor of the thyroid with basaloid differentiation: a lesion with a solid cell nest neoplastic component? Int J Surg Pathol. 2011;19:276–80.

Rare Follicular Tumours

3

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Introduction

The follicular thyroid tumours are usually easily identifiable in practice and their difficulty lies basically in the correct classification as benign or malignant tumours according to the identification of their infiltrative and/or angioinvasive character [1, 2]. This chapter addresses some rare follicular neoplasms in which diagnosis can be problematic for several reasons. In some cases, such difficulties are

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due to the existence of clear or mucinous cells that raises problems for the differential diagnosis with metastatic carcinomas, in other cases due to the lack of thyroid markers (e.g. oncocytic carcinoma negative for TTF-1 and thyroglobulin), the presence of unusual morphological patterns of growth (e.g. paraganglioma-like or glomeruloid) or even because the neoplasm appears to be hyperfunctioning in contrast to the well-established knowledge that hot tumours are, in principle, benign.

Oncocytic (Hürthle Cell, Oxyphilic) Tumours and Oncocytic Tumours with Clear Cells

Hürthle cell tumours are neoplasms composed of oncocytic cells which are usually encapsulated [1]. These tumours are called adenomas when they are not invasive and carcinomas if there is evidence of capsular and/or vascular invasion; the last edition of the WHO book (2017) stratifies Hürthle cell carcinoma, like follicular carcinoma (FTC) composed of common follicular cells, in three levels of invasiveness: minimally invasive (only capsular invasion); encapsulated, angioinvasive; and widely invasive [1]. For therapeutic purposes, "encapsulated, angioinvasive" carcinomas should be treated as widely invasive carcinomas (please read: total thyroidectomy and radioactive iodine). Tumours with a lower proportion of Hürthle cells have been designated as follicular neoplasms with Hürthle cell features [3]. Oncocytic tumours (see Chap. 1) are characterized by cells with abundant cytoplasm packed with eosinophilic granules (mitochondria), large centrally placed nuclei and prominent nuclei (Fig. 3.1). Although neoplastic C-cells may also

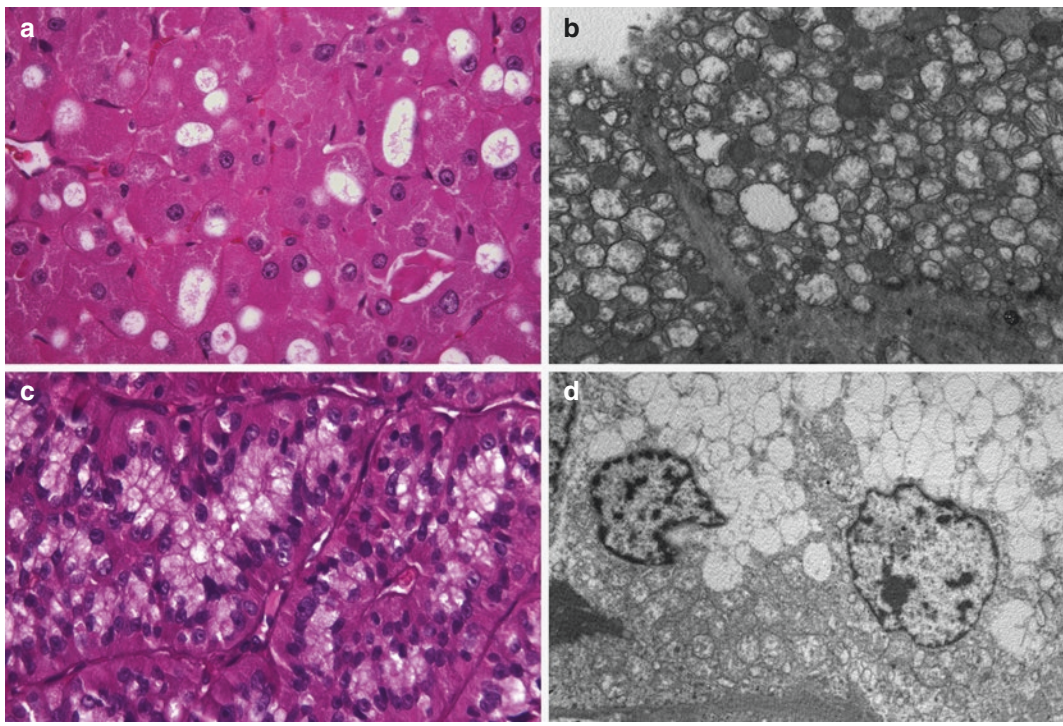

Fig. 3.1 Oncocytic (Hürthle cell, oxyphilic) tumour with clear cell features. Benign (**a**) and malignant oncocytic follicular tumours have abundant granular eosinophilic cytoplasm due to the accumulation of innumerable abnormal mitochondria (**b**). Widely invasive biphasic oncocytic clear cell carcinoma (**c**) in which the lower half of the cytoplasm of tumours cells is oncocytic, whereas the upper half is clear, as a consequence of the swelling of the abundant, mitochondria (**d**) (Electron micrographs: courtesy of Andrés Beiras Iglesias, Santiago de Compostela, Spain)

have oncocytic changes, the term oncocyte, when applied to the thyroid without a qualifier, refers to a variant of follicular cell [1]. Follicular oncocytic tumours are not uncommon and per se do not constitute a rare entity. Less frequently, benign and malignant Hürthle cell tumours can undergo secondary clear cell changes due to mitochondrial swelling (oncocytic clear cell tumours) [2]. Even rarer are the biphasic oncocytic clear cell tumours, in which the lower half of the cytoplasm is oncocytic while the upper half is clear [4] (Fig. 3.1).

Oncocytic (Hürthle Cell, Oxyphilic) Carcinoma Negative for TTF-1 and Thyroglobulin

A few cases of benign and malignant oncocytic tumours negative for TTF-1 and thyroglobulin have been described [5]. The case we selected is from a 76-year-old female with a history of long-standing goitre that has started growing fast causing slight dysphagia and apparently invading the local structures of the neck. Total thyroidectomy and left lymphadenectomy were performed (Courtesy of Ligia Castro, Coimbra, Portugal).

The left lobe was almost totally occupied by a large, poorly circumscribed tumour that invaded the anterior and posterior margins of the specimen (Fig. 3.2). The tumour is composed of cells organized in a solid-patterned fashion. The cells have abundant cytoplasm at variance with the small size of the normal follicular cells; mitoses are scarce. Despite the papillary areas, the nuclei are not PTC type (Fig. 3.3). Angio- and perineural invasion as well as prominent lymphoid infiltration are present. Neither necrotic foci nor node metastases were observed.

The neoplastic cells are negative for TTF1 and thyroglobulin (Fig. 3.4). Succinate dehy-

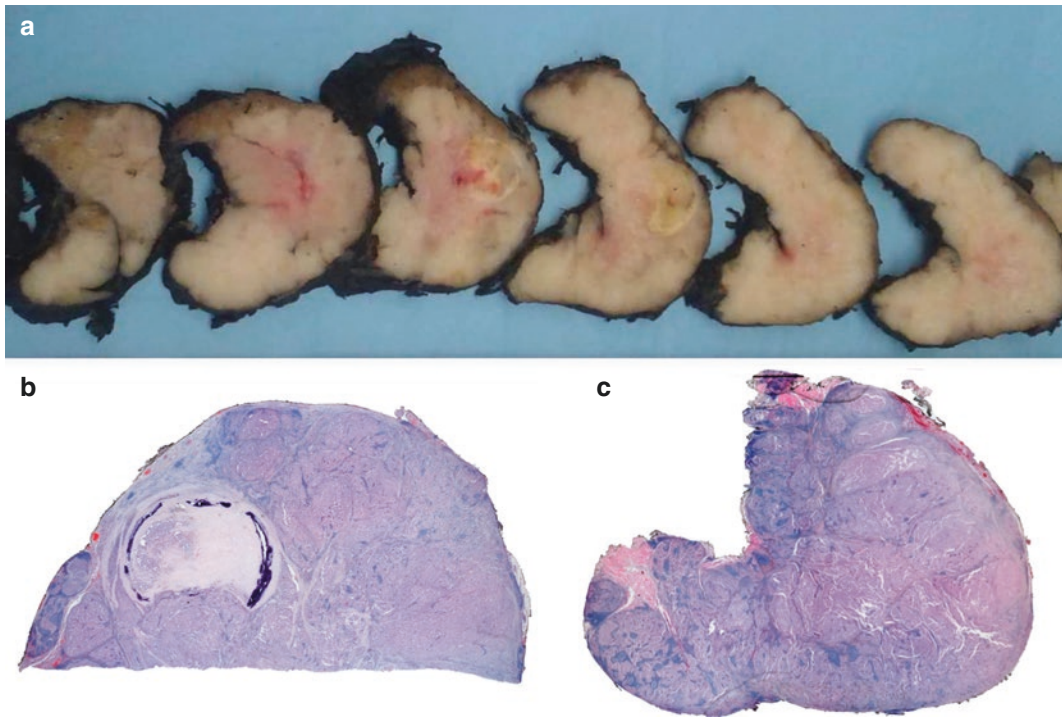

Fig. 3.2 Oncocytic (Hürthle cell, oxyphilic) carcinoma negative for TTF-1 and thyroglobulin. Multinodular lesion with a central fibro-calcified nodule (**a**, **b**) and with lymphoid infiltrate (**c**)

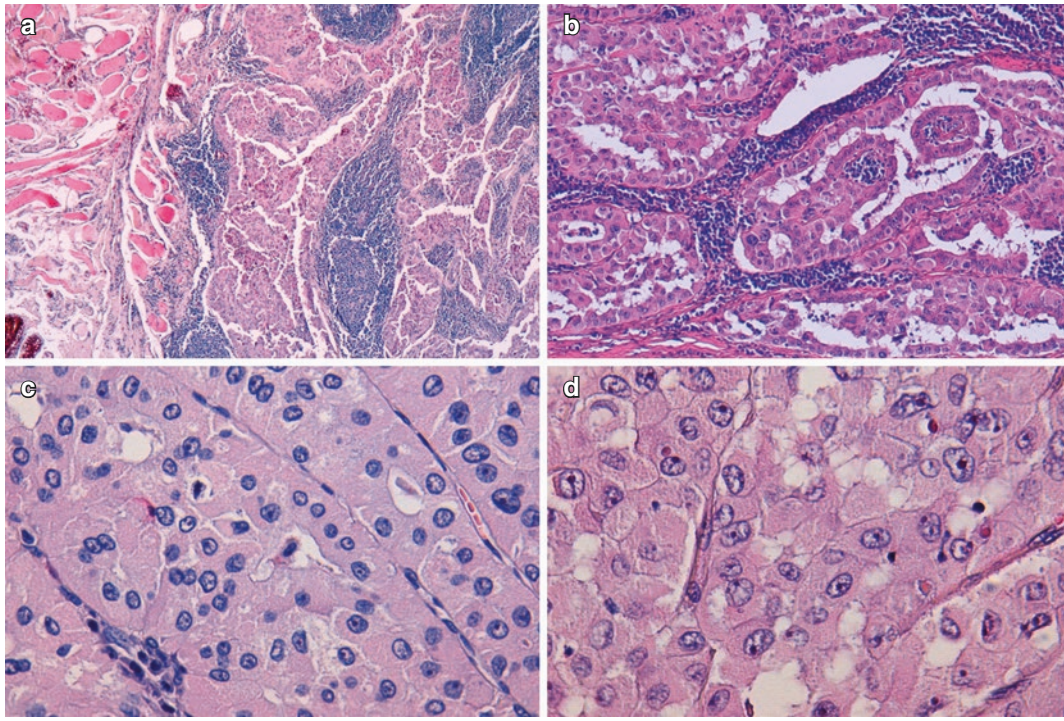

Fig. 3.3 Oncocytic (Hürthle cell, oxyphilic) carcinoma negative for TTF-1 and thyroglobulin. Tumour cells infiltrating skeletal perithyroid muscle (**a**). Marked lymphocytic infiltration (**b**) Hürthle cells with abundant finely granular cytoplasm and round to oval nuclei with prominent nucleoli (**c**, **d**). Scattered cells with irregular nuclei are not sufficient for the diagnosis of papillary carcinoma (**d**)

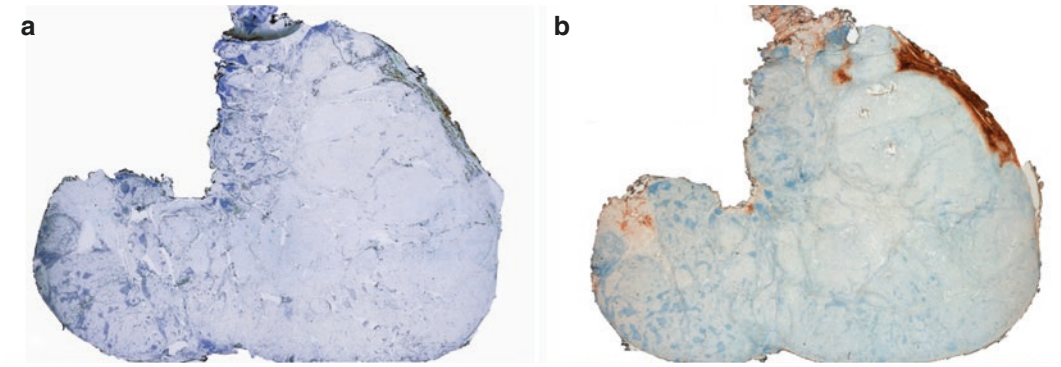

Fig. 3.4 Oncocytic (Hürthle cell, oxyphilic) carcinoma negative for TTF-1 and thyroglobulin. Tumor cells do not show reactivity for TTF-1 (**a**, **c**) and thyroglobulin (**b**) (positive internal control at the periphery). Normal follicles are positive for thyroglobulin and tumor cells disclose a strong positivity for SDHA (mitochondrial marker) (**d**)

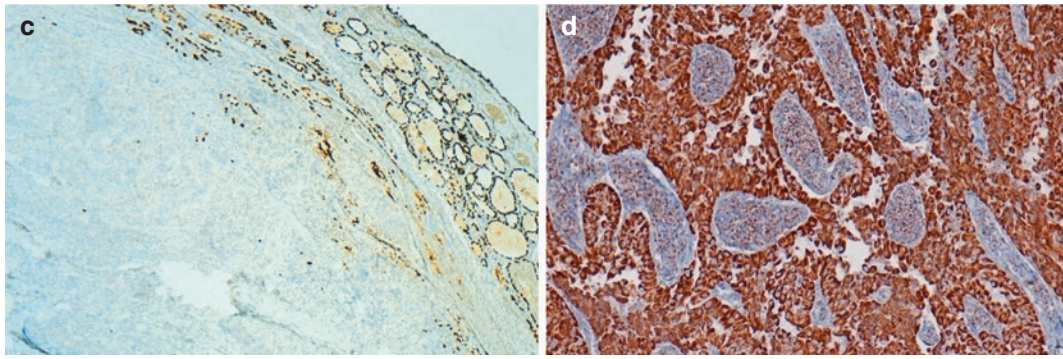

Fig. 3.4 (continued)

drogenase subunit A protein (SDHA), a mitochondrial marker, is strong and diffusely positive (Fig. 3.4). The most curious feature of the tumour regards the absence of immunoreactivity for TTF1, thyroglobulin and calcitonin. These unexpected negative findings prompted us to explore the possibility of a metastatic carcinoma that we have ruled out after an exhaustive imagiological search as well as a detailed and thorough immunohistochemical study. The carcinoma was classified as widely invasive because there was invasion of the perithyroid tissues and evidence of a central fibro-calcified nodule probably representing the original tumour. At variance with common FTCs in which it is usually easy to separate encapsulated from widely invasive neoplasms, Hürthle cell carcinomas tend to display a multinodular growth pattern without exhibiting an obvious centrally located tumour.

From the clinical standpoint, oncocytic carcinomas negative for thyroglobulin may preclude the use of serum thyroglobulin as a reliable tumour marker during the follow-up of patients harbouring these tumours (see Chap. 2, "Thyroglobulin Negative PTC"). This case has a number of negative prognostic parameters: incompleteness of surgery, old age of the patient, large size, extrathyroid extension of the tumour and signs of lymphovascular invasion. Molecular data provided no additional information regarding prognosis. The patient was treated with high doses of radioactive iodine and is alive and well 3 years after the diagnosis.

Oncocytic (Hürthle Cell) Tumour with Non-specific Immunoreactivity

Special care is required in interpreting the results of immunohistochemical analysis of oncocytic cell tumours to avoid false-positive results. Oncocytic cells frequently show non-specific immunoreactivity of the cytoplasm with various antibodies because of high endogenous biotin activity, which may be further enhanced by antigen retrieval procedures [6]. It manifests as coarsely granular staining limited to the cytoplasm that should not be confused with true positivity (Fig. 3.5). This false reactivity may be prevented in many, but not all cases, by endogenous biotin blocking procedures.

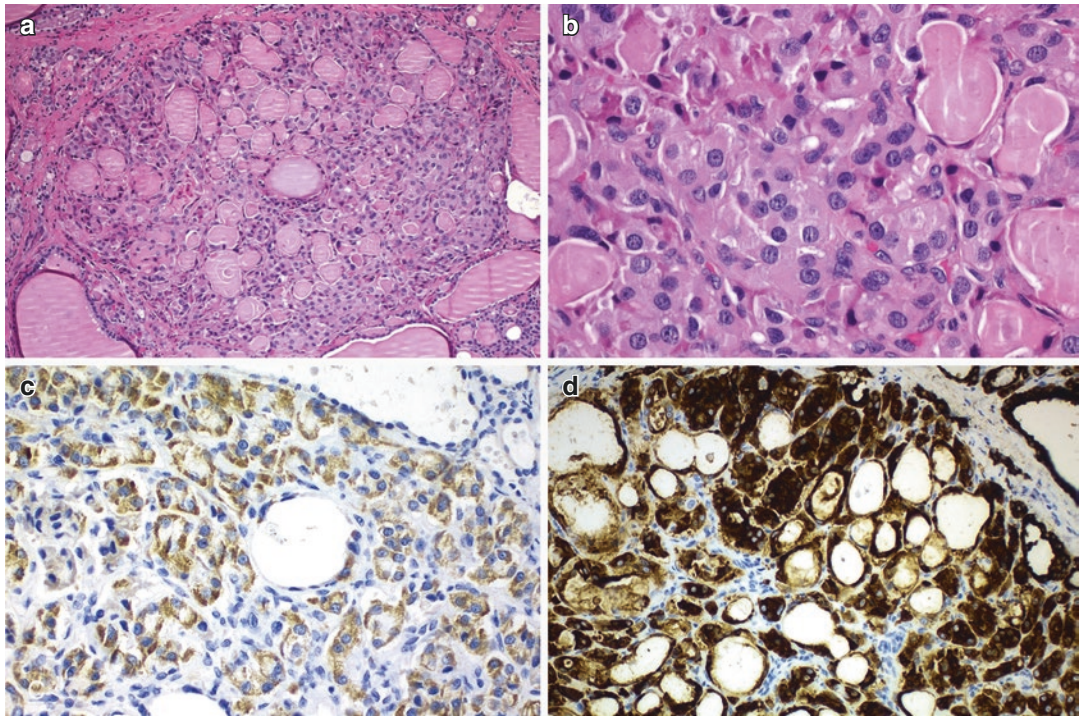

Fig. 3.5 Oncocytic (Hürthle cell) tumour with non-specific immunoreactivity for chromogranin. Oncocytic cells are prone to non-specific staining of the cytoplasm with various antibodies due to their high endogenous activity. It manifests as coarsely granular staining limited to the cytoplasm. In this oncocytic adenomatoid thyroid nodule (**a**, **b**) presented in a 46-year-old woman, false cytoplasmic immunostaining for chromogranin was observed (**c**). Negativity for calcitonin, calcitonin gene-related peptide, carcinoembryonic antigen, synaptophysin and CK20, with positivity for thyroglobulin, thyroperoxidase (**d**), TTF-1,and CK7 was found in the same tumour cells. mRNA in situ hybridization for thyroglobulin was also positive

Lipid-Rich Follicular Tumours

Single cases of benign and malignant follicular neoplasm with intracytoplasmic accumulation of lipid droplets have been documented [7, 8]. In these tumours, the cytoplasm of the vast majority of cells has a characteristic clear, microvesicular, foamy appearance (Fig. 3.6). Focally, a signet ring cell appearance can also be seen. These neoplasms should not be confused with adenolipoma, in which island of mature adipose tissue is mixed with the neoplastic epithelial cells (see Chap. 5, "PTEN Hamartoma Tumour Syndrome").

A lipid-rich follicular carcinoma has been described in a 41-year-old woman with McCune-Albright syndrome [8]; the tumour showed 90% of clear cells with capsular and vascular invasion, and immunohistochemistry demonstrated thyroglobulin positivity in the non-clear neoplastic cells, whereas most of the clear cells were negative.

The case illustrated in Fig. 3.6 is an angioinvasive lipid-rich follicular carcinoma displaying a solid pattern of growth, clear cells and diffuse immunoexpression for thyroglobulin, TTF-1 and PAX8, as well as numerous lipid vacuoles at the ultrastructural level.

In addition to lipid accumulation, there are several other mechanisms by which follicular thyroid cells acquire a clear cytoplasmic appearance when examined in haematoxylin and eosin-stained sections. Clear cell follicular tumours (Fig. 3.7) can also be the result of mitochondrial swelling (e.g. oncocytic tumours; see above); dilation of secretory vesicles, the endoplasmic reticulum or Golgi apparatus; and accumulation of glycogen (PAS

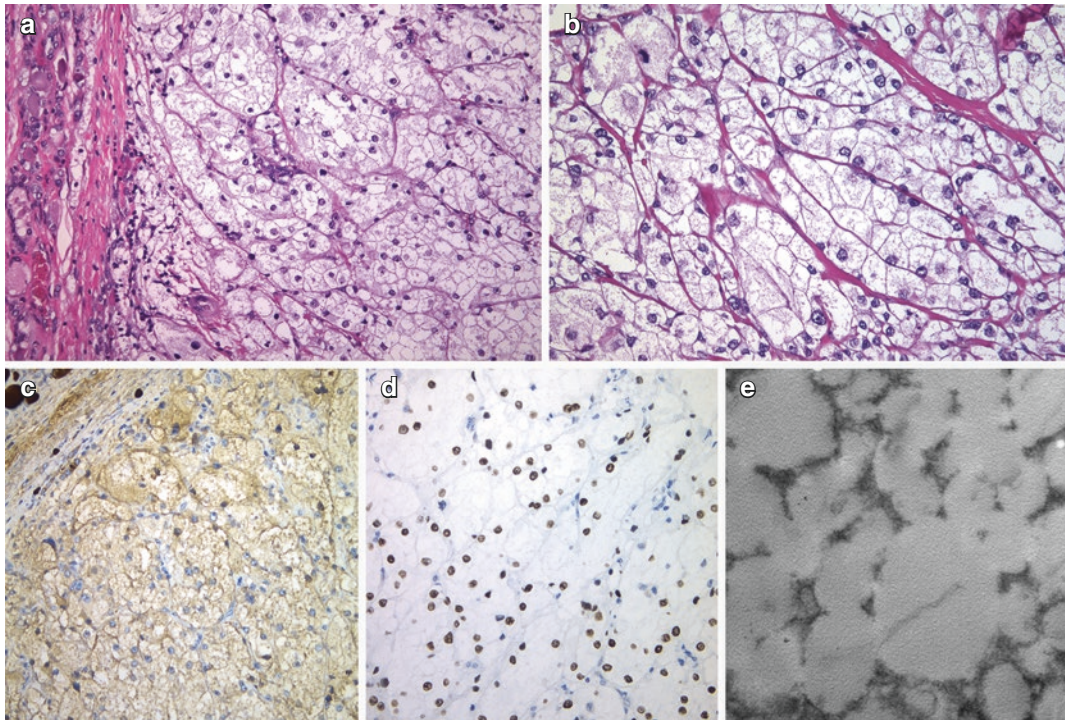

Fig. 3.6 Lipid-rich follicular carcinoma. This well-circumscribed angioinvasive carcinoma shows prominent cytoplasmic clear (foamy) cell features (**a**, **b**) and diffuse positivity for thyroglobulin (**c**) and TTF-1 (**d**). The ultrastructural study evidenced numerous intracytoplasmic lipid vacuoles (**e**) (Electron micrograph: courtesy of Andrés Beiras Iglesias, Santiago de Compostela, Spain)

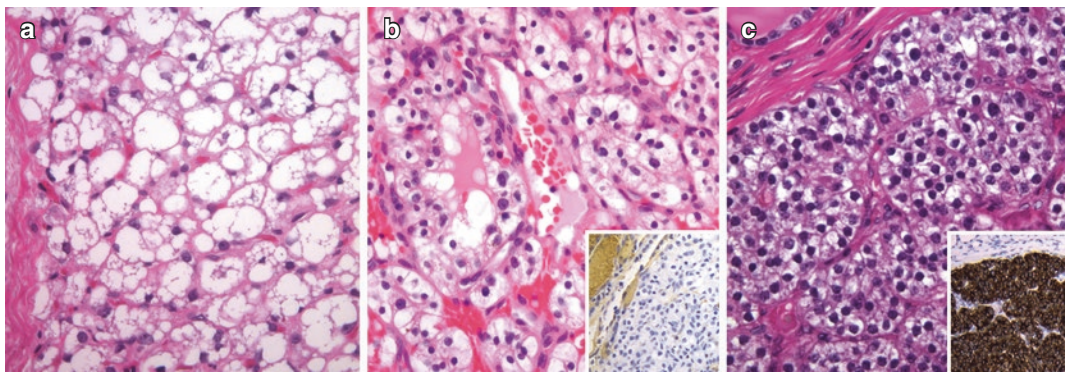

Fig. 3.7 Clear cell thyroid tumours. Benign and malignant follicular tumours with clear cells (**a**) should be distinguished from metastatic carcinoma, particularly from the kidney (**b**), and from parathyroid tissue (**c**). Thyroglobulin and TTF-1 are negative in renal cell carcinoma (**b**) and parathyroid tissue (**c**). In this intrathyroidal parathyroid adenoma, strong positivity for PTH can be observed (**c**, *inset*)

positive and diastase sensitive), thyroglobulin or mucin [1, 2]. Follicular tumours composed of clear cells should be distinguished from metastatic carcinoma, particularly from the kidney (Fig. 3.7), from clear cell papillary and medullary carcinoma and from normal or tumoural parathyroid tissues (Fig. 3.7). Thyroglobulin and TTF-1 immunoreactivity is helpful for distinguishing clear cell follicular

tumours from renal cell carcinoma, medullary thyroid carcinoma and parathyroid tissue. PTC is ruled out by the absence of characteristic nuclear features.

Follicular Tumours with Signet Ring Cells

In routine sections, this variant of follicular cell tumour is characterized by cells with large intracytoplasmic vacuoles that displace and compress the nucleus to the side [1, 2] (Fig. 3.8). Usually, signet ring cells alternate with others having more conventional features, contain large cytoplasmic vacuoles lined by microvilli and are strongly reactive for thyroglobulin [9] (Fig. 3.8). Less commonly, they may also be positive for mucin stains, a fact that has led to the designations of signet ring cell mucinous adenoma and mucin-producing microfollicular adenoma. In rare cases, large intracytoplasmic lipid vacuoles can also produce a signet ring cell appearance. The presence of signet ring cells is not a feature of malignancy by itself. The diagnosis of follicular carcinoma rests on the identification of capsular and/or vascular invasion. Signet ring carcinoma may be mistaken for metastatic carcinoma from the breast or stomach, which can be excluded by their negativity for thyroglobulin and TTF-1.

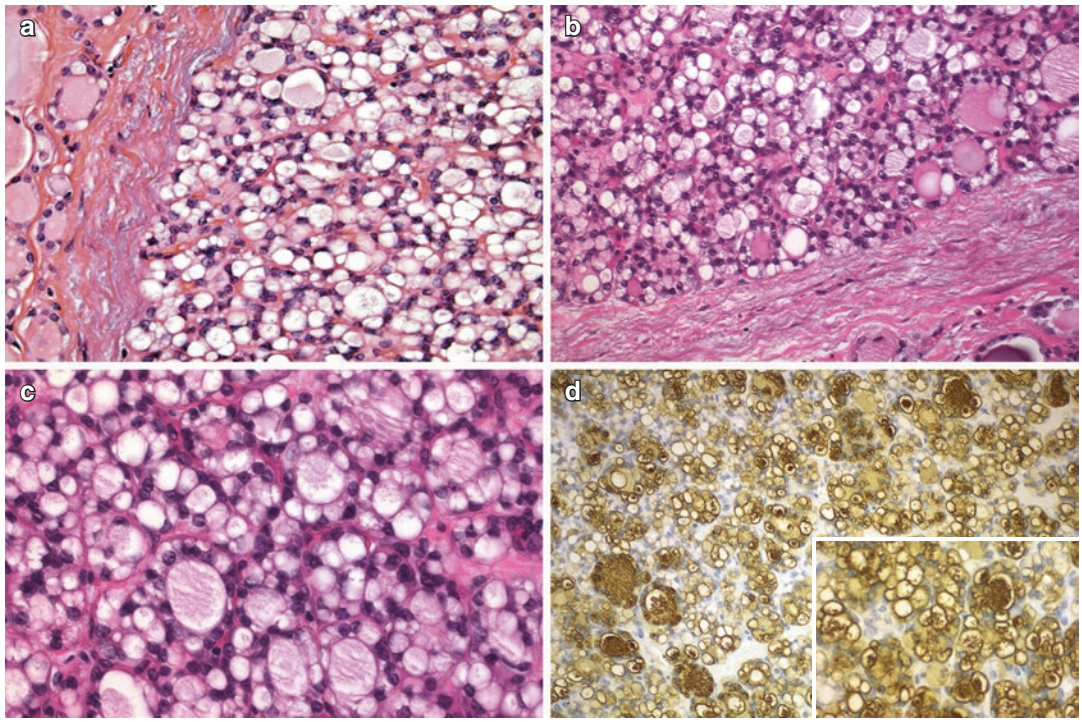

Fig. 3.8 Follicular tumours with signet ring cells. The cells in both adenomas (**a**, **b**) reveal large cytoplasmic vacuoles that displace the nuclei laterally, leading to a signet ring configuration. Signet ring cells alternate with follicular structures (**c**). Cytoplasmic vacuoles, whether small or large, are strongly immunoreactive for thyroglobulin (**d**)

Atypical Adenoma (Including Spindle Cell Adenoma)

Some pathologists use the wastebasket term of atypical adenoma to designate any follicular adenoma that looks peculiar or worrisome due to the presence of nuclear atypia (Fig. 3.9), high cellularity (cellular or hypercellular adenoma), spindle cells (spindle cell adenoma) (Fig. 3.9), a thick capsule, mitotic activity or necrosis without capsular or vascular invasion [1, 2]. In some adenomas, scattered huge, irregular and hyperchromatic nuclei tend to occur in cluster (adenoma with bizarre nuclei). The bizarre appearance of such nuclei is likely due to cell degeneration, the so-called endocrine atypia, and should not be taken, by itself, as a sign of malignancy. These worrisome features force us to make a meticulous examination of the entire capsule. If there is no invasion, the tumour is clinically benign and the term atypical follicular adenoma is not appropriate.

Some adenomas are predominantly composed of spindle cells (spindle cell adenoma) that show positivity for thyroglobulin and TTF-1 [10, 11]. The differential diagnosis in this setting includes spindle epithelial tumour with thymus-like elements (SETTLE); spindle cell variant of papillary, medullary and anaplastic thyroid carcinoma; and solitary fibrous tumour, as well as other mesenchymal lesions (see Chap. 6).

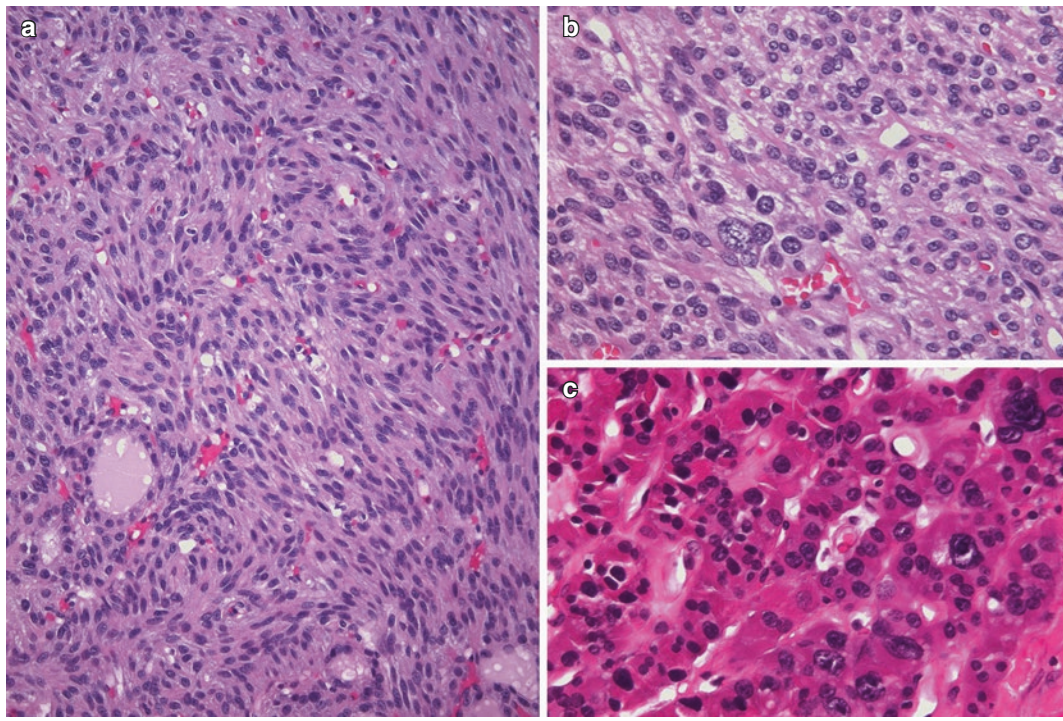

Fig. 3.9 Atypical adenoma (including spindle cell adenoma). Atypical adenoma is a vague and imprecise designation used to refer to any follicular adenoma that looks peculiar or worrisome due to the presence of spindle cells (**a**), nuclear atypia (**b**, **c**), a thick capsule, mitotic activity or necrosis without capsular or vascular invasion. The follicular nature of spindle cell adenoma (**a**, **b**) can be confirmed by its immunoreactivity for thyroglobulin and TTF-1. Tumour cells with giant nuclei (bizarre nuclei) (**b**, **c**) are not a sign of malignancy, indicating probably a degenerative phenomenon

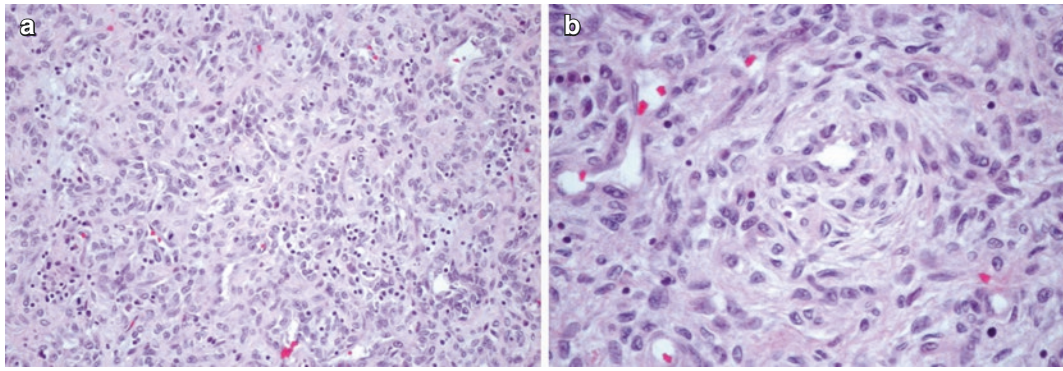

Fig. 3.10 Meningioma-like follicular adenoma. Spindle cells and a whorled pattern of growth are characteristic of this type of benign follicular cell tumour (**a**, **b**)

Meningioma-Like Follicular Adenoma

The spindle cell phenotype can also appear as the meningioma-like tumour of the thyroid or meningioma-like follicular adenoma [12] that is considered another morphological variant of follicular adenoma (Fig. 3.10).

As the name suggests, the meningioma-like follicular adenoma is an encapsulated tumour that can be potentially confused with primary (of the neck) or metastatic transitional meningioma or with other rare spindle cell tumours such as the spindle cell variants of PTC and MTC, the spindle cell tumour with thymus-like elements (SETTLE) or solitary fibrous tumour. The characteristic arrangement of bland-looking spindle to ovoid cells in a whorled pattern around blood vessels (Fig. 3.10) may also give the impression one is dealing with vascular tumours of the pericytic type. The immunohistochemical staining of the tumour cells for TTF-1 and thyroglobulin, and the coexistence of spindle cells with well-differentiated follicles, favours the interpretation that the meningioma-like tumour of the thyroid is a morphological variation of the spindle cell metaplasia occurring occasionally in follicular adenomas.

Pericytic-Like Follicular Adenoma

We proposed the descriptive designation of pericytic follicular adenoma for the tumour illustrated in Figs 3.11 and 3.12. It was an encapsulated nodule presented in the thyroid of a 45-year-old woman. Microscopically, the majority of tumour cells are spindle shaped and concentrically arranged around small- and medium-sized vessels in a pericytic-like form. Isolated follicular cells and follicles were also observed in small groups and/or scattered between spindle cells as a minor component of the tumour (Fig. 3.11). The nuclei were bland and oval with no significant mitotic activity (Fig. 3.12). There was no necrosis, capsular invasion or angioinvasion. Tumour cells disclosed immunopositivity for thyroglobulin, thyroperoxidase, TTF-1, pankeratins (clone AE1/AE3) and vimentin and negativity for calcitonin, CD31 and CD34 (Fig. 3.12). Collagen IV immunostaining highlighted the peculiar whorl-like arrangement of follicular cells around blood vessels (Fig. 3.12). The patient was alive and well 10 years after thyroidectomy.

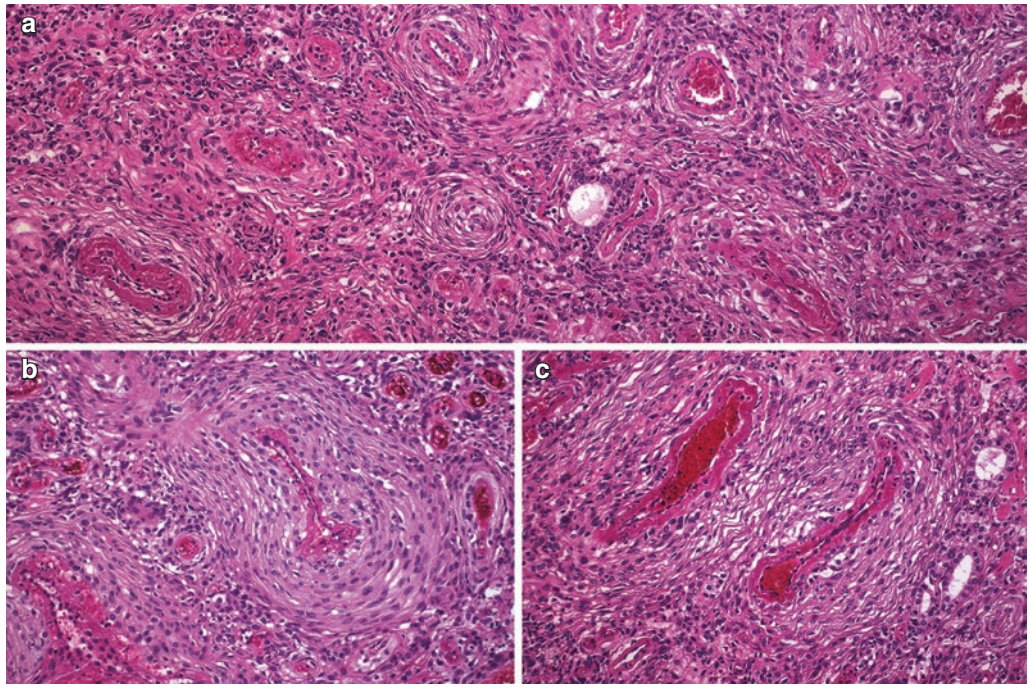

Fig. 3.11 Pericytic-like follicular adenoma. This benign lesion is microscopically characterized by a proliferation of spindle, follicular cells concentrically arranged around small and medium-sized vessels in a pericytic-like form (**a**–**c**). Scattered follicles between spindle cells can also be seen (**b**, **c**)

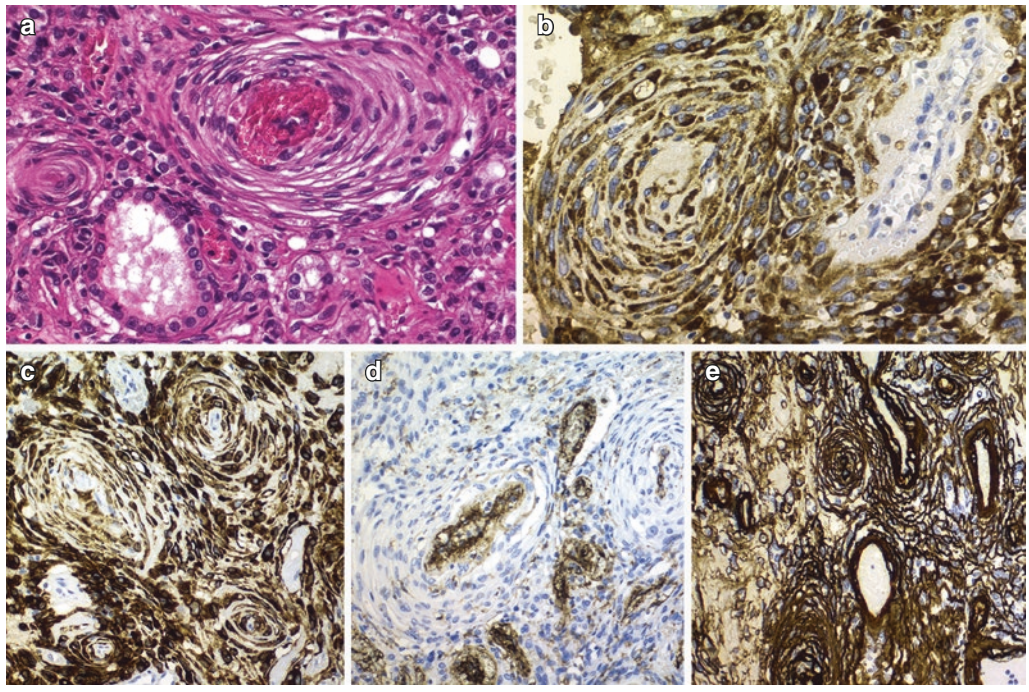

Fig. 3.12 Pericytic-like follicular adenoma. Tumour cells concentrically arranged around vessels in a pericytic-like fashion (**a**) are positive for thyroglobulin (**b**) and thyroperoxidase (**c**) and negative for CD34 and CD31 (**d**). Immunostaining for collagen IV highlights the concentric arrangement of tumour cells (**e**)

Hyalinizing Trabecular Neoplasms

Rare tumours morphologically indistinguishable from hyalinizing trabecular adenoma (HTA) may show infiltration, vascular invasion and/or metastasis [1, 13, 14]. Hyalinizing trabecular tumours are almost always benign neoplasms (Fig. 3.13), but due to their nuclear characteristics, they should be distinguished from a trabecular/solid variant of PTC, as well as from paraganglioma and paraganglioma-like variant of MTC (Fig. 3.14), because of their growth pattern. It is interesting to stress that, since desmoplasia is a reliable indicator of metastatic potential in MTC [15], paraganglioma-like variant of MTC and all MTCs lacking desmoplasia carry a better clinical behaviour than those associated with a desmoplastic stromal reaction. The prognostic importance of these microscopic features, however, is obscured by staging that remains the crucial key for prognosis.

