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Augusto Vaglio *Editor*

Systemic Fibroinflammatory Disorders

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To my sweet family

Contents

Introduction to Fibroinflammatory Diseases

The term *fibroinflammatory disorders* may be vague, as many conditions – idiopathic, infectious, neoplastic, or reactive – show histopathological evidence of fibrosis and inflammation. In addition, fibrosis is commonly considered to be a reparative response to inflammation, thus it is not surprising that these two processes partially overlap and that they can coexist in pathological samples of a variety of different disorders. However, there are specific conditions, affecting almost every organ, whose pathology is hallmarked by chronic inflammation and an exuberant fibrotic component. The label of *fibroinflammatory* conditions is therefore used in such cases to describe disorders to which the current paradigm considering fibrosis as a physiological response to inflammation does not necessarily apply. The pathology of such disorders is *dominated* by fibrosis, which often accompanies chronic inflammation and is therefore likely to represent an exuberant (rather than a physiological) response to inflammation. The clinical features of these diseases are often the consequence of this abnormal fibrosing response: they usually present with pseudotumoral, mass-forming lesions that infiltrate neighbouring structures. The fibroinflammatory infiltrate also tends to replace the normal parenchyma, thus leading to organ dysfunction [1].

The prototype of fibroinflammatory disorders is the so-called IgG4-related disease (IgG4-RD), an often systemic condition characterized by tissue infiltration by $IgG4^+$ plasma cells, abundant fibrosis with a storiform pattern, obliterative phlebitis, and frequent tissue eosinophilia. Chronic inflammation in IgG4-RD lesions is often organized in lymphoid aggregates with germinal centers, a finding commonly encountered in chronic autoimmune diseases [2]. Typical examples of IgG4-RD lesions include "autoimmune" pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, orbital pseudotumor, and chronic sialoadenitis (Mikulicz's disease).

However, the term IgG4-RD has not completely replaced the traditional nomenclature of these conditions. As a matter of fact, only those forms bearing infiltrates extremely rich in $IgG4^+$ plasma cells (or showing high serum IgG4 levels) and showing the aforementioned histopathological features should go under the umbrella IgG4-RD, whereas the rest of them are classified according to traditional definitions. The proportion of IgG4-related vs. IgG4-unrelated forms varies depending on the affected sites. For example, Riedel's thyroiditis, whose histopathology often fits the picture of an IgG4-related lesion, only occasionally shows $IgG4^+$ infiltrates,

whereas Hashimoto's thyroiditis more frequently shows IgG4-rich inflammation [3]. Likewise, retroperitoneal fibrosis is IgG4-related in less than 50 % of the cases, [1, 4, 5] while chronic sclerosing pancreatitis (now called type I autoimmune pancreatitis) is quite commonly IgG4-related [6]. In essence, it is very likely the conditions we deal with are part of a *disease continuum* with common histopathological features, with IgG4-RD representing one end of the spectrum. One of the major objectives of this textbook is indeed to redesign a correct nosology for these disorders; understanding the boundaries between IgG4-related and IgG4-unrelated forms is certainly difficult but could prove helpful to better capture the different etiologies and pathogenetic mechanisms underlying these diseases.

Beyond their micro- and macroscopic histopathological similarities, the different *fibroinflammatory disorders* also share clinical aspects. First, they can occur as organ-limited lesions but also overlap in the setting of a systemic condition, which is named IgG4-RD when the clinical, serological, and histological criteria for IgG4-RD are met, or "multifocal fibrosclerosis" when they are IgG4-unrelated. More intriguingly, most of these conditions can be associated with autoimmune disorders, either organ-limited or systemic. This is the case of retroperitoneal and mediastinal fibrosis, which have frequently been described in association with connective tissue disorders and systemic vasculitis, particularly antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and different types of glomerulonephritis [7]. This is an important message for the clinician, who should always treat these conditions as *potentially systemic* disorders.

The idea of an autoimmune origin behind this disease spectrum is also supported by other findings. Many fibroinflammatory disorders have documented associations with HLA polymorphisms, particularly of the HLA class II region [8]. An association with HLA variants is traditionally considered a hallmark of autoimmune diseases. In addition, some of these conditions are characterized by the presence of circulating autoantibodies: this is the case of antithyroperoxidase and antithyroglobulin antibodies in Hashimoto's thyroiditis, and antibodies against the plasminogen-binding protein of *Helicobacter pylori* in type I autoimmune pancreatitis [9]. Finally, as mentioned above, some of these diseases show histopathological evidence of ectopic lymphoneogenesis, a clear histopathological sign of chronic autoimmune diseases, also seen in prototypical autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus [2].

Although it appears clear that fibroinflammatory disorders have an immune-mediated pathogenesis, their exact pathogenic mechanisms are far from being elucidated. Disease-specific mechanisms certainly exist, but common traits can also be found. All these diseases histologically show infiltrates rich not only in plasma cells but also in T- and B-cells. $CD4^+$ cells are particularly enriched, and T-helper (Th) polarization studies showed Th2-skewed responses and regulatory T cell (Treg)-rich infiltrates. This has been demonstrated in IgG4-related lesions (particularly pancreatocholangitis) [10] but also in non-IgG4 related cases of retroperitoneal fibrosis, where Th2-responses also induce the secretion of chemokines such as eotaxin/CCL11, which in turn drive the recruitment of eosinophils and mast cells [11]. Interestingly, cytokines involved in Th2-responses such as interleukin(IL)-4, IL-5,

IL-10, and IL-13 also contribute to the switch from the production of IgG1 to IgG4 [12]. Such responses are usually associated with a "reparative" phenotype, i.e., they usually turn off effector responses and promote fibrosis. Notably, increased expression of the profibrotic mediator TGF-β was also detected in chronic pancreatocholangitis [10]. Nevertheless, the mechanisms regulating the impressive fibrogenic response in these disorders are obscure.

Despite the heterogeneous clinical presentation and the likely presence of distinct pathogenic mechanisms, many – albeit not all – fibroinflammatory diseases respond to common therapeutic strategies. Most of them are indeed steroid-sensitive diseases: this is particularly the case of chronic pancreatitis, cholangitis, sialoadenitis, lymphadenopathy, retroperitoneal, and mediastinal fibrosis [7, 13]. In some instances, drugs with potential antifibrotic and immunomodulatory properties such as tamoxifen have been shown to have therapeutic efficacy [14]. Conventional immunosuppressants such as methotrexate, cyclophosphamide, azathioprine, and mycophenolate mofetil are also widely used, [15] although the data are scarce and prospective studies are lacking. These findings are interesting as they confirm the hypothesis that common pathogenic mechanisms regulate this wide spectrum of diseases; to further corroborate this view is the observation that even "targeted" therapies such as the B-cell depleting antibody rituximab work in these conditions, as shown in patients with mediastinal and retroperitoneal fibrosis (either IgG4-related or not) and in those with full-blown IgG4-RD [16–18].

Significant advances have indeed been made in the field of fibroinflammatory diseases, particularly in the last two decades. However, their recognition remains challenging mainly due to their rarity, their puzzling clinical presentation, and the paucity (or absence in most cases) of diagnostic biomarkers. A wide variety of disorders with a strong fibroinflammatory accent but with definite etiology (e.g., malignant neoplasms, systemic histiocytoses, drug-induced fibrosing lesions, nephrogenic fibrosis) must be considered in the differential diagnosis.

This textbook offers a novel view on a group of rare disorders that share histopathological, pathogenetic, and clinical aspects, and whose common denominator is an abnormal fibrosing response that accompanies chronic inflammation. The authors of the different chapters are true experts in the field, and were able to accumulate over the past few years a considerable experience with fibroinflammatory diseases. They should be commended for their excellent contributions and for providing the readers with clear and easy-to-read reviews of the basic and clinical aspects of this enigmatic clinical spectrum.

Parma, Italy — Augusto Vaglio, MD, PhD
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Genetics of Fibroinflammatory Disorders

1

Davide Martorana, Francesco Bonatti, and Javier Martin

1.1 Introduction

Fibro-inflammatory disorders (FIDs) are a group of rare heterogeneous diseases dominated by inflammation and fibrosis and are frequently considered to be autoimmune conditions. FIDs may cause early mortality, organ failure, and chronic morbidity.

The causes of FIDs are unknown; they may be considered multifactorial diseases, because multiple genetic factors, combined with several environmental factors, influence susceptibility to their development and modulate their phenotypes. Ethnicity affects some types of FIDs, in fact several studies describe differences in disease incidence and phenotypes across populations. In this chapter, genetic aspects of FIDs will be discussed.

1.2 Familial Cases

In the era of the *-omics*, family history is still important, because it may represent the only indicator of a possible heritability in complex diseases [1].

The etiology of FID seems to involve both genetic susceptibility factors and environmental triggers. So far, very few familial cases have been described, suggesting that genetics has a low impact in the development of these disorders but

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raising the possibility that shared genetic factors between relatives (even if they have never been demonstrated) may contribute to the disorders.

Idiopathic retroperitoneal fibrosis (IRF) is a prototypical FID, with some familial cases reported; in 1973 a West Indian Black family with three siblings has been described [2]. Consanguinity was not reported; they also had sickle-cell trait (heterozygous hemoglobinopathy). The presence of IRF was demonstrated at laparotomy in two of the three siblings, while the third member of the family showed early radiological features of the disease.

A second case of familial IRF has been described in 1978 [3]. The individual was a black man, HLA-B27 positive. Being the HLA-B27 gene present in only 4% of black subjects, the authors suggested the HLA-B27 antigen as a possible susceptibility factor for IRF. However, this was not confirmed by other immunogenetic studies involving sporadic cases [4, 5]. Other IRF familial cases have been described, but unfortunately no genetic investigation was performed [6–8].

A Japanese family with two siblings affected by type 1 autoimmune pancreatitis (AIP) has been described [9]. The two male siblings showed characteristic IgG4-related sialoadenitis and retroperitoneal fibrosis but not high serum IgG4 concentration. In this case no genetic risk factors have been described.

Another family presenting the cases of two HLA identical siblings both DRB1*1501 positive exhibiting features of IgG4-associated cholangitis together with ulcerative colitis was reported. IgG4-associated cholangitis is known to be associated with AIP, but an association with inflammatory bowel disease (IBD) has not yet been described [10].

In order to further elucidate genetic background at the basis of FIDs, more familial cases need to be searched and investigated. New technologies, in particular next-generation sequencing, will be of great utility in this field.

1.3 Genetic Association Studies and Candidate Gene Studies: General Features

Genetic association studies typically investigate alleles conferring increased or decreased risk to the development of multifactorial disorders; in some cases a candidate gene approach can be chosen, investigating all the gene variants belonging to a specific biological pathway or with similar biological function. Candidate gene selection implies an *a priori* knowledge of the biological genes/pathways involved in the disease of interest. In some cases, not only a polymorphism but a mutation is involved in the development of the disease.

Genetic association studies are useful in order to investigate the presence of candidate genes or genomic regions associated with a given disorder [11]. Association studies can identify genetic markers conferring susceptibility to complex disorders. The term “complex” means that both genetic and environmental factors contribute to the risk of developing the disease. Genetic studies for many complex disorders (such as diabetes, heart disease, autoimmune diseases) demonstrate that many

different genetic variants influence disease risk, with each variant contributing only a small effect to the final phenotype.

In the pre-candidate gene approach era, several other methods were chosen to identify gene variants related to a specific disease; these methods were, for example, genetic linkage and positional cloning. Unfortunately, these methods were not useful with complex disorders, primarily because familial cases are rare; moreover, they are influenced by the age of onset and the severity of the disease and are not ideal for complex diseases, since they frequently involve different biological pathways.

In complex diseases, the most investigated genetic markers are single-nucleotide polymorphisms (SNP); differences in allele or genotype frequencies between patients with a given disease and control subjects can suggest that the studied variant increases the risk to develop the disease. SNPs are the most widely tested markers in case–control association studies, but recently also copy-number variants (CNVs) have been largely investigated, demonstrating their potential in the susceptibility to complex diseases [12].

Genome-wide association studies (GWAS) are case–control studies and currently represent a significant proportion of large-scale genetic association studies. In addition to GWAS, other approaches to genetic association include family-based association studies and quantitative trait locus studies.

Associations with polymorphisms in candidate genes have been confirmed in many different diseases [13] and GWAS; frequently, novel associations in genes that had not been previously hypothesized a priori have been demonstrated [14].

At statistical level, the small increase in susceptibility implies that large studies (of thousands of subjects) are required to detect and confirm genetic association.

The study design more often used to test for association is the case–control study, in which a cohort of subjects with the disease of interest is compared with a population of controls without that specific disorder. A well-defined identification of the disease phenotype is important in order to limit confounding factors, and applying strict clinical criteria is necessary to ensure homogeneous cohorts of patients. A screening with unaffected controls will have higher power to detect associations as compared with a study using population-based controls.

A more comprehensive and unbiased case–control approach is to employ markers encompassing the entire genome. These types of studies are named "hypothesis-free," because no prior knowledge is necessary in order to design the study. High-throughput genotyping microarrays have decreased the costs of genotyping in a whole genome scale. With this study design, several GWAS for complex diseases have recently been completed [15, 16]. The availability of genetic information in online databases allows researchers to examine existing data and web-based resources for new candidate genes. In recent years, several free online databases have become available [17, 18].

With the recent progress in the sequencing of both whole exome and genome, candidate gene studies may be overcome; nevertheless, large association studies and sequencing studies may be complementary, because they generate different information.

1.4 HLA Associations with Fibro-inflammatory Diseases

The mechanism by which exposure to environmental factors that cause no symptoms in a large proportion of the population leads to severe disease in a small subgroup is unknown. Evidences from several genetic studies demonstrated the importance of the HLA system in the predisposition of humans to FIDs, even if non-HLA genes may modulate the phenotype of these disorders. Identifying putative causal variants within this genetic background is challenging, because of the strong linkage disequilibrium and high SNP density in the HLA region.

Several possible mechanisms have been postulated to explain the link between specific HLA and the susceptibility to complex disorders. These hypotheses are based on the interaction between specific epitopes and environmental factors such as viruses, toxins, or other foreign substances. At the HLA level, one of the most studied FIDs is primary sclerosing cholangitis (PSC) (Table 1.1).

The first GWAS in PSC was performed in 2010, genotyping 443,816 SNPs in 285 Norwegian patients and 298 controls. Results from this discovery cohort were replicated in subjects from Scandinavia (137 cases and 368 controls), Belgium/the Netherlands (229 cases and 735 controls), and Germany (400 cases and 1832 controls). The strongest association identified was close to the HLA-B locus (SNP rs3099844). In non-HLA regions, genes involved in bile homeostasis and other inflammatory conditions were demonstrated to be associated with PSC [19].

In 2011 a GWAS of 2,466,182 genotyped SNPs in PSC patients was performed. The population studied consisted of 715 patients and 2,962 controls, followed by replication in 1,025 cases and 2,174 controls. No HLA regions were identified as disease associated, while non-HLA associations at rs3197999 in MST1 and rs6720394 near BCL2L11 were demonstrated [20].

After the first GWASs, replication studies of the most significant SNPs in other cohorts have been performed. In a single study, 45 SNPs in 1221 PSC cases and 3508 controls were analyzed. The results have been compared in a meta-analysis with previous studies, with 1936 PSC cases and 6470 controls. Furthermore, the researchers analyzed bile microbial community composition in 39 PSC patients by 16S rRNA sequencing. *FUT2* gene rs602662 SNP in the chromosome 19q13 was able to influence susceptibility to infectious agents. As a result, multiple new PSC risk loci were demonstrated [21].

In 2013, in a large multicenter study, 3,789 PSC cases of European ancestry and 25,079 controls were compared, genotyping 130,422 SNPs using Immunochip platform. Twelve genome-wide significant associations outside the HLA complex were demonstrated; association of nine of them was described for the first time, increasing the number of the associated loci. Six of the 12 loci are shared with inflammatory bowel disease, suggesting an overlap between these two disorders [22].

Genetic studies performed in PSC have suggested to stratify patients in four pathogenic groups, depending on inflammation, cholangiocyte function, fibrosis, and carcinogenesis. This subclassification promises to be an important tool in the management of patients in the clinic and in the development of new potential treatments [34].

Table 1.1 Genetic association studies providing statistically significant associations of gene variants with fibro-inflammatory disorders

Gene/locus and variation/allele	Population	Cases	Controls	Odds ratio	P-Value	Reference
HLA-B (rs3099844)	Norwegian	285 PSC	298	4.8	2.6×10^{-26}	Karlsen et al. [19]
GPC6 (rs9524260)	Norwegian	285 PSC	298	0.67	8.1×10^{-04}	Karlsen et al. [19]
MST1 (rs3197999)	[a]From four geographic regions	1,740 PSC	5,136	1.39	1.1×10^{-16}	Melum et al. [20]
BCL2L11 (rs6720394)	[a]From four geographic regions	1,740 PSC	5,136	1.29	4.1×10^{-08}	Melum et al. [20]
FUT2 (rs602662)	–	1,936 PSC	6,470	Not available	1.9×10^{-06}	Folseraas et al. [21]
MMEL1 (rs3748816)	European Ancestry	3,789 PSC	25,079	1.21	7.41×10^{-12}	Liu et al. [22]
2q33 (rs7426056)	European Ancestry	3,789 PSC	25,079	1.3	1.89×10^{-20}	Liu et al. [22]
MST1 (rs3197999)	European Ancestry	3,789 PSC	25,079	1.33	2.45×10^{-26}	Liu et al. [22]
4q27 (rs13140464)	European Ancestry	3,789 PSC	25,079	1.3	8.87×10^{-13}	Liu et al. [22]
6q15 (rs56258221)	European Ancestry	3,789 PSC	25,079	1.23	8.36×10^{-12}	Liu et al. [22]
10p15 (rs4147359)	European Ancestry	3,789 PSC	25,079	1.24	8.19×10^{-17}	Liu et al. [22]
PPP2R1B (rs7937682)	European Ancestry	3,789 PSC	25,079	1.17	3.17×10^{-09}	Liu et al. [22]
HDAC7 (rs11168249)	European Ancestry	3,789 PSC	25,079	1.15	5.49×10^{-09}	Liu et al. [22]
SH2B3 (rs3184504)	European Ancestry	3,789 PSC	25,079	1.18	5.91×10^{-11}	Liu et al. [22]
CD226 (rs1788097)	European Ancestry	3,789 PSC	25,079	1.15	3.06×10^{-08}	Liu et al. [22]
PRKD2 (rs60652743)	European Ancestry	3,789 PSC	25,079	1.25	6.51×10^{-10}	Liu et al. [22]
21q22 (rs2836883)	European Ancestry	3,789 PSC	25,079	1.28	3.19×10^{-17}	Liu et al. [22]
MMP-2 (rs243865)	–	132 PSC	Not available	Not available	0.031	Liu et al. [22]
GPR35 (rs3749171)	Northern European Ancestry	1,012 PSC	11,659	1.39	3.0×10^{-09}	Ellinghaus et al. [23]
TCF4 (rs1452787)	Northern European Ancestry	1,012 PSC	11,659	0.75	2.61×10^{-08}	Ellinghaus et al. [23]

(continued)

Table 1.1 (continued)

Gene/locus and variation/allele	Population	Cases	Controls	Odds ratio	P-Value	Reference
TGR5 (rs11554825)	Norwegian	1,109 PSC	3,593	1.14	0.010	Hov et al. [24]
KIAA1109 (rs13151961)	Caucasian	41 PSC	1,487	0.34	0.013	Stallhofer et al. [25]
KIAA1109 (rs13119723)	Caucasian	41 PSC	1,487	0.40	0.023	Stallhofer et al. [25]
IL21-AS1 (rs6840978)	Caucasian	41 PSC	1,487	0.46	0.043	Stallhofer et al. [25]
*HLA-DRB1*0405*	Japanese	40 AIP	201	4.97	2.9×10^{-06}	Kawa et al. [26]
*HLA-DQB1*0401*	Japanese	40 AIP	201	5.12	2.0×10^{-06}	Kawa et al. [26]
*HLA-DRB1*0405*	Japanese	43 AIP	213	3.20	6.3×10^{-05}	Ota et al. [27]
*HLA-DQBI*0401*	Japanese	43 AIP	213	3.29	4.6×10^{-05}	Ota et al. [27]
ABCF1 (C3-2-11 microsatellite, allele 219)	Japanese	43 AIP	213	2.96	0.0076	Ota et al. [27]
FCRL3-110	Japanese	59 AIP	97	7.45	0.012	Umemura et al. [28]
CTLA4 (49A)	Chinese	46 AIP	200	7.20	0.0001	Chang et al. [29]
CTLA4 (−318C/+49A/ CT60G)	Chinese	46 AIP	200	8.53	0.001	Chang et al. [29]
CTLA4 (+6230 G/G)	Japanese	59 AIP	102	2.48	0.011	Umemura et al. [30]
HLA-A2	Caucasian	19 MF	21,086	3.32	0.027	Peebles et al. [31]
*HLA-B*08*	Italian	35 CP	350	3.08	0.026	Martorana et al. [4]
*HLA-DRB1*03*	Italian	35 CP	350	3.18	0.0012	Martorana et al. [4]
CCL11 (haplotype TTCCAT)	Italian	142 CP	214	NA	0.00048	Mangieri et al. [32]
CCR5 (Δ32)	Italian	100 CP	180	2.8	0.017	Boiardi et al. [33]
*DRB1*1501*	–	Two Identical siblings (IAC)	No controls	Not available	Not available	Dastis et al. [10]

IAC IgG4-associated cholangitis, *PSC* primary sclerosing cholangitis, *AIP* autoimmune pancreatitis, *CP* chronic periaortitis, *MF* mediastinal fibrosis, *PSC* primary sclerosing cholangitis, *EA* European–American

[a]Scandinavia, Germany, Central Europe, United States

Based on the data that increased IgG4 serum levels have been reported in 9–15 % of patients with PSC, a genetic analysis of the HLA complex was performed in patients from Norway, Sweden, and the United States. The authors found that in patients with low IgG4 level, a diminished frequency of the HLA-B*08 and increased frequencies of HLA-B*07 and HLA-DRB1*15 were shown, suggesting HLA complex may influence the expression of IgG4 levels [35].

Autoimmune pancreatitis (AIP), a distinct disease entity whose type 1 subtype is characterized by high serum immunoglobulin G4 concentrations and tissue infiltration by IgG4+ plasma cells, has been investigated in Japanese patients. HLA-A, −B, −C, −DR, and -DQ gene typing and HLA-DRB1, −DQB1, and −DPB1 allele typing were performed in 40 patients compared with 201 controls. The authors found a significant association with DRB1*0405 and DQB1*0401 alleles and with the DRB1*0405-DQB1*0401 haplotype [26].

The same authors, 5 years later, investigated more deeply the HLA region in 43 AIP Japanese patients and 213 controls. The HLA-associated regions were restricted to HLA-DRB1*0405-DQB1*0401 in the HLA class II and ABCF1 proximal to C3-2-11, telomeric of HLA-E in the HLA class I regions [27].

In 2010, the role of single HLA genes in the development of AIP in transgenic mice was studied. HLA-DR*0405 transgenic mice developed AIP, whereas HLA-DR*0401, HLA-DQ8, and HLA-DR*0405/DQ8 transgenic controls did not. At the tissue level, the pancreas in HLA-DR*0405 transgenic mice showed destructive infiltration of the exocrine tissue with CD4(+) and CD8(+) T cells, B cells, and macrophages. Furthermore, mice with complete pancreatic atrophy lost weight, developed fatty stools, and had reduced levels of serum lipase activity. Finally, HLA-DR*0405 expression failed to protect mice from AIP. As a result, the HLA-DRB1*0405 allele was suggested to represent an important risk factor for AIP on the HLA-DRB1*0405-DQB1*0401 haplotype [36].

In a study of 40 AIP patients, genetic predictors of relapse were evaluated. The substitution of aspartic acid with another residue in position 57 of HLA-DQB1 showed a significant association with relapse of AIP, concluding that DQB57 may be an important genetic factor for relapse of AIP [37].

In chronic periaortitis (CP), a disease spectrum encompassing idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysms, genetic association studies are difficult to perform because of the low incidence of the disease. The largest HLA study was performed in 35 Italian patients compared with 350 controls [4]. The results showed an increased HLA-DRB1*03 and HLA-B*08 allele frequencies in CP patients as compared with controls. These two alleles are linked to several autoimmune disorders, adding further evidence to the autoimmune origin of CP. This study needs to be replicated in larger populations, also in order to stratify the disease in different subsets.

In addition, a study that analyzed the perianeurysmal forms of the disease (i.e., inflammatory abdominal aortic aneurysms) found the HLA-DRB1 as a genetic risk factor. The HLA-DRB1*15 and DRB1*0404 alleles were described as predisposing alleles [38, 39]. Taken together, these findings provide evidence for a role of the HLA system in conferring susceptibility to CP.

The HLA locus was also investigated in mediastinal fibrosis. Nineteen Caucasian patients were compared with 21,086 white controls (kidney donors). The authors found a statistically significant association with the HLA-A2 gene. Several diseases have been associated with this gene, such as rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis. Given the high prevalence of the HLA-A2 in the general population, the predictive value of this finding in the susceptibility to the disease is low [31].

1.5 Associations with Non-HLA Genetic Variants

Non-HLA genes have been poorly investigated in FIDs, because of the genetic heterogeneity of these diseases (Table 1.1).

In PSC, several genetic polymorphisms have been investigated. Matrix metalloproteinase-2 (−1306 C/T) and MMP-9 (−1562 C/T) gene promoter polymorphisms have been investigated in 132 PSC patients in a recent study, relating them to the severity of the disease [40]. MMP-9 genotype was demonstrated not to be associated with disease severity in PSC, while MMP-2 1306C>T gene promoter polymorphism has been postulated as an independent risk factor for PSC disease severity.

In a large GWAS, the authors investigated a first cohort of 392 PSC patients and 987 ulcerative colitis (UC) patients, compared with 3000 controls; the results were replicated in a cohort of 1,012 PSC patients, 4,444 UC patients, and 11,659 controls. Two novel SNPs were found to be disease associated: rs3749171 at 2q37 located in the G-protein-coupled receptor 35 (GPR35) gene and rs1452787 at 18q21 located in the transcription factor 4 (TCF4) gene. The first SNP causes a threonine to methionine amino acid change. Structural model showed that this SNP may alter the efficiency of signaling through the GPR35 receptor. GPR35 shows associations with both UC and PSC, while TCF4 SNP is a PSC risk locus not associated with UC. This study elucidated the difference in the genetic background between PSC and UC [23].

Based on the findings of previous studies, the TGR5 gene was investigated in PSC patients. TGR5 is a G-protein-coupled bile acid receptor 1 (GPBAR1), already linked to inflammatory pathways. The authors sequenced the TGR5 gene in 267 PSC patients and 274 healthy controls. Furthermore, they functionally analyzed the discovered variants, finding six nonsynonymous DNA variants linked to the disease. In a functional study using confocal microscopy, flow cytometry, and a cAMP-sensitive luciferase assay, a receptor model was studied, introducing the mutated TGR5 constructs into human epithelial cell lines. Five nonsynonymous variants (W83R, V178M, A217P, S272G, and Q296X) were found to reduce or abolish TGR5 function. This study demonstrated that TGR5 gene may represent a strong candidate gene for PSC [24]. The TGR5 gene maps to the chromosome 2q35, close to the rs3749171 SNP (located in 2q37), previously associated in a large GWAS [41].

The IL-2/IL-21 region was also investigated in PSC, because this region has been previously associated with UC and several autoimmune diseases. Four SNPs in the KIAA1109/TENR/IL-2/IL-21 linkage disequilibrium block were genotyped in 41

PSC subjects. The minor alleles of all four markers were associated with a decreased susceptibility to PSC. A haplotype of the four major alleles was independently associated with PSC when excluding the patients with concomitant inflammatory bowel disease. The authors concluded the IL-2/IL-21 region may be a susceptibility factor of PSC [25].

Another investigated condition was AIP. A group of genes called Fc receptor-like genes (FCRLs), which have high structural homology with classical Fc receptor genes, has been shown to be associated with several autoimmune diseases, such as rheumatoid arthritis, autoimmune thyroid disease, and systemic lupus erythematosus in Japanese populations; the authors found the FCRL3-110 alleles are related to susceptibility for AIP [28].

Another gene role investigated in AIP was cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene, which is a negative regulator of the T-cell immune response; the gene is highly polymorphic. Many positive associations between *CTLA4* SNP and various autoimmune diseases have been identified. In a study of Chinese patients, 46 patients with AIP were investigated and the *CTLA4* 49A variant was found to be a susceptibility factor in AIP patients [29]. In another study, the authors replicated the association with CTLA4 gene [30]. Another gene investigated in Japanese AIP patients has been the protease serine 1 (PRSS1). Two novel mutations (p.81Leu → Met and p.91Ala → Ala) were found in PRSS1 gene, suggesting that this gene is also linked to the susceptibility to AIP [42].

In idiopathic retroperitoneal fibrosis/CP, few non-HLA loci have been investigated. Prompted by the evidence that serum levels of eotaxin/CCL11 were increased in IRF patients compared to controls, immunohistochemical and immunogenetic studies were performed in an Italian cohort [32]. CCL11 was demonstrated to be produced at high levels by infiltrating mononuclear cells, and its receptor, CCR3, was found to be expressed by different tissue-infiltrating cells, such as eosinophils, mast cells, lymphocytes, and fibroblasts. Testing for genetic association, six CCL11 gene SNPs were analyzed in a case–control study, but no statistically signal was found. However, extending the analysis to the haplotype of the tested SNPs, a strong signal for the TTCCAT haplotype was found. The results suggested the eotaxin/CCL11-CCR3 axis is important in idiopathic retroperitoneal fibrosis pathogenesis and that it drives tissue infiltration of eosinophils and mast cells, promoting fibrosis.

Another study investigated idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysm [43]. Toll-like receptor 4 (TLR-4) and vascular endothelial growth factor (VEGF) polymorphisms were genotyped in 102 patients and 200 controls. In particular, TLR-4 gene polymorphism (+896 A/G) (rs4986790), VEGF mutations +936 C/T (rs3025039) and −634 C/G (rs2010963), and an 18 base pair (bp) insertion/deletion (I/D) polymorphism at −2549 of the VEGF promoter region were investigated. No statistically significant differences in the distribution of the polymorphisms were found. However, the +936 T polymorphism was more frequent in patients with idiopathic retroperitoneal fibrosis than in those with inflammatory abdominal aortic aneurysms [43].

In a similar study, the CC chemokine receptor 5 (CCR5) Δ32 polymorphism was investigated [33]; this study showed that it was associated with an increased risk of developing inflammatory abdominal aortic aneurysms.

Systemic histiocytoses are multifactorial diseases of yet unclear origin. Their histopathology, in particular in cases of Erdheim–Chester disease, a non-Langerhans cell histiocytosis, shows abundant fibrosis and a chronic inflammatory infiltrate, in addition to pathologic histiocytes. This is why such diseases are included in the differential diagnosis of primary FID. Genetic susceptibility factors to such conditions have not been extensively investigated. However, recent studies have demonstrated that mutations of proto-oncogenes such as BRAF are found in the lesions. In particular, the BRAF V600E mutation, which drives different neoplastic proliferations such as melanoma, was found in the biopsies of approximately 50–55 % of patients with Erdheim–Chester disease. Based on this observation, treatment with specific BRAF V600E inhibitors such as vemurafenib has been tried in patients with Erdheim–Chester disease and also in Langerhans cell histiocytoses bearing the specific mutations, with excellent clinical results. The search for this mutation has therefore become strongly advised in the management of such diseases [44–46].

1.6 Genetic Overlap Between Systemic Fibro-inflammatory Diseases and Meta-analysis

To date, there is no evidence of genetic markers shared by the different FIDs, both for HLA and non-HLA-associated loci. In order to find possible genetic markers associated with the different FIDs, it would be interesting to perform genetic association studies (GWAS or Immunochip) analyzing all FID patients recruited as a single entity and then stratifying them according to the single disease and to the IgG4 status. Such an analysis would require a multicenter approach. Different ethnicity would be a positive factor. As evidenced by a GWAS performed by the European Vasculitis Genetic Consortium for ANCA-associated vasculitis [15], after the genetic study new possible disease criteria of classification may originate; in this case, the goal would be to find a genetic marker linked to pathogenesis, in particular with IgG4 status or a common shared pathway.

Meta-analysis of genetic association studies is an important strategy useful for increasing the statistical power of different studies; it analyzes the effect of gene variants across groups of several ancestries and studies. Until now, no meta-analysis in FIDs has been performed. Once candidate gene association studies, Immunochip and GWAS data of FIDs become available, the possibility of meta-analyses will become feasible, determining which genes may predispose to different subsets of these diseases.

1.7 Future Perspectives

In complex multifactorial diseases such as FIDs, case–control studies are useful to search for novel associated loci. After this exploratory study, they need to be replicated in different cohorts and to find possible shared loci in the different FIDs. Novel variants may show low increases in susceptibility to the disease, but they

may indicate new pathogenic pathways. Until now, the HLA system has shown several genetic associations for FIDs, but an increasing number of different non-HLA genes also seem to be associated. In the following section we will describe several methods available for investigating more deeply genomic regions associated with complex diseases like FIDs.

1.7.1 Immunochip

In the last years, Illumina produced Immunochip genotyping microarray, a platform able to perform immunogenetic studies of the SNPs and CNVs previously associated with inflammatory and autoimmune diseases [47].

These SNPs have been selected on the basis of significant loci associated with autoimmune diseases in high-density GWAS. The first version of the Immunochip genotypes 196,524 polymorphisms, with 195,806 SNPs and 718 small insertion/deletions, screening for common and rare variants. Being immunogenetics highly involved in inflammatory and autoimmune disorders [48], Immunochip includes a dense coverage of the HLA SNPs; this enables sensitive replication and imputation of the major classical HLA loci.

Several autoimmune diseases have already been investigated with Immunochip, such as atopic dermatitis [49], ankylosing spondylitis [50], Crohn's disease [51], primary IgA deficiency [52], juvenile idiopathic arthritis [53], multiple sclerosis [54], rheumatoid arthritis [55], Sjögren syndrome [56], psoriasis [57], systemic sclerosis [58], giant cell arteritis [59], and Takayasu arteritis [60], showing a statistically significant association with immunogenetic variants. Such analysis may confirm the results obtained from the GWAS, further exploring the HLA system at higher density. An interesting study would be to perform Immunochip in the different FIDs and then compare the statistically associated loci between them, in order to search for common variants shared by the different diseases; such an analysis would allow to highlight evidences of common/distinct pathways at the basis of FIDs.

1.7.2 Targeted Sequencing

Targeted sequencing is a method useful to investigate a panel of several candidate genes. It investigates causative mutations, rare variants, or regions associated with the disease in previous studies, such as GWAS and Immunochip.

The search for rare variants at high penetrance requires large cohorts, frequently recruited in multicenter studies, involving deep sequencing in a large number of affected individuals.

Targeted sequencing can be performed with next-generation sequencers (NGS), which are able to produce billions of nucleotides in a single run. Because of the large number of genetic variants found with NGS, it is extremely important to get information about their possible role in the development of a specific disease. Several softwares have been developed in recent years, most of them based on the

assumption that protein sequences derived from living organisms have survived natural selection. The goal is to find if a genetic variant is a causative mutation or a common polymorphism. Examples of such softwares are Sorted Intolerant From Tolerant (SIFT) [61], PolyPhen-2 [62], and MutationTaster [63]. These softwares are free and easy to use [64].

In FIDs, targeted sequencing with gene panels will be feasible when several variants will be discovered from different GWAS or Immunochip analysis.

1.7.3 Whole Exome and Whole Genome Sequencing

In the human genome there are about 18,000 genes, with exons and introns. Exons are generally short, functional sequences of DNA which represent the portion of the genome translated in protein. Whole exome sequencing (WES) is a recent strategy designed to sequence only the coding regions of the genome (which represent 1 % of the human genome, about 30 megabases); this is an effective method alternative to whole genome sequencing, cheaper and less complicated in the bioinformatic/statistical analysis. The WES has the potential to identify the coding variants responsible for both Mendelian and common diseases [65].

Whole genome sequencing (WGS) allows to sequence the entire genomic DNA, both chromosomal and mitochondrial. Unlike WES, this method allows the sequencing of both exons and introns, for a total amount of three gigabases. If with WES the number of discovered variants requires a strong bioinformatic/biostatistical approach, with WGS these analyses are prohibitive for the greater part of the small laboratories [66].

WES and WGS may be applied to FIDs for several reasons, such as the study of rare familial cases, the investigation of extreme phenotypes or subsets within a particular disease, for the finding of causative mutations or rare variants of already known or novel susceptibility genes, and for pharmacogenomic studies. Furthermore, the increasing number of susceptibility genetic variants will improve bioinformatic pathway analyses.

Conclusions

FIDs are multifactorial diseases, with genetic and environmental factors which modulate the clinical presentation of a specific disorder. The knowledge of biological pathways at the basis of different FIDs is very important; the elucidation of these novel factors may have clinical relevance, because it may be included in genetic risk modeling approaches. Furthermore, new genetic factors might in the next future represent novel biomarkers for FIDs, allowing physicians to treat patients at risk. The susceptibility genetic variants previously identified as playing a role in the same pathway represent new potential therapeutic targets, not only for FIDs but also for other inflammatory diseases. The new age of the *-omics* has allowed the improvement of the knowledge of FIDs. By means of genetic fine mapping, targeted sequencing, transcriptomics, proteomics, and metabolomics, physicians may improve treatment and therapy tailored on the single patient.

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Basic Mechanisms Linking Inflammation and Fibrosis

2

Carlo Chizzolini

2.1 Introduction

Fibrosis is due to excess in extracellular matrix (ECM) deposition over reabsorption resulting in tissue distortion eventually leading to organ dysfunction, organ failure, and death. Central to any fibrotic response, myofibroblasts are contractile cells with high ECM synthetic capacity. The inflammatory response triggered by tissue damage and aiming at tissue repair is characterized by an array of factors and cells, which result in fibrosis with sustained and relentless myofibroblast recruitment and activation. In addition, macrophages and receptors belonging to the innate immune system are fundamental in initiating and maintaining myofibroblast activation. In some circumstances, cells of the adaptive immune system, namely, T and B cells, are thought to participate to fibrosis development. In this respect it is noteworthy that IL-4 and IL-13 produced by Th2 cells, often expanded in IgG4-related disease, provide direct pro-fibrotic stimulation. The basic mechanisms linking innate and adaptive immune responses and fibrosis are reviewed herein, with a particular focus on their participation in fibro-inflammatory disorders.

2.2 Definition of Fibrosis

Fibrosis is a process meant to repair tissues whose integrity has been altered by a wide variety of stimuli including trauma, infection, sterile inflammation, toxic exogenous compounds or endogenous metabolites whose inappropriate accumulation or composition exerts harmful effects on tissues, hypoxic/anoxic stress, ionizing radiation, as well as excessive tensile forces exerted on contractile tissues like the myocardium.

The physiology of the fibrotic response initiated to repair tissues is a finely tuned, homeostatic process which has inbuilt mechanisms aimed at termination and to

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some extent reabsorption of the freshly deposed ECM. However, unchecked fibroblast activation may lead to excessive ECM deposition that may cause disruption of the normal tissue architecture and function resulting in organ failure and eventually in death. Fibrosis may affect any organ or vascularized tissue including parenchymatous organs such as the liver, lung, heart, kidney, and exocrine glands but also the bone marrow as observed in myelofibrosis, the intestine, or the skin.

Given the wide variety of causes that elicit fibrosis, it is easily understandable that the fibrogenic mediators involved are many and possibly different in the various circumstances. However, they all converge on a single cell type – the fibroblast – that trans-differentiates into myofibroblast [1, 2] endowed with high synthetic capacity of ECM components, particularly, but not uniquely, collagens and possessing contractile properties useful to favor wound closure. However, the sustained ECM deposition and the isometric contraction of these cells contribute to the distortion of parenchymal architecture, which promotes disease and organ failure.

2.3 General Mechanisms Leading to Fibrosis

Taking advantage from studies designed to understand wound healing, the development of fibrosis can be subdivided into several and partly overlapping processes, which need to be well organized in space and time for optimal healing. They serve as the main framework to understand how pathological fibrosis develops in the skin and other organs. They comprise an inflammatory phase associated with angiogenesis, migration, and proliferation of fibroblasts, which lead to scar formation followed by connective tissue remodeling.

As already mentioned, fibroblasts and myofibroblasts are central to fibrosis development.

The precise origin of myofibroblasts is still debated, but they might derive from mesenchymal progenitor cells such as pericytes, liver stellate cells (Ito cells), pancreatic stellate cells, or resident fibroblasts, particularly those seating in perivascular areas. Other cell types, including fibrocytes (which are of hematopoietic origin) or epithelial cells via epithelial to mesenchymal transition (EMT) or endothelial cells via endothelial to mesenchymal transition (EndoMT) are thought to directly contribute to myofibroblast generation and fibrosis [3, 4], but these concepts have been recently disputed. Genetic cell fate mapping experiments have suggested that myofibroblasts are principally derived from cells of mesenchymal origin practically in all organs assessed [5–12]. This is not to dismiss a role for EMT and EndoMT or fibrocytes; however, these cells by acquiring a migratory phenotype and activating a more mesenchymal cell type of gene expression may direct the activation of pericytes and other resident fibroblasts to become myofibroblasts, rather than being themselves progenitors. Interestingly, mediators involved in the phenotypic changes of myofibroblast precursors are those also involved in neoangiogenesis and include transforming growth factor-beta (TGF-β), platelet-derived growth factor and its receptor-beta and receptor-alpha (PDGFR-β, PDGFR-α), and vascular endothelial growth factor (VEGF) and its receptor 2 (VEGFR2), in addition to signals

associated with angiopoietin and sphingosine kinase as well as developmental pathways WNT, Hedgehog, and Notch [9].

Myofibroblasts are structurally characterized by a pronounced rough endoplasmatic reticulum, stress fibers, and a large nucleolus. They are highly synthetic cells that produce large amounts of procollagens, matrix metalloproteinases, cytokines, chemokines, lipid mediators, and radical oxygen species. Interestingly, increasing levels of mechanical tension result in increased myofibroblast proliferation and ECM synthesis irrespective of tissue origin [13–15]. Fibroblasts/myofibroblasts and the mediators involved in their activation represent an interesting target for intervention when fibrosis needs to be halted or reversed and therefore are the object of intense scientific scrutiny [16].

Several lines of evidence indicate that fibroblasts/myofibroblasts are heterogeneous in terms of function, which reflects the particular organ they populate [17–19]. Furthermore they are capable of some degree of plasticity resulting in differential production of mediators, which variably shape the inflammatory response [20]. It is their responsiveness to environmental signaling cues that will finally determine whether or not excess ECM will be deposed and pathological fibrosis will ensue. When specific environmental situations last sufficiently, fibroblasts may become autonomous and maintain a pro-fibrotic phenotype over time. Indeed, fibroblasts isolated from fibrotic tissues can be distinguished from those isolated from healthy tissues in terms of collagen production, sensitivity to growth factors, loss of antiproliferative responses, sensitivity to inhibitory signals, impaired eicosanoid synthesis, and increased resistance to apoptosis, thus lending support to their central role in fibrosis development [16]. In this respect recent findings indicate a role for toll-like receptors (TLR) expressed on fibroblasts. For instance, fibronectin extracellular domain A (FN^{EDA}), expressed in high amounts in fibrotic skin, has been proposed to bind TLR4 and enhance collagen production in an in vivo murine model of scleroderma. FN^{EDA} production is induced by TGF-β and simultaneously enhances TGF-β production by fibroblasts, thus providing a positive feedback loop potentially able to maintain persistent fibroblast activation [21, 22].

As already stressed, neoangiogenesis is tightly associated with fibrosis, and to some extent pro-angiogenic factors are also pro-fibrotic factors. Angiogenesis is mediated by the migration and proliferation of endothelial cells from adjacent vessels, which are directed in their migration and proliferation by growth factor gradients. Alternatively, neoangiogenesis is associated with the recruitment of endothelial precursor cells of hematopoietic origin at sites of injury. Among the most important factors governing angiogenesis and vasculogenesis is the family of VEGF/VEGF receptor complex. In addition, the interaction between Notch and its ligands with the further intervention of a disintegrin and metalloproteinase domain-containing protein (ADAM) is tightly linked with neoangiogenesis [23]. The dysregulation of this complex of numerous ligands and receptors as well as intracellular signaling pathways may participate in excessive fibrosis. Of interest, vasculogenesis is completed by the recruitment of pericytes and smooth muscle cells mostly mediated by angiopoietins, TGF-β, and PDGF. Finally, integrins and matricellular proteins such as plasminogen activator and matrix metalloproteinases (MMPs) are also involved

in tissue remodeling during neoangiogenesis. Thus, pericytes that intervene in vasculogenesis may provide the cellular link with fibrosis further stressing the intertwining of these two processes.

2.4 Inflammation and Fibrosis

Inflammation is a dynamic process whose aim is to bring defensive and repairing elements to damaged vascularized tissues. Thus, inflammation and fibrosis are tightly associated when the integrity of a tissue is at stake and tightly associated when the fibrotic process goes beyond repair and becomes itself the source of pathology. In practical terms there is no fibrosis in the absence of inflammation. A variety of cell types and soluble mediators contribute to the initiation, full progression, and then the resolution of inflammation. A given cell type or a given soluble factor may play different roles (sometime opposite roles) in the inflammatory process according to the timing and environment in which it enters in action. Thus, it is important to keep in mind that there is not a unique role and function for the cells or the mediators involved in inflammation, but the context in which they operate ultimately dictates the outcome of their function. Furthermore, it should be stressed that mediators of inflammation such as cytokines or lipid-derived mediators can be produced by cells that are not conventionally considered inflammatory. Thus, besides cells of hematopoietic origin, also fibroblasts, endothelial cells, keratinocytes, and parenchymal cells of various organs (i.e., the liver, kidney, etc.) may produce mediators participating to inflammation.

In adult (as opposed to embryonic) tissues an influx of inflammatory cells initiates and favors the reparative processes when the integrity of the tissue is disrupted. It aims at the clearance of apoptotic and necrotic material and it promotes angiogenesis and recruitment of fibroblasts and generation of myofibroblasts, hence enhancing deposition of ECM and then remodeling. Neutrophils are the first cells to be recruited at wound, quickly replaced by macrophages. In rodents, in which the influx of macrophages is hampered by the neutralization of macrophage inhibitory protein-1α, the repair of skin wound is delayed [24]. This is also the case in mice deficient in ICAM-1 [25], which have defective cell trafficking. Similarly, impaired healing is also observed in humans with genetically determined leukocyte adhesion molecule deficiency [26]. It is interesting to note that the functional phenotype of macrophages appears to change with time during the fibrotic response [27]. During the early phases of this process, macrophages are mostly capable of producing pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) and are particularly good in phagocytosis and elimination of cellular debris as well as degrading ECM due to the production of MMPs and other ECM-degrading enzymes [28]; with time, under the influence of IL-4 and IL-13, they progressively assume a different phenotype prone to favor angiogenesis and ECM deposition [9]. Indeed, alternatively activated macrophages are good producers of TGF-β and other pro-fibrotic cytokines. It is therefore clear that macrophages play essential roles in the initiation and eventually abnormal perpetuation of the fibrotic process.

Macrophages may participate however to the resolution of the fibrotic response when they acquire a regulatory phenotype with high IL-10 production and downregulation of pro-fibrotic cytokine production [29, 30].

T cells, in particular T helper cells, are important contributors, in particular of pathological fibrosis, through their role in initiating/perpetuating the inflammatory response and the production of cytokines. However, T cells may as well be important in terminating or at least reducing fibrogenic responses. Transcriptome analysis in animal models has shown that genes involved in wound healing and fibrosis are associated with Th2-polarized responses, characterized by the production of IL-4, IL-5, and IL-13, as opposed to Th1-polarized responses characterized by IFN-γ production [31]. Considerable evidence indicates that indeed type 2 polarized responses are important for fibrosis development [32–34]. Among Th2 cytokines, IL-13 has been identified as a major mediator of fibrosis in various tissues. Its activity is modulated by the relative expression of two subunits of its receptor: IL-13Rα1, which transmits the signal, and IL-13Rα2, which acts as a decoy and inhibitory signal induced by IL-13 [35]. IL-13 may participate in the fibrotic response by directly stimulating ECM production by fibroblasts or indirectly by inducing the production of TGF-β by macrophages or PDGF by epithelial cells [36–38]. In this context, Th1 cells and IFN-γ are mostly seen as inhibitors of fibrosis. Indeed, IFN-γ has the capacity to inhibit collagen production by fibroblasts [39–41]. The role of Th17 cells in fibrosis is controversial with divergent evidence obtained in animal models and human cell cultures. Murine models of fibrosis have identified IL-17A to be involved in bleomycin-induced lung and skin fibrosis [42–45]. Furthermore, Th17-polarized responses mediated lung fibrosis in a model of chronic hypersensitivity [46], and IL-17A deficiency attenuated skin thickness in tight skin-1 (TSK-1/$^{+}$) mice [45]. Consistently, IL-17 increased TGF-β, connective tissue growth factor (CTGF), and collagen production by mouse skin fibroblasts [45] and promoted collagen production and EMT in mouse alveolar epithelial cells in a TGF-β-dependent manner [43]. In humans, IL-17 has been shown to enhance proliferation, IL-6 and IL-8 production, and ICAM-1 expression by fibroblasts and endothelial cells [47, 48]. However, IL-17A possesses direct anti-fibrogenic properties in normal human fibroblasts by downregulating CTGF and type I collagen production [49]. Furthermore IL-17 limits the differentiation of fibroblasts into pro-fibrotic myofibroblasts induced by TGF-β1, simultaneously favoring the production of IL-8, IL-6, monocyte chemotactic protein-1 (MCP-1), and MMP-1 [50–52]. In vivo studies are needed to fully understand the role of IL-17 family members in fibrosis development to distinguish between the pro-inflammatory and the potential anti-fibrotic role of this cytokine.

An important unanswered question, particularly in the context of IgG4-RD, is whether T cells infiltrating tissues undergoing fibrosis are recruited in an antigen-independent inflammatory-driven mode or whether they specifically respond to antigens or even autoantigens present in that tissue. It should however be mentioned that in several instances, particularly in the settings of fibrosing autoimmune disorders, T-cell receptors (TCRs) appear to be clonally distributed, thus providing support to the hypothesis of their role as driving cells in the fibrotic process [53, 54].

Innate lymphoid cells (ILCs) are a recently identified population of cells of hematopoietic origin, which do not express clonally distributed antigen receptors but similarly to CD4+ T cells may develop in discrete functional subsets according to the cytokine milieu where they mature. Thus, ILC1 mostly produce IFN-γ, ILC2 produce type 2 cytokines (IL-4, IL-5, IL-13), and ILC17 produce IL-17 and IL-22. They participate to homeostasis and inflammation and respond to environmental signals further influencing the differentiation of adaptive immunity [55, 56]. It is therefore logical to think that they may be involved in fibrosis initiation and regulation [57, 58]. Of interest, in scleroderma evidence generated studying the peripheral blood of affected individuals has shown that ILC2 cells are numerically increased [59]. Furthermore, ILC2 cells have been implicated in the pathogenesis of pulmonary fibrosis [60]. It is tempting to speculate that in IgG4-RD, ILC2 could be activated by signals generated by cellular stress in tissues undergoing damage for various reasons and converting them into a stereotyped response characterized by storiform fibrosis and high IgG4 production.

2.5 Soluble Mediators of Fibrosis

Numerous soluble factors have been reported to promote fibrogenesis by directly or indirectly upregulating fibroblast function. Among the most widely accepted soluble factors believed of importance in fibrogenesis, there are TGF-β, PDGF, CTGF, plasminogen activator inhibitor 1 (PAI-1), IL-4, and IL-13. A place apart is reserved to IL-6 and TNF. The effect of these cytokines on fibroblasts is schematically summarized in Fig. 2.1.

Transforming Growth Factor-Beta: TGF-β TGF-β is believed to play a crucial role in promoting fibrotic responses. Three isoforms of TGF-β exist, and in the context of fibrosis most of our knowledge is centered on TGF-β1 [61, 62]. TGF-β affects the behavior of a number of cellular types either of hematopoietic, mesenchymal, or epithelial origin. TGF-β is a powerful immunosuppressant, regulates inflammation, variably promotes or suppresses tumor growth, and is essential in wound healing [63]. The biological activities of TGF-β are mostly regulated by modifications of the released protein rather than by modifications of its synthesis. Indeed, TGF-β exists in a latent complex bound to the ECM. Following tissue injury, TGF-β is released from ECM and influences the cells in the immediate vicinity. Within the ECM, mature TGF-β exists as a dimer, forming a small latent complex with the latency-associated peptide (LAP), itself bound to a larger complex directly bound to ECM proteins. To become biologically active, the latent TGF-β complex needs to be activated by proteolytic mechanisms or by tractional forces mediated by integrins – most notably, the αVβ6, αVβ5, and αVβ3 integrins [64]. Following receptor binding, TGF-β implicates canonical and noncanonical signaling pathways. The SMAD pathway implicates the phosphorylation of SMAD2 and SMAD3 proteins and their association with the co-SMAD4 for

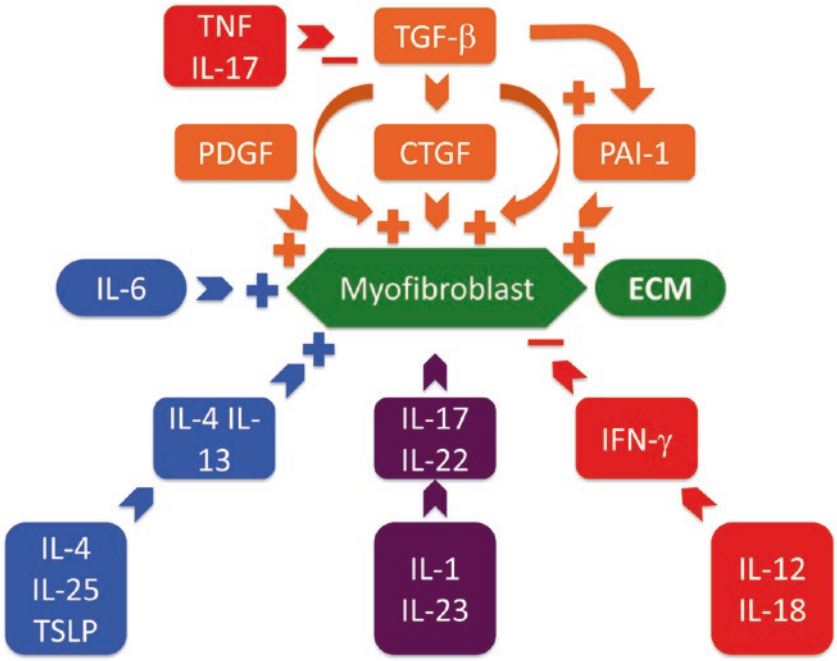

Fig. 2.1 *Myofibroblasts are central to fibrogenesis and are submitted to regulation by pro- and anti-fibrotic cytokines*. Schematic and simplified view of the network of cytokines influencing ECM deposition by myofibroblasts. In *orange*, pro-fibrotic cytokines mostly produced by cells of non-hematopoietic origin. In *blue*, pro-fibrotic cytokines mostly produced by cells of hematopoietic origin. In *red*, anti-fibrotic cytokines. In *purple*, cytokines known to enhance the pro-inflammatory activity of fibroblasts but with no direct pro-fibrotic activity. + denotes activation. − denotes inhibition. *CTGF* connective tissue growth factor, *ECM* extracellular matrix, *IL* interleukin, *PAI-1* plasminogen activator inhibitor 1, *PDGF* platelet-derived growth factor, *TGF-β* transforming growth factor-β, *TNF* tumor necrosis factor

nuclear translocation. This signaling cascade is negatively regulated by SMAD7 [65]. In fibrosis development, the noncanonical TGF-β signaling pathways may play a major role and involve MAPK, PI3K, and NFkB pathways as well as NADPH oxidase 4 (NOX4)/reactive oxygen species (ROS) pathways [66]. Key to avoid excessive ECM deposition, TGF-β signaling needs to be terminated once tissue is repaired and the synthesis of extracellular matrix should return to normal levels. Finely tuned homeostatic mechanisms are thought to be at play, but the molecular mechanisms that underlie the failure to limit TGF-β activity are poorly understood. However, recent work has highlighted the role of the orphan nuclear receptor NR4A1 in downregulating TGF-β signaling and participating to a negative feedback loop that limits excessive TGF signaling and could be exploited to attenuate fibrotic disorders [67].

Platelet-Derived Growth Factor: PDGF PDGF signals through two different PDGF receptors, alpha and beta, and comprises a family of homo- or heterodimeric growth factors including PDGF-AA, PDGF-AB, PDGF-BB, PDGFCC, and PDGF-DD [68]. After wounding, the expression of PDGF is increased; this growth factor participates in the recruitment of neutrophils, macrophages, fibroblasts, and smooth muscle cells into the wound [69]. PDGF also stimulates the formation of granulation tissue with direct effects on fibroblasts, resulting in collagen matrix contraction and fibroblast differentiation into myofibroblasts in vitro [70]. Tyrosine kinase inhibitors such as imatinib mesylate, dasatinib, and nilotinib exert potent anti-fibrotic effects in experimental models of fibrosis, most likely by inhibiting signaling induced by PDGF-receptor engagement [71].

Connective Tissue Growth Factor: CTGF or CCN2 CTGF is a member of the CCN proteins that are key signaling and regulatory molecules involved in cell proliferation, angiogenesis, tumorigenesis, wound healing, and fibrosis [72]. CTGF is a modular matricellular component produced by fibroblasts (among other cells) and induced in response to various stimuli including TGF-β, endothelin-1, and angiotensin-II and is thought to act mainly by favoring an environment which promotes fibrogenesis [73]. It acts mostly in an autocrine manner interacting with other matrix components and adhesion molecules [74]. It has been implicated in several fibrotic conditions including scleroderma, chronic heart failure, and proliferative diabetic retinopathy.

Plasminogen Activator Inhibitor 1 (PAI-1) PAI-1 is a member of the serine protease inhibitor (serpin) gene family and the major physiologic inhibitor of the serine proteases urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). Inhibition of uPA/tPA results in the inhibition of plasminogen-to-plasmin conversion as well as plasmin-dependent MMP activation. Thus, PAI-1 protects ECM proteins from proteolytic degradation and helps accelerate wound healing. However, sustained PAI-1 activation may contribute to excessive collagen accumulation [75]. Fibroblasts obtained from fibrotic tissues spontaneously produce higher amounts of PAI-1 compared to control fibroblasts, and inhibition of PAI-1 protects against fibrosis in the lung [76], heart, and kidney but not the skin [77] in animal models of fibrosis. Factors that may induce high production of PAI-1 are VEGF and TGF-β1. Thus, PAI-1 participation to fibrosis development exemplifies the role of an excessive brake directed against events aimed at ECM reabsorption.

Interleukin-4 (IL-4) and IL-13 Classical Th2 cell products, such as IL-4 and particularly IL-13, have been shown to have direct and indirect roles in fibrosis development. IL-4 and IL-13 enhance type I collagen production in dermal fibroblasts [78, 79]. IL-13 in vivo acts by inducing TGF-β production by macrophages and directly stimulating myofibroblast and fibroblast synthetic activities. IL-13 function is regulated by the relative expression of the two IL-13 receptor subunits, IL-13Rα1 (signaling component) and IL-13Rα2 (decoy component). When IL-13Rα2 levels are low, fibrotic responses are enhanced [80]. Consistent with the importance of

Th2-like response in fibrotic pathologies, the report shows increased eotaxin/CXCL13 serum levels in idiopathic retroperitoneal fibrosis [81].

Interleukin-6 (IL-6) IL-6 is rather a newcomer in the fibrosis field, whose importance has been highlighted by the availability of targeted biological therapies. IL-6 is a pleiotropic cytokine with direct pro-angiogenic and pro-fibrotic activities [82]. Its levels are increased in the serum and skin of scleroderma patients [83], and its inhibition attenuates bleomycin-induced experimental fibrosis in the murine lung and skin [84, 85]. Of importance, IL-6 blockade has shown beneficial effects in humans affected by idiopathic retroperitoneal fibrosis [86].

Tumor Necrosis Factor (TNF) Historically, TNF has been associated with the development of fibrosis in experimental models dominated by inflammation. In a pioneering work, Piguet and coworkers demonstrated that TNF blockade strongly attenuated the fibrotic response in the mouse with bleomycin-induced lung fibrosis [87]. However, when TNF inhibitors have become available in the clinics, their use in humans was not always associated with fibrosis halting; conversely, in some cases worsening of the fibrotic process was observed, particularly in individuals suffering from systemic sclerosis [88]. On the one hand, TNF is particularly important among inflammatory cytokines because it enhances the recruitment of inflammatory cells which mandatorily precede fibrosis; on the other hand, TNF inhibits the transcription of type I and type III procollagen mRNA [89, 90] and is a strong inducer, in fibroblasts and macrophages, of MMP production, in particular of the interstitial collagenase MMP1, which participates in ECM degradation [91] [92]. Thus, the net effect on fibrosis development of TNF may very well depend on the context and timing in which it operates, variably resulting in enhanced or decreased ECM deposition.

2.6 Fibrosis in IgG4-Related Disorder and Unresolved Questions

The pathological features currently used to identify IgG4-RD include a lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis, and mild-to-moderate tissue eosinophilia. Minor features include the presence of germinal centers, lymphoid follicles, non-obliterative phlebitis, and obliterative arteritis (usually in the lung) [93–96]. From the fibro-inflammatory point of view, specific and peculiar pathological characteristics of IgG4-RD are the presence of storiform fibrosis and a very rich inflammatory infiltrate composed largely by CD4+ T cells, macrophages, and plasma cells. The presence of eosinophils is also remarkable. Storiform fibrosis is rare if ever encountered in connective tissue diseases or other diseases characterized by organ fibrosis but sometimes described in association with solid tumors [97]. Thus, one of the unanswered questions is why collagen and ECM deposition in florid IgG4-RD assumes this typical disposition. It is known that myofibroblasts and spindle-shaped fibroblasts are tightly associated with freshly

deposed collagen fibers in IgG4-RD, therefore conforming to the paradigm that α-smooth muscle actin (SMA)$^+$ cells are central to fibrosis development [98]. It is also remarkable that under certain circumstances fibrosis associated to IgG4-RD can regress [99], or at least, the size of lesions, as assessed by imaging studies, definitely decreases; this leads to the hypothesis that collagen bundles are not extensively cross-linked and could undergo degradation, perhaps under the influence of MMPs. This notwithstanding, in several cases thick, acellular matrix results in permanent tumorlike masses.

When searched for, classical mediators involved in fibrosis including LAP (TGF-β1) are mostly expressed in macrophages, TGF-RII and PDGF-B are mostly expressed in myofibroblasts and epithelial cells, and PDGF-Rα and PDGR-Rβ have been documented in type I autoimmune pancreatitis [98]. In these settings, the strongest positivity for such mediators was observed in grade 3 histological pattern [100], when the inflammatory component is maximal.

As mentioned in previous paragraphs, Th2 cells and their products, particularly IL-4 and IL-13, are associated with fibrotic responses in many distinct pathological situations. Thus, the documentation of expanded Th2 cell responses in IgG4-RD may provide a pathogenically interesting link between inflammation and fibrosis [101–104]. However, Th2 cell responses have been documented only in a fraction of patients with IgG4-RD [105, 106]. Th2 cells produce also IL-5, which enhances eosinophil maturation, recruitment, and activation, and eosinophils are frequently present in fibroblastic tissues in IgG4-RD [107]. Eosinophils may release IL-13, TGF-β1, and PDGF, thus participating in the activation of fibroblasts [108]. The inflammatory infiltrate in IgG4-RD is also rich in macrophages, which may also release TGF-β1 and PDGF. Given the presence of B cells as well as of plasma cells particularly those producing the eponym IgG4, it is clearly tempting to speculate that these cells may produce factors that enhance the production of ECM by fibroblasts. B-cell contribution to fibrosis is an area of relatively scarce research. However, B cells were shown to induce contact-dependent human dermal fibroblast activation with upregulation of, among other mediators, type I collagen. This B-cell activity was enhanced by B-cell activation in the presence of anti-IgM and B-cell-activating factor (BAFF) [109]. Interestingly, BAFF levels are increased in IgG4-RD, positively correlating with IgG4 serum levels and decreasing after glucocorticoid therapy [110]. Thus, this remains an area of specific interest in IgG4-RD fibrosis.

Additional inflammatory cells identified in tissues undergoing IgG4-RD pathological transformation are Foxp3+ T regulatory cells [111]. These cells may produce TGF-β, and therefore they may be mechanistically associated with the development of fibrosis. However, no direct evidence has been gathered to back this hypothesis. Furthermore, in humans Foxp3 can be acquired in fully differentiated effector cells with no regulatory activity. This is the case in systemic sclerosis skin where Foxp3+ cells have been proved to produce high levels of IL-4, which has direct pro-fibrotic activities [112].

It should however be noted that no specific studies have been devoted in IgG4-RD to investigate the contribution of each cell type to the activation of fibroblasts.

Conclusions

An exuberant inflammatory infiltrate rich in CD4+ T cells, macrophages, and IgG4+ plasma cells in addition to storiform fibrosis participates to the pathological definition of IgG4-RD. It is reasonable to speculate that the inflammatory infiltrate drives fibroblast activation, myofibroblast recruitment, and subsequent ECM deposition in this disorder. The fundamental processes, mediators, and cells associated to fibrosis in general seem to be at play in IgG4-RD fibrosis. However, the mechanisms specifically involved in its generation remain elusive. This is particularly true taking into consideration the very heterogeneous clinical presentation of this condition and the difficulties we experience in understanding the relationship between the fundamental aspects of the disease and the variety of organs affected. Thus, we should try to answer the question whether indeed a single etiopathogenic event is at the base of all forms of IgG4-RD or whether IgG4-RD is a default reaction to a variety of different etiopathogenic events. The functional characterization of inflammatory cells present in early lesions, the hunting for an eventual antigen – autoantigen recognized by infiltrating T cells or B cells – and their interplay with cells of the innate immune system should bring new light and improve our knowledge of IgG4-RD in the next few years. This should allow to implement more targeted therapies or even more optimistically to adopt preventive strategies.

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The Pathology of Systemic Fibroinflammatory Disorders

3

Domenico Corradi and Maria Nicastro

3.1 Introduction

The systemic fibroinflammatory disorders encompass a series of exceedingly different lesions whose common denominator is the presence of varying amounts of newly formed fibrous tissue and different degrees of inflammatory cells. The nature of these disorders is various, ranging from reactive disorders to neoplastic lesions, and also including forms of uncertain nature. Based on the fibroinflammatory disorders described in this textbook, in this chapter we will analyze the pathology of sclerosing mesenteritis (SM), nephrogenic systemic fibrosis (NSF), IgG4-related disease (IgG4-RD), idiopathic retroperitoneal fibrosis (IRF), sclerosing forms of autoimmune thyroiditis, Erdheim-Chester disease (ECD), inflammatory myofibroblastic tumor (IMT), and the non-ECD histiocytoses.

3.2 Sclerosing Mesenteritis

SM is a pseudoneoplastic enlargement of the mesentery featuring varying degrees of fibrosis, chronic inflammation, and fat necrosis. This relative lack of homogeneity in terms of histological components would justify the various designations that this entity received in the past, depending on the predominant histologic feature (i.e., retractile mesenteritis, mesenteric lipodystrophy, and mesenteric panniculitis).

In the 1990s, Emory et al. [1] reviewed a large patient population affected by fibrosing lesions of the mesentery, which had been labeled as mesenteric lipodystrophy, mesenteric panniculitis, or retractile mesenteritis and SM. They concluded that these disorders represented histologic variants of the same lesion and that SM would be the most appropriate denomination.

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Grossly, SM may present as a single mass, multiple masses, or diffuse thickening of the mesentery (by increasing frequency). In the above-mentioned series, 69 % of SM cases affected the small bowel mesentery, 23 % the mesocolon, 2 % both the small and large bowel mesenteries, and 1 % the mesoappendix. The remaining cases occurred in various intra-abdominal sites, including the peripancreatic area, omentum, and pelvis. These masses were round or multilobulated and ranged from 1 to 40 cm in their major dimension (average value 10 cm). The cases with diffuse thickening ranged from 10 to 35 cm [1].

Histopathologically (Fig. 3.1), in the great majority of cases collagen bands replace the resident adipose tissue by infiltrating and surrounding lobules of fat, while a chronic inflammatory infiltrate – mainly composed of lymphocytes, with minor plasma cell and eosinophil component – is interspersed in both the fibrotic and adipose areas. In the most inflammatory zones, lymphoid follicles may be detected. Of note, neutrophils are only occasionally detectable throughout the lesion and vasculitic signs are not part of this abdominal disorder. Dystrophic calcifications or, much more rarely, heterotopic bone formation may sometimes be found

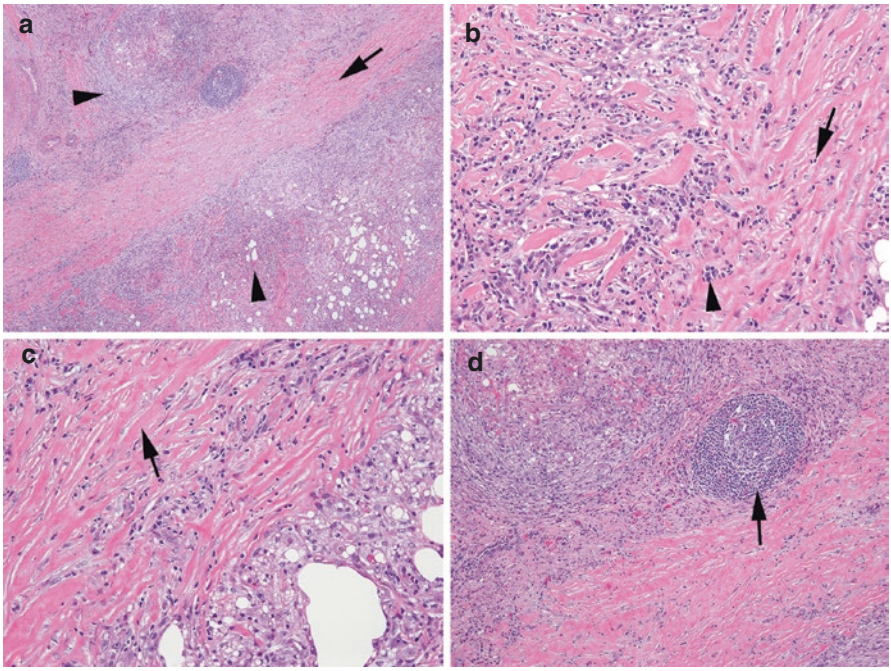


Fig. 3.1 Sclerosing mesenteritis. (**a**) On low-power view, sclerosing mesenteritis consists of a diffuse replacement of the resident mesenteric soft tissues (mostly adipose tissue) by a dense fibrous tissue (*arrow*) and several foci of chronic inflammatory infiltrate (*arrowheads*). (**b**) This inflammatory infiltrate is mainly made of lymphocytes (*arrow*) and plasma cells (*arrowhead*). (**c**) Large bands of collagen (*arrow*) replace the normal mesenteric soft tissues. (**d**) Often, the lymphocytes are organized into follicles with a germinal center (*arrow*) (Courtesy of Dr. Andrew L. Folpe, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN)

within the fibrous tissue. A few SM cases – those that had previously labeled as "mesenteric lipodistrophy" – showed predominant areas of fat necrosis and barely focal or even no fibrotic component. In SM cases involving *ab extrinseco* the bowel wall, the *muscularis propria* seems compressed rather than truly infiltrated. Interestingly, in about 20% of these latter SM cases, varying amounts of foamy histiocytes infiltrated the mucosal *lamina propria* [1].

The pathologic differential diagnosis includes lymphoma, well-differentiated liposarcoma (where, in addition to basic histopathology, immunohistochemistry for MDM2 and CDK4 or FISH for MDM2 may be helpful in diagnosing this mesenchymal neoplastic proliferation) [2], inflammatory myofibroblastic tumor, and a reactive process secondary to either carcinoma, foreign material or bowel perforation, fibromatosis, idiopathic retroperitoneal fibrosis and, sometimes, Whipple disease [1].

3.3 Nephrogenic Systemic Fibrosis

NSF – also known as "gadolinium-induced fibrosis" (GIF) – is an iatrogenic fibrosing disease primarily affecting patients with chronic kidney disease following exposure to gadolinium-based contrast agents in case of imaging procedures. GIF is characterized by skin thickening, tethering, and hyperpigmentation especially affecting the extremities; flexion contractures of joints; and extracutaneous fibrosis [3].

A skin biopsy is mandatory in order to confirm the clinical suspicion of GIF, and clinical data must be the guide for a correct histopathological interpretation of otherwise non-fully specific microscopic findings. The histopathologic picture largely depends on the timing in the disease course, with the general morphologic change of a fully developed lesion being a cell-rich dermal fibrosis that can sometimes extend to the underlying hypodermis. In the dermis there are thick and thin collagen bundles, which are often surrounded by clefts of $CD34^+$, $CD45RO^+$, and/or type I procollagen$^+$ spindle cells, these findings suggesting their origin from circulating fibrocytes. In addition, factor $XIIIa^+$ cells and CD68-$KP1^+$ multinucleated histiocytes can be observed. Prominent elastic fibers interweave among the above-mentioned dermal collagen bundles and mucin deposits. Additional less common histological features include bone metaplasia, calcification, and a mild chronic inflammatory infiltrate [3].

The skeletal muscle is often modified in the areas just below the affected skin segments, thereby suggesting that muscle participation in GIF is closely related to superficial involvement. In a series of five NSF cases, Levine et al. [4] found by computerized tomography scan fibrosis of the fascia and muscles in the most severely affected patients, and by electromyography mild-to-severe myopathic changes. Histopathologically (Fig. 3.2), a spectrum of mild-to-severe fibrosis, degenerating fibers, nonspecific changes, and/or chronic inflammatory cells can be detected. However, it cannot be ruled out that secondary signs of uremic nephropathy may be superimposed on the above skeletal muscle myopathic changes [5].

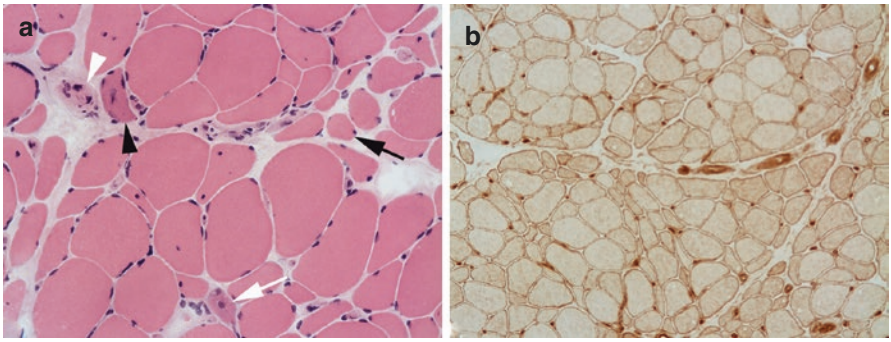


Fig. 3.2 Nephrogenic systemic sclerosis (skeletal muscle biopsy). (**a**) Medium-power view of a skeletal muscle in a patient with nephrogenic systemic sclerosis showing scattered atrophic fibers (*black arrow*), and occasional necrotic (*black arrowhead*) and regenerative fibers (*white arrow*). The small arteries (*white arrowhead*) and some capillaries have slightly thickened walls. (**b**) Immunohistochemical analysis showing HLA Class I overexpression in muscle fibers (Courtesy of Dr. Istvan Bodi, King's College Hospital, London, UK)

Interestingly, gadolinium has been detected by electron microscopy in the affected skin as well as in skeletal muscle, lymph node, heart, lung, liver, adrenal gland, kidney, ileal wall, thyroid, eye, dura mater, and cerebellum of patients with GIF [3].

Using data from the Yale International NSF Registry, Girardi et al. [6] have compiled diagnostic criteria and a compendium of images to assist the clinician in making this diagnosis. With regard to the histopathologic interpretation, they proposed a 0–4 score (as "inconsistent with NSF," "suggestive of NSF," "consistent with NSF," "highly consistent with NSF," or "NSF excluded," respectively) whose total is the sum of different histopathologic findings in a kind of weighted score: the presence of: (i) increased dermal cellularity, (ii) thick and thin collagen fibers, (iii) septal involvement, and (iv) $CD34^+$ cells, each correspond to +1; the presence of osseous metaplasia corresponds to +3; the absence (or reduction) of elastic fibers corresponds to −1.

Given the relatively nonspecific histopathologic changes, pathologic differential diagnosis is obviously wide and includes scleromyxedema, morphea/scleroderma, eosinophilic fasciitis (Shulman syndrome), eosinophilia-myalgia syndrome, lipodermatosclerosis, dermatofibrosarcoma protuberans, stiff skin syndrome/congenital fascial dystrophy, septal panniculitis, pseudoxanthoma elasticum, and calciphylaxis [6].

3.4 IgG4-Related Disease

IgG4-RD is an immune-mediated fibroinflammatory disorder characterized by the development of sclerotic masses reportedly rich in lymphocytes and $IgG4^+$ plasma cells. These masses may affect synchronously or metachronously the soft tissues

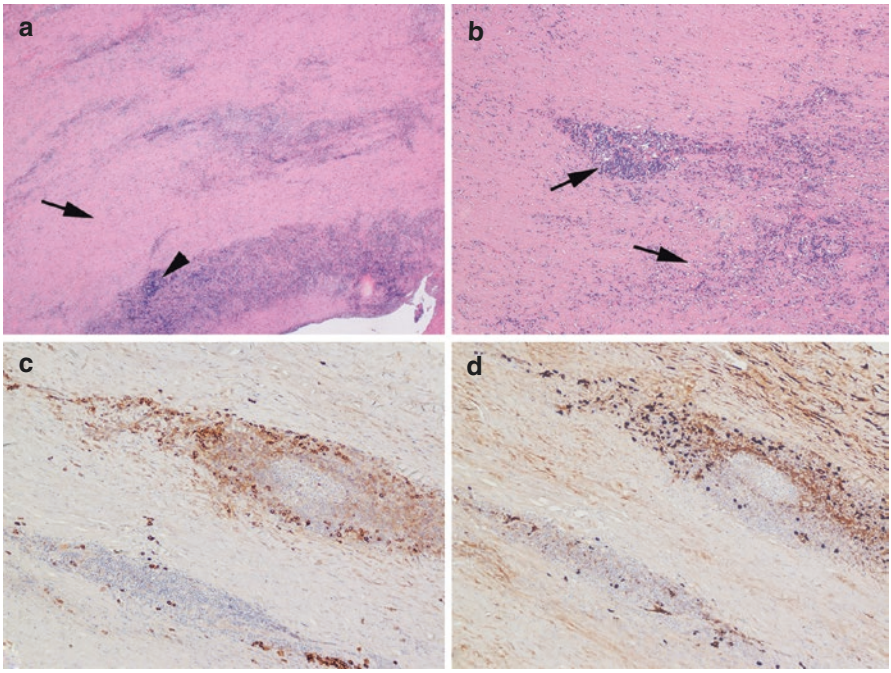


Fig. 3.3 IgG4-related disease. (**a**) Low-power view of a chronic periaortitis consisting of marked sclerotic replacement and expansion of the adventitial spaces (*arrow*), as well as foci of inflammation (*arrowhead*). (**b**) This inflammatory infiltrate (*arrows*) is mainly composed of lymphocytes and plasma cells. (**c**) Immunohistochemical analysis with an anti-CD138 antibody decorating the plasma cells. (**d**) Immunohistochemical analysis displaying the IgG4-positive plasma cells (overall, >50 % of the total plasma cells)

and/or different organs such as pancreas, lacrimal glands, salivary glands, gallbladder, and many other target locations including the cardiovascular system [7].

Very recently, a panel of experts has issued current strategies for managing and treating patients suffering from IgG4-RD. According to these recommendations, careful clinical assessment, laboratory tests, and imaging studies are initially imperative but often unsatisfactory in differentiating IgG4-RD from tumors or other tumefactive nonneoplastic lesions. In view of this, adequate biopsy material is fundamental to make a diagnosis of this fibroinflammatory disorder [8].

According to current guidelines on morphological interpretation of IgG4-RD tissue samples [9], key histopathological findings (Fig. 3.3) that are relevant to the diagnosis of IgG4-RD are: dense lymphoplasmocytic infiltrate, storiform-type fibrosis, and obliterative phlebitis. It should be noted that there are some exceptions to these general microscopic findings, in particular anatomical locations such as the lymph node, lung, salivary glands, and lacrimal glands where storiform fibrosis or obliterative phlebitis may be modest or even absent, and the inflammatory infiltrate may be qualitatively different. In lungs, obliterative arteritis signs are often seen. Moreover, in lymph nodes five histological patterns (always in the presence of other

IgG4-RD lesions) have been reported: (a) multicentric Castleman's disease-like, (b) follicular hyperplasia, (c) interfollicular expansion, (d) progressive transformation of germinal center, and (f) nodal inflammatory pseudotumor-like [9].

In addition to these qualitative characteristics, quantification of IgG4+ plasma cells by immunohistochemistry is crucial to make a diagnosis of IgG4-RD. IgG4 quantification should be performed in three histological fields – using a ×40 magnification objective lens – with the highest number of $IgG4^+$ plasma cells by: (a) counting the absolute number of $IgG4^+$ plasma cells (cut-off ranging from 10/hpf to 200/hpf, depending on the organ involved), or (b) calculating the $IgG4^+$ plasma cell-to-IgG^+ plasma cell ratio (with cut-off of 40 %). The above-mentioned board also proposed a terminology scheme – as "highly suggestive," "probable," or "insufficient" categories – for diagnosis of IgG4-RD, which is primarily based on the histopathological picture of the various biopsies [9]. In aortic biopsies, since some cases of atherosclerosis and giant-cell or infectious aortitis can sometimes display IgG4/IgG ratios close to 40 %, a cell ratio of >50 % should be considered as a threshold criterion for diagnosis of IgG4-RD [9, 10].

Overall, however, a number of vital points regarding IgG4-RD histopathological diagnosis are still pending. With regard to the general histopathological features in IgG4-RD, both storiform fibrosis and obliterative phlebitis cannot always be detected in the relevant biopsy material, even outside the above-mentioned organs that constitute an exception to the general rules. In fact the growth pattern of fibrosis may be different from one site to another and even from case to case, and the storiform pattern may merely be one of the possible morphologic manifestations of the newly formed fibrotic tissue. Furthermore, according to current understanding of IgG4-RD pathogenesis, IgG4 seems not to play a pathogenic role in the development of this disorder. In view of this, diagnostic criteria based on a pure dichotomic subdivision between IgG4-to-IgG plasma cell ratio of <40 % and >40 % would very likely miss a significant fraction of patients affected by this disease. Moreover, a distinction between organs in terms of different IgG4 cut-offs often seems somewhat arbitrary [11].

3.5 Idiopathic Retroperitoneal Fibrosis

IRF is a fibroinflammatory disorder included in the spectrum of "chronic periaortitis." In the great majority of cases, it develops around the infrarenal tract of a non-dilated aorta and the iliac arteries. IRF grows centrifugally and, in doing this, frequently entraps adjacent retroperitoneal structures such as the ureters and the inferior *vena cava* with obvious and severe *sequelae* [12, 13].

Grossly, IRF is a firm grayish noncapsulated mass, which stems from the adventitia of the aorta (or other arteries) and extends eccentrically towards the retroperitoneal soft tissues. Due to the infiltration of the resident adipose tissue, the peripheral areas of this mass often display a combination of grayish and yellow zones [12].

The histopathology of IRF is quite nonspecific (Fig. 3.4), especially if the various components are examined singularly. On the contrary, its microscopic picture as

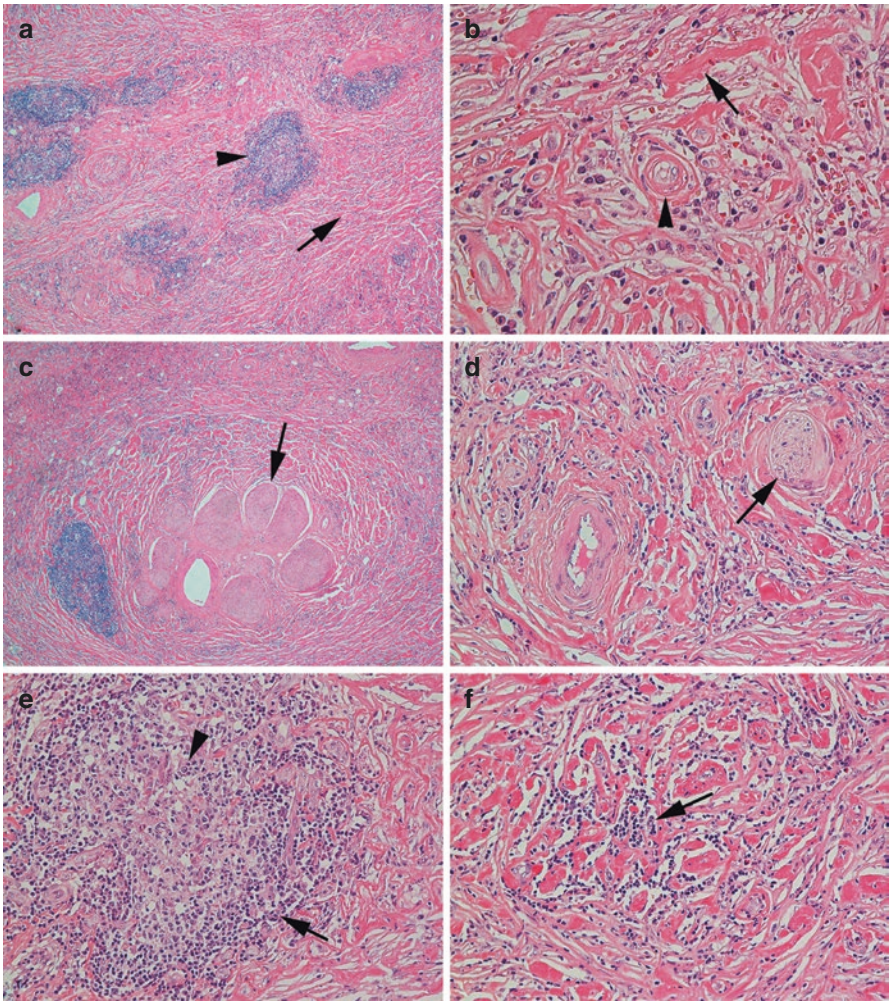


Fig. 3.4 Idiopathic retroperitoneal fibrosis. (**a**) Low-power view of an idiopathic retroperitoneal fibrosis constituted of a fibrous tissue (*arrow*) which replaces the resident soft tissues and an inflammatory component (*arrowhead*). (**b**) The fibrous component consists of thick keloid-like and haphazardly distributed collagen bands (*arrow*) with a peculiar onionskin distribution around the blood vessels (*arrowhead*). The inflammatory infiltrate is composed of lymphocytes, plasma cells, macrophages, and scattered eosinophils. (**c, d**). The fibroinflammatory proliferation may infiltrate and entrap large nerve trunks (**c**, *arrow*) as well as small peripheral nerves (**d**, *arrow*). (**e**) The perivascular pattern of the inflammatory infiltrate is characterized by a nodular aggregation of lymphocytes and plasma cells around the adventitia of small blood vessels (*arrow*). Sometimes, this component shows a germinal center (*arrowhead*). (**f**) The diffuse inflammatory pattern (*arrow*) consists of dispersed aggregates of the above-mentioned inflammatory cells

a whole bears morphologic characteristics which, when guided by informative clinicoradiologic information, very often allow the pathologist to make a correct diagnosis. Of course, the more adequate the biopsy (in terms of size and sampling site) the more accurate the diagnosis.

In broad terms, IRF consists of fibrous tissue and inflammatory infiltrate in various proportions from case to case and even within the same lesion. The fibrous component is characterized by thick keloid-like and irregularly distributed collagen bands (both immunohistochemically and ultrastructurally consistent with type I collagen) with quite a peculiar organization around the adventitia of small-sized blood vessels with an onionskin appearance. In addition, some nerves entrapped in the fibrous proliferation may be found. Closely associated to these collagen bands, there is a mild (sometimes moderate) proliferation of medium-sized fibroblasts/myofibroblasts with elongated and normochromatic nuclei. These spindle-shaped cells are immunohistochemically positive for vimentin and often smooth muscle actin (with a mild-to-moderate staining intensity suggesting a myofibroblastic phenotype), but do not express citokeratins, caldesmon, S100, CD34, ALK-1, beta-catenin, desmin, myogenin, or myoglobin. In addition, the MIB1 proliferation index in these cells is always negligible. Mitoses are absent or exceedingly rare and there are no signs of necrosis. Typically, the interface between IRF and the preexisting adipose tissue is poorly demarcated and displays a combination of IRF findings and resident soft tissues; in addition, the collagen fibers are often thinner than the above-mentioned ones, this fact suggesting that these areas represent the more recent ones within the fibroinflammatory proliferation. Congo red staining does not reveal any amyloid material deposition [12].

The fibrous background shows varying degrees of inflammatory infiltrate consisting of small lymphocytes, plasma cells, macrophages, and rare eosinophils; this inflammatory component is characterized by two main patterns: perivascular and diffuse. The inflammatory perivascular pattern consists of lymphocytes tightly packed within and around the adventitia of the small blood vessels; in a significant proportion of IRF cases, it is possible to identify a vasculitic process consisting of inflammatory cells infiltrating the wall of the above-mentioned blood vessels. On immunohistochemistry, the perivascular inflammatory infiltrates consist of similar proportions of CD3+ and CD20+ lymphocytes, with a CD4+/CD8+ cell ratio of about 3:1. Most of the perivascular inflammatory infiltrates have a peculiar target-like appearance (or even a germinal center), with the central portion occupied by CD20+ lymphocytes, and the periphery mainly consisting of CD4+ and CD8+ lymphocytes. The diffuse pattern is characterized by dispersed aggregates of lymphocytes, macrophages, and rare eosinophils infiltrating the narrow spaces between the collagen bands. Immunohistochemically, in the inflammatory areas with a diffuse pattern, there are more CD3+ than CD20+ lymphocytes, and the CD4+ and CD8+ cell percentages are quantitatively superimposable [12].

The above-described morphologic picture is also observed in the other forms of chronic periaortitis (i.e., perianeurysmal retroperitoneal fibrosis and inflammatory abdominal aortic aneurysms) as well as in thoracic periaortitis and in most of the secondary forms of retroperitoneal fibrosis.

3.6 Sclerosing Forms of Autoimmune Thyroiditis

The sclerosing forms of autoimmune thyroiditis are chronic disorders characterized by varying degrees of fibroinflammatory replacement of the thyroid gland parenchyma. They mainly encompass Riedel's thyroiditis, Hashimoto's thyroiditis, and the IgG4-related disease. Owing to the common inflammatory nature of these disorders and the relative nonspecificity of the different histopathologic findings, especially if considered singularly, a specific diagnosis may be challenging. This is why clinicopathologic correlation is vital to achieve a correct identification of the disease.

3.6.1 Riedel's Thyroiditis

Dr. Bernhard Riedel first described in 1896 this rare and – in some respects – still obscure thyroiditis [14]. Riedel's thyroiditis (RT) presents as a painless enlargement of thyroid gland with signs and symptoms secondary to frequent tracheal and esophageal fibrotic involvement. Like in HT, hypothyroidism and hyperthyroidism may manifest as a result of progressive replacement of the thyroid parenchyma by the newly formed fibrosclerotic tissue.

Grossly, the thyroid gland is grayish, nonlobulated, woody, and hard; in addition, it is typically fixed to the surrounding anatomic structures without any detectable cleavage plane.

Histopathologically (Fig. 3.5a, b), there is total loss of thyroid parenchyma, which is replaced by thick bands of hyalinized collagen. Interestingly, various degrees of phlebitis with consequent luminal obliteration of the small and large thyroid and extrathyroid veins may also be found.

The inflammatory infiltrate is frequently scattered in the sclerotic areas and more copious at the border of the lesion; it is composed of lymphocytes, monocytes, and granulocytes, with no evidence of giant cells, lymphoid follicles, oncocytes, and granulomas. Immunohistochemically, there are more T- than B-lymphocytes, with a similar ratio of CD4 and CD8 cells [15].

3.6.2 Hashimoto's Thyroiditis

First described in 1912 by Dr. Hakaru Hashimoto [16], Hashimoto's thyroiditis (HT) is an autoimmune disease affecting more commonly women than men (ratio 10:1, respectively) and characterized by the presence of a series of circulating autoantibodies to thyroid antigens (see Chap. 7 of this textbook).

The disease develops over a span of months to years and shows a transitory hyperthyroidism (mainly due to follicle rupture and consequent thyroid hormone release into the circulation) followed by possible clinical or subclinical hypothyroidism (secondary to various degrees of fibroinflammatory thyroid parenchyma replacement) [17].

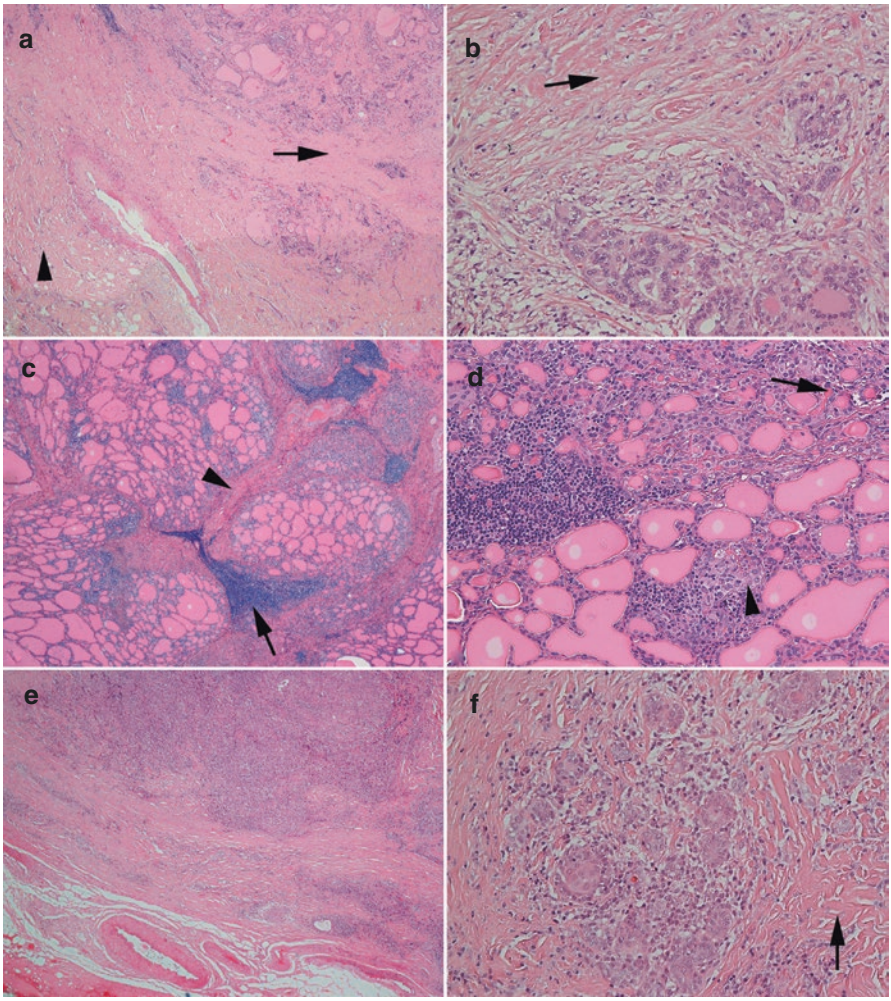


Fig. 3.5 Sclerosing forms of autoimmune thyroiditis. (**a**) Low-power view of Riedel's thyroiditis showing a significant and progressive replacement of the organ parenchyma by collagen fibers (*arrow*). Typically, this sclerotic tissue extends beyond the thyroid capsule (*arrowhead*) and is usually fixed to the surrounding structures. With time, the thyroid parenchyma is progressively replaced by the sclerotic tissue (**b**, *arrow*). (**c**) Hashimoto's thyroiditis consists of a mainly lymphocytic inflammation (*arrow*) of the thyroid gland with some degree of sclerosis (*arrowhead*). The involved thyroid follicles (**d**) are atrophic (*arrow*) and may show some oncocytic metaplasia (*arrowheads*). (**e**) The "fibrous variant" of Hashimoto's thyroiditis is characterized by marked sclerosis (usually, more than one third of the organ) which typically – unlike Riedel's thyroiditis – is confined within the thyroid capsule. The collagen bands (**f**, *arrow*) are thicker than those of Riedel's thyroiditis

Grossly, as a rule, the gland is homogenously enlarged and not fixed to the surrounding structures. On cut section, thyroid parenchyma displays varying degrees of lobulation and a spectrum of colors from pale pink to gray, depending on the amount of fibrous tissue.

The usual form of HT is microscopically characterized by different degrees of lymphocytic (with comparable amounts of B and T cells) and plasmacytic inflammatory infiltrates and, in the most active cases, formation of lymphoid follicles (Fig. 3.5c, d). With time, this inflammatory process induces follicle atrophy with focal or extensive oncocytic metaplasia (Hürthle's cell metaplasia), decreased or no colloid, and, finally, collagen fiber deposition. Of note, Hürthle metaplastic cells may often show nuclear pseudo-atypia that can be mistaken for malignancy. Likewise, the follicular cells entrapped into the lymphoplasmocytic process may display nuclear clearing, thereby simulating papillary carcinoma of thyroid gland.

The "fibrous variant" of HT (10–13 % of the HT cases) is characterized by marked fibrosis – from one-third to the majority of the parenchyma – which replaces the normal architecture of the thyroid gland (Fig. 3.5e, f). When this sclerotic replacement does not affect the entire organ, changes typical of otherwise usual HT in the remaining parenchyma are detectable, including islands of metaplastic squamous epithelium that may simulate foci of carcinoma cells. Unlike RT, the fibrotic process does not extend beyond the thyroid capsule. In addition, fibrosis is of dense hyaline type, thereby differing from the active proliferative fibrosis seen in RT [18]. Stromal fibrosis in HT has recently been classified into three main patterns which can also occur in various combinations: (a) interlobular fibrosis, in which fibrous tissue surrounds end extends between individual lobules (or a small group of follicles); (b) interfollicular fibrosis, in which the increased fibrous tissue occupies the interfollicular space, thereby separating individual follicles; and c. scar fibrosis, with keloid-like fibrosis [19].

3.6.3 IgG4-Related Disease

A small subtype of HT with lymphoplasmacytic fibrotic changes and an increased number of $IgG4^+$ plasma cells has recently been reported in the literature. Since this form shared similar microscopic features with IgG4-RD in other organs, it was proposed that Hashimoto's thyroiditis can be subdivided into two subgroups: "IgG4 thyroiditis" and "non-IgG4 thyroiditis" [20]. The HT subtype that displays closer similarities with the so-called IgG4 thyroiditis is its already discussed fibrous variant [19]. Even though with significant overlapping features, Li et al. [19] have recently found some histopathologic differences between fibrous variant of HT and IgG4 thyroiditis which allowed them to consider these two entities as quite separate. IgG4 thyroiditis is significantly associated with a prevalent interfollicular pattern of fibrosis, while non-IgG4 thyroiditis shows more commonly interlobular fibrosis. In addition, unlike non-IgG4 thyroiditis, IgG4 thyroiditis frequently shows the presence of small thyroid follicles, significant follicular cell degeneration, and increased giant cell/histiocyte infiltration [19]. Whether these differences are the consequence

of an a priori subdivision into IgG4 and non-IgG4 groups merely based on arbitrary IgG4+ plasma cell level cell cut offs (and, therefore, into more or less inflammatory cases), remains a critical challenge.

3.7 Erdheim-Chester Disease and Non-Erdheim-Chester Disease Histiocytoses

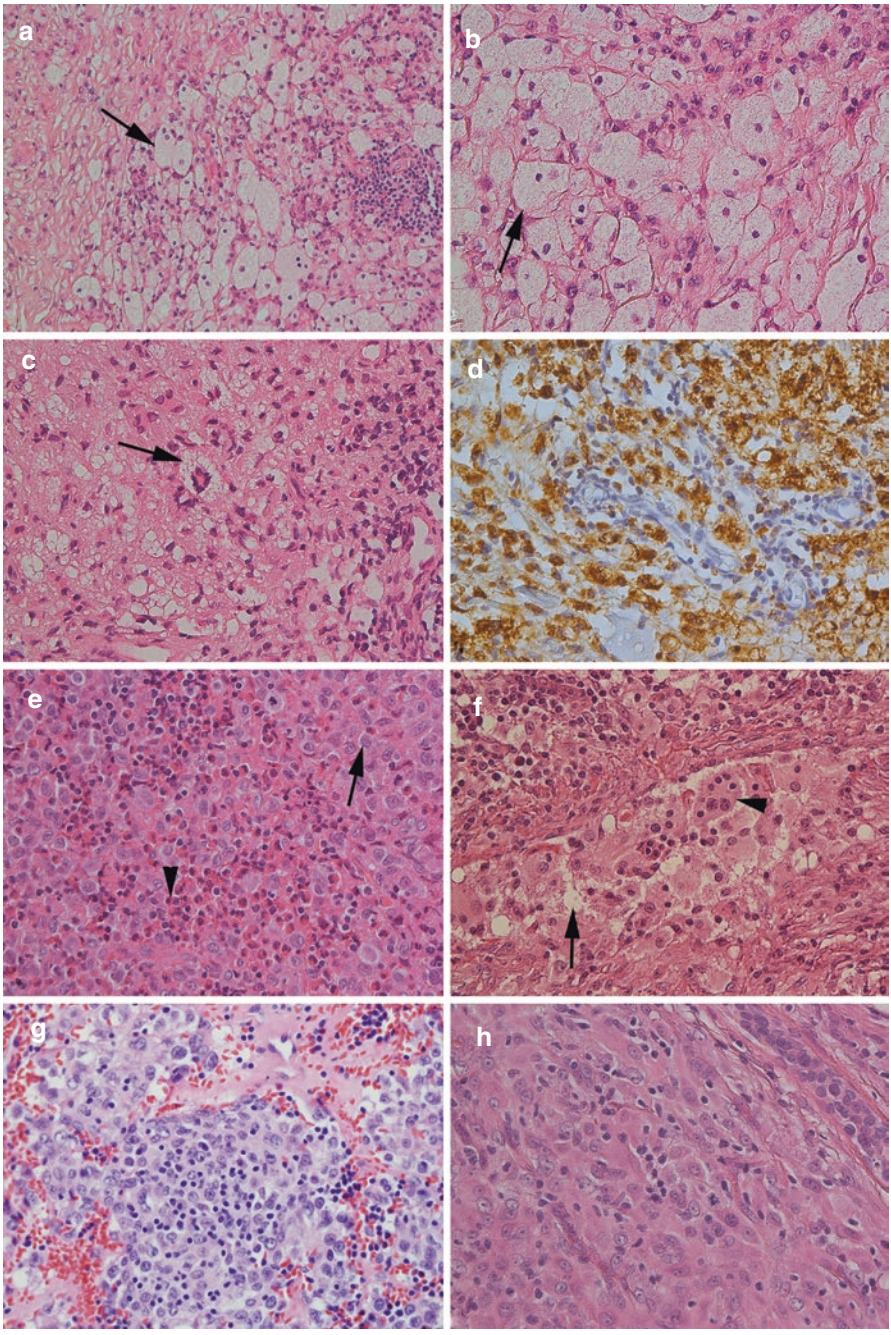
Histiocytoses are rare tumors characterized by the primary accumulation and tissue infiltration of histiocytes and dendritic cells. The main histologic types include Langerhans cell histiocytosis (LCH), Rosai-Dorfman disease (RDD), ECD, follicular dendritic cell sarcoma/tumor (FDCS), and histiocytic sarcoma (HS).

3.7.1 Erdheim-Chester Disease

ECD is an exceedingly rare form of non-Langerhans cell histiocytosis; it clinically presents with a broad spectrum of manifestations, ranging from focal to diffuse and infiltrative locations, which often affect multiple organ systems and display a high mortality rate [21]. Possible manifestations of this disorder include a very frequent skeletal involvement, diabetes insipidus, exophthalmos, xanthelasmas, retroperitoneal fibrosis with perirenal and/or periureteral involvement, interstitial lung disease, bilateral adrenal enlargement, renal function impairment, testis infiltration, and central nervous system and cardiovascular involvement [22].

The pathology of ECD (Fig. 3.6a, d) is characterized by skeletal and extraskeletal areas where the normal tissue architecture has been replaced by a proliferation of $CD68^+$ and $CD1a^-$ histiocytes organized in small nests and/or significant groups with, in between, a noteworthy amount of dense type I collagen with a usually

Fig. 3.6 Erdheim-Chester disease and other histiocytoses. (**a**) The pathology of Erdheim-Chester disease consists of foci of tissue infiltration by histiocytes (*arrow*) in a fibrous background often with varying amounts of chronic inflammatory cells. (**b**) These histiocytes (*arrow*) show typical foamy cytoplasms and small nuclei. (**c**) Sometimes, they display a kind of Touton-like appearance (*arrow*). (**d**) On immunohistochemistry, these histiocytes are decorated by an anti-CD68-KP1 antibody. (**e**) Langerhans cell histiocytosis consisting of Langerhans cells (*arrow*) and a significant amount of eosinophils (*arrowhead*). (**f**) Rosai-Dorfman disease with sinusoidal dilation (*arrow*) containing histiocytes, lymphocytes, and plasma cells. In this setting, phenomena of emperipolesis (*arrowhead*, lymphocytes within the cytoplasm of histiocytes) are a common finding. (**g**) Follicular dendritic cell sarcoma/tumor (Courtesy of Dr. Jennifer L. Oliveira, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN). (**h**) Histiocytic sarcoma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minor fibroblastic component. The histiocytes are foamy and roundly shaped; however, sometimes, they display a more elongated profile, especially in the more fibrous cases and in bone locations. Quite often, a mild-to-moderate reactive inflammatory infiltrate principally made of small lymphocytes and, to a lesser extent, plasma cells may be detectable throughout the histiocytic proliferation. Skeletal locations of ECD are usually characterized by sclerotic and hypertrophic bone lamellae and, in parallel, replacement of the intertrabecular space tissues by the above-described proliferation. Sometimes, these lesions are purely lytic with marked resorption of the lamellar component and mild sclerosis of the surrounding reactive bone. The main pathologic differential diagnosis includes nonspecific histiocyte-rich inflammatory infiltrates, true xanthomas, LCH, RDD, and histiocyte nests in fibrous dysplasia of bone [23].

3.7.2 Langerhans Cell Histiocytosis

LCH is a neoplastic proliferation whose main cells are Langerhans cells characterized by a consistent expression of CD1a and S100 proteins. In the great majority of cases this disorder is unifocal (so-called "solitary eosinophilic granuloma") and usually occurring in bones (e.g., skull, femur, pelvis, or ribs) and less frequently lymph nodes, skin, or lung. When multifocal and unisystem (so-called Hand Schüller-Christian disease), LCH occurs in multiple sites within a single system, almost always in bones. In its multifocal multisystem variant (so-called Letterer-Siwe disease), multiple systems are affected such as bones, skin, liver, spleen, and/or lymph nodes [24, 25].

Histopathologically (Fig. 3.6e), LCH appears as a mixture of Langerhans cells and eosinophils in different proportions. Typically, the Langerhans cell, 10–12 μm in size, displays a slightly eosinophilic and moderately abundant cytoplasm with or without very fine and clear spaces. Its nuclear shape ranges from reniform to oval, with fine chromatin, inconspicuous nucleoli, and thin nuclear membranes. In their classic description its nuclei have "grooves" or "lines," but in reality the nuclei are "cleaved" or "convoluted." In addition to Langerhans cells and eosinophils, varying amounts of histiocytes (mono- or sometimes multinucleated), neutrophils, and lymphocytes may be detected throughout the neoplastic proliferation. Sporadically, eosinophilic microabscesses with central necrosis can be found. Early cases are characteristically more cellular than older lesions which can display larger areas of fibrosis with foamy histiocytes [24, 25].

3.7.2.1 Rosai-Dorfman Disease

RDD – also called "sinus histiocytosis with massive lymphadenopathy" – was identified as a distinct clinicopathologic disorder in 1969 by Drs. Rosai and Dorfman [26]. Clinically, RDD presents with fever, leukocytosis, and nonpainful cervical lymphoadenopathy. It tends to affect the lymph nodes in the head and neck region; however, it can also present in almost any extranodal site (e.g., skin, soft tissue, central nervous system, and, less frequently, gastrointestinal tract) [27].

From a histopathological standpoint (Fig. 3.6f), the lymph node architecture is disrupted by massive sinusoidal dilation containing histiocytes, lymphocytes, and plasma cells. Emperipolesis within the histiocyte cytoplasm is a classical finding in this disorder: lymphocytes, plasma cells, and erythrocytes may be found in intracellular vacuoles within histiocytes, this fact very likely being a kind of escape from degradation by the cytolytic enzymes during their transit through the histiocyte cytoplasm [28, 29]. In addition, reactive lymphoid follicles may be frequently detected in the lymph node cortex. In the medullary lymph node region, increased plasma cells, small lymphocytes, and occasional lipid-laden macrophages are present [27]. In extranodal sites, RDD shows increased amounts of fibrosis, while fewer histiocytes may be detected [26, 28]. On immunohistochemistry, RDD histiocytes are positive for CD68-KP-1, CD163, and S100, while they stain typically negative for CD1a.

3.7.3 Follicular Dendritic Cell Sarcoma/Tumor

FDCS/T is a neoplastic proliferation of cells featuring morphologic and phenotypic characteristics of follicular dendritic cells. The World Health Organization (WHO) has proposed the designation "sarcoma/tumor" in view of the variable cytologic grade and indeterminate clinical behavior in a large number of FDCS/T cases [30].

FDCS/T affects lymph nodes in one-half to two-thirds of cases, with the cervical lymph nodes the most affected; axillary, mediastinal, mesenteric, and retroperitoneal lymph node stations are further locations of this neoplasia. Among the extranodal sites, tonsil, spleen, oral cavity, gastrointestinal tract, liver, soft tissue, skin, and breast are possible locations of the disease [30].

Histopathologically (Fig. 3.6g), the neoplastic cells are large (measuring at least 20 μm) and spindle shaped. They usually have an oval and central nucleus, with a delicate nuclear membrane, finely dispersed chromatin, and a small but prominent nucleolus. In some fields, ovoid and/or polygonal cells may also be seen. A variable number of binucleated, multinucleated, and/or vacuolated cells may be found in most cases. The mitotic count usually ranges between 1 and 5×10 HPF. The neoplastic cells form a whorled, fascicular or storiform pattern. In the background, there is a variable number of small lymphocytes, both isolated and in small clusters. Sclerotic bands may also be found. On immunohistochemistry, the neoplastic cells express FDC-associated antigens (CD21, CD35, and CD23); CD68-KP1 and S100 protein may variably be expressed [31].

3.7.4 Histiocytic Sarcoma

HS is a malignant proliferation of cells showing features similar to mature histiocytes. About one-third of HS cases occur in lymph nodes, one-third in the skin, and the remaining third in other extranodal sites (e.g., intestinal tract) [32].

From a histopathologic standpoint (Fig. 3.6h), tumor cells are large and ovoid cells with a diameter greater than 20 μm. Their nuclei – round or oval – are slightly

eccentric and with finely to moderately dispersed chromatin and one or more small, but distinct nucleoli. Cellular pleomorphism is usually moderate, but in some instances more pronounced, sometimes with multinucleated giant cells and rare spindle cells. HS tumor cells show a cohesive and diffuse growth pattern with a mitotic count ranging from 10 to 30/10 HPF. Neoplastic cells consistently express cytoplasmic CD68-KP1 and CD68-PGM1 in a granular pattern, lysozyme, CD11c, CD14, CD45, CD45RO, and HLA-DR [31, 32].

3.8 Inflammatory Myofibroblastic Tumor

IMT is a distinct neoplastic proliferation of fibroblasts/myofibroblasts associated with an inflammatory cell population composed of lymphocytes, plasma cells, and/or eosinophils. IMT shows slight female predominance; it predominantly affects children and young adults, and is rare in individuals older than 50 years of age [33, 34].

Lung, mesentery, omentum, retroperitoneum, abdominal soft tissues, mediastinum, and the head and neck region are the most common IMT locations, even though almost any site may be affected. Up to one third of patients develop a systemic syndrome in the form of fever, anemia, weight loss, hypergammaglobulinemia, thrombocytosis, elevated erythrocyte sedimentation rate, and/or elevated C-reactive protein [34].

Grossly, IMT is a nodular or multinodular lesion whose diameter ranges widely in size from 1 to more than 20 cm (average size 6 cm). Its cut section may be tan, whorled, fleshy, or myxoid with possible hemorrhagic, necrotic, or calcific areas [35, 36]. Histopathologically (Fig. 3.7), IMT consists of proliferating spindle cells that can be organized into three patterns: loosely arranged myofibroblasts in an edematous myxoid background, a compact fascicular proliferation in a variable collagenous or myxoid stroma, or a scar-like hypocellular spindle-cell proliferation. In about 50 % of cases, a population of ganglion-like myofibroblasts may also be

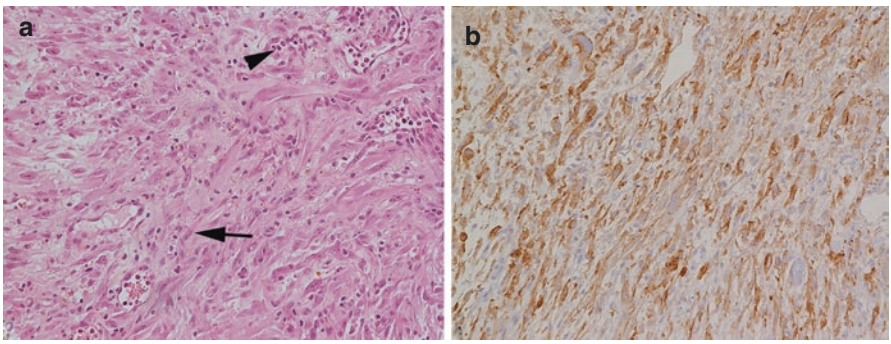

Fig. 3.7 Inflammatory myofibroblastic tumor. (**a**) Medium-power view showing a fibroblastic/myofibroblastic proliferation (*arrow*) associated with an inflammatory component (*arrowhead*) which varies in entity from case to case. (**b**) In about 50 % of cases, the spindle cells are immunohistochemically positive for ALK

detected. A prominent inflammatory infiltrate composed of lymphocytes, plasma cells, and/or sparse eosinophils permeating the fibroblast proliferation is one of the key morphological findings [33, 34, 37]. A distinctive variant of IMT – the "epithelioid inflammatory myofibroblastic sarcoma" – affects mesentery and omentum and consists of epithelioid cells with vesicular nuclei and large nucleoli, in a myxoid stroma. This form is associated with *RANBP2-ALK* gene rearrangement [38]. From the immunohistochemical standpoint, IMT is positive for smooth muscle actin in 80 % of cases, desmin in 60 %, and keratins in about one third of patients [36, 37]. Interestingly, about half of IMTs display cytoplasmic immunoreactivity for anaplastic lymphoma kinase (ALK), this finding correlating with the presence of *ALK* gene rearrangement [39]. The epithelioid inflammatory myofibroblastic sarcoma frequently shows a nuclear membrane ALK positivity [38].