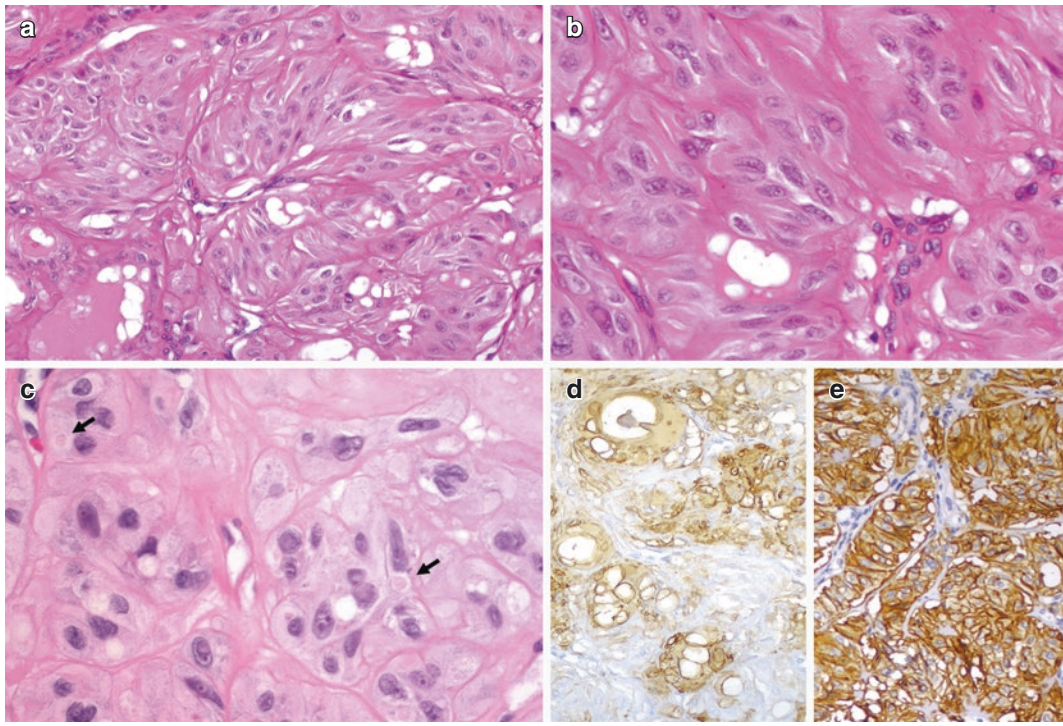

Fig. 3.13 Hyalinizing trabecular adenoma (paraganglioma-like adenoma). Hyalinizing trabecular tumour (HTT) is a follicular-derived neoplasm composed of large trabeculae of elongated or polygonal cells admixed with variable amounts of intratrabecular and intertrabecular hyaline material. Some of the tumour cells are arranged in compact clusters reminiscent of the "Zellballen" of paraganglioma, hence the alternative designation of this adenoma variant as paraganglioma-like (**a**–**c**). The nuclei are round, oval or elongated, sometimes showing grooves, pseudoinclusions and perinuclear vacuoles (**b**, **c**). In almost all cases, the so-called cytoplasmic yellow bodies can be seen (*arrows*) (**c**). Intraluminal and cytoplasmic positivity for thyroglobulin (**d**), and a very peculiar positivity of the cell membrane and cytoplasm of tumour cells with MIB1 (Ki-67) clone, is usually (but not always) seen (**e**)

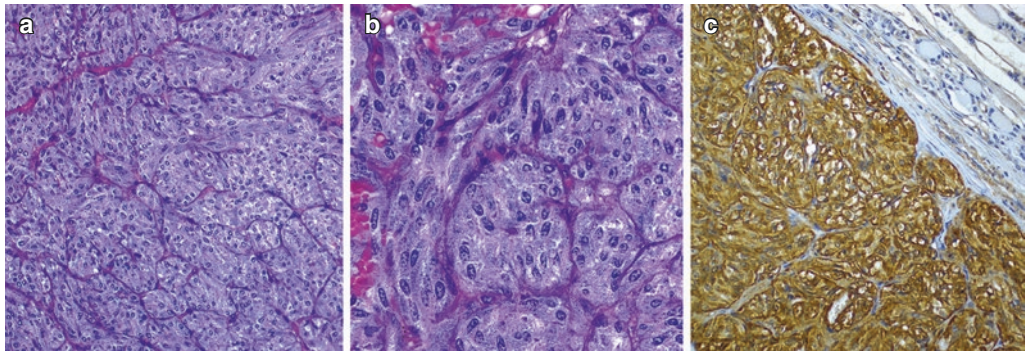

Fig. 3.14 Paraganglioma-like variant of medullary thyroid carcinoma. Occasional medullary thyroid carcinomas (MTCs) are encapsulated or well delimited and arranged in a broad trabecular pattern with an amyloid-negative hyalinized stroma, resembling hyalinizing trabecular adenoma (paraganglioma-like thyroid adenoma) (**a**). The cytoplasm is finely granular and the nuclei have coarse chromatin with inconspicuous nucleoli (**b**). Tumour cells in this variant of MTC are positive for calcitonin (**c**) and negative for thyroglobulin. Interestingly, this type of MTC lacking interstitial fibrosis has a better prognosis than those with desmoplastic stromal reaction

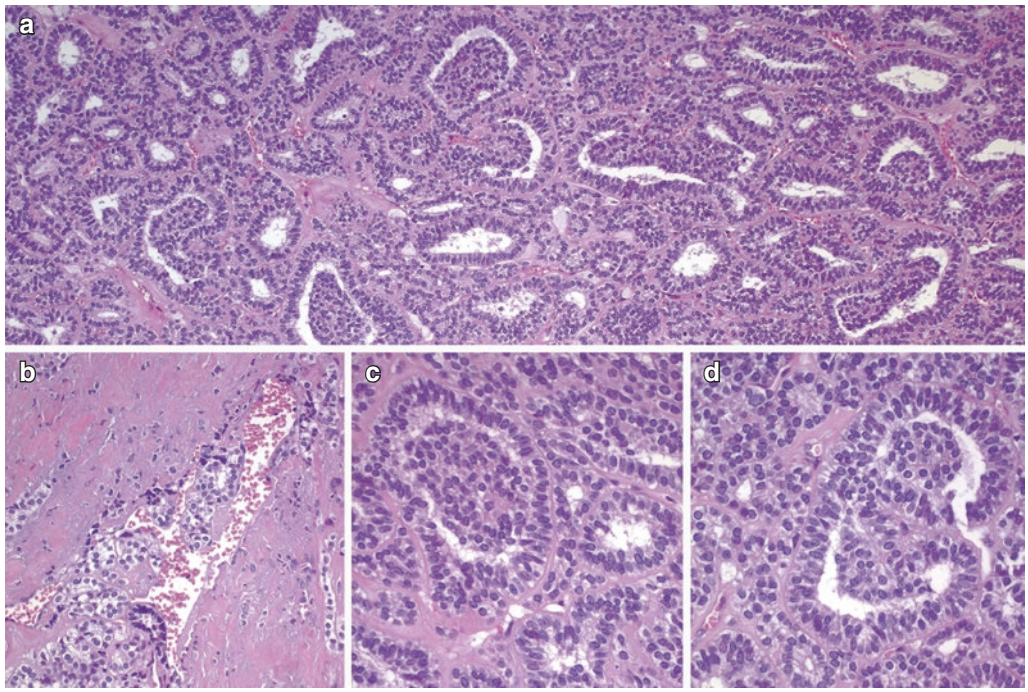

Fig. 3.15 Glomeruloid variant of follicular carcinoma. The tumour has a peculiar growth pattern with glomeruloid features (**a**, **c**, **d**) and vascular invasion (**b**)

Follicular Tumours with Glomeruloid Pattern of Growth

Some years ago, our group described a rare malignant thyroid tumour with an unusual glomeruloid pattern of growth [16]. The patient, a 56-year-old woman, presented with a right thyroid nodule of unknown duration. The widely infiltrating, angioinvasive tumour, 5 cm in diameter, exhibited a peculiar architectural growth pattern showing follicles with round to oval epithelial tufts growing within, often supported by a fibrovascular core mimicking the renal glomerulus (Fig. 3.15). Tubular or elongated follicles lacked colloid and were lined by

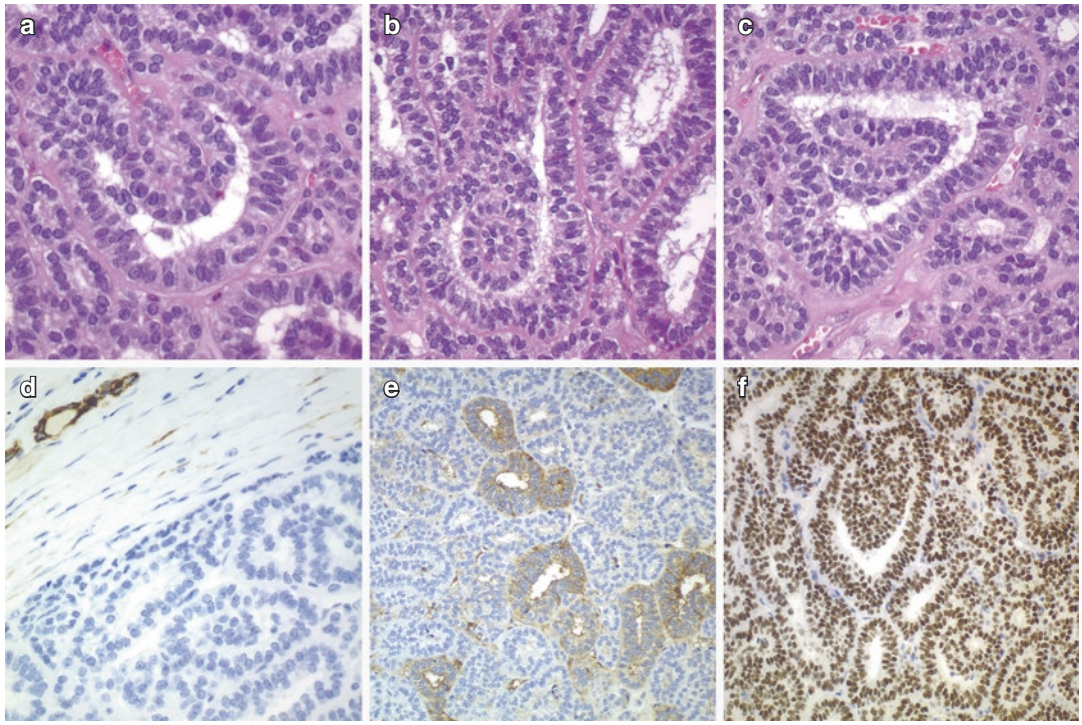

Fig. 3.16 Glomeruloid variant of follicular carcinoma. The glomeruloid structures have a layer of "visceral" epithelium covering the epithelial tuft sometimes with a vascular core (**a**–**c**). Tumour cells are negative for CK7 (**d**) and immunoreactive for CK18, thyroglobulin (**e**) and TTF-1 (**f**)

pseudostratified tall, columnar cells with clear cytoplasm. Nuclei were round to oval, with evenly distributed, slightly coarse chromatin. Neoplastic cells were positive for TTF-1, thyroglobulin, thyroperoxidase, CK18, Hector Battifora mesothelial cell 1 (HBME1) and vimentin (Fig. 3.16). Scattered cells positive for S100 and Wilms tumour 1 (WT1) were also detected. There were *N-RAS* mutation and *PAX8-PPAR gamma* rearrangement, but no mutations were found in *BRAF* or *APC* genes, nor were *RET/PTC* rearrangements detected. Because of the characteristic histologic features, we proposed naming this tumour follicular thyroid carcinoma with an unusual glomeruloid pattern of growth. More recently, a glomeruloid follicular thyroid adenoma [17] has also been reported.

Mucinous Carcinoma

Mucinous carcinoma (MC) is a rare malignant epithelial neoplasm characterized by clusters of neoplastic cells surrounded by extensive extracellular mucin deposition [1, 2] (Fig. 3.17). Postulated sources for MC include metaplastic follicles and ultimobranchial body remnants (solid cell nests) (see Chap. 6). Microscopic features of MC are identical to that of mucinous (colloid) carcinoma of other sites. By definition, features typical of other types of thyroid carcinoma should not be present. Focal areas of squamous differentiation may be detected. Mitotic figures are present but usually not numerous. MC frequently shows capsular invasion and angioinvasion. The mucinous material stains positively with the iron diamine method, mucicarmin, Alcian blue and PAS before and after diastase digestion (Fig. 3.17). The tumour cells are focally positive for thyroglobulin (Fig. 3.17), TTF-1, PAX8 and several mucins (MUC1, MUC2, MUC3 and MUC4) and negative for calcitonin and CGRP. MC of the thyroid should be distinguished from rare mucinous follicular adenoma [9, 18]; papillary (Fig. 3.18), follicular (Fig. 3.19) and medullary carcinoma; mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia of the thyroid (see Chap. 2); and metastatic mucinous carcinomas.

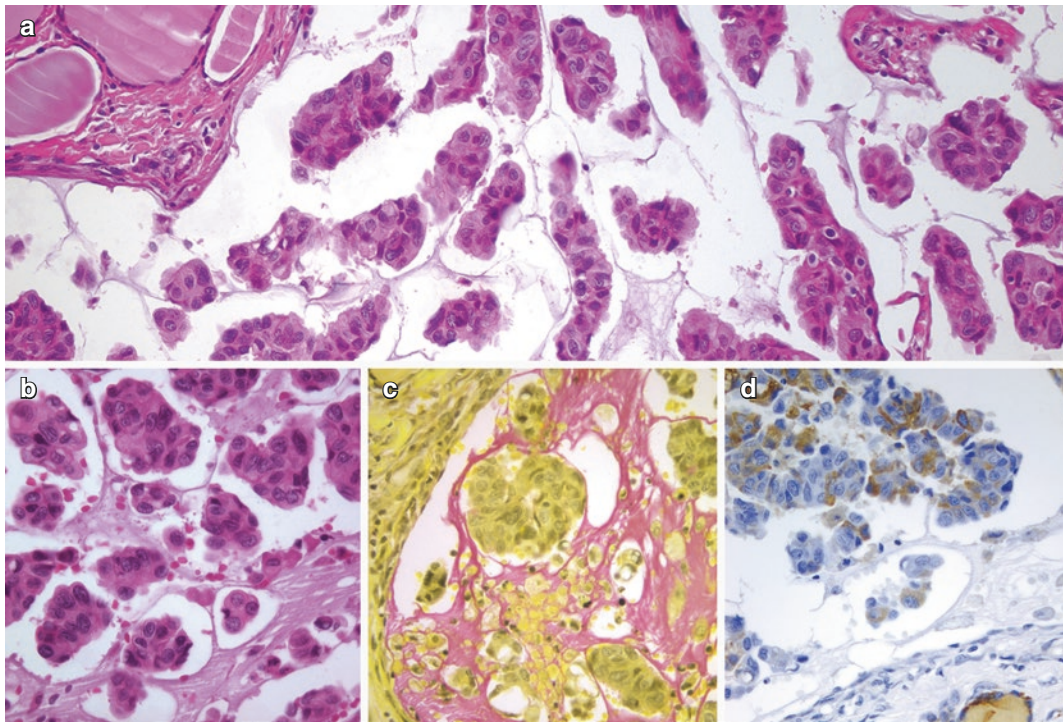

Fig. 3.17 Mucinous carcinoma (MC). MC contains pools of abundant mucoid material surrounding collections of epithelial neoplastic cells (**a**, **b**). The mucinous material stains positively with mucicarmin (**c**) and tumor cells are focally immunoreactive for thyroglobulin (**d**)

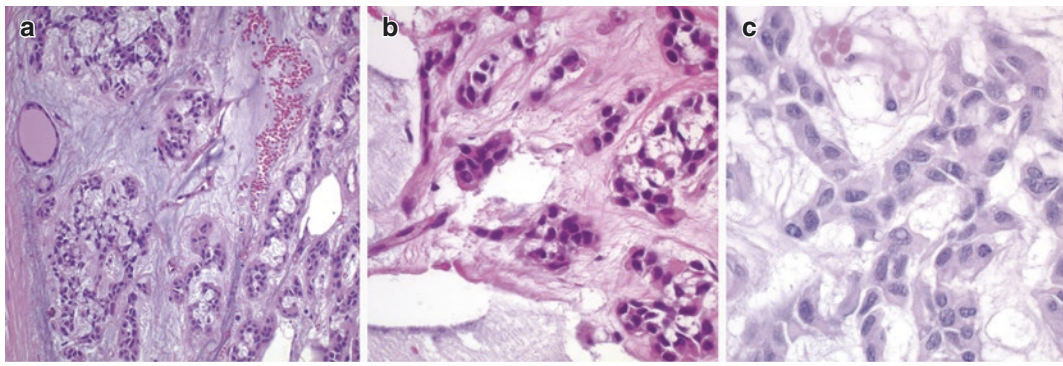

Fig. 3.18 Mucinous variant of papillary thyroid carcinoma (PTC). This tumour occurred in the thyroid isthmus of a 68-year-old woman with multinodular goitre (68 g). The neoplasia was well circumscribed and measured 15 mm in diameter. Histologically, it consisted of tumour cells arranged in a ribbon, trabecular or follicular pattern (**a**–**d**) with abundant mucoid stroma positively stained with Alcian blue (**e**) and mucicarmin. Most of the nuclei are large, oval and irregularly contoured with frequent intranuclear pseudoinclusions (**c**–**e**). Tumour cells were immunoreactive for CK7, CK19, TTF-1, galectin-3 and p63 with focal positivity for thyroglobulin (**f**) and thyroperoxidase. The Ki-67 index was less than 2%. No *BRAF* mutation was detected. The set of pathologic characteristics is consistent with a rare mucinous variant of PTC (Courtesy of José Mari Arrinda Yeregui, Hondarribia, Spain)

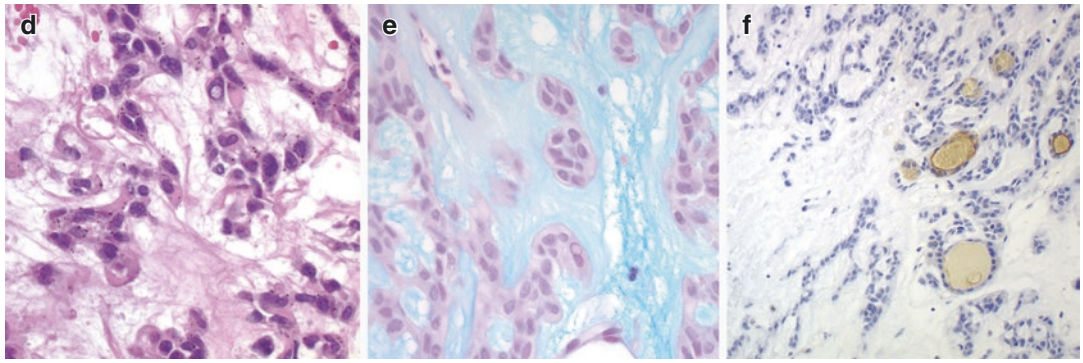

Fig. 3.18 (continued)

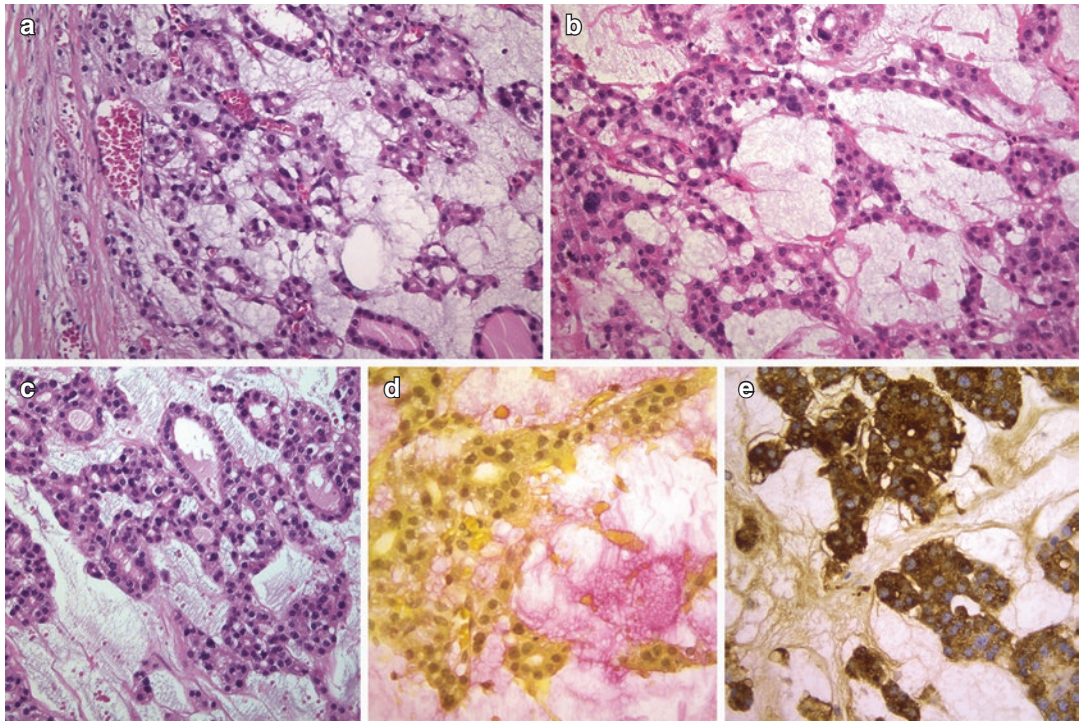

Fig. 3.19 Mucinous variant of oncocytic follicular carcinoma. This tumour presented as a fleshy, partially cystic nodule in the right thyroid lobe of a 51-year-old woman with Graves' disease. The neoplasia was encapsulated and measured 30 mm in diameter. Histologically, it consisted of oncocytic cells arranged in a follicular pattern (**a**–**c**) floating in abundant mucoid stroma positively stained with mucicarmin (**d**). Foci of capsular invasion but not vascular invasion were observed. Tumour cells were immunoreactive for CK7, TTF-1, thyroglobulin (**e**) and thyroperoxidase and negative for calcitonin

Hyperfunctioning (Hot) Follicular Thyroid Carcinoma

Hyperfunctioning nodules are almost always benign [1, 2]. Hyperfunctioning follicular adenomas are related to mutations in the TSH receptor (*TSHR*) gene (about 60%) and less frequently in the adenylate cyclase-stimulating G alpha protein (*GNAS1*) gene that activates the cAMP cascade (less than 5%) [19]. Follicular carcinomas (FTCs) usually concentrate radioiodine or other tracer less avidly than adjacent thyroid parenchyma.

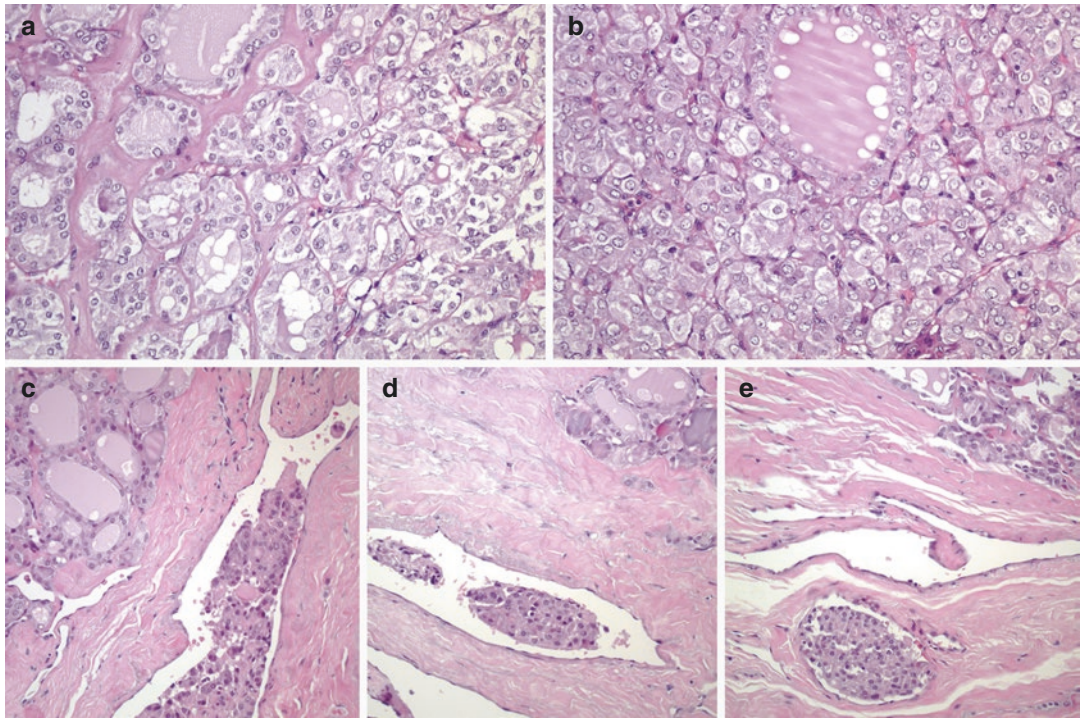

Fig. 3.20 Hyperfunctioning (hot) follicular thyroid carcinoma (FTC). This patient, a 55-year-old woman, underwent total thyroidectomy for goitre and hyperthyroidism. The thyroidectomy specimen showed an encapsulated, solid, reddish-yellow tumor measuring 50 mm in maximal dimension in the left lobe. The tumour combined well-formed colloid-containing follicles and solid/trabecular patterns of growth, with cuboidal cells showing round pale vesicular nuclei and moderate amount of cytoplasm (**a**, **b**). No nuclear overlapping, irregularity of nuclear contour, grooves or nuclear pseudoinclusions were observed. The mitotic index was less than 1 mitosis per 10 high-power fields. Foci of hyalinization and irregular calcifications were found, but not psammoma bodies or necrosis were detected. The tumor was encapsulated and displayed two foci of capsular invasion as well as multiple foci of angioinvasion (**c**, **d**, **e**). Tumor cells were positive for thyroglobulin, TTF-1, thyroperoxidase, E-cadherin and p53 and negative for calcitonin and HBME1. Somatic *TSHR*-activating mutation and the *PAX8-PPAR gamma* rearrangement mosaicism were detected; neither *RAS* nor *BRAF* mutations were found in the tumor cells

Hyperfunctioning (hot, toxic) follicular carcinomas of both conventional and oncocytic type are exceedingly rare. As in benign autonomously functioning thyroid nodules, mutations in either the *TSHR* gene or the *GNAS1* gene have been detected in a small number of thyroid carcinomas, with a handful of those being autonomously hyperfunctioning thyroid carcinomas. Most cases carry mutations in the *TSHR* gene pathway. Concurrent mutations in *RAS* and *TSHR* genes have been detected in a case of hyperfunctioning differentiated thyroid carcinoma. A case of autonomously hyperfunctioning FTC harbouring a somatic *TSHR*-activating mutation and a *PAX8-PPAR gamma* rearrangement was described by our group [20] (Fig. 3.20). Distant metastases may preserve the hyperfunction. Due to the rarity of these cases, the microscopic features of hyperfunctioning FTCs are not well characterized.

References

1. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization classification of tumours. pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
2. Rosai J, DeLellis RA, Carcangiu ML, Frable WJ, Tallini G. Tumors of the thyroid and parathyroid glands, AFIP Atlas of Tumor Pathology. Series 4. Fascicle 21. Silver Spring, MD: American Registry of Pathology; 2014.
3. Tsybrovskyy O, Rössmann-Tsybrovskyy M. Oncocytic versus mitochondrion-rich follicular thyroid tumours: should we make a difference? Histopathology. 2009;55(6):665–82.

4. Dickersin GR, Vickery AL Jr, Smith SB. Papillary carcinoma of the thyroid, oxyphil cell type, "clear cell" variant: a light- and electron-microscopic study. Am J Surg Pathol. 1980;4(5):501–9.
5. Bejarano PA, Nikiforov YE, Swenson ES, Biddinger PW. Thyroid transcription factor-1, thyroglobulin, cytokeratin 7, and cytokeratin 20 in thyroid neoplasms. Appl Immunohistochem Mol Morphol. 2000;8(3):189–94.
6. Bussolati G, Gugliotta P, Volante M, Pace M, Papotti M. Retrieved endogenous biotin: a novel marker and a potential pitfall in diagnostic immunohistochemistry. Histopathology. 1997;31(5):400–7.
7. Chetty R. Thyroid follicular adenoma composed of lipid-rich cells. Endocr Pathol. 2011;22(1):31–4. PMID: 21165779
8. Yang GC, Yao JL, Feiner HD, Roses DF, Kumar A, Mulder JE. Lipid-rich follicular carcinoma of the thyroid in a patient with McCune-Albright syndrome. Mod Pathol. 1999;12(10):969–73.
9. Gherardi G. Signet ring cell 'mucinous' thyroid adenoma: a follicle cell tumour with abnormal accumulation of thyroglobulin and a peculiar histochemical profile. Histopathology. 1987;11(3):317–26.
10. Vergilio J, Baloch ZW, LiVolsi VA. Spindle cell metaplasia of the thyroid arising in association with papillary carcinoma and follicular adenoma. Am J Clin Pathol. 2002;117(2):199–204.
11. Shikama Y, Mizukami H, Sakai T, Yagihashi N, Okamoto K, Yagihashi S. Spindle cell metaplasia arising in thyroid adenoma: characterization of its pathology and differential diagnosis. J Endocrinol Investig. 2006;29(2):168–71.
12. Magro G, Benkova K, Michal M. Meningioma-like tumor of the thyroid: a previously undescribed variant of follicular adenoma. Virchows Arch. 2005;446(6):677–9.
13. Sambade C, Franssila K, Cameselle-Teijeiro J, Nesland JM, Sobrinho-Simões M. Hyalinizing trabecular adenoma: a misnomer for a peculiar tumor of the thyroid gland. Endocr Pathol. 1991;2:83–91.
14. Carney JA, Hirokawa M, Lloyd RV, Papotti M, Sebo TJ. Hyalinizing trabecular tumors of the thyroid gland are almost all benign. Am J Surg Pathol. 2008;32(12):1877–89.
15. Koperek O, Scheuba C, Cherenko M, Neuhold N, De Micco C, Schmid KW, Niederle B, Kaserer K. Desmoplasia in medullary thyroid carcinoma: a reliable indicator of metastatic potential. Histopathology. 2008;52(5):623–30.
16. Cameselle-Teijeiro J, Pardal F, Eloy C, Ruiz-Ponte C, Celestino R, Castro P, Soares P, Sobrinho-Simões M. Follicular thyroid carcinoma with an unusual glomeruloid pattern of growth. Hum Pathol. 2008;39(10):1540–7.
17. Bosisio FM, Bickel JT. Glomeruloid follicular thyroid adenoma. Int J Surg Pathol. 2013;21(4):376.
18. Rigaud C, Peltier F, Bogomoletz WV. Mucin producing microfollicular adenoma of the thyroid. J Clin Pathol. 1985;38(3):277–80.
19. Palos-Paz F, Perez-Guerra O, Cameselle-Teijeiro J, Rueda-Chimeno C, Barreiro-Morandeira F, Lado-Abeal J, Galician Group for the Study of Toxic Multinodular Goitre, Araujo Vilar D, Argueso R, Barca O, Botana M, Cabezas-Agrícola JM, Catalina P, Dominguez Gerpe L, Fernandez T, Mato A, Nuño A, Penin M, Victoria B. Prevalence of mutations in TSHR, GNAS, PRKAR1A and RAS genes in a large series of toxic thyroid adenomas from Galicia, an iodine-deficient area in NW Spain. Eur J Endocrinol. 2008;159(5):623–31.
20. Lado-Abeal J, Celestino R, Bravo SB, Garcia-Rendueles ME, de la Calzada J, Castro I, Castro P, Espadinha C, Palos F, Soares P, Alvarez CV, Sobrinho-Simões M, Cameselle-Teijeiro J. Identification of a paired box gene 8-peroxisome proliferator-activated receptor gamma (PAX8-PPARgamma) rearrangement mosaicism in a patient with an autonomous functioning follicular thyroid carcinoma bearing an activating mutation in the TSH receptor. Endocr Relat Cancer. 2010;17(3):599–610.

Small Cell Tumours

4

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Introduction

Small cell tumours constitute a heterogeneous group of tumours that are difficult to distinguish from each other and for which there is no strict classification. In the setting of a tumour with a small cell phenotype in the thyroid, the first approach is to separate lymphomas from the other small cell tumours with the help of routine immunohistochemistry; afterwards, if the small cell tumour is

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not a lymphoma, one has to try to separate a primary from a metastatic neoplasm. The distinction between primary and metastatic tumours may require a solid collaboration with the clinical team, a broad panel of immunohistochemical and, sometimes, molecular tests, and often the second opinion of an experienced pathologist.

Poorly differentiated carcinoma (PDTC); the small cell variant of medullary carcinoma (MTC), including some atypical forms of MTC with a small cell component; and lymphoma are the most frequent thyroid tumour histotypes displaying a small cell phenotype. The other tumours that may present a small cell phenotype encompass squamous cell carcinoma, carcinoma showing thymus-like elements (CASTLE), primary small cell neuroendocrine carcinoma [1], primary extraskeletal Ewing family tumours (PEEFTs) [2, 3] and small cell secondary neoplasms, as well as some extremely rare primary tumours such as neuroblastoma [4], basaloid neoplasm with solid cell nest features [5] (see Chap. 2) and the recently described "primary carcinomas of the thyroid with Ewing family tumour elements" (CEFTE) [6].

Poorly Differentiated Carcinoma

Poorly differentiated thyroid carcinoma (PDTC) is not that rare and is morphologically defined by the Turin criteria [7–10]. Microscopically, PDTC usually discloses a thick capsule with impressive images of capsular and vascular invasion (Fig. 4.1). It is a tumour with solid/trabecular, microfollicular and/or the classic insular growth pattern (Fig. 4.2), with a mitotic index usually higher than 3 mitoses *per* 10 high-power fields, displaying foci of necrosis. PDTC can be difficult to distinguish from widely invasive follicular carcinoma with a predominant trabecular growth pattern as both lack the typical PTC-like nuclei. This distinction is not important in clinical terms as the treatment and prognosis of PDTC and those of widely invasive follicular carcinoma are similar. The nuclei of PDTC are either of the so-called "intermediate-type" or convoluted/raisin-like nuclei. In the latter situation, PDTC can present as a small cell tumour. The nuclear features of PDTC must be distinguished from those of the solid variant of PTC occurring mainly in young patients, as these two

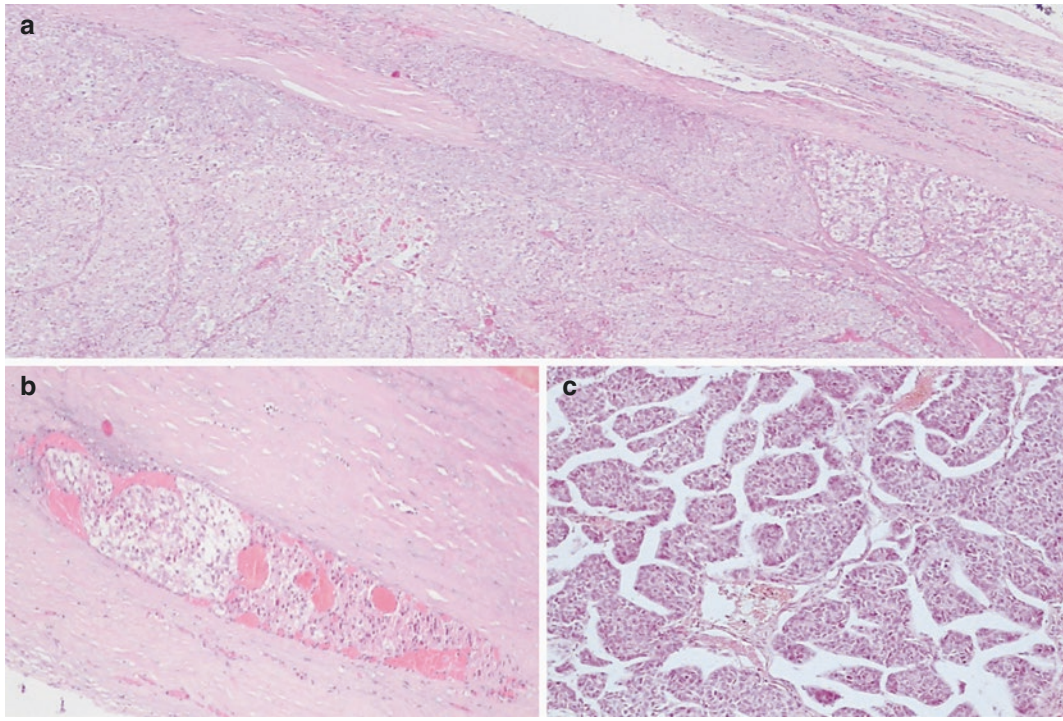

Fig. 4.1 Poorly differentiated thyroid carcinoma (PDTC). This case of PDTC discloses solid growth pattern, foci of necrosis and invasion of the capsule (**a**), as well as invasion of one large vessel of the capsule (**b**). The nested pattern is highlighted by artefactual retraction spaces that some PDTC can present (**c**)

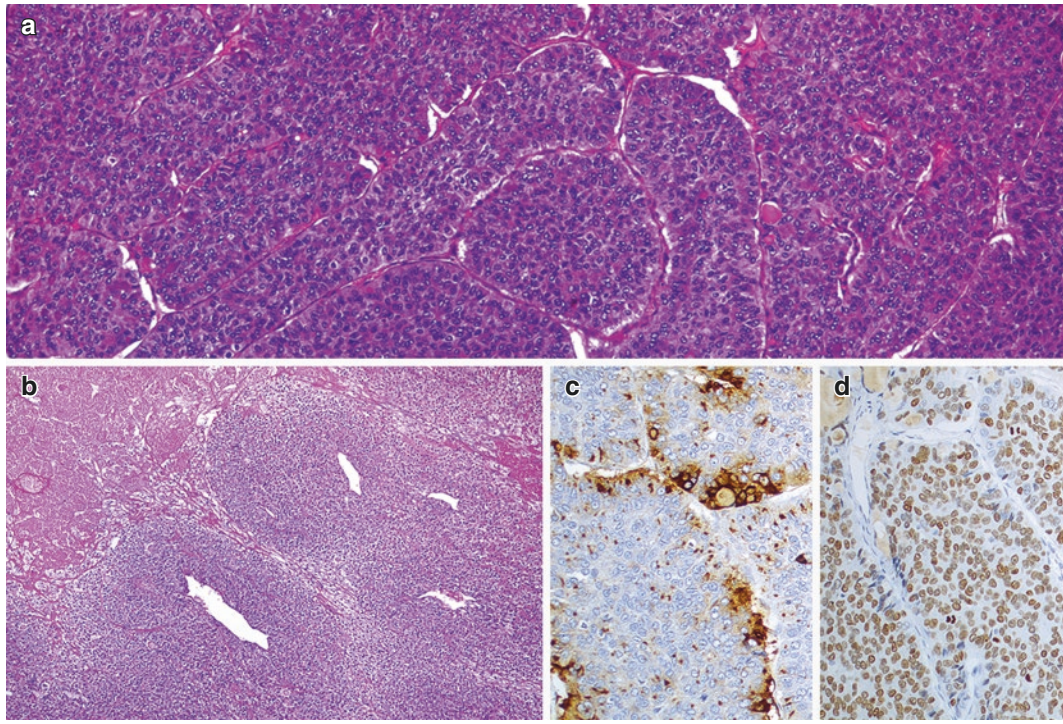

Fig. 4.2 Poorly differentiated thyroid carcinoma (insular carcinoma). This PDTC display a predominant growth pattern in solid nests (insular type) (**a**). There is tumour necrosis accompanied by preservation of the tumour cells surrounding the vessels resulting in a so-called perithelio-matous appearance (**b**). Immunohistochemically, PDTC show a characteristic pattern of microfollicular/paranu-clear dot-like staining for thyroglobulin (**c**) and expresses TTF-1 (**d**), TTF-2, PAX8 and BCL2. Focal expression of p53 is also frequently observed

entities are different concerning treatment and prognosis. The finding of an insular growth pattern, limited evidence of follicular cell differentiation (Fig. 4.2), p53 nuclear expression and high Ki-67 labelling index favour the diagnosis of PDTC.

The case depicted in Fig. 4.1 is a small cell PDTC diagnosed in a 53-year-old female. The nodule had 6 cm in largest dimension. Two years after the diagnosis, the patient developed bone metastases and refractoriness to radioactive iodine treatment.

Small Cell Variant of Medullary Thyroid Carcinoma

MTC is a thyroid tumour histotype that can present multiple aspects [8, 9], mimicking the most frequent follicular cell-derived tumours, as well as some rare entities such as vascular tumours and melanoma. The small cell phenotype of MTC is made by neoplastic C cells and frequently raises problems regarding the distinction from other tumours with small cell phenotype (Fig. 4.3). The immunoexpression of calcitonin is the key diagnostic feature. If calcitonin expression is not detected, one may be facing an atypical form of MTC (see below) or another small cell tumour with or without neuroendocrine features, including paraganglioma and metastatic carcinoma from elsewhere. Calcitonin and TTF-1 expression can be observed also in neuroendocrine carcinomas of the lung metastasizing to the thyroid.

The case illustrated here (Fig. 4.3) was from a 44-year-old male with a large thyroid nodule that was diagnosed as a small cell variant of MTC. The patient developed lymph node and lung metastases and died of the disease soon after the initial diagnosis.