The main pathologic differential diagnosis includes quite a large series of spindle cell sarcomas such as leiomyosarcoma, low-grade myofibroblastic sarcoma, dedifferentiated liposarcoma, fibromatosis, gastrointestinal stromal tumor (GIST), and dendritic-cell sarcomas [33].

IMT is characterized by an intermediate biologic potential, in view of its marked risk of local recurrence (<25 % in abdominal lesions while about 5 % in lungs) and quite a low rate of metastases (<5 %) [37]. The epithelioid inflammatory myofibroblastic sarcoma shows a particular aggressive clinical course [38]. Surgery is the treatment of choice in IMT, but targeted kinase inhibitor therapies may be beneficial in recurrent and metastatic cases [40].

Conclusions

Quite a wide range of microscopic findings characterize the pathology of systemic fibroinflammatory diseases, which in the majority of cases allow the pathologist to achieve a specific diagnosis. However, detailed clinicoradiologic information and adequate biopsies are the basis for a fruitful collaboration between pathologists and physicians who are in charge of a given patient.

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IgG4-Related Disease: A Prototypical Fibroinflammatory Disease. Overview on Clinical and Therapeutic Aspects

4

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4.1 Introduction

Among fibroinflammatory diseases, IgG4-related disease (IgG4-RD) has recently emerged as a prototypical one. Different entities have been unified within IgG4-RD because of common histopathological characteristics, despite their clinical, biological, and radiological presentations are variable and heterogeneous. In this chapter, we provide an overview on clinical and therapeutic aspects of the disease. Pathogenesis and pathology of IgG4-RD are analyzed in specific chapters of this book and will not be detailed in this section.

4.2 Definition and Nosology

IgG4-RD has emerged as a distinct clinicopathological entity during the last decade. The first description of the disease came from gastroenterologists. Sarles and colleagues described in 1961 chronic inflammatory sclerosis of the pancreas and raised the hypothesis of a new form of pancreatic disease [1]. They noted that patients presented inflammatory infiltrates in the pancreas and in some cases hypergammaglobulinemia. In 1997, Belgian and German authors reported the first anatomical series and clearly distinguished this entity as a nonalcoholic, duct-destructive chronic pancreatitis, showing that major histological changes were inflammatory infiltrates, comprising mainly T cells but also scattered aggregates of B lymphocytes and plasma cells centered around the ducts [2]. Yoshida and colleagues reported in 1995 that this chronic pancreatitis with hypergammaglobulinemia and

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not associated with Sjögren's syndrome responded to steroid therapy, and proposed the concept of "autoimmune pancreatitis" [3]. The hypothesis of the "autoimmune" nature of this pancreatitis was then reinforced by the association in some patients with antilactoferrin or anticarbonic anhydrase II antibodies, both against antigens expressed by pancreatic acinar and duct cells [4].

The link with immunoglobulin G4 (IgG4) came from the report in 2001 by Hamano and colleagues, who showed that most patients with sclerosing pancreatitis presented with elevated serum IgG4 levels [5]. This finding prompted to search for the source of IgG4 and led to the discovery of IgG4-positive plasma cells in the inflammatory lesions [6]. These characteristic pathological changes, usually with serum IgG4 elevation, have then been found in several clinical entities including sialadenitis, dacryoadenitis and Mikulicz's syndrome, cholangitis, retroperitoneal fibrosis (Ormond's disease), interstitial nephritis, pachymeningitis, aortitis, and prostatitis [7]. Their frequent association with type 1 "autoimmune" pancreatitis and other organ manifestations in a single patient has led to the concept of a systemic, IgG4-associated, disease. Eventually the term of "IgG4-related disease" (IgG4-RD) was retained and a nomenclature suggested for each organ manifestation [8]. At the same time general diagnostic criteria and pathological criteria were proposed [9–11].

4.3 Pathological Characteristics

The pathological characteristics include, aside the IgG4 plasmocyte infiltration, a dense polyclonal lymphoplasmocytic infiltrate associated with fibrosis (often with peculiar storiform pattern) and frequently obliterative phlebitis and sparse eosinophilic infiltrates [11]. Ectopic germinal centers were also observed in some cases and the polyclonal lymphocytic infiltrate includes numerous T lymphocytes. A specific section on histopathology of IgG4-RD has been detailed in Chap. 3. The clinical, imaging, and biological manifestations of the disease are the consequence of the pseudotumoral, often compressive, proliferation of the polyclonal lymphoplasmocytic infiltrate, and the fibrotic process.

4.4 Epidemiology

The prevalence and the incidence of IgG4-RD is largely unknown. Japanese authors have estimated its incidence to be 0.28–1.08/100,000 inhabitants/year, with 336–1300 newly diagnosed patients each year, whereas its prevalence is about 1/600,000 inhabitants in Japan [12]. There is a peak of age at disease onset between the fifth and the seventh decade [7]. Male gender is overrepresented in all series (ranging from 61 % to 80 %), but the sex ratio varies depending on the type of organ involvement [13, 14].

4.5 Clinical Characteristics

Clinical symptoms are extremely variable and depend on the type and number of organs involved. In our experience, general symptoms are rarely observed (weight loss in 32.6 % of patients, fatigue in 31.4 %, fever >38.5 °C in 7 % of a French case series of 86 cases [15]) and the symptoms noticed at diagnosis are mainly related to pancreatobiliary (abdominal pain in 26.7 %, jaundice in 12.8 %), salivary gland (enlargement in 18.6 %, sicca syndrome in 12.8 %), lacrimal gland (enlargement in 8.1 %), or lymph node (enlargement in 20.9 %) involvement, as in other series [16–19].

Major organs targeted by the disease have been reported in different retrospective case series from Europe, North America, and Asia (Table 4.1). There are clearly different forms of the disease that can be clinically distinguished as: localized versus systemic, and relapsing versus nonrelapsing. Relapses can occur at the initial site or metachronously in one or several other sites, as in other systemic diseases.

Besides these major prototypic organ involvements, several reports have indicated that other tissues (i.e., neural, skin, or bone) can present with characteristic pathological changes of the disease. Minimal criteria to propose IgG4-RD involvement of a new organ/site have been proposed: characteristic histopathological findings with high infiltrating $IgG4^+$ plasma cell numbers and a high $IgG4^+/IgG^+$ ratio and either (1) high serum IgG4 concentrations or (2) effective response to glucocorticoid therapy or (3) report of other organ involvement that is consistent with IgG4-RD in the same patient [11]. These criteria are however debatable.

Thus, the precise characterization of the clinical spectrum of the disease is not yet complete. This is also illustrated by the high rate of variation in the frequency of some major organ involvements (e.g., frequency of IgG4-related pancreatitis varying from 16 % to 44 %, see Table 4.1), reflecting probably a bias in case recruitment in major series. Moreover, the involvement of certain organs and some rare manifestations of the disease are probably underrecognized by physicians. This could explain the high proportion of systemic forms of the disease reported in the largest case series. Involvement of more than one organ was observed in 47–86 % of patients, and of more than three organs in 36–42 % (Table 4.1).

Common manifestations of IgG4-RD are shown in Fig. 4.1.

4.6 Laboratory Findings

The most characteristic biological finding associated with the disease is serum IgG4 elevation over 1.35 g/L (or 135 mg/dL). However, this elevation is neither specific for the diagnosis of IgG4-RD nor particularly sensitive [20, 21], as false negatives are observed in a range of 20–50 % of cases [13, 15]. There is no evidence at this time that IgG4 is by itself pathogenic. This is also based on previous works showing that IgG4 is not able to activate complement [22] and has a so-called antiinflammatory activity related to a dynamic process known as “Fab arm exchange” [23].

Table 4.1 Frequency (in %) of organ involvements in case series of IgG4-related disease

	Grados et al. [15]	Wallace et al. [13]	Fernandez-Codina et al. [19]	Campochiaro et al. [16]	Chen et al. [17]	Lin et al. [18]	Inoue et al. [14][a]
No. of patients	90	125	55	41	28	118	235
>1 organ	81	62	47	58	86	78 (>2)	58
>3 organs	36	38	–		42		
Pancreas	44	19	16	44	32	38	60
Biliary tree	27	9	4	10	29	17	13
Lymph nodes	58	27	2	12	43	65	14
Salivary glands	32	28	16	19	79	64	34
Lacrimal glands	9	–	22	–	46	50	23
Orbit	7	22	15	7	4	–	4
Kidney	32	12	7	2	11	24	9
RPF	28	18	27	19	11	26	4
Lung	14	17	9	2	4	27	5
IPT	30	–	–	–	11	8	–
Aorta	13	11	9	10	4	0	20
Meninges	2	2	4	7	–	0	–
Skin	–	2	0	0	–	4	–
Sinusitis	–	4	–	4	4	12	–
Mesentery	1	2	7	–	–	0	–
Prostate	6	3	–	–	14	35	–
Mediastinum	0	2	–	–	7	3	–
Thyroid	1	–	–	–	–	1	–

[a]In this study two inclusion criteria were used: the CDC for IgG4-RD and the International Diagnosis Criteria for autoimmune pancreatitis, *RPF* retroperitoneal fibrosis, *IPT* inflammatory pseudotumor (this item includes inflammatory pseudotumor from various organs)

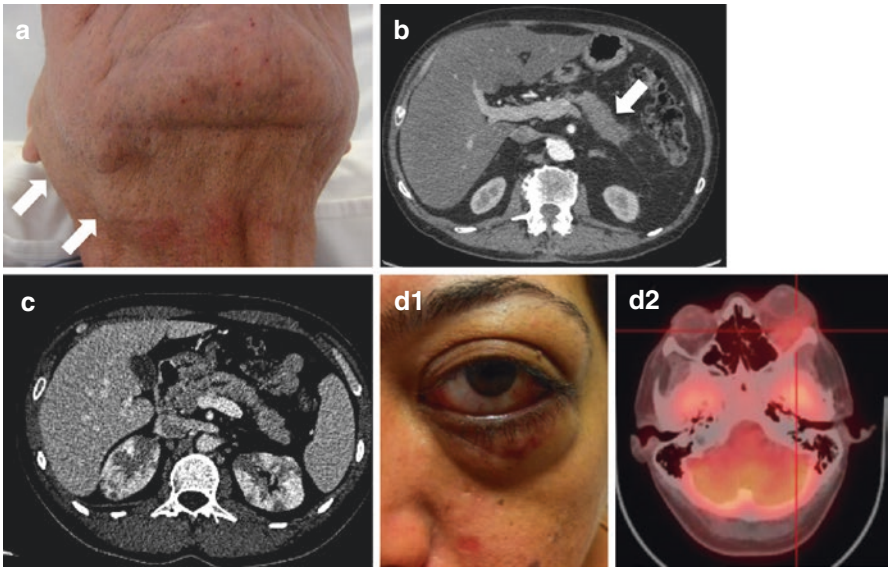

Fig. 4.1 (**a**) Parotid and submandibular gland involvement by IgG4-related disease. The *arrows* show the parotid and the submandibular enlargement in an 82-year-old man. (**b**) Abdominal CT scan showing an atypical caudal pancreatic enlargement (*arrow*) revealing IgG4-related pancreatitis. (**c**) CT scan showing bilateral pseudotumoral kidney masses revealing IgG4-related kidney involvement. (**d1**, **d2**) Unilateral exophthalmos with an orbital mass seen on PET (**d2**) revealing an IgG4-related orbitopathy

Table 4.2 Frequency of abnormal biological findings in IgG4-related disease patients

	Chen et al. [17]	Lin et al. [18]	Grados et al. [15]
n	28	118	90
IgG4 > 1.35 g/L	100 %	97.5 %	81 %
Elevated ESR	57 %	62 %	ND
Elevated CRP	25 % (>8 mg/l)	44 %	37 % (>15 mg/L)
Decreased Cpt	ND	ND	30 %
Elevated IgE	100 %	89 %	78 %
Eosinophilia	39 %	33 %	ND

This table provides the frequency of patients with abnormal biological values. Other series have reported variation of biological levels, however not as percentage of abnormal values but as mean levels

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *Cpt* complement levels (C3, C4, or CH50), *ND* not determined

Besides serum IgG4 elevation, an increase in other IgG subclasses is frequent [13, 24] and also contributes to the hypergammaglobulinemia observed in these patients. Abnormal k/λ ratios have also been reported [25]. IgE elevation is usual, probably resulting from the associated Th2 response, as is eosinophilia (Table 4.2). Eosinophilia is frequent with possible values over 1500 eosinophils/μL [13].

Antinuclear antibodies can be found at low titers, but usually anti-extractable nuclear antigen antibodies (and especially anti-SSA and anti-SSB) are negative. In most cases, the C-reactive protein level is normal or only moderately elevated. More recently, it has been proposed that total circulating and IgG4$^+$-plasmablast counts could be specifically increased and correlate with disease activity [26, 27].

4.7 Imaging

Radiological evaluation depends on clinical presentation and varies according to the affected organs [28]. Diffuse or patchy mass-forming lesions can develop in the involved organs with pseudotumoral presentation. Specific radiological abnormalities in pancreas and pancreatic ducts in IgG4-related pancreatitis and in bile ducts in IgG4-related cholangitis have been retained as diagnostic criteria for organ-specific forms [29, 30], and will be discussed in detail in Chap. 6 of this book.

For systemic and whole-body evaluation of the disease, ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET-CT) has been reported to be a useful tool [31, 32], especially for affected sites such as aorta/large arteries, salivary glands, and lymph nodes, with more sensitivity than conventional imaging studies for these organ lesions (Fig. 4.2). It has been suggested that this imaging modality can be useful not only for the initial disease evaluation but also during follow-up to assess response to treatment and detect relapses [31, 32]. Nevertheless, the utility of serial FDG PET-CT has not been clearly demonstrated, and the radiological follow-up must be tailored on patients' specific clinical features [28].

4.8 Diagnosis

The diagnosis or classification of IgG4-RD is currently based on the pathological consensus criteria [11] and general Comprehensive Diagnostic Criteria (CDC) [9]. These last criteria, based on clinical, biochemical (serum IgG4 > 1.35 g/L), and histological findings have been proposed by the Japanese IgG4 team. They include: (1) organ involvement (dysfunction, diffuse, or localized swelling); (2) serum IgG4 > 135 mg/dL; and (3) histopathological findings characteristic of IgG4-RD (e.g., lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis), with immunohistochemical evidence of a high proportion of IgG4$^+$ plasma cells (>40 % of total IgG$^+$ plasma cells, > 10 IgG4$^+$ plasma cells per hpf). If all three criteria are met, the diagnosis is considered to be *definite*; if 1 + 3 are met, the diagnosis is *probable*; finally, fulfillment of 1 + 2 makes the diagnosis of IgG4-RD *possible*. These criteria have been designed because former organ-specific criteria for type 1 autoimmune pancreatitis [29], IgG4-related dacryoadenitis/sialadenitis [33], and IgG4-related kidney disease [34] were unable to classify all patients with characteristic pathological findings of the disease. Pathological characteristics have been defined by a consensus of experts [11] (See Chap. 3 of this book).

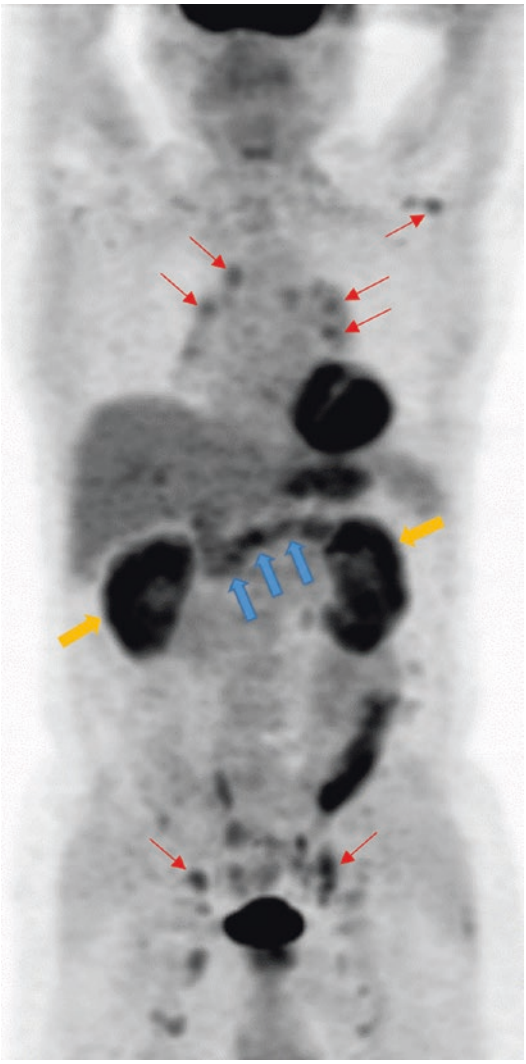

Fig. 4.2 PET-CT from a 72-year-old man presenting with a relapse of IgG4-RD. Relapse occurs after the tapering and stop of a 2-year treatment with prednisone and azathioprine. This PET-CT illustrates the systemic form of the disease, showing significant uptake of FDG of pancreas (*blue arrows*), both kidneys (*orange arrows*) and numerous mediastinal and pelvic lymph nodes (*red arrows*). Patient also presented with high serum IgG4 level (3.66 g/L) and complement decrease. IgG4-RD was proven by pathological analysis of kidney biopsy, showing tubulointerstitial nephritis with lymphoplasmocytic infiltrate, fibrosis, and IgG4+/CD138+ plasmocytes ratio of 50 % with 40 IgG4+ plasmocytes/HPF

It was also pointed out that several benign and malignant diseases should be systematically ruled out before a diagnosis of IgG4-RD can be made. Because serum IgG4 evaluation is associated with false negative and false positive results [20, 21], pathological documentation is highly recommended. Major differential diagnoses include: Sjögren syndrome, lymphoma and solid tumors, primary sclerosing cholangitis, ANCA-associated vasculitis, idiopathic and secondary retroperitoneal fibrosis, myofibroblastic tumors, Castleman disease, and sarcoidosis.

Currently, major unanswered questions regarding IgG4-RD definition and classification are: (1) the specificity and the weight of pathological changes and clinical/

imaging of organ involvement; and (2) the nosological boundaries with other idiopathic fibroinflammatory disorders. Future collaborative classification criteria should improve these points.

4.9 Overlap with Other (Fibroinflammatory) Disorders

The overlap with other fibroinflammatory diseases is a matter of debate. Because the pathogenesis of IgG4-RD and other idiopathic fibroinflammatory diseases is largely unknown, the nosological limit is unclear. Is the IgG4-RD pathological pattern unique to some fibroinflammatory IgG4-RD diseases or a pathological step for several yet unrelated fibroinflammatory disorders? For example, based on retrospective pathological analysis of case series, the frequency of IgG4-RD retroperitoneal fibrosis ranges between 28 % [35] and 57 % [36]. In idiopathic retractile mesenteritis, Akram et al. found that only 30 % of cases presented typical pathological findings of IgG4-RD [37]. Other retrospective studies on pathological specimens of aortitis [38] and pachymeningitis [39] have also evaluated the frequency of typical histological IgG4-RD criteria to clarify the overlap with these inflammatory diseases. For Hashimoto's thyroiditis there are controversial reports. Some case series reported that the fibrosing variant of Hashimoto's thyroiditis is an IgG4-RD based on pathological findings [40]. An increase in tissue $IgG4^+$ plasmocytes has been reported by several studies, but the exact overlap between IgG4-related thyroiditis and Hashimoto's thyroiditis needs to be further analyzed (see Chap. 7 of this textbook) [41].

Overlap with Rosai-Dorfman disease has also been investigated because numerous $IgG4^+$ plasmocytes can be observed in nodal and extranodal disease lesions, with variable degrees of fibrosis. It has been shown that some patients with Rosai-Dorfman disease harbor pathological characteristics of IgG4-RD, but large pathological series reported that the disease does not belong to IgG4-RD [42]. Likewise, differential diagnosis between IgG4-related lymphadenopathy and multicentric Castleman disease can be difficult, because of common histopathological characteristics and possible numerous $IgG4^+$ plasma cells in Castleman lymphadenopathy [43].

For these reasons, both characteristic pathological and clinical/imaging assessment are important for the diagnosis of IgG4-RD. Pathological assessment of the diseased lymph nodes can be challenging.

4.10 Treatment and Prognosis

Most data concerning the evolution and treatment of IgG4-RD come from studies performed in (IgG4-related) type 1 autoimmune pancreatitis [44–46]. Nevertheless, further data have been published these last years, based on cohorts of patients with various types of organ involvement [13, 14, 16, 18, 19, 24]. An international consensus paper on IgG4-RD management has recently been published by a multidisciplinary team of experts [28].

Favorable evolution and spontaneous regression without treatment have been described [47, 48]. Whether IgG4-RD always needs to be treated remains questionable. However, fibrosis is associated with the risk of organ dysfunction. This has been shown for salivary glands [49], for pancreas with exocrine and endocrine insufficiency [50], and for the kidneys. Moreover, severe and sometimes life-threatening evolution is possible especially in case of aortitis [51], kidney involvement [52], or meningitis [39]. For these reasons, treatment is usually required in these patients. A "wait and see" attitude can be considered in some peculiar situations: isolated and asymptomatic lymphadenopathy or mild salivary gland involvement.

First-line treatment is represented by corticosteroids. In type 1 AIP, it has been shown that remission was obtained more frequently and more rapidly with steroids than without steroids [50]. Response to steroids is usually excellent, and has been included as a diagnostic criterion of some organ involvements [29, 30, 34]. In different series, depending on the proportion of organ-limited versus systemic disease, steroids therapy induced remission in 82–100 % of patients (Table 4.3).

The initial steroid regimen is quite homogenous with an "attack treatment" of 3–4 weeks of prednisolone or prednisone at a dose of 30–40 mg/day or 0.4–0.6 mg/kg/day [44, 46]. Higher doses of steroids can be used, but such a strategy did not seem to be more effective in terms of renal function recovery than standard doses in IgG4-RD nephritis [59].

The tapering regimen and maintenance therapy differ among countries. Japanese consensus statement recommends a maintenance therapy between 2.5 and 5 mg/day until 3 years [46], whereas Mayo Clinic experts recommend treatment withdrawal after 11 weeks [45]. Depending on these strategies, relapse rates remain high in patients with type 1 AIP, being 23 % with maintenance therapy in Japanese studies versus 48 % at 1 year in Mayo Clinic series. In other studies with systemic and multiorgan involvement, this high rate of relapse during tapering or after stopping steroids has also been reported, with relapse in 24–60 % of patients among series (Table 4.3). Male sex and younger onset are associated with relapse in patients with IgG4-related dacryoadenitis and sialadenitis [60], and biliary involvement [44, 54], but strong evidence of risk factors for disease relapses is lacking.

Another major concern about steroid treatment is the poor tolerance and high rate of complications in this usually aged population. Side effects of steroids were noted in up to 67 % of these patients [24], with glucocorticoid-induced diabetes in up to 28 % of patients [16] and other complications such as infections, osteonecrosis, and osteoporosis in varying proportions of cases [55].

Different strategies are used to treat relapses. Retreatment by steroids is usually effective in these patients [28, 46]. The use of immunosuppressive treatments can also be used for relapses as steroid-sparing agents. Azathioprine, 6-mercaptopurine, cyclophosphamide, mycophenolate mofetil, or methotrexate have been used as steroid-sparing agents, despite the lack of robust evidence-based data. However, adjunction of such drugs to steroids at the time of relapse has not shown superiority to steroids alone for relapse free survival in a large retrospective monocentric study [45]. In a recent retrospective study, methotrexate has been shown to be effective in patients with relapse, insufficient response, or intolerance to steroids [56].

Table 4.3 Main available studies on treatment of IgG4-related disease

Study	Country	Number of patients	Design of the study	Organs involved	Steroids[a]	Other treatments[a]
Hart et al., *Gut*, 2013 [44] (Multicentric, International)	Asia, Europe and North America	*n* = 978 Type 1 AIP	Retrospective	Type 1 AIP (100 %) SG (7 %), RPF (2 %), K (1.2 %), LAD (0.8 %), Lung (0.6 %)	Steroids in *n* = 684: 99.6 % remission Relapse in 31 % (after withdrawal in 67 %)	Surgical resection in *n* = 127: 98.4 % remission Palliative surgical bypass in *n* = 23: 95.7 % remission Conservative in *n* = 67: 55.2 % remission
Hart et al., *Gut*, 2013 [45] (Mayo Clinic experience)	USA	*n* = 116	Retrospective	Type 1 AIP (100 %) Biliary (distal 47 %, prox 34 %) OOI (50 %)	Steroids in *n* = 77 Relapse in 48 % at 12 months (after withdrawal of steroids)	AZA in *n* = 31: 23 % remission, 30 % relapse on treatment 6-MP in *n* = 6: 50 % remission, 17 % relapse on treatment MMF in *n* = 11: 27 % remission, 27 % relapse on treatment RTX in *n* = 12: 83 % complete remission, relapse in 1 case
Sandanayake et al., *Clin Gastroenterol Hepatol*, 2009 [53]	UK	*n* = 28	Prospective	AIP (100 %) Associated-cholangitis (82 %)	Steroids in all: 82 % remission Relapse in 35 % (after withdrawal)	AZA in *n* = 10: 70 % remission

Huggett et al., *Am J Gastroenterol*, 2014 [54]	UK	$n=115$	Prospective	Type 1 AIP (92%) with IgG4-SC (56%) Isolated IgG4-SC (8%) Extrapancreaticobiliary (36%)	Steroids in $n=98$: 97% response Relapse in 50% (post steroids)	AZA in $n=41$: 20% relapse, 32% intolerant MMF in $n=5$ MTX in $n=4$ 6-MP in $n=2$
Yamamoto et al. (SMART database), *Mod Rheumatol*, 2015 [55]	Japan	$n=122$	Retrospective	IgG4-related dacryoadenitis and sialadenitis (100%) OOI by PET (61%)	Steroids (maintenance) in 92.1% Annual relapse rate: 11.5% ≈50% of relapse within 7 years	IS (AZA; Cyclo) in 9% of patients (associated with CS) RTX in $n=3$: steroid-sparing effect
Ebbo et al., *Medicine (Baltimore)*, 2012 [24]	France	$n=25$	Retrospective	Systemic involvement, with AIP (52%), SG (44%), K (44%), IgG4-SC (32%), RPF (32%)	Steroids in $n=23$: 90% response Side effects in 67% Could be stopped in 30% only	IS in 48% of patients AZA in $n=6$: 75% response, CYC in $n=3$: 33% response MTX in $n=2$: 50% response, RTX in $n=3$: 67% response
Campochiaro et al., *Scand J Rheumatol*, 2015 [16]	Italy	$n=41$	Retrospective	Single and multi-organ, with AIP (44%), RPF (19%), SG (19%), LAD (12%) Ao (10%), IgG4-SC (10%)	Steroids in $n=36$: response in all (55% complete, 45% partial) Relapse in 46% (median 8 months) GC-induced diabetes in $n=10$	IS in $n=17$ (41% of patients) AZA in $n=7$, MTX in $n=13$ CYC in $n=2$ RTX in $n=2$

(continued)

Table 4.3 (continued)

Study	Country	Number of patients	Design of the study	Organs involved	Steroids[a]	Other treatments[a]
Fernandez-Codina et al., *Medicine (Baltimore)*, 2015 [19]	Spain	$n=55$	Retrospective	Single and multi-organ (47 %), with RPF (27 %), orbit (22 %), SG (16 %), AIP (16 %), LG (15 %)	Steroids in $n=47$ Maintenance in 21 %	IS in $n=19$ (34.5 % of patients) MMF in $n=6$, AZA in $n=13$, MTX in $n=2$, CYC in $n=2$, RTX in $n=3$
Lin et al., *Rheumatology (Oxford)*, 2015 [18]	China	$n=118$	Retrospective	Multi-organ (96 %), with LAD (65 %), SG (64 %), LG (51 %), AIP (38 %), Ao/RPF (26 %), lung (27 %), K (18 %), IgG4-SC (18 %)	Steroids in $n=114$ Response in "majority" of patients	IS in $n=71$ Response data nonavailable
Wallace et al., *Arthritis Rheumatol*, 2015 [13]	US	$n=125$	Retrospective	Single (38 %) and multi-organ, SG (28 %), LAD (27 %), orbit (22 %), AIP (19 %), RPF (18 %), lung (18 %), K (12 %), Ao (11 %)	Steroids in $n=64$ (51 % of patients) Response in 86 % Relapse after stopping (40 %) or relapse during taper (23 %)	MTX in $n=7$, MMF in $n=3$, Tamoxifen in $n=3$, AZA in $n=5$ and CYC in $n=2$: ineffective disease control with discontinuation of IS in all patients RTX in $n=7$: response nonavailable

Inoue et al., *Medicine (Baltimore)*, 2015 [14]	Japan	$n=235$	Retrospective	Single and multi-organ (58%), AIP (60%), SG (34%), K (23%), LG (23%), Ao (20%)	Steroids in $n=162$ (69% of patients) Clinical remission in all cases Maintenance in most patients Relapse in 24% (median 24 months)	IS such as AZA or RTX: $n=0$ Relapse were treated by additional therapy with steroids
Della-Torre et al., *Rheumatology (Oxford)*, 2015 [56]	Italy	$n=10$	Retrospective	Meninges, RPF, lung, AIP	Steroids in all patients Initial response in all patients Relapse in 60% (at a mean steroid dose of 9.6 mg/d)	CYC or AZA in $n=3$ MTX in all patients ($n=10$): remission in $n=2$, partial response in $n=8$ at 6 months remission in $n=6$, partial response in $n=4$ at 12 months
Khosroshahi et al., *Medicine (Baltimore)*, 2012 [57]	US	$n=10$	Retrospective	AIP, IgG4-SC, Ao, SG, LG, LAD, thyroid, RPF	Steroids in all patients	AZA ($n=1$), MMF ($n=2$), 6-MP ($n=1$), MTX ($n=3$), tamoxifen ($n=1$) before RTX treatment RTX in all 10 patients: clinical response in 90%, discontinuation of steroids and IS in all patients, relapse in $n=2$ (4 disease flares)

(continued)

Table 4.3 (continued)

Study	Country	Number of patients	Design of the study	Organs involved	Steroids[a]	Other treatments[a]
Carruthers et al., *Ann Rhem Dis*, 2015 [58]	US	$n=30$	Prospective	AIP (60 %), IgG4-SC (33 %), LAD (60 %), SG (60 %), ophthalmic (27 %), ENT (23 %), lung (17 %), K (23 %), RPF (10 %), Ao (7 %)	Previous steroids in 73 % Relapse in all patients Only 13 % on GC at baseline	AZA ($n=3$), MMF ($n=3$), MTX ($n=1$), and RTX ($n=6$) with relapse in all cases before RTX treatment RTX in all 30 patients: response in 96 % at 6 months, complete in 60 %, without steroids in 90 % at 12 months 7 relapse over 12 months

Abbreviations: *AIP* autoimmune pancreatitis, *Ao* aorta, *AZA* azathioprine, *CS* corticosteroids, *CYC* cyclophosphamide, *Cyclo* cyclosporine, *ENT* ear, nose, and throat, *GC* glucocorticoids, *K* kidney, *LAD* lymphadenopathy, *IgG4-SC* IgG4-related sclerosing cholangitis, *IS* immunosuppressants, *LG* lacrimal glands, *MMF* mycophenolate mofetil, *MTX* Methotrexate, *OOI* other organ involvement, *PET* 18 F-fluorodeoxyglucose (FDG)-positron emission tomography, *prox* proximal, *RPF* retroperitoneal fibrosis, *RTX* Rituximab, *SG* salivary gland, *USA* United States of America, *6-MP* 6-mercaptopurine

[a]Depending on the study, the term of response or remission was used, without evident difference between the two terms (evaluation on clinical, biological, and radiological evolution under treatment)

Finally, encouraging results have been reported with B-cell depletion using rituximab. An early report described the use of rituximab in 10 patients at a single American center [57]. In this study, treatment was used in patients refractory to steroids or with intolerance to steroid treatment, with efficacy even in patients with fibrotic organ involvements. Since these first reports, other studies have been reported that described the use of rituximab for type 1 AIP [45] or for IgG4-RD with variable organ involvement [58]. In this latter study, treatment efficacy, evaluated by the IgG4-RD Responder Index [61], was noted in up to 90 % of patients. Tolerance was globally good in these patients. However, the uncontrolled design of the study and the short follow-up (12 months) must be taken into account. An important proportion of patients relapsed after treatment with rituximab [62, 63]. In our experience, 33 % of patients relapse with a median delay of 18 months [63].

Surgical or prosthetic treatments (biliary stenting in pancreato-cholangitis or urinary drainage in retroperitoneal fibrosis) are required in some patients in combination with medical treatment. Although the overall prognosis of IgG4-RD remains favorable under treatment, significant morbidity and increased mortality owing treatment complications but also to organ failure and malignancies have been reported [44, 54].

Conclusions

Despite data on IgG4-RD in medical literature have exploded during the last decade, the exact spectrum of this entity has not yet been completely clarified. While prototypic systemic presentations with classical organ involvements are now well recognized, other more atypical organ lesions are still debated. Characteristic histopathology is key for IgG4-RD diagnosis; nevertheless, this may also be not fully specific, given the frequent overlap with other fibroinflammatory diseases. Steroids are usually dramatically effective, but high rates of relapses and tolerance issues require further studies on steroid-sparing strategies.

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Pathophysiology of IgG4-Related Disease

5

Jochen Zwerina

5.1 Introduction

The concept of IgG4-related disease (IgG4-RD) as a systemic fibroinflammatory disease has been introduced in the very recent past. Many formerly thought "single-organ diseases" are now being summarized as organ manifestations of IgG4-RD. Therefore, much of the literature focusing on the causes of these disorders has been published on certain organ manifestations (e.g., autoimmune pancreatitis) rather than specifically on multisystemic IgG4-RD patients.

In general, IgG4-RD is a systemic fibroinflammatory disorder of unknown origin. Absence of infectious pathogens or malignancy, the clinical picture, and the usually prompt and good response to corticosteroids and other immunosuppressive drugs suggest IgG4-RD could be an autoimmune disease. In type 1 autoimmune pancreatitis, autoantibodies have been described. On the other hand, overall, there are only few data on immune system disturbances in IgG4-RD, and there is currently no reliable animal model of IgG4-RD. Also, the older age and frequent male affection is in contrast to many other autoimmune diseases.

5.2 Environmental and Occupational Triggers

There is evidence for the association of environmental triggers in autoimmune diseases. For instance, silica exposure has been linked to development of rheumatoid arthritis, systemic sclerosis, ANCA-associated vasculitides, and others [1–3]. Further, the association of smoking and several autoimmune diseases is well established [4]. A recent study in a Dutch IgG4-RD cohort consisting of IgG4-related cholangitis and

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pancreatitis patients reported that 88 % were blue-collar workers chronically exposed to solvents, oils, industrial and metal dusts, and others. These findings were similar in another IgG4-RD cohort from Oxford reported in the same study [5]. The role of occupational exposure and smoking has been investigated in a large retroperitoneal fibrosis (RPF) cohort form Italy. Asbestos and smoking were both independently and additively associated with RPF in this study, with relatively high odds ratios ranging from 2.93 to 4.22 [6]. Indeed, asbestos exposure has already been linked to RPF in another study from Finland [7]. However, RPF may only be partly associated with IgG4-RD, and therefore caution is mandatory to generalize these findings to IgG4-RD.

5.3 Genetics

Currently, there are no genetic association studies in IgG4-RD cohorts. There is however evidence for genetic associations of, e.g., HLA system in chronic periaortitis/retroperitoneal fibrosis and autoimmune pancreatitis patients discussed in detail in Chap. 2.

5.4 Atopy and IgG4-Related Disease

In IgG4-related sialoadenitis, pancreatitis, and cholangitis, studies have found a shift of the immune system towards a Th2 response, which is discussed in detail later. Moderate tissue and blood eosinophilia in IgG4-RD is not uncommon, and serum IgE elevation is also frequently observed [8]. While it was initially thought as possibly pathogenic for the disease itself, a recent study challenges this view. In a cohort of 70 biopsy-proven IgG4-RD patients, 31 % had a background of atopic disease, most commonly allergic rhinoconjunctivitis [9]. This is not different from the expected background frequency of atopic diseases in the USA according to the authors. IgE elevation and eosinophilia were much more frequent in patients with various atopic diseases. Also, circulating Th2 memory cells were found preferentially in the latter patients [10]. Thus, the Th2 immune response may be present in IgG4-RD patients with an additional atopic disease. Whether atopic disease is causally linked to IgG4-RD or not remains to be defined. In other clinical IgG4-RD cohorts, allergic diseases have however been described to occur more frequently (more than 50 % of patients) [11, 12].

5.5 T Cells

Alterations in the adaptive immune system have been investigated in detail in several studies. In biopsy specimens from IgG4-related pancreatocholangitis and other lesions, high expression of cytokines associated with a regulatory T-cell and Th2-cell phenotype such as IL-4, IL-5, IL-10, IL-13, and TGF-beta was noted [13]. These cytokines could therefore drive the major fibrotic disease phenotype and also

induce the immunoglobulin class switch to IgG4 production [13]. As discussed above, the frequent comorbid atopic diseases and elevated IgE levels in IgG4-RD patients are well in line with this theory. Another study also found increased IL-4 and IL-5 expression in bile of IgG4-related cholangitis patients. These cytokines disturbed barrier function of bile epithelial cells in vitro [14]. In IgG4-related sialoadenitis, increased local expression of, e.g., IL-4, IL-5, IL-10, and TGF-beta was also found when compared to disease controls such as Sjögren's syndrome [15].

However, whether these cytokines are truly produced by T cells is yet unclear. Moreover, other studies reported different findings challenging this theory. In IgG4-related sialoadenitis, increased expression of local Th1 and cytotoxic T cells but not Th2 cells was found as evidenced by intracellular cytokine flow cytometry. Also, increased IL-17 tissue expression was found [16]. Della Torre et al. investigated T-cell polarization in peripheral blood of IgG4-RD patients. They found increased Th2 immune responses only in IgG4-RD patients with concomitant atopic disorders, questioning a true relationship with IgG4-RD itself [10].

Very recently, the same authors extended their findings on T-cell polarization in IgG4-RD [17]. CD4 + CD27^{lo}CD62L^{lo} cells, indicative of effector memory T cells usually arising from chronic antigen stimulation, were highly increased in active IgG4-RD. Using a variety of analytical methods, including gene expression profiling, these cells seem to be of a modified Th1 type showing increased expression of T-bet along with SLAMF7 and 2B4. Interestingly, these cells have potent cytolytic activity in vitro after stimulation. These CD4 + SLAMF7+ cytotoxic T cells (CTLs) but not Th2 cells were oligoclonally expanded in active IgG4-RD patients. CD4 + SLAMF7+ CTLs were increased in peripheral blood samples but also abundant in tissue lesions of IgG4-RD patients, outnumbering Th2 cells. In vitro, these cells can produce profibrotic cytokines such as TGF-beta and IL-1beta. In patients successfully treated with rituximab, the concentration of these cells in the peripheral blood successfully decreased [17].

Another study linked IL-21 overproduction to the pathogenesis of IgG4-RD [18]. IL-21 is an important cytokine for the formation of germinal centers, the latter being frequently found in IgG4-related sialoadenitis. IL-21 was overexpressed in minor salivary glands from IgG4-RD patients. Both molecules indicating Th2 (IL-4, CCR4, and cMaf) and T follicular helper cell (Tfh) response were found in the same lesions representing possible IL-21 producers in IgG4-related sialoadenitis.

There is also evidence for alterations of regulatory T cells in IgG4-RD [13]. Miyoshi et al. analyzed the frequency of CD4 + CD25 high T cells and CD4 + CD25 + CD45RA+ (naïve) T cells in the peripheral blood of autoimmune pancreatitis patients. They found increased frequencies of Tregs, while naïve regulatory T cells were decreased [19]. Tregs can also be found locally in IgG4-related pancreatitis lesions as evidenced by immunohistochemical methods [20]. Another study also identified increased numbers of Tregs in the peripheral blood of IgG-related pancreatitis patients. They also described increased frequencies of IL-10 producing ICOS+ Tregs in these patients. Possibly, these cells could drive a B-cell response towards IgG4 production and represent an attempt to limit an uncontrolled inflammatory response [21].

5.6 B Cells and Plasma Cells

The efficacy of the anti-CD20 antibody rituximab in refractory IgG4-RD patients put B cells central in the pathogenesis of the disease [18]. Indeed, B cells are abundant in tissue lesions of IgG4-RD patients. Cytokines found to be produced in IgG4-RD patients such as IL-4, IL-10, and others could drive B-cell differentiation towards IgG4 production. In IgG4-related cholangitis, the B-cell receptor (BCR) repertoire was investigated in peripheral blood and tissue. In IgG4-RD but not in controls, IgG4+ B cell clones were identified that were selectively suppressed upon immunosuppressive therapy. These clones seemed to have undergone affinity maturation as evidenced by somatic hypermutation [22]. Well fitting, oligoclonal intrathecal IgG4 production has been described in IgG4-related pachymeningitis suggesting locally residing IgG4-producing plasma cells [23].

Though it is still unknown which antigens drive this process, a prominent process towards expansion of specific B cells and finally differentiation to IgG4-producing plasmablasts and plasma cells is evident. Plasmablasts are derived from B cells, produce antibodies, and still retain the ability to proliferate while having a short half-life. Plasmablasts can finally differentiate into plasma cells. Circulating plasmablasts, rare in healthy individuals, have been described in a variety of immune-mediated diseases including rheumatoid arthritis and systemic lupus erythematosus. In a recent study, a significant expansion of $CD19+CD27+CD20\text{-}CD38^{hi}$ plasmablasts in the peripheral blood of active IgG4-RD patients was found [24]. These plasmablasts were largely surface IgG4-positive, and next-generation sequencing revealed oligoclonal expansion in all tested samples. Interestingly, numbers of circulating plasmablasts seemed to be independent of serum IgG4 levels [25].

After administration of rituximab in IgG4-RD patients, not only CD20+ B cells were depleted but also plasmablast frequency decreased in the peripheral blood [23]. There was a high variability on the timing of repopulation of clonally divergent plasmablasts in the blood of the treated patients partially correlating with disease relapse. Somatic hypermutation was observed both before and after rituximab therapy in IgG4-RD patients, implying importance of T helper cell responses in this disease. CD20 depletion presumably depletes precursors of IgG4-producing plasmablasts and short-lived plasma cells. However, elevated serum IgG4 levels are frequently observed after therapy in patients, which suggests residual plasma cells in the bone marrow and/or affected tissue of patients after therapy.

5.7 Monocytes and Macrophages

Macrophages are multifunctional cells of the immune system potentially involved in IgG4-RD pathogenesis. Currently, macrophages are grossly divided into classically activated M1 macrophages and M2 macrophages. M1 macrophages are

generally regarded as proinflammatory, while M2 macrophages display a different phenotype: they are usually found as resident tissue macrophages and have been linked to wound healing and repair processes. M2 macrophages can produce significant amounts of IL-4, IL-10, and TGF-beta and thus could play a role in fibroinflammatory diseases such as IgG4-RD. In IgG4-related sialoadenitis, local macrophage infiltration preferentially of the M2 type could be demonstrated by immunohistochemistry [26]. These cells seem to produce for instance CCL18, a chemokine linked to fibrotic diseases such as pulmonary fibrosis and systemic sclerosis. Further, macrophage infiltration positively correlated with the severity of fibrosis in affected tissues.

In peripheral blood mononuclear cells (PBMCs) from healthy donors, activation of toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2) induced significant IgG4 production in vitro [27]. NOD2 activation was specifically able to trigger IgG4 production by B cells from healthy donors when these were cocultured with monocytes from IgG4-related pancreatitis patients. IgG4 production was dependent on monocyte production of B-cell activating factor (BAFF). These findings were independent of functional T-cell signaling in this in vitro system.

5.8 Other Cells

Mast cells have been described as important mediators of anaphylactic reactions and in allergic disorders. However, mast cells are currently considered to be involved in classical autoimmune diseases such as rheumatoid arthritis and bullous pemphigoid. Tissue mast cells have been found in IgG4-related sialoadenitis recently. Moreover, these cells colocalized with IL-4, IL-5, IL-10, and TGF-beta expression [28]. The same group reported recently that mast cells in IgG4-related sialadenitis may also produce IL-13 [29]. Interestingly, long-term treatment with an antihistamine drug was associated with regression of IgG4-related dacryoadenitis in one patient without immunosuppressive treatment [30]. In retroperitoneal fibrosis (RPF), tissue mast cell infiltration was well documented in a recent study [31]. Eotaxin/CCL11, a mediator involved in mast cell chemotaxis, is increased in serum of RPF patients and is locally produced in the inflamed tissue. Tissue infiltrating mast cells also seem to express the CCL11 receptor CCR3.

Basophils, the least abundant granulocyte type in peripheral blood, are involved in the pathogenesis of allergic and other disorders. Recently, basophils have also been implicated in pathogenesis of fibrosis. In an animal model of cardiac allograft fibrosis, basophils were important for myofibroblast activation leading to cardiac fibrosis [32]. A recent study demonstrated that activation of TLRs in basophils from healthy donors could induce IgG4 production by B cells through BAFF production in vitro. Basophils from IgG4-RD patients were even more effective in inducing an IgG4 response in B cells from healthy donors. This phenomenon was associated with increased IL-13 and BAFF production in vitro.

5.9 IgG4 Antibodies

Immunoglobulin 4 (IgG4) is the least abundant IgG subclass in serum of healthy individuals accounting usually for less than 5 % of total IgG. Its physiological relevance is currently unclear because IgG4 is not able to significantly activate the complement system. IgG4 antibodies are unique because of the possibility to exchange Fab arms between different IgG4 molecules resulting in so-called bi-specific antibodies. However, there is no evidence of the formation of immune complexes using this bi-specificity, and therefore the relevance of this finding is unclear. On the other hand, IgG4 is associated with Th2 immune response and allergic diseases. Further, induction of blocking allergen-specific IgG4 antibodies correlates with successful desensitization in immunotherapy [33]. Although the name IgG4-RD suggests a central role for IgG4 antibodies in the disease, this is currently unproven. There are a variety of diseases such as eosinophilic granulomatosis with polyangiitis, Castleman disease, and others that commonly have elevated serum IgG4 levels [34, 35]. Conversely, active IgG4-RD may present with normal IgG4 levels. Also, serum IgG4 levels usually decline with clinical response upon immunosuppressive treatment, but this is not specific and relapses may occur with normal serum IgG4 levels [36]. Moreover, although IgG4 does not seem to activate complement, decreased complement C3 and C4 levels suggesting complement activation are not uncommon in IgG4-RD [37].

Recently, an experimental study of passive transfer of IgG1 and IgG4 antibodies from IgG4-RD patients to neonatal mice showed pathogenicity in terms of pancreatic damage. Transfer of patient IgG but not control IgG induced pancreatic neutrophil infiltration, hemorrhage, and acinar cell necrosis. However, in this study, IgG1 antibodies were more harmful than IgG4 antibodies. Also, IgG4 antibodies acted counteractive in combination and attenuated damage. However, the histopathological findings in this model were not reminiscent of type 1 autoimmune pancreatitis, and further research is necessary [38].

5.10 Autoantibodies

The usually prompt and excellent response to corticosteroids could suggest that IgG4-RD is an autoimmune disease. Therefore, measurable systemic or organ-specific autoantibodies could play a role in the disease pathogenesis. Efficacy of CD20 depletion in difficult-to-treat IgG4-RD patients underlines this possibility. There is however currently not much evidence supporting this theory.

Testing of currently known autoantibodies is usually done during diagnostic evaluation for IgG4-RD. Recently published large cohorts on IgG4-RD patients from the USA, Europe, and Asia reported clinical features but also mostly on prevalence of antinuclear antibodies (ANA) and partially anti SS-A/SS-B antibodies [39–41]. In general, detecting ANA is not unusual, especially in low titers, while there is usually no signal arising from tests on antibodies against extractable nuclear antigens such as SS-A/SS-B antibodies. There are no systematic data on other autoantibodies such as rheumatoid factor, ANCA, and others. Organ-specific antibodies

have however been described in different organ manifestations of IgG4-RD, mainly before the introduction of the IgG4-RD concept as a systemic disease [42].

5.11 Summary

Overall, our understanding of the pathophysiology of IgG4-RD remains to date incomplete. When considering data from autoimmune pancreatitis, there could possibly be a genetic predisposition based on certain HLA types. There is little evidence on what could initiate and drive IgG4-RD. Possibly, environmental exposure could be important in disease initiation, but other triggers such as microbial antigens or auto-antigens could also be causative. As opposed to the scarce studies on innate immune system, there is increasing evidence for the role of adaptive immunity in IgG4-RD. Most studies focused to date on T-cell polarization and B-cell physiology. While there are several studies implicating a strong shift towards a Th2 immune response, this view has recently been challenged suggesting that this may be instead related to coexisting atopic disorders rather than IgG4-RD itself. Instead, a modified Th1 cytolytic cell type may be crucially involved in the pathogenesis of IgG4-RD. Regardless of the origin, the observed cytokine milieu (e.g., IL-4, IL-10, TGF-beta) could be responsible for the IgG class switch to drive IgG4 antibody production in IgG4-RD. There is evidence for the selection of dominant IgG4+ B-cell receptor clones in IgG4-RD, and immunosuppressive therapy decreases these clones. However, the driving antigens responsible are yet to be defined. Further, successful therapy decreases circulating plasmablasts and short-lived plasma cells in IgG4-RD. The strong and sometimes devastating fibrotic response in IgG4-RD is still enigmatic and is in contrast to many other immune-mediated inflammatory disorders. Identifying these mechanisms will possibly help to prevent irreversible tissue damage [43].

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Autoimmune (IgG4-Related) Pancreatitis

6

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6.1 Introduction

Autoimmune pancreatitis (AIP) is a peculiar form of chronic inflammatory disease of the pancreas with unique pathologic features, different from all other forms of pancreatitis. Although a possible autoimmune involvement of the pancreatic gland had been proposed since the early 1960s [1], the term AIP was introduced in 1995 by Yoshida et al. [2], based on a case report and the review of the available English and Japanese literature. However only in recent years was AIP finally accepted as a distinct nosographic entity. The more relevant clinical data and the main reason for introducing the term "autoimmune pancreatitis" were the dramatic response to steroid therapy, which represents one of the cardinal diagnostic criteria, like other gastrointestinal tract diseases (e.g., autoimmune hepatitis).

6.2 Pathogenesis

The etiopathogenesis of AIP is largely unknown. The major pathogenetic factors potentially contributing to the development of AIP include genetic predisposition, immunologic triggers, and the subsequent immune reaction [3]. Like other immune-mediated diseases, AIP may develop in genetically susceptible subjects after exposure to environmental factors through an immune-mediated reaction. The involvement of the immune system seems to be confirmed by the fact that about 40 % of AIP patients are positive for nonorgan-specific autoantibodies (e.g., antinuclear antibodies).

Organ-specific autoantibodies have been described in patients with AIP (directed against carbonic anhydrase II, lactoferrin, α_2-amylase, and/or pancreatic secretory

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trypsin inhibitor, plasminogen-binding protein), but it still unknown whether their production occurs primarily or secondary to pancreatic inflammation. Furthermore, these antibodies are not entirely specific for AIP and are sometimes detected in other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Despite the frequent association with high serum levels of IgG4 and tissue-infiltrating $IgG4^+$ plasma cells, IgG4 is not believed to play a critical role in the pathogenesis of AIP. Some authors suggested that IgG4 may reflect the attempt to downregulate the inflammatory process, since IL-10, an anti-inflammatory cytokine, is needed to drive the differentiation of IgG4-switched B cells to IgG4-secreting plasma cells [4]. High serum levels of IgG4 usually indicate patients with a more severe disease, with a deeper involvement of the pancreas and of other extra-pancreatic organs, and with a higher frequency of disease relapses. Indeed different studies reported a significantly higher frequency of relapses in AIP patients with high serum IgG4 as compared with those showing normal serum IgG4, with a risk ratio ranging between 5.5 [5] and 6 [6].

The pathogenesis of the disease may involve two phases, an "induction" phase and a "progression" phase [7]. An initial response to self-antigens might be induced by decreased naive regulatory T cells (Tregs), followed by a Th1 immune response with the subsequent release of proinflammatory cytokines (IFN-γ, IL-1-beta, IL-2, TNF-α). Then Th2 immune responses producing IgG, IgG4, and autoantibodies may drive disease progression. An excessive "induction" phase is thought to increase serum IL-10 and TGF-β production in the "progression" phase, both secreted from inducible memory Tregs, and, consequently, also serum and tissue IgG4 and fibrosis, in an attempt to downregulate the inflammatory process.

6.3 Pathology

AIP is histologically defined on surgical specimens of patients undergoing surgical resection for a suspicion of a pancreatic tumor, but with a final diagnosis of pancreatic inflammation (pancreatitis) [8]. It is estimated that approximately 10% of patients undergoing surgery for resectable pancreatic cancer have a final diagnosis of pancreatitis [9], and that AIP represents about a third of these patients [10]. The investigation of surgical specimens allowed to define the histological criteria of AIP and the differential diagnosis with other types of chronic pancreatitis. The most frequent and significant histological finding in AIP is an intense inflammatory cell infiltration, mainly comprising lymphocytes and plasma cells, usually arranged around the pancreatic ducts of medium and large size, while the involvement of secondary pancreatic ducts has been found in more advanced cases [8]. Additionally, the presence of aggression of pancreatic acinar cells by granulocytic cells ("granulocytic epithelial lesions – GEL") has also been described [8, 12].

In most cases, there is also an intense intra- and extralobular fibrosis, defined "storiform" as it is irregular and not oriented, different from the well-oriented fibrosis observed in "classic" chronic pancreatitis [8]. Intralobular fibrosis also shows

peculiar characteristics, around the acinar cells, with atrophy of the cells, and with the islets of Langerhans which appear as coated by fibrosis (encasement). The third main histological characteristic of autoimmune pancreatitis is vascular involvement, with obliterans arteritis and venulitis, both generally observed in areas where fibrosis is most represented.

In 2010, an International Consensus conference held in Honolulu (USA) established the main histological features that differentiate AIP from alcoholic chronic pancreatitis [12]. Furthermore, the diagnostic criteria for two main subtypes of AIP, type 1 (AIP type 1) and type 2 (AIP type 2) AIP, were defined as well.

Type 1 AIP, previously called *lymphoplasmacytic sclerosing pancreatitis* (LPSP), is characterized by periductal lymphoplasmacytic infiltration of $IgG4^+$ plasma cells, storiform fibrosis, and obliterative venulitis. Other organs (biliary ducts, lacrimal glands, salivary glands, kidney, retroperitoneum) may be involved by the inflammatory process, leading to consider type 1AIP as a manifestation of systemic IgG4-related disease.

Type 2 AIP, previously called *idiopathic duct-centered pancreatitis* (IDCP), is characterized by a neutrophilic infiltration in the ductal epithelium with duct destruction and occasionally microabscess formation. The periductal GEL and the absence or rare presence of $IgG4^+$ plasma cells are the specific features of type 2 AIP. Lymphoplasmacytic infiltration and storiform fibrosis, as well as venulitis, may be observed in this form, but they are less frequent than in type 1 AIP. Clinically, type 1 AIP is a more aggressive disease, with frequent relapses, association with involvement of other organs and need for maintenance therapy (immunosuppressants or rituximab).

6.4 Epidemiology and Clinical Features

AIP probably represents about 5 % of chronic pancreatitis [13], mainly affects the male sex, with an M/F ratio of 3:1, and the mean age at clinical onset of the disease is 60 years [14]. The estimated prevalence increased in Japan from 0.82/100,000 inhabitants in 2002 [15] to 2.2/100,000 inhabitants in 2007 [16], probably due to a better recognition of the disease and to the improvement of diagnostic capability. The incidence of AIP in Europe and the USA is still unknown, with only limited series published in the literature by tertiary reference centers. Type 1 AIP is the most frequent subtype of the disease (up to 90 % of cases) in Asian countries [14] and its prevalence is 60 % in Italy [17].

The most common manifestations are jaundice, weight loss, signs of classic pancreatitis, diabetes, and steatorrhea, with different frequencies reported around the world. Type 1 AIP is often characterized by painless jaundice, while type 2 by classic pancreatitis. Type 1 AIP is often associated with diseases of the biliary tract (sclerosing cholangitis), kidney, retroperitoneum, salivary gland, and, more generally, with other autoimmune diseases. The multiorgan involvement with elevated serum IgG4 allows to diagnose an IgG4-related disease [18]. On the other hand, type 2 AIP is often associated with inflammatory bowel disease (IBD), especially ulcerative colitis [5, 17].

6.5 Diagnostic Criteria

An international consensus was held in 2011 in Fukuoka (Japan) to define the diagnostic criteria of AIP [19]. There have been numerous attempts to define diagnostic criteria by different research groups, such as:

- *US*: based on a combination of individual criteria such as Histology, Imaging, Serology, Other organ involvement, and Response to therapy and therefore known by the acronym HISORt [20]
- *Japanese*: based mainly on endoscopic retrograde cholangiopancreatography (ERCP) [21];
- *Korean*: similar to Japanese criteria, from which they differ for a greater weight given to the classical imaging methods [11]
- *Asian*: based on a combination of Japanese and Korean criteria [22]
- *Italian*: based on the presence of three out of four diagnostic criteria (serology, imaging, response to steroids, histology/cytology) [6]

The Consensus Conference of Fukuoka defined the "International Consensus Diagnostic Criteria" for AIP (*ICDC*) [19], based on five diagnostic criteria that include: (a) *imaging*, differentiated in "parenchymal" (evaluated with CT and MRI) and "ductal" (evaluated by ERCP or MRCP) criteria; (b) *serology*; (c) *other organ involvement*, including extrapancreatic organs, such as the biliary tract, kidney, salivary glands, retroperitoneal, colon; (d) *histology*; (e) *response to steroid therapy.* These criteria have been further divided into Level 1 (higher) and Level 2 (lower), based on the diagnostic reliability. The combination of the various criteria allows to classify AIP into type 1 (definite or probable), AIP type 2 (definite or probable), AIP type NOS (not otherwise specified), and AIP probable. The ICDC criteria are now internationally accepted and represent an attempt to standardize the diagnosis of the disease, although they remain quite complex.