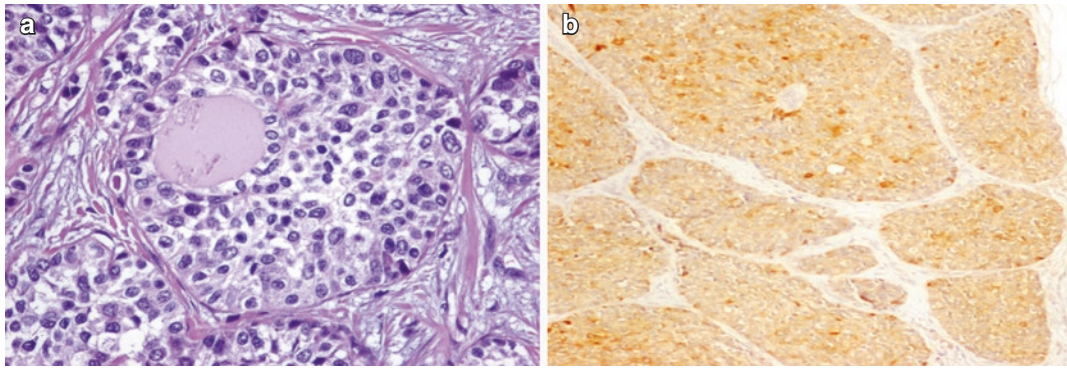

Fig. 4.3 Small cell variant of medullary thyroid carcinoma (MTC). Small cell variant of MTC disclosing a solid growth pattern around pre-existing benign follicles (**a**) and expressing calcitonin (**b**)

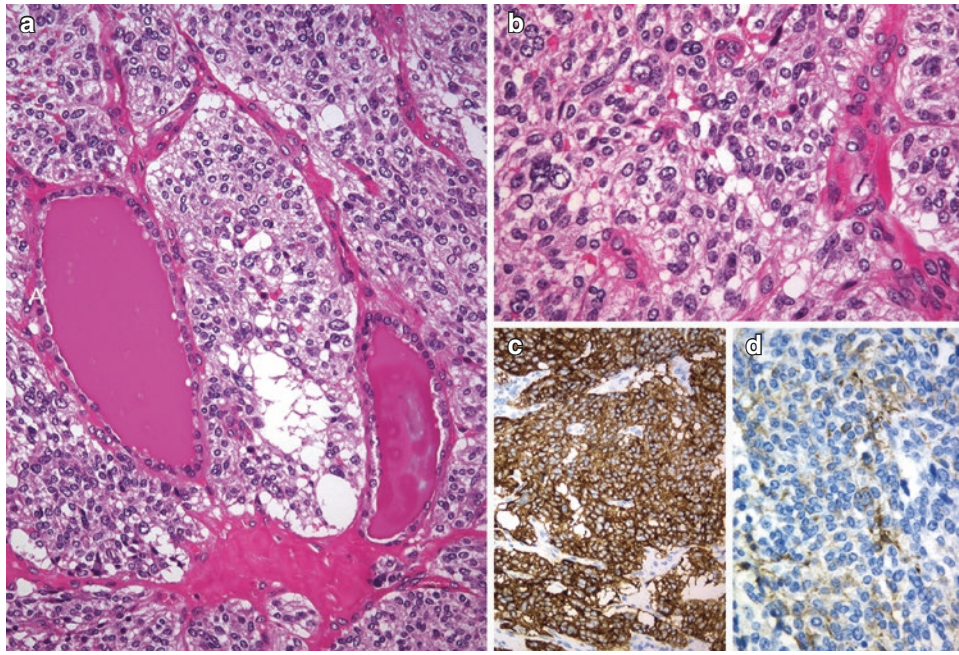

Fig. 4.4 Calcitonin negative (atypical) medullary thyroid carcinoma (MTC). The tumour was encapsulated and composed of neoplastic cells arranged in middle-sized nests separated by thin-walled blood vessels (**a**). Tumour cells are round to oval with mild to moderate atypia and have nuclei with slightly coarse chromatin and inconspicuous nucleoli (**b**). No immunoreaction for thyroglobulin and calcitonin was detected in any tumour cell. Positivity was found for chromogranin A (**c**), synaptophysin, TTF-1, PAX8, cytokeratins and calcitonin gene-related peptide (CGRP) (**d**)

Calcitonin-Negative (Atypical) Medullary Thyroid Carcinoma

In the thyroid gland, primary neuroendocrine tumours encompass MTC and, rarely, other tumours such as paragangliomas. MTCs are derived from C cells and express calcitonin and neuroendocrine tumours markers. Some reports have documented thyroid neuroendocrine displaying little, or no expression, of calcitonin that raise difficult diagnostic problems [10, 11]. Figures 4.4 and 4.5 illustrate two cases of

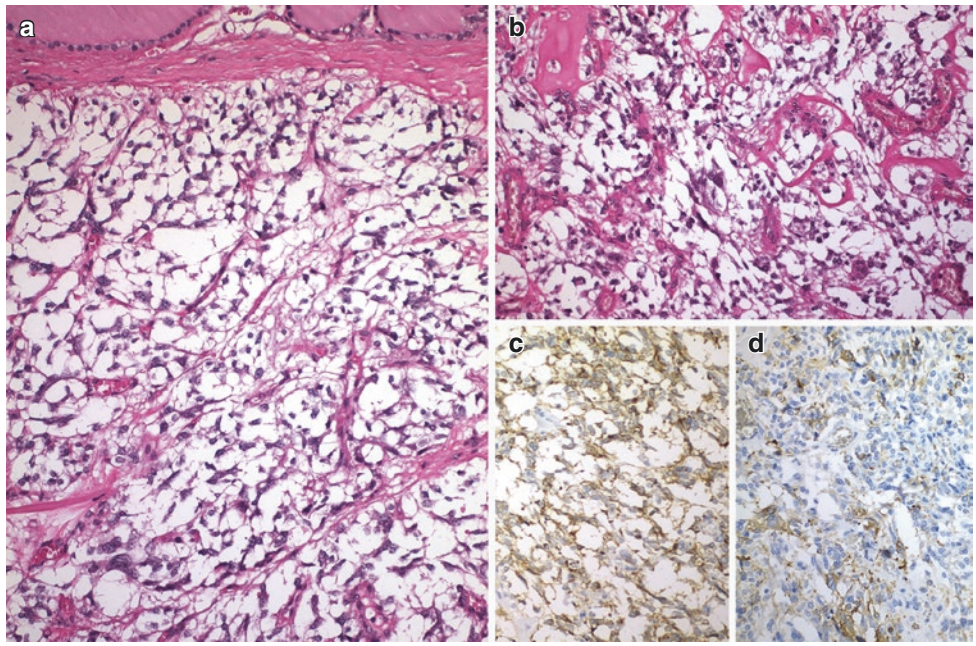

Fig. 4.5 Calcitonin negative (atypical) medullary thyroid carcinoma (MTC). This is a well-circumscribed, angioinvasive tumour without extrathyroid extension (**a**). There were fewer than 1 mitotic figure per 10 high-power fields, and no foci of necrosis (**b**). The tumour cells were positive for chromogranin A (**c**), synaptophysin, CD56, TTF-1, PAX8, cytokeratins and CGRP (**d**) and were negative for calcitonin, CEA and thyroglobulin. The patient remains free of disease 18 months after left lobectomy plus isthmectomy

C-cell-derived calcitonin-free neuroendocrine carcinoma of the thyroid. These cases presented in a 48-year-old woman and in a 76-year-old man, respectively, with no family history of MTC. In both cases, the tumours were solid and well circumscribed, measuring 28 and 60 mm in largest diameter. Histopathologically, the neoplastic cells formed solid nests surrounded by thin fibrovascular septa with an organoid ("Zellballen") pattern resembling the aspect of paraganglioma-like MTC. The immunohistochemical findings were similar in both cases. The tumour cells showed reactivity for chromogranin A, synaptophysin, TTF-1, PAX8, cytokeratins (clone AE1/AE3, CK7, CK8 and CK18) and calcitonin gene-related peptide (CGRP) and negativity for calcitonin, CEA, TTF-2 (FOXE1), thyroperoxidase and thyroglobulin. In situ hybridization showed that the neoplastic cells lacked calcitonin and thyroglobulin mRNA expression. Genetic analysis did not disclose any *RET* mutation. CGRP is a member of the calcitonin family of neuropeptides, which is generated as a consequence of tissue-specific mRNA alternative splicing of the *CALCA* gene-encoding calcitonin, CGRP and catakalcin (procalcitonin). CGRP is also produced in other organs; therefore, CGPR expression alone does not necessarily indicate the C-cell origin of the tumour cells. However, together with the expression of TTF-1 and PAX8, and despite the loss of calcitonin expression, the positivity for CGRP pointed to the C-cell origin of the two tumours leading to a diagnosis of calcitonin-negative MTC.

In the follow-up of patients with MTC, serum calcitonin level is a crucial tumour marker. The lack of calcitonin expression in MTC raises a problem similar to the absence of thyroglobulin expression in differentiated thyroid carcinomas: the marker (calcitonin) may not represent the tumour burden and may not be useful for the follow-up.

Thyroid Lymphoma

Lymphomas of the thyroid, including MALT-type B-cell lymphoma, T-cell lymphoma and follicular lymphoma, disclose also a small cell phenotype but are less frequent than the diffuse large B-cell lymphoma composed of larger lymphoid cells. Lymphomas may involve the thyroid as part of a systemic disease or, rarely, as a primary disease originating in the thyroid (primary lymphoma) [12]. Many patients are elderly women that complain of a rapidly growing mass and compressive symptom, simulating an anaplastic thyroid carcinoma. The histological features of each lymphoma type in the thyroid are similar to those of corresponding lymphomas in other locations. The overall destruction of the thyroid architecture and the prominent lymphoepithelial lesions, together with the coexistence of plasma cell differentiation, are morphological clues that favour the diagnosis of MALT-type B-cell lymphoma against the alternative diagnosis of florid Hashimoto thyroiditis (Figs. 4.6, 4.7 and 4.8). In most cases, the diagnosis of lymphoma involving the thyroid can be made by FNAB and flow cytometry. The case illustrated in Fig. 4.5 is from a 58-year-old female with an enlarged thyroid without nodules and a diagnosis of MALT-type B-cell lymphoma primary of the thyroid. No other foci of lymphoma were found in the patient.

Metastatic Small Cell Carcinoma

Secondary tumours of the thyroid are those resulting from the spread of a primary tumour at a distant location or those resulting from the direct extension of tumours arising in structures contiguous to the gland [9, 10]. Metastases to the thyroid are detected in up to one fourth of autopsies of elderly euthyroid patients with disseminated malignancies. The most common primary carcinoma sites giving rise to metastases in the thyroid are the kidney, lung, breast and oesophagus, but in the large majority of cases, the metastases do not display as a small cell phenotype.

Two patterns of growth can be observed in the metastases to the thyroid: an interstitial infiltration pattern that surrounds the follicles and a nodular pattern that can mimic a primary tumour. Figure 4.9 illustrates a case of metastatic invasive breast carcinoma disclosing an interstitial infiltration of the thyroid.

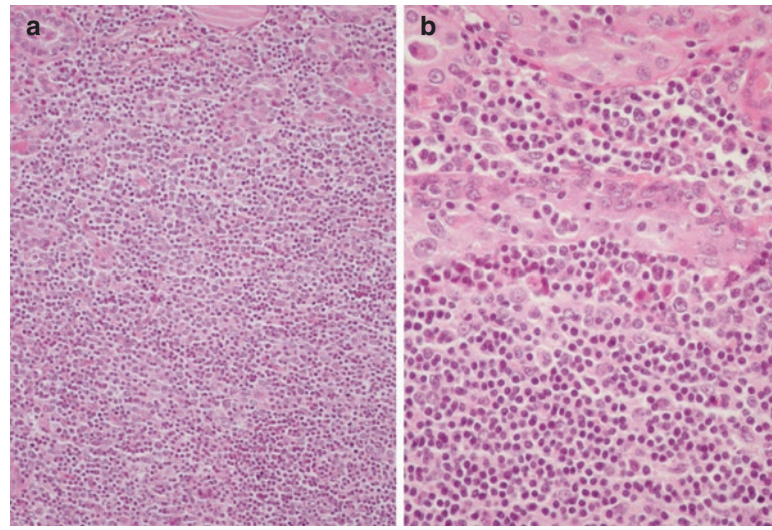

Fig. 4.6 Primary MALT-type B-cell lymphoma of the thyroid. The tumour discloses an extensive effacement of the thyroid architecture due to a diffuse proliferation of small lymphoid cells (**a**) and lymphoepithelial images that consist in the permeation by neoplastic B-cell lymphocytes of the epithelial cell nests that remain from the original thyroid tissue (**b**)

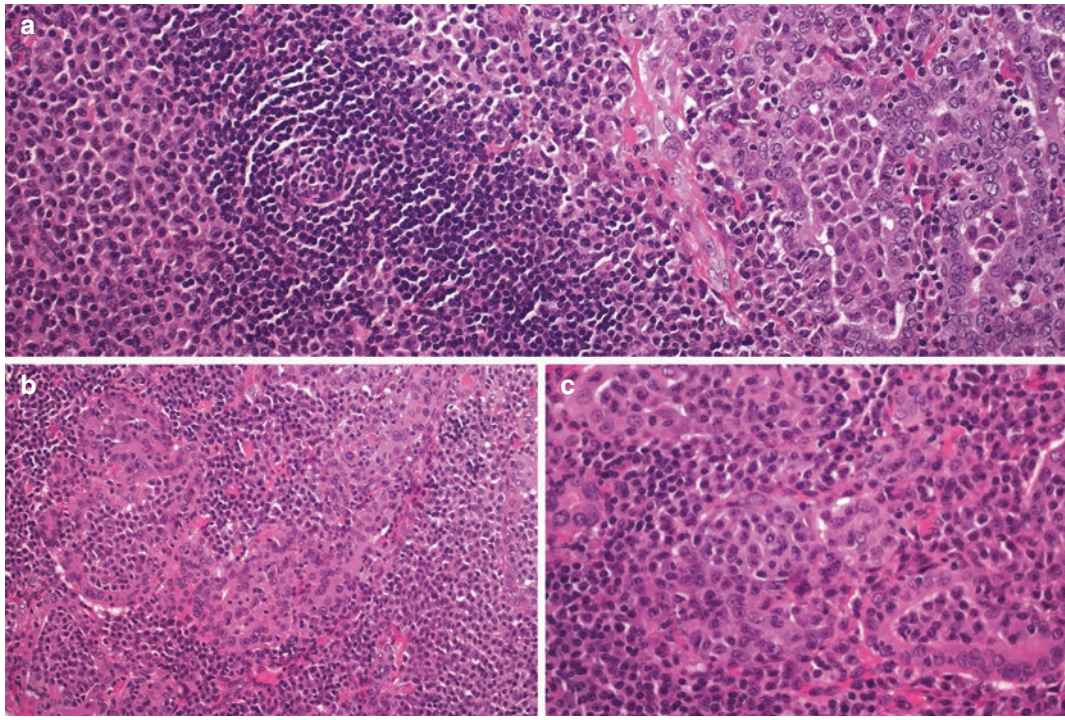

Fig. 4.7 Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) of the thyroid. This case presented in a 73-year-old woman with a history of lymphocytic thyroiditis and rapid enlargement of the thyroid. There was an extensive infiltration of the thyroid parenchyma by sheets of small lymphoid cells, centrocyte-like cells, monocytoid cells and plasma cells, often with interspersed reactive lymphoid follicles (**a**). Malignant cells tended to infiltrate and expand thyroid follicles forming lymphoepithelial lesions. The plasmacytoid nature of the infiltrate and the packing of follicles by the tumour cells are important diagnostic clues (**a**–**c**)

In Fig. 4.10, we present a case of a metastatic Merkel cell carcinoma with a small cell phenotype and a nodular pattern that might have create a big problem if the primary tumour was not known. It was a 56-year-old female with a clinical history of Merkel cell carcinoma of the left leg diagnosed 3 years before. The thyroid ultrasound, performed under surveillance of a long-standing nodular goitre, showed a multinodular thyroid. The patient was treated with surgery, and in the surgical specimen, the largest nodule measured 6.5 cm and was well-circumscribed, whitish and firm. The histological examination showed a tumour invading a thick capsule and displaying a solid pattern of growth and extensive areas of necrosis (Fig. 4.10). Immunohistochemistry disclosed a perinuclear dot-like staining for keratins CAM5.2 and CK20 and diffuse and strong expression for chromogranin A and synaptophysin (Fig. 4.10). Expression for CK7, TTF-1, thyroglobulin and calcitonin was absent.

The absence of thyroglobulin expression in some primary thyroid tumours, as well as the expression of thyroglobulin in entrapped follicles that may diffuse into the adjacent structures and be absorbed by metastatic cells, constitutes two well-known pitfalls. The expression of TTF-1 expression can also be observed in a subset of metastatic lung carcinomas that may be difficult to separate from primary thyroid tumours.

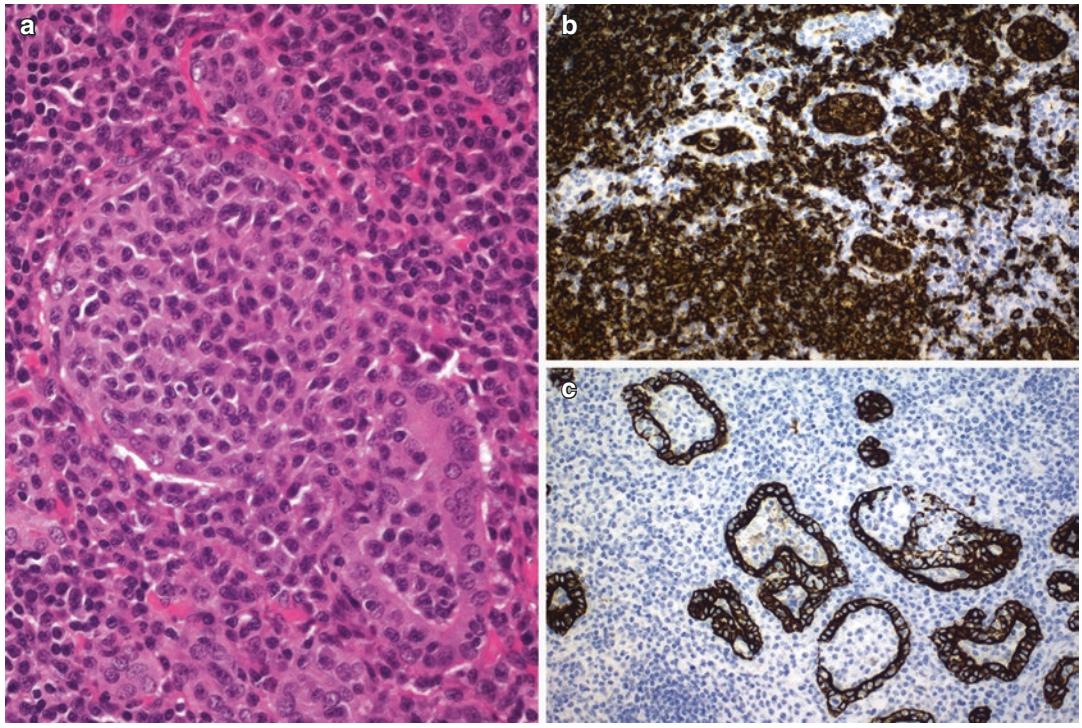

Fig. 4.8 Lymphoepithelial lesions in marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) of the thyroid. Same case as Fig. 4.7. Two main forms of lymphoepithelial lesions can be seen. In one, neoplastic cells invade the follicular epithelium but not the colloid. In the other form, lymphoma cells invade into the colloid portion of the follicle, leaving the epithelium relatively well preserved (**a**–**c**). The neoplastic cells are positive for CD20, including those located within the entrapped follicles (**b**). Immunostaining for keratin (clone AE1/AE3) illustrates the entrapment and distortion of the epithelial follicular cells by the lymphoma cells (**c**)

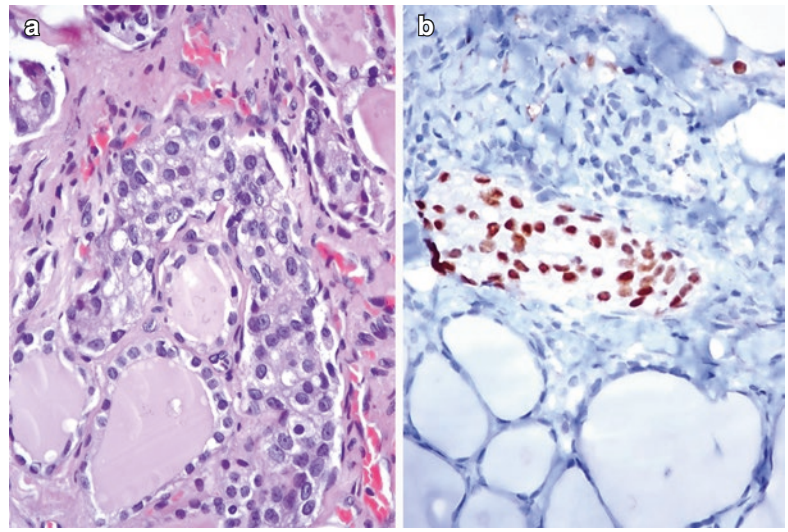

Fig. 4.9 Metastatic breast carcinoma. Metastatic invasive breast carcinoma displaying an interstitial infiltration of the thyroid (**a**) and positivity for oestrogen receptors (**b**)

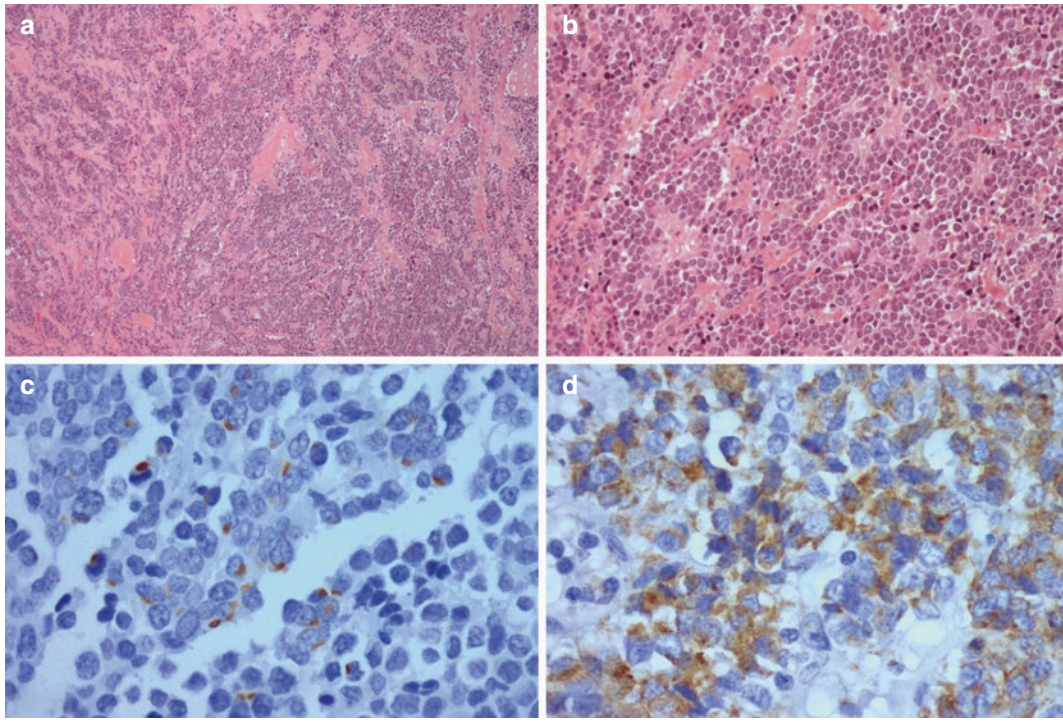

Fig. 4.10 Metastatic Merkel cell carcinoma. Metastasis of Merkel cell carcinoma of the skin to the thyroid displaying a solid growth pattern and a small cell phenotype (**a**). The neoplastic small cells disclose abundant mitotic figures (**b**) and express dot-like CK20 (**c**) and cytoplasmatic chromogranin (**d**) (Courtesy of António Polónia, Porto, Portugal)

Carcinoma of the Thyroid with Ewing Family Tumour Elements (CEFTE)

The existence of true small cell primary thyroid tumours, with or without neuroendocrine features, has been a matter of debate for many years. After the first description in the pre-immunohistochemistry era by Meissner and Lahey and until the 1980s, the small cell carcinoma of the thyroid was considered a morphological variant of anaplastic carcinoma. Later on, immunohistochemical studies provided evidence that allowed to identify, within the umbrella descriptive group of small cells tumours of the thyroid, lymphomas and MTC and PDTC composed of small cells.

In 2011 [13], our group reported a non-endocrine small cell carcinoma primary of the thyroid with basaloid pattern and vascular invasion (Fig. 4.11). An extensive clinical search did not reveal any other tumour elsewhere. The case was from a 42-year-old woman with an unencapsulated tumour that displayed a nesting growth pattern consisting of well-defined, variable-sized insulae, as well as trabeculae and solid areas, composed of small (basaloid) cells with regular, round nuclei and scanty cytoplasm with ill-defined boundaries (Fig. 4.11). Additionally, epidermoid-like areas coexisted with neoplastic follicular cell foci with PTC-like nuclear features (Fig. 4.11). The small cells disclosed strong and diffuse immunoreactivity for p63, CK19, CK8/18, CKs AE1/AE3 and CKs CAM5.2 (Fig. 4.12).

Immunoreactivity for TTF-1, thyroglobulin, calcitonin, CK5, CK7, actin, chromogranin A, synaptophysin, NSE, GCDFP-15, HMB-45 and S100 protein was not detected. Later on, during the study of a second case with similar features,

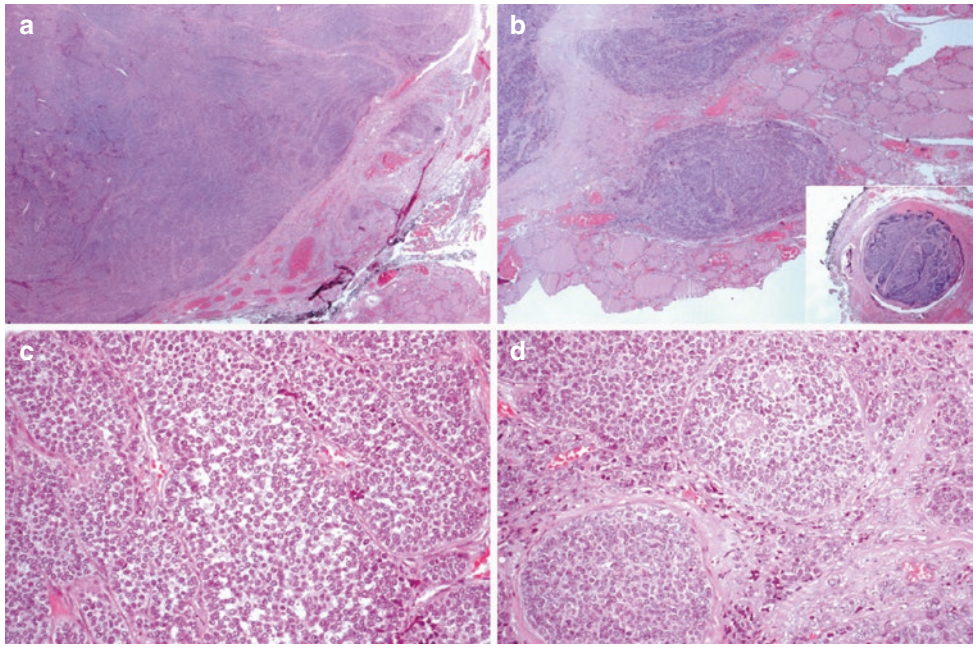

Fig. 4.11 Carcinoma of the thyroid with Ewing family tumour elements (CEFTE). Please notice the expansive growth pattern (**a**) and the infiltrative invasive front (**b**) of the first reported case of CEFTE that also disclosed vascular invasion (**b**, *inset*). Tumour cells showed a solid/trabecular (**c**) and nested growth pattern (**d**)

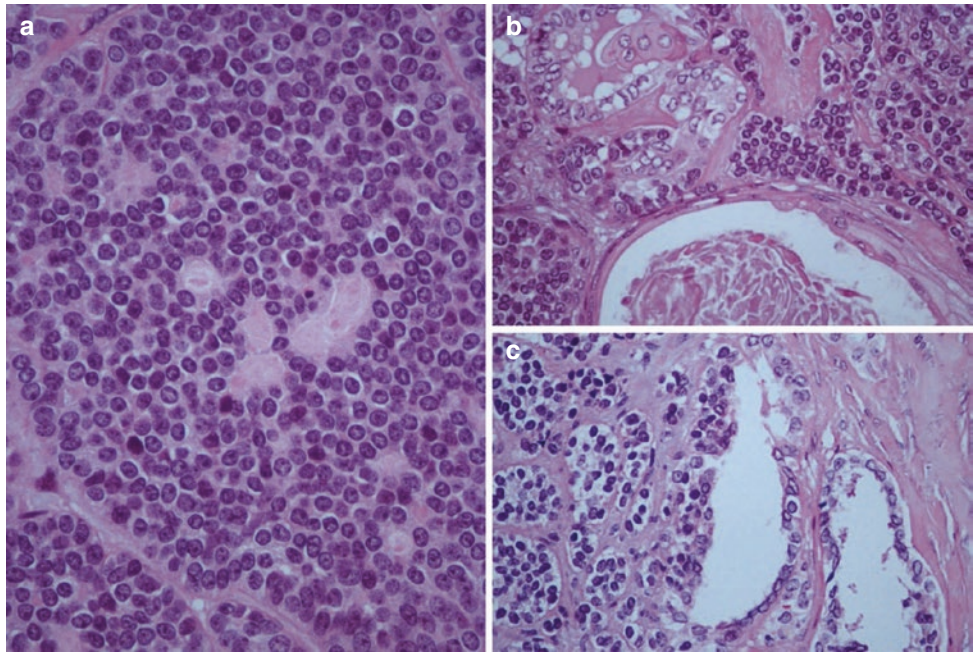

Fig. 4.12 Carcinoma of the thyroid with Ewing family tumour elements (CEFTE). The small cell component is characterized by cells with scant cytoplasm, monotonous, roundish nuclei with low mitotic index and foci of necrosis (**a**). The small cell component coexists with PTC foci (disclosing a follicular organization and typical PTC-like nuclei) and squamoid nests (**b**, **c**)

the expression CD99, together with the presence of *EWSR1/FLI1* rearrangement, was detected in this and in the previous case [14, 15]. Both patients are alive and well after more than 6 years of follow-up after being treated with total thyroidectomy and, in the second case, followed by radioactive iodine. In summary, CEFTE is a special type of small cell thyroid carcinoma with primary extraskeletal Ewing family tumour features, foci of papillary thyroid carcinoma and apparently good prognosis. There is another case of CEFTE with neuroendocrine differentiation (Fig. 4.13), a feature that can also be detected in primary extraskeletal Ewing family tumour (PEEFT).

The distinction between CEFTE and typical PEEFT is difficult and uses mainly the absence of vimentin expression, the prominent epithelial differentiation, the coexistence of PTC foci (Fig. 4.14) and the favourable prognosis of the former in comparison with PEEDT.

CEFTE is a small cell tumour with uncertain histogenesis. Based upon the morphological and immunohistochemical features of the neoplastic cells, two putative histogeneses have been advanced [6, 15]:

- From PTC cells that "dedifferentiate" acquiring the *EWSR1-FLI1* rearrangement and loosing thyroid differentiation (negativity for TTF-1 and thyroglobulin), taking in consideration the close topographical relationship between CEFTE and PTC foci
- From main cells of solid cell nests (SCN), taking in consideration the diffuse expression of p63

Recently, a study of our group has shown that *EWSR1* rearrangements are frequently detected in PTC and not detected in SCN, favouring the interpretation that CEFTE probably arises from "dedifferentiation" of PTC [16] .

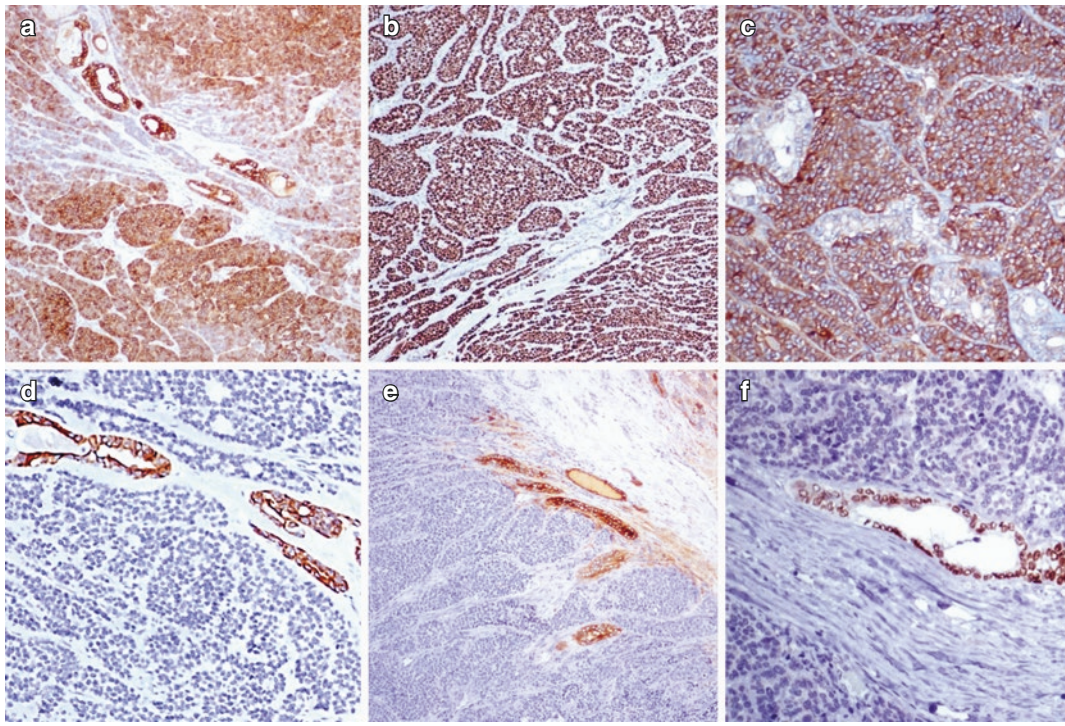

Fig. 4.13 Immunohistochemical features of a case of CEFTE. The small cells express CAM5.2 (**a**), p63 (**b**) and CD99 (**c**), while the PTC cells express CK7 (**d**), thyroglobulin (**e**) and TTF-1 (**f**)

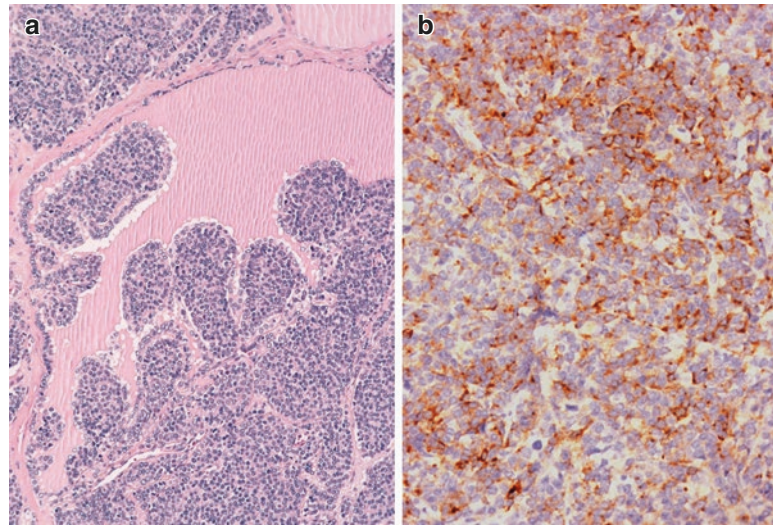

Fig. 4.14 CEFTE with neuroendocrine features. In this case of CEFTE, the small cells coexist with PTC areas disclosing a papillary growth (**a**). The small cells express chromogranin (**b**) (Courtesy of Sandra Sapia, Elche, Spain)

References

1. Beach DF, Klump WJ, Haddad G, Reid LM, Schwarting R, Hageboutros A. Extrapulmonary small cell: a novel case of small cell carcinoma of the thyroid gland. Med Oncol. 2012;29(3):1405–8.
2. Chan JM, Bilodeau E, Celin S, Nikiforov Y, Johnson JT. Ewing sarcoma of the thyroid: report of 2 cases and review of the literature. Head Neck. 2013;35(11):E346–50.
3. Maldi E, Monga G, Rossi D, Tosoni A, Mezzapelle R, Boldorini R. Extra-osseous Ewing sarcoma of the thyroid gland mimicking lymphoma recurrence: a case report. Pathol Res Pract. 2012;208(6):356–9.
4. Kumar M, Gupta P, Chaubey A. The thyroid: an extremely rare primary site of neuroblastoma. Hum Pathol. 2006;37(10):1357–60.
5. Eloy C, Vinagre J, Cameselle-Teijeiro J, Paiva ME, Soares P, Sobrinho-Simões M. Tumor-in-tumor of the thyroid with basaloid differentiation: a lesion with a solid cell nest neoplastic component? Int J Surg Pathol. 2011;19(2):276–80.
6. Eloy C, Cameselle-Teijeiro JM, Rousseau E, Sobrinho-Simões M. Small cell tumors of the thyroid gland: a review. Int J Surg Pathol. 2014;22(3):197–201.
7. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, Lloyd RV, LiVolsi VA, Papotti M, Sobrinho-Simoes M, Bussolati G, Rosai J. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 2007;31(8):1256–64.
8. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
9. Rosai J, DeLellis RA, Carcangiu ML, Frable WJ, Tallini G. Tumors of the thyroid and parathyroid glands, AFIP Atlas of Tumor Pathology. Series 4. Fascicle 21. Silver Spring, MD: American Registry of Pathology; 2014.
10. Kasajima A, Cameselle-Teijeiro J, Loidi L, Takahashi Y, Nakashima N, Sato S, Fujishima F, Watanabe M, Nakazawa T, Naganuma H, Kondo T, Kato R, Sasano H. A calcitonin non-producing neuroendocrine tumor of the thyroid gland. Endocr Pathol. 2016;27(4):325–31.
11. Nakazawa T, Cameselle-Teijeiro J, Vinagre J, Soares P, Rousseau E, Eloy C, Sobrinho-Simões M. C- cell-derived calcitonin-free neuroendocrine carcinoma of the thyroid: the diagnostic importance of CGRP immunoreactivity. Int J Surg Pathol. 2014;22(6):530–5. PMID: 24599901.
12. Widder S, Pasieka JL. Primary thyroid lymphomas. Curr Treat Options in Oncol. 2004;5(4):307–13.
13. Cruz J, Eloy C, Aragüés JM, Vinagre J, Sobrinho-Simões M. Small-cell (basaloid) thyroid carcinoma: a neoplasm with a solid cell nest histogenesis? Int J Surg Pathol. 2011;19(5):620–6.
14. Eloy C, Oliveira M, Vieira J, Teixeira MR, Cruz J, Sobrinho-Simões M. Carcinoma of the thyroid with ewing family tumor elements and favorable prognosis: report of a second case. Int J Surg Pathol. 2014;22(3):260–5.
15. Eloy C, Cameselle-Teijeiro J, Vieira J, Teixeira MR, Cruz J, Sobrinho-Simões M. Carcinoma of the thyroid with Ewing/PNET family tumor elements: a tumor of unknown histogenesis. Int J Surg Pathol. 2014;22(6):579–81.
16. Oliveira G, Polónia A, Cameselle-Teijeiro JM, Leitão D, Sapia S, Sobrinho-Simões M, Eloy C. EWSR1 rearrangement is a frequent event in papillary thyroid carcinoma and in carcinoma of the thyroid with Ewing family tumor elements (CEFTE). Virchows Arch. 2017;470(5):517–52.

Rare Familial Tumours

5

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Introduction

Approximately 3–9% of non-medullary thyroid carcinomas occur on a familial basis [1]. About 5% of these tumours are syndromic, whereas the remaining 95% of all cases of familial non-medullary thyroid carcinomas (FNMTCs) are non-syndromic with less well-defined genetic susceptibility [1].

The genetic details of non-syndromic FNMTC are summarized in Table 5.1, including the *HABP2* gene whose role in familial PTC has

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recently been questioned [1–3]. Usually there is a family history of thyroid nodules, and although the histology of non-syndromic FNMTC is not different from that of sporadic tumours, most cases are PTCs characterized by an early onset, increased multifocality and bilaterality and association with multinodular goitre and/or follicular adenoma(s) [1, 3]. At variance with this, the syndromic FNMTCs have well-defined driver germline mutations including familial adenomatous polyposis (FAP), DICER1 syndrome, Werner syndrome, Carney complex type 1 and PTEN hamartoma tumour syndrome (PHTS) which includes Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS) (Table 5.2).

Table 5.1 Non-syndromic familial non-medullary thyroid carcinomas

Chromosomal location	Gene	Thyroid tumour/s	Additional lesions
19p13.11	*GRIM-19* (*NDUFA13*)	Multifocal Hürthle cell (oncocytic) adenoma, PTC and/or FTC	
19p13.2	*TCO* (unknown)	Multifocal Hürthle cell (oncocytic) adenoma, PTC and/or FTC	
1q21	*PTCPRN* (*fPTC/PRN1*) (unknown)	PTC	Papillary renal neoplasia
9q22.33	*FOXE1* (*TTF-2*)	PTC	
9q34.13	*TTF-1* (*NKX2-1*)	MNG, PTC	
12q14.2	*SRGAP1*	PTC	
10q25.3	*HABP2*	PTC	
8p23.1-p22	Unknown	MNG, follicular adenoma, PTC	
2q21	*NMTC1* (unknown)	PTC (classical and follicular variant)	
6q22	Unknown	PTC	
8q24	Unknown	PTC	

PTC papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *MNG* multinodular goitre

Table 5.2 Syndromic familial non-medullary thyroid carcinomas

Syndrome	Gene and location	Thyroid tumour/s	Main additional lesions
Familial adenomatous polyposis	*APC* 5q22.2	Cribriform-morular variant of PTC	Multiple colonic adenomatous polyps, colorectal cancer, desmoid tumours and osteomas (Gardner syndrome), medulloblastoma (Turcot syndrome), hepatoblastoma, congenital hypertrophy of the retinal epithelium
PTEN hamartoma tumour syndrome (Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome)	*PTEN* 10q23.31	MNG, multiple adenomatous nodules ("microadenomas"), follicular adenoma, lipoadenoma, PTC, FTC, lymphocytic thyroiditis, foci of adipose infiltration, C-cell hyperplasia	Fibrocystic breast disease, breast hamartoma, breast cancer, trichilemmomas, keratosis, oral papillomas, cutaneous papules, pigmentation of penis, endometrial carcinoma, upper and lower gastrointestinal (hyperplastic, adenomatous, hamartomatous, lipomatous, ganglioneuromatous and inflammatory) polyps and cancer, macrocephaly, Lhermitte-Duclos disease, mental retardation, autism, renal carcinoma, glycogenic acanthosis, storiform collagenoma, lipomas

Table 5.2 (continued)

Syndrome	Gene and location	Thyroid tumour/s	Main additional lesions
DICER1 syndrome	*DICER1* 14q32.13	MNG, differentiated thyroid carcinoma	Pleuropulmonary blastoma, cystic nephroma, ovarian Sertoli-Leydig cell tumours, gynandroblastoma, juvenile granulosa cell tumours, pituitary blastoma with infant Cushing disease, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma, embryonal rhabdomyosarcoma of the cervix, anaplastic sarcoma of kidney
Werner syndrome (adult progeria)	*WRN* 8p12	PTC, FTC, undifferentiated (anaplastic) carcinoma	Prematurely aged facies, scleroderma-like skin changes, cataracts, premature arteriosclerosis, type 2 diabetes, osteosarcoma, soft tissue sarcomas, melanoma, meningioma, myeloid disorders
Carney complex type 1	*PRKAR1A* 17q24.2	Follicular adenoma, PTC	Skin and mucosal pigmentary abnormalities (blue nevi), atrial myxoma, mucocutaneous myxomas, pigmented nodular adrenocortical disease, large-cell calcifying Sertoli cell tumour, psammomatous melanotic schwannomas, pituitary adenomas

PTC papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *MNG* multinodular goitre

Due to its rarity and importance for the understanding of thyroid carcinogenesis, this chapter focuses on the characteristics of cribriform-morular variant of PTC which is usually associated with FAP but can also be sporadic, as well as on tumours arising in the context of PHTS and DICER1 syndrome. The peculiar morphological and immunohistochemical characteristics of some of such thyroid tumours allow pathologists to play a crucial role in the recognition of the respective hereditary conditions.

Cribriform-Morular Variant of Papillary Thyroid Carcinoma

Cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC) is the peculiar form of thyroid carcinoma associated with familial adenomatous polyposis (FAP) that can also occur as a sporadic tumour [3–5]. The name "cribriform-morular variant" of PTC was coined by our group in 1999 to describe the sporadic morphological counterpart of FAP-associated familial non-medullary thyroid carcinoma [5]. About 60% of the cases are associated with FAP, and in these cases, the diagnosis of thyroid carcinoma precedes that of FAP in up to 40%. CMV is a tumour with a striking prevalence in women (female-to-male ratio of 61:1) in contrast to a female-to-male ratio of colonic tumours of about 1:1 in FAP. The mean age of primary diagnosis is 26.5 years (median 26, range 8–61 years) with no significant difference between FAP-associated and sporadic CMV of PTC [6].

Most tumours are well-circumscribed or encapsulated, white to tan, fleshy and solid, although cystic areas can be seen in some cases. In FAP patients, the tumours are more often multifocal and/or bilateral than in the sporadic cases (63% versus 13%) (Fig. 5.1).

CMV of PTC is usually encapsulated or well circumscribed and partially divided in lobules by sclerotic septa. It is characterized by a blending of cribriform, follicular, papillary, trabecular and solid patterns of growth, with morular (squamoid) structures [4, 5] (Figs. 5.2, 5.3 and 5.4). Cribriform areas are formed by anastomosing bars and arches of cells in the absence of fibrovascular stroma and typically merge with small tubular follicles. Both large follicles (cribriform pattern) and tubular structures are frequently devoid of colloid or may contain foamy and/or multinucleated histiocytes. Nonarbourizing papillary and pseudopapillary elements are usually focal and lined by columnar

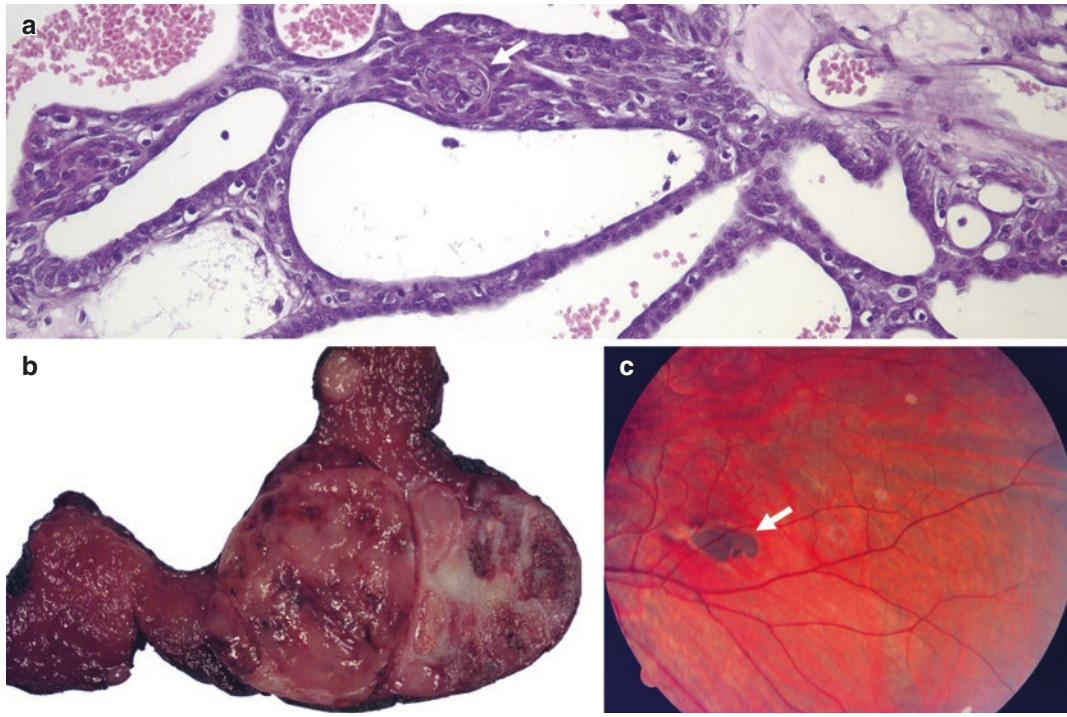


Fig. 5.1 Familial adenomatous polyposis (FAP)-associated cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). CMV is characterized by a combination of cribriform pattern of growth and morular (arrow) structures (**a**). FAP-associated CMV of PTC is often multiple and bilateral (**b**). In these patients, the germline mutations usually occur in exon 15 before codon 1220; curiously, the same codons are implicated in the development of thyroid carcinoma and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Fundoscopy showing CHRPE (*arrow*) is therefore a good way to confirm the hereditary nature of the CMV of PTC before the genetic study (**c**, courtesy of Rosario Touriño Peralba, Santiago de Compostela, Spain)

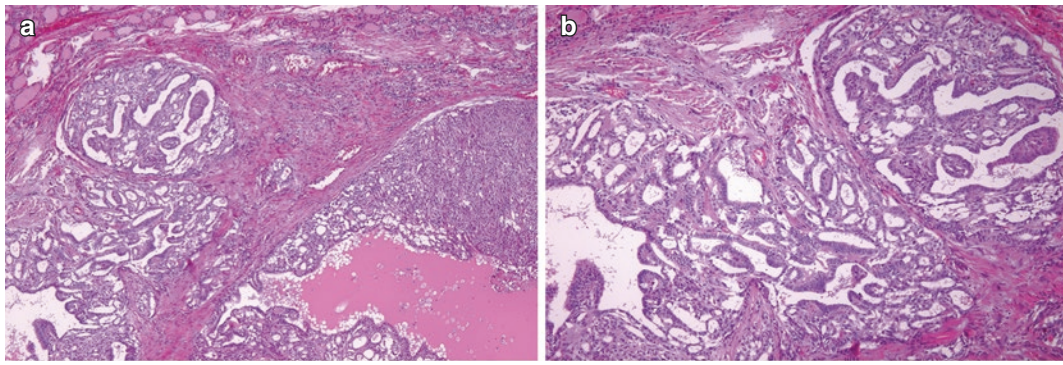
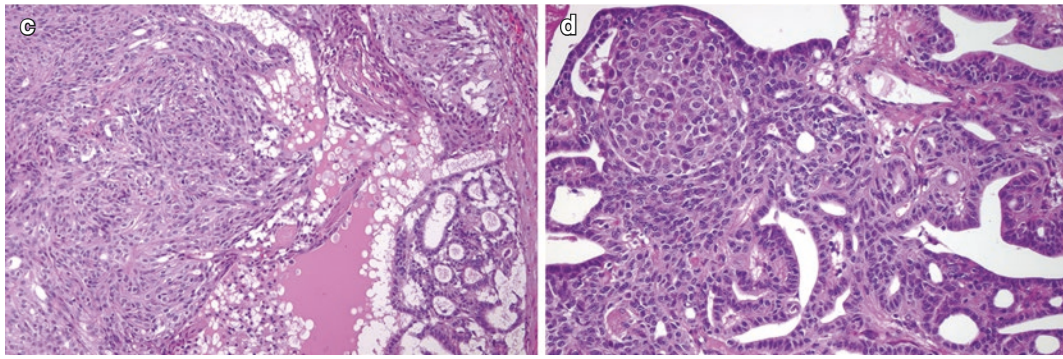


Fig. 5.2 Cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). This sporadic case is from a 31-year-old female. CMV of PTC is usually well circumscribed and partially divided in lobules by sclerotic septa (**a**). It is microscopically characterized by an intricate blending (**a**) of cribriform, follicular, papillary (**b**) and solid (**c**) patterns of growth, with morular (squamoid) structures (**d**). Colloid is rarely seen in the follicular lumina



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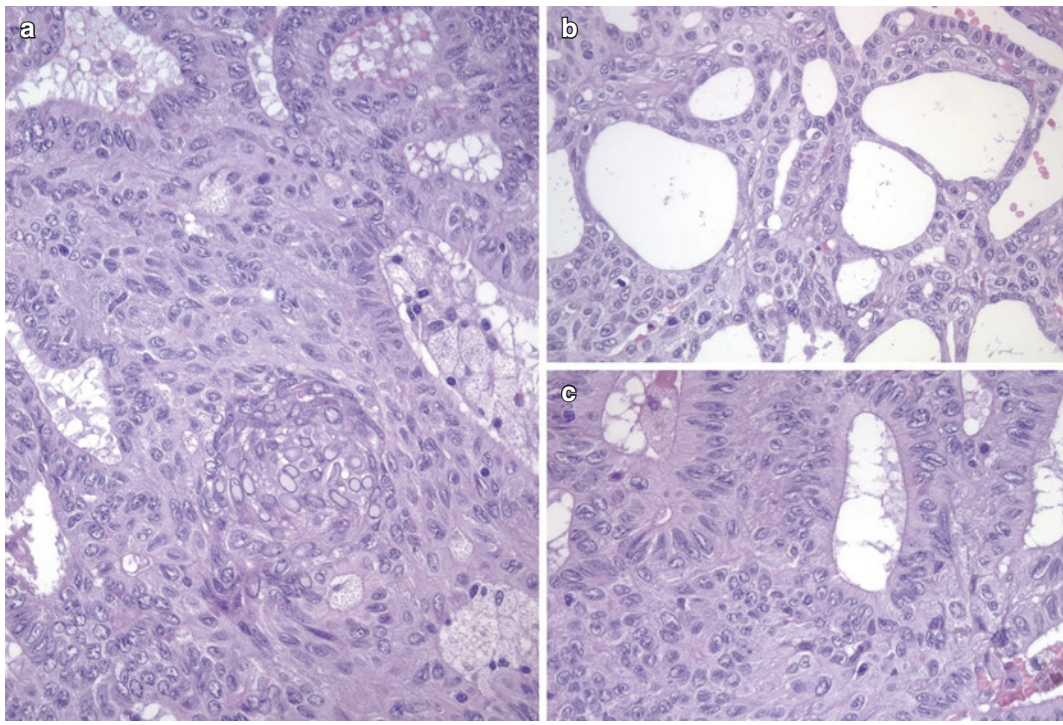

Fig. 5.3 Cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). Familial adenomatous polyposis-associated case of CMV of PTC observed in a 29-year-old female. The tumour showed the typical admixture of solid (**a**), cribriform (**b**) and follicular architecture (**c**), as well as morular structures (**a**). The nuclei of tumour cells are not particularly clear but show a round to oval shape with prominent grooving (**a**–**c**) and pseudoinclusions. In the morular structure shown in (**a**), numerous biotin-rich, optically clear nuclei can be identified

cells. Areas with trabecular arrangement of plump spindle cells with the nuclei aligned perpendicular to the long axis are reminiscent of the so-called hyalinizing trabecular tumour (Fig. 5.4). The tumour cells are cuboidal or tall, with frequent nuclear pseudostratification and abundant amphophilic to oxyphilic cytoplasm. The nuclei are usually hyperchromatic, variably displaying the

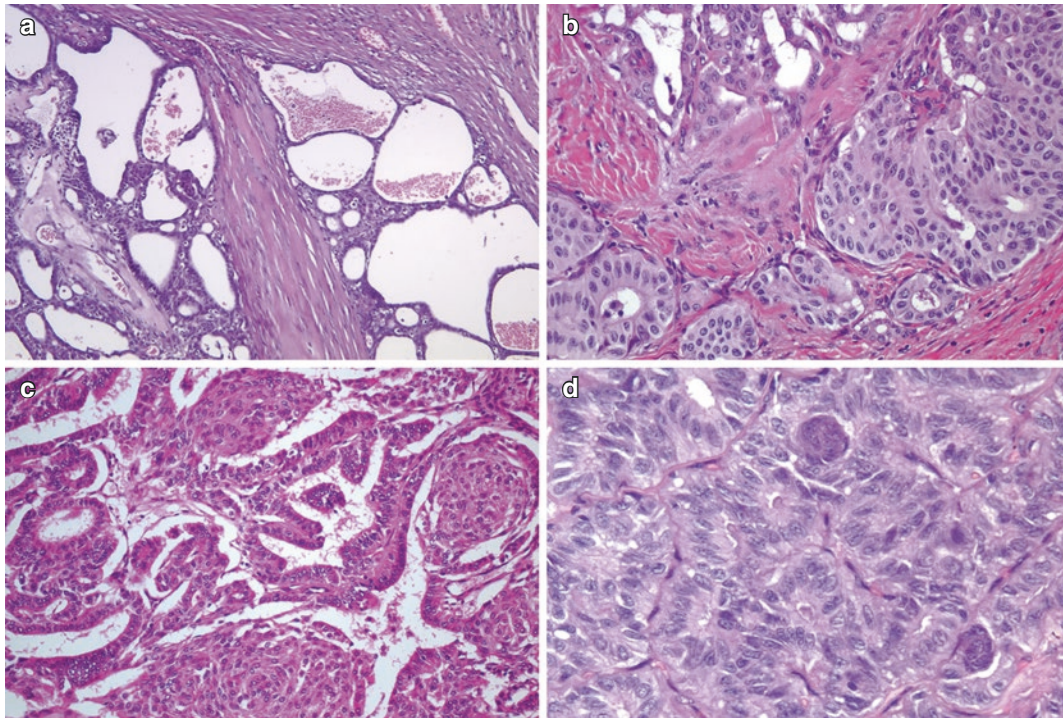

Fig. 5.4 Cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). CMV of PTC may show a highly variable combination of cribriform, papillary, solid, trabecular and morular growth patterns (**a**–**d**). In some cases the cribriform growth pattern may mimic mammary cribriform carcinoma (**b**). A trabecular pattern reminiscent of hyalinizing trabecular adenoma of the thyroid can also be seen (**d**)

nuclear features of classic PTC. In the solid areas, tumour cells become oval to plump and spindly and commonly show nodular whorls resembling squamoid nests (morules). Morules lack keratinization and show scattered or groups of cells with peculiar nuclear clearing, characterized by replacement of the chromatin by a homogeneous, light eosinophilic material throughout the entire nucleus (Fig. 5.5). These morules are also seen interspersed among the other trabecular and cribriform areas, but they can be difficult to find in some cases. Alcian blue (pH 2.5) and Mayer's mucicarmine stains are negative. Psammoma bodies are rarely found [7]. Foci of necrosis can be seen, and capsular and vascular invasion were reported in about 40% and 30% of cases, respectively [4–10].

Additional areas with an adamantinous-like pattern of growth, atypical mitotic figures and hyaline globules (thanatosomes) were detected in one case with neuroendocrine differentiation and aggressive behaviour [6]. Another rare case of CMV of PTC combining an adenoid cystic carcinoma-like growth pattern due to deposition of basement membrane-like material has also been reported [11].

Tumour cells may be focally positive or totally negative for thyroglobulin, but they are consistently positive for thyroid transcription factor-1 (TTF-1) and consistently negative for calcitonin and CK20 and always show strong nuclear and cytoplasmic reactivity for β-catenin [4–21] (Fig. 5.5). A rare case with tumour cells positive for TTF-1 and also positive for chromogranin and synaptophysin in 40% of the tumour mass but negative for thyroglobulin and calcitonin was reported by our group [6]. CMV of PTC is characteristically positive for oestrogen receptors α and β and progesterone receptor and can show focal positivity for androgen receptor; these features seem to be the result of crosstalk between WNT/β-catenin and oestrogen signalling pathways and are probably related to their female predominance (Fig. 5.6). The proliferative (Ki-67) index is generally less than 5% but can reach up to 60% in aggressive (poorly differentiated) tumours [6, 9]. A rare case

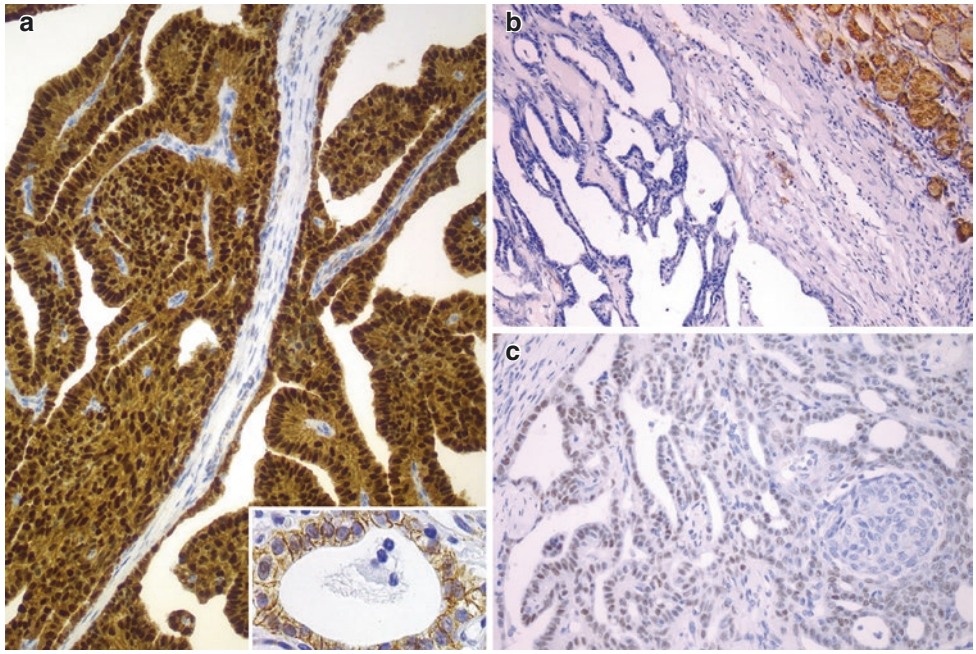

Fig. 5.5 Immunohistochemical features of the cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). Beta-catenin is the hallmark of the CMV of PTC. Immunohistochemistry demonstrates a change in beta-catenin expression from the membranous pattern found in normal follicular cells (*inset*) to the cytoplasmic and nuclear staining in tumour cells of CMV of PTC (**a**). Neoplastic cells may be totally negative for thyroglobulin (**b**), but they are consistently positive for TTF-1 (**c**)

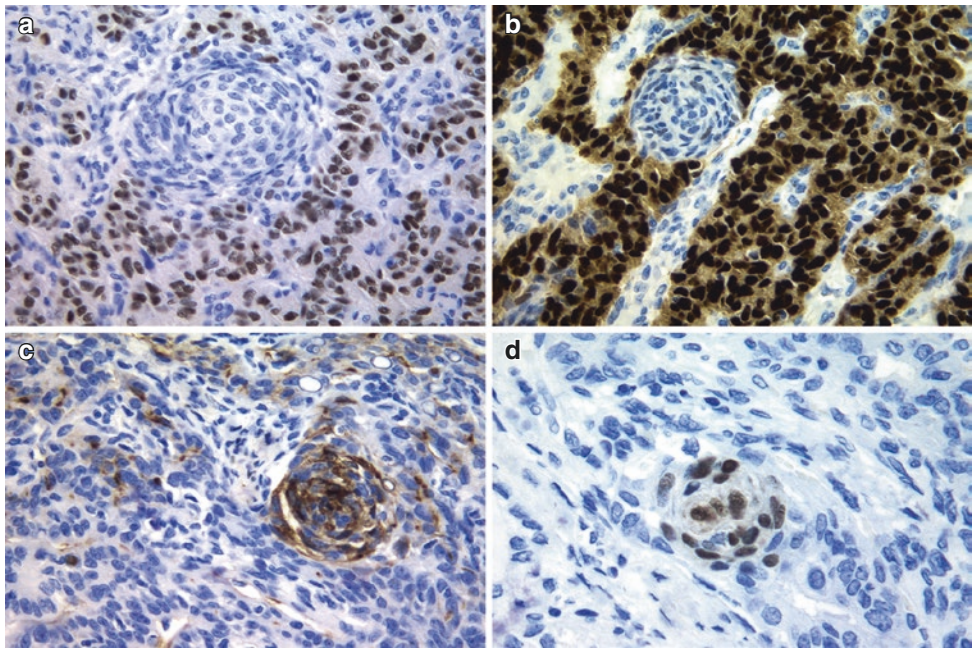

Fig. 5.6 Immunohistochemical features of the cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). Tumour cells in CMV of PTC are positive for oestrogen (**a**) and progesterone receptors (**b**), but these immunomarkers are negative in the morular component. The morular structures are selectively stained for CD10 (**c**) and CDX2 (**d**)

with positivity for β-human chorionic gonadotropin has been reported [19]. No reactivity was found for carcinoembryonic antigen (CEA), CA125, epidermal growth factor receptor, Wilms tumour protein (WT1), c-kit (CD117), p63 or calretinin.

The morular component of CMV has a distinctive immunohistochemical profile with positivity for β-catenin, CKs AE1/AE3, E-cadherin, bcl-2, cyclin D1, CA19.9 and galectin-3, as well as negativity for TTF-1, thyroglobulin, calcitonin, vimentin CEA, CK7, CK20, CK 34βE12 and CA125. The characteristic optically clear nuclei contain biotin; due to their high endogenous biotin content, false-positive reactions in the nuclei of morular cells are highly probable whenever using immunohistochemical systems containing (strep) avidin [5]. CD10 is a useful tool in identifying morules not only in the CMV of PTC but also in all biotin-rich optically clear nuclei family tumours [22], all of them sharing alterations in the WNT/β-catenin signalling pathway (Fig. 5.6). Interestingly, CDX2, an intestine-specific homeobox gene transcription factor, is also selectively expressed in the CMV morules [23] (Fig. 5.6).

In contrast to morular structures, the true foci of squamous metaplasia lack nuclear staining for β-catenin, are negative for Bcl-2 and show numerous S100 protein-positive dendritic cells, especially at the periphery [14] (Fig. 5.7).

The peculiar cribriform pattern of growth along with the positivity for oestrogen and progesterone receptors, as well as the tubulo-glandular pattern of the CMV of PTC, can mimic metastatic carcinoma from the breast and colon, but positivity for TTF-1, which is always positive in CMV of PTC, can help in the differential diagnosis. Columnar cell variant of PTC shows significant morphologic overlap with the CMV of PTC (nuclear pseudostratification, solid areas

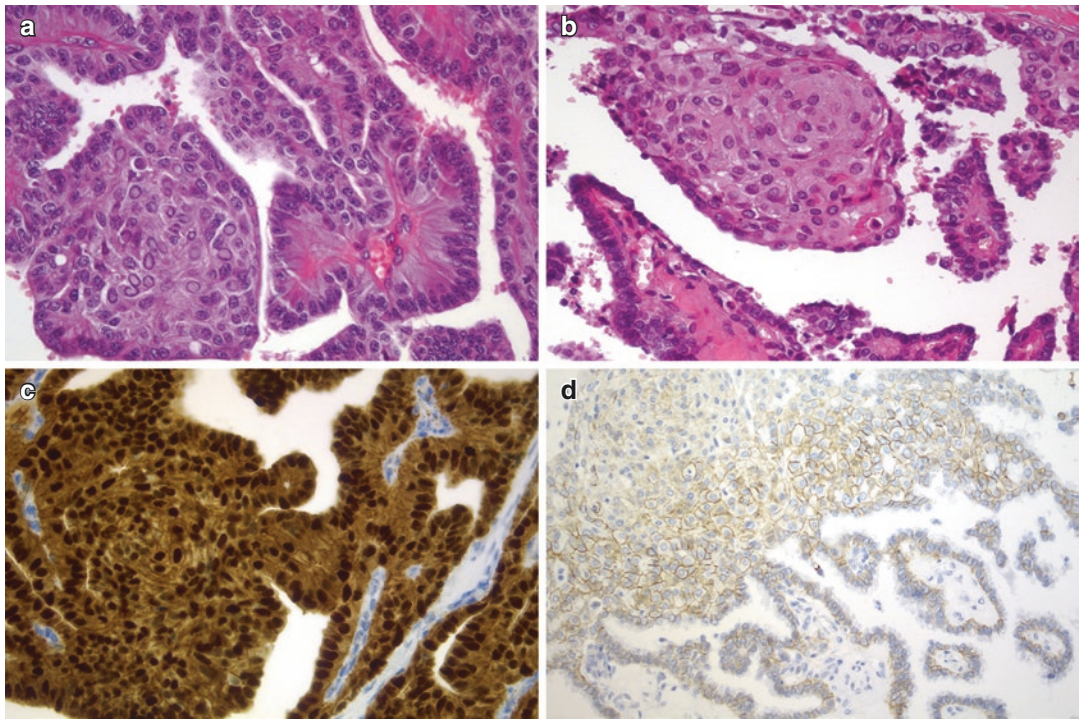

Fig. 5.7 Morules and squamous metaplasia in papillary thyroid carcinoma (PTC). In this figure, a case of CMV of PTC (**a**) is compared with a classic PTC with squamous metaplasia (**b**). While in CMV both the nucleus and cytoplasm of all tumour cells are strongly stained for beta-catenin (**c**), there is only a limited staining, with membrane pattern, in classic PTC cells (**d**)

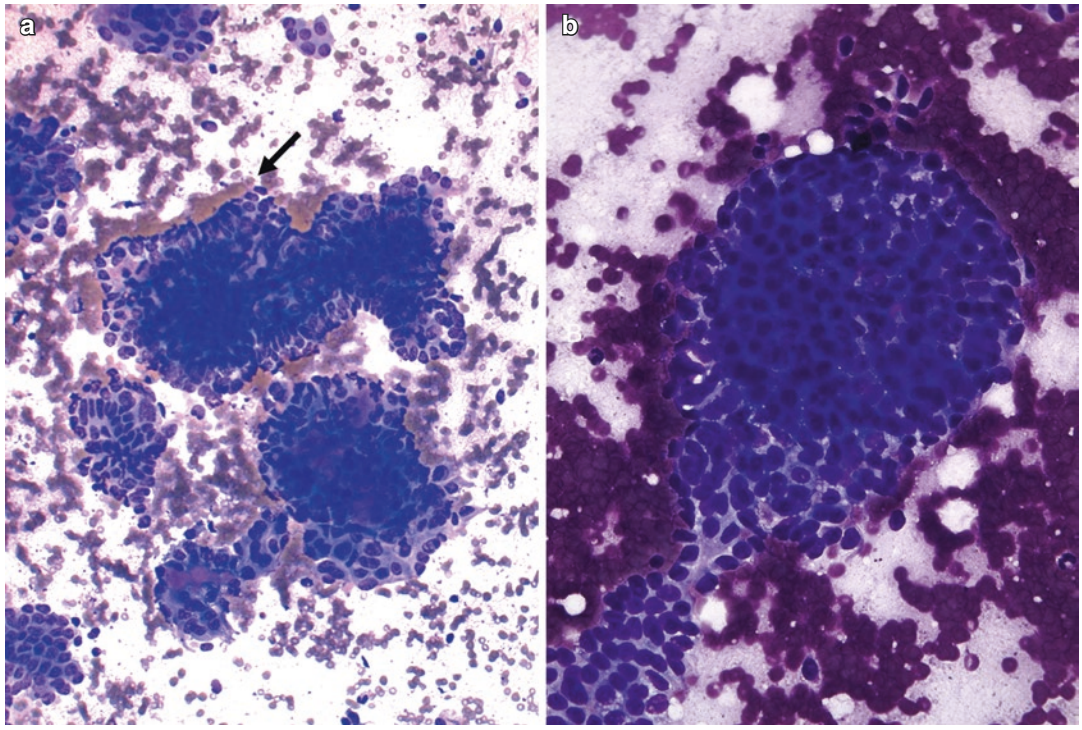

Fig. 5.8 Cytologic features of the cribriform-morular variant (CMV) of papillary thyroid carcinoma (PTC). Papillary arrangement with tall, columnar cells at the periphery (*arrow*) (**a**, Diff-Quik stain). Sheet of cells with morular arrangement (**b**, Diff-Quik stain). This case of CMV of PTC is from a 20-year-old woman with a multicentric, bilateral tumour (T3N0M0) with familial history of adenomatous polyposis. Total thyroidectomy was performed. The patient has no evidence of disease at 84 months of follow-up

and elongated, empty follicles resembling tubular glands); however, tumour cells in the columnar cell variant have nuclear hyperchromasia, may contain supranuclear and subnuclear cytoplasmic vacuoles reminiscent of those of early secretory endometrium and are positive for thyroglobulin.

Fine needle aspiration biopsy (FNAB) is an effective method for diagnosing thyroid malignancy and is even able to make a diagnosis of CMV of PTC [8, 10, 12, 17–19, 21, 24–26] (Figs. 5.8 and 5.9). The smears are typically hypercellular, disclosing cohesive papillary fragments lined by epithelial cells with nuclear stratification and nucleomegaly as well as solid flat monolayers. Tumour cells are usually tall and columnar with obscure ground-glass nuclei and abundant spindle cytoplasm with distinct cell borders (Fig. 5.8). Typical nuclear features of classic PTC are commonly seen, but prominent nucleoli are absent (Fig. 5.9). Frequent acinar/cribriform formations devoid of colloid and less common dense cellular (squamoid) morules composed of epithelial cells in a tightly haphazard or whorly arrangement can be seen (Figs. 5.8 and 5.9). The background is generally clean with no multinucleated giant cells, lymphocytes or colloid. Although the detection of cribriform fragments, cellular morules and columnar cells in cytological samples is highly indicative of CMV of PTC, there is much overlap between the architectural and nuclear features of conventional PTC and CMV of PTC. Positive nuclear β-catenin immunostaining plays a definitive role for diagnosing a CMV of PTC [17, 24, 25].

In more than 90% of FAP-associated thyroid carcinomas, the tumours have a typical CMV histology. Therefore, clinicians should be alerted to the possibility of FAP whenever a diagnosis of CMV of PTC is made, namely, when there is not a familiar setting.

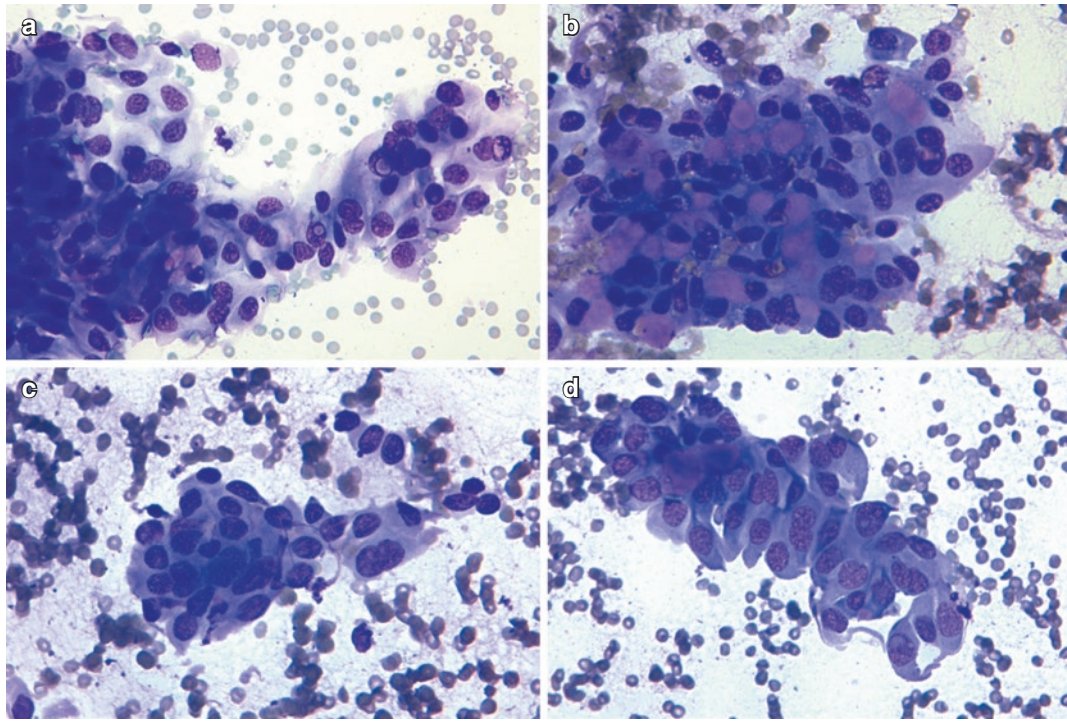

Fig. 5.9 Cytologic features of the cribriform-morular variant of papillary thyroid carcinoma. Nuclear groves and pseudoinclusions (**a**). Cluster with hyaline material (**b**). Morular structure (**c**). Tall, columnar cells (**d**). Same case as in Fig. 5.8 (Diff-Quik stain)

CMV of PTC is the typical thyroid tumour occurring in FAP, an autosomal dominant disorder caused by a germline mutation in the adenomatous polyposis coli (*APC*) gene, which is located on 5q21–22. *APC* gene encodes the tumour suppressor APC protein that acts as an antagonist of the WNT/β-catenin signalling pathway. Overall, somatic mutation of the *APC* gene appears in more than 30% of the sporadic CMV of PTC examined. Additional somatic *APC* mutation have been detected in 50% of the tumours of patients with germinal *APC* mutation. ("Second hit" of the Knudson's two hit model) [27] (Table 5.3).

Whether this neoplasm is just another variant of PTC or rather a distinct category of thyroid carcinoma is controversial. Although this rare tumour shares some characteristics with classical PTC, we, like others, tend to consider that it may be a form of thyroid carcinoma distinct from conventional papillary and follicular carcinoma, with a peculiar primitive endodermal (intestinal-like) phenotype and permanent activation of the wingless (WNT/β-catenin) signalling pathway. This assumption fits with the recently discovered position of CMV in the group of non-*BRAF*-non-*RAS* subtype of the new molecular classification of thyroid tumours [34].

Because the CMV of PTC frequently does not express thyroglobulin, the use of serum thyroglobulin as a tumour marker in the follow-up of patients may be unreliable [10] (see Chap. 2—Thyroglobulin Negative PTC—and Chap. 3, Oncocytic Carcinoma Negative for TTF-1 and Thyroglobulin).

Table 5.3 Main somatic mutations in the cribriform-morular variant of papillary thyroid carcinoma

Reference	F/M	FAP/SPO	*APC*	*CTNNB1*	*AXIN1*	*BRAF*	*RET/PTC*	*PAX8/PPARγ*	*K/N/HRAS*	*PIK3CA*	*TERT*
Soravia et al. [7]	3/0	3/0	1/3[a]	ND	ND	ND	3/3[b]	ND	ND	ND	ND
Miyaki et al. [28]	2/0	2/0	2/2[c]	ND	ND	ND	ND	ND	ND	ND	ND
Cetta et al. [29]	6/0	6/0	0/6	ND	ND	ND	4/5[d]	ND	ND	ND	ND
Xu et al. [13]	5/0	1/4	0/5	5/5[e]	ND	ND	ND	ND	ND	ND	ND
Kameyama et al. [15]	2/0	2/0	1/2	ND	ND	ND	ND	ND	ND	ND	ND
Uchino et al. [30]	1/0	1/0	1/1[d]	0/1[e]	ND	ND	ND	ND	ND	ND	ND
Jung et al. [8]	5/0	3/2	ND	1/4[f]	ND	0/5	ND	ND	ND	ND	ND
Schuetze et al. [31]	ND	1/3	ND	ND	ND	0/4	ND	ND	ND	ND	ND
Rossi et al. [16]	1/0	1/0	0/1	ND	ND	0/1	0/1	ND	0/1 *KRAS*	ND	ND
Nakazawa et al. [9]	1/0	1/0	1/1	0/1	ND	0/1	ND	ND	0/1 *N/HRAS*	ND	ND
Giannelli et al. [18]	1/0	1/0	ND	ND	ND	0/1	0/1	0/1	1/1 *KRAS*	ND	ND
TCGA [32]	ND	ND	0/2	0/2	ND	0/2	0/2		0/2	0/2	0/2
Kwon et al. [20]	3/0	0/3	ND	0/3	ND	0/3	ND	ND	0/3 *KRAS*	3/3	ND
Kumamoto et al. [33]	3/0	3/0	3/3	ND	ND	ND	ND	ND	ND	ND	ND
Oh et al. [10]	1/0	0/1	ND	ND	ND	0/1	ND	ND	0/1 *K/N/HRAS*	0/1	1/1 C228T
Our group	8/2	3/6[g]	3/10[h]	0/9	2/10[i]	0/10	1/2[j]	0/2[i]	1/7 *KRAS* 0/10 *NRAS* 0/2 *HRAS*	ND	0/4[k]
Total	42/2	28/19	12/36	6/25	2/10	0/28	8/14	0/3	2/26	3/6	1/5
Total (%)			33.3%	24%	20%	0%	57%	0%	7.6%	50%	20%

F female, *M* male, *SPO* sporadic, *FAP* familial adenomatous polyposis, *ND* not done, *TCGA* the cancer genome atlas

[a]The case with concurrent germline and somatic *APC* gene mutation also showed a *RET/PTC1* rearrangement

[b]*RET/PTC1* in all cases, with additional *RET/PTC3* rearrangement in one of them

[c]With multicentric tumours, each carcinoma had a different somatic mutation

[d]*RET/PTC1* in all cases

[e]Case with multiple tumours and not germline or somatic *APC* mutations

[f]*CTNNB1* mutation occurred in one sporadic case

[g]Unknown in one case

[h]Includes one case with concurrent germline and somatic *APC* gene mutation

[i]Includes one sporadic and another familial case

[j]Negative in a sporadic case and positive in a family case

[k]All cases were sporadic

PTEN Hamartoma Tumour Syndrome (PHTS)

PHTS is a rare autosomal dominant spectrum of disorders secondary to germline-inactivating mutations in the *PTEN* tumour suppressor gene. PHTS includes several clinical syndromes such as Cowden syndrome (CS), presenting in adulthood, Bannayan-Riley-Ruvalcaba syndrome (BRRS) in children, Lhermitte-Duclos disease in adult and autism spectrum alterations associated with macrocephaly [35–42]. Individuals with PHTS have an increased risk for carcinomas of the thyroid, breast, endometrium, colorectum, kidney and melanoma, as well as for benign lesions (Table 5.2).

About 14% of patients with PHTS have thyroid cancer, while in patients with germline PTEN mutation and thyroid pathology, such incidence raises to 75% [36, 37, 39]. The main subtypes of thyroid carcinoma in PHTS are PTC (60–80%), FTC (14–45%) and undifferentiated (anaplastic) carcinoma (6%) [36, 37]. Abnormal distribution of C cells and/or C-cell hyperplasia but not medullary carcinoma was detected in some of these patients [35, 37, 43]. In the thyroid of children and adults with PHTS, the combination of multiple and bilateral cellular follicular adenomas, adenomatous nodules and multiple tiny foci of follicular cell proliferations composed of small follicles (the so-called microadenomas) is characteristic, in a background of lymphocytic thyroiditis. The presence of foci of adipose infiltration in the parenchyma and/or within the adenoma(s) (adenolipomas) is also characteristic, especially when detected in children and young adults (Fig. 5.10). Oxyphilic (Hürthle cell) and clear cell changes, as well as tumours with features of hyalinizing trabecular adenoma (tumour), occur occasionally [35, 36].

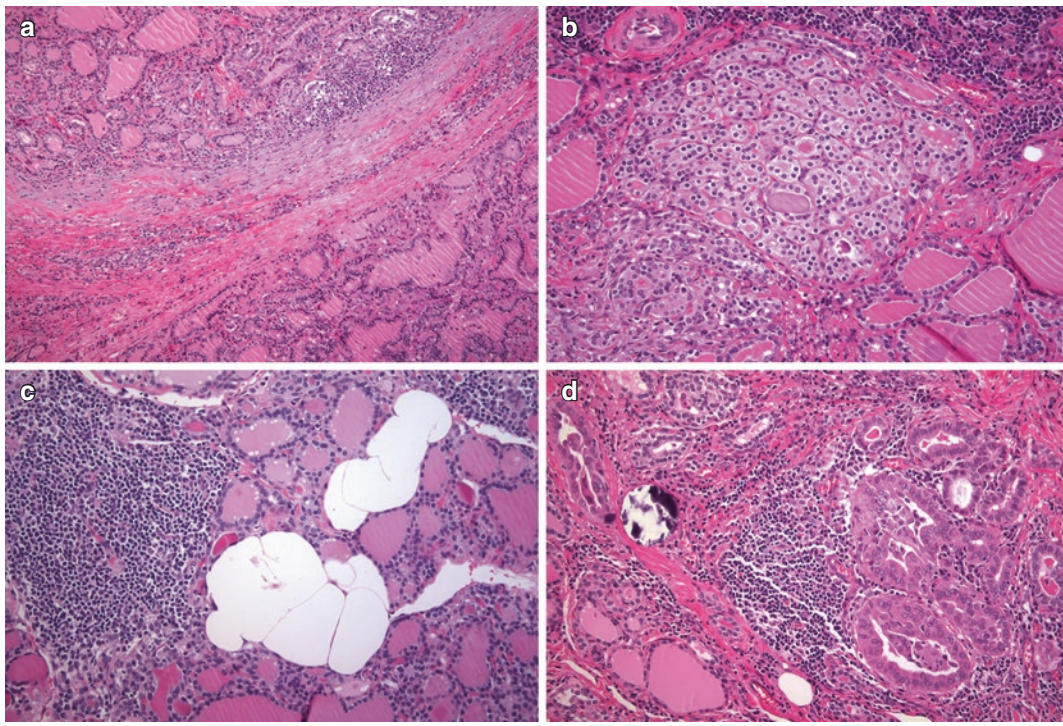

Fig. 5.10 Thyroid pathology in PTEN hamartoma tumour syndrome. Thyroid gland of patients with PTEN hamartoma tumour syndrome (Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome) typically shows multiple and bilateral follicular adenomas, hyperplastic nodules (**a**) and tiny adenomatous nodules (so-called microadenomas) (**b**). The presence of foci of adipose infiltration in the parenchyma (**c**) and increased risk for follicular carcinoma and papillary thyroid carcinoma (**d**) is also characteristic

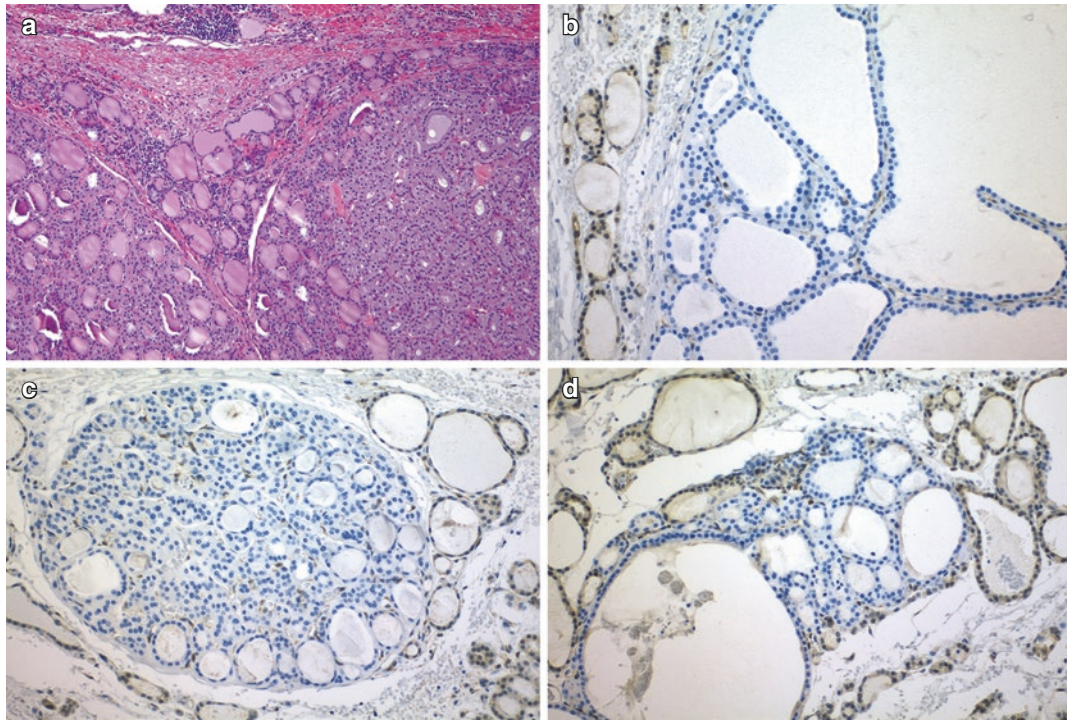

Fig. 5.11 Thyroid pathology in PTEN hamartoma tumour syndrome. In these patients, the presence of multiple and bilateral nodules (**a**) is characteristic . Most of the benign (**b**) and malignant tumours, including tiny adenomatous nodules (so-called microadenomas) (**c**, **d**), are negative for PTEN protein

All the aforementioned follicular cell tumours are positive for thyroglobulin and negative for calcitonin. Immunohistochemical staining for PTEN may help in the identification of patients with PHTS [36, 44]. Loss of PTEN immunoexpression in adenomatous thyroid nodules, whether in all the nodules or just in a subset, is both sensitive and specific for PHTS [44] (Fig. 5.11).