6.6 Laboratory Findings

Serum IgG4 is the only specific serological test available to diagnose type 1AIP, whereas no serological tests are available for type 2 AIP. However, up to 30 % of patients with type 1 AIP have normal serum IgG4 concentrations, and an elevated serum IgG4 concentration is observed in 5 % of healthy persons and 10 % of patients with pancreatic carcinoma [23]. Therefore, the sensitivity of serum IgG4 using a cutoff of 135 mg/dl is only 76 % and specificity 93 % in the diagnosis of AIP [24]. A meta-analysis evaluating the usefulness of serum IgG4 in diagnosing AIP showed variation in sensitivity (67–94 %) and specificity (89–100 %) [25].

The diagnostic value of serum IgG4 concentration increases with a higher cutoff level. Using a cutoff of serum IgG4 of 240 mg/dl, the specificity reaches 100 % but sensitivity decreases to 53 % [24]. Therefore, serum IgG4 alone cannot be used to make the diagnosis of AIP.

It has been reported that most patients with AIP have antibodies against the plasminogen-binding protein (PBP) of *Helicobacter pylori* [26]. These antibodies are presumed to act as autoantibodies by molecular mimicry in genetically predisposed individuals. The sensitivity and specificity of anti-PBP antibodies for differentiating between AIP and pancreatic cancer were reported in one study to be 94 % and 95 %, respectively. However, no further studies have been published, and the test cannot be used yet in clinical practice.

Other nonspecific antibodies have also been proposed for the diagnosis of AIP, such as antilactoferrin, anticarbonic anhydrase-II/IV, antipancreatic secretory trypsin inhibitor, antiamylase α, rheumatoid factor, antinuclear antibody, and anti-smooth muscle antibody. However, the clinical significance of these autoantibodies in AIP remains unclear.

6.7 Imaging

Imaging findings at diagnosis and after steroid therapy are the most important diagnostic criteria for AIP diagnosis. One of the limitations of the imaging techniques is their inability to differentiate AIP subtypes (23). Indeed, parenchymal and ductal criteria at imaging by ICDC are the same for AIP type 1 and type 2.

The imaging modalities to evaluate AIP include CT scan for the parenchyma evaluation, MRI with MRCP sequences for both parenchyma and ductal evaluation, and ERCP for the evaluation of the pancreatic ductal system. However, diagnostic ERCP is used only in Asia, since in Western countries this technique can be used only for therapeutic purposes.

CT scan with administration of contrast medium is the imaging modality most widely available and used for the diagnosis of AIP, able to accurately assess the glandular morphology [27–30]. The pancreas can be entirely (*diffuse form*) or focally (*focal form*) involved [27, 31]. In the diffuse form, the pancreas is enlarged, hypodense with a "sausage-like" appearance, sometimes with the presence of a peripheral hypodense rim in about half the cases, without dilation of the main pancreatic duct. In focal forms, pancreatic involvement is limited, sometimes with the presence of a hypodense mass, mimicking pancreatic adenocarcinoma. The Wirsung duct is generally mildly dilated upstream the focal mass (Fig. 6.1).

The involved pancreas is hypodense (hypovascular) in the early arterial phase, with a progressive enhancement in subsequent contrastographic phases (especially venous and portal phases). In focal AIP, this contrastographic pattern allows to differentiate inflammation (hypovascular in arterial and hypervascular in late phases) from pancreatic adenocarcinoma (hypovascular both in arterial and late phases).

Abdominal MRI with MRCP sequences is the most accurate method for evaluating the pancreas in AIP [31–35], since it allows both parenchymal and ductal pancreatic assessment (Fig. 6.1). In AIP, the involved pancreas is hypointense in T1-weighted and hyperintense in T2-weighted sequences. Contrast-enhancement dynamics is similar to that observed in CT.

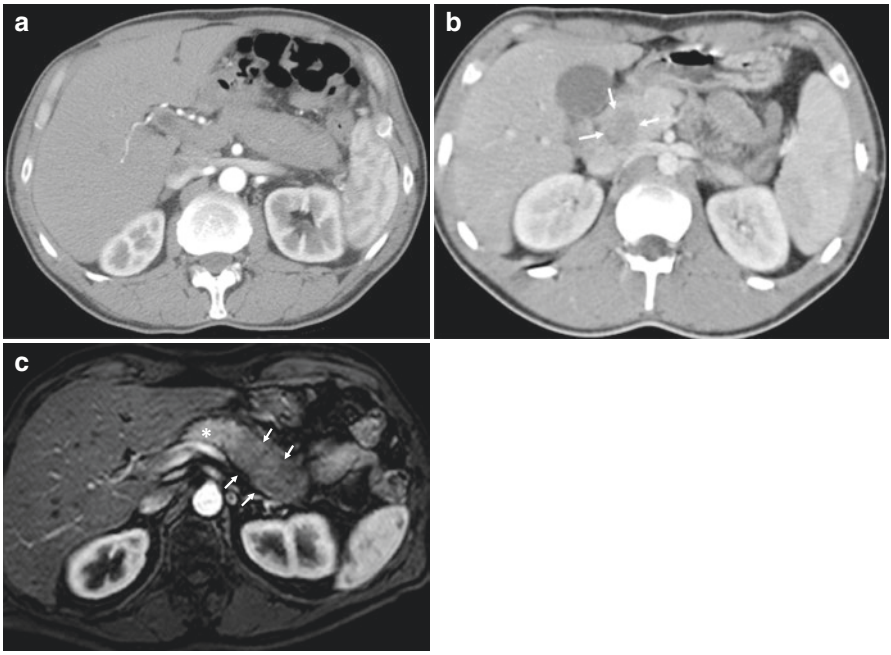

Fig. 6.1 (**a**) Computed tomography (CT) appearance of diffuse AIP: the pancreatic parenchyma appears diffusely hypodense in the body-tail of the pancreas on arterial phase. (**b**) CT appearance of focal AIP: focal hypodensity in the head of the pancreas on pancreatic phase. (**c**) Magnetic resonance findings in focal AIP: the pancreatic parenchyma (*arrows*) appears hypointense at tail on pancreatic phase compared to body (*asterisk*) ("*black and white*" sign) at axial T2-weighted image

MRCP sequences after administration of secretin increase the definition of pancreatic ductal system morphology, in particular the number and length of ductal stenosis. In the diffuse forms, the main pancreatic duct is compressed and reduced in diameter, with the presence of multiple stenoses. In focal forms, a ductal stenosis at the level of the pancreatic mass is generally observed with mild upstream dilatation. The visibility of the duct at the level of the stenosis after secretin administration (so-called duct penetrating sign) is frequently observed in AIP, whereas the duct generally remains not visible after secretin in pancreatic adenocarcinoma.

CT and MRI may also evaluate the possible abdominal involvement of extrapancreatic organs (biliary tract, kidney, retroperitoneum) which further supports the diagnosis of AIP.

Abdominal contrast-enhanced ultrasound (CE-US) [36, 37] and the endoscopic-ultrasound with contrast medium administration (CE-EUS) [38, 39] are useful in AIP diagnosis. In precontrastographic phase, the involved pancreas is hypoechoic, with a progressive enhancement after contrast medium injection, a sign highly suggestive of inflammation. The dynamics is similar to that of other imaging modalities (CT and MRI), but the continuous visualization of the pancreas ("real time") by CE-US or CE-EUS allows a better assessment. In focal forms, pancreatic

adenocarcinoma that remains hypoechoic after contrast medium injection can be easily diagnosed versus focal AIP [40]. However, in focal AIP, fine needle aspiration/biopsy is mandatory to diagnose AIP and/or exclude the presence of a tumor, before using steroids.

The evaluation of the response to steroid therapy by the normalization of the pancreas in diffuse AIP and the disappearance of the pancreatic lesion in focal AIP can be carried out by any imaging method. However, abdominal MRI, as it is pan exploring (vs. CE-US), free of radiation (vs. CT), and noninvasive (vs. CE-EUS), is probably the modality of choice. After steroid withdrawal, the disease recurs (often asymptomatic) in 30 to 60 % of the cases across different studies, involving in most cases the pancreas, but sometimes extrapancreatic organs (kidney, bile ducts) [14]. MRI with RMCP sequences is the radiological method recommended for the follow-up of patients, generally 3 months after steroid withdrawal and then yearly, although timing is based only on clinical experience. MRI characteristics of the pancreas in the presence of relapse are similar to those observed at clinical onset of the disease, with an increase in size of the gland, which can be focal or diffuse [31].

6.8 Other Organ Involvement

Extrapancreatic manifestations have been reported in up to 40 % of patients with type 1 AIP [41]. The most common extrapancreatic site in type 1 is the biliary tree. Chest (including mediastinal fibrosis), retroperitoneum (chronic periaortitis, retroperitoneal fibrosis), salivary glands, kidneys (tubulointerstitial nephritis) may be also affected, but the spectrum of IgG4-related disease is even larger [42]. IgG4-lymphoplasmacytic infiltrate is often found in affected organs. Involvement of the biliary tree in autoimmune pancreatitis, called or "IgG4 sclerosing cholangitis" (IgG4-SC), can be confused with primary sclerosing cholangitis or cholangiocarcinoma.

6.9 Treatment and Prognosis

Although steroids are the treatment of choice in AIP, there is no consensus on the optimal dose and tapering schedule. Initial prednisone doses range from 0.5 mg/kg/day (as proposed by Asian studies) to 1 mg/kg/day (Italy, Germany) or 40 mg regardless of the weight (the USA, the UK). This dose should be kept for at least 2–4 weeks, then tapered by 5 mg/week [14]. The efficacy ranges from 95 to 100 % and is now considered as a standard induction therapy. The relapse rate after discontinuation of steroid treatment varies from 30 to 60 %; in such cases, most investigators recommend a second course of steroid therapy for induction followed by maintenance therapy with immunosuppressants (Europe, the USA) [43] or with low-dose steroids (Asia) [14]. Azathioprine is considered the most effective drug for maintenance therapy at a dose of 2–2.5 mg/kg/day. Other immunosuppressive drugs (methotrexate, mycophenolate mofetil) seem to be less effective. Rituximab, an

anti-CD20 antibody able to deplete B cells, has been recently proposed [43, 44]. Although a hematologic regimen (4 weekly doses of 375 mg/m^2 followed by drug reinfusion every 2 months) has been proposed, we experienced a good clinical and morphological response with a rheumatologic regimen (two infusions of 1 g each at time 0 and 2 weeks, with repetition of the cycle to 6 months) (unpublished data). After the introduction of biologics, the problem of step-up vs. top-down therapy arises, similar to other diseases of the gastrointestinal tract (e.g., IBD). Based on our center experience on 231 AIP patients (at June 2015), of whom only 10 were treated with rituximab (while the remaining received mainly steroids), we suggest a step-up strategy, even for a cost-benefit assessment.

The natural history of AIP is still not clarified. Spontaneous remission can occur in patients with lower serum IgG4 levels and focal rather than diffuse enlargement of the pancreas. Steroids probably modified the natural history of the disease, particularly when the treatment is started in an early phase of the disease. Untreated AIP probably progresses from lymphoplasmacytic inflammation to extensive fibrosis that may result in permanent organ dysfunction and evolution toward an "ordinary" chronic pancreatitis [45]. Some studies have also suggested a slightly increased risk of malignancy (pancreatic, lung, colon, lymphoma) [46, 47].

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Sclerosing Forms of Autoimmune Thyroiditis: Hashimoto's, Riedel's, and IgG4-Related Forms

7

Graziano Ceresini and Michela Marina

7.1 Introduction

Hashimoto's thyroiditis (HT) has been considered for many years a well-defined clinicopathological condition. However, the recent observation, in some HT cases, of marked fibrosis and thyroid inflammation rich in immunoglobulin G4 (IgG4)-positive plasma cells, has led to the notion that subtypes of HT may exist. The increased IgG4-positive plasma cell infiltration suggests that this type of HT may have a close relationship with IgG4-related disease (IgG4-RD). This subgroup of HT, now called IgG4-thyroiditis, can be differentiated from non-IgG4 thyroiditis on the basis of clinical, sonographical, and serological findings. In addition, not only some cases of classical HT but also the well-known fibrous variant of HT has been included the IgG4-thyroiditis spectrum. It is still under investigation whether Riedel's thyroiditis (RT) as well may be considered as an IgG4-thyroiditis. As a matter of fact, RT is characterized by thyroid inflammatory lesions which involve the surrounding tissues, a finding not reported in IgG4-thyroiditis. However, according to some reports, RT with increased IgG4-positive plasma cells may represent the first clinical manifestation of an underlying IgG4-RD.

Clinically, IgG4-thyroiditis has been associated with increased thyroid volume leading to mass symptoms, younger age, lower female/male ratio, higher levels of circulating antithyroid autoantibodies, more diffuse hypoechogenicity, more frequent loss of thyroid function, and a more rapid progression to surgery. According to some reports, serum IgG4 concentrations are elevated in IgG4-thyroiditis and decrease after thyroidectomy.

As compared with non-IgG4 thyroiditis, the IgG4-related forms are histologically characterized by higher grades of stromal fibrosis, lymphoplasmacytic infiltration,

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and follicular cell degeneration. IgG4-thyroiditis has therefore been proposed to represent an IgG4-RD of the thyroid gland, because it shares histopathological characteristics with IgG4-RD in other organs.

Improving the knowledge on IgG4-thyroiditis may open new perspectives for the diagnosis of this rapidly progressive and destructive type of autoimmune thyroiditis and may also provide clues for new therapeutic approaches.

7.2 Relationship Between IgG4-Related Disease (IgG4-RD) and the Thyroid Gland

The relationship between IgG4-RD and the thyroid is an area of active study. IgG4-RD was first proposed in relation to autoimmune pancreatitis (AIP) by Hamano et al. in 2001 [1]. Since then, IgG4-related lesions similar to AIP have been reported in various organs in which they may occur without AIP, in various combinations and in systemic forms [2]. It is interesting to note that a high prevalence of hypothyroidism has been reported in patients with AIP [3], and this finding led authors to investigate the relationship between thyroid disease and IgG4-RD.

It is well known that regardless of the organs affected, IgG4-RD manifestations have common pathological features, such as lymphoplasmacytic infiltration, fibrosis, obliterative phlebitis, and increased numbers of IgG4-positive plasma cells [4]. In this regard, the thyroid represents a very interesting organ to be studied because it can be affected by lymphoplasmacytic inflammation and fibrosis as a result of other diseases which can cause hypothyroidism.

7.3 Hashimoto's Thyroiditis (HT) and IgG4-RD

HT represents a form of chronic autoimmune thyroiditis, also known as chronic lymphocytic thyroiditis or *struma lymphomatosa*, first reported in 1912 by Hakaru Hashimoto, who described four women with enlarged thyroid glands that showed abundant lymphocytic infiltration [5]. HT is the most common cause of hypothyroidism in geographic areas where dietary iodine is sufficient, and is defined by the presence of goiter and positivity of serum thyroid autoantibodies [6]. Typical histological features of HT include lymphoplasmacytic infiltration, lymphoid follicles with germinal center formation, and the presence of large follicular cells with abundant granular eosinophilic cytoplasm (oxyphilic cells).

The pathology of HT was formerly considered to be uniform, but currently more and more findings indicate that it has to be considered as varying [7]. Therefore, HT includes various subtypes which exhibit distinct clinicopathological characteristics [8]. The hypothesis has been proposed that different types of immunopathogenetic mechanisms may be involved in the disease processes of HT in addition to autoimmune inflammation. Therefore, several subclassifications of HT have been introduced [9–11].

Based on immunohistochemistry of IgG4, in 2009, Li and coworkers hypothesized that HT can be divided into two main groups, one termed IgG4-thyroiditis (characterized by IgG4-positive plasma cells) and the other non-IgG4 thyroiditis (characterized by rare IgG4-positive plasma cells) [12].

IgG4-thyroiditis was characterized by histological findings that were almost indistinguishable from those of IgG4-RD in other organs. It was also demonstrated that IgG4-thyroiditis is associated with a lower female-to-male ratio and more rapid progression with more frequent occurrence of subclinical hypothyroidism [8]. Based on these findings, the hypothesis was made that the morphological characteristics with the presence of IgG4 at immunohistochemistry can explain those cases of patients with aggressive and progressive type of HT who develop more frequently and more rapidly subclinical hypothyroidism [8].

Some authors also proposed that the IgG4-thyroiditis subgroup of HT may be an organ-limited form of IgG4-RD, because none of the cases of IgG4-thyroiditis they studied showed systemic involvement of IgG4-RD in other organs [2].

In 1974, Katz and Vickery redefined the fibrous variant of HT (FVHT) [13]. Patients with the FVHT present with neck enlargement and pressure on local tissues often causing diagnostic confusion with malignancy [13]. FVHT demonstrates the same female predominance of HT, with hypothyroidism occurring in almost all patients. The histological characteristics of FVHT include marked fibrous replacement of the thyroid parenchyma and changes typical of HT in the remaining thyroid tissue. In contrast to RT, the fibroinflammatory lesion in FVHT is confined to the thyroid parenchyma and does not extend beyond the thyroid capsule. This suggested the hypothesis of a link between FVHT and IgG4-thyroiditis. Recently, Deshpande and coworkers evaluated 28 consecutive cases of HT and nine cases of FVHT. Hypothyroidism was noted in 62 % of HT and 86 % of FVHT. FVHT demonstrated an exaggerated lobular pattern with lobules separated by cellular storiform-type fibrosis, resembling fibrosis seen in other forms of IgG-RD. The median IgG4 counts per high power field in HT and FVHT were 2.3 and 22, respectively. The median tissue IgG4:IgG ratios in HT and FVHT were 0.11 and 0.58, respectively. Altogether, these findings led the authors to propose that FVHT belongs to the spectrum of IgG4-RD [14].

Elevated numbers of IgG4-positive plasma cells are identified in a wide variety of conditions that belong to the spectrum of IgG4-RD, including sclerosing cholangitis, lymphadenopathy, lymphoid interstitial pneumonia, inflammatory pseudotumor of the lung, orbital pseudotumor, sclerosing sialoadenitis, tubulointerstitial nephritis, inflammatory aortic aneurysm, and pachymeningitis [2]. An increased number of IgG4-positive plasma cells have also been demonstrated in retroperitoneal fibrosis [15, 16]. Related to the latter findings, it is of interest to note the recent report of an association between retroperitoneal fibrosis and autoimmune thyroiditis observed examining both the antithyroid antibody positivity and the ultrasound findings of autoimmune thyroiditis. In a case-control setting, this study showed not only that HT is more common in patients with retroperitoneal fibrosis than in controls but also that a substantial proportion of retroperitoneal fibrosis patients (~25 %) ultimately develop hypothyroidism requiring L-tiroxine [16]. These data, together with the

whole scenario described above about HT and IgG4-RD, led to the hypothesis that, like retroperitoneal fibrosis, HT may also be histologically characterized by a continuum of lesions ranging from an almost absent plasma cell infiltration to a typical IgG4-associated tissue damage.

7.4 IgG4-RD and Riedel's Thyroiditis (RT)

RT is a rare chronic thyroid fibrosing disorder that has been studied by many authors with the attempt to verify whether it may be considered as being part of the spectrum of IgG4-RD. It is characterized by proliferative fibrosis, which involves the thyroid parenchyma and the surrounding structures [17, 18].

The morphological similarities between RT and IgG4-RD suggest that these entities are closely related. Some authors have hypothesized that RT with increased infiltrating IgG4-positive plasma cells, with or without elevated serum IgG4 levels, may be the first clinical manifestation of an underlying IgG4-RD [19, 20]. It is of interest that at histological examination, RT shows obliterative phlebitis in addition to fibrosclerotic changes [18], and this is the reason why it has been suggested that RT may be one of the thyroid manifestations of IgG4-RD. Some authors also suggested a significant link between obliterative phlebitis and extracapsular fibrosis; in fact, it has been postulated that the presence of obliterative phlebitis is essential for the disease to become systemic [2].

It has been hypothesized that when IgG4-RD develops as a multisystemic disease, thyroid involvement usually presents as RT rather than HT. In contrast to RT, IgG4-related forms of HT may be an organ-specific form of IgG4-RD, because they are generally not associated with other organ manifestations of IgG4-RD.

However, cases of IgG4-related RT are not frequent. Recent data support the concept that RT-type of IgG4-thyroiditis is rare or even exceptional [12, 21]. In a recent review of RT in Japan, Takeshima and coworkers [22] identified only ten patients diagnosed with this form of thyroiditis during a 25-year period. In two patients, the infiltration of IgG4-positive plasma cells was confirmed; one of these two patients promptly responded to steroid therapy. Although these clinicopathological features suggest that IgG4-RD may be the underlying condition in some patients with RT, the etiology of RT in relation to IgG4-RD is not yet established.

7.5 Histological Findings of IgG4-Thyroiditis

The majority of thyroid glands show diffuse symmetric enlargement without any dominant mass. The thyroid gland from patients with IgG4-thyroiditis is usually elastic-soft in consistency and ivory-white or pinkish-white in color on cut surface, which indicates replacement of the thyroid parenchyma by fibrous tissue. The thyroid lobes are demarcated by a capsule that is nonadherent and that can be easily separated at the surgical intervention from the surrounding structures. Therefore,

the diagnosis of RT or extrathyroid extension of malignant disease beyond the thyroid capsule can be macroscopically ruled out.

Literature reports of IgG4-thyroiditis show histological features indicative of HT with prominent lymphoplasmacytic sclerosing changes and increased numbers of IgG4-positive plasma cells. IgG4-thyroiditis has been reported to show a significantly higher grade of lymphoplasmacytic infiltration and stromal fibrosis than the non-IgG4 thyroiditis subtype [8, 12].

In line with these reports, other authors have described histological features of IgG4-RD in a subset of patients with Hashimoto's thyroiditis [8, 12, 23–26], whereas other studies suggest that increased IgG4 counts can be seen in nonspecific inflammatory infiltrates [27] and that there is no relationship between IgG4 counts and thyroid fibrosis [28].

Obliterative phlebitis is one of the characteristic features of IgG4-RD. However, some authors reported either a very low prevalence or even the absence of obliterative phlebitis in IgG4-thyroiditis [29]. However, the lack of obliterative phlebitis has not been considered to conflict with the conclusion that IgG4 thyroiditis is one of the thyroid manifestations of IgG4-RD. In fact, obliterative phlebitis has been hypothesized to be linked with extracapsular fibrosis which almost never occurs in IgG4-thyroiditis.

There are several possible explanations for the above-reported discrepancies between studies.

Most of the published studies on IgG4-thyroiditis come from Asian populations with only a few representative studies from Europe or North America [14]. Therefore, differences in population genetics, dietary (iodine), or other environmental factors may underlie the heterogeneous histopathological and pathophysiological characteristics of HT as well as IgG4-RD [30, 31]. Also, several studies have used a range of arbitrary thresholds to define increased IgG4-positive plasma cell counts, contributing to the heterogeneity of the results.

7.6 Immunohistochemistry of IgG4-Thyroiditis

Patients with HT are generally subclassified into IgG4-thyroiditis or non-IgG4 thyroiditis groups based on the immunostaining of IgG4 and IgG, and the cutoff value of >20/HPF IgG4-positive plasma cells and >30 % IgG4/IgG ratio [8, 12]. Immunohistochemically, IgG4-thyroiditis shows diffuse or nodular dense infiltration of IgG4-positive plasma cells with a high ratio of IgG4/IgG positive plasma cells. On the contrary, in the non-IgG4 thyroiditis, only a few IgG4-positive plasma cells are found although many IgG-positive plasma cells may be present in the stroma. However, discrepancies between studies exist. For example, no correlation between IgG4-positive plasma cell counts and fibrosis or other histological findings typical of IgG4-RTD was identified in a North American cohort [29]. In fact, a retrospective review of 38 thyroidectomy specimens from patients with chronic thyroiditis over a 3-year period demonstrated a wide range of IgG4-positive plasma cell counts, lymphoplasmacytic inflammation, and fibrosis with

no correlation between IgG4 plasma cell levels and fibrosis. Therefore doubts still exist, at least according to some authors, on the involvement of the thyroid gland in IgG4-RD [29].

7.7 Laboratory Findings

Studies have been conducted in order to define whether serum levels of IgG4 may be of thyroid origin in patients with hypothyroidism and IgG4-related thyroid lesions. It has been demonstrated that serum concentrations of IgG4 from IgG4-thyroiditis patients are significantly higher as compared to those measured in non-IgG4 thyroiditis patients [2]. An interesting report on eight patients affected by IgG4-thyroiditis demonstrated that serum IgG4 concentrations significantly decreased after total thyroidectomy, which indicates that the origin of serum IgG4 must be the thyroid gland, or that the thyroid is the target organ against which IgG4 antibodies are produced. Marked reductions of more than twofold were detected after thyroidectomy in five out of the eight cases. One patient with a normal preoperative serum IgG4 concentration showed a relatively stable value. The remaining two cases of IgG4-thyroiditis showed a slight elevation after surgery. In these three cases, the thyroid glands could not have been the major origin of serum IgG4, while probably other affected sites could account for IgG4 production. Review of these three patients failed to identify any systemic involvements of IgG4-RD in the other organs, and no reasonable explanations for the source of IgG4 in these patients could be made. Circulating levels of thyroid autoantibodies, directed against both thyroid peroxidase and thyroglobulin, have been shown to be significantly higher in patients with IgG4-thyroiditis than in those with non-IgG4 thyroiditis [8, 12, 24].

7.8 Clinical Findings

Patients with IgG4-thyroiditis have been demonstrated to be younger than those affected by non-IgG4 thyroiditis. In HT, the female-to-male ratio is about 8–9:1; this ratio has been demonstrated to be lower in IgG4-thyroiditis. Patients with IgG4-thyroiditis have been reported to present with an enlarged thyroid with mass effect [32]. In some cases, thyroid enlargement may be characterized by a constant increase. A history of previous autoimmune thyroid disease, such as Graves' disease, has been reported in some cases [26]. A differential diagnosis with thyroid malignancy, especially with lymphoma, may be required. As compared with patients with non-IgG4 thyroiditis, those ones with IgG4-thyroiditis have been shown to be characterized by significantly shorter disease duration of HT before they underwent total thyroidectomy. Also, the thyroid functional status has been demonstrated to differ between IgG4- and non-IgG4 thyroiditis with findings consistent with a more frequent loss of the thyroid function being associated with IgG4-thyroiditis [8].

A summary of the main findings of original studies focusing on IgG4-thyroiditis is reported in Table 7.1.

Table 7.1 Main findings of original studies focusing on IgG4-thyroiditis

Author, year	Number of patients	Type of study	Main results
Li et al. (2010) [8]	70	Histological case-control study of IgG4-thyroiditis and non-IgG4 thyroiditis	IgG4-thyroiditis and non-IgG4 thyroiditis are distinct entities
Li et al. (2009) [12]	17	Histological cohort study	Immunostaining of IgG4 can help subclassify HT
Ceresini et al. (2015) [16]	144	Prospective ultrasonographic and laboratory case-control study	Patients with idiopathic retroperitoneal fibrosis have a higher risk of HT compared to controls
Dahlgren et al. (2010) [20]	3	Retrospective histological study	Riedel's thyroiditis is part of the IgG4-related systemic diseases
Watanabe et al. (2013) [23]	114	Retrospective study in patients with IgG-4-related disease	Serum IgG4 are higher in hypothyroid subjects
Li et al. (2012) [24]	105 cases of HT	Retrospective histological study	In IgG4 HT histopathological features are distinct from non-IgG4 HT
Kawashima et al. (2014) [26]	24 HT patients with elevated serum IgG	Measure of serum IgG-4 in a prospective study	Serum IgG-4 elevated in five patients
Zhang et al. (2014) [25]	53 cases of HT patients	Histological and laboratory cohort study	HT can be divided into IgG4-positive and IgG4-negative

HT Hashimoto's thyroiditis

7.9 Imaging

Sonographic studies have revealed that IgG4-thyroiditis is significantly associated with diffuse low echogenicity, whereas non-IgG4 thyroiditis seems to be associated with diffuse coarse echogenicity.

Several sonographic patterns have been reported in HT [33–35] and studies aimed at the identification of an association between sonographic findings and the degree of thyroid function impairment have been conducted [36, 37]. Data have been reported demonstrating that patients with remarkable hypoechogenicity of the thyroid gland (i.e., the echogenicity of the thyroid was almost equal to or less than that of the adjacent muscles) had abnormally low T4 and abnormally high TSH more frequently than patients with coarse echogenicity. Thus, the observation that IgG4-thyroiditis is significantly associated with diffuse low echogenicity is likely to suggest that this form is more frequently associated with hypothyroidism and follicular degeneration [2]. See Fig. 7.1 for representative ultrasound images of normal thyroid and chronic Hashimoto's thyroiditis.

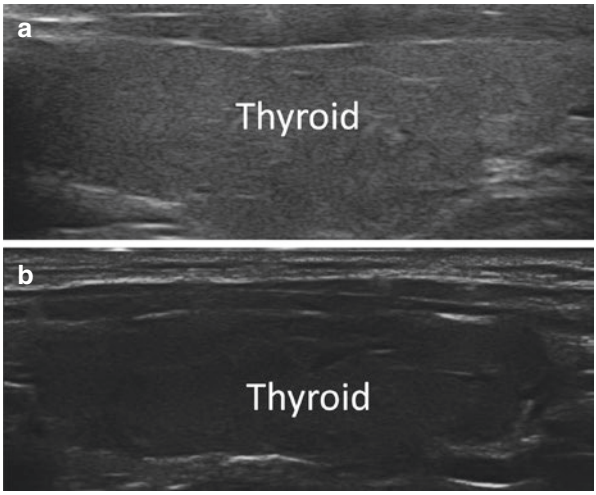

Fig. 7.1 Representative ultrasound images of normal thyroid (**a**) with homogeneous texture, and chronic autoimmune (Hashimoto's) thyroiditis (**b**) characterized by hypoechogenicity and inhomogeneous texture

7.10 Future Perspectives and Hypothesis of Treatment

The potential association between IgG4-RD and thyroid disease represents a matter of increasing interest. There is no doubt that larger studies are needed in order to better define this relationship. Identifying subsets of patients with IgG4-thyroiditis, based either on tissue or serum findings, could be important for several clinical aspects. The more rapid progression towards surgery due to thyroid gland enlargement in the IgG4-thyroiditis subgroup could lead investigators to explore whether this subset warrants immunosuppressive therapy, and whether immunosuppression may halt disease progression. In addition, a more rapid loss of thyroid function of IgG4-thyroiditis patients may lead to earlier interventions in treating hypothyroidism. Finally, from an investigative perspective, IgG4-related and -unrelated forms of thyroiditis may recognize different proteins as target antigens of autoantibody production, and may reveal different immunopathogenic patterns leading to thyroid inflammation and fibrosis.

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Retroperitoneal Fibrosis and the Spectrum of Chronic Periaortitis

8

Federica Maritati, Gabriella Moroni, and Augusto Vaglio

8.1 Introduction

Retroperitoneal fibrosis (RPF) is a rare condition of variable etiology characterized by the presence of an aberrant fibroinflammatory tissue in the periaortic retroperitoneum that frequently entraps neighboring structures such as the ureters, causing obstructive uropathy and renal failure. RPF is idiopathic in more than two thirds of the cases, while the remaining third is secondary to many causes, such as drugs, neoplasms, infections, trauma, radiotherapy or surgery [1].

Idiopathic RPF may develop around an undilated or a dilated aorta, therefore "nonaneurysmal forms" and "perianeurysmal forms" of RPF can be distinguished. In addition, it also frequently affects the thoracic aorta [2, 3]. For these reasons, in the 1980s the more appropriate term "chronic periaortitis" was coined in order to describe all these clinical conditions. Chronic periaortitis (CP) includes idiopathic RPF (the nonaneurysmal form), inflammatory abdominal aortic aneurysms (IAAA) (without ureteral involvement), and perianeurysmal fibrosis (with ureteral involvement); the two latter conditions are clinically and histologically similar to idiopathic RPF except for aortic aneurysmal dilatation [4].

CP, especially its nonaneurysmal form, may be isolated or develop in the setting of a systemic immune-mediated disease, such as systemic lupus erythematosus, rheumatoid arthritis, and small- and medium-sized-vessel vasculitides. It can also be found associated with organ-specific autoimmune disorders such as autoimmune thyroiditis [1].

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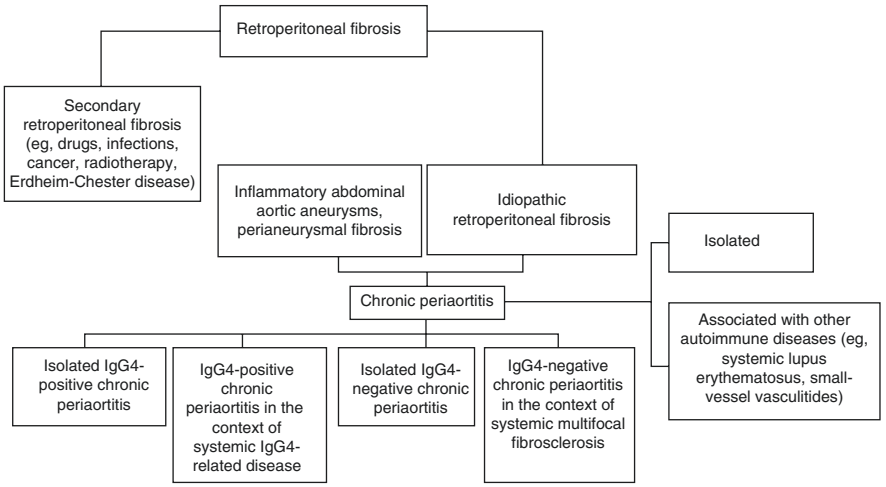

Fig. 8.1 Schematic representation of the clinical spectrum of retroperitoneal fibrosis and chronic periaortitis

Finally, idiopathic RPF may occasionally arise in the context of the IgG4-related disease, a fibroinflammatory disorder affecting different structures (e.g., pancreas, biliary tract, lymph nodes), histologically hallmarked by extensive T-lymphocyte- and IgG4-bearing plasma-cell infiltration associated with storiform fibrosis, tissue eosinophilia and obliterative phlebitis, and also characterized by increased levels of serum IgG4 in a significant proportion of cases [5, 6] (Fig. 8.1).

8.2 Secondary Forms of RPF

The clinical entities included in the spectrum of CP are idiopathic. About one third of RPF, particularly if nonaneurysmal, are instead secondary to different etiologies, including drugs, malignancies, infections, and external-beam radiation [1, 7].

The drugs most frequently associated with RPF are derivatives of ergot alkaloids (e.g., methysergide, ergotamine) and dopamine agonists (e.g., pergolide, methyldopa). Methysergide and other ergotamine-derived agents increase the levels of endogenous serotonin that can lead to fibrous reactions through stimulation of myofibroblast proliferation and increase in collagen matrix deposition. This fibrogenic effect is often not limited to the retroperitoneum, but may involve pericardium, pleura, and lungs [8, 9]. Other medications reported as associated with RPF include beta-blockers, hydralazine, and phenacetin, but the pathogenesis of this process is still unclear [10]. Recently, some case reports described the relation between RPF and the previous or concomitant use of biological agents. In particular, the drugs involved are infliximab, a monoclonal antibody directed against tumor necrosis factor-alpha (TNF-alpha) and etanercept, a soluble receptor that acts as a TNF-alpha blocker, both widely employed in the treatment of rheumatic diseases. It was already

reported that they may trigger a number of autoimmune conditions, but the mechanisms through which they may stimulate fibrotic reactions are still unknown [11].

Malignancies are a frequent cause of secondary forms of RPF. In most of these cases, RPF is the consequence of an exuberant desmoplastic response to retroperitoneal metastases (e.g., carcinoma of the prostate, breast, colon) or is due to primary retroperitoneal neoplasms (e.g., Hodgkin and non-Hodgkin lymphomas, various types of sarcomas, and well-differentiated liposarcoma sclerosing variant) [12]. The only exception are carcinoids, where RPF can arise in absence of metastasis or primitive retroperitoneal lesions, probably through a mechanism mediated by serotonin or by the release of fibrogenic growth factors such as platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and the family of transforming growth factors alpha and beta [13].

Infection-related RPF is usually secondary to the local spread of a contiguous infectious focus (e.g., spinal or paraspinal abscesses), or to an immune response triggered by a remote infection. The primary infections more often reported are tuberculosis, actinomycosis, or histoplasmosis [14].

Finally, other potential causes of RPF include radiotherapy, trauma, major abdominal surgery, proliferative disorders such as Erdheim–Chester disease, and other histiocytoses [15].

8.3 Association with Autoimmune or Fibroinflammatory Diseases

The association with autoimmune disorders is an interesting aspect of idiopathic RPF and highlights the relevance of autoimmune mechanisms in the pathogenesis of the disease. Autoimmune thyroiditis is the most frequently associated autoimmune condition: in a recent case–control study, idiopathic RPF patients had a prevalence of antithyroperoxidase antibodies of 24.7 % (versus 10.6 % in healthy controls) and a significantly higher frequency of ultrasound signs of chronic thyroiditis; after a median follow-up of 45 months, 25 % of RPF patients developed hypothyroidism requiring L-thyroxine. Where available, histology most often showed typical Hashimoto thyroiditis or its fibrous variant [16]. Cases of Riedel's thyroiditis were also described [17].

Idiopathic RPF can also arise in the context of a systemic fibroinflammatory condition recently reclassified as IgG4-related disease (IgG4-RD), a heterogeneous disorder whose spectrum of manifestations include sclerosing (autoimmune) pancreatitis and cholangitis, chronic sialoadenitis, fibrosing mediastinitis, orbital pseudotumor, and tubulointerstitial nephritis. These organ manifestations can be variably associated and can develop simultaneously or metachronously. Histologically, the affected organs reveal similar aspects to those seen in idiopathic RPF (abundant fibrosis and a chronic inflammatory infiltrate), but more specific manifestations include an intense infiltration by IgG4-bearing plasma cells, fibrosis with a storiform pattern, tissue eosinophilia, and – rarely – obliterative phlebitis [18]. An increase in serum IgG4 levels is also often detected in these patients [19]. Recent

studies have demonstrated that, based on histologic findings (e.g., IgG4+ plasma cell infiltration), approximately 50 % of idiopathic RPF can be histologically classified as "IgG4-related" even when the disease is not associated with other IgG4-RD lesions. However, these data have not yet been confirmed. IgG4-related and IgG4-unrelated RPF do not appear to differ clinically, except for a higher frequency of extraretroperitoneal manifestations in the former group; in particular, they have similar demographic and laboratory characteristics, comparable mass location and thickness, and comparable rates of ureteral involvement. Therefore, it is likely that they represent different ends of the same disease spectrum [5].

Idiopathic RPF has also been found in association with different types of glomerulonephritis (GN), particularly membranous nephropathy (MN) [20, 21]. Idiopathic MN is also mediated by glomerular deposition of IgG4. Notably, target antigens in MN associated with RPF or IgG4-RD differ from those (e.g., phospholipase A2 receptor) detected in idiopathic MN [22, 23].

Finally, other associations reported in the literature include rheumatoid arthritis, ankylosing spondylitis, ANCA-associated vasculitis, systemic lupus erythematosus, and psoriasis [24–27].

8.4 Epidemiology

CP is a rare disease and data about its epidemiology are not well known and limited to idiopathic RPF and IAAA. The incidence of idiopathic RPF is estimated to be 0.1–1.3 per 100,000 person-years and its prevalence 1.4 per 100,000 inhabitants [7, 28]. Data available about IAAAs show that they represent 4–10 % of all abdominal aortic aneurysms. No data are available about the incidence of secondary RPF. Idiopathic RPF most commonly occurs in individuals aged 50–60 years and has a male predominance (male/female ratio of 2:1 to 3:1) [29, 30]. Pediatric cases are rare, with up to 30 patients described in the literature [31].

8.5 Pathogenesis

The first studies on the pathogenesis of the disease, carried out during the 1980s and 1990s by Parums and Mitchinson, defined CP as an exaggerated localized reaction to antigens contained in the atherosclerotic plaques of the abdominal aorta. These authors postulated that plaque macrophages process oxidized low-density lipoproteins (LDLs) and, migrating from the intima-media to the adventitia (especially when there is medial thinning as it occurs in atherosclerosis), they present such lipids to lymphocytes and plasma cells, triggering adventitial and periadventitial inflammation and fibrosis [4, 32].

However, the observation of idiopathic RPF in patients who do not suffer from atherosclerosis and, at the same time, the high frequency in these patients of constitutional symptoms, high concentrations of acute-phase reactants, autoantibodies, and the association with other autoimmune diseases, have led to the hypothesis that

CP is a manifestation of a systemic autoimmune disease [33]. This systemic immune-mediate theory is also in line with the evidence that idiopathic RPF usually shows a good response to immunosuppressive therapy [34]. Idiopathic RPF could arise as a primary aortitis that subsequently elicits a periaortic fibroinflammatory response. In keeping with this hypothesis is the observation that inflammation predominates in the adventitia and is often associated with *vasa vasorum* vasculitis together with adventitial lymphoid follicles with germinal centers [35]. The pathogenesis of the disease is multifactorial. Genetic studies have demonstrated that CP is associated with human leucocyte antigen (HLA) DRB1*03, an allele linked to other autoimmune diseases such as type 1 diabetes, myasthenia gravis, and Hashimoto's thyroiditis [36]. A more recent study also described an increased susceptibility to develop CP, especially its aneurysmal form, in patients carrying the delta 32 (Δ32) polymorphism of the CC-chemokine receptor 5 (CCR5) gene. CCR5 is expressed on many immune cells, especially Th1 cells, and this SNP may produce a nonfunctional receptor that could shift T-cell response towards a Th2 pattern [37].

Environmental factors also play a definite role. A recent case–control study confirmed the predisposing role of asbestos exposure and also identified smoking as a risk factor. Smoking and asbestos had a multiplicative effect on disease risk, with an odds ratio of 12.04 (95% confidence interval, 4.32–38.28) in those subjects exposed to both risk factors [38]. Microbial agents such as *Mycobacterium tuberculosis* may also act as disease triggers [14], while the role of viruses is still uncertain.

The molecular mechanisms underlying the development of CP are still unclear. Studies performed on aortic biopsies in these patients revealed the expression of gene transcripts of interferon-γ (IFN-γ), interleukin-1α (IL-1α), IL-2, and IL-4, suggesting lymphocytic activation [39]. A number of chemokines have certainly a pathogenetic role. A recent study showed that serum levels of eotaxin/chemokine (C-C motif) ligand 11 (CCL11) are significantly higher in CP patients than in healthy controls and this chemokine is also highly expressed by mononuclear cells in the inflammatory infiltrates of retroperitoneal biopsies obtained from CP patients. Eotaxin/CCL11 induces tissue recruitment of eosinophils and mast cells which have been found in periaortic biopsies. In addition, the receptor for eotaxin/CCL11, CCR3, has been demonstrated to be diffusely expressed by eosinophils, mast cells, and fibroblasts, suggesting that this chemokine may have a peculiar pathogenetic role not only by inducing tissue influx of eosinophils and mast cells, but also by directly stimulating collagen-producing cells [40]. Fibroblast proliferation and collagen production are also stimulated by eosinophil and mast cell products (e.g., eosinophil granule proteins, tryptase) [41]. Fibroblasts activation is also induced by CCL18, a marker of fibrotic activity in pulmonary idiopathic fibrosis, whose serum levels were found to be increased also in CP and correlated with tissue shrinkage after therapy [42].

The recent considerations about the association of idiopathic RPF or IAAAs with IgG4-RD, together with the frequent observation of intense infiltration by IgG4+ plasma cells in both aneurysmal and nonaneurysmal forms of CP, led to new pathogenetic hypotheses [43]. In fact, because IgG4-skewed immune responses are

commonly driven by T-helper 2 (Th2) cytokines such as IL-4, IL-5, IL-10, and by TGF-β, it is likely that such reactions play a pathogenetic role both in IgG4-RD and in CP, with TGF-β that promotes fibrosis and IL-5 inducing eosinophil maturation and tissue infiltration [44]. IL-4, IL-10, and IL-13 instead can boost B-cell responses and humoral immunity. B cells are abundant in CP tissue [45]. Their pathogenetic role is still unclear, but it is known that these cells are critical for antigen presentation to Th2 effector cells or CD4+ effector memory cells and have an important role in the persistence of the disease, modulating immunity independently of antibody production, both as effective antigen-presenting cells and as source of cytokines. In addition, in CP, it has been shown that T cells locally produce IL-6, which can activate B cells and fibroblasts [46].

The pathogenic importance of the IL6-mediated axis and of B cells was confirmed in vivo by the efficacy of therapies targeting the IL-6 receptor (tocilizumab) and the B-cell marker CD20 (rituximab), but these data are limited to small case series and need to be confirmed by larger studies [46, 47].

8.6 Clinical Manifestations and Laboratory Tests

CP is a rare and severe disease that may progress until kidney failure due to the complete obstruction of the ureters and/or of the blood vessels of the kidney peduncle involved by the process. A prompt diagnosis and an appropriate treatment may prevent the development of irreversible complications. Unfortunately, the clinical presentation of CP is often vague and insidious and an early diagnosis is usually difficult. The most common presenting symptoms of CP are abdominal, lower back, or flank pain. The pain is usually dull and constant. A colicky pain due to ureteral encasement may occur but is not mandatory. Renal failure due to bilateral ureteral obstruction resulting in hydronephrosis is seen in about 42–95 % of the cases [28, 30]. Ureteral encasement can frequently be unilateral and, for this reason, renal function may remain normal for a long time. In these cases, the correct diagnosis is made tardily and the chronic entrapment of the ureter can lead to a severe and sometimes irreversible damage to the corresponding kidney.

Retroperitoneal blood and lymphatic vessel involvement is less frequent (one-quarter of the cases) and manifests typically as edema (rarely thrombophlebitis) of the lower limbs, while arterial encasement may cause – although not frequently – claudication. Other complications include scrotal swelling, varicocele or hydrocele, due to the compression of the gonadal vessels, and constipation, nausea, and vomiting. Constitutional manifestations such as fever, weight loss, fatigue, and night sweats often occur [1, 7]. If the thoracic aorta or the periaortic arteries are involved, patients may suffer from hoarseness, secondary to recurrent laryngeal nerve paralysis, dry cough, or upper limb claudication [3].

Acute-phase reactants, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are elevated in more than half of the patients but they lack sensitivity and specificity for the diagnosis of RPF and are not able to distinguish idiopathic from secondary forms. However, ESR and CRP correlate with the

symptoms and the amount of mass shrinkage after therapy, thus they are useful to monitor the clinical course of the disease [48].

Renal function is variably impaired in patients with ureteral encasement, depending on the severity of obstruction. Urinary sediment and proteinuria should be checked to exclude an underlying glomerulonephritis. Even in absence of any parenchymal renal disease, macroscopic and microscopic hematuria may be found, probably as a result of ureteral involvement. Anemia is quite frequent, due to chronic inflammation and/or renal dysfunction [49].

Antinuclear antibodies (ANAs) and anti–smooth muscle antibodies are the most frequently positive autoantibodies. They can be positive even in patients without any associated autoimmune disorder and their presence may support the autoimmune origin of the disease [34].

Serum IgG4 levels may be raised in patients with both nonaneurysmal and aneurysmal forms of CP [19]. However, these findings do not always allow to classify the disease as part of IgG4-RD; high serum IgG4 levels are also found in approximately 5 % of healthy controls and in patients with other diseases such as eosinophilic granulomatosis with polyangiitis (EGPA), Castelman's disease, and eosinophilic pneumonia [50, 51]. Thus, the finding of high serum IgG4 needs to be interpreted within the clinical context.

8.7 Pathology

The macroscopic findings of the idiopathic and the secondary forms of RPF are often similar [1]. The lesion appears as a hard and white mass of varying thickness without a capsule, which infiltrates the retroperitoneal adipose tissue surrounding the abdominal aorta and iliac vessels, as well as the inferior vena cava and the ureters.

The microscopic observation of idiopathic RPF samples reveals the presence of two components: a fibrous tissue and a chronic inflammatory infiltrate. The fibrous component consists of an extracellular matrix composed of type I collagen fibers organized in thick irregular bundles and a population of spindle-shaped cells characterized immunohistochemically as fibroblasts and myofibroblasts (positive for vimentin and α-smooth muscle actin, respectively). The fibroblast population rarely shows mitoses, although these cells have been shown to undergo clonal proliferation. The collagenous stroma contains varying quantities of nerves and small blood vessels that often show a prominent perivascular hyalinization. The inflammatory component infiltrates the fibrous tissue and consists of B and T lymphocytes, macrophages, plasma cells, and rare eosinophils. It can be diffuse or organized into a perivascular pattern. In the former case, inflammatory cells are interspersed within the collagen bundles; in the latter, aggregated lymphocytes surround the small retroperitoneal vessels and tend to have a central core of B cells and a periphery of CD4+ and CD8+ T cells [45]. In the late stages of the disease, histology shows especially pronounced sclerosis with scattered calcifications and a reduction of the inflammatory component [1].

In IgG4-related RPF, the microscopic findings are very similar to those of the idiopathic form, with associated obliterative phlebitis, a mild-to-moderate eosinophilic infiltrate, and fibrosis with a storiform pattern. As in idiopathic RPF, the inflammatory infiltrate is composed of T and B lymphocytes, whereas B cells are typically organized in germinal centers and T cells are distributed diffusely. Although IgG4-bearing plasma cells may be also found in the inflammatory infiltrate of idiopathic RPF, a ratio of IgG4-bearing plasma cells to total IgG-bearing plasma cells higher than 30–50 % is essential for the diagnosis of IgG4-related RPF [18].

8.8 Imaging Studies and Role of Biopsy

Imaging procedures are essential for the diagnosis and follow-up of CP [52]. Ultrasonography is usually the first-line study performed at the disease onset to assess the presence of hydronephrosis and aortic dilatation/aneurysm; sometimes a hypoechoic periaortic tissue may be observed [53].

Abdominal CT and MRI are currently considered the investigations of choice to reach a correct diagnosis [53]. CP appears at CT as a homogeneous periaortic and peri-iliac mass isodense to muscle that can compress neighboring structures and displace the ureters medially. Unlike secondary forms of RPF due to neoplasms or lymphomas that appear as lobulated or nodular masses infiltrating or destroying psoas muscles or bones, idiopathic RPF is usually characterized by a mass of soft-tissue density and a plaque-like appearance, located distal to the kidney hilum, anteriorly and laterally to the aorta. In aneurysmal CP (IAAAs or PRF), the aorta has aneurysmal dilatation and the tissue usually encircles its entire circumference. Some localized lymphadenopathies adjacent to the mass can occur in idiopathic forms but they are never confluent (Fig. 8.2).

On MRI, CP appears hypointense in T1-weighted images; in T2-weighted images, its intensity is low in the quiescent phases of the disease and high in the active stages, when there is abundant tissue edema and hypercellularity [54]. If renal function is not compromised, it is useful to perform CT or MRI with contrast medium. The contrast-enhancement on CT or MRI of the retroperitoneal mass correlates with disease activity, and can be used to evaluate the response to treatment [53].

Nuclear medicine is a suitable complement to radiographic imaging because it provides an easy visualization of almost the entire body. Specifically, fluorodeoxyglucose-positron emission tomography (FDG-PET) is a nuclear medicine technique able to identify accurately in vivo areas characterized by elevated glucose metabolism, such as inflammatory, infectious, and neoplastic lesions. In patients with CP, FDG-PET is able to show a vasculitic process in the large branches of the aorta, both abdominal and thoracic [55]. The presence of atherosclerotic plaques or of other large-vessel vasculitides such as giant cell arteritis or Takayasu's arteritis can also produce a positive vascular FDG uptake, reducing the specificity of this technique for the diagnosis of CP. Recent studies showed the abnormal FDG uptake by the retroperitoneal mass in active disease phases tends to reduce parallel

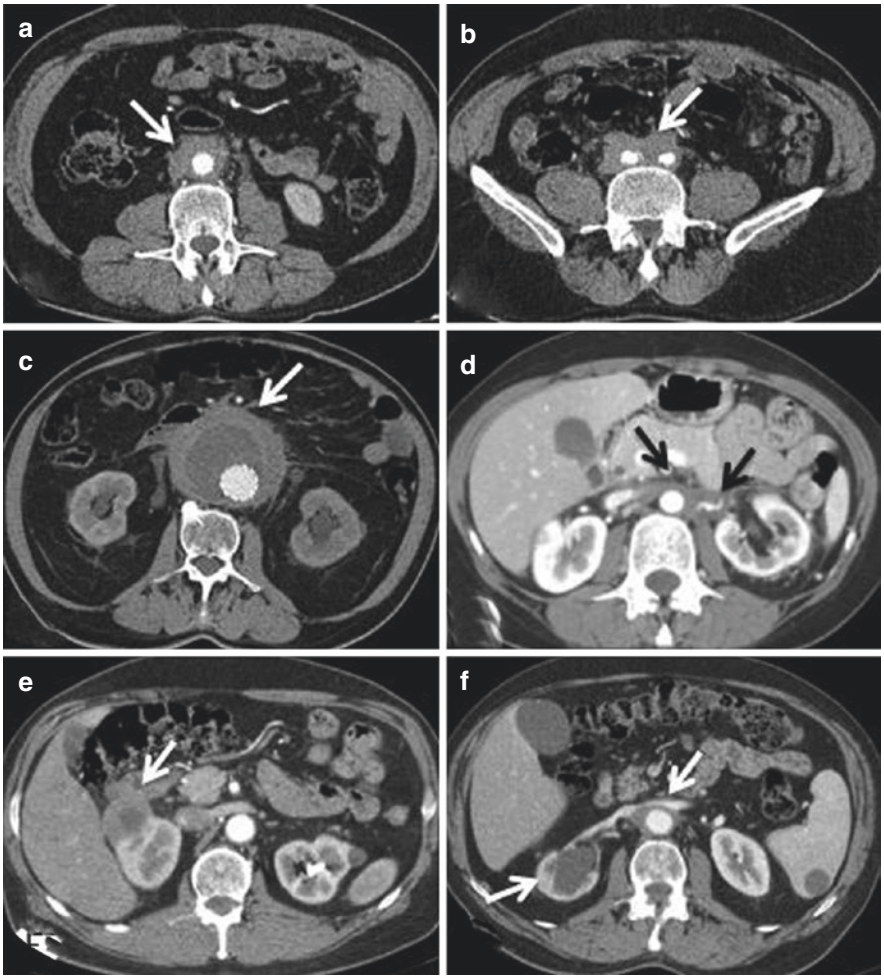

Fig. 8.2 Computed tomography findings in chronic periaortitis. (**a**, **b**) Typical aspects of periaortic (**a**, *arrow*) and peri-iliac (**b**, *arrow*) idiopathic retroperitoneal fibrosis (RPF). The retroperitoneal tissue develops around the anterior and lateral sides of the abdominal aorta and the common iliac arteries. (**c**) Typical case of perianeurysmal RPF, with the periaortic tissue surrounding an aneurysmal aorta (*arrow*). Endovascular aortic prosthesis can be seen. (**d**) Idiopathic RPF surrounds the abdominal aorta (*left arrow*) and encases the origin and the left renal artery (*right arrow*). (**e**) Renal inflammatory pseudotumor in a patient with chronic periaortitis (*arrow*). (**f**) In a patient with idiopathic periaortic (*right arrow*) and peri-iliac retroperitoneal fibrosis (not shown), chronic hydronephrosis determined right kidney atrophy (*left arrow*)

to ESR and CRP through remission [56, 57]. In clinical practice, FDG-PET is used to assess disease activity. In addition, it can also reveal active vasculitis in other vascular territories and may disclose other affected areas, such as those observed in IgG4-RD, or occult neoplastic or infectious processes, thus turning very useful in differential diagnosis with secondary forms of RPF [55]. If imaging studies are not

completely diagnostic for CP, tissue biopsy becomes mandatory. Biopsy may be recommended in cases with atypical localization (e.g., periureteral, perirenal) [58, 59], or with clinical or imaging findings consistent with neoplastic RPF [60] and in patients refractory to conventional steroid therapy. Multiple biopsy techniques have been used in sampling CP, including open, laparoscopic, or transcaval retroperitoneal biopsy, and fine-needle aspiration.

8.9 Treatment and Outcome

The first aim of treatment of CP is reversing ureteral obstruction and preserving kidney function [1]. In all cases of renal failure and severe bilateral hydronephrosis, ureteral decompression should be promptly performed in order to avoid permanent kidney damage. Surgical ureterolysis with intraperitonealization and omental wrapping of the ureters is no longer the first-line approach, while conservative procedures (e.g., double-J stent or nephrostomy placement) followed by medical therapy are preferred [61, 62]. Surgical approach is often mandatory also in the perianeurysmal forms of RPF when the aortic diameter exceeds 5–5.5 cm; in these cases, open repair is the traditional method, although the less invasive endovascular prosthesis placement is now widely used with good efficacy. No clear differences between inflammatory and noninflammatory abdominal aortic aneurysms are reported in terms of risk of rupture, postoperative complications, and long-term outcome [1]. Some case reports describe the possibility of a complete regression of the perianeurysmal mantle [63]. However, several studies indicate that it frequently persists or even progresses after surgery or endovascular treatment. For this reason, medical treatment might be the treatment of choice when there are no surgical indications for aneurysm repair, to improve the symptoms and to reduce the risks of obstructive complications. In the other cases, the need for starting medical therapy will be considered depending on patient condition and, however, a strict follow up is mandatory [1].