There is no correlation between the specific *PTEN* germline mutations and the pathologic findings in either Cowden (Figs. 5.12 and 5.13) or Bannayan-Riley-Ruvalcaba syndrome [37, 39] (Figs. 5.14, 5.15 and 5.16). Patients with PHTS can develop thyroid nodules and thyroid cancer in early childhood [39]. Because early detection improves the outcome of thyroid cancer, ultrasound surveillance for all patients upon the confirmation of a germline *PTEN* mutation seems appropriate, regardless of the age. Although the tumours are usually benign and well circumscribed, total thyroidectomy should be recommended due to their multicentricity, increased risk of recurrence and progression to carcinoma.

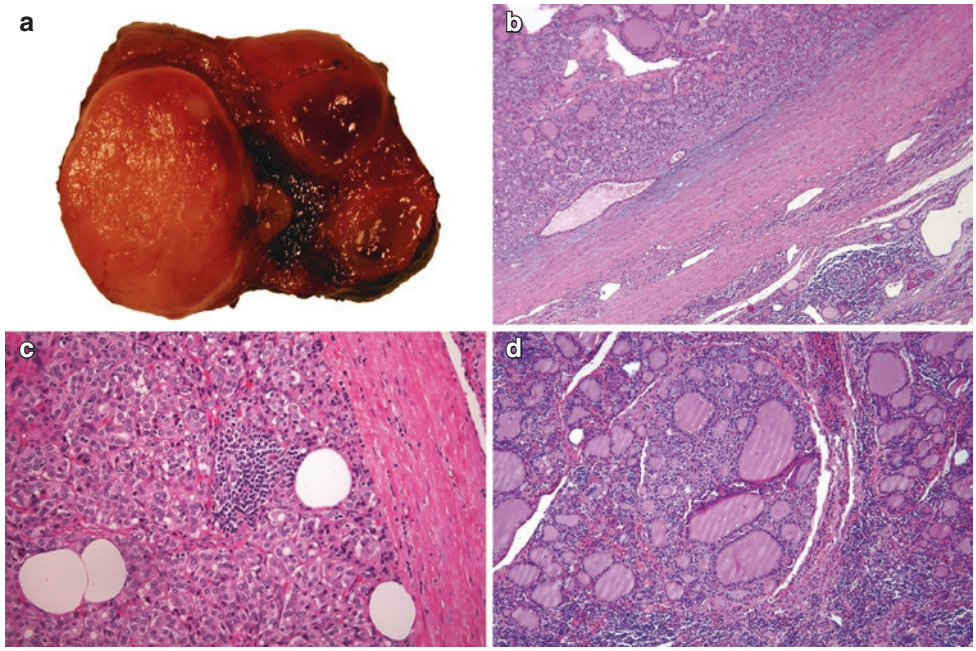

Fig. 5.12 Thyroid pathology in Cowden syndrome. Total thyroidectomy specimen typically shows multiple and bilateral, both encapsulated and well-circumscribed nodules (**a**). Microscopic examination shows a characteristic combination of multiple follicular adenomas (**b**), adenolipomas (**c**), adenomatous nodules and tiny foci of follicular cell proliferation (the so-called microadenomas) (**d**), in a background of lymphocytic thyroiditis

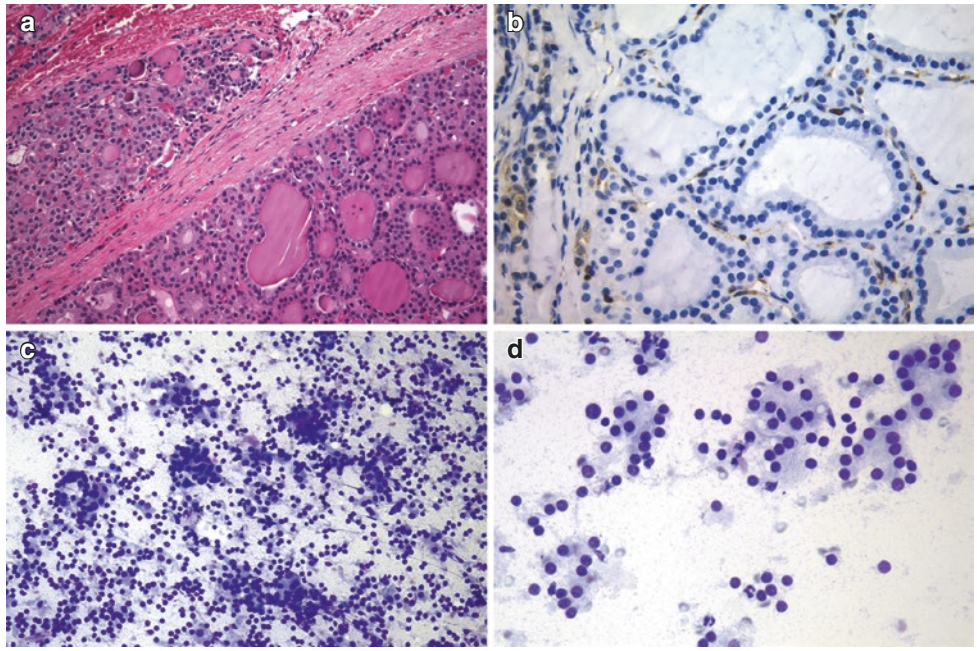

Fig. 5.13 Thyroid pathology in Cowden syndrome. All adenomas and adenomatous nodules (**a**) were negative for PTEN protein in the immunohistochemical study (**b**). The cellular smears on fine needle aspiration biopsy are composed of uniform follicular cells with follicular pattern, no pleomorphism and sparse colloid, compatible with follicular lesion or follicular neoplasia (**c**, **d**)

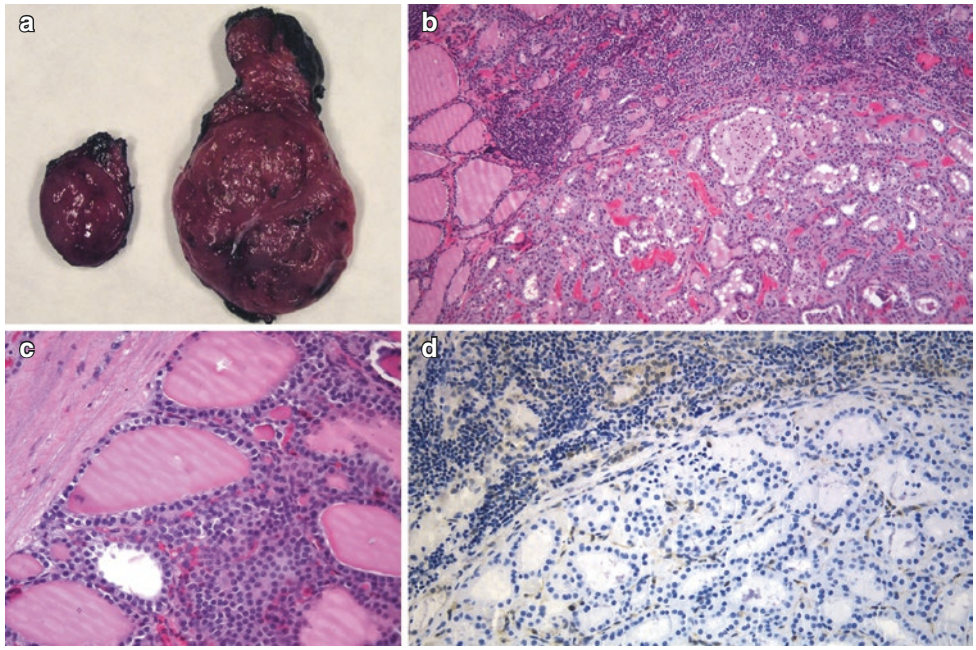

Fig. 5.14 Thyroid pathology in Bannayan-Riley-Ruvalcaba syndrome. Total thyroidectomy specimen of a 14-year-old boy with Bannayan-Riley-Ruvalcaba syndrome typically showing several nodules in both lobes (**a**). Microscopic examination showed multiple hyperplastic nodules (**b**) and adenomas (**c**). The immunohistochemical study was negative for the PTEN protein in the hyperplastic nodules and follicular adenomas (**d**)

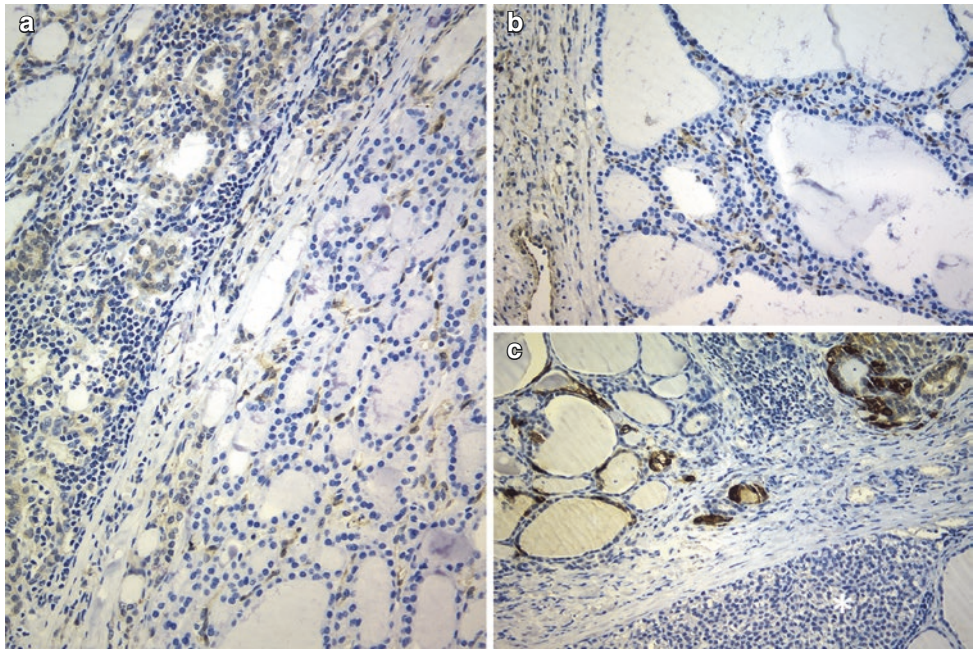

Fig. 5.15 Thyroid pathology in Bannayan-Riley-Ruvalcaba syndrome. Characteristic loss of PTEN protein immunoexpression in a hyperplastic adenomatous nodule (**a**) and in one macrofollicular adenoma (**b**) in the thyroid of a boy with Bannayan-Riley-Ruvalcaba syndrome (same case as in Fig. 5.14); normal follicular cells and endothelial cells (internal positive control) are positive for PTEN (**a**, **b**). C-cell hyperplasia was demonstrated by the immunohistochemical search for calcitonin (**c**), and one intrathyroidal parathyroid gland (*asterisk*) was also found (**c**)

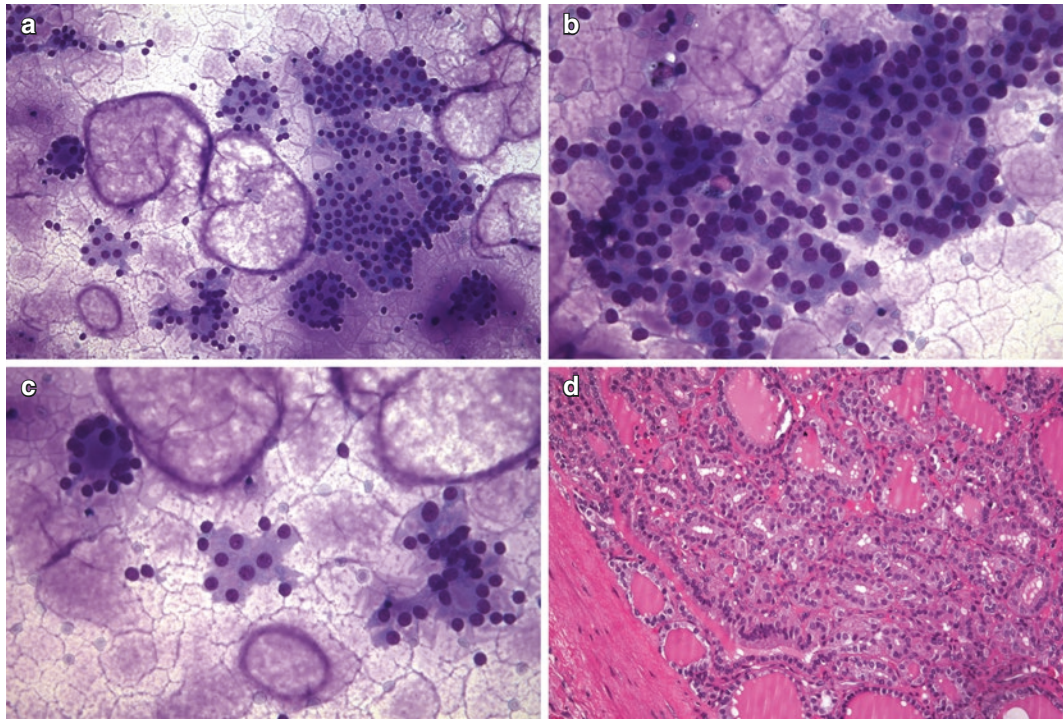

Fig. 5.16 Cytopathology features in Bannayan-Riley-Ruvalcaba syndrome. The thyroid cytologic smears of a dominant nodule in a patient with Bannayan-Riley-Ruvalcaba syndrome (same case as in Figs. 5.14 and 5.15) showed abundant colloid and sheets of follicular cells with some microfollicles (**a**–**c**). Histological examination revealed a follicular adenoma (**d**)

DICER1 Syndrome

The case we selected (courtesy of Dr. Irene Gullo, Porto, Portugal) highlights the problems raised by DICER1 syndrome thyroid tumours [45–50], as well as by most hereditary thyroid neoplasms and thyroid neoplasms with familial clustering.

It was a multinodular lesion in a 12-year-old girl who had had a botryoid-type embryonal rhabdomyosarcoma of the cervix at the age of 7. The patient was treated with surgery and adjuvant chemotherapy and 5 years later developed a bilateral multinodular enlarged thyroid gland. The diagnosis of FNAB of the two largest nodules was benign (Bethesda II) and follicular neoplasm (Bethesda IV). The patient was submitted to total thyroidectomy (61 g). On cut surface, multiple and heterogeneous nodules were identified (Fig. 5.17).

The nodules were mostly well circumscribed and, occasionally, encapsulated, displaying the morphologic characteristics of adenomas/adenomatous nodules (Figs. 5.18 and 5.19). In one of the nodules with a thicker, although incompletely formed, capsule, there were signs of angioinvasion (Fig. 5.20). The nuclei of the neoplastic cells of this nodule were larger and more irregular than follicular cell nuclei, but they did not exhibit the typical features of PTC nuclei. This type of "quasi-PTC-like" nuclei is often designated as intermediate-type nuclei (Fig. 5.20). In this case, putting the microfollicular architecture and the intermediate-type nuclei together with the invasion of a large vessel in the capsule, a diagnosis of "Well circumscribed, partly encapsulated, 1.4 cm well differentiated thyroid carcinoma (WDTC), not otherwise specified (NOS) and with angioinvasion" was made.

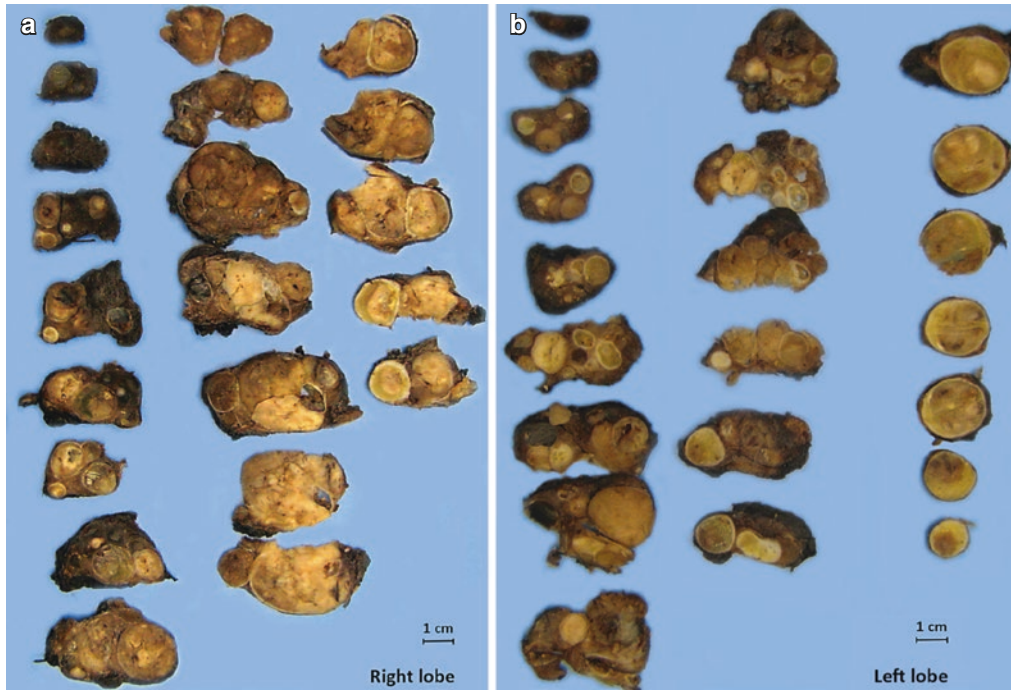

Fig. 5.17 DICER1 syndrome. Total thyroidectomy specimen showing multiple and bilateral heterogeneous nodules, many of them displaying a well-formed capsule

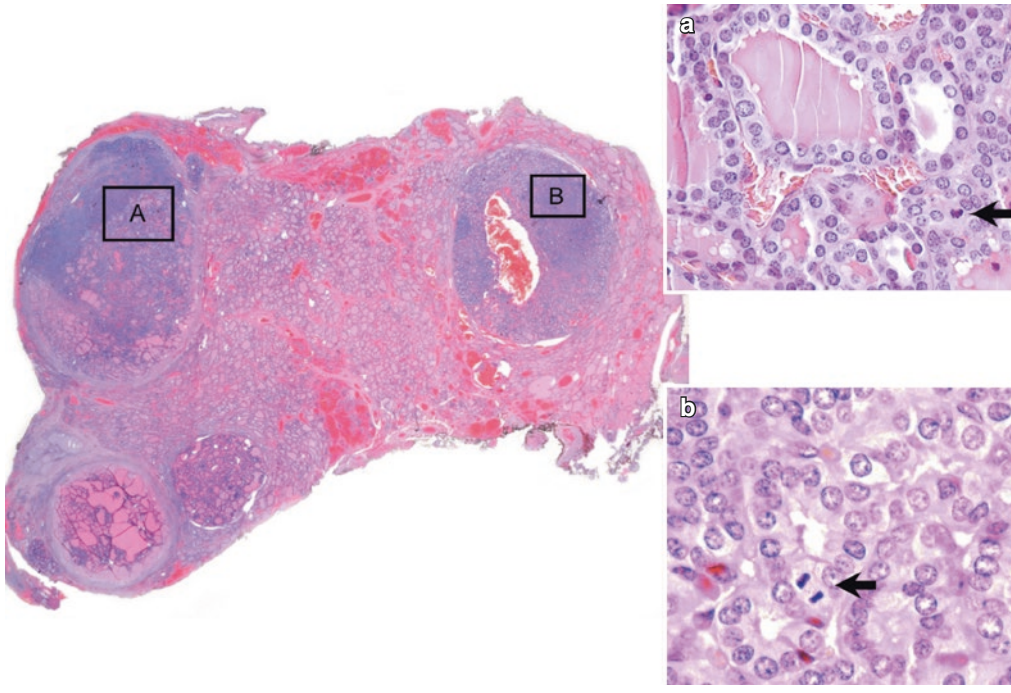

Fig. 5.18 DICER1 syndrome. Microscopic appearance of adenomas/adenomatous nodules with regular nuclei and frequent mitoses (*arrows*) (**a**, **b**)

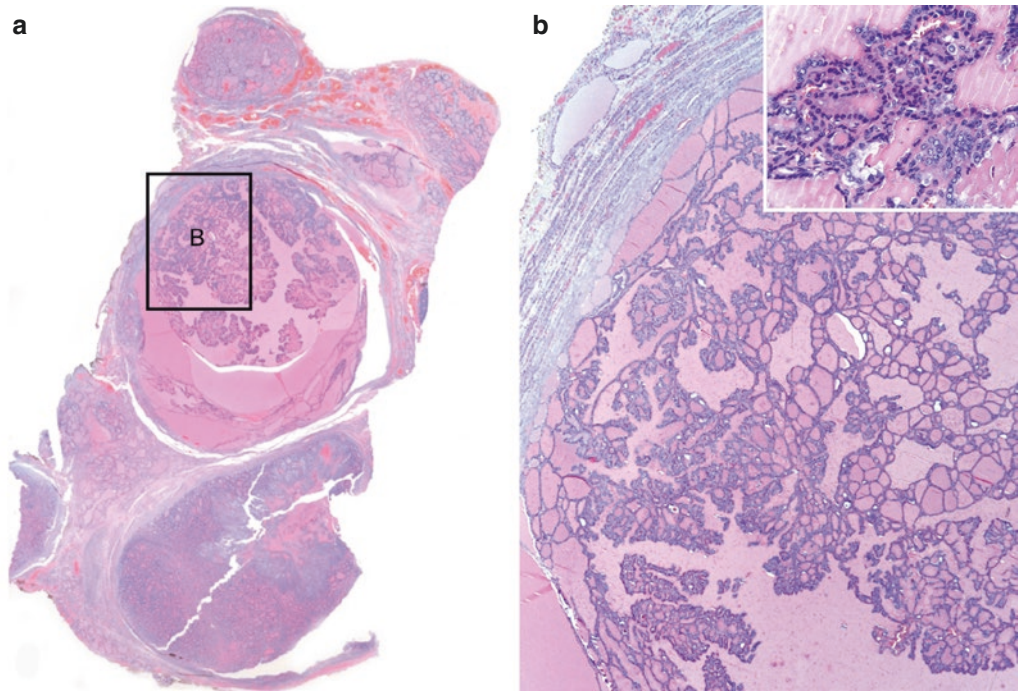

Fig. 5.19 DICER1 syndrome. One adenomatous nodule displaying papillary hyperplasia at the microscopic level (**a**, **b**). The higher magnification also showed the lack of typical features of papillary thyroid carcinoma (*inset*) (**b**)

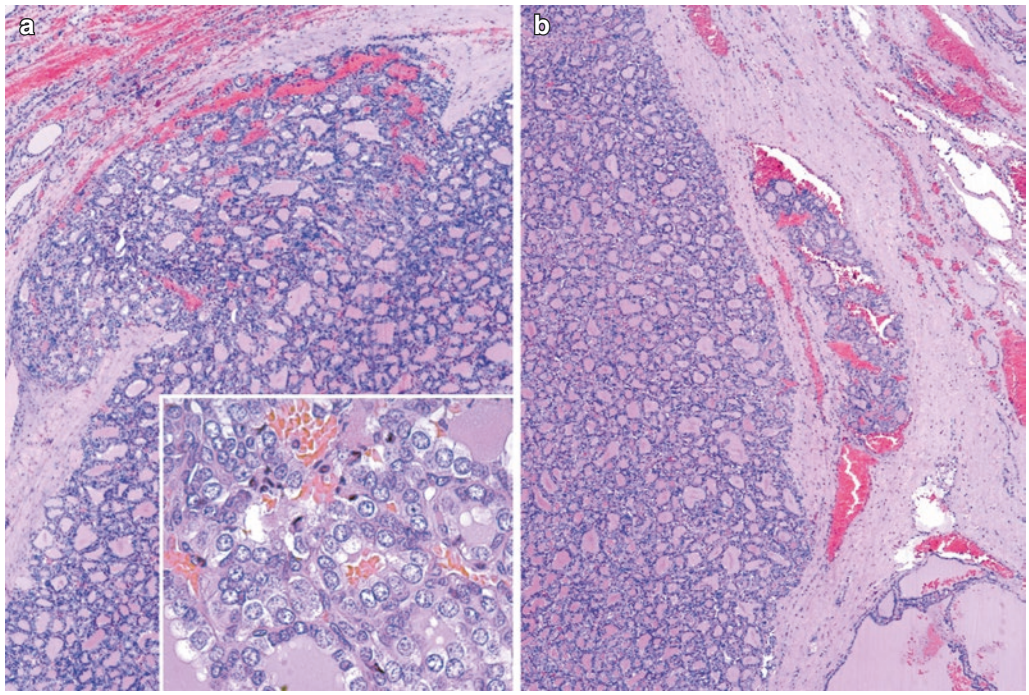

Fig. 5.20 DICER1 syndrome. Well-differentiated thyroid carcinoma, not otherwise specified (NOS) (**a**). Partly encapsulated follicular patterned tumour with questionable capsular invasion and intermediate nuclei (**a**). Nuclei are larger, clearer and more irregular than those of follicular cells (PTC like) (**a**, *inset*). Well-differentiated thyroid carcinoma, NOS, with vascular invasion (**b**)

We considered the association of botryoid rhabdomyosarcoma and multinodular goitre in a young girl highly suggestive of DICER1 syndrome. The genetic testing, performed in this case, confirmed the presence of a germline pathogenic (nonsense) DICER1 mutation (p. Arg1060Ilefs*7). Familial multinodular goitre is the most frequent manifestation of germline *DICER1* mutation in the thyroid gland. Despite being usually considered as "rare", the occurrence of well-differentiated thyroid carcinoma is emerging as a not so rare phenotype.

Ten cases of thyroid malignant neoplasms have been reported previously in the context of germline *DICER1* mutations: three cases of FTC and seven PTC. Curiously, there was a description of a case of FTC that, when revisited by other authors, was reclassified as PTC [46], underlying the difficulty of diagnosing *DICER1* thyroid tumours using the classic dual classification. Our specimen showed morphological features that did not match follicular carcinoma nor papillary carcinoma; hence, we preferred the term "well-differentiated thyroid carcinoma, NOS".

The distinctive morphologic appearance of these tumours also corresponds to distinctive molecular alterations. As reported by several authors, we did not find any of the molecular alterations that are characteristically associated to FCT or PTC (*BRAF*^{V600}, *NRAS61*, *HRAS12/61*, *TERT* promoter mutations and *PAX8/PPARγ*, *RET/PTC1* and *RET/PTC3* rearrangements). Furthermore, it is worthy to mention that in the recently proposed three-tiered molecular classification (including BRAF-like, RAS-like and non-BRAF-non-RAS tumours), *DICER1* is one of the driver genes defining the novel non-BRAF-non-RAS molecular subgroup. It looks like that thyroid carcinomas arising in the background of DICER1 syndrome may reflect a carcinogenic process different from the classical pathways towards PTC or FTC.

Unfortunately, the cytological and histological characteristics of the tumours arising in the context of DICER1 syndrome, like in the large majority of hereditary non-medullary thyroid tumours—the exception is the CMV of PTC—are unspecific, regardless of being benign (adenomas/adenomatous nodules) or malignant (FTC, PTC or WDTC, NOS). In these cases, it is the clinicopathological context (familial history, more or less typical syndromic associations, age of the patients and bilaterally/multicentricity) that raises the possibility of a hereditary condition and leads to the search of the appropriate genetic alteration(s).

References

1. Peiling Yang S, Ngeow J. Familial non-medullary thyroid cancer: unraveling the genetic maze. Endocr Relat Cancer. 2016;23(12):R577–95.
2. Colombo C, Muzza M, Proverbio MC, Ercoli G, Perrino M, Cirello V, Vicentini L, Ferrero S, Fugazzola L. Segregation and expression analyses of hyaluronan-binding protein 2 (HABP2): insights from a large series of familial non-medullary thyroid cancers and literature review. Clin Endocrinol. 2017;86(6):837–44.
3. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World health organization classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
4. Harach HR, Williams GT, Williams ED. Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm. Histopathology. 1994;25(6):549–61.
5. Cameselle-Teijeiro J, Chan JK. Cribriform-morular variant of papillary carcinoma: a distinctive variant representing the sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma? Mod Pathol. 1999;12(4):400–11.
6. Cameselle-Teijeiro J, Menasce LP, Yap BK, Colaco RJ, Castro P, Celestino R, Ruíz-Ponte C, Soares P, Sobrinho-Simões M. Cribriform-morular variant of papillary thyroid carcinoma: molecular characterization of a case with neuroendocrine differentiation and aggressive behavior. Am J Clin Pathol. 2009;131(1):134–42.
7. Soravia C, Sugg SL, Berk T, Mitri A, Cheng H, Gallinger S, Cohen Z, Asa SL, Bapat BV. Familial adenomatous polyposis-associated thyroid cancer: a clinical, pathological, and molecular genetics study. Am J Pathol. 1999;154(1):127–35.
8. Jung CK, Choi YJ, Lee KY, Bae JS, Kim HJ, Yoon SK, Son YI, Chung JH, Oh YL. The cytological, clinical, and pathological features of the cribriform-morular variant of papillary thyroid carcinoma and mutation analysis of CTNNB1 and BRAF genes. Thyroid. 2009;19(8):905–13.
9. Nakazawa T, Celestino R, Machado JC, Cameselle-Teijeiro JM, Vinagre J, Eloy C, Benserai F, Lameche S, Soares P, Sobrinho-Simões M. Cribriform-morular variant of papillary thyroid carcinoma displaying poorly differentiated features. Int J Surg Pathol. 2013;21(4):379–89.
10. Oh EJ, Lee S, Bae JS, Kim Y, Jeon S, Jung CK. TERT promoter mutation in an aggressive cribriform morular variant of papillary thyroid carcinoma. Endocr Pathol. 2017;28(1):49–53.

11. Baloch ZW, Segal JP, Livolsi VA. Unique growth pattern in papillary carcinoma of the thyroid gland mimicking adenoid cystic carcinoma. Endocr Pathol. 2011;22(4):200–5.
12. Cameselle-Teijeiro J, Ruiz-Ponte C, Loidi L, Suarez-Peñaranda J, Baltar J, Sobrinho-Simões M. Somatic but not germline mutation of the APC gene in a case of cribriform-morular variant of papillary thyroid carcinoma. Am J Clin Pathol. 2001;115(4):486–93.
13. Xu B, Yoshimoto K, Miyauchi A, Kuma S, Mizusawa N, Hirokawa M, Sano T. Cribriform-morular variant of papillary thyroid carcinoma: a pathological and molecular genetic study with evidence of frequent somatic mutations in exon 3 of the beta-catenin gene. J Pathol. 2003;199(1):58–67.
14. Hirokawa M, Kuma S, Miyauchi A, Qian ZR, Nakasono M, Sano T, Kakudo K. Morules in cribriform-morular variant of papillary thyroid carcinoma: Immunohistochemical characteristics and distinction from squamous metaplasia. APMIS. 2004;112(4–5):275–82.
15. Kameyama K, Mukai M, Takami H, Ito K. Cribriform-morular variant of papillary thyroid carcinoma: ultrastructural study and somatic/germline mutation analysis of the APC gene. Ultrastruct Pathol. 2004;28(2):97–102.
16. Rossi ED, Revelli L, Martini M, Taddei A, Pintus C, Panunzi C, Fadda G. Cribriform-morular variant of papillary thyroid carcinoma in an 8-year-old girl: a case report with immunohistochemical and molecular testing. Int J Surg Pathol. 2012;20(6):629–32.
17. Boonyaarunnate T, Olson MT, Bishop JA, Yang GC, Ali SZ. Cribriform morular variant of papillary thyroid carcinoma: clinical and cytomorphological features on fine-needle aspiration. Acta Cytol. 2013;57(2):127–33.
18. Giannelli SM, McPhaul L, Nakamoto J, Gianoukakis AG. Familial adenomatous polyposis-associated, cribriform morular variant of papillary thyroid carcinoma harboring a K-RAS mutation: case presentation and review of molecular mechanisms. Thyroid. 2014;24(7):1184–9.
19. Alikhan M, Koshy A, Hyjek E, Stenson K, Cohen RN, Yeo KT. Discrepant serum and urineβ-hCG results due to production of β-hCG by a cribriform-morular variant of thyroid papillary carcinoma. Clin Chim Acta. 2015;438:181–5.
20. Kwon MJ, Rho YS, Jeong JC, Shin HS, Lee JS, Cho SJ, Nam ES. Cribriform-morular variant of papillary thyroid carcinoma: a study of 3 cases featuring the PIK3CA mutation. Hum Pathol. 2015;46(8):1180–8.
21. Uchino S, Ishikawa H, Miyauchi A, Hirokawa M, Noguchi S, Ushiama M, Yoshida T, Michikura M, Sugano K, Sakai T. Age- and gender-specific risk of thyroid cancer in patients with familial adenomatous polyposis. J Clin Endocrinol Metab. 2016;101(12):4611–7.
22. Cameselle-Teijeiro J, Alberte-Lista L, Chiarelli S, Buriticá C, Gonçalves L, González-Cámpora R, Nogales FF. CD10 is a characteristic marker of tumours forming morules with biotin-rich, optically clear nuclei that occur in different organs. Histopathology. 2008;52(3):389–92.
23. Cameselle-Teijeiro J, Alberte-Lista L, Peteiro-González D, Abdulkader-Nallib I, Reyes-Santías R, Soares P, Sobrinho-Simões M. CDX2 expression in some variants of papillary thyroid carcinoma. Am J Clin Pathol. 2012;138(6):907–9.
24. Hirokawa M, Maekawa M, Kuma S, Miyauchi A. Cribriform-morular variant of papillary thyroid carcinoma--cytological and immunocytochemical findings of 18 cases. Diagn Cytopathol. 2010;38(12):890–6.
25. Koo JS, Jung W, Hong SW. Cytologic characteristics and β-catenin immunocytochemistry on smear slide of cribriform-morular variant of papillary thyroid carcinoma. Acta Cytol. 2011;55(1):13–8.
26. Priyani AA, Opatha ST, Gunathilake NW, Lokuhetty MD. Cribriform morular variant of papillary thyroid carcinoma: cytomorphology, differential diagnosis and diagnostic implications in patients with adenomatous polyposis coli. J Cytol. 2016;33(4):235–8.
27. Cameselle-Teijeiro J, Peteiro-González D, Carreira M, Abdulkader I, Reyes-Santías R, Celestino R, Romero Rojas A, Ruíz-Ponte C, Soares P, Casanueva F, Sobrinho-Simões M. Molecular alterations in the cribriform-morular variant of papillary thyroid carcinoma. Virchows Arch. 2016;469(Suppl 1):S72.
28. Miyaki M, Iijima T, Ishii R, Hishima T, Mori T, Yoshinaga K, Takami H, Kuroki T, Iwama T. Molecular evidence for multicentric development of thyroid carcinomas in patients with familial adenomatous polyposis. Am J Pathol. 2000;157(6):1825–7.
29. Cetta F, Curia MC, Montalto G, Gori M, Cama A, Battista P, Barbarisi A. Thyroid carcinoma usually occurs in patients with familial adenomatous polyposis in the absence of biallelic inactivation of the adenomatous polyposis coli gene. J Clin Endocrinol Metab. 2001;86(1):427–32.
30. Uchino S, Noguchi S, Yamashita H, Yamashita H, Watanabe S, Ogawa T, Tsuno A, Murakami A, Miyauchi A. Mutational analysis of the APC gene in cribriform-morular variant of papillary thyroid carcinoma. World J Surg. 2006;30(5):775–9.
31. Schuetze D, Hoschar AP, Seethala RR, Assaad A, Zhang X, Hunt JL. The T1799A BRAF mutation is absent in cribriform-morular variant of papillary carcinoma. Arch Pathol Lab Med. 2009;133(5):803–5.
32. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159:676–90.
33. Kumamoto K, Ishida H, Ohsawa T, Ishibashi K, Ushiama M, Yoshida T, Iwama T. Germline and somatic mutations of the APC gene in papillary thyroid carcinoma associated with familial adenomatous polyposis: analysis of three cases and a review of the literature. Oncol Lett. 2015;10(4):2239–43.
34. Yoo SK, Lee S, Kim SJ, Jee HG, Kim BA, Cho H, Song YS, Cho SW, Won JK, Shin JY, Park do J, Kim JI, Lee KE, Park YJ, Seo JS. Comprehensive analysis of the transcriptional and mutational landscape of

follicular and papillary thyroid cancers. PLoS Genet. 2016;12(8):e1006239.
35. Harach HR, Soubeyran I, Brown A, Bonneau D, Longy M. Thyroid pathologic findings in patients with Cowden disease. Ann Diagn Pathol. 1999;3(6):331–40.
36. Cameselle-Teijeiro J, Fachal C, Cabezas-Agrícola JM, Alfonsín-Barreiro N, Abdulkader I, Vega-Gliemmo A, Hermo JA. Thyroid pathology findings in Cowden syndrome: a clue for the diagnosis of the PTEN hamartoma tumor syndrome. Am J Clin Pathol. 2015;144(2):322–8.
37. Laury AR, Bongiovanni M, Tille JC, Kozakewich H, Nosé V. Thyroid pathology in PTEN-hamartoma tumor syndrome: characteristic findings of a distinct entity. Thyroid. 2011;21(2):135–44.
38. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96(12):E2063–71.
39. Smith JR, Marqusee E, Webb S, Nose V, Fishman SJ, Shamberger RC, Frates MC, Huang SA. Thyroid nodules and cancer in children with PTEN hamartoma tumor syndrome. J Clin Endocrinol Metab. 2011;96(1):34–7.
40. Orloff MS, He X, Peterson C, Chen F, Chen JL, Mester JL, Eng C. Germline PIK3CA and AKT1 mutations in Cowden and Cowden-like syndromes. Am J Hum Genet. 2013;92(1):76–80.
41. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C. Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations. J Clin Oncol. 2014;32(17):1818–24.
42. Nizialek EA, Mester JL, Dhiman VK, Smiraglia DJ, Eng C. KLLN epigenotype-phenotype associations in Cowden syndrome. Eur J Hum Genet. 2015;23(11):1538–43.
43. Zambrano E, Holm I, Glickman J, Huang S, Perez-Atayde A, Kozakewich HP, Shamberger RC, Nosé V. Abnormal distribution and hyperplasia of thyroid C-cells in PTEN-associated tumor syndromes. Endocr Pathol. 2004;15(1):55–64.
44. Barletta JA, Bellizzi AM, Hornick JL. Immunohistochemical staining of thyroidectomy specimens for PTEN can aid in the identification of patients with Cowden syndrome. Am J Surg Pathol. 2011;35(10):1505–11.
45. Shin SH, Yoon JH, Son MH, Kim SJ, Park SY, Kim HY, Lee HS, Park HJ, Park BK. Follicular thyroid carcinoma arising after hematopoietic stem cell transplantation in a child with pleuropulmonary blastoma. Thyroid. 2012;22(5):547–51.
46. de Kock L, Sabbaghian N, Soglio DB, Guillerman RP, Park BK, Chami R, Deal CL, Priest JR, Foulkes WD. Exploring the association between DICER1 mutations and differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2014;99(6):E1072–7.
47. Foulkes WD, Priest JR, Duchaine TF. DICER1: mutations, microRNAs and mechanisms. Nat Rev. Cancer. 2014;14(10):662–72.
48. Rutter MM, Jha P, Schultz KA, Sheil A, Harris AK, Bauer AJ, Field AL, Geller J, Hill DA. DICER1 mutations and differentiated thyroid carcinoma: evidence of a direct association. J Clin Endocrinol Metab. 2016;101(1):1–5.
49. Lumbreras C, Chueca MJ, Arribas L, Randamie R, Alonso Á, Fernández P, Berrade S, Anda E, Regojo RM, Mendiola M, Moreno JM. Germline and somatic DICER1 mutations in familial papillary thyroid carcinoma and multinodular goiter. Eur Thyr J. 2016;5:70.
50. Durieux E, Descotes F, Mauduit C, Decaussin M, Guyetant S, Devouassoux-Shisheboran M. The co-occurrence of an ovarian Sertoli-Leydig cell tumor with a thyroid carcinoma is highly suggestive of a DICER1 syndrome. Virchows Arch. 2016;468(5):631–6.

Other Rare Tumours and Tumour-Like Lesions

6

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Introduction

In this chapter, we describe peculiar thyroid structures of supposed branchial origin such as the so-called solid cell nests (SCNs) and other related lesions, as well as a number of rare tumours and tumour-like lesions with branchial pouch or thymic derivation. The knowledge of SCNs and this heterogeneous group of tumours is important not only for diagnostic purposes but also for understanding the strange phenotype of such lesions within the thyroid gland. Rare

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benign and malignant mesenchymal thyroid neoplasms and tumour-like conditions are also addressed.