Medical treatment for idiopathic RPF should be initiated as soon as possible. There is evidence that treatment with glucocorticoids, sometimes associated with immunosuppressive agents, is highly effective in the vast majority of patients [30, 64, 65]. Initial doses of 1 mg/kg/day of prednisone for the first month appear to be the best option to induce remission, which is defined as resolution of symptoms and hydronephrosis, acute-phase reactant normalization, and/or reduction of mass thickness at CT or MRI control. After 1 month of therapy, if remission is obtained, prednisone may be progressively tapered to 5–10 mg daily within 3–4 months, and then maintained for an additional 6–9 months [30]. Remission rates after steroid therapy range between 75 and 95 % [30, 65] with a mean mass thickness reduction reported around 50 % [30]. Patients with CP undergoing treatment should be monitored clinically, by laboratory tests including inflammatory markers and serum creatinine, and by imaging techniques. There is no evidence-based rule to dictate the frequency of assessments, but it is reasonable to monitor blood tests every 1–2 months, while imaging studies should be repeated 2–4 months after starting therapy [28, 48].

FDG-PET may be repeated at the end of the treatment or in case of suspected relapse. Patients who satisfactorily respond to treatment usually show a decrease in inflammatory markers, reduced or absent enhancement, and shrinkage of the retroperitoneal mass and a complete or near-complete normalization of FDG uptake at PET [55]. Nephrostomic tubes or double-J stents can be removed when cross-sectional imaging demonstrates that ureters are no longer encased. Once these devices are removed, kidney ultrasound should be frequently performed in order to early identify recurrent hydronephrosis.

Relapses are common upon glucocorticoid tapering [62, 65] and this is the reason why the clinician should follow the patient also after remission. There are no guidelines on how to follow these patients up, but we consider appropriate to test acute-phase reactants and kidney function every 3 months and to repeat CT or MRI 6 months after remission and thereafter every 6–12 months [53].

In those patients who experience repeat relapses requiring long-term glucocorticoid therapy or in patients with contraindications to glucocorticoid therapy, a valid steroid-sparing alternative is still missing. The antiestrogen agent tamoxifen has been proposed as an alternative to glucocorticoids because of its potential antifibrotic activity. This drug is thought to be effective in fibrosing disorders such as RPF or desmoids for its capacity to down-regulate the release of growth factors involved in fibroblast proliferation and collagen production [66–68]. In the only randomized controlled trial performed in idiopathic RPF patients, 36 of 39 patients who obtained remission after induction therapy with 1 mg/kg/day of prednisone were randomized to prednisone tapering or to switch to tamoxifen (0.5 mg/kg/day) for an additional 8 months. Relapses were more frequent in the tamoxifen group, with the between-group difference in relapse rates being significant both at the end of treatment (month 8) and at 26 months follow-up [30]. Therefore, to date, the efficacy of tamoxifen is not supported by controlled trials and its superiority to other agents is still unproven.

After remission, patients have to be carefully followed using laboratory tests, ultrasound, and periodic CT or MRI studies, in order to early detect relapses. Relapse rate is up to 72 % [65] and relapsing patients often experience multiple relapses [69]. In such cases, long-term maintenance therapy with immunosuppressants can be considered.

Several immunosuppressive drugs (e.g., mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, and cyclophosphamide) have been employed for refractory or relapsing forms of idiopathic RPF with favorable outcome, but so far there is no evidence that a particular immunosuppressive agent is superior to others [70–73]. Therefore, the choice of the steroid-sparing agents to be used in the individual patients should probably be best based on the patient's profile.

In one of the few prospective studies available, comprising 28 patients treated with 40 mg/day of prednisone tapered over 6 months and mycophenolate mofetil 1 g twice daily for a mean of 24 months, all patients attained remission of constitutional manifestations and normalization of ESR and creatinine levels. A shrinkage of the periaortic mass greater than 25 % was observed in 25 patients [73].

Recently, methotrexate plus low doses of prednisone has been employed in a prospective trial including 16 patients with relapsing disease. Patients were treated with methotrexate at the dosage of 15–20 mg/week for 12 months and prednisone at the initial dosage of 0.5–1 mg/kg/day and then rapidly tapered. Of the 14 patients that continued the treatment until the end of the year, 79 % achieved remission and had an excellent renal outcome. Moreover, the patients who continued the treatment after month 12 showed a longer relapse-free survival, confirming the efficacy of methotrexate in maintaining remission [69].

The successful use of biologic agents in cases of refractory CP has been reported anecdotally. B-cell depletion with rituximab at the dose of 375 mg/m^2/weekly for four consecutive weeks has been shown to be effective in two cases, one refractory to standard treatment and one receiving low-dose glucocorticoids [47]. RTX has been also successfully used in patients with IgG4-related RPF and no differences in the response to this therapy have been demonstrated so far [74, 75]. Finally, the anti-IL6 receptor monoclonal antibody tocilizumab was also reported as effective in two difficult-to-treat cases of CP [46]. Further studies are needed to validate these preliminary observations.

Despite its chronic-relapsing course, idiopathic RPF has good patient and renal outcomes. The mortality rate reported in studies with long-term follow-up (median, 48–61 months) ranges between 3.3 and 7.3 % [28, 30]. Varying degrees of chronic kidney failure occur in up to 32 % of the patients, but end-stage renal disease is extremely rare [28].

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Diffuse (Thoraco-Abdominal) Periaortitis

9

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9.1 Introduction

Chronic periaortitis (CP) is usually referred to as a spectrum of rare diseases characterized by the presence of an aberrant fibroinflammatory tissue usually located around the infrarenal portion of the abdominal aorta and around the iliac arteries [1]. A recent study showed that in approximately one third of cases CP may also involve other vascular districts, particularly the thoracic aorta and its major branches, which reinforces the view that CP may be a systemic fibroinflammatory disease [2].

A systemic immune-mediated etiopathogenesis of diffuse CP that has replaced the classical theory according to which CP was due to a localized inflammatory response to aortic atherosclerosis plaque antigens; the "systemic immune-mediated" theory is also supported by other findings including the association with other autoimmune diseases and with HLA-DRB1*03 and the presence of systemic clinical manifestations [3–5]. Another important element which may support the autoimmune etiology comes from the histological examination of CP biopsies, given that the pattern of vascular and perivascular inflammation in CP is consistent with an inflammatory vascular disease: as in giant cell arteritis (GCA) and Takayasu arteritis (TA), inflammation in CP predominates in the adventitia where the *vasa vasorum*, a possible port of entry for disease-triggering pathogens, are often inflamed [3, 6].

In some cases, diffuse CP could be included in the spectrum of IgG4-related disease (IgG4-RD) due to immunohistochemistry revealing the presence of IgG4-positive plasma cell infiltration [7] and/or in cases of serum IgG4 elevation.

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9.2 Large Vessel Involvement in Chronic Periaortitis

CP is considered to be confined to the abdominal aorta and the iliac arteries but, since the 1970s, anecdotal cases of involvement of other vascular districts have been reported. Autopsy studies performed in patients with CP involving the abdominal aorta provided evidence of mild inflammation and fibrosis in the adventitial layer of the thoracic aorta, suggesting the presence of widespread aortic disease and implying a transition from adventitial inflammation to fibrosis [8, 9]. Subsequent reports have also documented the involvement of coronary arteries: in these cases, coronary artery pathology revealed abnormalities similar to those seen at the aortic level, such as adventitial and periadventitial fibrosis and fibrous intimal hyperplasia [10, 11].

Recently, some reports provided evidence of involvement of other large- and medium-sized arteries in patients with CP. In 2009, Scheel and Feeley described renal artery involvement as a possible clinical feature of CP; 15 of the 48 observed CP patients (31 %) had extension of the fibroinflammatory tissue to the renal hilum, with encasement of the renal arteries and/or veins [12]. Subsequently, Salvarani et al. described 5 CP patients that, at disease onset, showed gastrointestinal symptoms, such as ischemic gastritis, duodenitis, and colitis; these features were related to the involvement of the superior and inferior mesenteric arteries and of the celiac axis [13].

The development of imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), CT- and MRI-angiography, and especially fluorodeoxyglucose-positron emission tomography (FDG-PET) has offered the opportunity to assess disease activity and to provide an accurate visualization of the large vascular districts of the body: thanks to these imaging techniques, it has been demonstrated that CP can involve several vascular districts [14, 15] (Fig. 9.1). In 2005, in a pilot case–control study using FDG-PET, we found that three of seven patients with active CP (41 %) – as compared with none of the 14 controls – had abnormal FDG uptake at the thoracic aorta level similar to that observed in other large-vessel vasculitides, particularly GCA [15, 16].

In a recent study, we retrospectively investigated the thoracic aorta and epiaortic artery involvement in a large cohort of CP patients [2]. CP patients were eligible for this study if they had appropriate imaging studies examining the inflammatory involvement of the thoracic (and abdominal) large vessels, which included contrast-enhanced chest CT or MRI and whole-body FDG-PET. We found thoracic vessel involvement in approximately one third of the cases (28 of the 77 eligible patients, 35 %). More specifically, three main patterns were observed: thoracic periaortitis, periaortitis with thoracic aorta aneurysm, and thoracic aorta aneurysm without periaortitis. In 15 of the 28 CP patients (54 %) with thoracic periaortitis, the perivascular tissue surrounded a thoracic aorta of normal caliber; tissue enhancement was variable on CT or MRI, probably reflecting disease activity. The median FDG uptake grade at PET studies was similar at the abdominal aorta and thoracic aorta levels. Seven of these 15 patients also showed epiaortic artery involvement, commonly of the origin of the carotid arteries. Periaortitis surrounding a thoracic aortic aneurysm was observed in six patients (21 %), two of them with epiaortic artery involvement. The remaining seven cases (25 %) had a thoracic aortic aneurysm without periaortitis; this pattern was included as a

disease-related manifestation because it is a potential complication of large-vessel vasculitides where it is thought to be due to chronic inflammation of the aortic wall.

This study has also offered the possibility to analyze thoracic vascular/perivascular biopsies of three patients (two after carotid endarterectomy and one after surgical repair of thoracic aortic aneurysm) that showed a histologic pattern strikingly similar to that found in abdominal CP [6]. Vascular inflammation predominated in the adventitia and consisted of lymphocytes, histiocytes, plasma cells, and eosinophils; this adventitial infiltrate was often organized in follicular aggregates, sometimes with germinal centres rich in lymphocytes, which clustered around adventitial *vasa vasorum*. The aggregates are considered examples of ectopic lymphoneogenesis that is an expression of a highly structured immune-mediated response, as observed in many autoimmune diseases. These histological findings, together with the imaging features, suggest that CP may arise as a primary large-artery inflammatory disease that in some cases may involve not only the abdominal aorta but also other large vessels. In these cases we should always keep in mind that same patterns of thoracic CP may be seen in other large vascular disease, especially GCA and TA that generally lack the thick periaortic cuff seen in CP but, as discussed below, differential diagnosis sometimes is challenging.

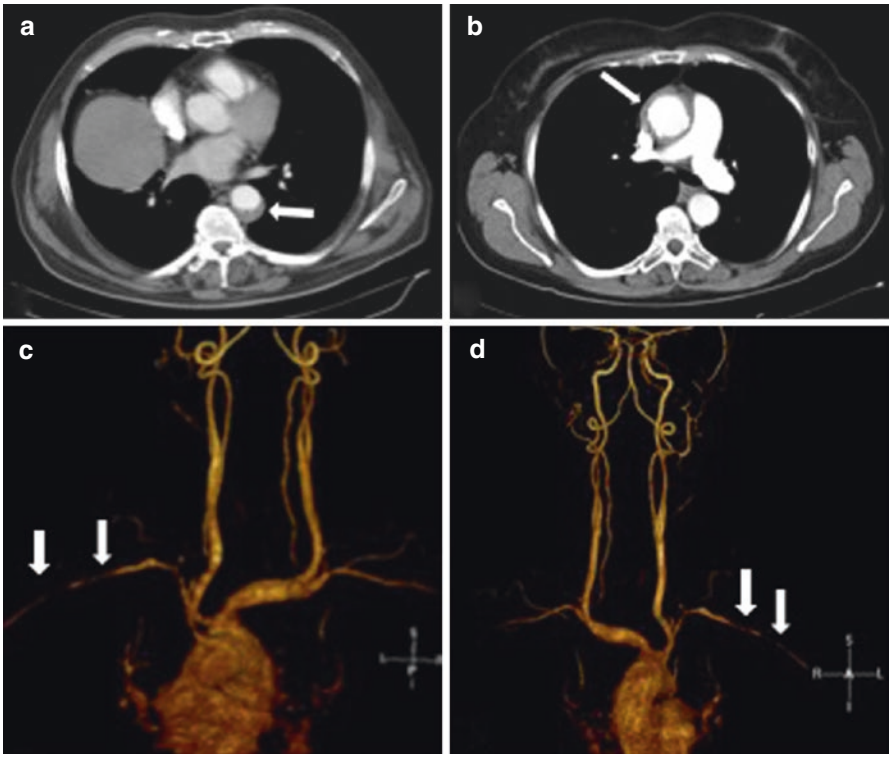

Fig. 9.1 (**a**, **b**) Computed tomographic (CT) appearance of thoracic periaortitis. The perivascular tissue surrounds (**a**) the upper portion of descending aorta (*arrow*), and (**b**) the ascending thoracic aorta (*arrow*). (**c**, **d**) Magnetic resonance (MR) angiography of thoracic periaortitis with epiaortic artery involvement. The scans show diffuse caliber reduction of the right subclavian artery (*arrows*) (**c**) and significant caliber reduction of left subclavian artery (*arrows*) (**d**).

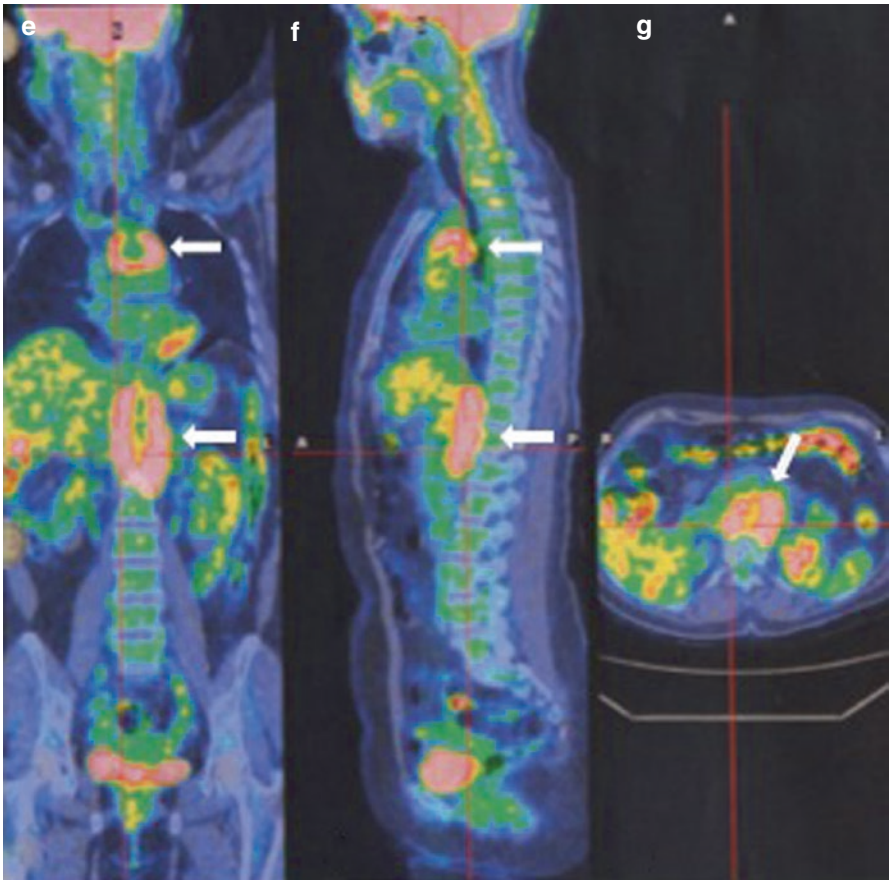

Fig. 9.1 (Continued) (**e**–**g**) ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT evidence of active chronic periaortitis. The scans (**e**), coronal view, (**f**), sagittal view, and (**g**) axial view show increased uptake of FDG at the thoracic aorta and upper abdominal aorta levels (*arrows*)

9.3 Complications of Thoracic Periaortitis

Complications of thoracic involvement in CP have never been illustrated in literature. The only well illustrated data concern the inflammatory thoracic aorta aneurysms that, less frequently than the atherosclerotic ones, tend to produce acute dissection needing prompt surgical repair [17, 18]. This aspect was also confirmed in our group of patients: only 4 of the 13 thoracic aortic aneurysms (either with or without periaortitis) underwent surgical or endovascular repair [2]. By reviewing our published cohort of patients with diffuse periaortitis, we interestingly disclosed that thoracic disease was asymptomatic in about 85 % of the cases and, in the few symptomatic ones, the clinical pattern was related to epiaortic artery involvement: two patients had hoarseness secondary to recurrent laryngeal nerve paralysis, two patients had unilateral deficit in arm strength and

asymmetrical pulses/blood pressure values, three patients had upper limb claudication, upper limb paresthesias, and dry cough.

9.4 Chronic Periaortitis with Thoracic Aorta Involvement: A Distinct Subset?

Until 2015, the anecdotal published cases of diffuse CP had not provided any detailed information about the clinical aspects of this new disease pattern. Our recent study also explored demographic, laboratory, and clinical features in patients with and without thoracic disease (28 and 49 patients respectively) [2]. Patients with thoracic disease had a significantly higher female prevalence, a greater age at disease onset, and a higher prevalence of disease-related symptoms, namely systemic symptoms (e.g., fatigue, anorexia, weight loss) and back or abdominal pain. Patients with thoracic disease also tended to have higher levels of inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) than patients without thoracic disease, although the differences were not statistically significant. No differences in the two groups were found in terms of prevalence of autoantibodies, associated autoimmune diseases, atherosclerotic risk factors, and established atherosclerotic diseases.

By keeping in mind the recent hypothesis that CP, especially when there is thoracic involvement (as an expression of systemic disease), should be included in the spectrum of IgG4-related disease (IgG4-RD) we analyzed, where available (45 of the 77 cases), the levels of serum IgG4 in patients with and without thoracic disease [7, 19]. Only about 20 % of patients in both groups exhibited high serum IgG4 levels with no difference between the two groups. Nevertheless, immunohistochemistry on thoracic CP biopsies revealed in two of the three cases a significant $IgG4^+/CD138^+$ plasma cell ratio (>40 %) suggesting that in such cases CP may be considered IgG4-related. These patients, however, showed no other organ lesions typical of IgG4-RD.

The female prevalence as well as the advanced age at disease onset in patients with thoracic aorta involvement is a feature similar to other large-vessel vasculitides, particularly GCA. These clinical aspects, in addition to the histopathologic finding of active adventitial inflammation lend further support to the hypothesis that in a subset of patients CP may be considered a primary large-vessel inflammatory disease.

9.5 Differential Diagnosis with Other Large-Vessel Diseases

When managing CP patients with thoracic aorta involvement, it is mandatory to exclude other diseases that diffusely affect the aorta and its branches. First, diffuse CP normally refers to idiopathic clinical entities and does not include cases secondary to different etiologies such as use of drugs, cancer (primary or metastatic disease), carcinoid syndrome, radiotherapy, trauma, major abdominal surgery, and infections. These conditions, illustrated in detail in Chap. 15, always need to be considered when approaching a CP patient [20].

There are numerous inflammatory/autoimmune conditions that diffusely affect the aorta and its major branches (Table 9.1). These are defined as “aortitis” and typically lack the periaortic fibroinflammatory reaction that hallmarks CP.

Table 9.1 Main differential characteristics of conditions that may cause diffuse large artery disease

	Diffuse chronic periaortitis	Giant cell arteritis	Takayasu arteritis	Erdheim-Chester disease	Infectious aortitis
Demographic characteristics					
Female-to-male ratio	1:1	3:2	7:1	1:3	3:1
Age, median at the onset	>60 years	> 50 years	< 40 years	> 30 years	All age groups
Clinical manifestations					
Constitutional symptoms[a]	++	++	++	+	++
Abdominal symptoms[b]	+++	−	+	+	+
Ureteral obstruction	++	−	−	++	−
Upper limb symptoms[c]	±	++	+++	+	−
Cranial symptoms[d]	−	+++	−	+	−
Autoimmunity					
Associated immune-mediated diseases	Various	Polymyalgia rheumatica	Rare	Rare	None
Positive ANA	++	+	+	±	−
Other positive auto-antibodies	++	±	±	±	−
Laboratory findings					
High ESR	++	+++	++	+	++
High CRP	++	+++	++	+	++

Main histopathological findings					
	Marked fibrosis and chronic inflammatory infiltrate in the adventitial and periadventitial soft tissues	Granulomatous inflammation at the media adventitia, intimal hyperplasia	Acutely, granulomatous inflammation typically found in the media and adventitia; chronically, fibrotic thickening of the intima and media	Foamy histiocytes (CD68+, CD1a-) and chronic inflammation	Neutrophilic infiltrate with profound injury to the underlying vessel Chronic dissection, atheromatous changes with no signs of vasculitis
Imaging findings					
CT scan	Concentric wall thickening of the thoracic aorta with periaortic fibroinflammatory cuff	Thickening of the aortic wall with no periaortic mass. Chronically, possible progression to the aneurysmatic dilatation of the aortic wall	Thickening of the wall of the vessel and smooth or segmental luminal narrowing and occlusion	Periaortic fibrosis involving the whole aorta and leading to a "coated aorta" aspect	Periaortic nodularity, gas collection
PET scan	Increased uptake	Increased uptake	Increased uptake	Mildly increased perivascular uptake	Nonspecific uptake

Abbreviations: *ANA* antinuclear antibodies, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *CT* computed tomography, *PET* positron emission tomography

[a]Constitutional symptoms include fatigue, anorexia, weight loss, fever

[b]Abdominal symptoms include side, back, or abdominal pain; constipation, claudication, and intestinal ischemia

[c]Upper limb symptoms include claudication and upper limb paresthesias

[d]Cranial symptoms include headache, visual symptoms, jaw claudication, swallowing claudication or dysphagia, tongue claudication

The distinction between aortitis and periaortitis is important for clinical and therapeutic implications. Aortitis is a pathological term that refers to the presence of areas of wall thickening and inflammation; it is generally mainly lymphoplasmacytic or lymphohistiocytic, with giant cells and well-formed granulomas in the context of the medial layer. Atherosclerosis is often found in the intima, whereas, unlike in periaortitis, the adventitia rarely shows inflammation and fibrosis [3].

The most frequent causes of aortitis include two large-vessel vasculitides, GCA and TA. GCA involves cranial arteries with the presence of typical symptoms such as headache, visual abnormalities, jaw claudication, and scalp tenderness. In case of aortic involvement (mainly thoracic), GCA may lead to the development of aortic aneurysms. The presence of pronounced periaortic thickening is uncommon in GCA, whereas in CP it is one of the main characteristics. CP patients do not present the typical GCA-related cranial symptoms and, on the other hand, GCA patients do not have obstructive uropathy. The differential diagnosis between GCA and CP is not always easy and becomes more challenging when the patients lack typical manifestations and present with fever of unknown origin and nonspecific systemic manifestations such as fatigue or weight loss. A subset of patients with GCA or even TA indeed has such a presentation, without clear signs of organ ischemia but with pronounced systemic manifestations.

TA typically affects young women with symptoms related to arterial occlusive disease of the aorta, aortic arch, and large vessels (e.g., pulse deficits, vascular bruits, hypertension, claudication of the extremities), and constitutional symptoms (such as fever, malaise and arthralgias). Abdominal aorta involvement is frequent and it is characterized by stenosis and aneurysm; similarly, subclavian, renal, innominate, and common carotid arteries are often involved. TA frequently causes thickening of the arterial wall and, in absence of other clinical features, it is difficult to distinguish it from CP in its early stages, although TA almost never shows obstructive uropathy [21].

Aortitis may often develop during the course of infections. Bacterial aortitis usually affects elderly men and involves a segment of the aortic wall with atherosclerotic plaque or aneurysm. *Salmonella*, *Staphylococcus*, and *Streptococcus pneumoniae* are the most common organisms associated with infectious aortitis. Tuberculous aortitis should be suspected in patients with inflammation of the aorta or atypical aortic aneurysm presenting with pulmonary or extrapulmonary tuberculosis [22]. Syphilitic aortitis typically involves the ascending aorta and is associated with thoracic aortic aneurysm [23].

When approaching a patient with abdominal CP and thoracic aortitis it is mandatory to exclude (systemic) IgG4-related sclerosing disease, characterized by extensive T-lymphocyte- and IgG4-bearing plasma-cell infiltration of various organs in association of fibrosis and obliterative phlebitis [24]. Between 10 and 50 % of cases of inflammatory aortitis are associated with an intense infiltration of $IgG4^+$ plasma cells. The thoracic aorta involved in IgG4-RD most commonly exhibits aneurysm and only rarely shows dissection; the aortic arch is the aortic segment most frequently affected [17, 24]

Finally, another disease presents with features similar to those of diffuse CP: Erdheim-Chester disease (ECD), a non-Langerhans cell histiocytosis which usually

affects the aorta circumferentially may involve the entire aorta, from its origin to the iliac vessels ("coated aorta"); this disease often presents with symmetrical long bone involvement and often perirenal fibrosis which is usually absent in CP [25, 26].

9.6 Treatment and Prognosis

There is no one immunosuppression regimen that has been shown to be superior to other treatments in patients affected by diffuse CP and, to date, no published reports give indications how to treat patients with diffuse disease. The goals of therapy are to improve the symptoms, both systemic and localized, to stop the fibrosing process, to decrease the size of the mass, and to prevent relapses once remission is achieved. The first-line therapy for CP is based on glucocorticoids, which are usually used at high doses (1 mg/kg/day for the first month and progressively tapered) to curb disease activity. When high-dose-glucocorticoid therapy is contraindicated, a good alternative may be the use of several immunosuppressive drugs such as mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, cyclophosphamide, and tamoxifen [27].

Recently there have been some reports of a successful use of biologic agents in case of difficult-to-treat cases of CP. The agents employed are rituximab, infliximab (anti-TNF-monoclonal antibody), and tocilizumab (anti-interleukin-6 receptor antibody) [28].

After the beginning of medical therapy the prognosis is usually good with improvement of the symptoms and reduction of the fibrous mass. However, relapses are common (25–50% of treated patients) upon tapering of the glucocorticoid dose, and patients often need long-term therapy, which may cause morbidity [20]. To date, regarding the outcome of the disease, there are no data of comparison between patients with and without thoracic involvement. Further studies may be useful to understand if patients with diffuse involvement need a distinct therapeutic approach.

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Idiopathic Mediastinal Fibrosis

10

Giovanni M. Rossi and Giacomo Emmi

10.1 Definition and Nosology

Fibrosing mediastinitis, also known as mediastinal fibrosis or sclerosing mediastinitis, is a clinical entity characterized by abnormal proliferation of fibrous tissue within the mediastinum. The compression of mediastinal vital structures by the fibroinflammatory tissue determines the clinical presentation [1]. Primitive and secondary forms have been described.

The latter are mainly secondary to infectious triggers (particularly, fungal and mycobacterial infections), neoplastic processes, drugs, and radiotherapy [2].

Cases have been reported in association with aspergillosis, mucormycosis, blastomycosis, criptococcosis, tuberculosis, nontubercular mycobacterial infection as well as lymphomas, desmoblastomas, sarcoidosis, methysergide-maleate assumption, radiation therapy, and posttraumatic hemorrhage [3–8].

Mediastinal fibrosis has also been described in the setting of autoimmune disorders such as Behçet disease, rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, and ANCA-associated vasculitides [3, 9–14].

Reports of cases of mediastinal fibrosis associated with other idiopathic fibroinflammatory diseases (in particular, retroperitoneal fibrosis, Riedel thyroiditis, sclerosing cholangitis, sclerosing pancreatitis, and pseudotumor of the orbit) corroborate the notion that idiopathic mediastinal fibrosis might be part of the IgG4-RD spectrum [15–24].

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10.2 Epidemiology

Mediastinal fibrosis is rare. Accurate epidemiological data is lacking as the disorder has only been described in small case series and case reports [1, 3]. In the largest cohort study published to date, which comprised a total of 83 cases, the disease was most frequently secondary to *Histoplasma capsulatum* infection [1]. However, in the largest histoplasmosis outbreak, which occurred in Indianapolis in 1978–1979, only 3 out of 100,000 people infected developed mediastinal fibrosis [25].

Among all forms of mediastinal fibrosis, the idiopathic one, occurring alone or in conjunction with other fibroinflammatory diseases or systemic autoimmune disorders such as ANCA-associated vasculitides, is probably the rarest. The description of familial cases, the rarity of mediastinal fibrosis even in the setting of known potential triggers such as histoplasmosis, and the clinical, histological, and imaging similarities between idiopathic and secondary forms make it reasonable to think they might share a common pathogenesis [3, 15, 23].

10.3 Pathogenesis

Data regarding the pathogenesis of IMF are largely lacking. The similarities in histological features with retroperitoneal fibrosis suggest that a dysregulation of the immune system towards fibrogenesis might play a major role.

As already stated, histoplasmosis-related fibrosing mediastinitis develops only in 3 out of 100,000 infected people in endemic *H. capsulatum* areas [25]. This suggests that an abnormal immune host response to infection is needed in order to develop mediastinal fibrosis.

A recent case–control study investigated the association between HLA subtypes and the development of mediastinal fibrosis in 34 patients of European-American ancestry with mediastinal fibrosis and positive serology for histoplasmosis. A significant increase in HLA-DQB1*03:02 carriage was found in affected patients compared to control cohorts [26].

The authors speculated that their findings were consistent with a pathogenic role of CD20+ B lymphocytes, which are found in mediastinal fibrous tissue biopsies in patients affected by mediastinal fibrosis [1]. Particularly, an HLA class II molecule like HLA-DQB1*03:02 could prompt a response by CD4+ Th2 helper cells through antigen presentation. Th2 cytokines could then activate myofibroblasts, while B-cell activation could lead to the secretion of profibrotic cytokines such as IL-6 and also to the production of autoantibodies. In turn, activated macrophages and monocytes produce TGF-beta which stimulates mesenchymal cell transformation in myofibroblasts and the production of procollagen I and III. These processes are similar in fashion to what happens in other fibroinflammatory conditions [26–29].

In the study with the largest cohort (83 patients), all but 13 had a diagnosis of prior histoplasmosis. The adopted diagnostic criteria were arbitrary. A “conclusive” diagnosis was made whether the patients had a positive fungal stain or culture of the biopsy tissue and/or serological titer $\geq$1/32; a “suggestive” diagnosis was made in

the presence of a serological titer >1/8 or merely based on radiographic features suggestive of previous granolumatous infection. These criteria are in contrast with the EORTC/MSG consensus criteria for the diagnosis of fungal infections [1, 30].

Furthermore, considering the high prevalence of histoplasmosis in the area of origin of the cohort and the benign course of the infection in immunocompetent hosts, serological proof alone does not seem appropriate and one cannot exclude that some of those patients had indeed idiopathic mediastinal fibrosis. It is therefore tempting to think that the immunological mechanisms underlying the development of mediastinal fibrosis in histoplasmosis are the same at play in the idiopathic form of the disease.

10.4 Pathology

The histological differential diagnosis of idiopathic mediastinal fibrosis includes fungal and mycobacterial infections and drug-associated and neoplastic forms capable of causing mediastinal fibrosis. Infective forms might be confirmed if biopsy cultures are positive and/or fungal structures are directly observed. Histoplasmosis can lead to diffuse mediastinal fibrosis or to granulomatous disease associated with fibrosis: the observation of granulomas excludes idiopathic mediastinal fibrosis [31]. Neoplastic forms, such as sclerosing non-Hodgkin lymphoma, the nodular sclerosis variant of Hodgkin disease, fibrous tumors of the pleura, diffuse desmoplastic mesotheliomas, metastatic carcinomas with fibrogenic response, thymoma, and thymic carcinoid, are generally excluded easily because they have peculiar pathological and immunostaining characteristics [2]. Although according to some authors histologic differences between the various forms of mediastinal fibrosis can be appreciated on microscopic examination, these are probably too subtle to differentiate idiopathic mediastinal fibrosis from secondary infectious forms [32].

Recent studies showed that prior histoplasmosis and idiopathic mediastinal fibrosis share common histopathological characteristics. The constant finding is extensive tissue fibrosis which infiltrates and obliterates adipose tissue with or without patchy mononuclear immune cell infiltration [1]. Furthermore, a subset of patients with prior histoplasmosis had histological characteristics compatible with a definite diagnosis of IgG4-RD: lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis/arteritis, ≥50 IgG4-positive plasma cell/hpf, and ≥40 % IgG4/IgG-positive plasma cells [33] (Fig. 10.1).

This finding further suggests the possibility of common pathogenetic mechanisms in idiopathic and infective secondary forms of mediastinal fibrosis.

10.5 Clinical Characteristics

The clinical presentation and the severity of the disorder are determined by the compression of vital mediastinal structures, i.e., central airways, superior or inferior vena cava, pulmonary veins, and arteries. However, patients are often asymptomatic.

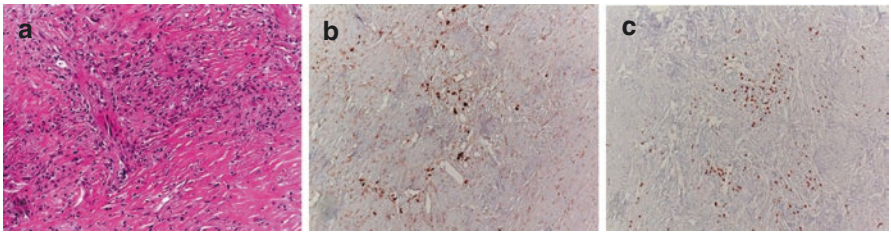

Fig. 10.1 Mediastinal tissue biopsy of a patient affected by idiopathic mediastinal fibrosis with elevated serum IgG4 levels. The pictures show fibrotic tissue with linfo-plasmacellular infiltration (**a**). IgG4 (**b**) and CD138 (**c**) immunohistochemical stainings demonstrate that a significant proportion of total plasma cells are IgG4+. (**a**) Hematoxylin and eosin; (**b**) IgG4 immunostaining; (**c**) CD138 immunostaining. Original magnification is × 10 in (**a**) and (**b**) and × 4 in (**c**)

When present, typical symptoms include dyspnea, cough, hemoptysis, and pleuritic chest pain [1]. The occlusion of airways can lead to recurrent or persistent pneumonia with or without lung atelectasis distal to the occlusion [2]. If the compression of the superior or inferior vena cava is significant, superior or, much less frequently, inferior vena cava syndromes can occur, with their typical signs [34]. The compression of pulmonary veins and less frequently of pulmonary arteries can lead to secondary pulmonary hypertension and subsequent right heart failure [35, 36].

Less frequent complications, such as pulmonary infarcts, myocardial infarction, and pulmonary edema, have also been reported [37–40].

10.6 Laboratory Findings

Laboratory findings are usually nonspecific or absent. Elevation of ESR and/or of CRP can be observed. A case has been reported of idiopathic mediastinal fibrosis with high serum IgG4 level [41]. However, in a recent series of 40 cases of idiopathic mediastinal fibrosis, none had high serum IgG4 level. The authors concluded that since mediastinal fibrosis is a focal process, the quantity of IgG4-producing plasma cells might not be sufficient to cause an increase in serum IgG4 levels [42].

10.7 Imaging

Chest radiograph Chest radiographs usually show nonspecific widening of the mediastinum (most frequently the middle mediastinum). Findings consistent with superior vena cava obstruction, compression of central airways, pulmonary arterial obstruction, or pulmonary venous obstruction can be seen if these structures are involved [2].

Computed tomography The typical manifestation on computed tomography (CT) scans is an infiltrative mass of soft-tissue attenuation obliterating normal mediastinal planes, invading or encasing adjacent structures. The middle mediastinal

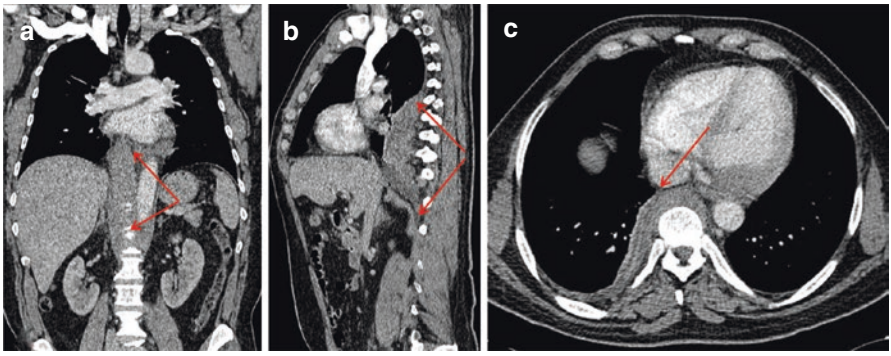

Fig. 10.2 Coronal (**a**), sagittal (**b**), and axial (**c**) views of contrast-enhanced CT scans of the chest showing mediastinal fibrosis from D4 to D12 (*red arrows*)

compartment is frequently involved, although involvement of the posterior mediastinum is not uncommon [2].

Several authors highlighted two different patterns on CT scans: a focal pattern, usually located in the hila or in the right paratracheal/subcarinal regions; and a diffuse pattern, which consists of a diffuse infiltration of multiple mediastinal compartments. The focal pattern is the most frequent and is probably associated with histoplasmosis, while the diffuse pattern is more frequently associated with the idiopathic form, a finding that is consistent with CT scan appearance of other disorders such as retroperitoneal fibrosis or Riedel thyroiditis [2, 29, 43] (Fig. 10.2).

As already stated for chest radiographs, complications due to the compression of mediastinal structures by the mediastinal mass can be seen on CT scans. Contrast-enhanced CT scans are particularly useful if arterial or venous obstruction are present, with or without pulmonary infarcts [2].

Magnetic resonance Magnetic resonance (MR) imaging can help distinguish between mediastinal fibrosis and neoplastic forms, as the latter typically show increased signal intensity on T2-weighted images [2].

18FDG Positron emission tomography Increased metabolic activity can be seen, either focal or diffuse, and a case has been reported of immunosuppressive therapy response of idiopathic mediastinal fibrosis associated with idiopathic retroperitoneal fibrosis monitored through serial 18FDG-PET evaluation [44–46].

10.8 Diagnosis

The diagnosis of idiopathic mediastinal fibrosis is a diagnosis of exclusion. As patients are often asymptomatic, mediastinal masses can be incidental findings on CT scans or chest radiographs. Whether symptoms are present or not, neoplastic and infective forms must be carefully excluded if idiopathic mediastinal fibrosis is

suspected. The association with other fibroinflammatory disorders makes the diagnosis more likely. Nonetheless, if feasible a biopsy should always be performed. As already noted, the histological features of mediastinal fibrosis are not unique to the idiopathic form. Thus, a final diagnosis can be made only by integrating clinical, histological, and imaging findings.

10.9 Overlap with Other Disorders

As already noted, cases of idiopathic mediastinal fibrosis associated with retroperitoneal fibrosis, Riedel thyroiditis, pseudotumor of the orbit, and sclerosing cholangitis have been reported since the 1960s [17–20, 24, 47]. Familial cases have also been reported [15, 23]. Such fibroinflammatory disorders are now thought to be part of the IgG4-RD spectrum and to share a common pathogenesis [22, 48]. However, it is still unclear which proportion of cases of idiopathic mediastinal fibrosis can actually be classified as being IgG4-related, because systematic histological studies are lacking and also because patients with idiopathic mediastinal fibrosis are not routinely screened for other conditions belonging to the spectrum of IgG4-RD. It seems clear, however, that IgG4-RD lesions and idiopathic mediastinal fibrosis share many histological features, such as a chronic inflammatory infiltrate rich in plasma cells, B cells, and CD4+ T cells, abundant and irregular fibrosis.

In addition, the frequently reported association with autoimmune disorders such as ANCA-associated vasculitides, Behçet disease, and others further suggests the systemic nature of the disease and the central role of an abnormal immune response in the pathogenesis of idiopathic mediastinal fibrosis [9–13].

10.10 Treatment and Prognosis

It has been reported that idiopathic mediastinal fibrosis, in contrast with neoplastic forms and similarly to prior histoplasmosis form, has a relatively benign course, even when left untreated. However, compression of vital mediastinal structures can lead to life-threatening complications. Once believed to be frequent, probably because only the most severe cases were reported in literature, these complications (airway obstruction with or without recurrent pulmonary infections, superior vena cava syndrome, secondary pulmonary hypertension and *cor pulmonale*, inferior vena cava syndrome, pulmonary infarcts, myocardial infarction) are usually best addressed with surgical procedures or nonsurgical procedural interventions [1].

Immunosuppressive therapy seems to be effective in reducing the mass and thus preventing complications, but larger data is necessary to confirm this claim. Cases have been reported of successful therapy with rituximab and/or glucocorticoids, tamoxifen, and mycophenolate mofetil [1, 19, 33, 41, 49].

10.11 Surgical Management of Complications

When the disease is refractory to immunosuppressive therapy, surgical procedures or nonsurgical interventions become mandatory. However, they are both associated with high complication and mortality rates.

Surgical procedures include: debulking procedures; superior vena cava bypass procedures such as positioning of spiral vein grafts, PTFE grafts, conduits between right ventricle to pulmonary artery; pulmonary resection for uncontrollable hemoptysis (lobectomies and pneumonectomies); and pulmonary vein reconstruction [1, 50].

Nonsurgical procedural interventions include: superior vena cava angioplasty and/or stenting; endobronchial balloon dilatation and/or stenting; pulmonary artery angioplasty and/or stenting; and pulmonary vein angioplasty [1, 50].

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Sclerosing Mesenteritis

11

Eric F.H. van Bommel and Nienke van Putte-Katier

11.1 Introduction

Sclerosing mesenteritis (SM) is a rare, idiopathic disorder of unknown etiology that involves the adipose tissue of the mesentery, being characterized by chronic and nonspecific fibrous inflammation [13, 42]. A PubMed search at the time of writing (October 2015)[1] revealed 517 publications on the subject of SM, the majority being anecdotal case reports and small case series. This suggests that SM is still considered to be a rare or at least uncommon disease or that the disease is underrecognized in clinical practice [39, 41, 42]. Much can be learned from some large case series and prevalence studies published over the last four decades from single-center experience or from cumulative literature data [1, 10, 13, 15, 42, 59]. In this chapter, we provide an overview of this intriguing disease, including its potential pathogenesis, the possible association with other fibroinflammatory disorders, and outline the

[1] PubMed search strategy:
("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("mesenteric"[All Fields] AND "panniculitis"[All Fields]) OR "mesenteric panniculitis"[All Fields]) OR ("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("sclerosing"[All Fields] AND "mesenteritis"[All Fields]) OR "sclerosing mesenteritis"[All Fields]) OR ("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("mesenteric"[All Fields] AND "lipodystrophy"[All Fields]) OR "mesenteric lipodystrophy"[All Fields])

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diagnostic and therapeutic approach, with emphasis on imaging and medical treatment.

11.2 Definition and Nosology

First described by Jura in 1924 as "retractile mesenteritis" [26], numerous other terms have been used to describe this disease depending on the predominant histology, including mesenteric lipodystrophy, sclerosing mesenteritis, mesenteric Weber-Christian disease and mesenteric fibrosis [13, 15, 30, 32, 42]. The variety of terms, used particularly in older literature, in part reflects the variable proportion of histologic changes from case to case (i.e., chronic inflammation, fat necrosis and fibrosis) and the absence of a unifying concept [15]. It is now increasingly accepted that these different terms or diagnostic entities represent a spectrum of a single disease characterized by nonspecific inflammation of the mesenteric fat that may ultimately lead to fibrosis and retraction, and that SM is probably the most appropriate encompassing term [13, 15, 24].

11.3 Epidemiology

SM is being recognized with increasing frequency at computed tomography (CT) imaging due to the increased use of abdominal diagnostic imaging and the identification of typical signs for SM on CT [59]. Data on the prevalence of SM are scarce with conflicting results. One study reported a prevalence of 0.6 % among patients who underwent CT scanning for various reasons [10], while others reported a much higher prevalence ranging from 3.4 to 7.8 % depending on the CT-criteria used [8]. Other studies reported a lower prevalence, ranging from 0.16 to 0.6 % among patients who underwent CT scanning [19, 53, 63]. However, these studies were all based on a keyword search instead of actually reanalyzing all CT scans for signs of SM, which may lead to underreporting. Reanalyzing all CT scans for signs of SM in 3,820 patients using very strict CT criteria and exclusion criteria, a prevalence of 2.5 % was found by van Putte et al. [59]). SM typically presents in patients between the 6th and 7th decades of life with a male predominance [13, 15, 59, 61]. However, it may occur in every age group and pediatric cases have been described [1, 13]. SM seems more common in Caucasian men [7, 59].

11.4 Etiopathogenesis

11.4.1 General Comments

The etiology of SM remains obscure. The disease may occur independently or in association with other disorders, suggesting that the pathogenic mechanism may be

a nonspecific response to various stimuli [13, 15, 42]. Various causal factors have been suggested, notably malignancy and abdominal trauma (including surgery) [1, 7, 44, 50]. Mesenteric ischemia may also play a role in the pathogenesis of SM [13, 15, 41, 42]. Anecdotally, SM has been associated with auto-immune disorders, certain infections, granulomatous disease and fibrosis at other sites [13, 15, 42]. Recent data suggest that SM may in some cases be a manifestation of immunoglobulin G4-related disease (IgG4-RD) [37, 49, 64]. Environmental factors may also be involved, smoking being linked to the development of SM [12]. Given the frequency of smoking in the population at large, this needs further investigation. Some authors suggest that a high prevalence of SM explains the spontaneous association with numerous and probably unrelated clinical situations/disorders found in the literature [7, 44, 50].

11.4.2 Malignancy

SM has a poorly understood association with underlying malignancy with conflicting results in the literature, which suggests that it may at least in some patients be a paraneoplastic phenomenon [10, 19, 53, 63]. Reported prevalence of malignancies, usually discovered before the onset/diagnosis of SM, is high and ranges from 23 to 49 % [19, 32, 59, 63]. Kipfer et al. suggested that SM may be a nonspecific response to an underlying abdominal malignancy [32]. As SM occurs typically in older and male patients, it inevitably increases the likelihood of cancer development in general and more specific prostatic cancer. Therefore, its possible association with malignancy should be taken with care. To date, only 2 CT-directed prevalence studies performed a matched pair analysis to correct for potential confounding by age and sex [19, 59]. Following matched pair analyses, van Putte et al. found a significantly higher prevalence of malignancy (48,9 % vs. 46.3 %; $P < 0.05$) and metastasis (37 % vs. 26.4 %; $P < 0.05$) in SM patients at the time of the initial CT scan compared to the control group [59]. Prostatic carcinoma was the most frequent coexisting malignancy, which was also reported by others [7]. The chance of future cancer development during the 5-year follow-up period was also significantly higher in SM patients compared to that in the control group (14,6 % vs. 6,9 %; $P < 0.05$). Conversely, Gögebakan et al. did not find any relation between SM and malignancy in their matched pair analysis [19]. However, it is unclear whether extensive follow-up of the control group was performed in this study. In addition, follow-up imaging was available in only 35 of 77 SM patients [19]. In the study by van Putte et al. follow-up was performed in all SM and control patients during a 5-year period using information from follow-up imaging and medical records [59]. These and other findings suggesting an association with malignancy [19, 32, 63] indicate that SM may be relevant in terms of clinical predictivity of an associated neoplasm, particular for prostatic carcinoma. However, further study is needed to substantiate this point.

11.4.3 Previous Abdominal Surgery or Trauma

Previous abdominal surgery and associated intraabdominal pathology may have influenced the development of nonspecific inflammation in the adipose tissue. Percentage of SM patients who had previous abdominal surgery in large case series varies from 5 to 35 % (Table 11.1). Prevalence studies noted previous abdominal surgery for several conditions in up to 50 % of identified SM patients, with time interval from surgery to SM diagnosis varying from weeks to many years [59]. Besides direct trauma, use of powdered surgical gloves before the mid-1980s, retainement of suture material and abdominal hemorrhage are speculated to play a role in the development of SM [1, 13, 41, 42].

11.4.4 IgG4-Related Disease

In recent years, it is argued that in a subset of patients SM may be part of the spectrum of IgG4-RD, an immune-mediated disorder that may affect many different organs, notably pancreas, salivary glands, lacrimal glands and lungs [43, 54]. IgG4-RD is characterized by a lymphoplasmocytic infiltrate, predominantly consisting of IgG4-bearing plasma cells, storiform fibrosis, tissue eosinophilia and obliterative phlebitis. Concurrently raised serum levels of IgG4 are often seen, but low serum levels do not exclude the presence of IgG4-RD [43, 54]. Some cases of SM indeed have such histologic features and concomitant involvement at other sites, suggesting that these may be manifestations of IgG4-RD (see Sect. 11.5.2).

11.5 Pathology

11.5.1 Macroscopic Findings

The pathology of SM is usually limited to the mesentery of the small intestine and involves the root or a segment of the mesentery [15, 42]. The lesions are described as yellow/gray and hard with gritty consistency [15]. Typically, the lesions appear as diffuse thickening of the mesentery or as a single rubbery nodular mass or multiple masses [15, 42]. In addition, extensive scarring and shortening of the mesentery in addition to thickening may be observed [15, 42]. In rare cases, the omentum, mesoappendix, mesocolon, and large bowel mesentery may be involved [13, 15, 42]. The inflammatory process may extend to the retroperitoneum and involve the inferior vena cava, pancreas, duodenum, hepatic peduncle and bladder [1, 15, 42, 51].

Table 11.1 Major characteristics of patients with sclerosing mesenteritis

Characteristic	Durst [13]	Emory [15]	Akram [1]
Year of publication	1977	1997	2007
Study design	Cumulative literature data[a]	Retrospective, single-center[b]	Retrospective, single-center[c]
Study period	1955–1972	1970–1993	1982–2005
No. of cases	68	84	92
Age at diagnosis, *yr* (*range*)	53 (7–82)	60 (23–87)	Median 64.5 (IQR 55–72)
Male–female ratio	1.8:1	1.9:1	2.3:1
Previous abdominal surgery/ trauma, *n* (%)	12 (18)	4/78 (5)	32 (35)
Associated conditions, *n* (%)			
Rheumatologic disorders	N/A	1/78 (1.2)	5 (6)
Fibrosis at other sites	N/A[d]	4 (5)	4 (4)
Duration of symptoms, *mo* (*range*)	N/A (24 h to 2 years)	12 (days to 10 years)	N/A
Symptoms, *n* (%)			
Abdominal pain	46 (68)	27/78 (35)	65 (70)
Diarrhea or constipation	11 (16)	N/A	33 (41)
Bloating/distension	N/A	N/A	24 (26)
Weight loss	10 (15)	N/A	21 (23)
Nausea and vomiting	22 (32)	N/A	18 (21)
Fever	11 (16)	N/A	5 (6)
Physical examination, *n* (%)			
Palpable abdominal mass	34 (50)	24/78 (31)	14 (15)
Signs of bowel obstruction	22 (32)	24/78 (31)	22 (24)
Elevated ESR, *n* (%)	N/A	N/A	13 (14)
Concurrent other intra-abdominal pathology	17 (25)	N/A	17 (18)
Malignant disease	4 (6)	N/A	7 (8)
Nonmalignant disease	13 (19)	N/A	10 (10)

Unless noted otherwise, data are mean and range and counts and percentages
N/A not available
[a]Data collected from case reports and small case series in the literature and personal experience with six cases;
[b]Cases retrieved from the files of the Armed Forces Institute of Pathology, Washington, DC, USA; clinical information was available from 78 cases;
[c]Cases ($n=64$) were retrospectively identified through the Mayo Clinic Diagnostic Index and Department of Pathology database from the Mayo Clinic, Rochester, Minnesota, USA; 28 cases were prospectively identified as referrals to the gastroenterology outpatient department;
[d]Retroperitoneal extension of SM was noted in 7 cases (10%)

11.5.2 Microscopic Findings

The microscopic picture is that of a mild to moderate infiltration of the fat by macrophages with an abundant foamy cytoplasm [13, 15, 42]. The macrophages are distributed in thin and broad interconnecting bands. Focal collections of lymphocytes are seen, usually adjacent to small vessels and frequently without follicle formation with fewer plasma cells and scattered eosinophils [13, 15, 42]. Focal or multifocal venulitis and (obliterative) phlebitis may be observed, predominantly affecting small- to medium-sized venous channels and in rare cases large veins [6]. Polymorphonuclear leukocytes are uncommon. The mesenteric inflammatory process may progress to include necrosis, fibrosis and calcification [13, 15, 42]. A zone of lipid-laden macrophages oriented about a central lymphoid aggregate or lymph node with an interposed zone of normal fat may be seen, the so-called halo-effect [9]. In patients with cavitation, areas of amorph material containing cholesterol were present [13]. Depending on the predominant histologic appearance, it was thought that SM presented in three distinct and sequential histologic stages with accordingly appropriate and different naming of the disease: (1) the presence of lipid-laden foamy macrophages infiltrating the mesenteric fat, *mesenteric lipodystrophy*; (2) predominant chronic inflammatory infiltrate, *mesenteric panniculitis*; and (3) prominent fibrosis with scant inflammation and fat necrosis, *retractile mesenteritis/mesenteric fibrosis/sclerosing mesenteritis* [1, 13, 15, 42]. However, the diagnostic groups all share the presence of fibrosis, chronic inflammation and fat necrosis and, in addition, have common demographic and clinical characteristics [15]. Upon statistical analysis of the three major histologic components, the amount of fibrosis was found to be the main feature of the different stages. Hence, the term "sclerosing mesenteritis" was proposed as the most accurate naming of the disease in the majority of cases [15].

Immunohistochemical staining typically shows a mixed population of CD3-positive T cells and CD19/CD20-positive B cells. Keratin, S-100, bcl-2, CD117/c-kit immunostain and T-cell receptor gene rearrangement studies are all negative [1]. MDM-2 immunohistochemistry may differentiate SM from well-differentiated liposarcoma, negative MDM-2 immunoexpression essentially ruling out the latter [62]. The connection between SM and IgG4-RD has not been studied extensively [1, 4, 6, 38, 40]. Abundant tissue infiltration of IgG4-positive plasma cells was observed in 4 of 12 SM cases (33 %) [1]. In a pathologic study of tissue material from 9 SM patients, IgG4-reactive plasma cells ranged in number from 0 to >100 per hpf, in 4 cases IgG4-positivity of plasma cells being between 11 and 20 per hpf and in 2 cases >100 per hpf [6]. The ratio of IgG4-positive/IgG-positive plasma cells varied from 3 to >100 per hpf in 6 cases studied, in 3 of these 6 cases (50 %) being ≥60/hpf [6]. In a 82-year-old woman with SM [40], microscopic examination showed abundant stromal fibrosis and obstructive phlebitis. Numerous IgG4-positive plasma cells were observed with a IgG4/IgG ratio of

76 %. IgG4 serum level, examined post-surgery, was high. In another case report of a 53-year-old man with extensive SM, storiform fibrosis, obliterative phlebitis and infiltration of many IgG4-positive plasma cells was observed [38]. The IgG4/IgG ratio amounted to 64 %, and the ratio of forkhead box protein 3 (Foxp3)-positive/CD4-positive cells was elevated (13 %) [38]. Foxp3 + cells are typically observed in auto-immune pancreatitis (AIP), the most prominent manifestation of IgG4-RD and are a good marker of CD4 + CD25 + regulatory T cells, which are thought to participate in the pathogenesis of the IgG4 reaction in AIP [64, 65]. These combined findings suggest that in a subset of patients, SM may be a manifestation of IgG4-RD.

11.6 Clinical Characteristics

SM typically affects middle-aged to older adults and is twice as common in men (Table 11.1). The clinical manifestations are largely nonspecific. SM may be asymptomatic and diagnosed incidentally on CT examination for other indications. In symptomatic patients, duration of symptoms vary from 24 h to 10 years (Table 11.1). In our experience, SM may present as an acute disease with often raised acute-phase reactant levels and as a chronic disease with usually unremarkable laboratory investigation. This may relate to the predominant (histologic) stage of the disease, i.e., inflammation or fibrosis [13]. The most common symptom is abdominal pain, often accompanied by diarrhea or constipation, weight loss, nausea and vomiting (Table 11.1). There does not seem to be a specific abdominal pain locus and every quadrant can be affected. Although uncommon, fever may be present. Physical examination frequently reveals a palpable mass and may reveal signs of bowel obstruction (Table 11.1). Bowel obstruction typically involves the small bowel but focal large bowel obstruction may occur [1, 13]. In most patients however, physical examination is unremarkable but for local abdominal tenderness or abdominal distention [13, 15, 42]. In rare cases, SM is complicated by (chylous) ascites, gastrointestinal bleeding, superior mesenteric vein thrombosis, and pleural or pericardial effusion [13–15, 42].

11.7 Laboratory Findings

Laboratory investigation is usually unremarkable. There may be raised acute-phase reactant levels (Table 11.1), sometimes accompanied by mild anemia. Usually mild leukocytosis may be found in the absence of other inflammatory disease and occasionally, leucopenia may be seen [13, 42]. A raised serum IgG4 level is sometimes observed [40].

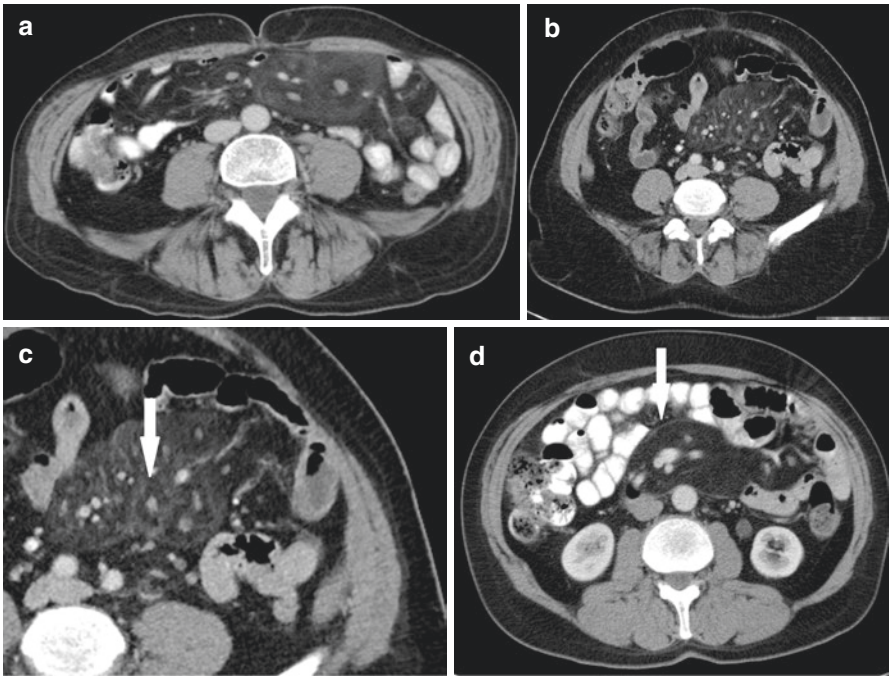

Fig. 11.1 (**a**): Sclerosing mesenteritis: the mesenteric fat is hyperdense compared to the subcutaneous or retroperitoneal fat and displaces surrounding small bowel loops. (**b**): Sclerosing mesenteritis in another patient. (**c**): Sclerosing mesenteritis with the characteristic "fat-ring" sign. The mesenteric vessels, which are surrounded by normal fat, are enveloped by hyperdense mesenteric fat. (**d**): Sclerosing mesenteritis with "tumoral pseudo-capsule", a dens stripe in the peripheral region differentiating normal mesentery from the inflammatory process

11.8 Imaging

11.8.1 Computed Tomography

Most cases of SM are asymptomatic and incidentally detected on abdominal CT examination. CT features vary from subtle increased attenuation (attenuation values of −40 to −60 Hounsfield Units [HU]) of the mesentery to a more solitary well-defined soft tissue mass at the root of the small bowel mesentery [7, 10, 24, 29]. There is engulfment of superior mesenteric vessels and displacement of the bowel loops without infiltration (Fig. 11.1a,b). Small lymph nodules (short axis <10 mm) are often seen within the region of mesenteric fat stranding. Typically, the mesenteric vessels and soft tissue nodes show a "fat-ring" sign (Fig. 11.1c), referring to preservation of fat nearest to the mesenteric vessels and nodes [24, 56, 61]. A "tumoral pseudocapsule" (Fig. 11.1d), a dense stripe in the peripheral region differentiating normal mesentery from the inflammatory process is also suggestive for SM [10, 48]. Although uncommon, calcifications may be seen [23, 34, 59]. Table 11.2 shows the prevalence of the main CT features of SM in two large studies [10, 59].

Table 11.2 CT features in patients with sclerosing mesenteritis

Variable	Daskalogiannaki [10]	Van Putte-Katier [59]
Number of patients, *n*	49	94
Prevalence sclerosing mesenteritis, *%*	0.6	2.5
Transverse diameter, *cm*	9.5 ± 1.4	9.5 ± 1.9
Orientation transverse diameter, *n* (%)		
Leftward	48 (98)	91 (96.8)
Rightward/central	1 (2)	3 (3.2)
Density mesenteric fat, *HU*	−54 ± 2	−56.8 ± 10.8
Density retroperitoneal fat, *HU*	−116 ± 9	−105,0 (8)
Density subcutaneous fat, *HU*	NA	−109.2 ± 6.7
Fat ring sign, *n* (%)	42 (85.7)	88 (93.6)
Density, *HU*	−106 ± 4	−105.5 (12)
Stripe or pseudocapsule, *n* (%)	29 (59.2)	53 (56.4)
Lymph nodes, *n* (%)		
None	10 (20.4)	2 (2.1)
<5 mm	39 (79.6)	81 (86.2)
5–10 mm	N/A	11 (11.7)
Calcifications, *n* (%)	N/A	4 (4.3)

Values are mean ± standard deviation, median and interquartile range or numbers and percentages, where appropriate
N/A not available

11.8.2 Other Imaging Techniques

Ultrasound may reveal a well-defined homogeneous hyperechoic (fatty) mass at the mesenteric root with in most cases a clear interface between the normal fat and the inflammatory fat in SM [46]. Ultrasound findings may be subtle, easily missed, and findings are nonspecific and may be seen in other conditions involving the mesentery [58]. Magnetic resonance imaging (MRI) findings are similar to the CT features. On MRI, a mesenteric mass is seen with intermediate signal intensity on T1-weighted images and with slightly higher signal intensity on T2-weighted images [27]. ^{18}Fluorodeoxyglucose-(FDG) positron emission tomography (PET) has been proven useful mainly for the differentiation between SM (not FDG-avid) and malignant mesenteric involvement (FDG-avid), especially in patients with tumoral or lymphomatous involvement of the mesentery. A negative PET scan has a high diagnostic accuracy in excluding lymphomatous or tumoral involvement of the mesentery [66].

11.9 Diagnosis (Including Differential Diagnosis)

A definite diagnosis of SM can only be made by biopsy and pathologic analysis; however the incidental and often asymptomatic nature does not justify biopsy in most cases. Diagnosis can be made by imaging features, especially CT examination

(see Sect. 11.8). The term SM is solely reserved for idiopathic inflammation leading to infiltration of the mesentery and must be differentiated from any alternative causes altering density of the mesenteric fat ("misty mesentery") [24, 37, 52, 56, 58]. This includes mesenteric edema, hemorrhage, inflammation (e.g., pancreatitis and other inflammatory diseases of the gastrointestinal tract), retroperitoneal fibrosis (RPF), and neoplasm involving the mesentery including lymphoma and primary mesenteric neoplasm. When fibrosis dominates in SM, imaging features may overlap with carcinoid tumors, desmoid tumors, and peritoneal carcinomatosis. Lymphoma is the most common tumor involving the mesentery and is a challenging differential diagnosis to exclude, particularly in the early stage when bulky lymphadenopathy may still be absent [24, 37]. The "halo sign" and pseudocapsule favors SM, but can be seen in lymphoma. Any lymphadenopathy outside the mesenteric regions favors early stage lymphoma. Lymphoma will not contain calcifications, unless previously treated [24]. The CT appearance of SM and carcinoid can be identical. Both can appear as an infiltrating mass in the root of the mesentery with desmoplastic reaction and calcifications [7, 23, 24]. The "halo sign" favors SM, a discrete enhancing bowel mass and hypervascular liver metastases favor carcinoid tumor.

11.10 Overlap with Other (Fibroinflammatory) Disorders

Concomitant RPF and sclerosing pancreatitis has occasionally been noted in SM patients, suggesting that SM may sometimes be part of multifocal fibrosis [1]. In addition, typical histopathologic and immunohistochemical features of IgG4-RD has been observed in some cases of SM (see Sect. 11.5.2). However, SM may extend per continuitatem into the retroperitoneal space to involve the (peri-) pancreatic region, where histologic features of autoimmune pancreatitis are not present [13, 51]. In our extensive experience with RPF patients, concomitant noncontiguous CT-documented SM was noted on several occasions. Of interest, smoking has been linked to the development of both SM and RPF [12, 20].

11.11 Treatment and Prognosis

11.11.1 General Approach

The aims of treatment of SM are to relieve gastrointestinal symptoms, to relieve bowel obstruction if present, to induce regression of the fibroinflammatory reaction, and to avoid recurrence. Treatment should be guided by the severity of signs and symptoms and may include different drugs, surgical procedures, or both. Of note, many patients often have only mild symptoms, and SM may even be an incidental finding in otherwise asymptomatic patients. Medical treatment is usually not warranted for these patients. A novel nonpharmacological treatment option for cases refractory to medical treatment may be (repeated) endoscopic ultrasonography-guided celiac plexus block [2].

11.11.2 Surgical Treatment

The primary surgical approach should be limited to exploration with biopsy and, in cases of intractable bowel obstruction, palliative colostomy or bypass [1, 13, 15, 42]. In some cases, partial or complete resection of the mesenteric mass with the adjacent bowel may be possible [1, 42]. However, resection may be hazardous and often not feasible because of extensive encasement of the bowel or mesenteric blood vessels [1, 13, 15]. In addition, attempted surgical resection or debulking usually does not result in resolution of symptoms [1]. In some cases, segmental bowel resection may be required as a result of severe vascular compromise from the affected mesentery [1]. In case of coexistent intraabdominal diseases, additional surgical procedures may be needed [1, 42].

11.11.3 Medical Treatment

The medical treatment of SM is empiric and various pharmacological agents have been used to treat the disease. Already in the 1950s, treatment directed at the presumed inflammatory component was used with corticosteroids and azathioprine, either alone or combined [3, 42, 55]. Anecdotal case reports have described the use of cyclophosphamide [5], but we do not advocate its use because of the associated increased risk of infection, especially sepsis. Over the last decades, several other drugs have been used in the treatment of SM, notably tamoxifen (TMX) [1, 21, 35, 51, 60], colchicine [16, 17, 25], and thalidomide [1, 18]. Although often used in conjunction with other agents, notably corticosteroids, TMX has also been used successfully as monotherapy [21]. TMX down-regulates growth factors involved in fibroblast proliferation, has anti-inflammatory and immunomodulatory effects, and has antiangiogenic properties [21, 57]. We have also treated several SM patients successfully with TMX monotherapy (20 mg b.i.d.), with amelerioration of symptoms and CT-documented improvement at follow-up (Fig. 11.2). Adding colchicine to corticosteroid treatment allowed for tapering of steroids in previously steroid-dependent cases with maintenance of clinical remission [16, 25, 27]. Colchicine is thought to act through downregulation of inflammation and modulation of innate immunity. It also has antifibrotic activities and various effects on endothelial function [33]. Thalidomide has potent anti-inflammatory, immunomodulatory, and anti-angiogenic properties and suppresses TNF-α [18]. In an open-label pilot study, five patients with symptomatic SM received oral thalidomide (200 mg nightly) for 12 weeks. Thalidomide was well tolerated and symptoms ameliorated in four of the five patients (80 %) within this period with concurrent decrease in acute-phase reactant levels and stable mass at CT follow-up [18]. In a case of refractory symptomatic SM, despite steroid and azathioprine treatment, anti-TNFα therapy (Infliximab®) led to dramatic clinical as well as (subsequent) radiological improvement [47]. Recently, low-dose naltrexone proved useful in patients with symptomatic SM [45].

Given the paucity of published data on medical treatment of SM in larger case series and the absence of a direct comparison of different agents, it is hard to assess

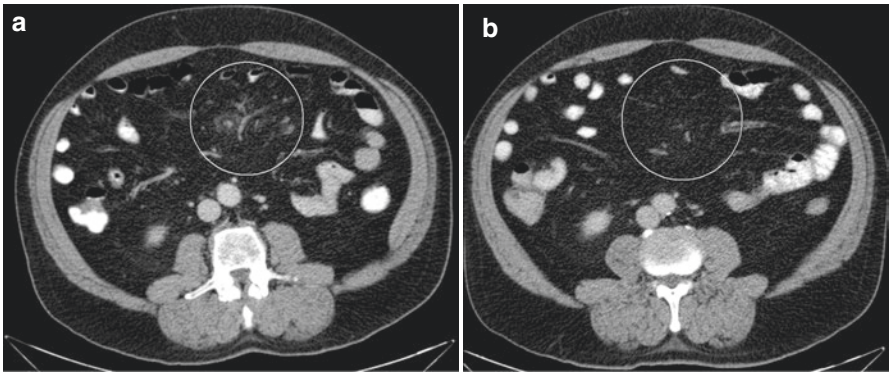

Fig. 11.2 (**a**): Contrast-enhanced abdominal CT scan in a 64-year-old man with chronic pain in the lower left abdomen and postprandial diarrhea showing discrete sclerosing mesenteritis. (**b**): Follow-up CT scan after 4 months of tamoxifen treatment (20 mg b.i.d.) showing complete disappearance of intraabdominal abnormalities. His symptoms had resolved within 4 weeks of treatment

the "true" success rate of different treatment regimens. The retrospective study of Akram et al. gives us a good impression as to the overall effect of different treatment regimens in SM [1]. From analyzing their data of individual patients receiving medical therapy without surgical intervention we constructed Table 11.3.[2] Overall, the disease was responsive to medical treatment in 9 of 22 patients (41 %). Data suggest that corticosteroids alone may not be sufficient to treat the disease. However, treatment regimens which included both initial high-dose prednisone and TMX proved successful in 8 of 12 cases (75 %) (Table 11.3). In these 12 cases, mean (initial) dose and duration of prednisone amounted to 38 (range 10–60) mg/day for 10 (range 2–24) months and of TMX 19 (range 10–20) mg/day for 24 (range 4–33) months. From the study it could not be derived if and to what extent CT-documented improvement was observed following treatment initiation in these patients. Persistent to progressive disease was seen more often in patients who did not receive medical treatment post-surgery compared to those who received additional medical treatment post-surgery (8/10 vs. 4/8 patients) [1]. Based on above mentioned data and our own experience, we suggest that medical treatment should be individualized according to presentation and severity of disease. As the disease usually has a benign course and may resolve spontaneously, medical treatment should usually not be offered to asymptomatic or mildly symptomatic patients. In patients with uncomplicated SM who are moderately symptomatic, TMX monotherapy (20 mg b.i.d.) may suffice as first-line therapy. Note that this dose is higher than used by others [1,

[2] From their study [1], we analyzed data of individual patients receiving medical treatment without surgical intervention with follow-up ≥ one month and categorized patients according to four different treatment regimens. Per treatment category we calculated the number of patients, mean age (y), male sex (*n*), response rate (*n*, %) and mean follow-up (range). We also calculated dose range per drug and mean (initial) dose (mg/day) and duration (month) of prednisone and tamoxifen in those patients who received medical treatment including both prednisone and tamoxifen.

Table 11.3 Results of medical treatment without surgical intervention in patients with sclerosing mesenteritis[a]

Medical treatment	Patients, *n*	Mean age, y/ male sex, *n*	Response to therapy			Follow-up, *mo*
			Responsive[b], *n* (%)	Persistent, *n* (%)	Progressive, *n* (%)	
PDN	6	64/4	0 (0)	4 (67)	2 (33)	25 (4–46)
PDN/TMX	9	70/7	5 (56)	3 (33)	1 (11)	30 (10–89)
PDN/ TMX + AZA/Col	3	63/0	3 (100)	0 (0)	0 (0)	19 (3–41)
Miscellaneous[c]	4	59/4	1 (25)	2 (50)	1 (25)	21 (8–60)
All treatment	22	66/15	9 (41)	9 (41)	4 (18)	26 (3–89)

Values are counts and percentages or mean and range, where appropriate
Abbreviations: *AZA* azathioprine (range 50–100 mg/day), *Col*, colchicine (range 1.2–1.8 mg/day), *PDN* initial high-dose prednisone/prednisolone (range 10–60 mg/day), *TMX* tamoxifen (range 10–20 mg/day)
[a]Table constructed from analyses of individual patient data from Akram et al. [1]
[b]Response to treatment was assessed by symptom evaluation and abdominal CT scanning at follow-up
[c]Treatment included TMX ($n=1$), TMX/C ($n=1$) or combined PDN/A with thalidomide ($n=1$) or colchicine ($n=1$)

21, 51, 60]. Extrapolating our results with TMX in RPF [57], we advocate long-term use of this fixed-dose regimen for up to 2 years in patients with satisfactory initial response. TMX is usually well tolerated with few side effects, albeit with an increased risk of thromboembolic events [57]. In patients with severe symptoms and/or signs of bowel obstruction, a trial with more aggressive therapy with combined TMX (20 mg b.i.d.) and initial high-dose corticosteroids (40–60 mg) seems appropriate. In responsive patients, corticosteroids can be tapered and discontinued after 6–12 months with continued long-term use of TMX. In refractory cases or intolerance/contraindications for corticosteroids or TMX, colchicine (1–2 mg/day) may be added. Thalidomide, anti-TNF therapy, and naltrexone should probably be withheld as "rescue" therapy until more data are available.

11.11.4 Prognosis

Because of the rarity of SM and the paucity of long-term follow-up data in larger patient groups, its natural course remains unclear. However, it does seem to have a benign course in most cases with little chance of recurrence, often with stable radiological abnormalities. Spontaneous resolvement of the mesenteric mass has been reported anecdotally [11, 22, 36]. Many cases therefore do not require any treatment. In some cases, however, it may be associated with significant morbidity and

a chronic debilitating course [1, 3, 13, 15]. Although rare, death from recurrent SM-related complications and its (surgical) sequelae has been reported [13, 15, 28, 31]. Overall mortality in larger case series of SM patients with long-term follow-up varied from 20 to 45 %, death usually being unrelated to SM [1, 15]. An important issue is whether follow-up in patients with SM should include repeat abdominal CT scanning. Some suggest that treatment is best assessed by symptomatic improvement alone [1]. However, it is unknown if clinical improvement with stable radiological abnormalities following treatment ultimately has another prognosis (e.g., chance of recurrence) than patients who have both clinical and radiological improvement at follow-up. Although further study is needed, SM may be a paraneoplastic phenomenon. We argue that CT follow-up is therefore justified, but proposing its frequency and timing is difficult and should probably be guided by SM-related and other signs and symptoms during follow-up.

Conclusions

SM is a rare disease characterized by chronic, nonspecific inflammation of the adipose tissue of the mesentery of the small intestine. Although several potential etiologic factors have been identified, its precise etiopathogenesis remains obscure. After careful age-appropriate cancer screening, a diagnosis of SM can be made with near-certainty with abdominal CT scanning, thereby obviating the need for routine biopsy. Although unproven, physicians should keep in mind that SM may be associated with (future) malignancy and other chronic (fibro) inflammatory disorders. Its course is usually favorable but severe complications may occur, notably bowel obstruction. Medical treatment should be offered to patients with moderate to severe symptoms, surgery usually being confined to palliative bypass in cases of bowel obstruction. Long-term follow-up is indicated.

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Erdheim-Chester Disease and Other Histiocytoses

12

Julien Haroche, Davide Gianfreda,
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12.1 Introduction

Erdheim-Chester disease (ECD) was first described as "lipoid granulomatosis" by Jakob Erdheim and William Chester in 1930 [1]. This non-Langerhans histiocytosis of unknown origin is rare, with less than 1000 cases as of December 2015 [2–5]. ECD, morphologically and immunohistochemically, appears to be a member of the juvenile xanthogranuloma (JXG) family that involves the long bones in a bilateral fashion. ECD can be distinguished from Langerhans cell histiocytosis (LCH) by the characteristic xanthogranuloma immunostaining, which is factor XIIIa+/CD68+/CD163+/fascin+ and S100−/CD1a−/Langerin−/Birbeck granules− [6].

ECD appears to be a true multisystemic disease, as almost all tissues may be infiltrated by histiocytes: patients may present with skeletal involvement with bone pain, diabetes insipidus, exophthalmos, xanthelasmas, interstitial lung disease, bilateral adrenal gland enlargement, retroperitoneal fibrosis with perirenal and/or ureteral obstruction, renal impairment, testis infiltration, and involvement of the central nervous system (CNS) and/or cardiovascular system [4, 7]. The extent and distribution of the disease determine the clinical course. Some cases present only asymptomatic bone lesions, whereas others have multisystemic, potentially life-threatening forms.

Histiocytoses are heterogeneous diseases and different histiocytic disorders may occur in association (overlap forms) [8–10]. This situation is most frequently observed for ECD and LCH, but Rosai-Dorfman disease (RDD), a non-Langerhans

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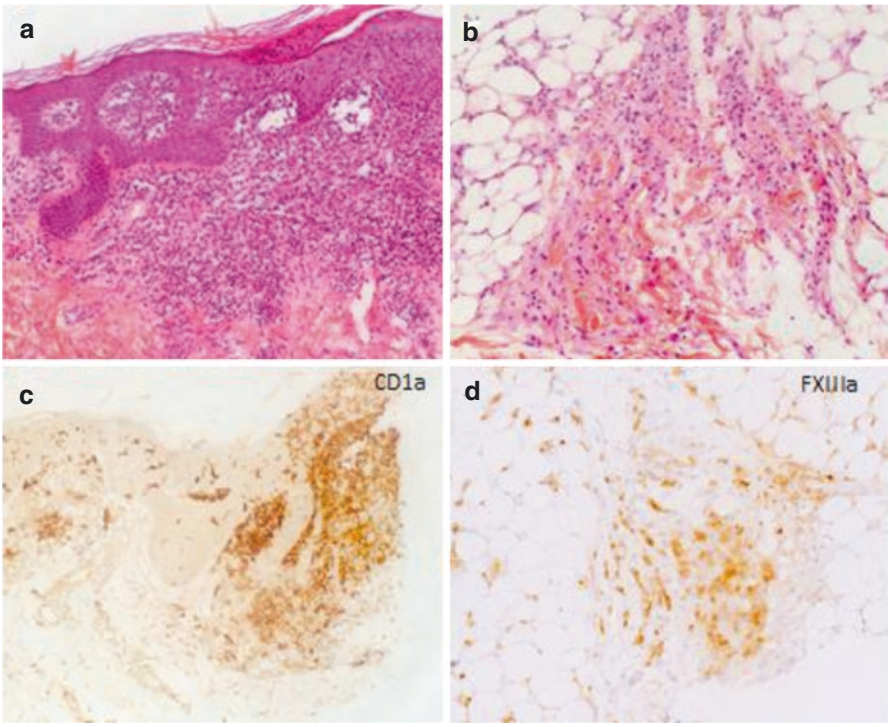

Fig. 12.1 Skin biopsy of an overlap case of histiocytosis (Langerhans cell histiocytosis, LCH, and Erdheim-Chester disease, ECD). (**a**) LCH, Langerhans cells infiltrating the superficial dermal and the epidermal layers (hematoxylin and eosin, H&E, ×100); (**b**) ECD: histiocytes with foamy cytoplasm infiltrating the adipose tissue of the hypoderma, associated with fibrosis (H&E, ×100); (**c**) LCH, typical immunostaining of CD1a by Langerhans cells (immunoperoxydase, ×100); (**d**) ECD, foamy histiocytes are positive for FXIIIa (immunoperoxydase, ×100)

form of histiocytosis that generally has a more favorable outcome, may also be present. The frequency of these overlap forms is too high to be considered coincidental and implies a common cause for the various histiocytoses [11].

12.2 Diagnostic Criteria

The diagnosis of ECD is based on histopathologic findings within an appropriate clinical and radiological context. The typical histological pattern is a polymorphic granuloma infiltrated with $CD68^+$ and $CD1a^-$ foamy histiocytes, fibrosis, or xanthogranulomatosis [6, 7] (Figs. 12.1 and 12.2). These characteristic histiocytes may be found in virtually any tissue in ECD patients. Lesional tissue usually shows foamy or lipid-laden histiocytes with surrounding fibrosis or xanthogranulomatosis; Touton giant cells are often present. Immunohistochemistry shows histiocytes that

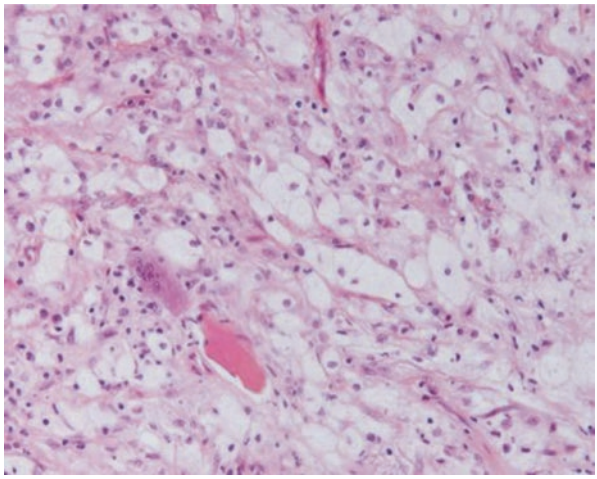

Fig. 12.2 Femoral biopsy from a patient with ECD: the medullary spaces of the spongious bone are infiltrated by foamy histiocytes, along with some small lymphocytes admixed with mild fibrosis. A residual bone trabecula with an adjacent multinucleated osteoclast can also be seen (H&E, ×200)

are factor XIIIa$^+$/CD68$^+$/CD163$^+$/fascin$^+$ and CD1a$^-$/Langerin$^-$/Birbeck granules$^-$. Positivity for S100 is rarely observed (~20 % cases).

The radiographic finding of bilateral and symmetric diaphyseal and metaphyseal osteosclerosis in the legs is present in almost all patients. This is one of the iconic features of ECD, and is best seen on ^{99}Tc bone scintigraphy, which reveals radiotracer uptake by the distal ends of the femurs and the proximal and distal tibia (in 96 % of a series of 53 patients published in 2011) [12, 13], and less sensitively by positron emission tomography (PET). Bone lesions may be missed on plain films but can be visualized more sensitively on computed tomography (CT) or magnetic resonance imaging (MRI). Abdominal CT may show dense infiltration of perinephric fat, or "hairy kidneys," in 57 % of cases [14, 15]. A biopsy is always necessary to establish the diagnosis of ECD, and when "hairy kidney" aspect is present, a CT-guided biopsy of the perirenal infiltration is the recommended approach [16]. Biopsy of skin lesions, such as xanthelasmas, is also feasible, but the findings cannot be easily distinguished from those of non-ECD xanthelasmas. Biopsy is also helpful to establish the *BRAF* mutational status, which has major therapeutic implications.

The diagnostic criteria generally used for ECD include:

1. Characteristic histological findings: foamy histiocytic infiltration of polymorphic granuloma and fibrosis or xanthogranulomatosis, with histiocytes CD68$^+$ and CD1a$^-$ on immunostaining;
2. Characteristic skeletal abnormalities: (a) bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal parts of the long bones on X-ray and/or (b) symmetric and abnormally intense labeling of the distal ends of the long bones of the legs and, in some cases, arms, on ^{99}Tc bone scintigraphy. Although very typical of ECD, long bone involvement may be absent in up to 5 % of the cases.

Table 12.1 Frequency of the main clinical and radiological characteristics of Erdheim-Chester disease

	From the literature	Personal experience[a]
Bone pain	50	39
Periaortic infiltration	60	55
"Coated aorta" (sheathing of the whole thoracoabdominal aorta)	30	43
Pericardial involvement	45	30
"Pseudotumoral" infiltration of the right atrium	NA	31
Exophthalmos	27	21
Diabetes insipidus	27	26
Xanthelasma	19	25
"Hairy kidney" aspect	NA	57
CNS involvement	15–25	40
Pulmonary involvement	22	34

Data are expressed as percentages
NA no data available
[a]122 consecutive ECD patients seen at least once in hospitalization in the internal medicine department of Pitié-Salpêtrière Hospital

12.3 Epidemiology

Although between 700 and 1000 ECD cases have been reported in the literature until December 2015 since the seminal description of the disease in 1930, the number has dramatically increased in the last decade due to increased awareness of the disease [3–5, 7]. ECD affects predominantly adults between the age of 40 and 70 years (mean age being approximately 55 years), and it is more frequently diagnosed in men (M:F ratio usually being 3:1) [4]. Pediatric cases of ECD have rarely been described (~15 cases reported to date), none of whom displayed cardiac involvement, as opposed to adult patients [17, 18].

This chapter will mainly rely on our own experience with 122 patients followed at our center. This series was presented at the second medical symposium on ECD held in September 2014 in Bethesda (Table 12.1). This is the largest series worldwide. All these patients attended our center at least once since 1991, and we have followed most of them regularly. Most of these patients live in France (80 %), but 25 live elsewhere, mostly in Europe, but also in Israel, South Africa, and Kazakhstan. Twenty-seven of these patients have died (22 %). Most of them were men (75 %), and the mean age at diagnosis was 56.1 ± 14.7 years (range, 5–80 years). In an early study in 2006, the time between the onset of symptoms and diagnosis was between a few months and several years (up to 25 years). Since then, this time interval has substantially decreased, probably due to increasing recognition of the disease [13].

12.4 Clinical Manifestations

12.4.1 Bone Involvement

Skeletal involvement is extremely frequent (96 % of the 53 patients included in a 2011 series), but only 39 % of patients suffer bone pain, which is, nevertheless, the most common clinical feature of ECD [13]. It is usually mild, may start at any time during the course of the disease and mostly affects the legs. X-ray evidence of bilateral, symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions of the long bones is an idiosyncratic feature of ECD, and abnormally strong, symmetric labeling of the distal ends of the long bones of the legs, and sometimes the arms, is also often revealed by ^{99}Tc bone scintigraphy (Fig. 12.3) [6, 7]. The axial skeleton and the mandible are often involved in LCH, but not in cases of ECD. In recent years, positron emission tomography (PET) with ^{18}F-labeled fluorodeoxyglucose (PET-CT) has gradually been replacing bone CT scans [19, 20]. MRI of the long bones can be informative in some cases, because it may reveal epiphyseal involvement of the long bones and periostitis not detected on X-ray [21]. MRI may also be valuable in the rare cases of ECD showing no abnormalities on bone CT scans.

12.4.2 Cardiovascular Involvement

Progresses in radiological imaging has facilitated the detection of cardiovascular involvement. The most frequent cardiovascular sign is the circumferential periaortic sheathing of the thoracic or abdominal aorta (55 and 57 % of cases, respectively) [4, 7]. Serratrice et al. described cases in which the whole aorta was sheathed, showing a "coated aorta" appearance, and this has become one of the iconic features of ECD (43 % of cases) [13, 22]. Periarterial infiltration may extend to the main aortic branches. Its clinical consequences are usually not severe, apart from renovascular hypertension due to renal artery involvement (16 % of cases), a complication that can be treated by renal artery stenting [7].

With respect to heart involvement, pericardial lesions are the most frequent (30 %) (Fig. 12.3), sometimes with tamponade, but myocardial and endocardial infiltrations may also be observed [7, 23]. Abnormal heart imaging was detected by cardiac MRI in 70 % of the 37 patients undergoing systematic retrospective cardiovascular screening (MRI and/or heart CT scan) in a study published in 2009: Abnormal infiltration of the right heart was found in 49 %, including "pseudotumoral" infiltration of the right atrium in 30 %, and infiltration of the auriculoventricular sulcus in 19 % [24].

More than 20 patients with myocardial infarction secondary to pericoronary infiltration have been reported, with this condition leading to death in some cases [7, 25, 26]. In one series of 53 patients, 17 % had symptomatic heart valve disease (aortic and mitral regurgitations) [4], although valve replacement was required very rarely [7, 27]. This operation is technically difficult, due to the extensive infiltration

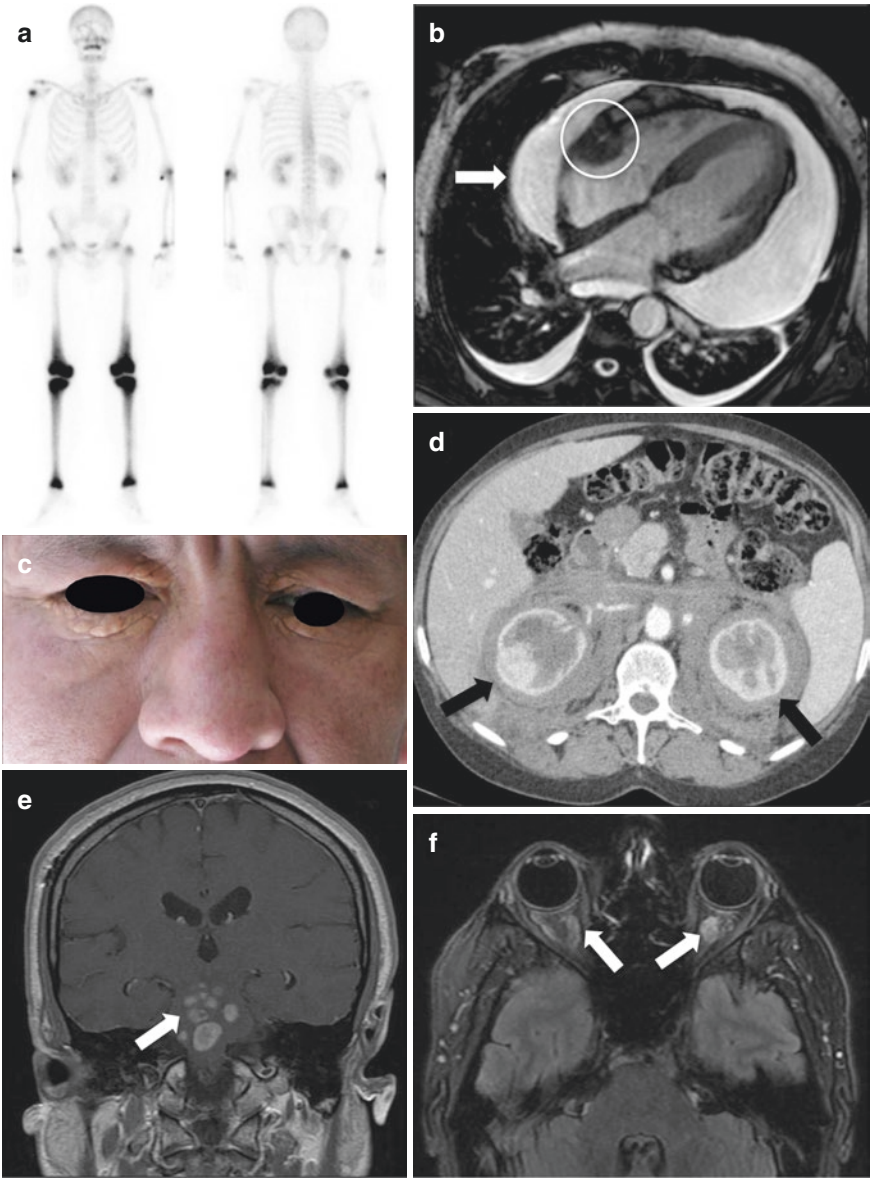

Fig. 12.3 Typical clinical and imaging findings in ECD. (**a**) ^{99}Tc Bone scintigraphy showing bilateral and symmetric tracer uptake of the distal femurs and of the proximal and distal tibias. (**b**) Cardiac magnetic resonance (MR) scan showing massive pericardial effusion (*arrow*) and infiltration of the right atrium (*circle*). (**c**) Bilateral xanthelasmas involving the upper and lower eyelids. (**d**) Abdominal computed tomography scan showing retroperitoneal infiltration, around the kidneys (*arrows*) but also involving the abdominal aorta and the renal arteries. (**e**) Brain MR (coronal view) showing multiple lesions involving the encephalic trunk (*arrow*). (**f**) Brain MR (axial view) showing bilateral infiltration of the retro-orbital space (*arrows*).

of the heart *tunicae*, and should therefore be performed only in appropriately selected cases, at specialized centers.

12.4.3 Retro-Orbital Infiltration

Twenty-five percent of ECD patients develop exophthalmos, which is often bilateral and due to infiltration of the retro-orbital soft tissues (Fig. 12.3) [28, 29]. This infiltration may be massive in a small number of cases, rendering it refractory to conventional therapy, such that surgical debulking is required.

12.4.4 Endocrine Involvement

Diabetes insipidus, due to pituitary gland infiltration, is the most frequent endocrine manifestation of ECD (26 % of patients). Rare cases of pituitary or hypothalamic infiltration with other endocrine consequences have been reported, including hyperprolactinemia, gonadotropin insufficiency, and abnormally low levels of IGF-1 [30, 31].

We performed a single-center observational study between October 2007 and May 2013 with systematic endocrine evaluation in 64 consecutive ECD patients [32]; 36 of the studied patients also had follow-up assessments. Diabetes insipidus was found in 33.3 % of patients, frequently inaugural of ECD. Anterior pituitary dysfunction was found in 91.3 % of patients with full anterior pituitary evaluation, including somatotropic deficiency (78.6 %), hyperprolactinemia (44.1 %), gonadotropic deficiency (22.2 %), thyrotropic deficiency (9.5 %), and corticotropic deficiency (3.1 %). Thirty-five patients (54.7 %) had two anterior pituitary dysfunctional axes, rising to 69.6 % (16/23) when only considering patients with complete evaluation. Two patients had pan-hypopituitarism. Infiltration of pituitary and stalk was found on MRI in 24.4 % of cases. Testicular insufficiency was found in 53.1% of patients, with sonographic testicular infiltration in 29 % of men, mostly bilateral. Imaging signs of adrenal infiltration were found in 39.1 % of patients, and one case of adrenal insufficiency was observed. No patient was free of endocrine hormonal or morphological involvement. Endocrine dysfunctions were most often permanent, and new deficits appeared during follow-up. Therefore, endocrine involvement is very frequent in ECD and should carefully be evaluated at diagnosis and during follow-up.

12.4.5 Skin and Mucosal Involvements

Xanthelasmas, generally involving the eyelids or periorbital spaces, affected 25 % of our patients (Fig. 12.3). Papulonodular lesions [33] and infiltrations of the vulva and clitoris may also be observed, but they are less frequent [1]. In a recent study,

we described the clinical, pathological, and molecular features of the cutaneous manifestations of 40 patients with ECD identified from a cohort of 123 patients [34]. Clinical and pathological cutaneous features were analyzed and *BRAF*^{V600E} mutation was determined. The most frequent ECD cutaneous manifestations were xanthelasma-like lesions (XLLs), which occurred in 31 (25 %) patients. Other ECD cutaneous lesions were patchy or papulonodular lesions. Mixed forms of ECD and cutaneous LCH presented with crusty papules in some patients. Compared with classic xanthelasma palpebrarum, ECD XLL pathology more frequently involved the reticular dermis, displayed more multinucleated or Touton cells, and showed less extensive fibrosis. The *BRAF*^{V600E} mutation was more frequently detected in patients with cutaneous involvement than in those without (76 % vs. 52 %; $P = .005$) and constantly found in 10 XLLs. XLLs are the most frequent cutaneous ECD manifestations and might be targeted both for pathology and determination of the *BRAF* mutational status.

12.4.6 Urological and Nephrological Complications

About one third of ECD cases present with "pseudoretroperitoneal fibrosis," in some cases complicated by bilateral hydronephrosis, which may require ureteral stenting (Fig. 12.3) [35]. This situation was observed in 25 % of the cases in our series. Involvement of the pelvic ureters has never been described, and the inferior vena cava is rarely affected in ECD. The "fibrosis" observed in ECD patients sheaths the walls of the aorta completely and circumferentially, whereas the posterior aortic wall is rarely affected in the idiopathic form of retroperitoneal fibrosis [7].

12.4.7 Lung Involvement

In 2008, we performed a retrospective analysis of lung involvement in 34 consecutive patients with ECD [36]. High-resolution thoracic CT scans demonstrated involvement of the lung parenchyma in 53 % of cases, and of the pleura in 41 % [37]. The lesions mostly affected the interlobular septa. Lung involvement was not a significant prognostic factor for ECD in this series, contrasting with previous findings emerged from studies on smaller number of patients. A MEDLINE search identified reports of lung involvement in 70 (22 %) of the 319 ECD cases published before November 2008, but most of the descriptions were incomplete.

12.4.8 CNS Involvement

CNS involvement is common in ECD patients (15–25%) [13] and was described in detail in a French neurological series [38]: this multicenter literature review was

carried out in 2006 and analyzed 66 ECD patients (including six personal cases) with neurological involvement. Cerebellar and pyramidal syndromes were the most frequent neurological signs (41 and 45 % of cases, respectively), and the other features described included seizures, headaches, neuropsychiatric signs or cognitive impairment, sensory disturbances, cranial nerve paralysis, and asymptomatic lesions. Neurological involvement led to severe functional disability in almost all patients. CNS involvement is a major prognostic factor in ECD, as survival analysis has identified this factor as an independent predictor of death (hazard ratio = 2.51; 95 % confidence interval, 1.28–5.52; $P = 0.006$) [4]. The most damaging (and difficult to treat) neurological condition is the pseudodegenerative involvement of the cerebellum, which is present in 17 % of our patients. The overall frequency of CNS involvement is 40 %.

We reviewed brain MRI findings for 33 ECD patients followed at Pitié-Salpêtrière Hospital until 2009. Only three patients had normal imaging results [39], and two or more different anatomic sites were affected in most patients. Lesions of the brain, meninges, facial bones, and orbits are frequent in ECD patients (Fig. 12.3). MRI and CT should therefore be carried out systematically, to investigate the brain, in all ECD patients, even those without symptoms.

12.5 Other Infiltrations and Organ involvements

A broad range of organs has been reported to be involved in ECD. Autopsy has demonstrated involvement of the testes, thyroid, and lymph nodes [40]. There are also numerous case reports describing breast infiltration [41–43] and macrophage activation syndrome.

12.6 Disease Activity

The clinical course of ECD seems to be typical of a chronic disease but has not been described in detail. Lesions accumulate in the affected organs and systems and rarely regress spontaneously. Serum C-reactive protein (CRP) levels are high in more than 80 % of cases, but with little impact on outcome after diagnosis. Disease activity in ECD patients is assessed by regular clinical, biological, and radiological investigations (about every six months), and imaging to assess morphological changes. No disease activity score has yet been established.

PET is particularly informative for the assessment of ECD activity [19]. PET scans can detect CNS involvement, and can reveal early responses of CNS lesions to treatment, when no change in such lesions are apparent on MRI. PET scans can also be used to investigate the cardiovascular system – the heart and the entire vascular tree- which can be studied during a single session. PET studies are therefore recommended for ECD patients, because no other single technique provides as much information as does PET in ECD.

12.7 Treatment

12.7.1 Interferon Alpha (IFNα) and Other Nonmutation-Driven Approaches

Before 2005, the standard treatments for ECD included steroids, cytotoxic agents [44], and double autologous hematopoietic stem-cell transplantation [45, 46]. The efficacy of these treatments was difficult to establish, because had been administered to only small numbers of patients, or in combination with other drugs. The follow-up periods were also short. Braiteh et al. reported rapid, marked, and persistent regression of retro-orbital infiltration and a progressive improvement of bone lesions, pain, and diabetes insipidus in three ECD patients given IFNα [47]. However, in eight patients with ECD treated with low-dose IFNα (3 MU X 3/week), we found that the efficacy differed according to the involved sites [16]. In some cases, the symptoms failed to respond to such low doses of IFNα; this was particularly true in patients with severe multisystem forms of ECD (CNS and cardiovascular involvement in particular). We therefore recommend higher doses, up to 9 MU X 3/week if tolerated, because such doses may be more effective against meningeal infiltrations, sub- and retrosellar masses, and pericardial and pseudoatrial infiltrations. IFNα is necessarily a long-term treatment, but it may lead to adverse effects, including depression and fatigue. IFNα treatment has also given disappointing results in cases of pseudodegenerative cerebellar involvement (similar to that observed in LCH).

Nevertheless, IFNα appears to be the best choice for the initial treatment of ECD. Survival analysis on a series of 53 patients indicated that treatment with IFNα and/or PEGylated IFNα was a major independent predictor of survival (HR = 0.32; 95 % CI, 0.14–0.70; P =0.006) [4]. We generally begin treatment with PEGylated forms of IFNα because such forms are better tolerated than IFNα in the long term.

Imatinib mesylate was reported to be effective in cases of histiocytosis in 2010 [48]. However, a small trial with this treatment in six ECD patients yielded disappointing results [49]. The treatment of two ECD patients (with neither cardiovascular nor CNS involvement) with recombinant human interleukin-1 receptor (anakinra) was described, and this treatment appeared to be promising [50]. In a larger experience with 12 cases treated with anakinra, the drug efficacy was poor overall, particularly for the severe forms of the disease (cardiovascular and CNS involvement) [51]. Other groups have shown this treatment to be effective only for mild forms of the disease (mostly bone pain). Cladribin may be useful for treating CNS involvement at sites not responsive to IFNα [44]. Infliximab treatment was shown to be beneficial after 12–18 months, in two ECD patients with cardiac involvement [52]. Recently, sirolimus combined with prednisone was reported in an open-label trial of ten consecutive patients: most patients achieved disease stabilization or objective responses; one died due to disease progression and one due to small-cell lung cancer. Overall, this therapy was well tolerated [53].

12.7.2 BRAF Inhibition

The etiology of ECD has been a matter of debate for many years; in particular, it was unclear whether the disease could be considered primarily inflammatory or neoplastic. The RAS-RAF-MEK-ERK pathway is a key cellular signaling pathway that has been found implicated in diverse tumors [54, 55]. Many human tumors carry the *BRAF*^{V600E} mutation [56], causing activation of the RAS-ERK pathway independently of RAS activation. The inhibition of BRAF activation by vemurafenib improves the survival of patients with metastatic *BRAF*^{V600E}–positive melanomas [57]. In 2010, recurrent somatic activating mutations of the *BRAF*^{V600E} type were found in 57 % of archived LCH lesions [58]. Targeted pyrosequencing of paraffin-embedded samples from 127 patients with histiocytoses identified mutually exclusive *BRAF*^{V600E} mutations in 54 % of ECD samples and 38 % of LCH samples, but none of the other non-LCH samples [59]. The frequency of *BRAF*^{V600E} mutations in ECD is currently considered to range between 57 and 75 % of the cases, depending on the techniques used [60].

Vemurafenib inhibits the mutant BRAF protein and displays some efficacy against both *BRAF*^{V600E}-associated melanoma and hairy-cell leukemia [61]. In 2012, we conducted a pilot study of vemurafenib treatment for three patients with multisystemic and refractory ECD who carried the *BRAF*^{V600E} mutation [54]. Two of the patients also had skin or lymph node LCH. Vemurafenib treatment led to rapid, substantial clinical and biological improvement in all three cases, as shown by clinical, biological (CRP values), histological (skin biopsy), and imaging (PET, CT, and MRI) findings during follow-up. The tumor response assessed by PET, CT, and/or MRI was detected as early as one month after the beginning of treatment. For one patient, serial PET assessments of the response to treatment showed continuous improvement during the first four months of treatment.

The study was extended to five additional patients: This study confirmed sustained efficacy of vemurafenib [62]. One patient developed squamous cell carcinoma after six months of treatment, but no other major adverse effects were reported in the others. Therefore, vemurafenib can be considered as the ideal treatment for all patients with severe and refractory BRAF^{V600E}-positive histiocytoses, particularly if life threatening. The importance of BRAF inhibition has been confirmed and extended to larger series of patients, both by our group [63] and by many other groups worldwide. At the time of writing, BRAF inhibitors have been used to treat more than 60 patients in total.

In 2013, Diamond et al. described one patient with ECD and *NRAS* mutation [64]. It is likely that ECD patients with *NRAS* mutations would also benefit from targeted anti-MEK therapy, as do some patients with metastatic melanomas. Moreover, the possible benefits of combined treatment (anti-MEK and anti-BRAF) should also be investigated in histiocytoses, as this approach might be more effective and less toxic, as already demonstrated in melanoma patients. We nevertheless strongly recommend that BRAF inhibitors only be used in patients harboring a BRAF mutation. A summary of the main treatment options for ECD is presented in Table 12.2.

Table 12.2 Treatment recommendations for ECD patients

Therapy	Treatment	Indications and tolerability
First-line	Interferon-α/ pegylated interferon-α	Best choice as frontline treatment of ECD. Tolerance issues (fatigue, depression); pegylated form is better tolerated Major independent predictor of survival. Higher doses (9 million units X 3/week) are recommended in cases with meningeal infiltration, sub- and retrosellar masses, pericardial, and pseudoatrial infiltrations [4, 5, 16, 47]
First-line in BRAF V600E carriers with severe and diffuse disease. Second-line in other cases	Vemurafenib and other BRAF inhibitors	Most impressive responses in ECD treatment, if BRAFV600E is present (57–70%), in multisystemic and refractory disease despite IFN-α therapy (CNS, cardiovascular ECD). Safety issues (in particular squamous cell carcinoma); optimal duration of treatment to be determined in future studies; less efficacious in pseudodegenerative neurologic forms of the disease [54, 62, 63]
Second-line	Steroids	Classically not effective in ECD, except in severe exophthalmos or macrophage activation syndrome
Second-line	Anakinra	Effective in mild ECD (bone pain, systemic symptoms). Disappointing in severe cases such as CNS and heart (cardiac tamponade occurring under therapy) [5, 50, 51]
Second-line	Double autologous stem-cell transplant	Anecdotal efficacy reported, but 5 cases with lack of efficacy in our center experience [45, 46]
Second-line	Cladribine	Potential benefit in treating CNS ECD refractory to IFN-α. However, unfavorable outcome in our small experience [44]
Second-line	Infliximab	Beneficial after 12–18 months in 2 ECD patients with cardiac involvement; needs to be studied further [52]
Second-line	Imatinib	Effective in 3 histiocytosis cases in 2010. However, discouraging results seen in 6 ECD patients [48, 49]
Second-line	Sirolimus	Objective responses or disease stabilization seen recently when combined with prednisone; good tolerability [53]

12.8 Follow-Up

We reported two series from before the "IFNα era," and these studies provided evidence of the poor prognosis of ECD [6, 7]. In 2004, 35 (60%) of the 58 patients for whom data were available had died, and the mean survival after diagnosis was 19.2 months (range, 0 to 120 months). By contrast, a survival analysis of 122 patients followed in our centers in 2014 indicated that overall mortality following treatment with IFNα and, more recently, vemurafenib, was only 22%, with a 5-year survival of 82.8% [65].

12.9 Pathophysiology, Overlap Histiocytoses

Little was known about the pathogenesis of ECD before 2006, largely because previous studies included only small numbers of patients. Stoppacciaro et al. reported an immunohistochemical study of three patients, showing that a complex network of cytokines and chemokines regulate histiocyte recruitment and accumulation in the lesions [66]. Dagna et al. studied both spontaneous and stimulated cytokine production by mononuclear cells in biopsy fragments from a single patient: Tumor necrosis factor α was produced after stimulation, and IL-6 and IL-8 were secreted spontaneously, with IL-8 being able to act as a chemoattractant for polymorphonuclear cells and monocytes [67]. Aouba et al. reported evidence from two patients indicating that targeting of the IL-1 pathway might be beneficial [50]. In a larger study published in 2011, we assayed serum samples from 37 ECD patients for 23 cytokines [68] and found high IFNα, IL-1/IL1-RA, IL-6, IL-12, and MCP-1 levels, indicating strong, systemic immune activation. There is, therefore, evidence to suggest that ECD is associated with systemic immune Th-1-oriented responses. Further studies on this aspect might lead to the development of targeted therapeutic agents.

The recent finding that 57–75 % of all ECD patients carry *BRAFV600E* mutations shows that the pathophysiology of this disorder is even more complex than previously suspected. This finding should prompt us to look for the putative clonal proliferation (associated with the *BRAFV600E* mutation) in addition to the non-clonal accumulation of histiocytes in affected tissues (probably driven by circulating chemokines and proinflammatory cytokines). Other mutations of the MAP kinase pathway have recently been identified in ECD patients. Indeed, in a large collaborative study between Pitié-Salpêtrière hospital in Paris, and the Memorial Sloan Kettering Cancer Center (MSKCC) in New York [69], *PIK3CA* and *NRAS* mutations were found to be recurrent in 11 and 4 % of ECD patients with wild-type *BRAF* status, respectively. More recently, this fruitful collaboration allowed the identification through combined whole exome and transcriptome sequencing, of recurrent kinase fusions involving BRAF, ALK, and NTRK1, as well as recurrent, activating MAP2K1 and ARAF mutations in BRAF-wild-type, non-LCH patients [70]. In addition to MAP kinase pathway lesions, recurrently altered genes involving diverse cellular pathways were characterized.

Mixed histiocytoses have been described simultaneously in patients at different sites of biospy, or in the same lesion or as one disease preceding another; this mixed pattern can occur as LCH/ECD (the most prevalent of all), LCH/JXG, LCH/RDD, or ECD/RDD. In 2014, a multicenter study of 23 patients reported an association between LCH and ECD, linked to the $BRAF^{V600E}$ mutation [11]. ECD either followed LCH (n =12) or was diagnosed simultaneously (n =11), but never preceded LCH. The $BRAF^{V600E}$ mutation was found in 11/16 LCH lesions (69 %) and 9/11 ECD lesions (82 %). These findings indicate that the association of LCH and ECD is not fortuitous, and suggest a link between these diseases involving the $BRAF^{V600E}$ mutation. Berres et al. recently proposed that LCH could be redefined as an inflammatory myeloid neoplasia [71]. There are, indeed, genetic, molecular, and functional data implicating ERK signaling pathway activation at critical stages of

Table 12.3 Differential diagnosis between ECD, retroperitoneal fibrosis (RPF), and Takayasu arteritis

	ECD	Retroperitoneal fibrosis (RPF)	Takayasu arteritis
Periaortic infiltration	Circumferential, regular sheathing of the whole aorta (coated aorta) without clear stenosis	Involvement of lateral and anterior sides of the aorta, usually sparing its posterior side	Segmental sheathing of the aorta, long stenosis or occlusions, and sometimes aneurysm
Parietal aortic wall thickening	Absent, infiltration involving only adventitial and periadventitial spaces	Absent. In some patients, RPF surrounds abdominal aortic aneurysm	Present
Inferior vena cava	Usually not affected	Commonly involved with stenosis or occlusion	Absent
Bilateral infiltration of the perirenal fat ("hairy kidney")	Often present	Absent	Absent
Pelvic ureteral involvement	Absent	Often present	Absent
Bone scintigraphy	Long bone hyperfixation, almost always present	Negative	Negative

myeloid differentiation, as an essential and universal driver of LCH. Given the high frequency of associations between LCH and ECD and the similar mutations affecting the MAP kinase pathway found in both conditions, we also speculate that ECD could be redefined as an inflammatory myeloid neoplasia.

12.10 Differential Diagnosis

Parietal aortic wall thickening with diffusion to the main aortic branches can be observed in Takayasu arteritis, which mainly affects young women. However, the radiologic findings of Takayasu arteritis and ECD are different (Table 12.3). The entire wall, that is, adventitia, media, and intima, is affected in Takayasu arteritis, whereas the adventitial and periadventitial periaortic spaces but not the wall itself is affected in ECD patients. Radiologic abnormalities can also be used to distinguish ECD from mediastinal and retroperitoneal fibrosis. Typically, retroperitoneal fibrosis is not circumferential and infiltrates the anterior and the lateral sides of the aorta, sparing the posterior side [7]. Retroperitoneal fibrosis, but not ECD, may involve the inferior vena cava (which may be stenosed or occluded) or the pelvic ureters. Extravascular images observed in ECD and not in retroperitoneal fibrosis, such as bilateral infiltration of the perirenal space ("hairy kidneys" appearance), can be useful for differential diagnosis.

Another differential diagnosis (and easy to rule out) is relapsing polychondritis (via periaortitis) but the clinical context is totally different. Hyper IgG4 syndrome can as well be discussed, as some overlap forms of RDD have been reported and a few ECD infiltrated tissues may also contain abundant IgG4+ plasma cells. Mesenteric panniculitis is also occasionally discussed in the differential diagnosis and can be even misdiagnosed as ECD is associated in scarce observations. Finally, anecdotic case reports of pseudotumoral infiltrations of the right atrium linked to RDD have been reported.

12.11 Conclusions: Emerging Concept of Inflammatory Myeloid Neoplasia

ECD is a rare, orphan disease. Having long been largely under-recognized, numerous cases have recently been diagnosed, and more than 300 new cases have been published in the last 10 years. This increase in diagnosis rates is due mostly to a greater awareness among pathologists, radiologists, and clinicians of various aspects of this previously obscure disease. Substantial progress has been made in recent years, with the demonstration of efficacy for IFNα, the description of systemic proinflammatory cytokine signatures, and the demonstration that BRAF inhibition is highly effective in severe cases of *BRAFV600E* mutation-associated ECD, in a sustained and reproducible manner. More than half the ECD patients tested have been found to carry the $BRAF^{V600E}$ mutation. Other recurrent, somatic mutations of the MAP kinase and AKT pathways have been found, including mutations of *NRAS*, *MAP2K1*, and *PIK3CA*. Further studies of this disease and improvements in our understanding of its pathogenesis should lead to the development of better targeted, more effective treatments. We also suggest that ECD should be redefined as an inflammatory myeloid neoplasia, as recently proposed for LCH.

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Malignant Diseases Mimicking Retroperitoneal and Mediastinal Fibrosing Disorders

13

Tristan Mirault

13.1 Definition and Nosology

Retroperitoneal and mediastinal fibrosing disorders refer to clinicopathologic entities characterized by a mainly sclerotic tissue that develops in the periaortic retroperitoneal space or in the mediastinum and often encases neighboring structures, such as the ureters, the inferior vena cava, or the pulmonary arteries. Retroperitoneal and mediastinal fibrosing disorders do not identify a single disease entity but rather include a wide spectrum of diseases. Among them malignancy is associated with up to 8 % of retroperitoneal fibrosis (RPF) cases [1, 2] and may mimic idiopathic RPF or mediastinal fibrosis.

Spread or diffusion of a disease is generally interpreted as a sign of malignancy. However, it is worth to note that, in RPF, up to 15 % of patients have additional fibrotic processes outside the retroperitoneum; occasionally, several organ systems are involved simultaneously [3]. The most commonly recognized associated conditions are mediastinal fibrosis/fibrosing mediastinitis, Riedel fibrosing thyroiditis, sclerosing cholangitis, and orbital pseudotumors [4]. Other associated fibrotic processes can occur in virtually every organ, from the frontal lobe of the brain to the parenchyma of the testes [1, 2]. The diagnosis of malignancy is to be considered particularly when RPF is found in other than its typical retroperitoneal location: RPF may occur in the pelvic area in females and simulate cervical carcinoma [5], may obliterate the peripancreatic fat planes and resemble pancreatic carcinoma, and may infiltrate the root of the mesentery, which may be mistaken for an intraperitoneal tumor [6].