Solid Cell Nests (SCNs) and Related Lesions

SCNs are considered remnants of the ultimobranchial body (UB) that appear in the interfollicular space as clusters of squamoid cells designated as main cells, with a minor proportion of C cells [1–5]. Most SCNs measure 0.1 cm in diameter but occasionally can achieve 2 mm or more. They are present in 3% of routinely examined thyroid glands and in more than 60% of thyroid glands when blocked serially at 2–3 mm. Sometimes, SCNs are totally cystic while in other cases SCNs combine solid, cystic and/or papillary architecture (Fig. 6.1). The main cells of SCNs are polygonal to ovoid, with round to oval nuclei with nuclear grooving and frequent overlapping that mimic the nuclei of PTC. Intranuclear pseudoinclusions, however, are very rare in SCNs, whose cells, compared to PTC, are negative for thyroglobulin and TTF-1 (Fig. 6.2). SCNs may show mixed follicles composed of follicular cells along with main SCN cells, columnar cells, ciliated cells and/or squamous cells (Fig. 6.3). Alcian blue positive mucinous material may be seen in microcysts or in some cells of SCNs. (Fig. 6.4). Oncocytic (Hürthle cell) transformation was observed in main cells of rare SCNs [6] (Fig. 6.5). Scattered T-lymphocytes positive for CD5 are commonly associated with SCNs, probably due to a common embryologic origin of SCNs and thymus (Fig. 6.5).

Ultrastructurally, the main cells of SCNs have many desmosomes and hemidesmosomes at the cell surface. Filaments are the only cytoplasmic evident organelles while other are poorly developed, as it happens in stem cells. Main cells are

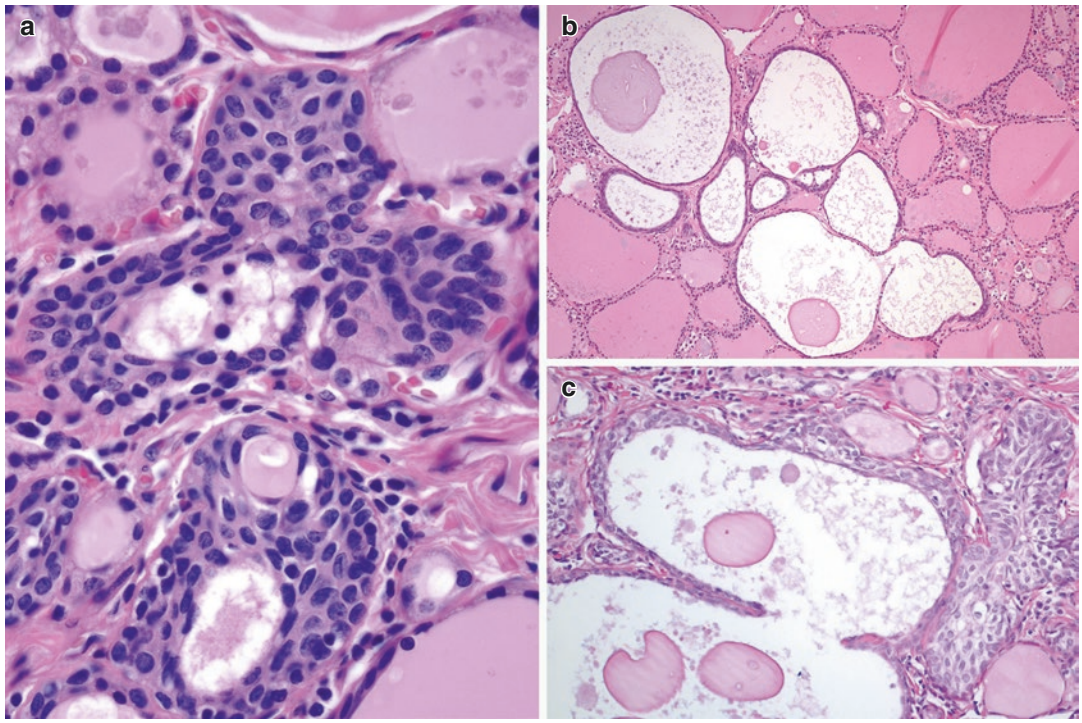

Fig. 6.1 Solid cell nests (SCNs) of the human thyroid. SCNs appear as cellular clusters with a lobulated configuration within the interstitium of the thyroid gland (**a**–**c**). They are usually solid squamoid nests (**a**) mainly composed of main cells with a minor proportion of C cells. Sometimes, however, SCNs are totally cystic (**b**) or combine solid, cystic and/or papillary architecture (**c**)

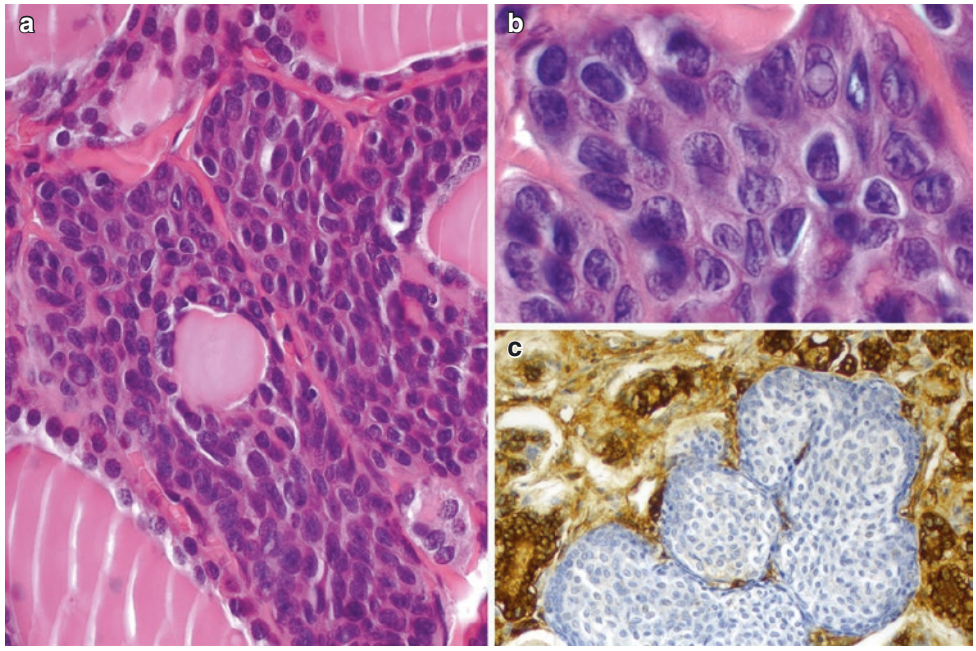

Fig. 6.2 Nuclear features in solid cell nests (SCNs). The nuclei of main cells of SCNs are round to oval with grooving and frequent overlapping (**a**), but intranuclear pseudoinclusions are very rare (**b**). Although these vestigial structures can be misinterpreted as papillary thyroid microcarcinoma, they are negative for thyroglobulin (**c**) and thyroid transcription factor-1 (TTF-1)

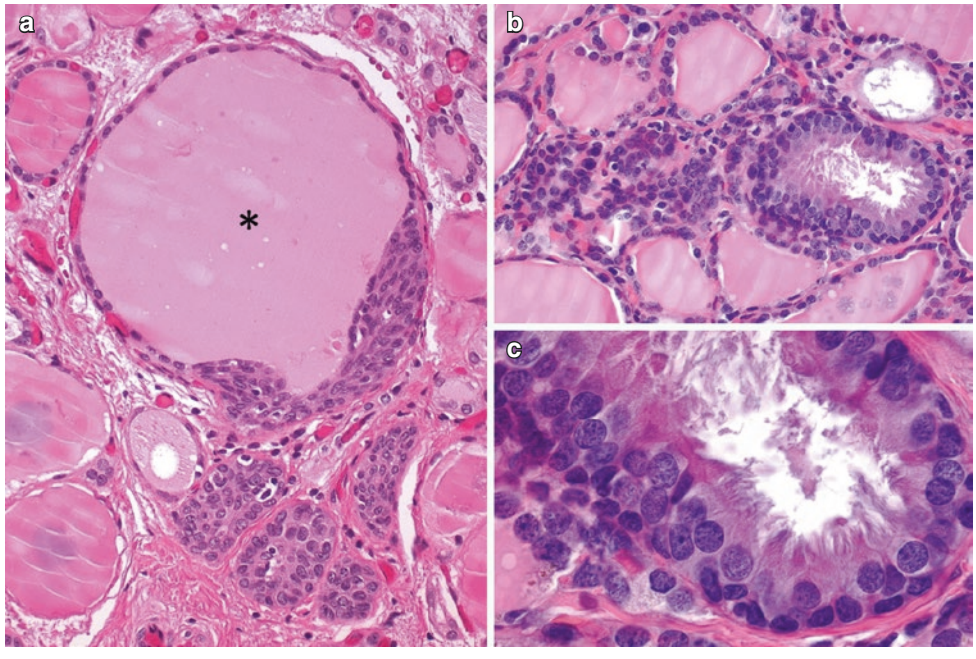

Fig. 6.3 Mixed follicles and ciliated cells in solid cell nests (SCNs). Occasional SCNs are connected to thyroid follicular cells to form mixed follicles (*asterisk*) (**a**). Approximately 20 percent of the cystic structures in SCNs are lined by ciliated columnar cells (**b**, **c**)

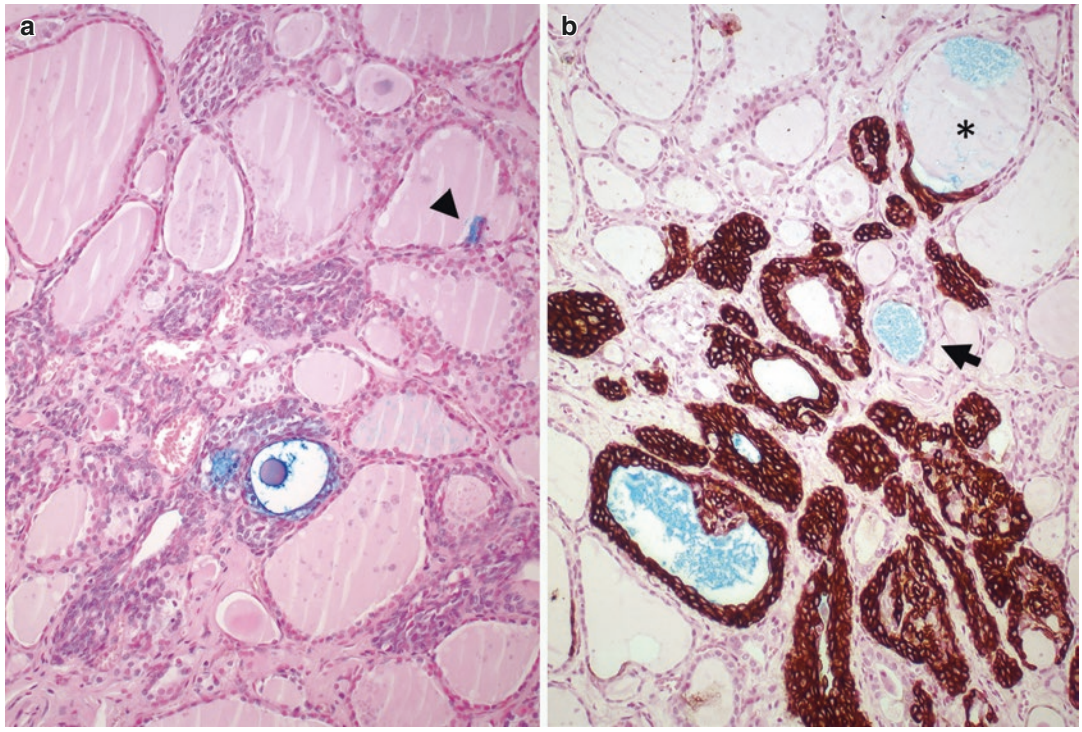

Fig. 6.4 Thyroid follicles with mucins in solid cell nests (SCNs). The SCNs may contain isolated cells (*arrowhead*) and small cysts with intraluminal accumulation of acidic mucins demonstrable with the Alcian blue stain (**a**, **b**). In the human thyroid gland, follicles with acid mucins (*arrow*) are almost always confined to the sections that also contain SCNs (**b**). A mixed follicle containing acidic mucins and colloid (*asterisks*) can be spotted easily in the upper part of the photograph because of the positivity of main cells for keratins (clone 34βE12) (**b**). It has been suggested that the histogenesis of some mucin-producing thyroid tumours could be linked to "ultimobranchial" thyroid follicles with acid mucins

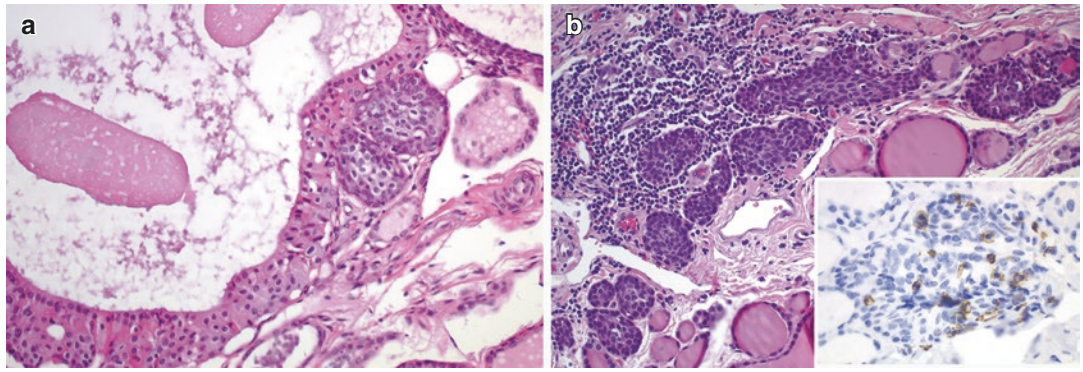

Fig. 6.5 Oncocytic change and lymphocytic infiltration in solid cell nests (SCNs). It has been reported the existence of rare cases of main cell of SCNs with oncocytic (Hürthle cell) changes (**a**). This finding indicates that SCNs may acquire mitochondrial alterations similar to those seen in follicular and C cells, as well as in their respective tumours (**a**). A variable proportion of scattered T-lymphocytes positive for CD5 (*inset*) are usually associated with SCNs, probably due to a common embryologic origin of SCNs and thymus (**b**)

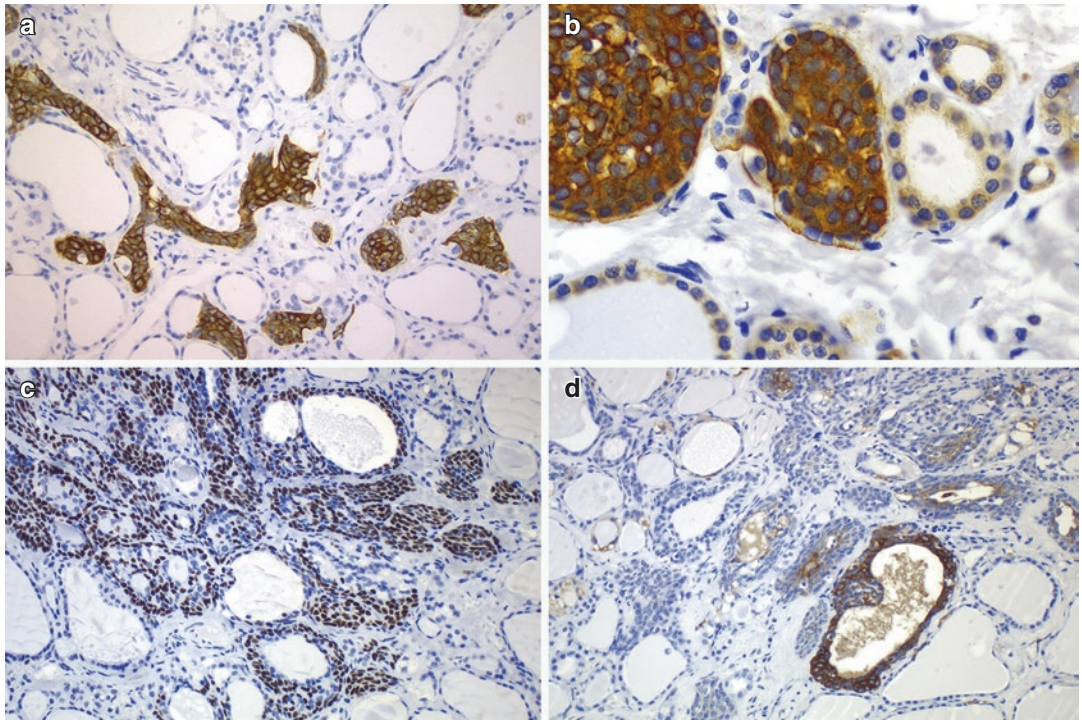

Fig. 6.6 Immunohistochemical features of solid cell nests (SCNs). Main cells of human SCNs have strong cytoplasmic positivity for cytokeratin 19 (**a**) and BCL-2 protein (**b**). They are also immunoreactive for p63 (**c**) and carcinoembryonic antigen (CEA) (**d**)

positive for high and low molecular weight keratins, p63, p40, galectin-3, Bcl-2 and carcinoembryonic antigen (CEA) (Fig. 6.6), and negative for TTF-1, PAX8, thyroglobulin, calcitonin, chromogranin and synaptophysin. Calcitonin and neuroendocrine pan-markers are only positive in the associated C cells (Fig. 6.7).

SCNs are thought to be remnants of the fifth branchial arch (UB) [1, 2]. The UB origin of SCNs is supported by similarities with the UB of mammals, its relation with C cells (Fig. 6.8), production of mucins [7], association with branchial-like cysts (Figs. 6.9 and 6.10), presence in some piriform sinus fistula as well as the occurrence of SCNs along with thymic, parathyroid, adipose, fibrous, cartilaginous and salivary gland-type tissues (Fig. 6.11).

In contrast to foci of squamous metaplasia which are generally associated with inflammatory or reparative phenomena, SCNs usually appear in normal thyroid tissue accompanied by C cells (Fig. 6.12). Squamoid cell nests of Hashimoto's thyroiditis [8] share some nuclear features with PTC, but they are neither neoplastic structures nor true SCNs. Such squamoid cell nests are usually smaller than SCNs and display floret-like features, surrounded by a collection of lymphocytes, having weak TTF-1 positivity and negativity for HBME-1 and galectin-3 and lacking associated C cells [8] (Fig. 6.13). The squamoid cell nests of Hashimoto's thyroiditis seem to represent ductal metaplasia, a type of phylogenic regression to an exocrine structure, secondary to chronic injury [9]. Rare cases of Hashimoto's thyroiditis massive squamous metaplasia of follicular cells [10] and multiple branchial cleft-like cysts (cystic variant of Hashimoto's thyroiditis) [11] may occur (Fig. 6.14). True isolated intrathyroid branchial cysts have also been reported (Fig. 6.10). In comparison to branchial derived cysts, true keratinizing cysts similar to

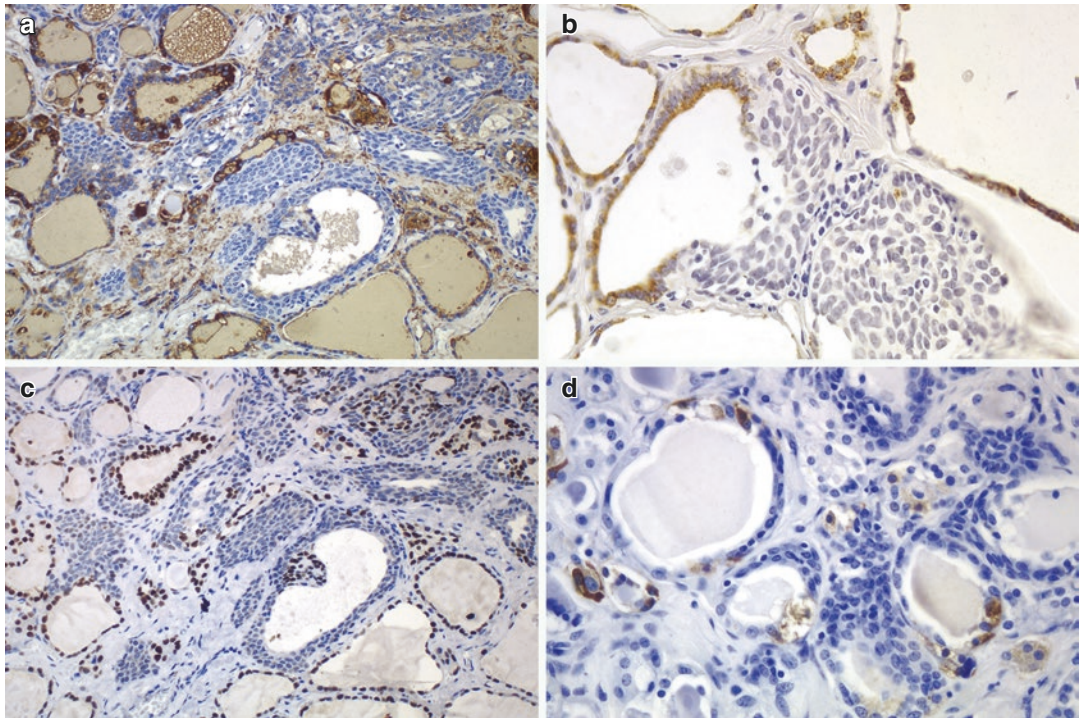

Fig. 6.7 Immunohistochemical features of solid cell nests (SCNs). SCNs show negativity for thyroglobulin by immunohistochemistry (**a**) and in situ hybridization (mRNA) (**b**). TTF-1 is also negative in main cells of SCNs (**c**). Positivity for calcitonin is limited to the C cells usually associated to the SCNs (**d**)

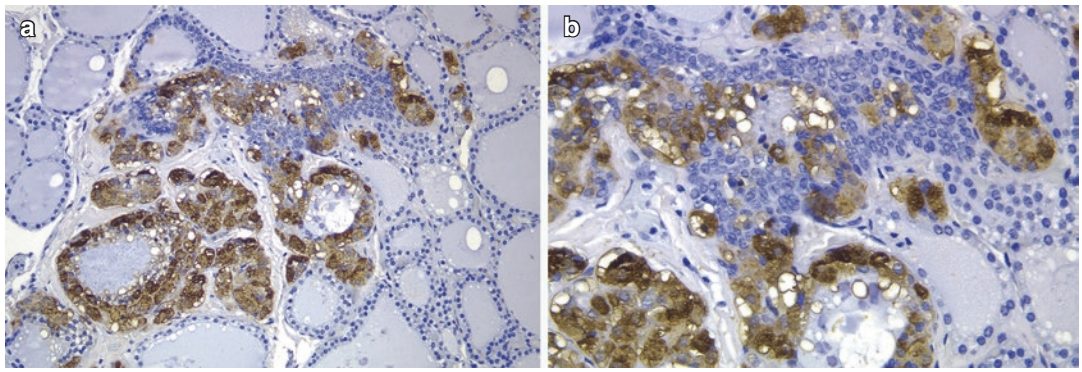

Fig. 6.8 Solid cell nests in a patient with multiple endocrine neoplasia type 2A (MEN 2A). In this case associated to MEN 2A, calcitonin staining showed a very high number of C cells associated with SCNs (**a**, **b**). Primary C-cell hyperplasia is associated with heritable forms of medullary thyroid carcinoma. In fact, there is evidence to support the view that primary C-cell hyperplasia in patients with MEN2 syndromes and in some sporadic microcarcinomas represents a thyroid intraepithelial neoplasia of C cells

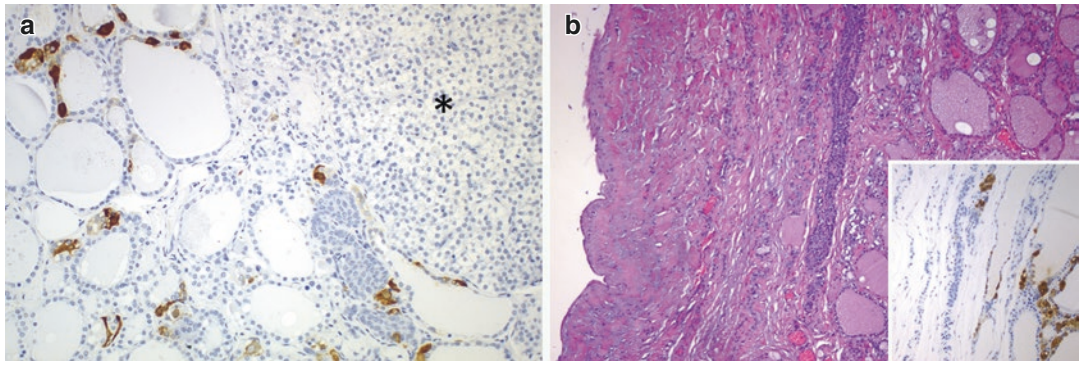

Fig. 6.9 C cells in solid cell nests (SCNs) and branchial-like cysts. Numerous C cells stained for calcitonin are associated with SCNs adjacent to the ectopic (intrathyroidal) parathyroid tissue (*asterisk*) (**a**). SCNs accompanied by numerous calcitonin-positive C cells (*inset*) are seen on the wall of this case of intrathyroidal branchial-type cyst (**b**)

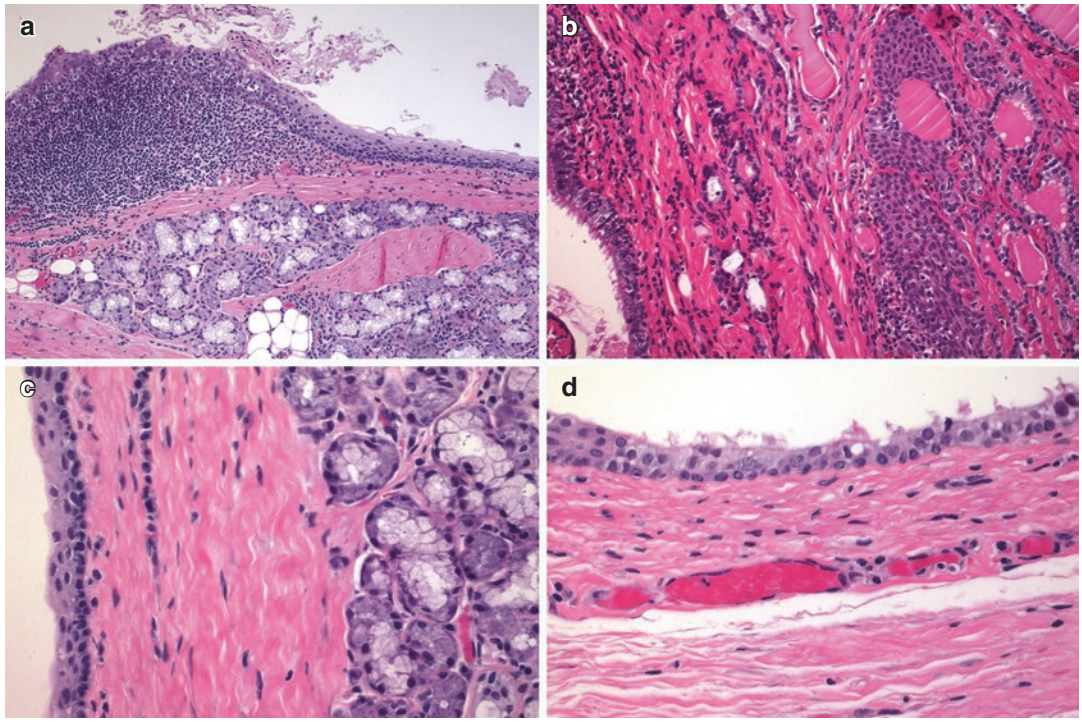

Fig. 6.10 Intrathyroidal branchial cleft cyst. Lymphoid aggregates (**a**), solid cell nests (**b**) and salivary gland-type tissue (**c**) were found in the wall of a branchial cleft cyst occurring in the right thyroid lobe of a children. The wall of the cyst was lined by stratified squamous (**a**, **c**) and ciliated respiratory (**b**, **d**) epithelium

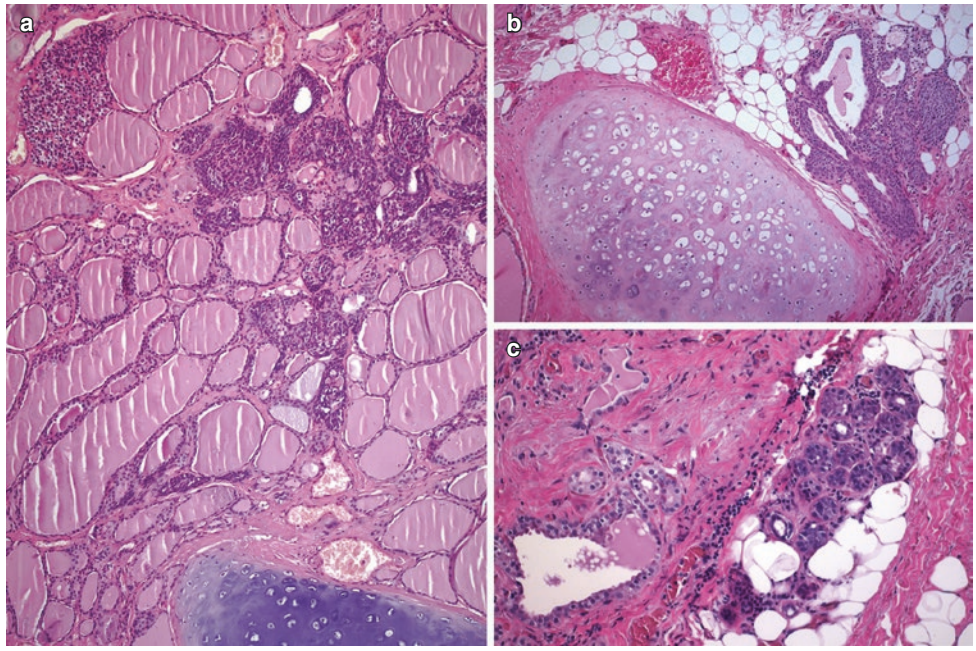

Fig. 6.11 Solid cell nests (SCNs) with intrathyroidal parathyroid, cartilage and salivary gland tissue. The presence of tissues of the branchial apparatus such as parathyroid tissue (**a**), islands of cartilage (**a**, **b**) and salivary gland-type tissue (**c**) around SCNs supports the assumption of a branchial origin for SCNs

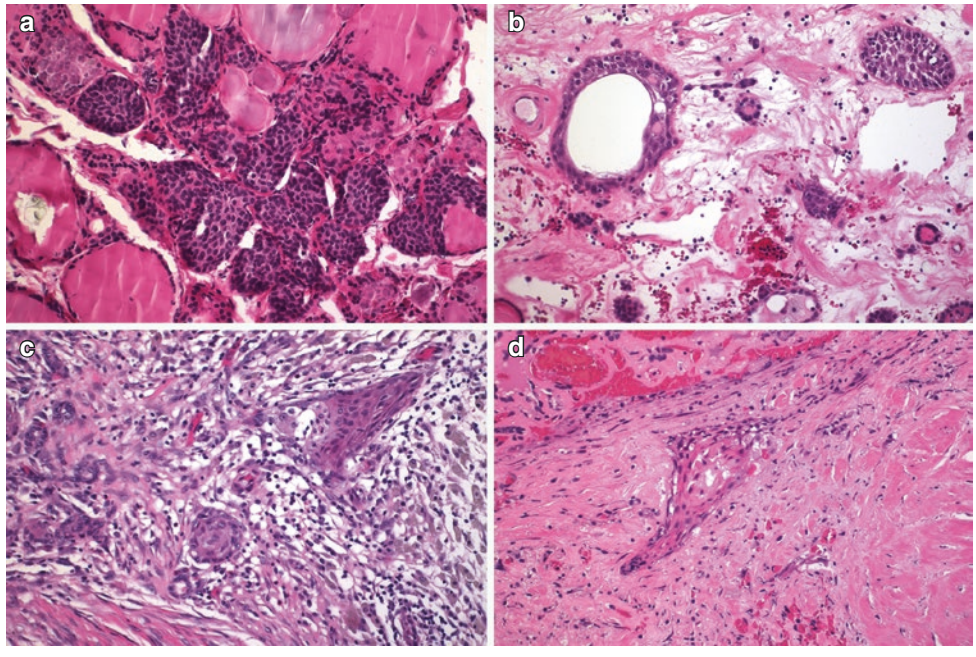

Fig. 6.12 Solid cell nests (SCNs) and squamous metaplasia. SCNs usually appear in normal thyroid tissue, sometimes accompanied by scattered lymphocytes (**a**). In contrast, nests of squamous metaplasia of follicular cells usually appears in a stroma with oedema, fibrin, dense mixed inflammatory infiltrate with abundant histiocytes and variable fibrosis (**b**–**d**)

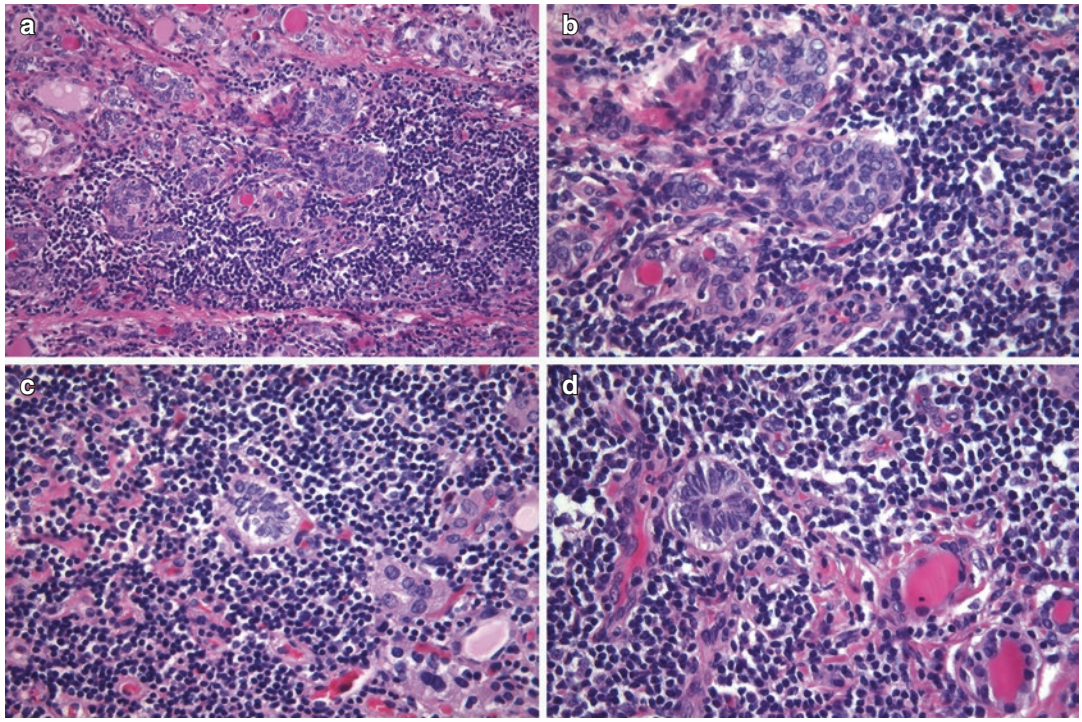

Fig. 6.13 Ductal metaplasia in chronic lymphocytic thyroiditis. Compared to branchial-derived SCNs, the cell nests that occur in thyroiditis are usually smaller squamoid nests of cells with "floret-like" features, surrounded by a collection of lymphocytes and lacking associated C cells (**a**–**d**). These squamoid nests of Hashimoto's thyroiditis are considered to represent ductal metaplasia, secondary to chronic injury. Ductal metaplasia cells are strongly positive for p63, stain weakly for TTF-1 and are negative for thyroglobulin, HBME-1 and calcitonin. These immunophenotypic features can be used to distinguish ductal metaplasia from papillary thyroid microcarcinomas (strongly positive for thyroglobulin, TTF-1 and HBME-1 and variably positive for p63) associated with Hashimoto's thyroiditis

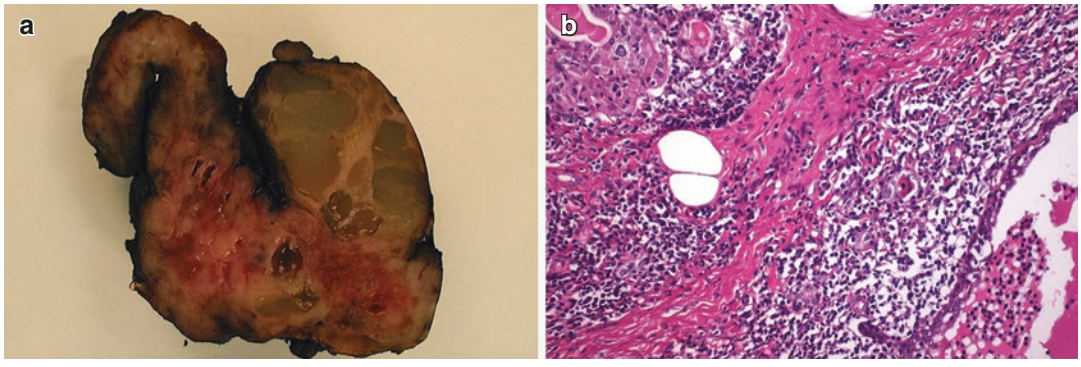

Fig. 6.14 Cystic variant of chronic lymphocytic (Hashimoto) thyroiditis. Rare cases of chronic lymphocytic thyroiditis show numerous cystic formations some of which are evident in macroscopic examination (**a**). In this case of a 50-year-old woman, microscopic examination revealed several branchial cleft-like cysts containing dense eosinophilic material with cholesterin clefts and lymphocytes. The cysts were lined by stratified epithelium of variable thickness. In the stroma, areas of diffuse lymphoplasmacytic infiltration, germinal centres and oncocytic metaplasia alternated with marked fibrosis, follicular atrophy and squamous metaplasia (**b**–**d**)

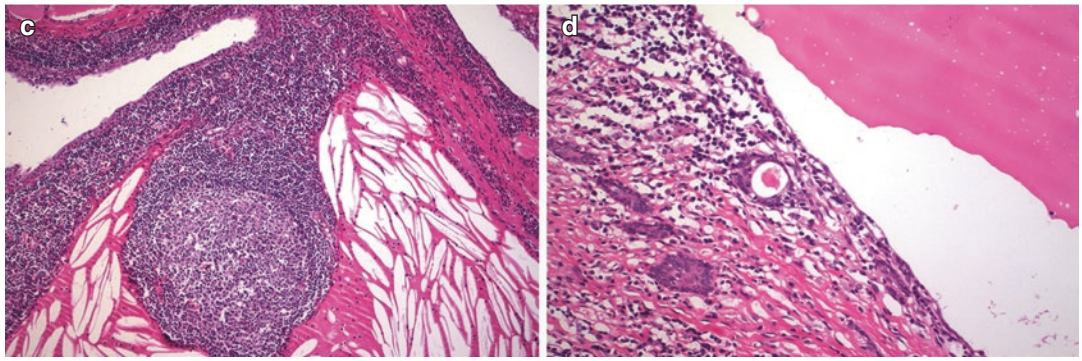

Fig. 6.14 (continued)

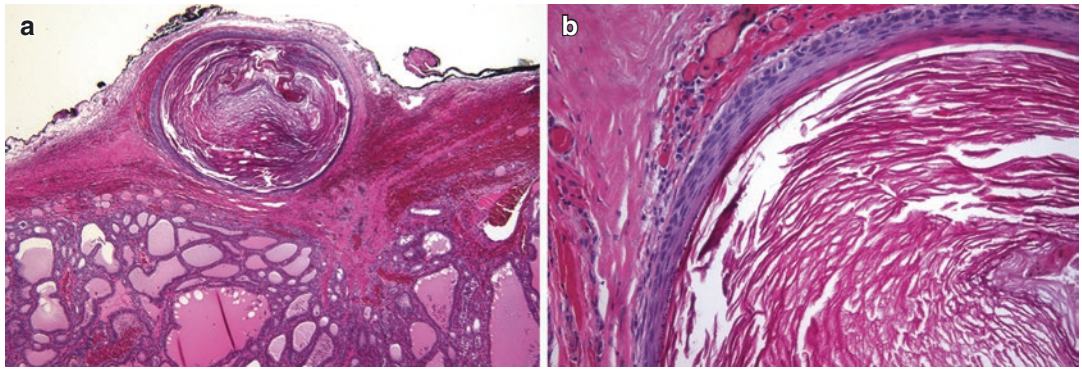

Fig. 6.15 Keratinous (epidermoid type) cyst. Keratinous cyst located on the surface of the gland surrounded by fibrous tissue of the capsule (**a**). This cyst is similar to an epidermoid type inclusion cyst; it is lined by cornified epithelium, has a distinct granular layer and contains lamellated keratin (**b**). Since the patient had a previous fine needle aspiration biopsy (FNAB), it is tempting to propose that the cyst has resulted from traumatic inclusion of epidermis secondary to the FNAB

epidermoid type inclusion cyst are extremely rare in the thyroid (Fig. 6.15).

It is possible that mixed follicles [12] may represent a phenomenon of asymmetric division (Fig. 6.16). We found positivity for CD133 in SCNs and in some follicles in the vicinity of a case of SCNs (unpublished observations) (Fig. 6.16). OCT4 protein expression, however, was only detected in a few cases of SCNs [13]; further research is therefore required to confirm their stem cell role.

One hyperplastic (giant) SCN case has been described [14]. Although no *BRAF* gene mutations are found in normal SCNs, $BRAF^{V600E}$ mutation has been reported in a case of diffuse and bilateral SCN hyperplasia with a contiguous papillary microcarcinoma also having the same $BRAF^{V600E}$ mutation [15]. In this case, two PTCs and the SCNs associated with the first microPTC showed the same *BRAF* mutation, while the follicular adenoma, the normal follicular cells and three other samples of SCNs showed no mutation. These findings support the assumption that SCN hyperplasia may be a precursor lesion of PTC [15]. In a similar way, our group reported in the centre of a follicular variant of PTC a second neoplastic lesion featuring a SCN-like appearance sharing a Q61R mutation in the *N-RAS* gene with the follicular variant of PTC [16]; this finding supports also a histogenetic relationship between these two lesions (see Chap. 2). Other studies have also supported a histogenetic link between SCNs and PTC, as well as with sclerosing mucoepidermoid carcinoma [4, 8]. A case of papillary thyroid microcarcinoma coexisting

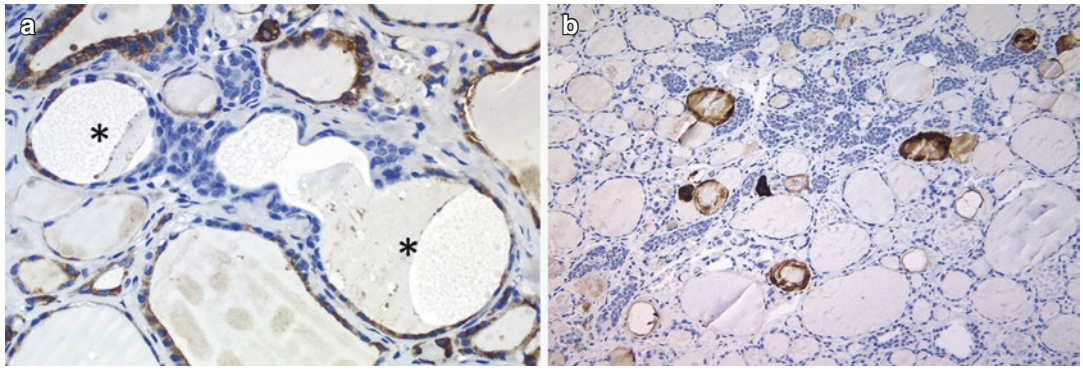

Fig. 6.16 Stem cell features in solid cell nests (SCNs). Main cells of the SCNs apparently harbour the minimal properties of a stem cell phenotype (telomerase activity and differentiation to one or more than one type of specialized cells) and may thus represent a pool of stem cells of the adult thyroid. In SCNs, the follicles (*asterisk*) lined by main cells and follicular epithelium positive for thyroperoxidase (mixed follicles) could represent the so-called asymmetric division of stem cells (**a**). CD133, thought to be a stem cell marker, is also positive in SCNs (**b**)

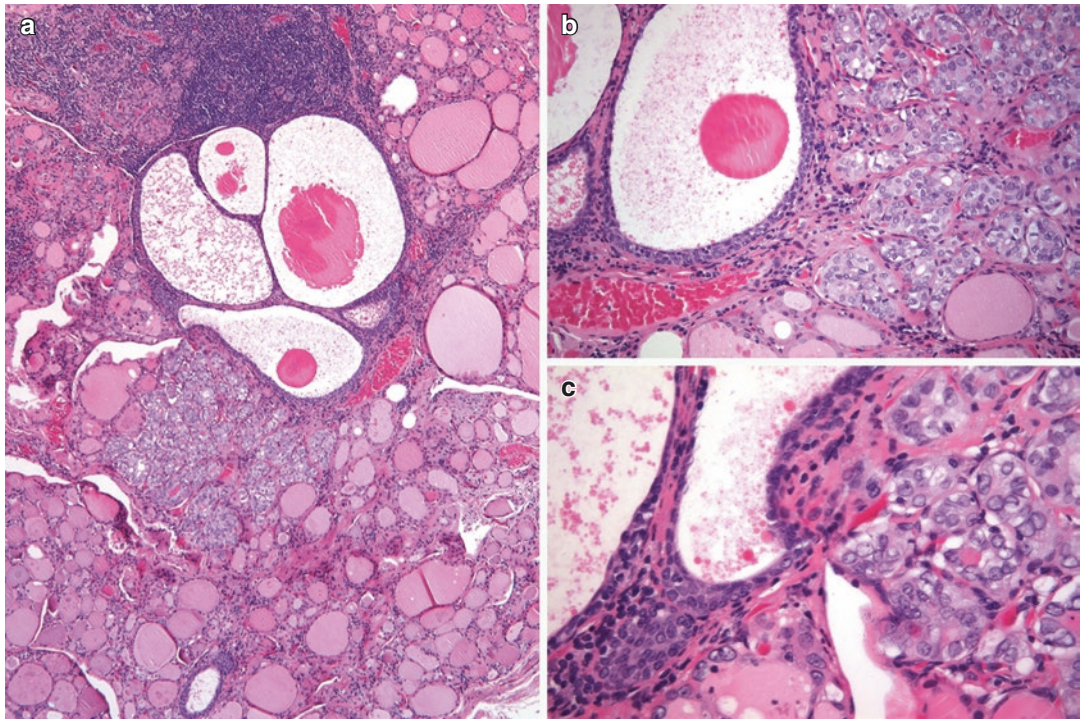

Fig. 6.17 Solid cell nests (SCNs) and papillary thyroid carcinoma. This figure illustrates a case of papillary thyroid microcarcinoma coexisting in intimate relationship with SCNs (**a**–**c**). In comparison to SCNs, the papillary microcarcinoma shows a pattern of microfollicular growth and larger nuclei with clearer chromatin

in intimate relationship with SCNs is illustrated in Fig. 6.17.

An additional relationship between SCNs and carcinoma showing thymus-like differentiation of the thyroid (CASTLE) has recently been reported [17]. Regardless of whether or not the main cells of SCNs serve as neoplastic stem cells, the broad spectrum of differentiation of SCNs may explain conceptually the existence of primary thyroid tumours with "aberrant" phenotypes.

A case of thyroid-type SCNs associated with struma ovarii has been reported supporting a histogenetic link between the main cells of SCNs and thyroid tissue [18]. Cystic tumour of the atrioventricular node of the heart [19] and the so-called complex choristoma of the gyrus rectus in central nervous system [20] are two intriguing lesions, morphologically and immunophenotypically equivalent to SCNs of the thyroid.

Spindle Epithelial Tumour with Thymus-Like Differentiation (SETTLE)

SETTLE is a rare, malignant tumour of the thyroid characterized by a lobulated architecture and biphasic cellular composition featuring spindly epithelial cells that merge into glandular structures [5, 21–23] (Figs. 6.18, 6.19, 6.20 and 6.21). It is thought that this tumour is derived from the branchial pouches or thymic remnants and shows primitive thymic differentiation [22]. It occurs predominantly in euthyroid children and young adults. SETTLE are usually limited by a continuous capsule with fibrous septa although they may also have an infiltrative growth pattern. Vascular invasion is rarely observed. The spindle cells are usually bland, and the epithelial (or epithelioid) cells may form tubules, small papillae, trabeculae or squamoid nests (Figs. 6.18, 6.19 and 6.20). Occasional cases comprise almost exclusively spindly cells or glandular structures, the so-called monophasic variant of SETTLE. The epithelial cells are cuboidal to columnar and are sometimes mucinous or ciliated (Figs. 6.20 and 6.21). The spindle cell component expresses low and high molecular weight cytokeratins, CK5, p63, vimentin and, often, CD99, while the epithelioid

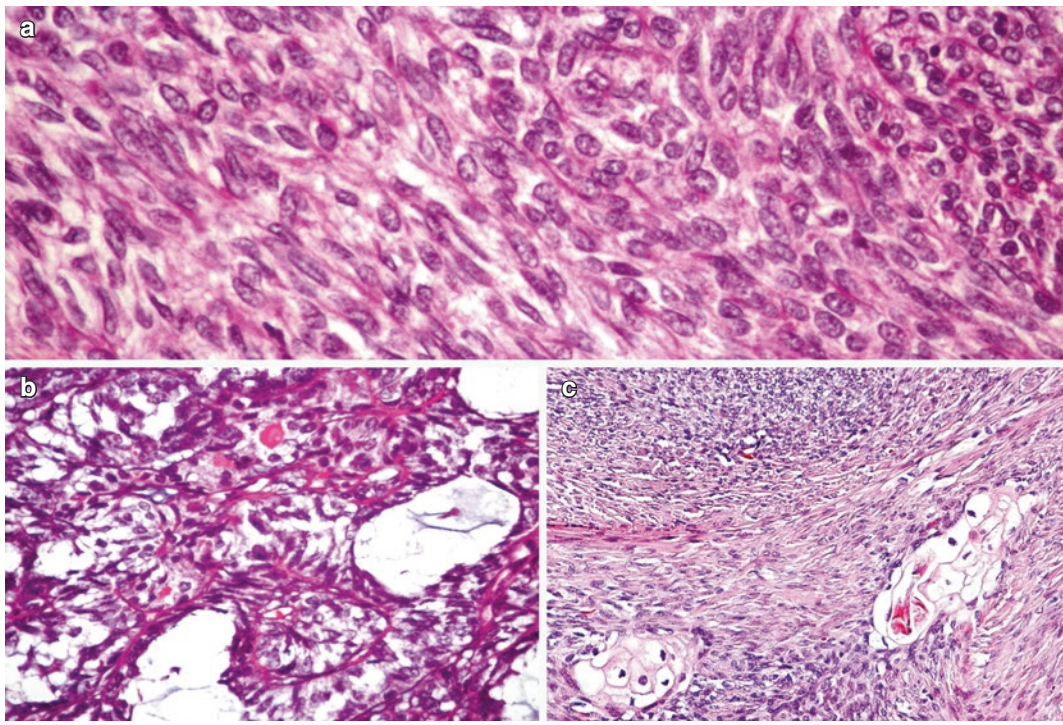

Fig. 6.18 Spindle epithelial tumour with thymus-like differentiation (SETTLE). Biphasic pattern of SETTLE including a bland spindle cell component (**a**) and an epithelial component that may disclose glandular structures with mucin cysts (**b**) and squamoid nests (**c**)

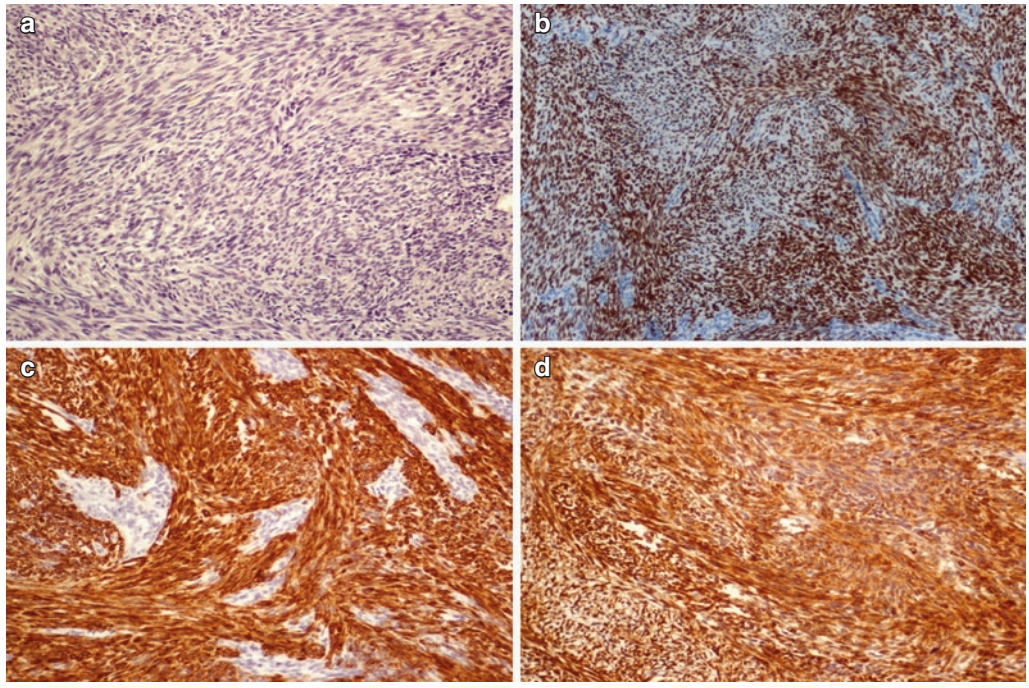

Fig. 6.19 Immunohistochemical features of SETTLE. The bland spindle cell component of SETTLE does not express thyroglobulin (**a**) and expresses p63 (**b**), pankeratins (clone AE1/AE3) (**c**) and Bcl-2 (**d**)

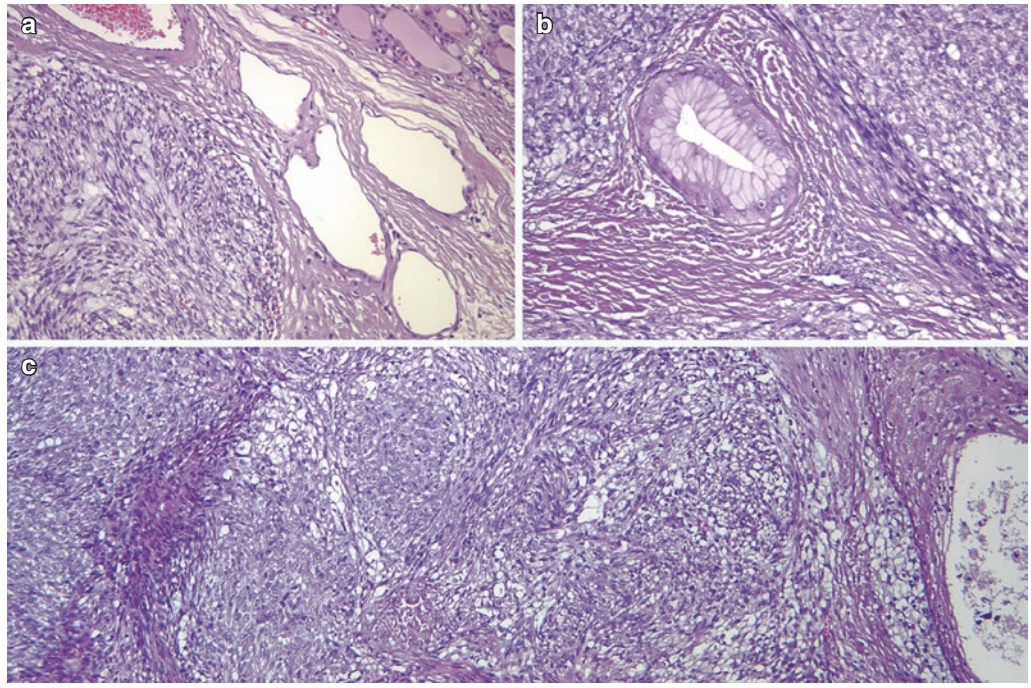

Fig. 6.20 SETTLE. This neoplasm is characterized by a lobulated architecture (**a**) and biphasic cellular composition featuring spindly epithelial cells that merge into glandular (**b**) and squamous (**c**) epithelium. The hypercellular and monotonous quality of the spindle cell component may lead to a misdiagnosis of synovial sarcoma

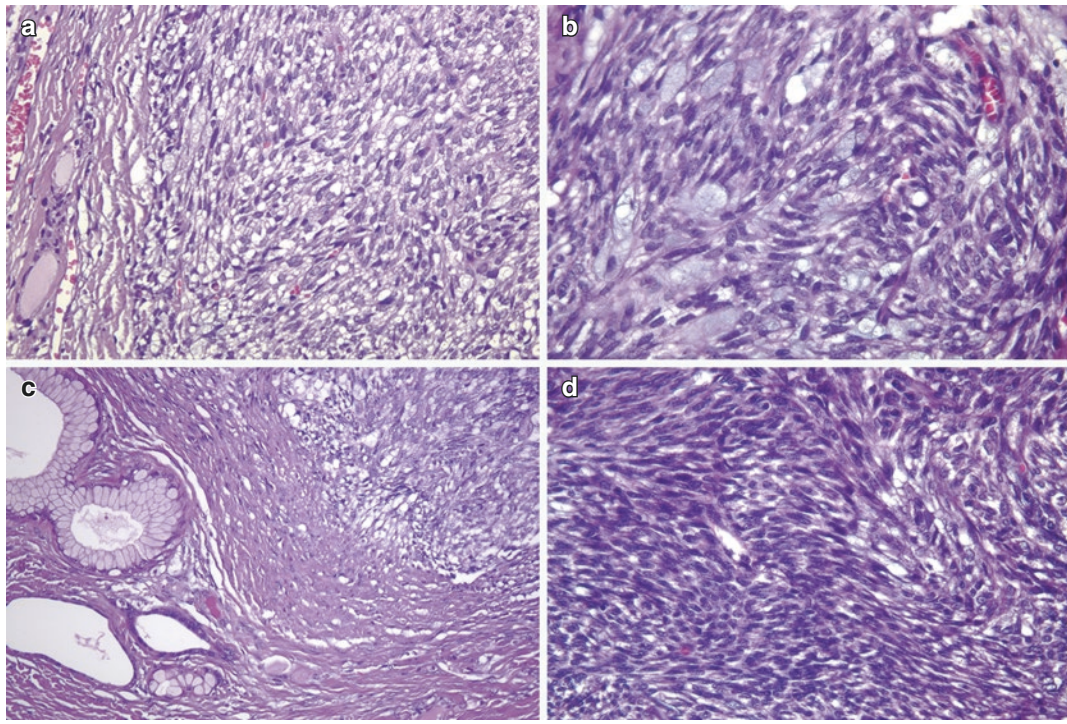

Fig. 6.21 SETTLE. The spindle cells often assume a reticulated appearance (**a**, **b**). Spindle cells, sclerotic bands and mucinous glands are typical features of SETTLE (**c**). The tumour is highly cellular with fascicular arrangement (**d**)

component usually lacks vimentin and CD99 expression (Fig. 6.19). Thyroglobulin, calcitonin, TTF-1, carcinoembryonic antigen, CD5 and CD34 are usually negative in both components. The differential diagnosis of SETTLE includes spindle cell variant of follicular adenoma (Fig. 3.9), spindle cell variant of PTC (Fig. 2.10) and spindle cell variant of MTC, ectopic thymoma, solitary fibrous tumour (Figs. 6.25 and 6.26) and synovial sarcoma. The distinction between SETTLE and synovial sarcoma may be achieved only after the exclusion of the t(X,18) rearrangement typical of synovial sarcoma.

The case illustrated in Figs. 6.18 and 6.19 is from a 13-year-old male child who had a 3 cm nodule in the thyroid (courtesy of Daniella Vieira, Florianopolis, Brazil). The nodule was whitish and firm. Microscopically, the tumour had a thick and calcified capsule without signs of invasion. It was a biphasic tumour composed of a spindle cell component and an epithelioid component.

Carcinoma Showing Thymus-Like Differentiation (CASTLE)

Intrathyroid epithelial thymoma (ITET)/carcinoma showing thymus-like differentiation (CASTLE) is a rare malignant epithelial tumour of the thyroid displaying thymic epithelial differentiation [5, 21, 24]. It is thought to represent the malignant counterpart of an ectopic thymoma of the thyroid gland or remnants of the branchial pouches that differentiate along the thymic line [22]. CASTLE usually develops in the lower poles of the thyroid. It is a solid, well circumscribed and slightly lobulated, not encapsulated tumour (Fig. 6.22, courtesy of Jesús Alberto Veiga Barreiro, A Coruña, Spain). Microscopically, CASTLE is basically a squamous cell carcinoma with lymphocyte-rich stroma characterized by a lobulated pattern of growth, evident perivascular spaces, low mitotic count and immunopositivity for CD5, c-kit (CD117), PAX8, Bcl-2, EGFR, GLUT-1, p63 and p53 (Fig. 6.23). The tumour cells have large vesicular nuclei,

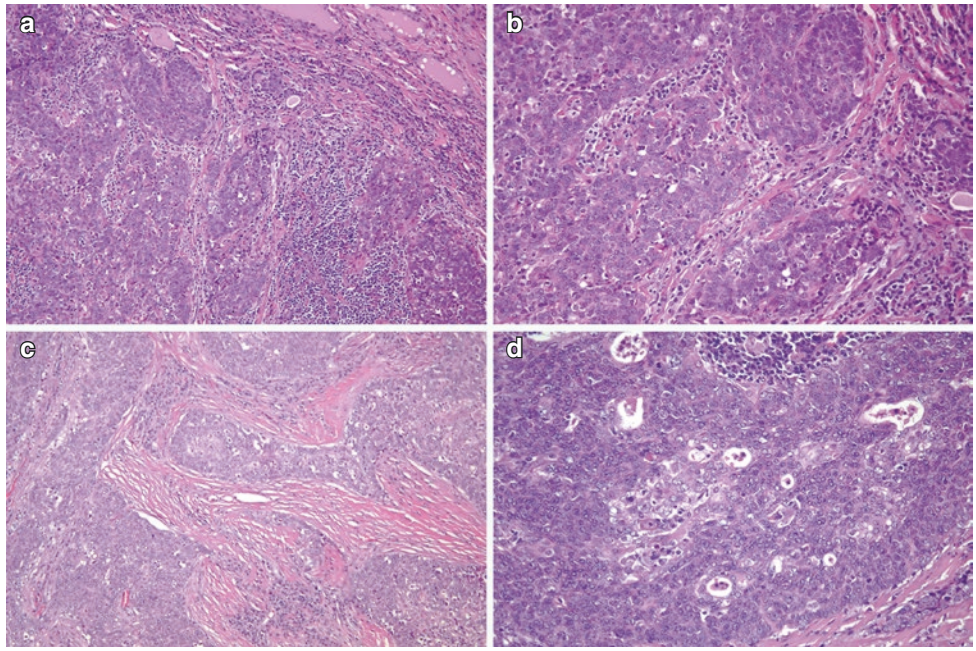

Fig. 6.22 Carcinoma showing thymus-like differentiation (CASTLE). The tumour cell nests, separated from each other by collagenous bands infiltrated by lymphocytes and plasma cells, are similar to those seen in conventional thymic carcinoma of mediastinum (**a**–**d**). Foci of squamous differentiation with structures reminiscent of Hassall's corpuscles may be seen (**d**)

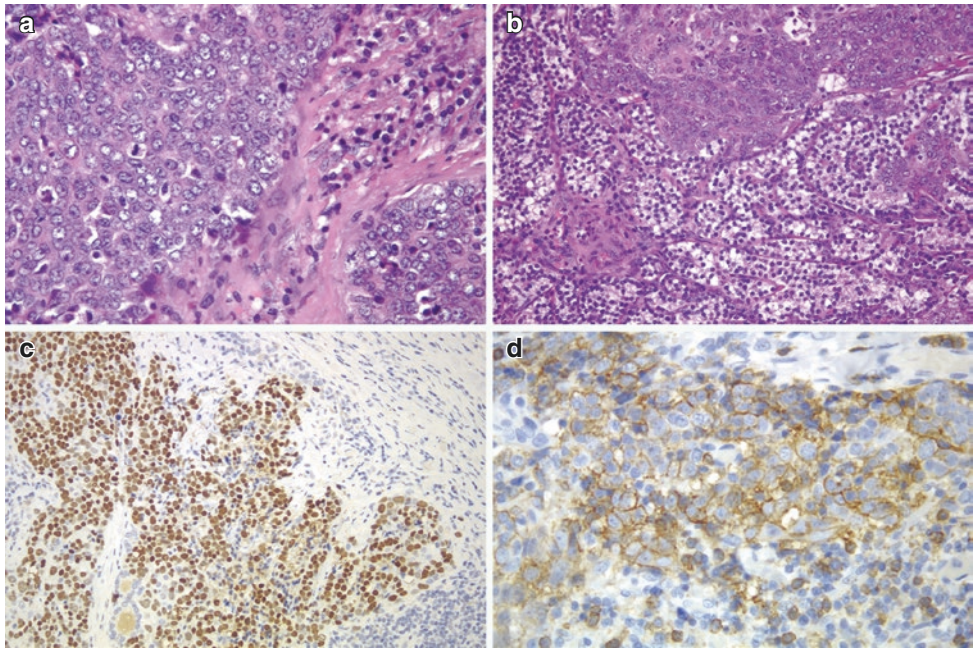

Fig. 6.23 CASTLE. The tumour cells are squamoid and syncytial, with pale to eosinophilic cytoplasm (**a**, **b**). The nuclear chromatin is vesicular with small but easily identifiable nucleoli (**a**). The tumour may invade the parathyroid at advanced stages (**b**). The tumour cells are typically immunoreactive for p63 (**c**) and CD5 (**d**)

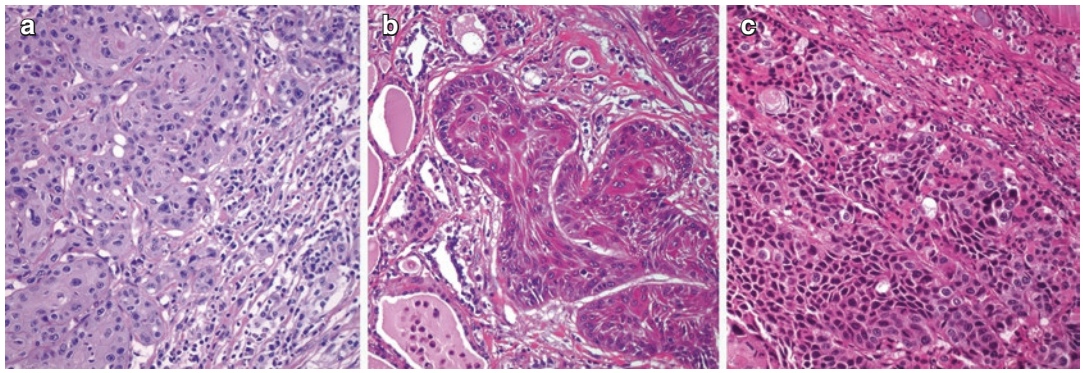

Fig. 6.24 Squamous cell carcinoma. Photomicrographs of SCCs primary of the thyroid (**a**), from larynx (**b**) and metastatic from lung (**c**). By definition, SCC of the thyroid should be composed predominantly, or entirely, of tumour cells with squamous differentiation. PAX8 staining may help for distinguishing between primary thyroid SCC and invasion or metastasis from extrathyroidal SCC. CASTLE must be distinguished from squamous metaplasia arising in benign thyroid lesions (e.g. chronic lymphocytic thyroiditis), squamoid variant of undifferentiated (anaplastic) carcinoma, primary SCC and SCC of other sites. Compared to CASTLE, squamous cell carcinomas have more obvious keratinization, higher proliferative activity and negativity for CD5

prominent nucleoli, fairly abundant cytoplasm and indistinct cell borders (Fig. 6.23). They are negative for thyroglobulin, TTF-1, calcitonin, chromogranin A, synaptophysin and leucocyte common antigen (CD45RB). The Ki-67 labelling index is lower (about 10–30%). Because of the better prognosis of CASTLE, it is important to separate it from undifferentiated (anaplastic) carcinoma (remarkable pleomorphism, atypical mitoses, necrosis, Ki-67 index >50% and prominent invasiveness) and from primary [25] or metastatic squamous cell carcinoma (more keratinization, Ki-67 index > 50% and negativity for CD5) (Fig. 6.24). Lymphoepithelial carcinoma is strongly associated with Epstein-Barr virus (EBV), whereas CASTLE is negative for EBV-encoded RNA (EBER). Follicular dendritic sarcoma may have a lobulated pattern of growth, but it is negative for keratins and CD5.

Solitary Fibrous Tumour

Solitary fibrous tumour (SFT) of the thyroid [5, 21] is a mesenchymal neoplasm indistinguishable from pleural and other extrapleural SFTs. Most tumours present as a well-circumscribed, usually unencapsulated mass. At the microscopic level, typical features include a haemangiopericytic or desmoid-like arrangement of spindle bland cells, alternation of hypercellular and hypocellular (keloid-like collagen) areas, branching and haemangiopericytoma-like vessels (Fig. 6.25). Myxoid change and inflammatory cells, namely, mast cells, can be seen. Cystic changes are rare. A lipomatous (adipocytic) variant of SFT has been reported [26] (Fig. 6.26). The neoplastic cells are immunoreactive for CD34, CD99, BCL-2, vimentin and STAT6 (Fig. 6.26), whereas S100 protein may highlight the lipomatous foci. Positivity for factor XIIIa, progesterone and oestrogen receptors was also detected in some SFTs. The neoplastic cells are negative for cytokeratins, desmin, CD31, FVIII-Ag, CD117, TTF-1, thyroglobulin and calcitonin. The behaviour is generally benign, but exceptional cases showing unequivocal signs of clinical aggressiveness and displaying histopathological features of malignancy (numerous mitoses and marked cellular atypia) have been reported. The differential diagnosis includes all spindle cell mesenchymal tumours, post-FNAB spindle cell nodules (Fig. 6.27), follicular adenoma (Fig. 3.9) and adenomatous goitre with spindle cell features, Riedel thyroiditis [27] (Fig. 6.28), spindle cell variant of MTC, spindle cell and paucicellular variants of undifferentiated (anaplastic) carcinoma (Fig. 6.29) and SETTLE (Figs. 6.18, 6.19, 6.20 and 6.21).

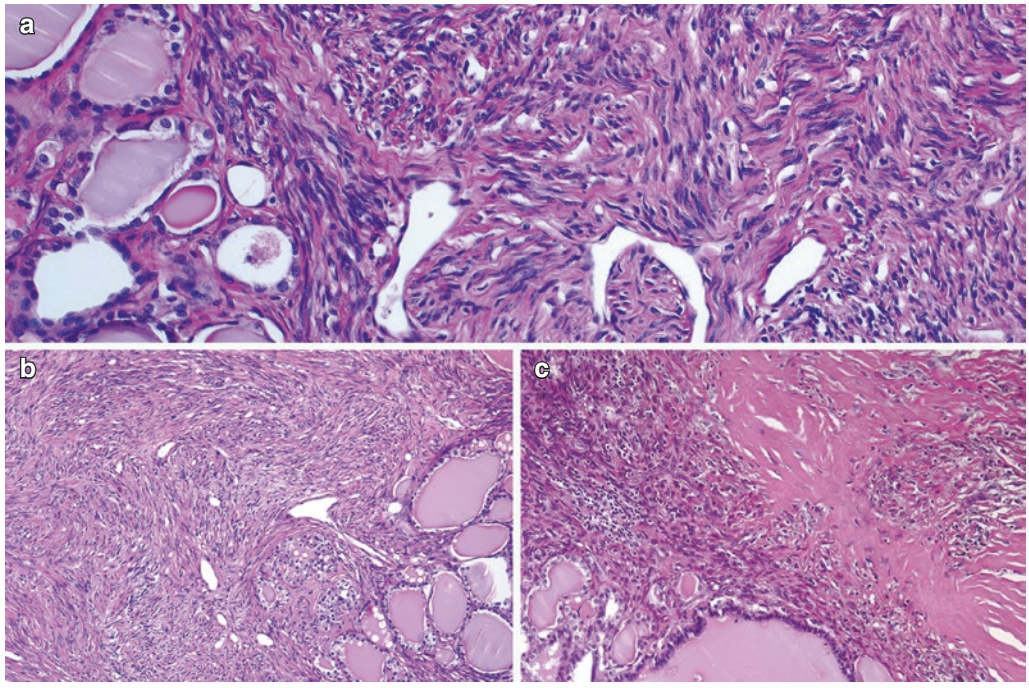

Fig. 6.25 Solitary fibrous tumour (SFT). SFT displays typically a hemangiopericytomatous pattern of growth displaying monotonous, bland, spindle-shaped cells (**a**, **b**) that alternate with hypocellular areas with increased keloid-like collagen deposition (**c**). These tumours are usually benign with no atypia, mitotic figures or necrosis

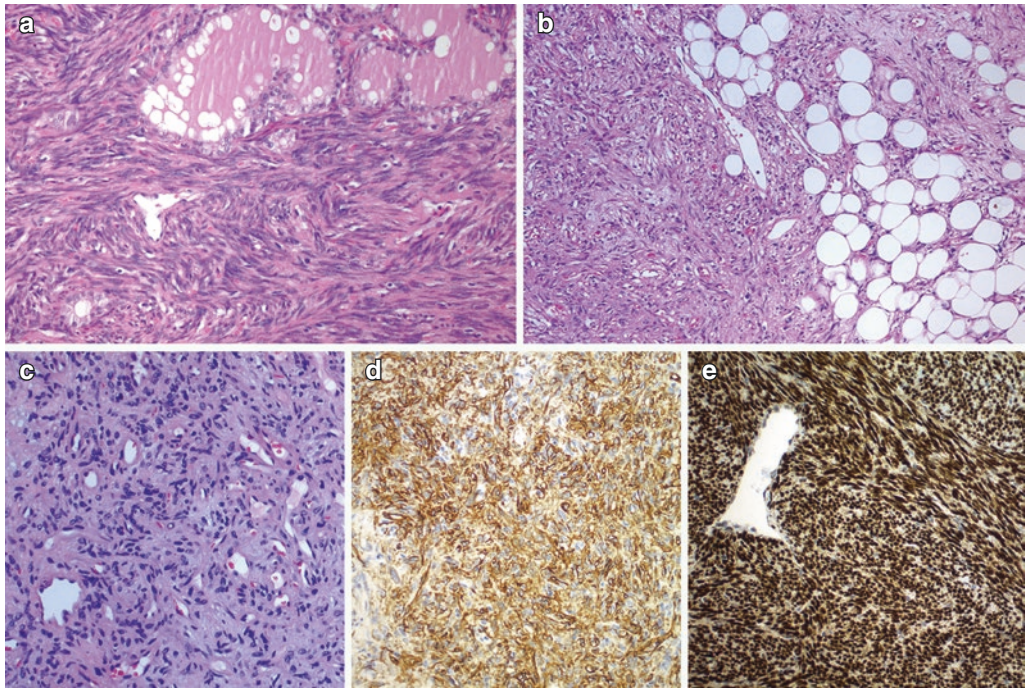

Fig. 6.26 SFT and lipomatous (adipocytic) variant of SFT. SFT may show areas of haemangiopericytoma-like (**a**), adipocytic (**b**), fascicular, storiform, keloid-like and myxoid (**c**) growth pattern. Tumour cells are characteristically immunoreactive for CD34 (**d**) and STAT6 (**e**) and negative for epithelial and thyroid markers

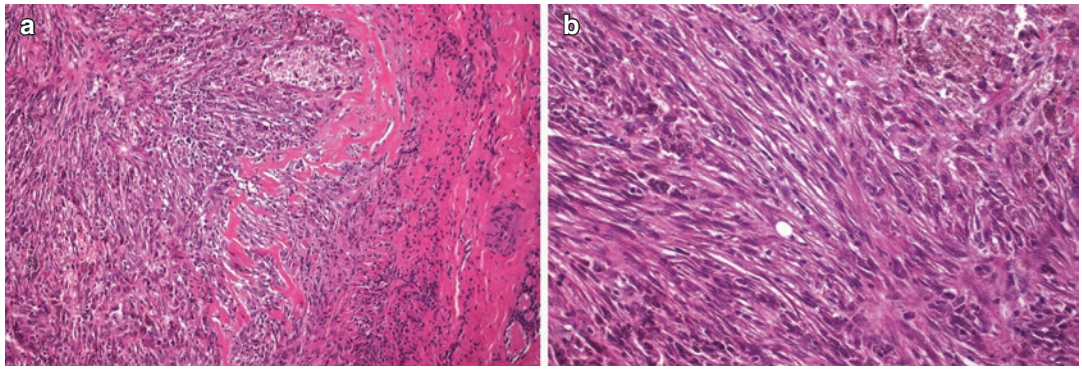

Fig.6.27 Fibroblastic proliferation post-FNAB. Following FNAB, the thyroid tissue appearance is similar to that of a healing wound (**a**, **b**). There is reactive fibroblastic proliferation, fibrin and new capillary blood vessels, followed by maturation of the fibrous tissue, areas of old haemorrhage and foci of squamous metaplasia of entrapped or adjacent epithelium. In this case, numerous hemosiderin-laden macrophages are typically present, supporting a reparative response to needle trauma with haemorrhage (**b**)

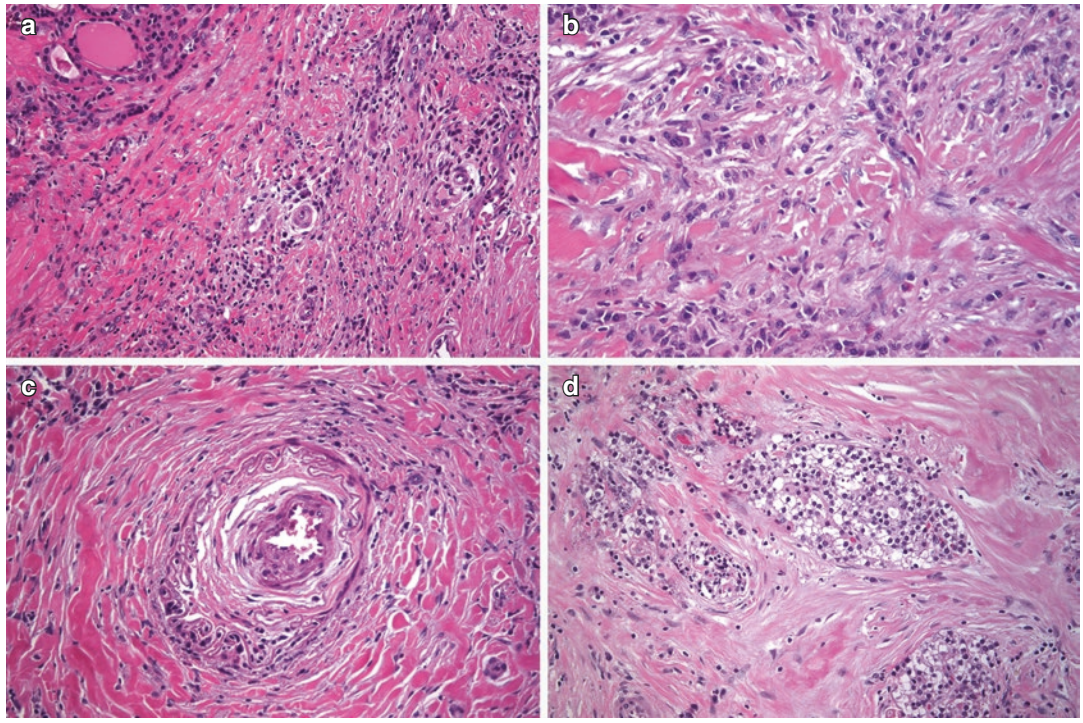

Fig. 6.28 Invasive fibrous (Riedel) thyroiditis. Riedel thyroiditis (RT) typically shows an extensive storiform fibrosis with almost complete atrophy of the follicles (**a**) and prominent inflammatory cells (plasma cells, lymphocytes and eosinophils) (**b**). Obliterative phlebitis (**c**) and extrathyroidal fibrosis with involvement of the parathyroid glands (**d**) and/or recurrent laryngeal nerves are characteristic. Recent studies include RT within the spectrum of IgG4-related thyroid disease

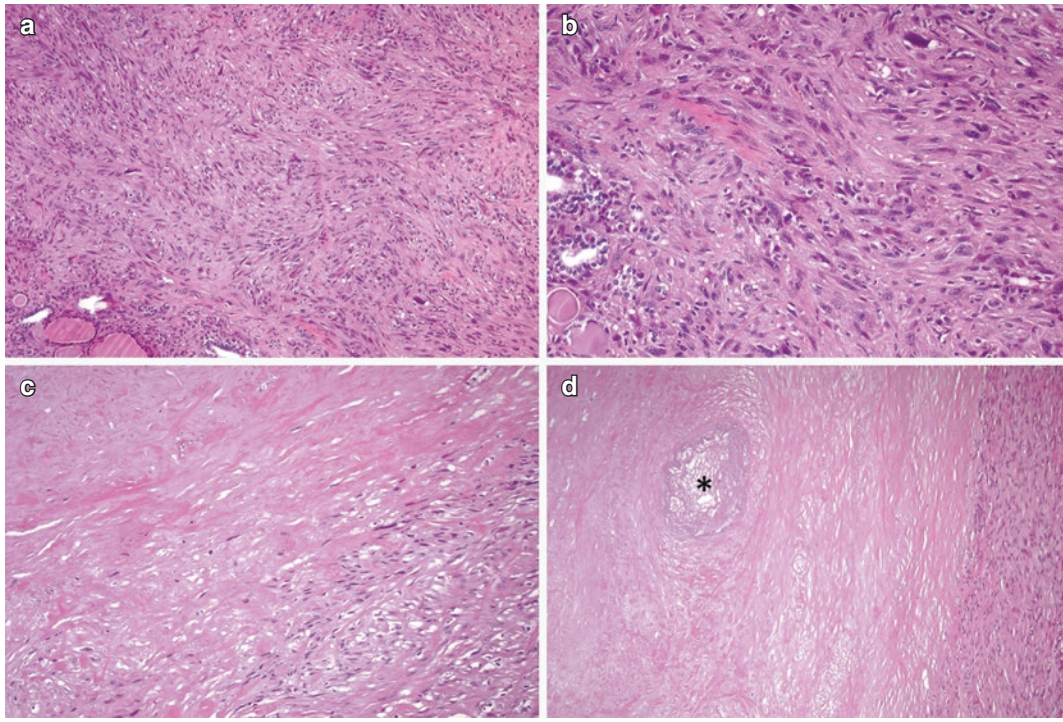

Fig. 6.29 Spindle cell and paucicellular variants of undifferentiated (anaplastic) carcinoma. Undifferentiated carcinoma (UC) is a highly aggressive thyroid malignancy formed by undifferentiated follicular thyroid cells typically showing necrosis, high mitotic activity and widely invasive growth. UC is broadly categorized into three main patterns (spindle cell, pleomorphic giant cell and squamoid cell) that occur singly or in any combination. Spindle cell is the most common histologic pattern (**a**, **b**). Paucicellular variant of UC is characterized by a dense fibrohyaline stroma with only scattered atypical spindle tumour cells (**c**, **d**). Heavy hyaline background in paucicellular variant of UC is probably secondary to extensive infarction due to vessel wall infiltration (*asterisk*) (**d**). These features could lead to an erroneous diagnosis of Riedel's thyroiditis

Florid Papillary Endothelial Proliferation

Papillary endothelial hyperplasia occurring within or around the capsule of thyroid neoplasms is rare [5, 28]. Such Masson-like lesions, which have been attributed to FNAB-induced injury and thrombosis, can mimic tumour angioinvasion or vascular neoplasms. Intravascular endothelial hyperplasia is associated with thyroid carcinoma but can also be seen in follicular adenomas with a lower frequency. This intravascular endothelial hyperplasia with a papillary configuration and/or with a Kaposi-like appearance should not be considered true vascular invasion (Fig. 6.30). The vessels within the papillary fronds are positive for CD31, CD34 and D2-40. In contrast to Masson's lesions that develop within blood vessels as a result of thrombosis, pericapsular papillary endothelial hyperplasia associated with thyroid neoplasms develops within lymphatics, possibly related to lymphangiogenic factors secreted by the thyroid neoplastic cells.