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Multiple imaging findings have been proposed as indicators of a malignant cause such as anterior displacement of the aorta by the retroperitoneal mass, marginal lobulation of the mass, and edema, Doppler flow, contrast enhancement, and isotope uptake on functional metabolic studies. However, results of imaging studies are often suboptimal in making this distinction, and biopsy may be required to definitively exclude malignancy [7, 8].

Most benign secondary forms of RPF (e.g., RPF related to the ingestion of drugs) are radiologically indistinguishable from the idiopathic form of the disease. For the sake of simplicity, I will use in this chapter the term *benign RPF*, including idiopathic and benign secondary forms of RPF, in contrast to *malignant RPF*, designing the malignant forms.

13.2 Epidemiology

The main epidemiologic characteristics of benign RPF were investigated in a 2004 study conducted in Finland, which reported an annual incidence of 0.1 per 100,000 people and a prevalence of 1.4 per 100,000 inhabitants [9]. This study is strengthened by previous publications with an incidence of 0.5 per 100,000 [10, 11]. Most (over 70 %) cases are thought to be idiopathic [2, 12, 13], the remainder occur in association with inflammatory disorders, medications, or malignancies. Malignancy has been estimated to be associated with up to 8 % of RPF cases [1, 2].

13.3 Etiopathogenesis

The pathogenesis of the malignant RPF largely depends on the underlying cause. In most cases, fibrosis is the consequence of an exuberant desmoplastic response of retroperitoneal metastases (e.g., carcinoma of the prostate, breast, colon) or of a primary retroperitoneal tumor (e.g., Hodgkin's and non-Hodgkin lymphomas, well-differentiated liposarcoma sclerosing variant, and various types of sarcomas) [14]. In some cases, the neoplastic disorder does not metastasize to the retroperitoneum but rather (as in the case of carcinoid) causes retroperitoneal fibrosis by releasing fibrogenic compounds, such as serotonin and growth factors [13, 15].

13.3.1 Nodular Sclerosing Variant of Hodgkin's Disease

Primary mediastinal Hodgkin's disease is usually located in the middle or anterior mediastinal compartments and is the most common mediastinal lymphoma [16, 17]. The absence of Reed-Sternberg (RS) cells, lacunar cells, and associated clinical features such as young age and mediastinal adenopathy are helpful in excluding this entity. In addition, immunohistochemical stains for CD30 and CD15 can be performed on core biopsy material in an effort to identify RS cells and their variants [18].

Table 13.1 Differential diagnosis of a mediastinal mass

Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Thymoma	Lymphoma	Neurogenic tumor
Teratoma, seminoma	Pericardial cyst	Bronchogenic cyst
Lymphoma	Bronchogenic cyst	Enteric cyst
Carcinoma	Metastatic cyst	Xanthogranuloma
Parathyroid adenoma	Systemic granuloma	Diaphragmatic hernia
Lipoma	Leiomyosarcoma	Meningocele
Lymphangioma	Malignant fibrous histiocytoma	Paravertebral abscess
Intrathoracic goiter		Synovial sarcoma
Angiosarcoma		Chondrosarcoma
Sarcomatoid mesothelioma		Sarcomatoid mesothelioma
Malignant fibrous histiocytoma		Malignant fibrous histiocytoma

13.3.2 Non-Hodgkin Lymphoma

Lymphoma represents the most common malignancy of the retroperitoneum [19]. In the presence of an infiltrative, predominantly lymphocytic process, non-Hodgkin's lymphoma must also be considered. The identification of mixed inflammatory elements, particularly granulocytes, is helpful in excluding this possibility. Confirmatory immunophenotyping, by either flow cytometry or by immunohistochemical staining, revealing a mixed rather than clonal population of B and T cells, can help exclude non-Hodgkin's lymphoma [18, 20].

13.3.3 Primary Neoplasms

Malignant RPF can result from infiltration of the retroperitoneum or the mediastinum by malignant cells, which produces desmoplastic and sclerotic reactions [14, 21–23].[24]. A large variety of tumors can invade or develop into the mediastinum or the retroperitoneal space [16, 25–27]. Tables 13.1 and 13.2 summarize the numerous differential diagnoses according to the location of the tumor.

13.3.4 Metastatic Infiltrate

Metastases from primary malignancies anywhere in the body can spread to the retroperitoneum or the mediastinum; the sites of origin mentioned in the literature most frequently are the breast, stomach, colon, prostate, lung, and kidney [14, 21, 22, 28, 29].

Table 13.2 Differential diagnosis of retroperitoneal masses

Lymphoma (particularly non-Hodgkin's lymphoma)
Plasma cell neoplasms (multiple myeloma, plasmacytoma, plasma cell leukemia)
Malignant mesenchymal tumors
Malignant peripheral nerve sheath rumor
Liposarcomas
Teratomas
Liposarcomas
Leiomyosarcoma
Fibrosarcoma
Malignant hemangiopericytoma
Neuroblastoma
Ganglioneuroblastoma
Ewing sarcoma extra-osseous form
Angiosarcoma
Malignant paraganglioma
Rhabdomyosarcoma
Osteosarcoma
Chondrosarcoma
Synovialosarcoma
Soft tissue alveolar sarcoma
Malignant mesothelioma
Primitive neuroectodermal tumor
Malignant granular cells tumor
Malignant fibrous histiocytoma
Carcinoid
Metastatic carcinomas
Testicular embryonal carcinoma
Prostatic adenocarcinomas and small cell carcinomas
Uterine cervical squamous cell carcinomas
Ovarian carcinomas
Breast adenocarcinoma
Lung adenocarcinoma or squamous cell carcinoma or small cell carcinomas
Thyroid adenocarcinoma
Gastric adenocarcinoma
Extra-gastrointestinal stromal tumor
Hepatocellular carcinoma
Nodal metastases from pancreas ductal adenocarcinoma
Bile duct adenocarcinomas
Colonic adenocarcinomas
Renal transitional cell carcinoma
Adenocarcinoma or squamous cell carcinoma of unknown origin
Benign mesenchymal tumors
Lymphangiomas
Hemangiopericytoma
Ganglioneuromas
Paraganglioma
Neurofibroma
Schwannoma
Pheochromocytoma
Lipomas
Mesothelioma
Myxoma
Chondroma
Angiomyolipoma
Solitary fibrous tumor
Castelman disease
Erdheim–Chester disease
Nonneoplastic lesion
Caseous granuloma
Amyloidosis
Retroperitoneal abscess
Retroperitoneal cyst
Retroperitoneal hematoma
Idiopathic RPF

13.3.5 Carcinoids

Carcinoids are likely to induce RPF in the absence of metastases, or primary localizations in the retroperitoneum, probably through a mechanism mediated by serotonin or by the release of fibrogenic growth factors such as platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and the family of transforming growth factors alpha and beta [30]. Mesenteric fibrosis and associated

ischemia, caused by a characteristic desmoplastic reaction, is often present in association with small bowel carcinoids. These tumors are also frequently associated with buckling or tethering of the intestine caused by extensive mesenteric involvement [31, 32].

13.3.6 Desmoid Tumors

Desmoid tumors are uncommon, with an estimated incidence of 2.4–4.3 per million per year, accounting for less than 3% of soft-tissue lesions. Although there is some variability, there is a 2–3.5-fold increased incidence in women. Most cases occur between the ages of 15 and 60 years with an average age of 36.7 years. The majority of cases are sporadic with no known predisposing factors, except the genetic syndrome familial adenomatous polyposis or in association with pregnancy or trauma. Desmoid tumors are benign tumors of soft tissue, locally invasive and highly recurrent, equivalent to low-grade fibrosarcoma but without metastatic potential [33]. They represent less than 3% of soft tissue tumors. In principle, desmoid tumors can affect all parts of the body: extra-abdominal injury (neck, shoulders, upper extremities, gluteal region), abdominal (from the fascia to the abdominal/chest wall, and rarely in the mesenteric or retroperitoneal space. Smooth and firm masses are usually detected by palpation. Desmoid tumors result from the proliferation of well-differentiated myofibroblasts, and their pathogenesis is driven by the Wnt/beta-catenin pathway. The diagnosis is confirmed by biopsy of the tumor showing an abundant collagen surrounding elongated fusiform cells with small nuclei and regular and clear cytoplasm. The immunohistochemical examination reveals the expression of beta-catenin and the absence of CD34, c-kit, desmin, and S-100. In addition, the diagnosis can be confirmed by screening for mutations of *CTNNB1*, the beta-catenin gene. Indeed, approximately 85–90% of sporadic desmoid tumors are associated with somatic mutations in *CTNNB1*. Differential diagnosis is wide, ranging from fibrosarcoma, gastrointestinal stromal tumor, solitary fibrous tumor, inflammatory myofibroblastic tumor, sclerosing mesenteritis, benign RPF to hypertrophic keloid scars [34].

Finally, RPF may also arise as a sclerotic response to radiotherapy, trauma, or surgical injury. Less common causes include rare infiltrative diseases, such as the non-Langerhans histiocytosis form named Erdheim–Chester disease (Chap. 12).

13.4 Pathology

The secondary forms of RPF caused by malignancies are characterized by the presence of neoplastic cells scattered into an abundant fibrous tissue; disruption or infiltration of neighboring muscle and bone structures is commonly found. However, microscopic (rather than macroscopic) characteristics drive the diagnosis toward a malignant form of RPF. For example, clonality of the inflammatory infiltrate or the presence of Reed-Sternberg cells suggest the presence of an underlying lymphoma [35]. The presence of lipoblasts may suggest the diagnosis of well-differentiated liposarcomas with sclerosing and inflammatory features [18]. For comparison,

benign RPF manifests on gross examination, as a pale, grayish, rubbery plaque-like mass with poorly defined margins enveloping adjacent viscera, including the ureters and the inferior vena cava; benign RPF usually extends from the origin of the renal arteries to the caudal portion of the common iliac vessels [2].

13.5 Clinical Characteristics

All the forms of (retroperitoneal and/or mediastinal) fibrosing disorders have similar clinical manifestations, thus their clinical presentation is often of no help in the differential diagnosis. Malignancies of the retroperitoneum cannot be identified by any specific laboratory test. However, it is recommended to perform an age-appropriate cancer screening, when exploring a patient with a RPF, especially because constitutional symptoms, such as low-grade fever, weight loss, anorexia, and fatigue classically related to malignancy, often herald the onset of idiopathic RPF in addition to pain [36]. In cases with advanced bilateral obstructive uropathy, manifestations related to uremia may predominate: hypertension, fluid and electrolyte disturbances, anemia, nausea, and vomiting [37]. Involvement of the biliary tree by the fibrotic tissue may cause obstructive jaundice [38].

Patients with benign RPF have a median age of 50 to 55 years [39–41] whereas malignant retroperitoneal RPF may affect older people: in a study by Rosenkrantz et al., retroperitoneal lymphomas affected patients aged 72.4 ± 13.3 years [39]; in a study of ours, malignant RPF patients had a median age of 63.6 years [8].

There is a 3:1 male-to-female preponderance in benign RPF, whereas sex ratio may be more balanced in case of malignancy [8, 39, 42].

13.6 Laboratory Findings

Age-appropriate cancer screening, when exploring a patient with a RPF, may include laboratory tests, and elevated prostatic specific antigen, beta2-microglobulin, or lactate dehydrogenase, for example, would turn toward a prostatic carcinoma or a lymphoma. Autoantibodies are often detected in patients who have benign and not in malignant RPF [37, 43]. The degree of renal failure generally depends on the extent of ureteral involvement. Renal dysfunction and the systemic inflammatory response contribute to the development of a normochromic, normocytic anemia [13].

13.7 Imaging Features in Favor of Malignant Fibrosing Disorders

As detailed above, a wide spectrum of neoplastic and nonneoplastic proliferative conditions may involve the mediastinal, retroperitoneal, or perirenal space either in isolation or as part of a systemic disease. Although some tumors and pseudotumors of these spaces (e.g., angiomyolipoma, hemangioma, and lymphangioma) have

characteristic imaging findings that permit their diagnosis, biopsy and histopathologic evaluation are required in most cases to establish a definitive diagnosis. Nevertheless, familiarity with the spectrum of imaging features may facilitate accurate diagnosis [44].

13.7.1 General Anatomic Features

Fibrosing mediastinitis usually presents as an extensively calcified, infiltrative mediastinal mass. Calcification of mediastinal or hilar nodes is present in up to 86 % of the patients [45]. The typical morphologic findings of idiopathic and most benign secondary forms of RPF include a well-defined but irregular soft-tissue periaortic mass, which extends from the level of the renal arteries to the iliac vessels and often progresses through the retroperitoneum to envelop the ureters and the inferior vena cava. The mass usually lies anterior and lateral to the aorta, sparing the posterior periaortic space and not causing aortic displacement.

The extent of the mass may be distinctive, as lymphomas often are found higher in the retroperitoneum and in the posterior mediastinum, while benign RPF is mainly located distal to the kidney hilus [6]. The results of one study suggested that the presence of confluent soft tissue completely surrounding the kidney may be considered virtually pathognomonic of lymphoma [46]. The kidney is indeed one of the organs most commonly involved by extranodal spread of lymphoma, and a perirenal distribution of lymphoma in the abdomen has been described in multiple reports [46–49]. Comparing nine cases of lymphoma to 22 cases of benign RPF Rosenkrantz et al. retrieved from a retrospective analysis of their magnetic resonance imaging (MRI), that patients with lymphoma had a higher frequency of perirenal extension (66.7 % *vs.* 13.6 %) and suprarenal predominance (33.3 % *vs.* 0 %) [39].

RPF is believed to typically begin below the aortic bifurcation at the level of the sacral promontory or lower lumbar spine [8, 39, 50]. We described that the extension of the RPF from above the renal arteries to below the aortic bifurcation was only found in patients with malignant RPF (47 % vs. 0 % in benign RPF) ($P = 0.001$) [8]. Rosenkrantz found a higher proportion of cases of benign RPF (with respect to lymphoma) with pelvic extension below the aortic bifurcation ($P = 0.004$) [39]. Similarly, we reported that extension below the aortic bifurcation was present in 22 % of benign RPF vs. 6 % of malignant RPF, but without reaching significance ($P > 0.05$).

Localized lymphadenopathies adjacent to RPF occur in benign forms, but when they become confluent and tend to surround the large vessels they are likely to be malignant. Retroperitoneal lymphoma typically begins as discrete nodes, which then form confluent soft-tissue masses as the disease progresses [39, 51].

The presence of additional discrete nodes is a classical finding observed in cases of lymphoma [39, 51]. In a multivariate logistic regression analysis of MRI features of the abdomen including 9 cases of lymphoma and 22 cases of benign RPF, only the presence of additional lymph nodes ($P = 0.001$, odds ratio [OR] = 50.67) was identified as an independent predictor of a diagnosis of lymphoma [39]. However,

in benign RPF, localized lymphadenopathy adjacent to the fibroinflammatory mass has been described in 25 % of cases. It is characterized by multiple subcentimetric lymph nodes, which are probably related to the retroperitoneal reaction [52].

In terms of mass size, benign RPF, unlike lymphomas and metastases, is usually located anteriorly and laterally to the aorta, that is not displaced forward [51]. Malignant RPF has a tendency to be larger and bulkier, displaying mass effect and displacing the aorta and inferior vena cava anteriorly from the spine [53]. The occurrence of this vascular displacement is likely related to enlargement of the lymph nodes lying posterior to the aorta and inferior vena cava. In contrast, the purely fibrotic process involved in benign RPF results in tethering of these structures to the underlying vertebrae. However, the sensitivity and specificity of these features are poor and exceptions are encountered. Thus, several cases of biopsy-proven benign RPF presented anterior displacement of the aorta from the spine caused by the presence of fibrous tissue posterior to the aorta [8, 39, 54, 55]. In our study comparing characteristics of 18 benign RPF to 17 malignant RPF, we described a wider extension of RPF behind the aorta in benign RPF than in malignant RPF ($P = 0.03$) [8].

The macroscopic characteristics of the soft-tissue mass have also been suggested as possibly allowing differentiation of benign from malignant RPF. Benign RPF has a tendency to manifest as a plaque-like mass with peripheral infiltration, whereas the presence of neoplasia results in peripheral nodularity and lobulation [7, 56, 57]. Occasionally, malignant adenopathy in the retroperitoneal area can become confluent, surround the great vessels, and resemble RPF [51]. The metastatic deposits also can take the form of solitary masses or infiltrating mantles of tissue that obliterate adjacent tissue planes [58]. Of 59 patients in whom computerized tomography demonstrated large para-aortic masses engulfing the aorta, Chisholm et al. reported that non-Hodgkin's lymphoma was found in 32 (54 %): the mass appeared confluent in 22 (69 %) while some nodularity could be discerned in the 10 left (31 %). Thirty-five of the 59 patients were known to have an underlying malignancy at the time of the CT; in every case, the underlying malignancy proved to be responsible for the mass. Among 24 patients in whom the CT abnormality was found at initial diagnosis, lymphoma proved to be responsible in 11 (46 %), periaortitis in 4 (17 %), and various malignancies in 9 (38 %) [51].

The classic triad observed in benign RPF combines medial deviation of the middle third of the ureters, tapering of the lumen of one or both ureters in the lower lumbar spine or upper sacral region, and proximal unilateral or bilateral hydroureteronephrosis with delayed excretion of contrast material [2, 59]. From the analysis of 18 patients with biopsy-proven benign RPF compared to 17 patients with malignant RPF, we found that the medial ureteral attraction was significantly more frequent in benign RPF than in malignant RPF, with 83 % sensitivity, 76 % specificity, and a positive likelihood ratio of 4.5 for benign RPF [8]. The medial ureteral bowing was also described more frequently in cases of RPF than in cases of lymphoma ($p < 0.001$) [39].

Malignancies generally appear as fibrous mass dislocating the psoas muscles or destroying the bone whereas benign RPF does not include any of these features. The extent of the mass may be distinctive, as lymphomas often are found higher

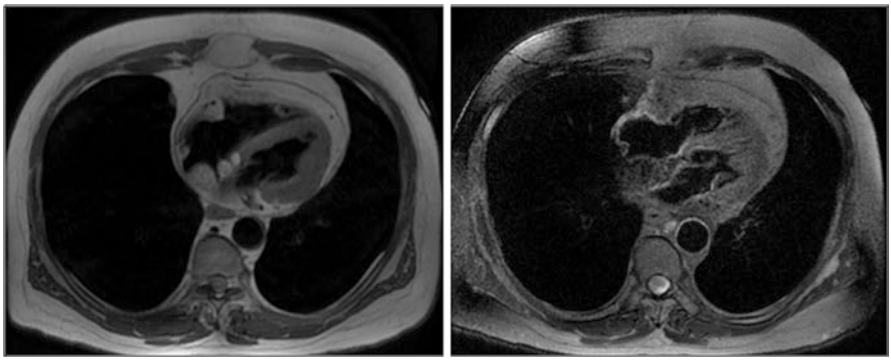

Fig. 13.1 Mediastinal lipoma. Biopsy-proven lipoma of the mediastinum and the pericardium. *Left panel*: gradient-echo T1-weighted MRI sequence; *right panel*: T2-weighted MRI sequence

in the retroperitoneum and in the posterior mediastinum, while benign RPF is mainly located distal to the kidney hilus. Furthermore, in this study of 23 patients, in cases of benign RPF, Brun et al. have not seen the fibrous mass dislocate the psoas muscles like in severe cases of lymphomas and sarcomas. Bone destruction did not appear in any patient in this study, while it often occurs in sarcomas and metastases [6].

13.7.2 Characteristic Tumor Components

The presence of fat is easily recognized owing to its low density at computerized tomography (CT) or its high signal intensity at T1-weighted MRI with loss of signal intensity on fat-suppressed images. A mass that is homogeneous and well defined and consists almost entirely of fat represents lipoma (Fig. 13.1) whereas if the mass is irregular and ill-defined, the diagnosis of liposarcoma or teratoma should be considered. Liposarcomas are the most common sarcomas of the retroperitoneum [60].

Calcium is easily detected by CT due to its very high density. Tumors that commonly contain calcium are ganglioneuroma, neuroblastoma, ganglioneuroblastoma, osteosarcoma, hemangioma, teratoma, and malignant fibrous histiocytoma [26]. When an extensively calcified, infiltrative mediastinal mass is seen at CT in a young patient from an area endemic for histoplasmosis, histoplasmosis-related fibrosing mediastinitis is the most likely diagnosis. When the mass is not calcified, however, idiopathic fibrosing mediastinitis cannot be confidently differentiated from other lesions: Hodgkin's disease, lung cancer, metastatic carcinoma, mediastinal sarcoma (Fig. 13.2), or, in rare cases, mediastinal desmoid tumors.

A limited number of tumors commonly contain myxoid stroma, which is characterized pathologically by a mucoid matrix that is rich in acid mucopolysaccharides. Myxoid stroma appears hyperintense on T2-weighted MRI sequences and shows delayed enhancement after injection of contrast medium. Neurogenic tumors commonly contain myxoid stroma (schwannomas, neurofibromas, ganglioneuromas,

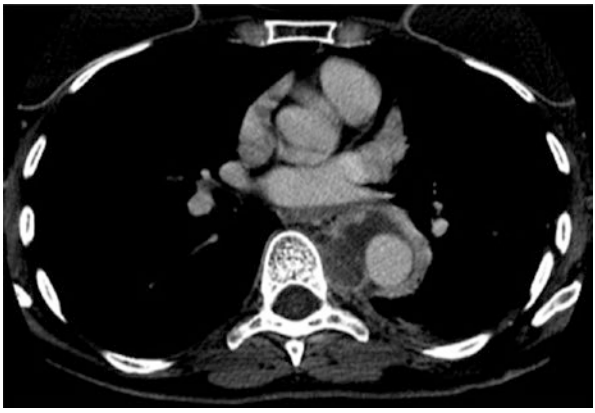

Fig. 13.2 Synovial sarcoma. Heterogeneous mass with a low attenuation core and peripheral enhancement on CT scan, surrounding the descending aorta and appended to the thoracic vertebral body. Pathology of the CT-guided biopsy sample led to the diagnosis of synovial sarcoma

ganglioneuroblastomas, malignant peripheral nerve sheath tumors) but also myxoid liposarcomas, and myxoid malignant fibrous histiocytoma [61]. Tumors that less commonly contain myxoid stroma include desmoid tumors, hemangiopericytomas, leiomyomas, leiomyosarcomas, malignant pericytomas, rhabdomyosarcomas, and malignant mesenchymomas [62].

Necrotic portions within tumors have low attenuation without contrast-enhancement at CT and are hyperintense at T2-weighted MRI. Necrosis is usually seen in tumors of high-grade malignancy such as leiomyosarcomas [25] or rhabdomyosarcoma [27].

Tumors composed of small round cells appear as homogeneous masses at T2-weighted MRI with relatively hypointense areas representing densely packed cellular components. Lymphomas are the most commonly encountered tumors composed of small round cells. They are homogeneous, with minimal contrast enhancement at CT and relatively low signal intensity at T2-weighted MRI [26].

Vascularity is an important feature of retroperitoneal tumors. Extremely hypervascular tumors include paragangliomas and hemangiopericytomas. Moderately hypervascular tumors include myxoid malignant fibrous histiocytomas, leiomyosarcomas, and many other sarcomas. Hypovascular tumors include low-grade liposarcomas, lymphomas, and many other benign tumors [25].

Some tumors grow and extend into spaces between preexisting structures and surround vessels without compressing their lumina. Lymphangiomas and ganglioneuromas are examples of such tumors [63]. Tumors of the sympathetic ganglia (paragangliomas, ganglioneuromas) tend to extend along the sympathetic chain and have an elongated shape [25]. Spread or diffusion of a disease is generally interpreted as a sign of malignancy. However, it is worth to note that in retroperitoneal and mediastinal fibrosing disorders, up to 15 % of patients have additional fibrotic processes outside the retroperitoneum; occasionally several organ systems are involved simultaneously [3].

13.7.3 Ultrasonography

Ultrasonography (US) has poor overall sensitivity in detection of RPF [13, 64]. Subtle or early changes of RPF can be missed at US because of overlying gas- or fluid-filled bowel loops [50].

The US findings of benign RPF consist of an extensive retroperitoneal, extrarenal, hypo- or anechoic, well-marginated, and with a smooth-bordered irregularly contoured mass [56, 65, 66]. It is visualized as a mass anterior to the sacral promontory or the para-aortic region [64, 66]. Abdominal US may reveal varying degrees of unilateral or bilateral hydronephrosis or hydroureter due to entrapment of the ureters. US may also be useful for detection of conditions frequently associated with benign RPF, such as primary biliary cirrhosis, bile duct dilatation due to sclerosing cholangitis, and focal or diffuse pancreatic distortion due to sclerosing pancreatitis [7, 36]. US features such as caudal extension beyond the sacral promontory and absence of lobulation suggest a benign cause; however, these signs are nonspecific and do not allow exclusion of malignancy, given that malignant RPF and most cases of malignant lymphadenopathy can have similar US features [7, 50, 65]. At US, demoid tumors appear as masses of low, medium, or high echogenicity with smooth sharply defined margins. The lateral borders may appear ill-defined or irregular [67].

13.7.4 Intravenous Urography

Intravenous urography and retrograde pyelography, once considered the techniques of choice for the evaluation of RPF, have been obviated in many instances because of improvements in cross-sectional imaging.

Intravenous urography usually demonstrates in idiopathic RPF the classic triad of medial deviation of the middle third of the ureters, tapering of the lumen of one or both ureters in the lower lumbar spine or upper sacral region, and proximal unilateral or bilateral hydroureteronephrosis with delayed excretion of contrast material [2, 59]. Nevertheless, this approach has limited sensitivity and specificity. Primary ureteral tumors, periureteral lymph nodes, or inflammatory strictures of the ureter can result in similar radiologic findings [50]. In addition, medial deviation of the ureters on intravenous urography has been identified in 20 % of subjects without any RPF, and some patients with idiopathic RPF may have their ureters entrapped in their normal anatomic position [68].

13.7.5 Computed Tomography

Fibrosing mediastinitis usually presents as an extensively calcified, infiltrative mediastinal mass. Calcification of mediastinal or hilar nodes is present in up to 86 % of patients [45]. In the absence of calcification, fibrosing mediastinitis cannot be confidently differentiated from tumoral lesions such as lymphoma, metastases, adenocarcinoma, or sarcoma. Thus, because the chest radiographic findings of

fibrosing mediastinitis are nonspecific and because MRI poorly depicts calcification, CT is considered the mainstay for diagnostic evaluation of patients suspected of fibrosing mediastinitis [45, 69, 70]. For the retroperitoneum, CT may not be as good to differentiate of benign from malignant RPF forms, even if several features have been described that may help in the suggestion of the presence of an underlying neoplasia. That is why Rubenstein wrote that "despite the attention of a number of investigators, attempts to define CT characteristics that may allow confident differentiation of benign from malignant RPF have proven futile" [65]. It is worth to note also that a considerable number of patients with RPF may have renal impairment secondary to obstructive uropathy, which precludes administration of intravenous contrast agents.

Degesys et al. observed homogeneous CT attenuation in case of benign RPF, although this finding was not specifically compared with the CT appearance of lymphoma [53]. In parallel, malignancies of the retroperitoneal space may have a variety of precontrast CT density appearance: ovarian fibroma or necrotic fibrosarcoma did not appear hyperdense as did breast cancer metastases or urothelial metastases in a retrospective series on 21 patients with surgically verified retroperitoneal fibrous lesions [65]. Desmoid tumors show attenuation similar to that of muscles [67, 71]. Thus, attenuation differences are not significant enough to help in the differential diagnosis of lymphoma or benign RFP or fibrosing mediastinitis [6, 72].

The contrast-enhancement of RPF has been variable and is generally related to the stage of disease [50, 73]. Heckmann et al. observed minimal enhancement of RPF in the late fibrotic stage [73], and Burn et al. observed a decrease in enhancement after therapy in three patients who were imaged before and after treatment [74]. To synthetize, active inflammation, which is predominant in early benign RPF, may be recognized as early contrast-enhancement. Conversely, the late inactive stage is relatively acellular and hypovascular, with predominant fibrosis; thus, it usually demonstrates little or absent contrast-enhancement [75]. Metastatic lesions may show higher enhancement than benign RPF, depending on the vascularity of the underlying primary neoplasm [53, 76]. Depending on the varying amount of collagen deposition, desmoid tumors may show moderate or avid enhancement after contrast enhancement [34, 67].

13.7.6 Magnetic Resonance Imaging

The manifestation of malignant RPF on MRI may be variable and often difficult to differentiate from benign causes of this entity (Fig. 13.3) [77]. Fibrosing mediastinitis typically manifests on T1-weighted MRI as a heterogeneous, infiltrative mass of intermediate signal intensity [78]. Benign RPF typically has low signal intensity on T1-weighted images [75, 76] even lower than in lymphoma, at least at low field strengths [79].

MRI has been proved to be superior to other imaging modalities, when characterizing desmoid tumors, showing tumor infiltration into muscle and distinguishing

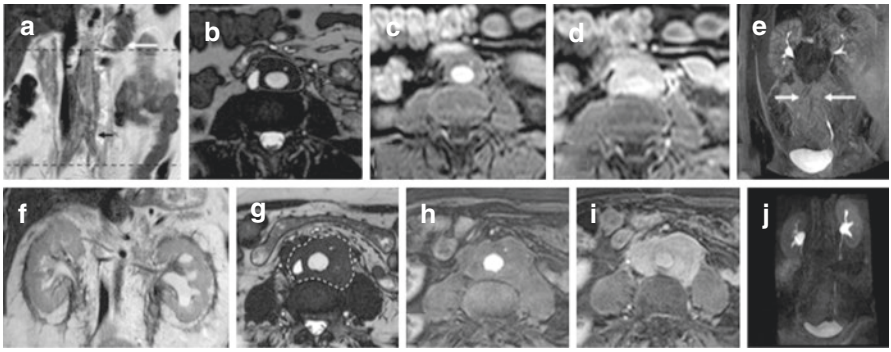

Fig. 13.3 (*upper row*): Characteristics of benign RPF. Abdominal MRI depicts extension of periaortic disease (image **a**, *dotted lines*; image **b**, *dotted white contour*) between the renal arteries (*white arrow*) and the aortic bifurcation (*black arrow*) on T2-w spin-echo coronal (**a**) and axial T2-w BFFE (**b**) images. The periaortic disease prevails at the anterior part of the aorta on axial images (**b–d**); intense but progressive enhancement is seen on gradient-echo T1-w fat-saturated dynamic contrast-enhanced series (**c** and **d** at early and late phases of injection, respectively), together with medial ureteral attraction (image **e**; *white arrows*) on late urogram. (*lower row*): *Characteristics of malignant RPF in two different patients*. (**f**) in a case of Erdheim–Chester Disease (ECD), perirenal fibrosis is seen on T2-w coronal view. (**g–j**) biopsy proven non-Hodgkin lymphoma with extensive fibrosis from below the renal arteries to the iliac bifurcation, involving the retroperitoneal space in front and behind aorta (***g****; white dotted contour*) on axial T2-w (**g**), T1-w dynamic contrast enhanced at early (**h**) and late (**i**) phases of injection, without attraction of ureters on the MR-urogram (**j**), and, in this case, no upper tract enlargement. Larger extension behind aorta is also visible

boundaries between vital structures and fascial planes. T1-weighted images reveal hypointense or isointense lesions [34].

Fibrosing mediastinitis appearance on T2-weighted MRI is also variable; regions of both increased and markedly decreased signal intensity are frequently seen in the same lesion [80, 81]. Although careful MRI–histopathologic correlation has not been performed, areas of decreased signal intensity are thought to indicate the presence of calcification or fibrous tissue, and areas of increased signal intensity may indicate more active inflammation. Extensive regions of decreased signal intensity within the lesion, when present, help differentiate fibrosing mediastinitis from other infiltrative lesions of the mediastinum, such as metastatic carcinoma and lymphoma that typically have increased signal intensity on T2-weighted images. Heterogeneous enhancement of the mass may be seen after administration of a gadolinium-based contrast medium.

Arrive et al., in a retrospective study, compared nine malignant vs. eight nonmalignant RPF (four idiopathic, two periaortitis, and two postsurgical). T1-weighted imaging did not differ from the two groups. T2-weighted imaging significantly differed in case of malignant RPF with a higher contrast of RPF compared to muscle. Signal intensity, the presence or absence of soft-tissue edema, and the degree of contrast-enhancement may be quite nonspecific, rendering tissue characterization by MRI inaccurate in many cases. Moreover, the morphologic findings at MRI were

similar for both malignant and nonmalignant RPF. Location and relation to retroperitoneal structures were the same for both entities. However, the lesion margin was always sharply delineated in nonmalignant RPF, while it was ill-defined in five of the nine patients with malignant RPF. Hydronephrosis was shown in both conditions [77].

It has also been recognized that benign RPF also can have a high signal intensity on T2-weighted images [76, 82]. Thus, a high signal on T2-weighted images cannot be used to differentiate malignant from benign RPF, but rather reflects only the presence of inflammatory edema in the plaque, because of the high free water content and hypercellularity in either benign or malignant RPF [82]. Similarly, Bakir et al. did not find significant signal intensity difference on T2-weighted images between benign and malignant RPF [42]. There was no significant difference of signal intensity values on T2-weighted images between chronic RPF and active RFP or malignant RPF [42]. Signal intensity values on T2-weighted images were not useful for differentiating malignancy vs. idiopathic RPF either active or chronic [42]

Better than the T2-weighted hyperintensity, T2 heterogeneity may be helpful in differentiating malignant forms. Rosenkrantz et al. found that MRI features that differed in 9 cases of lymphoma as compared to 22 cases of benign RPF were T2-heterogeneity (44.4 % vs. 9.1 %); however, no significant difference for the presence of hyperintensity on T2-weighted imaging (55.6 % vs. 31.8 %) was found [39].

Amis et al. suggested that a plaque showing low signal on both T1- and T2-weighted images was most likely benign RPF, because it would be unusual for the malignant variety to mature so completely [50]. But Semelka et al. also observed hypo- to isointensity on T2-weighted imaging in cases of retroperitoneal lymphoma with perirenal extension [83]. Although Negendank et al. suggested that lymphoma is often hyperintense to muscle on T2-weighted imaging, these authors observed a trend toward greater brightness on T2-weighted imaging for Hodgkin lymphoma than for non-Hodgkin lymphoma and for cases of lymphoma in the mediastinum [84]. In comparison, benign RPF on T2-weighted imaging has been variably described as hypo-, iso-, or hyperintense in prior case reports or small case series [76, 77, 85, 86].

This variable signal intensity on T2-weighted imaging relates to variability in stage, maturity, or histologic composition of benign RPF [50, 53, 54, 76, 77, 82, 85, 86]; decreased signal intensity on T2-weighted imaging is characteristic of the dense fibrocollagenous stroma of mature RPF [1, 50, 77]. Desmoid tumors show mixed hyperintense lesions on T2-weighted images [34].

In a retrospective study, diffusion-weighted imaging (DWI) features and signal intensity values at T2-weighted MRI were evaluated for the differential diagnosis of benign RPF and plaque-like retroperitoneal malignant neoplasms. Lesions in the malignant group and active RPF group had similar enhancement patterns, while those in the chronic RPF group demonstrated a higher apparent diffusion coefficient but less enhancement [42]. Rosenkrantz et al. found a trend toward greater frequency of visual hypertensity on high-b-value DWI in cases of lymphoma ($P = 0.077$) [39].

A significantly lower apparent diffusion coefficient (ADC) value in cases of lymphoma in comparison with idiopathic RPF or other malignant mesenchymal lesions was found in retrospective series [24, 39, 42] and may be attributed to the tumor cellularity of lymphomas, higher than in benign RPF, whose inflammatory cellular component declines after the early phase [50, 53, 54]. However, other authors did not find this difference between lymphoma and idiopathic RPF [87] or between malignancy and active idiopathic RPF [42].

13.7.7 Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)

FDG-PET is a functional imaging modality allowing whole-body examination. It has been well established in oncology and infectious diseases and is now used for the assessment of the full extent and distribution of vascular and perivascular inflammatory involvement in idiopathic RPF [88–90]. It can also reveal remote diseases such as multifocal fibrosclerosis or may demonstrate infectious, neoplastic, or other autoimmune processes with which RPF may be associated [90–93]. FDG-PET may also be useful in identifying more appropriate sites for biopsy [94]. The sensitivity of FDG-PET is very high, which allows detection and quantification of the metabolic activity of retroperitoneal lesions, but irrespective of a benign or malignant underlying cause (Fig. 13.4). Moreover, fibrosing mediastinitis may either show markedly increased uptake at FDG-PET in case of active disease [95] or negative FDG uptake in a stable stage [96, 97]. Thus, because of its low specificity, FDG-PET is not discriminant for diagnosis between idiopathic or other secondary benign forms of RFP and malignant forms of RPF [7, 98–101].

13.8 Diagnostic Approach

Malignancies of the mediastinum or the retroperitoneum cannot be identified by any specific laboratory test but, when approaching a patient with a suspected RPF, it is mandatory to perform an age-appropriate cancer screening.

As detailed above, current imaging techniques are insufficiently specific to allow confident differentiation between idiopathic RPF and RPF due to malignancy, infection, or other causes. This is why tissue biopsy is often required, when imaging studies do not show typical findings of benign RPF. Moreover, biopsy may also be recommended in patients refractory to conventional steroid therapy [2, 50, 92, 102]. When a mediastinal mass is not calcified, fibrosing mediastinitis cannot be confidently differentiated from other lesions: Hodgkin disease, lung cancer, metastatic carcinoma, mediastinal sarcoma, or, in rare cases, mediastinal desmoid tumors. Biopsy and culture of affected tissues is then required [69, 103, 104]. It is essential that the lesion be sampled extensively to confidently exclude an underlying neoplasm as the tumoral growth may occur in association with a fibrotic process [105]. For these reasons, surgical sampling performed during mediastinoscopy,

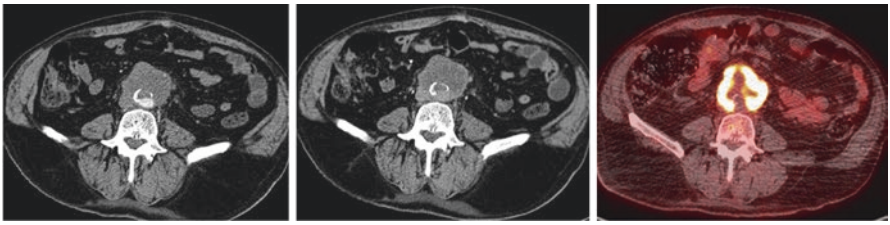

Fig. 13.4 Large B cell non-Hodgkin lymphoma. Contrast-enhanced CT shows a heterogeneous mass surrounding the abdominal aorta with a low attenuation core (*left panel*), poorly enhanced at a later passage (*middle panel*), with a hyperintense signal on 18F-FDG PET (*right panel*). Suspicion of infection led to a replacement of the abdominal aorta by an allogenic tissue graft. Pathology of the removed aorta provided the diagnosis of large B cell non-Hodgkin lymphoma

thoracoscopy, or open thoracotomy may be preferred to transthoracic fine-needle aspiration biopsy [106]. The role of percutaneous large-bore core needle biopsy has not been evaluated in this context [45].

Similarly, multiple biopsy techniques have been used in sampling RPF, including open, laparoscopic or transcaval retroperitoneal biopsy [107], and fine-needle aspiration [18]. In malignant RPF, multiple deep surgical biopsies are also often needed as the metastatic cells are usually diffusely dispersed in the fibrotic plaque [50, 108]. CT-guided fine-needle aspiration or core biopsies, because of the small amount of tissue sampled, are considered far less effective [58]. A diagnostic and management dilemma may arise because even when negative needle biopsies are obtained, a diagnosis of benign disease may erroneously be made because of the paucity of malignant cells in their surrounding desmoplastic reaction [108]. However, Koep and Zuidema found that if no malignancy was present on biopsy material, the patient could be given a fairly optimistic prognosis with a cumulative mortality rate of 9 %. Those authors suggested that when suboptimal improvement occurs, surgical reexploration may be indicated and further search for malignancy should be undertaken [2].

13.9 Treatment and Prognosis

The prognosis for patients with benign RPF is generally considered to be good, depending on the identification and nature of the underlying cause. On the contrary, malignant RFP carries a poor prognosis, with a mean survival of as little as 3–6 months [2, 38, 109]. Patients may have organ dysfunction and poor performance status, being unsuitable for palliative chemotherapy. There is no evidence in the literature that chemotherapy may help reducing malignant RPF. The decision to offer chemotherapy must be done from case to case, taking into consideration performance status and organ dysfunction. Similarly, there is no evidence of effectiveness of corticosteroid therapy in malignant RPF, whereas this is the first choice in idiopathic RPF. The only exception is RPF related to carcinoid tumors, which can achieve great response to corticosteroids [91]. Sarcomas of the mediastinum are

also of poor prognosis with a 5-year survival rate of approximately 50 %. Adenopathy or metastases are poor prognostic indicators, with a 5-year survival rate of less than 20 % [27]. Lymphoma are the mediastinal tumors with a better prognosis with a 5-year overall survival rate over 90 % [110]. Painkillers have also a place in the prescription, because pain management must be of great importance.

Despite the lack of effective systemic options for the management of malignant RPF, these patients might draw benefit from palliative surgical approaches in order to relieve obstructive complications. Drainage of the upper urinary tract may be required as a temporary measure to facilitate improvement in renal function. Percutaneous nephrostomy and double-J ureteral stenting are the current preferred approach, providing short-term relief of symptoms until the effects of appropriate management are seen.

Surgical intervention may be required to relieve vessels, urinary tract, mediastinum of the compression by the malignant tissue. However, this approach is not without hazard and ureteral devascularization, tears, and strictures with ureteral leakage or urinary fistula formation, vessels tears may occur. Several authors have reported successful laparoscopic approach offering the potential for less invasive surgical treatment options [111, 112].

Conclusions

In summary, mediastinum and retroperitoneal fibrosing disorders secondary to malignant disease are rare conditions associated with a dismal prognosis except maybe for lymphomas. Organ dysfunction and poor performance status usually preclude the use of systemic chemotherapy. RPF is an uncommon entity for which an underlying cause is found in less than 30 % of cases, with 8 % of causes relating to malignancy. CT and MRI offer superb delineation of the extent and complications of this disease process, though they fare poorly in the differentiation of benign from malignant causes. Sonography and scintigraphy are similarly unhelpful. Thus, biopsy and culture of affected tissues is often required, either by CT-guided biopsy or through surgical sampling. It is essential that the lesion be sampled extensively to confidently exclude an underlying neoplasm as the tumoral growth may occur in association with a fibrotic process.

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Drug-Induced Fibrosing Lesions

14

Nicolò Pipitone

14.1 Introduction

A number of medications have been linked to an increased risk of developing fibrosing disorders affecting a single or multiple organs. Many reports are based on single cases or limited case series, but over time case-controlled studies have been conducted, which have allowed a more reliable risk estimate. In turn, the recognition that some drugs were able to induce fibrosing reactions prompted investigations into the possible pathogenic mechanisms involved.

14.2 History

In the mid-1960s, Graham noted the development of pleuropulmonary fibrosis in a patient who had been taking the ergot alkaloid methysergide for 2 years for migraine. He subsequently collected and published similar cases which he had seen or had been brought to his attention [1]. Graham proposed several theories to explain the fibrosing effect of methysergide, including serotoninergic effect, prolonged vasoconstriction, hypersensitivity mechanism, local inflammatory mast cell degradation, and impairment of lymphatic drainage. Although at that time no theory was favored over another, the similarity between methysergide-induced and carcinoid-related fibrosis appeared to support a serotoninergic effect of methysergide as the cause of organ fibrosis.

Ergotamine-related heart valve disease was first reported in 1974 by Seiler et al. [2], while in 1997 from the Mayo Clinic came the first report of heart valvular disease associated with fenfluramine use [3].

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14.3 Pathogenesis

Activation of the serotonin 5-HT5B receptor is thought to be the main mechanism involved in drug-induced fibrosis of the heart and other organs [4–6]. 5-HT5B receptors are expressed in multiple tissues including heart valves and mediate proliferation of fibroblasts [7]. Studies performed in rats have demonstrated that longstanding treatment with serotonine causes valvular lesions similar to those observed in humans exposed to serotoninergic drugs. Echocardiographic changes are similar to those seen in human carcinoid heart disease, while histopathological examination reveals shortened and thickened aortic cusps characterized by a collection of myofibroblasts within an extracellular matrix of collagen [8]. Bioprostheses also appear to be susceptible to fibrotic changes following exposure to serotoninergic drugs like native cardiac valves [9]. Norfenfluramine, the metabolite of fenfluramine, and methylergonovine, the active metabolite of methysergide and ergotamine, have a high affinity as well as agonist or partial agonist effect on the 5-HT2B receptor [10], suggesting that their profibrotic action is mediated by this receptor. In contrast, the affinity for the 5-HT2B receptor of pramipexole and ropinirole is about hundred times weaker [11], which may explain why these latter drugs are not typically involved in organ fibrosis [12]. Finally, blockade of the 5-HT2B receptor with its antagonist cyproheptadine was able to prevent the development of drug-induced valve fibrosis in a model of Wistar rats exposed to serotonin or pergolide [13], further reinforcing the central role of the 5-HT2B receptor in inducing fibrosis.

14.4 Drugs Associated with Organ Fibrosing Lesions

14.4.1 Anorectic Agents Metabolized into Norfenfluramine

Numerous, controlled [14–18] (Table 14.1) and uncontrolled [19, 20], studies have found an association between fenfluramine (as well as dexfenfluramine) and fibrotic valvular heart disease. In 1998, Khan et al. [14] determined the prevalence of cardiac valvular insufficiency by transthoracic echocardiography in 233 patients treated with dexfenfluramine, fenfluramine, phentermine alone or in combination and in an equal number of matched controls. The presence of cardiac valve abnormalities, defined by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention as at least mild aortic-valve or moderate mitral-valve insufficiency, was independently assessed by at least two cardiologists. Multivariate logistic regression analysis was used to identify factors associated with cardiac valve abnormalities. The odds ratio (OR) for such cardiac valve abnormalities was 12.7 (95% confidence interval [CI], 2.9–56.4) with the use of dexfenfluramine alone, 24.5 (5.9–102.2) with the use of dexfenfluramine and phentermine, and 26.3 (7.9–87.1) with the use of fenfluramine and phentermine.

An increased risk of heart valve abnormalities at echocardiography was also found by Weissman et al. in obese patients taking dexfenfluramine compared to unexposed controls in the setting of a randomized controlled study [15]. In this

Table 14.1 Main controlled studies on fibrotic heart valvulopathy induced by appetite suppressants

Reference	Subjects	Treatment duration	Main findings
[14]	257 patients 239 controls (unexposed)	4.9 months (dexfenfluramine) 26.5 months (dexfenfluramine and phentermine)	Odds ratio for cardiac valve abnormalities 12.7 for dexfenfluramine, 24.5 for dexfenfluramine/phentermine, and 26.3 for fenfluramine/phentermine
[15]	718 patients 354 controls (placebo)	78 months	Mitral regurgitation found in 5.4 % of dexfenfluramine patients and 3.6 % of controls; aortic regurgitation found in 6.9 % of dexfenfluramine patients and 4.5 % of controls
[16]	412 patients 172 controls (unexposed)	6.9 months	Odds ratio for aortic/mitral regurgitation 3.82
[17]	1163 patients 672 controls (untreated for 5 years)	11.2 months	Odds ratio for cardiac valve abnormalities 6.2 for treatment duration greater than 720 days
[18]	711 patients 431 controls (untreated)	6.1 months (dexfenfluramine) 12 months (phentermine and fenfluramine)	Aortic regurgitation in 7.8 % of dexfenfluramine and 4.4 % of phentermine/fenfluramine patients versus 1.9 % of controls

study, the prevalence of any degree of aortic regurgitation was significantly higher in exposed versus unexposed individuals (17.0 % versus 12 %) and similar results were obtained when mitral regurgitation of any degree was considered (61 % versus 54 %). Of note, the degree of aortic or mitral regurgitation was often minimal to mild, perhaps owing to the limited duration of treatment (mean 72 days) with dexfenfluramine.

Shively et al. [16] evaluated by echocardiography (interpreted by at least three independent assessors) the prevalence and determinants of valvulopathy in 172 patients treated with dexfenfluramine and 172 matched controls. FDA grade regurgitation (at least mild aortic regurgitation or at least moderate mitral regurgitation) was significantly more frequent in dexfenfluramine patients (7.6 % versus 2.1 %), with an OR of 3.82. Older age, higher diastolic blood pressure, and shorter time from drug discontinuation to echocardiography appeared to be related to heart valve regurgitation. These findings suggest that dexfenfluramine-induced heart valve changes can be aggravated by older age and higher blood pressure, and that cardiac valvulopathy can at least partially regress following the withdrawal of the offending drug.

Jollis et al. examined 1163 patients who had taken fenfluramine-phentermine and 672 controls who had not taken the drug combination within 5 years. Aortic regurgitation of mild or more severe degree was found to be significantly more frequent in treated patients (8.8 %) than in controls (3.6 %). Moderate or greater mitral regurgitation was found in 2.6 % of treated patients and 1.5 % of controls, but the

difference did not reach significance. Duration of treatment was an important determinant of heart valvulopathy, since the adjusted OR compared with controls of aortic regurgitation significantly increased according to duration of treatment (181–360 days, 2.4; 361–720 days, 4.6; >720 days, 6.2).

A multicentric study aimed to investigate the prevalence of valvular abnormalities, as assessed by clinical cardiovascular parameters and echocardiography, in patients treated for obesity with dexfenfluramine or the combination phentermine/fenfluramine [18]. Four hundred and seventy-nine and 455 individuals had taken dexfenfluramine and the combination phentermine/fenfluramine, respectively, continuously for 30 days or more over the previous 14 months, while 539 untreated matched subjects were chosen as controls. In this study, cardiovascular signs and symptoms were similar among patients and controls. Aortic regurgitation was more prevalent in subjects treated with appetite suppressants (8.9 % in the dexfenfluramine group and 13.7 % in the phentermine/fenfluramine group versus 4.1 % in the untreated group), whereas no differences in prevalence were observed for mitral regurgitation, thickening or decreased mobility of any valve leaflet, pulmonary artery systolic pressure, left ventricular ejection fraction, or serious cardiac events.

Taken together, the findings derived from controlled studies suggest that dexfenfluramine and fenfluramine may induce cardiac valve regurgitation that is associated with longer disease duration and may regress, at least in part, following cessation of exposure to the medications. In line with these data, a meta-analysis of observational studies has shown that 1 of 8 patients treated for longer than 3 months with fenfluramine develop drug-induced cardiac valve disease [21]. Both fenfluramine and dexfenfluramine have been taken off the drug market in the USA following the ascertainment of their link with fibrosing heart valve disease.

14.4.2 Ergot Alkaloids

14.4.2.1 Ergotamine

Ergotamine intake has been linked to fibrosing changes of the pleura [22, 23], lung [23], pericardium [22], peritoneum and retroperitoneum [24–27], and heart valves [28] in uncontrolled observations.

14.4.2.2 Methysergide

The ergot alkaloid methysergide has been linked to a number of fibrosing disorders. A review of 481 cases of retroperitoneal fibrosis found that 12 % of them were attributable to methysergide intake [29]. Methysergide has also been linked to myocardial [30] and endocardial [30–32] fibrosis, valvular heart disease [30, 32–34], and pleuropulmonary fibrosis [1, 35–37].

14.4.2.3 Ergot-Derived Dopamine Agonists

An association with heart fibrosing disorders has been found with ergot-like dopamine agonists, such as bromocriptine, cabergoline, and pergolide [2, 38–45], but not with nonergot dopamine agonists (apomorphine, pramipexole, ropirinole, rotigotine) [12]. Lisuride, an ergolinic dopamine receptor agonist with 5-HT2B receptor

Table 14.2 Main controlled studies on fibrotic heart valvulopathy induced by ergot dopamine agonists

Reference	Subjects	Treatment duration	Main findings
[44]	36 patients 36 controls (treated with nonergot dopamine agonists)	Not stated	Patients had more frequent aortic, mitral, and tricuspidal valvulopathy
[40]	49 patients 38 controls (untreated) and 36 taking nonergot dopamine agonists	>9 months	Aortic regurgitation found in 12 % versus 0 % Mitral regurgitation found in 14 % versus 3 %
[41]	58 patients 20 controls (untreated)	39 months (bromocriptine) and 54 months (pergolide)	Aortic regurgitation found in 4.5 % (bromocriptine) and 11 % (pergolide) versus 0 %
[42]	75 patients 49 controls (untreated), 33 treated with ropirinole or pramipexole	30 months (cabergoline) and 61 months (pergolide)	Valvular regurgitation found in 47 % (cabergoline) and 31 % (pergolide) versus 10 % (untreated) and 13 % (nonergot dopamine agonists)
[38]	78 patients 18 controls (untreated)	18.2 months	Any restrictive heart valve disease found in 33 % of patients versus none of the controls
[43]	113 patients 90 controls (untreated) and 42 treated with nonergot dopamine agonists	24 months (cabergoline) and 63 months (pergolide)	Valvular regurgitation found in 23 % (pergolide) and 29 % (cabergoline) versus 0 % of nonergot dopamine agonists treated and 5.6 % of untreated controls
[39]	*82 patients* *85 controls (untreated) as well as 16 pramipexole treated and 27 past-treated*	*35 months (cabergoline) and 52 months (pergolide)*	Valvulopathy found in 69 % of cabergoline group and 29 % of the pergolide group versus 18 % of the controls

antagonist properties, has not been mapped to heart valve disease [46]. Likewise, a meta-analysis found no increased risk of fibrosis with nicergoline, a semisynthetic ergot derivative [47].

Numerous controlled studies have investigated the association of ergot-like dopamine agonists with heart fibrosing disorders (Table 14.2).

Van Camp et al. investigated by echocardiography 78 patients with Parkinson's disease treated with pergolide and 18 controls that had never been treated with an ergot-derived dopamine agonist [38]. Restrictive valvular heart disease of any type was found in 26 (33 %) patients in the pergolide group, but in none of the controls. For the mitral valve, tenting distance and tenting areas were measured as indicators for apical displacement of the leaflet coaptation and leaflet stiffness, similarly to what is done for mitral regurgitation in ischemic heart disease. A significant correlation was noted between cumulative doses of pergolide and tenting areas of the mitral valves. Mean systolic pulmonary artery pressure was significantly higher in

pergolide-exposed versus unexposed subjects. The reversibility of pergolide-induced cardiac lesions could not be assessed in the setting of this study.

Peralta and coworkers investigated by transthoracic echocardiography the prevalence of heart valve regurgitation in 75 patients with Parkinson's disease treated with pergolide ($n=29$), cabergoline ($n=13$), pramipexole or ropinirole ($n=33$), and 49 age-matched unexposed controls [42]. Valvular regurgitation was graded from 1 to 3 based on parameters of regurgitation volume, regurgitation fraction, and effective regurgitation orifice following the recommendations issued by the American Society of Echocardiography. The exposure to pergolide and cabergoline was associated with higher frequencies of valvular regurgitation grades 2 and 3 (31 % and 47 %) compared with age-matched controls (13 %), while there was no increase of valvular regurgitation grades 2 and 3 in patients treated with nonergot compounds (10 %). Evidence for restrictive valvulopathy was rare, being found in one patient treated with pergolide and cabergoline each.

Junghanns et al. evaluated by transthoracic echocardiography the effects of four dopamine agonists (pergolide, cabergoline, ropinirole, and pramipexole) on the morphology and function of heart valves in patients with Parkinson's disease [40]. Fibrotic valvular heart disease was diagnosed in 22 % of ergot dopamine agonists (pergolide and cabergoline) patients versus 3 % of nonergot dopamine agonists (ropinirole and pramipexole) patients and none of controls. The authors found no correlations of echocardiographic findings with duration or cumulative dose of treatment, age, or vascular risk factors, but the small number of patients enrolled per group significantly hampered the statistical analysis.

Yamamoto et al. obtained transthoracic echocardiography in 210 consecutive patients with Parkinson's disease with the aim of determining the frequency of cardiac valvulopathy in patients treated with or without dopamine agonists [39]. The frequency of valvulopathy was significantly higher in the cabergoline-treated group (69 %) than in the dopamine agonist nontreated controls (18 %), yielding an adjusted OR of 13. The cumulative dose and treatment duration of cabergoline in patients with valvulopathy were significantly higher than in those without valvulopathy. Of interest, the frequency of valvulopathy in past-treated patients was similar to that ascertained in controls, suggesting that drug withdrawal may reverse its noxious cardiac effects.

Kim and coauthors studied by echocardiography 58 patients with Parkinson's disease treated with ergot derivatives (22 bromocriptine and 36 pergolide) and compared them with 20 age-matched controls [41]. Aortic, mitral, and tricuspid valvular thicknesses, as well as tenting areas and tenting distance of the mitral valve, were measured. The authors found no significant increase in the frequency of valvulopathy in patients taking bromocriptine or pergolide. However, in this study the drug dosage was lower than that used in other reported cases, suggesting a dose-harm relationship between exposure to dopamine agonists and cardiac valve disease.

In an Italian study, echocardiography was performed in 155 patients taking dopamine agonists for Parkinson's disease (pergolide, 64 patients; cabergoline, 49; and nonergot-derived dopamine agonists, 42) and 90 control subjects [43]. Valve regurgitation and mitral-valve tenting area were assessed. Moderate to severe regurgitation in any valve was found with significantly greater frequency in patients taking pergolide (23.4 %) or cabergoline (28.6 %) but not in patients taking nonergot-derived dopamine

agonists (0 %), as compared with control subjects (5.6 %). The mean mitral tenting area was significantly larger in ergot-treated patients and displayed a linear relationship with the severity of mitral regurgitation. Mean cumulative dose of pergolide or cabergoline was higher in patients with moderate to severe cardiac valve regurgitation than in patients with less severe regurgitation.

Taken together, the findings derived from controlled studies indicate that ergot dopamine agonists carry a significantly higher risk than nonergot dopamine agonists for cardiac valve disease. Overall, a dose-harm relationship was demonstrated in studies of sufficiently large size.