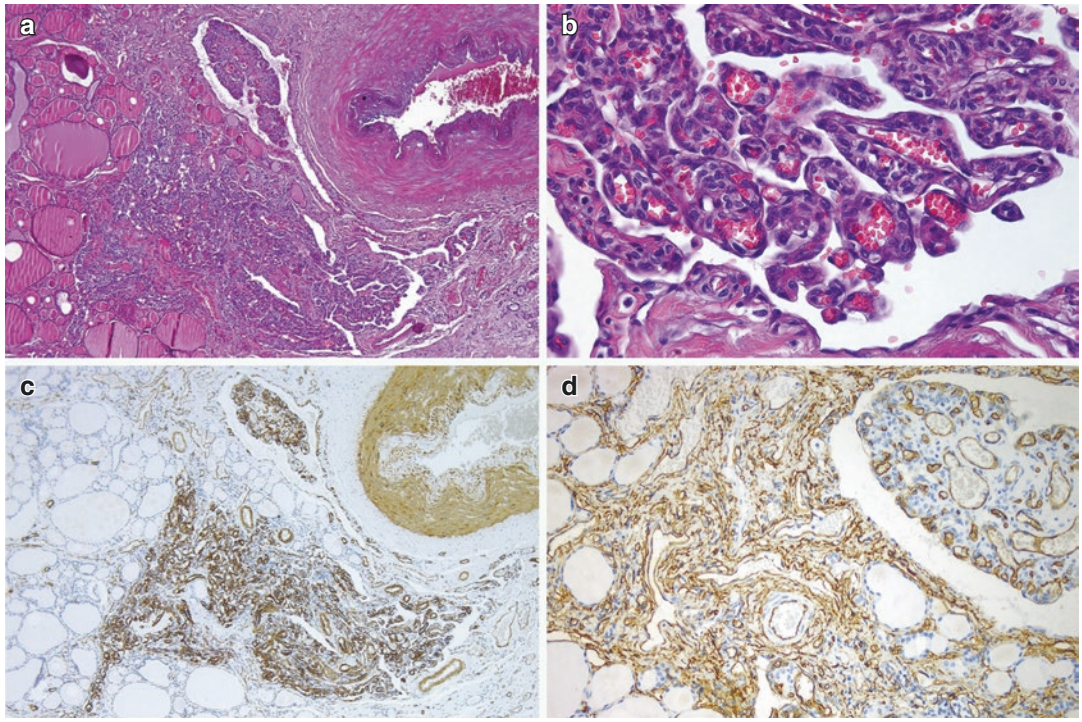

Fig. 6.30 Florid endothelial proliferation. Intravascular endothelial hyperplasia is associated with benign and malignant thyroid neoplasms. This type of hyperplasia may have a papillary configuration and/or a Kaposi-like appearance and should not be considered true vascular invasion (**a**). Higher magnification demonstrates the lack of bizarre cells and atypical mitoses (**b**). The vessels within the papillary fronds are positive for smooth muscle actin (**c**), CD31, CD34 (**d**) and D2-40

Spindle Cell Haemangioma

Spindle cell haemangioma (SCH) can exceptionally occur in the thyroid or involve the gland from a starting point located in the neck [29]. The morphological and immunohistochemical features of SCH of the thyroid are the same as those reported for other organs (Fig. 6.31). The major difficulties in the diagnosis of thyroid SCH include the difficult preoperative diagnosis by FNAB due to haemorrhage and the differential diagnosis with other spindle cell lesions in this location. The SCH of the thyroid with scant vascular spaces can be confused with the spindle cell variant of follicular cell tumours, such as follicular adenoma and PTC, angiomatoid variant of PTC, spindle cell variant of MTC, SETTLE and solitary fibrous tumour, among others. The distinction between solitary fibrous tumour and SCH can be hard as both express CD34 and vimentin but only solitary fibrous expresses CD99. After the confirmation that the spindle cells of this type of tumour have vascular differentiation, the differential diagnosis is with the malignant counterparts of spindle cells haemangioma, namely, angiosarcoma, and with exuberant reactive vascular proliferations. Angiosarcoma is a high-grade tumour composed of atypical cells that disclose mitotic figures at variance with the bland looking and resting cells of SCH.

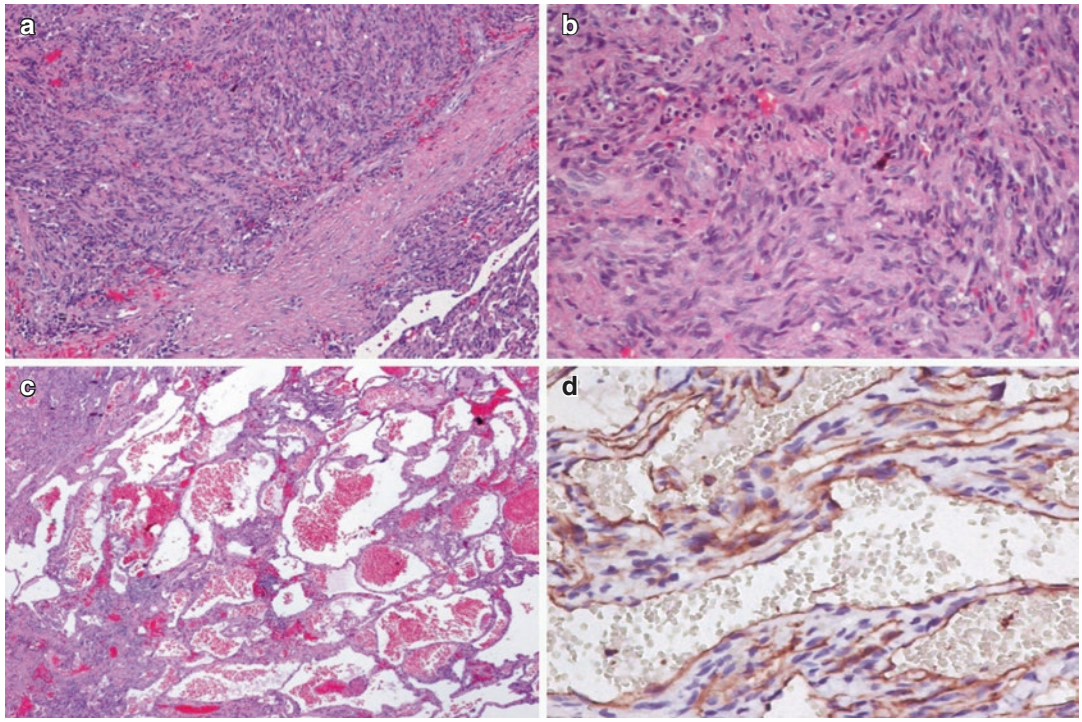

Fig. 6.31 Spindle cell haemangioma (SCH). This SCH of a 67-year-old female presented as a 34 mm nodule in the left lobe and isthmus of the thyroid. Preoperative FNAB was non-diagnostic due to abundant haemorrhage. The nodule was composed by solid spindle cell areas (**a**, **b**) and vascular spaces of the capillary and cavernous type (**c**) without atypical features of the lining cells. The spindle cells expressed CD31(**d**) and CD34

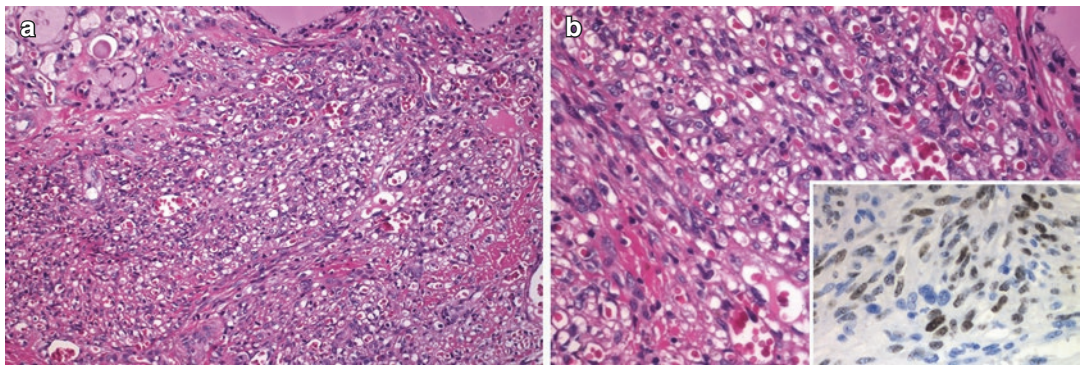

Fig. 6.32 Kaposi sarcoma (KS). This case of KS affecting the thyroid gland has been found at autopsy of an 82-year-old male with skin and visceral KS involvement. Cytologically bland spindle cells are associated with narrow vascular spaces (**a**). Notice the numerous erythrocytes (**b**). Nuclear positivity for HHV8 was also found (**b**, *inset*)

Kaposi Sarcoma

Kaposi sarcoma (KS) is a locally aggressive endothelial tumour or tumour-like lesion that usually occurs as cutaneous lesions in the form of multiples patches, plaques or nodules but may also involve different mucosal sites, lymph nodes and visceral organs. Involvement of the thyroid has been reported in very rare cases of HIV-positive and HIV-negative patients [30, 31] (Fig. 6.32).

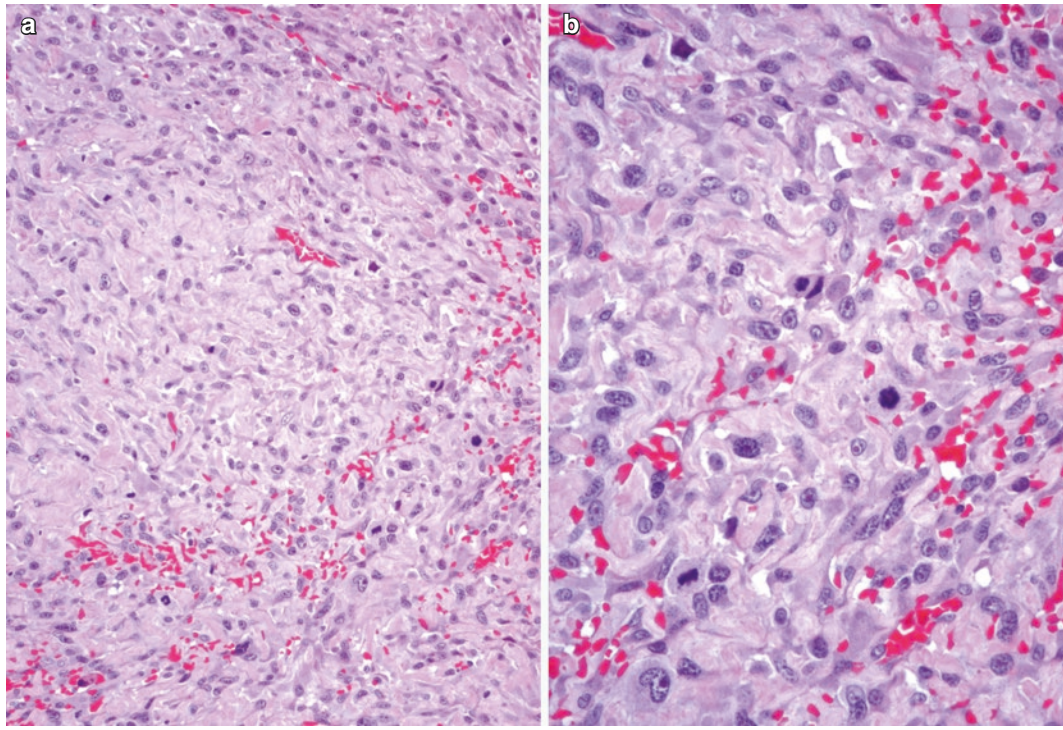

Fig. 6.33 Epithelioid haemangioendothelioma. This malignant vascular neoplasm (**a**, **b**) is characterized by an epithelioid proliferation in a background of chondromyxoid-collagenous stroma. The epithelioid cells are atypical, have mitotic figures and disclose intracytoplasmatic lumina filled with red blood cells

In a thyroid KS case, the smears of FNAB were composed of spindle and plasmocytoid cells, raising the possibility of MTC. KS is histologically composed of cellular bundles and fascicles of spindle cells as well as slit- and sieve-like vascular spaces. Extravascular erythrocytes and siderophages are numerous and hyaline globules are also frequently observed (Fig. 6.32). The lining cells of vessels and spindle cells are positive for endothelial markers (CD31, CD34 and ERG), as well as for lymphatic markers such as podoplanin (D2-40). KS is also positive for human herpes virus 8 (HHV8) (Fig. 6.32).

Epithelioid Haemangioendothelioma

Epithelioid haemangioendothelioma (EH) is a malignant angiocentric vascular neoplasm composed of cords of epithelioid endothelial cells in a distinctive myxo-hyaline stroma. Thyroid EHs are malignant tumours that occur in a setting similar to that reported for angiosarcomas [36]. EHs are characterized by an epithelioid and spindle endothelial cell proliferation in a background of a chondromyxoid stroma. The tumour cells are atypical and disclose intracytoplasmatic lumina filled with red blood cells (Fig. 6.33). The immunohistochemical profile of angiosarcoma and EH is similar.

Angiosarcoma

Thyroid angiosarcoma is a malignant primary thyroid tumour showing evidence of endothelial cell differentiation [5, 21, 32]. It manifests usually as cold masses in elderly women with long-standing nodular goitre. The majority of angiosarcomas of the thyroid have been reported from European Alpine regions, linked to dietary iodine deficiency, but they can also occur outside those regions. Angiosarcoma usually presents as a painful, largely invasive and rapidly growing mass that causes pressure symptoms or as a metastatic disease. Thyroid angiosarcomas are similar microscopically to angiosarcomas of deep soft tissues (Figs. 6.34, 6.35 and 6.36). The immunohistochemical profile of thyroid angiosarcoma cells includes the expression of vascular markers such as CD31, ERG, CD34, FLI-1 and factor VIII and the expression of low molecular weight cytokeratins (Figs. 6.34 and 6.36). The expression of cytokeratins can be exuberant and often more extensive than the one observed in ATC. Differential diagnosis between angiosarcomas and ATC with angiomatoid features can be difficult, but immunohistochemical stains for endothelial markers usually solve the diagnostic dilemma. In the post-FNAB setting, a peculiar endothelial hyperplasia termed "worrisome alterations following fine needle aspiration of the thyroid" (WHAFFT) [33] may mimic malignancy, but this reactive lesion is well delimited, lacks cytologic atypia and lacks freely anastomosing vessels.

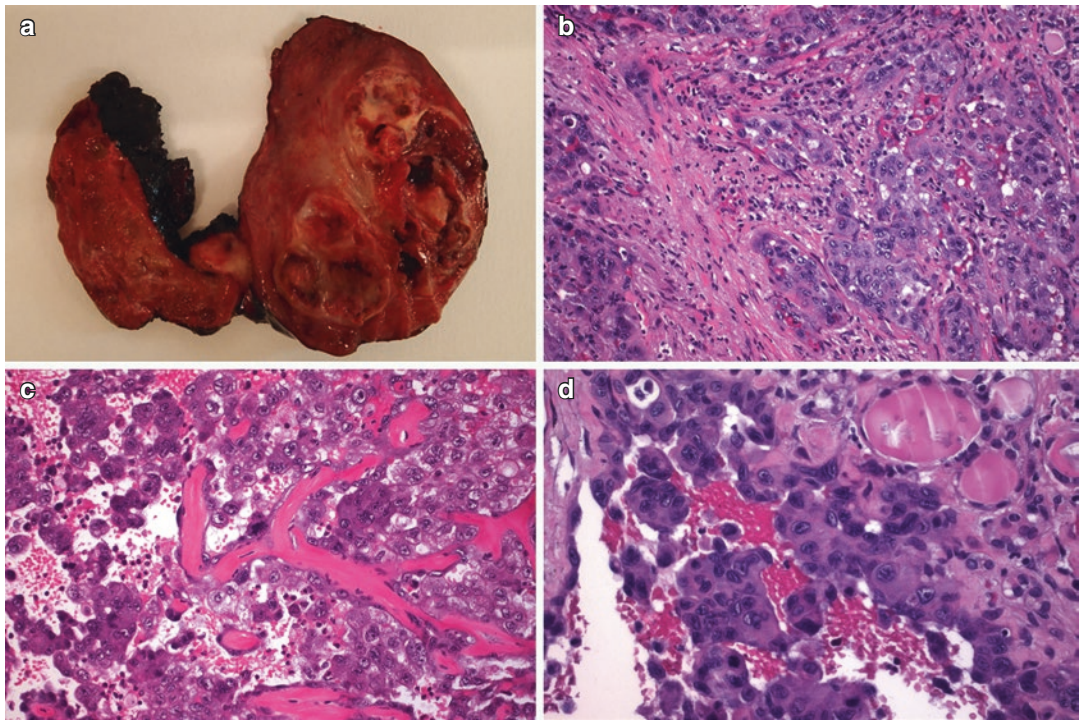

Fig. 6.34 Angiosarcoma. In this case of an 85-year-old man, the cut surface of the thyroidectomy specimen showed a tumour with cystic, haemorrhagic and necrotic areas (**a**). Microscopically, there was a sheet-like tumour cell growth mimicking undifferentiated carcinoma (**b**) and anastomosing channels containing papillary fronds lined by endothelial cells (**c**, **d**). The tumour cells had an epithelioid appearance with prominent nucleoli (**c**, **d**)

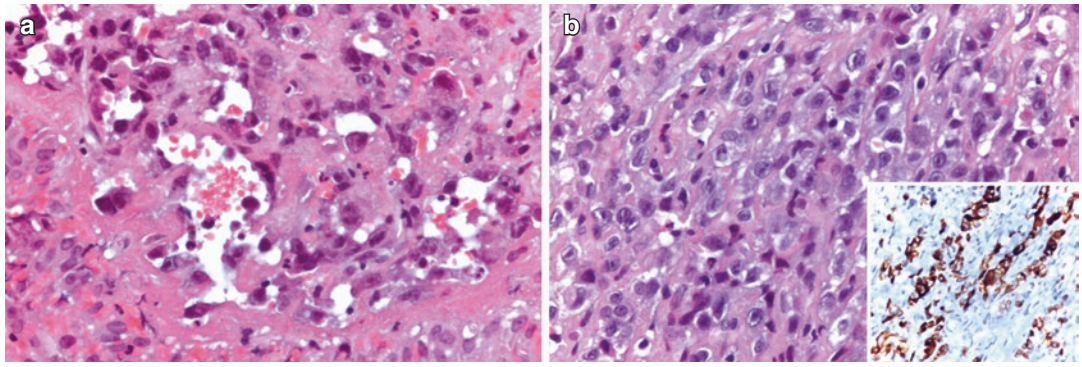

Fig. 6.35 Angiosarcoma. The anastomosing abnormal vascular channels (**a**) and the epithelioid solid pattern (**b**) of angiosarcoma of the thyroid are made of atypical cells displaying mitotic figures. The neoplastic cells are also positive for pankeratins with the clone AE1/AE3 (*inset*)

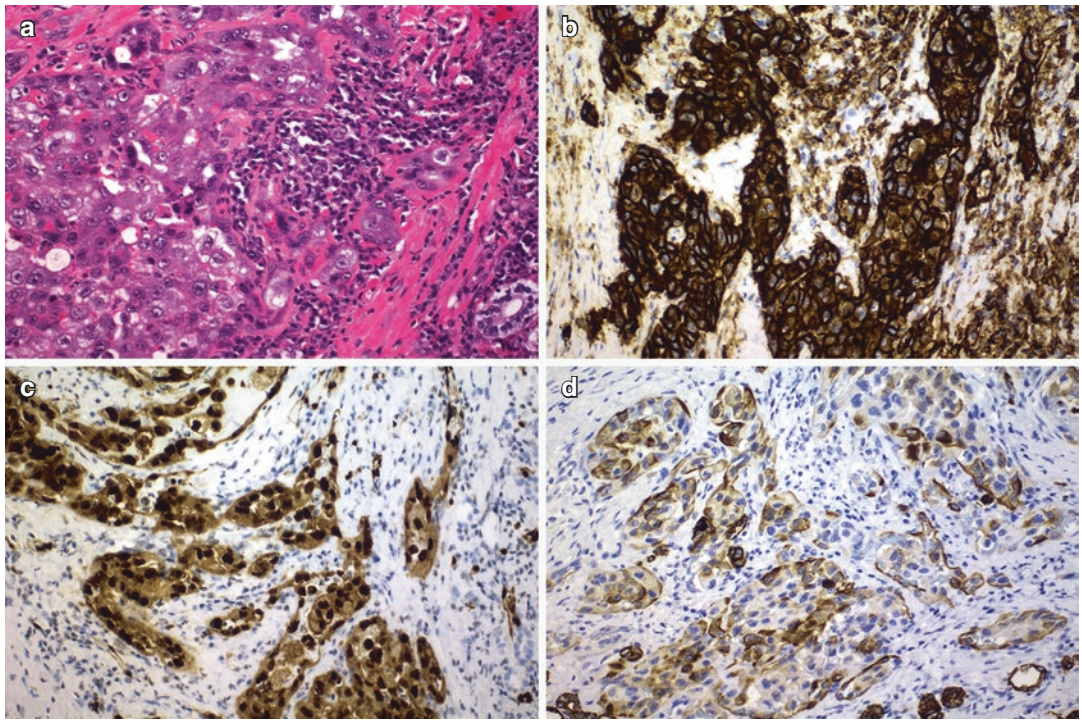

Fig. 6.36 Immunophenotype of angiosarcoma. Thyroid angiosarcomas (**a**–**d**) express the typical vascular markers: factor VIII related antigen, *Ulex europaeus* lectin receptors, CD34, FLI-1, CD31 (**b**) and ERG (**c**). Out of these markers, CD31, FLI-1 and ERG are regarded nowadays as the most useful for the immunohistochemical detection of endothelial differentiation. Angiosarcomas are also immunoreactive for pankeratins AE1/AE3 (**d**) and negative for thyroglobulin and TTF-1

Diffuse Lipomatosis

Diffuse lipomatosis (DL) of the thyroid is a rare condition characterized by diffuse infiltration of an otherwise normal thyroid by mature adipose tissue without evidence of encapsulation [34, 35] (Fig. 6.37). It presents as a diffuse or nodular goitre, with or without compressive symptoms. The patients may be euthyroid, hypothyroid or hyperthyroid. Thyroid DL must be distinguished from other lesions with adipose tissue content of the thyroid or of the neck, namely, adenolipoma, amyloid goitre, stromal adipose metaplasia, PTC with adipose stromal accumulation, benign and malignant adipocytic tumours and parathyroid tumours with adipose stroma. The infiltration of the neck by adipose tissue can also occur in multiple symmetric lipomatosis that can be associated with mitochondrial DNA mutations. The preoperative diagnosis by FNAB of this entity is difficult and may be helped by core needle biopsy.

The case illustrated in Fig. 6.36 presented a 47-year-old male with hypothyroidism and a slow-growing mass in the right region of the neck. Ultrasound examination disclosed a hypoechoic and heterogeneous mass in the right thyroid region that measured 15 × 6.5 × 4.9 cm. FNABs were repeatedly performed and were inconclusive. The patient underwent excision of the mass that weighted 250 g (Fig. 6.37). Histologically, the mass was composed by thyroid parenchyma composed by atrophic follicles extensively infiltrated by mature adipose cells without atypia. The immunohistochemical study of the expression of succinate dehydrogenase A (SDHA) highlighted the mitochondrial content in follicular cells while the study of succinate dehydrogenase B (SDHB) revealed loss of expression of this protein (Fig. 6.37). A large *SDHB* deletion was detected suggesting that the mitochondrial DNA alterations may be implicated in the genesis of diffuse lipomatosis of the thyroid, as it is in multiple symmetric lipomatosis of the neck.

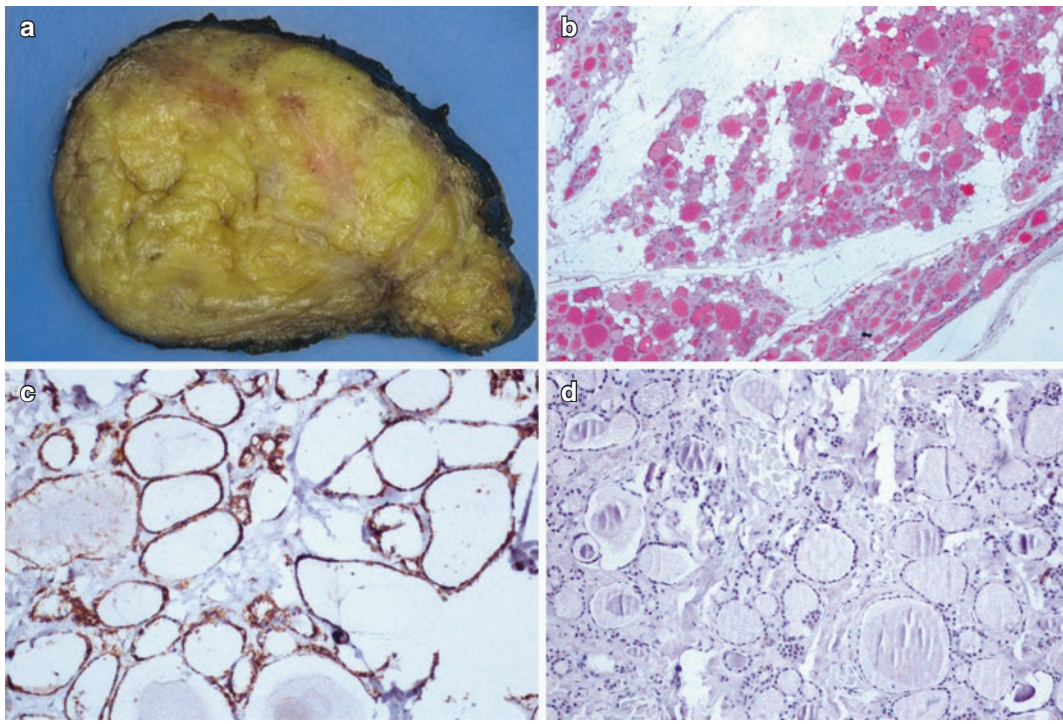

Fig. 6.37 Diffuse lipomatosis. Yellowish aspect of the specimen in a case of diffuse lipomatosis of the thyroid (**a**). Microscopically, the thyroid tissue was substituted by abundant mature adipose tissue (**b**). Expression of succinate dehydrogenase A (SDHA) protein was preserved (**c**) indicating the presence of a mitochondrial complex II whereas SDHB was not expressed (**d**) indicating a probable genetic alteration in this complex. See text

References

1. Harach HR, Vujanić GM, Jasani B. Ultimobranchial body nests in human fetal thyroid: an autopsy, histological, and immunohistochemical study in relation to solid cell nests and mucoepidermoid carcinoma of the thyroid. J Pathol. 1993;169(4):465–9.
2. Cameselle-Teijeiro J, Varela-Durán J, Sambade C, Villanueva JP, Varela-Núñez R, Sobrinho-Simões M. Solid cell nests of the thyroid: light microscopy and immunohistochemical profile. Hum Pathol. 1994;25(7):684–93.
3. Reis-Filho JS, Preto A, Soares P, Ricardo S, Cameselle-Teijeiro J, Sobrinho-Simões M. p63 expression in solid cell nests of the thyroid: further evidence for a stem cell origin. Mod Pathol. 2003;16(1):43–8.
4. Preto A, Cameselle-Teijeiro J, Moldes-Boullosa J, Soares P, Cameselle-Teijeiro JF, Silva P, Reis-Filho JS, Reyes-Santías RM, Alfonsín-Barreiro N, Forteza J, Sobrinho-Simões M. Telomerase expression and proliferative activity suggest a stem cell role for thyroid solid cell nests. Mod Pathol. 2004;17(7):819–26.
5. Rosai J, DeLellis RA, Carcangiu ML, Frable WJ, Tallini G. Tumors of the thyroid and parathyroid glands. AFIP atlas of tumor pathology. Series 4. Fascicle 21. Maryland: Silver Spring; 2014.
6. Cameselle-Teijeiro J, Ferreira R, Caramés N, Abdulkader I, Máximo V, Soares P, Sobrinho-Simões M. Absence of the BRAF and the GRIM-19 mutations in oncocytic (Hürthle cell) solid cell nests of the thyroid. Am J Clin Pathol. 2012;137(4):612–8.
7. Harach HR. Thyroid follicles with acid mucins in man: a second kind of follicles? Cell Tissue Res. 1985;242(1):211–5.
8. Asioli S, Erickson LA, Lloyd RV. Solid cell nests in Hashimoto's thyroiditis sharing features with papillary thyroid microcarcinoma. Endocr Pathol. 2009;20(4):197–203.
9. Caillou B. Ductal metaplasia in chronic lymphocytic thyroiditis as a manifestation of phylogenic regression to an exocrine structure. Am J Surg Pathol. 2006;30(6):774–81.
10. Ryska A, Ludvíková M, Rydlová M, Cáp J, Zalud R. Massive squamous metaplasia of the thyroid gland: report of three cases. Pathol Res Pract. 2006;202(2):99–106.
11. Nakazawa T, Kondo T, Oishi N, Tahara I, Kasai K, Inoue T, Mochizuki K, Katoh R. Branchial cleft-like cysts involving 3 different organs: thyroid gland, thymus, and parotid gland. Medicine (Baltimore). 2015;94(42):e1758.
12. Cameselle-Teijeiro J, Preto A, Soares P, Sobrinho-Simões M. A stem cell role for thyroid solid cell nests. Hum Pathol. 2005;36(5):590–1.
13. Ríos Moreno MJ, Galera-Ruiz H, De Miguel M, López MI, Illanes M, Galera-Davidson H. Immunohistochemical profile of solid cell nest of thyroid gland. Endocr Pathol. 2011;22(1):35–9.
14. Fellegara G, Dorji T, Bajineta MR, Rosai J. Images in pathology. "Giant" solid cell rest of the thyroid: a hyperplastic change? Int J Surg Pathol. 2009;17(3):268–9.
15. Cameselle-Teijeiro J, Abdulkader I, Pérez-Becerra R, Vázquez-Boquete A, Alberte-Lista L, Ruiz-Ponte C, Forteza J, Sobrinho-Simões M. BRAF mutation in solid cell nest hyperplasia associated with papillary thyroid carcinoma. A precursor lesion? Hum Pathol. 2009;40(7):1029–35.
16. Eloy C, Vinagre J, Cameselle-Teijeiro J, Paiva ME, Soares P, Sobrinho-Simões M. Tumor-in-tumor of the thyroid with basaloid differentiation: a lesion with a solid cell nest neoplastic component? Int J Surg Pathol. 2011;19(2):276–80.
17. Reimann JD, Dorfman DM, Nosé V. Carcinoma showing thymus-like differentiation of the thyroid (CASTLE): a comparative study: evidence of thymic differentiation and solid cell nest origin. Am J Surg Pathol. 2006;30(8):994–1001.
18. Cameselle-Teijeiro J, Caramés N, Romero-Rojas A, Reyes-Santías R, Piso-Neira M, Bernabeu I, Abdulkader I. Thyroid-type solid cell nests in struma ovarii. Int J Surg Pathol. 2011;19(5):627–31.
19. Cameselle-Teijeiro J, Abdulkader I, Soares P, Alfonsín-Barreiro N, Moldes-Boullosa J, Sobrinho-Simões M. Cystic tumor of the atrioventricular node of the heart appears to be the heart equivalent of the solid cell nests (ultimobranchial rests) of the thyroid. Am J Clin Pathol. 2005;123(3):369–75.
20. Abel TW, Curtis M, Lin DD, Burger PC, Cummings TJ. Complex choristoma of the gyrus rectus: a distinct clinicopathologic entity? Am J Surg Pathol. 2006;30(5):625–9.
21. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World health organization classification of tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2017.
22. Chan JK, Rosai J. Tumors of the neck showing thymic or related branchial pouch differentiation: a unifying concept. Hum Pathol. 1991;22(4):349–67.
23. Cheuk W, Jacobson AA, Chan JK. Spindle epithelial tumor with thymus-like differentiation (SETTLE): a distinctive malignant thyroid neoplasm with significant metastatic potential. Mod Pathol. 2000;13(10):1150–5.
24. Wang YF, Liu B, Fan XS, Rao Q, Xu Y, Xia QY, Yu B, Shi SS, Zhou XJ. Thyroid carcinoma showing thymus-like elements: a clinicopathologic, immunohistochemical, ultrastructural, and molecular analysis. Am J Clin Pathol. 2015;143(2):223–33.
25. Suzuki A, Hirokawa M, Takada N, Higuchi M, Yamao N, Kuma S, Daa T, Miyauchi A. Diagnostic significance of PAX8 in thyroid squamous cell carcinoma. Endocr J. 2015;62(11):991–5.
26. Cameselle-Teijeiro J, Manuel Lopes J, Villanueva JP, Gil-Gil P, Sobrinho-Simões M. Lipomatous haemangiopericytoma (adipocytic variant of solitary fibrous tumour) of the thyroid. Histopathology. 2003;43(4):406–8.

27. Cameselle-Teijeiro J, Ladra MJ, Abdulkader I, Eloy C, Soares P, Barreiro F, Sobrinho-Simões M, Beiras-Iglesias A. Increased lymphangiogenesis in riedel thyroiditis (immunoglobulin G4-related thyroid disease). Virchows Arch. 2014;465(3):359–64.
28. Schmitz BA, Singh C, Gulbahce HE, Manivel JC, Pambuccian SE. Florid capsular and pericapsular papillary endothelial proliferation associated with poorly differentiated thyroid carcinoma. Int J Surg Pathol. 2011;19(1):110–2.
29. Kumar R, Gupta R, Khullar S, Dasan B, Malhotra A. Thyroid hemangioma: a case report with a review of the literature. Clin Nucl Med. 2000;25(10):769–71.
30. Poniecka A, Ghorab Z, Arnold D, Khaled A, Ganjei-Azar P. Kaposi's sarcoma of the thyroid gland in an HIV-negative woman: a case report. Acta Cytol. 2007;51(3):421–3.
31. Cherqaoui R, Shakir KM, Shokrani B, Madduri S, Farhat F, Mody V. Histopathological changes of the thyroid and parathyroid glands in HIV-infected patients. J Thyroid Res. 2014;2014:364146.
32. Tanda F, Massarelli G, Bosincu L, Cossu A. Angiosarcoma of the thyroid: a light, electron microscopic and histoimmunological study. Hum Pathol. 1988;19(6):742–5.
33. LiVolsi VA, Merino MJ. Worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT). Pathol Annu. 1994;29(Pt 2):99–120.
34. Ge Y, Luna MA, Cowan DF, Truong LD, Ayala AG. Thyrolipoma and thyrolipomatosis: 5 case reports and historical review of the literature. Ann Diagn Pathol. 2009;13(6):384–9.
35. Lau E, Freitas P, Costa J, Batista R, Máximo V, Coelho R, Matos-Lima L, Eloy C, Carvalho D. Loss of mitochondrial SDHB expression: what is its role in diffuse thyroid lipomatosis? Horm Metab Res. 2015;47(3):165–7.
36. Egloff B. The hemangioendothelioma of the thyroid. Virchows Arch A Pathol Anat Histopathol. 1983;400(2):119–42.

Therapeutic Options

7

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Introduction

Taking care of patients with rare tumours of the thyroid gland is a clinical challenge. Some of the variants discussed in this book are known to be associated with a guarded prognosis, namely, with increased recurrence rate and disease-specific mortality. Nonetheless, the small number of cases precludes the design of clinical trials to assess if a specific therapeutic strategy is valuable for those patients. The clinical challenge increases when physicians treat patients with tumours that are considered to be 'the rarest of the rare', a situation in

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which much of the evidence comes from anecdotal case reports.

In general, the treatment of patients with rare thyroid tumours follows the same principles used to guide the treatment of all the patients with thyroid cancer. For follicular cell-derived thyroid carcinomas, surgery, radioiodine and suppressive levothyroxine treatment are the cornerstones of the therapeutic approach [1–4]. For C cell-derived thyroid carcinomas, surgery and replacement levothyroxine treatment are the usual initial approach [5]. In selected cases of both follicular cell-derived and C cell-derived carcinomas, external beam irradiation and chemotherapy may also play a role. In recent years, the use of tyrosine kinase inhibitors to treat progressive, radioiodine-refractory differentiated thyroid tumours has been increasing, and they are now recommended as a preferential option to treat patients with diffuse and progressive disease. Tyrosine kinase inhibitors have also been approved for the treatment of patients with progressive medullary thyroid carcinoma.

In this context, clinical guidelines and recommendations from different scientific societies advocate that the initial treatment should be based on a risk stratification that takes into consideration clinical, biochemical, histologic and radiologic factors. More recently, molecular alterations of tumours were added to refine risk assessment. Patients with a higher risk of recurrence or disease-specific mortality should be submitted to more aggressive treatments, including extensive surgery, postsurgical radioiodine treatment with higher activities and suppressive TSH treatment with levothyroxine. Some of the variants discussed in this book have been recognized as important determinants of risk and incorporated in clinical recommendations. In this chapter, from the previously discussed rare tumours, we will highlight those that have already been incorporated in clinical recommendations, as well as those that should be submitted to a specific treatment.

Hobnail Variant of Papillary Thyroid Carcinoma

The hobnail variant of papillary thyroid carcinoma (PTC) is associated with aggressive clinical behaviour, including increase in disease recurrence and more frequent local (70%) and distant (30%) metastases [6, 7]. The 2015 American Thyroid Association (ATA) guidelines include the hobnail variant of PTC in the intermediate risk of recurrence category and recommend that patients harbouring these tumours have a favoured indication for postsurgical radioiodine treatment. It is also suggested that higher activities of radioiodine should be used to treat these patients. After the initial treatment approach (surgery plus radioiodine), a close follow-up of patients with the hobnail variant of PTC is recommended, even if they are considered to be disease-free.

Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

This variant is characterized by a higher rate of local and distant metastases and a lower disease-free survival than classic PTC [8]. However, since this variant is mainly found in younger patients in whom response to treatment is high, the overall mortality is low, with a disease-specific survival of approximately 93% at 10 years of follow-up [9]. Patients with the diffuse sclerosing variant of PTC are included in the intermediate risk category of the ATA [1]; postsurgical radioiodine treatment is generally favoured in this group.

Oncocytic (Hürthle Cell) Carcinoma

It is possible that oncocytic carcinomas have a higher rate of recurrence and disease-specific mortality, but this issue is currently under debate

[10]. A possible explanation for the poorer outcome of patients with oncocytic carcinoma may be its lower ability to uptake radioiodine. From the biologic standpoint, it is now recognized that oncocytic carcinoma are distinct from other thyroid tumours because they harbour specific molecular alterations [11].

Cribriform-Morular Variant of Papillary Thyroid Carcinoma

Contrary to the aforementioned variants, the CMV of PTC seems to have a less aggressive behaviour than conventional PTC, being associated with a lower frequency of both local and distant metastases [12]. In accordance, the overall outcome is better, with lower rates of recurrence and disease-specific mortality. As discussed in Chap. 5, the CMV of PTC seems to be a distinct entity within the spectrum of thyroid carcinomas, with specific characteristics like the permanent activation of the WNT signalling pathway and high expression of oestrogen and progesterone receptors. In the future, the latter may be the target of therapies to be used in cases that are unresponsive to conventional therapy (surgery with or without radioiodine).

PTC with *TERT* Promoter Mutations (with or Without *BRAF* Mutations)

PTC harbouring *TERT* promoter (*TERTp*) mutations have been associated with aggressive clinicopathologic features, namely, larger size, older patients and distant metastases [13–15]. Of note, the relationship with distant metastases has been reproductively reported in the literature [16]. *TERTp* mutations have also been associated with disease persistence and increased disease-specific mortality. There is also evidence that tumours harbouring these mutations may be less responsive to radioiodine [17]. In some series, the prognosis of patients with tumours harbouring both *TERTp* and *BRAF* mutations was even worse than the prognosis of patients with a single-mutated tumour [18].

Poorly Differentiated Thyroid Carcinomas

The prognosis of poorly differentiated thyroid carcinomas is guarded, with a 10 years disease-specific survival rate of less than 50% [19, 20]. This is a heterogeneous group of tumours that generally occur in older people, progress rapidly and frequently present with local and distant metastases. Poorly differentiated thyroid carcinomas are usually radioiodine refractory. The treatment of these patients must be individually tailored to address patient's characteristics and may include a combination of treatment modalities, including surgery, radioiodine (when responsive), external beam irradiation and tyrosine kinase inhibitors.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
2. Pacini F, Castagna MG, Brilli L, Pentheroudakis G. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v214–9.
3. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154(6):787–803. Erratum in: Eur J Endocrinol. 2006;155(2):385
4. Melo M, Vicente N, Ventura M, Gaspar Da Rocha A, Soares P, Carrilho F. The role of ablative treatment

in differentiated thyroid cancer management. Expert Rev. Endocrinol Metab. 2017;12:109–16.
5. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG, American Thyroid Association Guidelines Task Force on Medullary Thyroid C. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610.
6. Asioli S, Erickson LA, Righi A, Lloyd RV. Papillary thyroid carcinoma with hobnail features: histopathologic criteria to predict aggressive behavior. Hum Pathol. 2013;44(3):320–8.
7. Lubitz CC, Economopoulos KP, Pawlak AC, Lynch K, Dias-Santagata D, Faquin WC, Sadow PM. Hobnail variant of papillary thyroid carcinoma: an institutional case series and molecular profile. Thyroid. 2014;24(6):958–65.
8. Koo JS, Hong S, Park CS. Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. Thyroid. 2009;19(11):1225–31.
9. Lam AK, Lo CY. Diffuse sclerosing variant of papillary carcinoma of the thyroid: a 35-year comparative study at a single institution. Ann Surg Oncol. 2006;13(2):176–81.
10. Chindris AM, Casler JD, Bernet VJ, Rivera M, Thomas C, Kachergus JM, Necela BM, Hay ID, Westphal SA, Grant CS, Thompson GB, Schlinkert RT, Thompson EA, Smallridge RC. Clinical and molecular features of Hurthle cell carcinoma of the thyroid. J Clin Endocrinol Metab. 2015;100(1):55–62.
11. Maximo V, Lima J, Prazeres H, Soares P, Sobrinho-Simoes M. The biology and the genetics of Hurthle cell tumors of the thyroid. Endocr Relat Cancer. 2016;23(12):R131–47.
12. Lam AK, Saremi N. Cribriform-morular variant of papillary thyroid carcinoma: a distinctive type of thyroid cancer. Endocr Relat Cancer. 2017;24(4):R109–21.
13. Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, Celestino R, Almeida A, Salgado C, Eloy C, Castro P, Prazeres H, Lima J, Amaro T, Lobo C, Martins MJ, Moura M, Cavaco B, Leite V, Cameselle-Teijeiro JM, Carrilho F, Carvalheiro M, Maximo V, Sobrinho-Simoes M, Soares P. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab. 2014;99(5):E754–65.
14. Vinagre J, Almeida A, Populo H, Batista R, Lyra J, Pinto V, Coelho R, Celestino R, Prazeres H, Lima L, Melo M, Rocha AG, Preto A, Castro P, Castro L, Pardal F, Lopes JM, Santos LL, Reis RM, Cameselle-Teijeiro J, Sobrinho-Simoes M, Lima J, Maximo V, Soares P. Frequency of TERT promoter mutations in human cancers. Nat Commun. 2013;4:2185.
15. Liu R, Xing M. TERT promoter mutations in thyroid cancer. Endocr Relat Cancer. 2016;23(3):R143–55.
16. Gandolfi G, Ragazzi M, Frasoldati A, Piana S, Ciarrocchi A, Sancisi V. TERT promoter mutations are associated with distant metastases in papillary thyroid carcinoma. Eur J Endocrinol. 2015;172(4):403–13.
17. Yang X, Li J, Li X, Liang Z, Gao W, Liang J, Cheng S, Lin Y. TERT promoter mutation predicts radioiodine refractory in distant metastatic differentiated thyroid cancer. J Nucl Med. 2017;58(2):258–65.
18. Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, Pai S, Bishop J. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol. 2014;32(25):2718–26.
19. Ibrahimpasic T, Ghossein R, Carlson D, Nixon I, Palmer F, Shaha A, Patel S, Tuttle R, Shah J, Ganly I. Outcomes in patients with poorly differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2014;99(4):1245–52.
20. Eloy C, Ferreira L, Salgado C, Soares P, Sobrinho-Simoes M. Poorly differentiated and undifferentiated thyroid carcinomas. Turk Patoloji Derg. 2015;31(Suppl 1):48–59.

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