There is more limited data on fibrotic changes other than cardiac valvulopathy induced by ergot dopamine agonists. In a review of the adverse events attributable to dopamine agonists identified through the United States Adverse Event Reporting System database between 2004 and September 30, 2007, 4 cases of endocardial fibrosis were ascribed to the use of ergot-derived dopamine agonists [12]. Similarly, 25 of 27 (93 %) cases of pericardial fibrosis/pericarditis, 72 of 81 (89 %) cases of pleural fibrosis/pleuritis, and 16 of 16 (100 %) cases of retroperitoneal fibrosis were mapped to the use of ergot dopamine agonists, with the remaining cases being associated – most likely by chance – with nonergot dopamine agonists.

14.5 Clinical Findings

Clinical symptoms and signs related to cardiac valve disease are similar to those encountered in other valvulopathies. Shortness of breath on exertion and sometimes at rest may be reported, while cardiac murmurs may be heard on auscultation [17].

In patients with serosal (pleura and/or pericardium) involvement, chest pain and shortness of breath have been described as initial manifestations, while lung auscultation can reveal dullness, mainly at the lung bases [22, 48].

Drug-induced retroperitoneal fibrosis typically presents with abdominal and/or flank pain and tenderness, but lower limb edema [49–52] has also been reported. Other manifestations potentially associated with retroperitoneal fibrosis include hydronephrosis secondary to obstruction of the ureters by the retroperitoneal mass, claudication of the lower limbs due to encasement of the abdominal arteries, as well as varicocele, hydrocele, and scrotal swelling, all of which are also attributable to ab extrinseco compression of vascular segments, while some patients may complain of abdominal bloating or nausea [53].

14.6 Investigations

Echocardiography is the procedure of choice to assess and grade severity of drug-induced heart valve disease [54], although progression of fibrotic changes may be difficult to evaluate if echocardiography has not been performed prior to onset of treatment with the offending drug. Typical echocardiographic findings are valvular regurgitation of various degrees as well as thickening of valve leaflets and subvalvular structures, both of which are attributable to fibrosis [54]. Valve thickening is

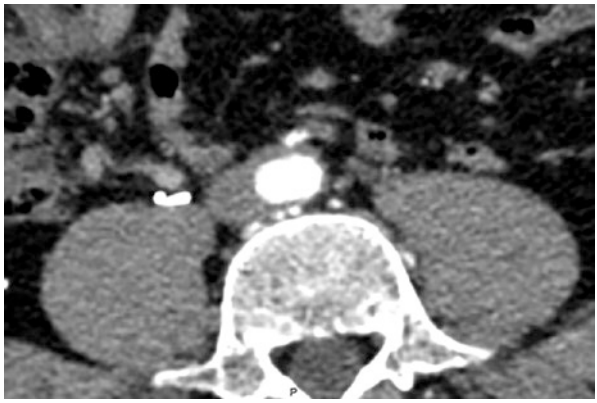

Fig. 14.1 Retroperitoneal fibrosis induced by pergolide treatment. Note the periaortic mass

usually more pronounced in affected mitral than in aortic valves [55]. In contrast, marked valvular stenosis is not a recognized complication [55]. Calcifications and marked commissural fusion, which are found in acute rheumatic fever, are also characteristically absent [55]. Tricuspid valve fibrosis is uncommon, but when present, is broadly similar to that observed in the other cardiac valves [55]. Tenting distance and tenting areas of the mitral valve are sometimes measured as indicators for apical displacement of the leaflet coaptation and leaflet stiffness [38]. Withdrawal of the medications implicated in inducing fibrosis usually results in lack of further progression of heart valve lesions [18].

Macroscopic pathological changes of affected valves include diffuse and irregular cusp thickening and retraction, while the subvalvular chordae appear shortened and fused [56]. Histopathology reveals proliferation of myofibroblasts and smooth muscle cells in the absence of inflammatory changes within a myxoid stroma [10, 57].

Endocardial fibrosis, pericardial fibrosis, and pericardial effusion are easily amenable to be investigated by means of echocardiography [22, 58, 59]. Pleural involvement can be demonstrated by plain X-rays or, more accurately, by computerized tomography (CT) of the chest [22, 37]; typical changes include pleural effusion and thickening, while histology reveals fibrotic changes in the absence of signs of inflammation [22]. Fibrosis of lung parenchyma is distinctively uncommon but reported [23], and can be also visualized by chest X-rays or better CT.

CT lends also itself well to demonstrate drug-induced fibrotic lesions in the retroperitoneum, with magnetic resonance imaging (MRI) being a reasonable alternative technique [51, 53, 60], while ultrasonography is less sensitive. ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET), which is currently coregistered with CT (PET/CT), usually shows high FDG uptake in idiopathic (inflammatory) retroperitoneal fibrosis [61], whereas in a case of pergolide-induced retroperitoneal fibrosis FDG uptake was not augmented [62], in keeping with the notion that inflammation (detected by PET) is not a feature of drug-induced retroperitoneal fibrosis (Figs. 14.1 and 14.2).

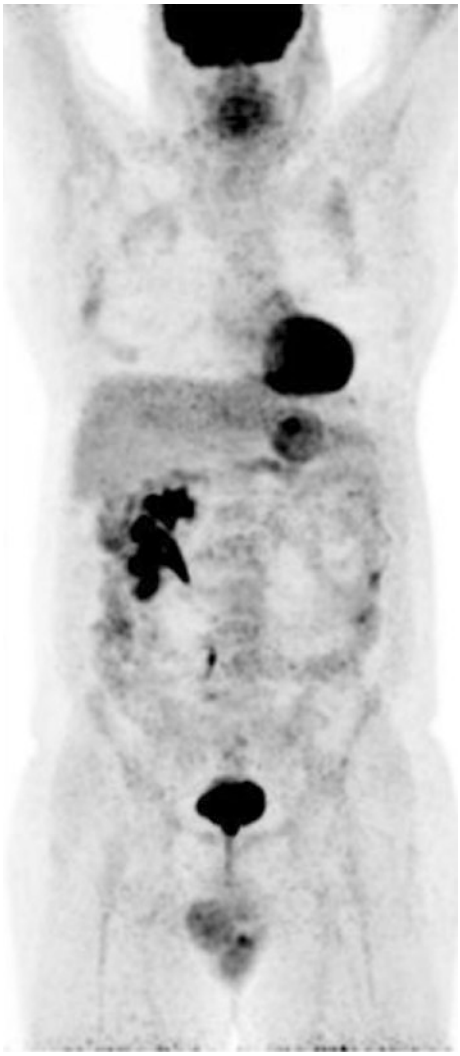

Fig. 14.2 PET/CT of the same patient depicted in Fig. 14.1. The scan is unremarkable, in particular there is no uptake in the periaortic area

14.7 Risk Factors for Fibrosing Complications

Both dosage [7, 39] and treatment duration [15, 17, 21, 63] appear to be risk factors for the development of drug-induced fibrosing disorders. Comorbidities such as asbestosis [64] and older age [16] might arguably play a contributory role in selected patients.

14.8 Management of Fibrosing Complications

The management of fibrosing disorders is mainly based on withdrawal of the offending drug. Sometimes glucocorticoids are given empirically to enhance recovery [48, 58]. Improvement has been noted in many [22, 23, 48, 58], but not all cases [57, 65] following suspension of the drug implicated in the fibrosing process.

14.9 Conclusions

Fibrosing disorders can be drug induced. Knowledge about offending agents can assist in the differential diagnosis of fibrosing disease.

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Gadolinium-Induced Fibrosis

15

Derrick J. Todd and Jonathan Kay

15.1 Historical Perspective and Nosology

Since their introduction into clinical practice in the late 1980s, gadolinium-based contrast agents (GBCAs) have greatly improved the diagnostic capabilities of magnetic resonance imaging (MRI). Gadopentetate dimeglumine (Magnevist®) was the first GBCA to be approved for use by the US Food and Drug Administration (FDA) in 1988, followed shortly thereafter by formulated gadodiamide (Omniscan®) in 1993. Additional GBCAs have since been approved by the FDA, the European Medicines Agency (EMA), and other regulatory agencies. Collectively, these GBCAs have been used in hundreds of millions of MRI studies globally.

Early data from published studies showed that, within a few days of their administration, GBCAs were well tolerated by the vast majority of patients [1]. Importantly, GBCAs were not associated with the same risk of severe nephrotoxicity that had been observed with iodinated contrast agents (ICAs). Thus, to avoid the risk of developing contrast-induced nephropathy (CIN) from ICAs, GBCA usage increased quickly among patients with moderate-to-severe kidney disease. Throughout the 1990s and early 2000s, it became common for clinicians to request GBCA-enhanced

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MRI *in lieu* of ICA-enhanced computed tomography (CT) for patients with any degree of renal impairment.

Soon after GBCAs became widely used in medical practice, a new fibrosing disease was first described, occurring exclusively in patients with moderate-to-severe renal impairment. Although not recognized at the time, GBCAs would later be implicated as the cause of this severely disabling condition. First reported in 2000 as a "scleromyxedema-like cutaneous disease" with prominent features of cutaneous fibrosis [2], this condition was initially named *nephrogenic fibrosing dermopathy* (NFD) [3]. The only characteristic commonly shared among the patients originally described with NFD, other than cutaneous fibrosis, was that of dialysis-dependent kidney disease. Within a few years of the initial report, many dozens of NFD cases had been reported around the world. Several early publications demonstrated systemic multi-organ fibrosis in patients with NFD, which prompted a change in nomenclature from NFD to *nephrogenic systemic fibrosis* (NSF) [4–6].

In the early 2000s, before GBCAs were known to be the cause of NSF, a growing anxiety swelled within the medical community as the number of NSF cases continued to rise among patients with moderate-to-severe renal disease. In the early 2000s, in our rheumatology clinical practice at a large academic tertiary care hospital (Massachusetts General Hospital, Boston, Massachusetts, USA), we diagnosed dozens of new cases of NSF among patients with advanced renal disease. We observed that many of these patients died from complications related either directly or indirectly to their NSF [7, 8]. Clearly, something new was happening in this vulnerable patient population.

In 2006, Thomas Grobner, a nephrologist in Wiener Neustadt, Austria, reported five cases of NSF that developed in patients with dialysis-dependent kidney disease within weeks of receiving the GBCA-formulated gadodiamide [9]. This seminal observation triggered an avalanche of epidemiologic studies that, over the next few years, established a strong association between prior GBCA exposure and NSF among patients with advanced renal disease [8, 10–15]. In 2006, the FDA issued "Dear Doctor" letters warning medical providers about the association of GBCAs with NSF. In May 2007, the FDA required a "black box" warning to be put in the labeling of all GBCAs [16].

Additional scientific and experimental data supported this association between NSF and the least stable GBCAs (especially formulated gadodiamide). Free gadolinium (Gd) uncoupled from its inorganic chelate was identified in lesional skin of patients with NSF [17, 18]. Both free Gd and GBCAs induce pro-fibrotic cytokine production in vitro [19] and cutaneous lesions resembling those of NSF in animal models [20, 21]. Most importantly, restricted use of the least stable GBCAs in patients with advanced renal disease prevented the development of new cases of NSF [22]. Collectively, these findings have led to the broadly accepted hypothesis that NSF is triggered in patients with advanced kidney disease by the release of free gadolinium cations from the least stable GBCAs.

Based on this preponderance of epidemiologic and scientific evidence, and also on our experience with over 100 cases of NSF that we have now diagnosed and/or managed over the years, we have determined that the term NSF is in need of yet

another revision [23]. We have proposed that the term *gadolinium-induced fibrosis* (GIF) more accurately reflects the current understanding of this disease and its pathogenesis than does the term *nephrogenic systemic fibrosis*. According to the Merriam-Webster dictionary, "nephrogenic" describes something that either is [1] "originating in the kidney" or is "caused by factors originating in the kidney" (e.g., nephrogenic diabetes insipidus) or is [2] "developing into or producing kidney tissue" (e.g., nephrogenic metaplasia of the bladder) [24]. The adjective *nephrogenic*, when used to describe NSF, fits neither of these definitions: kidney tissue is not the source of disease, and the disease does not produce kidney tissue. This chapter will review the preponderance of epidemiologic and experimental data, which prove that the disease known as NSF is *gadolinium induced*. Thus, the name *gadolinium-induced fibrosis* (GIF) better characterizes the known etiopathogenesis of the disease and succinctly describes both its cause and its clinicopathological features. Many patients with GIF have organ involvement, whereas others present only with cutaneous manifestations. We propose that the term "systemic" can be included as an added descriptor of GIF: when multisystem involvement is present, the term *gadolinium-induced systemic fibrosis* (GISF) is applicable.

For those readers who may be uncomfortable with another change in terminology for GIF, we point out that many diseases have undergone changes in nomenclature over the years, often reflecting an improved understanding of disease pathogenesis. For example, the term *Pneumocystis carinii* pneumonia has rapidly and broadly been replaced by *Pneumocystis jiroveci* pneumonia, based upon the re-categorization of its causative organism. Also, the overarching label of *IgG4-related disease* (IgG4RD) reflects the incrementally improved pathophysiologic understanding of what previously was a poorly understood collection of diseases with shared histologic features, including chronic sclerosing sialadenitis, Riedel thyroiditis, autoimmune pancreatitis, retroperitoneal fibrosis, and others [25]. In each of these examples, the name change has provided greater clarity regarding the etiopathogenesis of the disease. Likewise, our new term of *gadolinium-induced fibrosis* also accomplishes this objective. We encourage the medical community to embrace the term GIF as a more accurate description of this chronic fibrosing disorder that is triggered by Gd.

The term GIF also permits greater scientific plasticity when considering the larger universe of fibrosing disorders and what has yet to be learned about Gd toxicity. Tissue Gd deposition may even cause unrecognized adverse effects in patients with normal renal function, as might occur with cutaneous infiltration during the intravenous administration of a GBCA or with Gd deposition in bone or brain tissue of patients who received less stable GBCAs [26, 27]. In our opinion, supported by the scientific literature, the term *gadolinium-induced fibrosis* better characterizes the causative role of GBCAs in this disease, which should help to eliminate the inadvertent administration of high-risk GBCAs to at-risk patients. Indeed, the use of less stable GBCAs has been markedly restricted among patients with moderate-to-severe renal disease. Most fortunately for patients, and contributing to the proof of causation, there has been an almost complete disappearance of newly diagnosed cases of GIF now that measures intended to prevent administration of unstable GBCAs to patients with moderate-to-severe renal disease have been adopted widely.

In this chapter, we describe the epidemiologic, histopathologic, and clinical features of GIF, including a description of GBCA chemistry as it pertains to the understanding of GIF. We also review the data that support the causative relationship between administration of the less stable GBCAs and the development of GIF, based on Bradford Hill criteria [28]. We summarize the proposed pathogenesis of GIF, incorporating current knowledge about the biology and chemistry of GBCAs and tissue fibrosis. We then review published classification criteria for GIF and highlight the differential diagnosis of GIF. We conclude with a discussion of measures that have effectively prevented the onset of GIF and address the limited therapeutic options available to patients afflicted with GIF. However, unfortunately for many patients with GIF, the condition is often relentlessly progressive and frequently fatal.

15.2 Demographics and Epidemiology

By 2006, the demographic features of GIF had largely been described. The only known unifying feature among patients with GIF was renal dysfunction. Most cases of GIF have occurred in patients with stage 5 chronic kidney disease (CKD), defined as requiring chronic dialysis treatment or having a stable glomerular filtration rate (GFR) <15 ml/min. However, an early observation was that stage 5 CKD (also known as end-stage renal disease [ESRD]) was not a prerequisite for developing GIF. GIF was also described in patients with stage 4 CKD (GFR 15–29 ml/min) and even rarely in those with stage 3 CKD (GFR 30–59 ml/min) [29, 30]. GIF also was not restricted by dialysis modality. It afflicted patients with stage 5 CKD who were receiving either hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) [31]. Importantly, CKD also was not a requirement for GIF, since cases were reported in patients who had suffered severe acute kidney injury (AKI) but recovered and never developed CKD [32]. In our experience, these patients with AKI-associated GIF had been exposed to a GBCA while renally impaired.

GIF was described in patients with many causes of severe renal impairment: hypertensive nephropathy, diabetic nephropathy, glomerulonephritis, polycystic kidney disease, and others [8]. GIF was not restricted according to traditional demographic characteristics of age, gender, or race. It was reported in patients of all ages, from those as young as age 8 [33] to the elderly. In the early 2000s, investigators studied whether various comorbid disease states that occurred among patients with CKD might be associated with the onset of GIF: concurrent surgical procedures, thromboembolic events, infectious illnesses, and liver transplantation (among others) [34]. However, none of these conditions adequately explained the appearance of GIF as a novel disease entity. In addition, there was no reproducible association of GIF with medications, such as exposure to erythropoietin or sevelamer or the lack of ACE inhibitor therapy [13, 35–37]. Most troubling were the reports of an increased mortality rate associated with GIF, compared that which would be expected for similar patients without GIF [5, 8, 38].

After Grobner's 2006 report, there was an explosion of epidemiologic research into the relationship between GBCAs and GIF. Many epidemiologic studies showed a very strong association between GIF and antecedent exposure to the less stable GBCAs (Table 15.1). Most of these cases developed after patients had received formulated gadodiamide, which is the least thermodynamically stable GBCA. Gadopentetate dimeglumine was associated with the next highest number of GIF cases, followed by the relatively less stable gadoversetamide. At that time, gadoversetamide had a much smaller share of the GBCA market than did either gadodiamide or gadopentetate dimeglumine, which likely in part explained the lower absolute number of GIF cases associated with gadoversetamide [56].

When a case of GIF occurred after administration of only a single GBCA product (regardless of exposure dose or number of individual exposures), it is considered to be an "unconfounded case." In contrast, when GIF developed in a patient who received more than one GBCA product prior to disease onset, it is considered to be a "confounded case." Almost without exception, unconfounded cases of GIF have been associated with formulated gadodiamide, gadopentetate dimeglumine, or gadoversetamide. In confounded cases, when GIF was associated with any other GBCA, the patient almost always also had been administered formulated gadodiamide, gadopentetate dimeglumine, or gadoversetamide prior to the onset of GIF. In 2010, based on these observations and the relative kinetic and thermodynamic stability of the various GBCAs, the FDA and the EMA both issued a risk stratification in which gadodiamide, gadopentetate dimeglumine, and gadoversetamide were classified as "high risk" for the development of GIF, whereas the other GBCAs were deemed to be "medium risk" or "low risk" (Fig. 15.1) [58, 59].

Many factors made it difficult for investigators to determine the strength of the association between GBCAs and GIF. Most importantly, retrospective chart review studies often depended upon documentation of GIF in the medical record by treating physicians, other than the investigators. In the early 2000s, GIF was largely unknown to the general medical community; many cases of GIF likely were never recognized or documented in studies that included this time frame. For this reason, many retrospective chart-based studies likely underestimated prevalence and incidence rates. Notably, a much higher prevalence of GIF was reported in both a cross-sectional cohort study [60] and a retrospective study [14] in which patients received their care from healthcare providers who were familiar with the GIF epidemic. Although many cases of GIF developed within days to weeks after exposure to a high-risk GBCA, some cases were not diagnosed until years after the GBCA exposure [10, 18, 31]. Thus, potential cases of GIF might not have been captured in a study if GIF was not diagnosed until after the dates studied.

An additional confounding factor to consider when interpreting epidemiologic studies of GIF is that patients with CKD may receive medical care at multiple healthcare institutions. Thus, a GBCA exposure might not be documented in the medical records available to investigators. This phenomenon has been observed in epidemiologic studies [39] and likely explains the very infrequent reports of patients

Table 15.1 Epidemiologic studies associating high-risk gadolinium-based contrast agents with gadolinium-induced fibrosis

Study (location)	Year	GBCA exposure	Cases of GIF/GBCA exposed patients with renal disease	Notes
Marckmann (Denmark)	2006	Gadodiamide	13/370 (3.5 %)	Retrospective chart review: strong association of gadodiamide exposure with GIF (OR 32.5)
Broome (Loma Linda, CA)	2007	Gadodiamide	N/A	Retrospective chart review: 12/168 HD patients (7.1 %) had GIF, and all had been exposed to gadodiamide (OR 22.3)
Collidge (Scotland)	2007	Gadodiamide	13/421 (3.1 %)	Retrospective chart review: significant association between gadodiamide exposure and GIF (rate ratio 6.35). Dose response observed
Deo (Bridgeport, CT)	2007	Gadodiamide	3/87 (3.4 %)	Retrospective chart review
Lauenstein (Atlanta, GA)	2007	Gadodiamide	8/312 (2.6 %)	Retrospective chart review
Othersen (Charleston, SC)	2007	Gadodiamide	4/261 (1.5 %)	Retrospective chart review
Todd (Boston, MA)	2007	Gadopentetate	16/54 (29.6 %)	Cross-sectional cohort study: strong association between gadopentetate exposure and GIF (OR 14.7). Increased mortality among GIF patients *vs.* controls (HR 4.1)
Prince (New York, NY)	2008	Gadodiamide Gadopentetate Gadobenate Gadoteridol	15/786 (1.9 %)	Retrospective chart review: 15 GIF cases among 786 patients with eGFR <30 or AKI. Of these, 14/653 (2.1 %) patients exposed to gadodiamide developed GIF
Reilly (Dallas, TX)	2008	Gadoteridol	0/141 (0 %)	Retrospective chart review: 141 HD patients who had 198 exposures to gadoteridol. No GIF cases reported
Rydahl (Denmark)	2008	Gadodiamide	18/102 (17.6 %)	Retrospective chart review
Wertman (Chapel Hill, NC)	2008	Gadodiamide Gadopentetate	N/A	Retrospective chart review: four academic centers. GIF rates greater at institutions that used gadodiamide, (32/82,260) compared to gadopentetate (4/135,347), with denominator being all patients regardless of renal function

Abujudeh (Boston, MA)	2009	Gadobenate	0/250 (0%)	Retrospective chart review: no incident cases of GIF among patients (mostly stage 3 CKD)
Altun (Chapel Hill, NC)	2009	Gadodiamide Gadopentetate Gadobenate	37/1237 (3.0%)	Retrospective chart review: all cases of GIF were associated with gadodiamide. No cases of GIF in 549 patients after switch to gadopentetate or gadobenate for at-risk patients
Chen (Taiwan)	2009	Gadodiamide	1/127 (0.8%)	Retrospective chart review
Chrysochou (the United Kingdom)	2009	Gadodiamide Gadopentetate Gadofosveset	0/1659	Retrospective chart review: 1659 patients had stage 3, 4, or 5 CKD. No cases of GIF were reported, but, of the patients with stage 4 or 5 CKD, only 14 received gadodiamide, and only 246 received gadopentetate dimeglumine. None of the other patients received a "high-risk" GBCA
Heinz-Peer (Austria)	2009	Gadodiamide Gadopentetate Gadoterate Gadobutrol Gadoteridol Gadobenate Gadoxetate	6/367 (1.6%)	Retrospective chart review
Hope (N. California)	2009	Gadopentetate	1/530 (0.2%)	Retrospective chart review
Lee (Rochester, MN)	2009	Gadodiamide Gadopentetate Gadobenate Gadoteridol Gadoxetate	8/827 (1%)	Retrospective chart review
Perez-Rodriguez (Baltimore, MD)	2009	Gadodiamide Gadopentetate	N/A	Retrospective chart review: 33 cases of GIF. GBCA exposure was gadodiamide [20], gadopentetate [7], and "unknown" [6]. Incidence rates dropped after 2007, with restrictions on GBCA usage in patients with renal disease

(continued)

Table 15.1 (continued)

Study (location)	Year	GBCA exposure	Cases of GIF/GBCA exposed patients with renal disease	Notes
Lemy (Belgium)	2010	Gadodiamide	5/33 (15.2 %)	Retrospective chart review: 705 patients who had undergone renal transplantation, only 33 of whom had been exposed to a GBCA over a 7-year period
Martin (Atlanta, GA)	2010	Gadodiamide Gadobenate	8/1096 (0.7 %)	Retrospective chart review: 8 of 312 (2.6 %) HD patients developed GIF after gadodiamide exposure (dose response). None of 784 HD patients developed GIF after the institution switched to the more thermodynamically stable GBCA, gadobenate
Chow (Los Angeles, CA)	2011	Gadodiamide Gadopentetate	1/357 (0.3 %)	Retrospective chart review: 2142 patients who had undergone liver transplantation. Of these, 200 had stage 3 CKD, 60 had stage 4 CKD, and 97 had stage 5 CKD. One case of GIF occurred in a patient with stage 5 CKD who had received gadodiamide
Kendrick-Jones (New Zealand)	2011	Gadodiamide Gadopentetate Gadobenate Gadobutrol	5/522 (1.0 %)	Retrospective chart review: 522 chronic HD patients who had a total of 748 GBCA exposures. GIF was observed following 5 (1.3 %) of 392 gadodiamide-enhanced MRI studies and none of 356 studies using an alternative GBCA
Wang (Boston, MA)	2011	Gadopentetate Gadobenate	N/A	Retrospective chart review: Restrictions placed on GBCA use in patients with renal disease (2008). Before, there were 1287 GBCA exposures among patients with GFR < 30 ml/min and 34 cases of GIF. After 2008, there were only 36 GBCA exposures and no cases of GIF

Alhadad (Sweden)	2012	Gadodiamide Gadopentetate Gadoterate Gadobenate Gadoxetate Gadoteridol	0/272	Retrospective chart review: 143 patients with stage 4 CKD and 129 with stage 5 CKD who had been exposed to one or more GBCAs
Amet (France)	2014	Gadoterate	0/255 (0%)	Prospective cohort study: Assessment of dialysis patients getting GBCA. No cases of GIF were observed among those who received gadoterate (89% of patients)

References: [8, 10–15, 22, 29, 39–55]

Abbreviations: *AKI* acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *GBCA* gadolinium-based contrast agent, *GIF* gadolinium-induced fibrosis, *HD* hemodialysis, *HR* hazard ratio, *MRI* magnetic resonance imaging, *N/A* not available, *OR* odds ratio

Gadolinium-based contrast agent (trade name): gadodiamide = formulated gadodiamide (Omniscan®); gadoversetamide (OptiMARK®); gadopentetate = gadopentetate dimeglumine (Magnevist®); gadobenate = gadobenate dimeglumine (MultiHance®); gadoxetate = gadoxetate disodium (Eovist®, Primovist®); gadofosveset = gadofosveset trisodium (Vasovist®, ABLAVAR®); gadoteridol (ProHance®); gadobutrol (Gadovist®); gadoterate = gadoterate meglumine (Dotarem®)

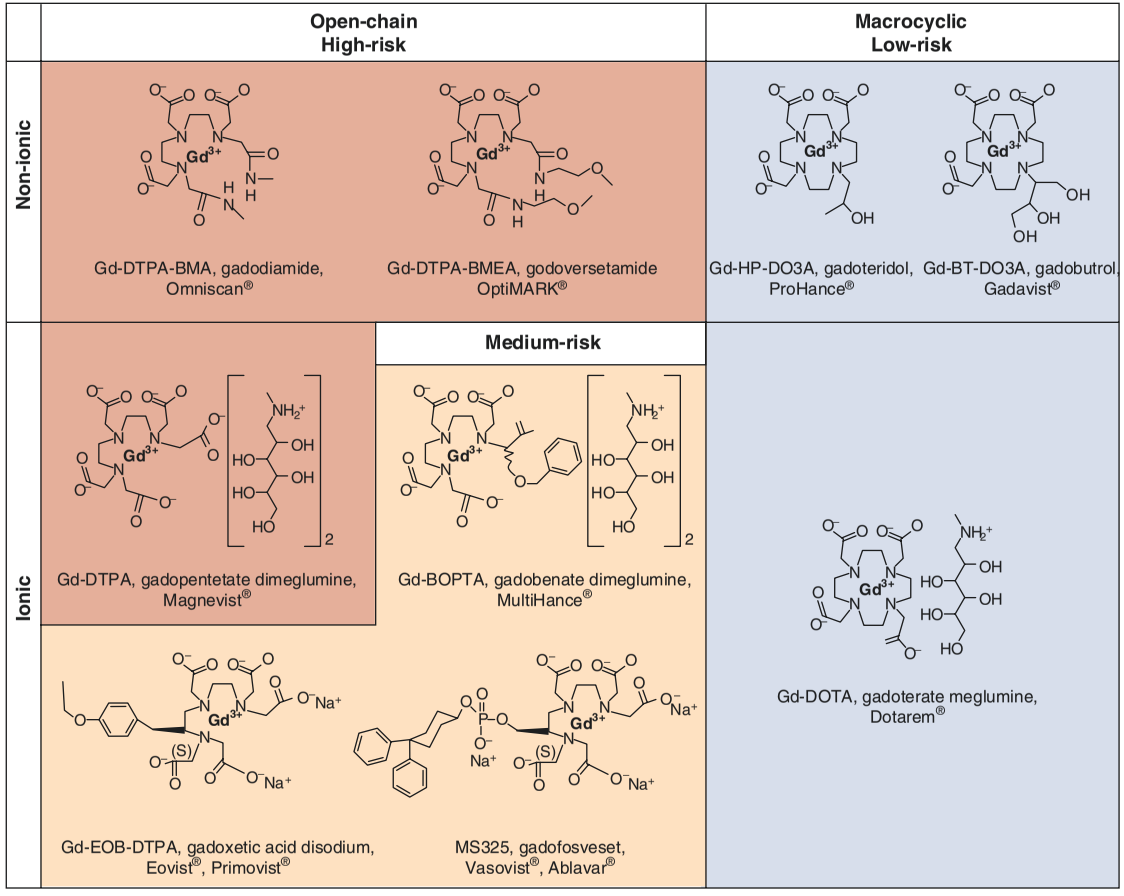

Fig. 15.1 Gadolinium-based contrast agents (GBCAs) categorized based on properties of structure (open chain and macrocyclic) and charge (ionic and nonionic). Shading indicates the categorization for risk of causing gadolinium-induced fibrosis (European Medicines Agency, 2010) (Modified from Bernstein and Kay [57] and reproduced with permission from Todd and Kay [23])

who developed GIF with no known GBCA exposure [61–63]. Gd has been detected in biopsy tissue from GIF patients for whom GBCA exposure was not documented in available medical records [64]. Gd is not otherwise present in the human body so one can presume that tissue Gd must have resulted from prior GBCA exposure, even if none was documented in the record or recalled by the patient. One reason why investigators might overlook an exposure is that patients could have received the GBCA during an imaging study other than MRI, such as a fistulogram or another vascular imaging study [40].

Before 2006, the specific type and dose of GBCA were not consistently documented in medical records [39, 41]. Contributing to this was the perception that GBCAs were so harmless that their identification was not significant enough for inclusion in the medical record [65, 66]. Prior to Grobner's 2006 publication, GIF was largely unknown to the radiology community [66]. Thus, investigators often had to rely upon institutional GBCA prescribing patterns to determine the brand and the dose of GBCA that was administered, making it difficult to show dose–response relationships between GBCA exposure and the onset of GIF in epidemiologic studies [39]. It is now standard practice (including at our respective institutions) that the specific type and dose of GBCA administered are included in the report of each GBCA-enhanced imaging study.

15.3 Histopathology and Pathogenesis

Histopathological assessment of GIF involves sampling affected tissue, which often requires a full-thickness skin biopsy that contains deep dermal and subcutaneous tissues. Biopsies from other organs can also be analyzed for evidence of systemic fibrosis. Regardless of the organ affected, several histological features are hallmarks of GIF. Reticular bundles of dermal collagen are thickened and surrounded by clefts, and dermal mucin is increased with intact elastic fibers (Fig. 15.2). $CD68^+$ factor $XIIIa^+$ dendritic cells and spindle cells that have a $CD34^+$ $CD45RO^+$ type I procollagen$^+$ phenotype infiltrate the dermis [3, 5]. Lesions of established GIF are less cellular than those of early disease and contain abundant collagen. Dystrophic calcification is a well-recognized histologic characteristic of late GIF lesions, and osseous metaplasia and calcified sclerotic bodies have been suggested to be histologic features highly specific for GIF [4, 68, 69]. However, in the absence of characteristic clinical features, it may be difficult to distinguish GIF from scleromyxedema based only upon histopathological analysis [70].

To better conceptualize the etiopathogenesis of GIF, it is important to understand the chemical and molecular properties that distinguish among the various GBCAs. Gd is a lanthanide series rare earth metal with seven unpaired electrons, which makes it highly paramagnetic and an ideal contrast agent for MRI. In solution, however, trivalent Gd^{+3} ("free gadolinium") is highly toxic [71, 72]. There are multiple mechanisms by which Gd is toxic, including blockage of voltage-gated calcium channels [73], formation of inorganic Gd-phosphate precipitates [74], and induction of cytokines associated with tissue fibrosis (discussed later) [19].

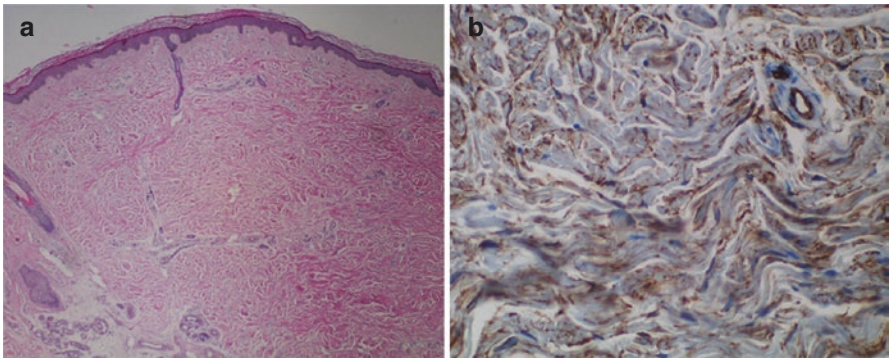

Fig. 15.2 Skin biopsy from the leg of a patient with gadolinium-induced fibrosis demonstrating typical histologic changes: hypercellular dermis (hematoxylin–eosin stain, *left*) with thick and thin collagen bundles surrounded by clefts with spindle cells intercalated between the collagen bundles throughout the reticular dermis and extending into the septa of subcutaneous fat. These spindle cells are dermal fibrocytes that stain with antibodies to CD34 (*right*) (Reproduced with permission from Kay [67])

To reduce the potential toxicity of Gd when used as a contrast agent, it is bound to an inorganic carrier molecule ("chelate"). It is this chelate that distinguishes among the various GBCAs approved for use in humans (Fig. 15.1). In 2006, five GBCAs were commercially available in the United States: formulated gadodiamide (gadodiamide with 5 % excess sodium caldiamide chelate, Omniscan®), gadoversetamide (OptiMARK®), gadopentetate dimeglumine (Magnevist®), gadobenate dimeglumine (MultiHance®), and gadoteridol (ProHance®). Additional GBCAs were available outside of the United States at that time or have become commercially available since 2006: gadoxetate disodium (Eovist®, Primovist®), gadofosveset trisodium (Vasovist®, ABLAVAR®), gadobutrol (Gadovist®), and gadoterate meglumine (Dotarem®).

GBCAs can be categorized by whether they have a linear or macrocyclic structure and whether they have an ionic or nonionic charge (Fig. 15.1). These two properties determine the kinetic stability and thermodynamic stability of each GBCA and largely explain the propensity for Gd to disassociate from its chelate to become toxic free Gd^{+3}. Those GBCAs that are linear and nonionic (formulated gadodiamide and gadoversetamide) are the least stable. In contrast, macrocyclic GBCAs (gadoteridol, gadobutrol, and gadoterate meglumine), whether ionic or nonionic, are the most stable GBCAs. Intermediate in stability are those GBCAs that are linear but ionic (gadopentetate dimeglumine, gadobenate dimeglumine, gadoxetic acid disodium, and gadofosveset trisodium). These properties are noteworthy when considering that the vast majority of reported GIF cases developed after patients had been exposed to the least stable GBCA: linear nonionic formulated gadodiamide.

All GBCAs are large molecules that remain extracellular. Most are highly water soluble and excreted by the kidneys [75]. Two GBCAs (gadobenate dimeglumine and gadoxetic acid disodium) are more lipophilic, such that a sizeable fraction is excreted via the hepatobiliary system [76]. In patients with intact renal function, the

half-life ($t_{½}$) of formulated gadodiamide is 70 min: 95% of a single dose is eliminated in the urine after 72 h [77]. However, the clearance of gadodiamide declines dramatically in patients with impaired renal function. The mean $t_{½}$ of formulated gadodiamide is 34.3 h in non-dialysis-dependent patients with stage 5 CKD and 52.7 h in patients receiving CAPD [78]. Only an average of 68.0% of formulated gadodiamide is cleared after one HD treatment, and only an average of 72.3% of the original amount is removed after four HD sessions [78]. In patients with GFR <20 ml/min, <70% of a single intravenous gadopentetate dimeglumine dose was recovered in urine by 48 h after administration [79]. Further, Gd tissue deposition has been observed in biopsies of multiple organs from patients with GIF, even years after the last known GBCA exposure [18]. Notably, in patients with normal renal function, Gd has been shown to deposit and accumulate in the brain and bone, with higher bone Gd content after the administration of formulated gadodiamide than of an equivalent dose of gadoteridol [26, 27, 80].

After their administration, GBCAs persist for many more hours in patients with advanced renal disease than in individuals with normal renal function. In patients with compromised renal function who have received a GBCA, free Gd is more likely to dissociate from its chelate and be released as Gd^{+3}, especially with the less stable (high-risk) agents. Altered phosphate levels may affect the release of Gd^{+3} from unstable linear chelates, but published data are inconsistent [11, 81, 82]. When a GBCA dissociates, not only does it release free Gd^{+3} but also it releases the empty chelate, which then is able to associate with other cations, such as Fe^{+2} and Zn^{+2}. This process is called transmetallation [83].

An early study described the toxicity of gadopentetate dimeglumine in 151 patients with renal disease [84]. Mostly, only mild adverse effects were reported. However, this was a retrospective chart review with short-term follow-up (30 days for outpatient MRIs or until hospital discharge for inpatient MRIs). Only 71 of the 151 patients (47%) had serum creatinine values >2.5 mg/dL, and only 15 patients (10%) were receiving HD. GIF had not yet been described in the medical literature at the time of this study. Thus, it is not surprising that neither cutaneous nor systemic fibrosis was reported in this relatively small study with a brief duration of follow-up.

Two additional factors must be considered regarding the use of GBCAs during the early 2000s. First, since its introduction in 1994 [85], GBCA-enhanced MR angiography was being performed with increasing frequency. In this procedure, patients often were administered twice or three times the standard 0.1 mmol/Kg dose of GBCA used for MRI [85]. Second, according to the FDA Office of Surveillance and Epidemiology (OSE), two GBCAs dominated the United States market during the mid-2000s: gadopentetate dimeglumine had an approximately 50% share of the GBCA market, and formulated gadodiamide followed with a market share of almost 40% [56]. The vast majority of patients who were reported to have developed GIF had been exposed to formulated gadodiamide, the least stable of the various GBCAs; many fewer patients were reported to have developed GIF after exposure to the slightly more stable GBCA gadopentetate dimeglumine. Thus, its thermodynamic instability, rather than its market share, likely accounted for the perceived greater propensity of formulated gadodiamide to cause GIF.

Many molecular, cellular, and animal studies have provided the framework to help understand the mechanism by which high-risk GBCAs likely cause GIF (Fig. 15.3). Many lines of evidence support the hypothesis that, with prolonged tissue exposure such as that which occurs in patients with significant renal dysfunction, formulated gadodiamide and other high-risk GBCAs dissociate into free Gd^{+3} and chelate [86]. Investigators have used microanalytical scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDS), synchrotron X-ray fluorescence (SXRF) microscopy, extended X-ray absorption fine structure (EXAFS) spectroscopy, and inductively coupled plasma-mass spectrometry (ICP-MS) to characterize and to quantify Gd in insoluble deposits found in tissue obtained from GIF lesions [17, 18]. In these deposits, Gd^{+3} cations associate with complexes of inorganic phosphate, calcium, and sodium [87].

The amount of free Gd^{+3} released is the primary determinant of tissue toxicity [88]. Several factors favor the release of free Gd^{+3} from its chelate, including an acidic environment (as might be found in the phagolysosome of macrophages) [89] and transmetallation, whereby other cations, such as Fe^{+2}, Zn^{+2}, Ca^{+2}, and Cu^{+2}, may displace Gd^{+3} from its chelate [95]. The increased mobilization of iron that is observed after exposure of patients with dialysis-dependent renal disease to formulated gadodiamide provides evidence that transmetallation occurs in patients at risk for developing GIF [96].

In lesional tissue of GIF patients, mRNA for TGBβ1 (a pro-fibrotic cytokine) is increased [5]. In vitro, the release of free Gd^{+3} from GBCAs promotes the production of TGBβ1 and other pro-fibrotic cytokines, chemokines, and growth factors by monocyte-derived macrophages and peripheral blood monocytes [19, 90]. GBCAs also stimulate fibroblast proliferation and increased synthesis of extracellular matrix components, such as hyaluronic acid, fibronectin, and type I and III collagens [93, 94]. Formulated gadodiamide produces these pro-fibrotic effects at much lower concentrations than the more stable macrocyclic GBCAs [97, 98]. These effects are likely mediated by signaling through toll-like receptors (TLR) 4 and 7 [99] with activation of nuclear factor-kB (NF-κB) [90]. Free Gd^{+3}, gadodiamide, and gadopentetate dimeglumine each activate the NLRP3 inflammasome in vitro to produce IL-1β; these molecules preferentially activate pro-fibrotic IL-4-polarized M2 macrophages [91].

Animal models of GIF demonstrate pro-fibrotic effects of various GBCAs, especially gadodiamide. Early studies, conducted before the first cases of GIF appeared, revealed toxic effects of $GdCl_3$ in mice, but these were due mostly to mineral deposition in vascular and reticuloendothelial tissues [72]. Rats given high doses of gadodiamide developed skin ulceration, an effect that was attributed to abnormal zinc metabolism [100]. After the association between GBCAs and GIF was recognized, investigators revisited animal models, administering GBCAs intravenously to rats that had or had not undergone partial nephrectomy [20, 21, 101, 102]. Although animal models do not recapitulate human GIF perfectly, several common themes emerged from these studies. First, formulated gadodiamide induced cutaneous changes in rats that were similar histologically to those of GIF, displaying increased cellularity and tissue fibrosis with increased collagen

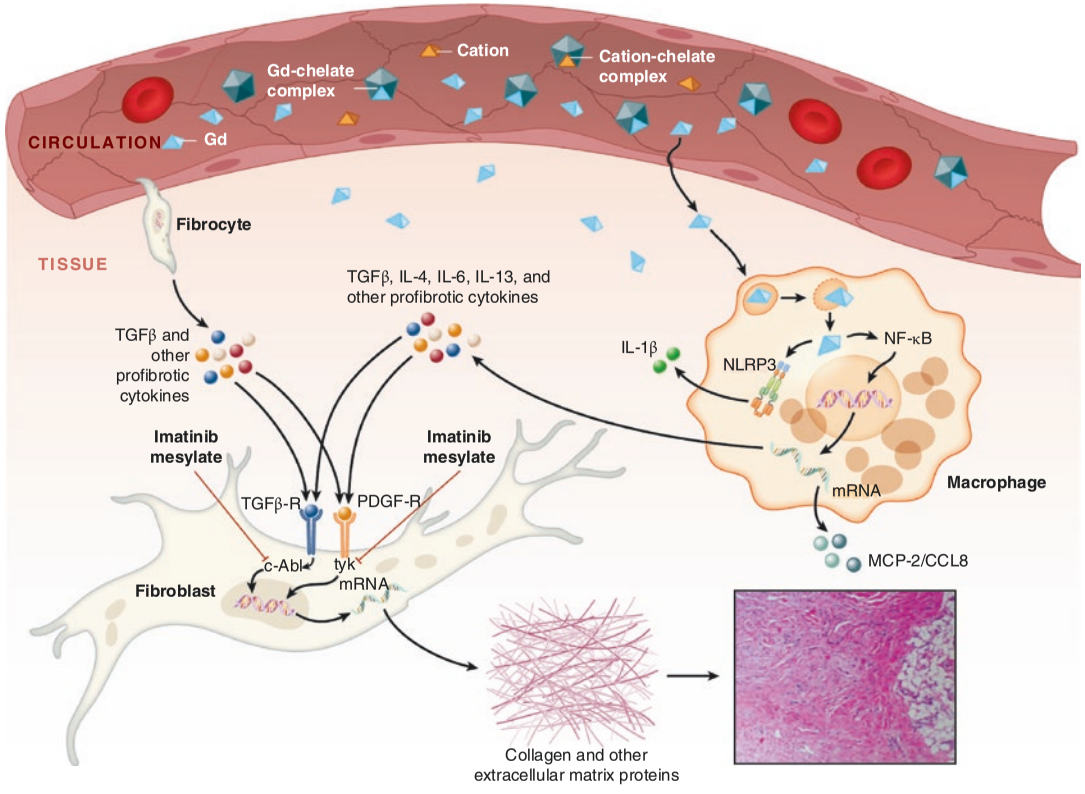

Fig. 15.3 Hypothesized pathophysiologic mechanism for gadolinium-induced fibrosis. In patients with renal dysfunction exposed to high-risk gadolinium-based contrast agents (e.g., formulated gadodiamide), free gadolinium is released into the tissues [86–89], where particulate Gd is internalized into macrophages by phagocytosis. These Gd particles are internalized into phagosomes that may rupture, releasing Gd into the cytosol, where it activates nuclear factor-κB [90] and preferentially stimulates M2 macrophages by way of the NLRP3 inflammasome [91]. This triggers production of pro-fibrotic cytokines [19, 90], which stimulate fibroblasts through tyrosine kinases [92] to upregulate the transcription, translation, and processing of extracellular matrix proteins [93, 94] (Reproduced with permission from Todd and Kay [23])

Table 15.2 Bradford Hill criteria for causation

Criterion	Supporting evidence
Strength of association	Very strong odds ratio associating GBCA exposure and GIF
Consistency	Many independent investigators from different institutions and different countries have found a similarly strong association
Specificity	GIF not proven to occur in the absence of GBCA exposure
Temporality	GBCA clearly precedes the onset of GIF, sometimes by years
Biological gradient	Many studies have shown a greater risk of GIF with exposure to higher doses of or repeated exposures to GBCAs
Biological plausibility	Many lines of molecular, cellular, and animal data support the "free gadolinium" hypothesis that Gd^{+3} in high-risk GBCAs dissociates from its chelate to trigger a cascade of events that result in GIF
Coherence	GIF has not been shown to result from any exposure other than to GBCAs
Experiment	Animal exposed to formulated gadodiamide develop a fibrosing condition that resembles GIF Avoiding use of GBCAs in patients with renal dysfunction has essentially eliminated incident cases of GIF
Analogy	Historically, environmental toxins caused Spanish toxic oil syndrome and eosinophilia-myalgia syndrome

See corresponding text for applicable references
Abbreviations: *GBCA* gadolinium-based contrast agent, *Gd* gadolinium, *GIF* gadolinium-induced fibrosis

deposition and dermal thickening. Second, formulated gadodiamide was the only one of the eight GBCAs tested that induced these changes to any significant degree. Third, among rats that had received GBCAs, the highest tissue concentrations of Gd were detected in tissues of those that received formulated gadodiamide [20, 101, 102]. TGF-β1 was detected in lesional skin from rats treated with gadodiamide but not from those treated with gadoteridol [101], as it had been in the skin of patients with GIF [5].

Previously, we and others have applied Bradford Hill criteria [28] to contend that the relationship between high-risk GBCAs and GIF is not just an association but rather implies causation [103–106] Todd and Kay [23]. We readdress this line of reasoning in Table 15.2, updating the nine criteria with additional data presented in this review. With regard to *strength of association*, a meta-analysis of seven epidemiologic studies calculated an odds ratio of 27 for the association between GBCA exposure and the subsequent development of GIF [103], which is comparable to the odds ratio associating heavy cigarette smoking with lung cancer [28]. *Consistency* also has been fulfilled, since many investigators working at different institutions in different countries have each identified similarly strong associations between exposure to high-risk GBCAs and GIF [8, 10, 11, 14, 31]. *Specificity* is fulfilled by the absence of convincing cases of GIF occurring without known GBCA exposure; Gd has been detected in lesional skin even from patients with GIF who recalled no prior GBCA exposure [64].

Almost all reports of GIF cases have confirmed *temporality* of the relationship, in that GBCA exposure occurred prior to the development of GIF. The time to onset may be days to years after the last GBCA exposure [9, 10, 31]. The *biological gradient* criterion is fulfilled by the many studies that have shown an inverse relationship between the cumulative GBCA dose and the time to disease onset. Many cases of GIF occurred after only a single dose of a high-risk GBCA, but studies have also shown a dose response for the development of GIF following exposure to high-risk GBCAs: patients were at greater risk of developing GIF if a single high-risk GBCA had been administered at higher-than-standard dose or after multiple doses of one or more high-risk GBCAs [10, 11, 15, 40, 42, 43]. *Biological plausibility* is supported by the many molecular, cellular, and animal studies substantiating the hypothesis that free Gd^{+3} dissociates from the least stable GBCAs and triggers a series of cellular events that result in tissue fibrosis. We are not aware of any strong data that would contradict the conclusion that high-risk GBCAs cause GIF, thus fulfilling the Bradford Hill concept of *coherence*.

Clearly, it would be unethical to attempt to fulfill the Bradford Hill *experiment* criterion with a randomized, clinical trial administering high-risk GBCAs to patients with renal dysfunction. However, guidelines that proscribe the administration of high-risk GBCAs to patients with renal dysfunction have effectively eliminated incident cases of GIF [22, 40–46]. Data from animal models of GIF also contribute to fulfillment of the *experiment* criterion: formulated gadodiamide induces GIF-like changes in the skin and other organs of treated rats [20, 101, 102]. Finally, the *analogy* criterion is fulfilled by the historical observations that other environmental triggers, such as contaminated rapeseed oil and L-tryptophan, caused the fibrosing disorders Spanish toxic oil syndrome and eosinophilia-myalgia syndrome, respectively [107, 108].

Fulfilling the Bradford Hill criteria for causation strongly supports that high-risk GBCAs are necessary for the development of GIF, but it does not imply that GBCA exposure alone is sufficient to cause the disease. Not all patients with renal dysfunction develop GIF following GBCA exposure, and, in those who develop GIF, the time to the appearance of clinical features of disease is highly variable. Thus, one must assume that other factors influence the risk of developing GIF and the time to its onset after exposure to a high-risk GBCA. Many permissive factors have been postulated, such as recent infection, surgical procedures, liver transplantation, certain medications, and altered serum phosphate levels. No such factor has been confirmed, but a pro-fibrotic milieu may provide the permissive state in which high-risk GBCAs cause GIF [91].

Perhaps the most compelling evidence that high-risk GBCAs cause GIF is the temporal relationship between GBCA usage and the appearance (and subsequent disappearance) of GIF. Before the introduction of GBCAs, GIF did not exist as a disease entity. Shortly after GBCA use in patients with renal dysfunction became widespread, GIF appeared. After restrictions were placed on the use of high-risk GBCAs in patients with renal dysfunction, GIF essentially ceased to exist. Thus, the history of GIF parallels those of Spanish toxic oil syndrome and

eosinophilia-myalgia syndrome, each of which appeared after the exposure of many people to a toxic chemical and disappeared completely after the environmental trigger was identified and removed.

15.4 Clinical Characteristics

GIF presents in a characteristic clinical manner. The earliest symptoms are often vague and nonspecific: weakness, pruritus, or pain (typically burning in nature) that begins in the distal extremities [7, 109]. Early cutaneous signs are also nonspecific and frequently include indurated erythematous papules and plaques and soft-tissue edema [7, 109]. Thus, many clinicians may overlook these early lesions of GIF.

In established GIF, the skin acquires a brawny hyperpigmented appearance with a texture that is hardened ("woody"), thickened, and tethered to underlying soft tissues (Fig. 15.4) [7, 109]. Around hair follicles, the skin takes on a "peau d'orange" appearance. Involvement of periarticular tissues by GIF causes joint contractures because of tightening of skin and fascia, which result in contractures of muscles, tendons, and joints. These joint contractures can cause severe pain and be very disabling. GIF almost always affects the lower extremities, and upper extremity involvement is common [8, 15, 40]. Often, extremities are

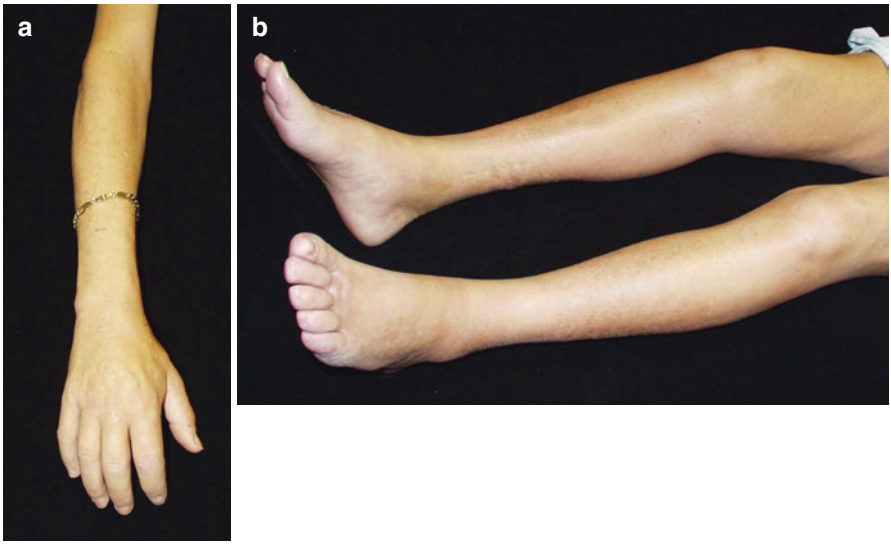

Fig. 15.4 Typical skin changes of gadolinium-induced fibrosis on the arms and legs, with brawny induration, hyperpigmentation, hardened "woody" texture, and thickened skin that is tethered to deep dermal tissues, resulting in flexion contractures of the fingers, elbows, and knees (Reproduced with permission from Kay [67])

affected symmetrically, and changes of GIF progress from distal to proximal. Even the trunk can be affected [5, 15]. However, in contrast to systemic sclerosis (scleroderma) and scleromyxedema, GIF has not been observed to affect the skin of the face.

As its name implies, GIF (also termed GISF) is not limited to the skin. Involvement of skeletal muscle (including esophagus and diaphragm), cardiac muscle, vasculature, pleural tissue, lung, rete testis, renal tubules, dura mater, and ocular sclera have been described [4, 5]. Scleral involvement presents as a thickened yellow plaque on the sclera, which consists of calcium phosphate salts surrounded by collagen [110]. Increased risk of mortality is a well-established consequence of GIF, frequently resulting from complications of respiratory failure, pneumonia, or other infection [5, 8, 38]. Diaphragmatic involvement may cause respiratory failure and hasten death [111].

No laboratory finding is consistently abnormal in patients with GIF, other than those that might occur in patients with CKD. Despite some clinical resemblance to systemic sclerosis (SSC, scleroderma) and scleromyxedema, GIF is not associated with autoantibodies or paraproteinemia. Imaging findings in GIF are nonspecific: MRI, bone scintigraphy, and positron emission tomography (PET) each show enhancement of involved areas, mostly corresponding to subcutaneous tissue, fascia, and muscle [112, 113].

15.5 Diagnosis and Differential Diagnosis

A clinicopathological definition of GIF was published in 2011 to provide criteria by which GIF could be classified for the purpose of further study [109]. This definition employs a two-part scoring system in which salient clinical and histopathological features of GIF are both considered. Combining clinical and histopathological scores, the likelihood of GIF can be designated as "definitive," "consistent," "suggestive," "inconsistent," or "not" GIF [109]. Patients with an "alternative diagnosis" are excluded from this classification.

When evaluating a patient with suspected GIF, one must also consider the many other conditions that can present with cutaneous fibrosis or sclerosis (Table 15.3). Of these, only β_2-microglobulin amyloidosis occurs exclusively in patients with advanced renal disease. Besides most patients having underlying impaired renal function, other characteristics distinguish GIF from its many mimics. For example, Raynaud's phenomenon and facial skin involvement are not features of GIF but occur commonly among patients with SSC. Upper extremity involvement, which often is observed in GIF, is not characteristic of lipodermatosclerosis. Thus, careful clinical evaluation can distinguish most, if not all, of the conditions that resemble GIF; histopathological analysis of affected tissue provides further support for the clinical impression. However, biopsies of affected tissue do not always demonstrate diagnostic features, especially when early lesions are sampled.

Table 15.3 Differential diagnosis of gadolinium-induced fibrosis

Scleromyxedema Monoclonal gammopathy or paraproteinemia often present Frequently involves face
Systemic sclerosis (scleroderma) Autoimmune condition with autoantibodies and Raynaud's phenomenon Frequently involves face
Lipodermatosclerosis Complication of chronic venous stasis Affects gravity-dependent tissues and spares the arms Does not cause joint contractures
Eosinophilic fasciitis Primarily a fasciitis histologically, with eosinophilia in blood and tissues Steroid responsive when treated early Associated with localized morphea and myelodysplastic syndromes
Scleredema (diabeticorum) Most commonly affects upper back and shoulders Associated with streptococcal infection or diabetes mellitus (scleredema diabeticorum)
Spanish toxic oil syndrome Historic entity caused by exposure to contaminated rape seed oil
Eosinophilia-myalgia syndrome Historic entity caused by exposure to contaminated L-tryptophan
Graft versus host disease Occurs in appropriate clinical context of bone marrow transplantation
Radiation-induced fibrosis Produced by exposure to causative agent
Bleomycin-induced fibrosis Produced by exposure to causative agent
Morphea profunda (diffuse type) Starts on trunk and progresses distally Generally spares hands and feet
Fibroblastic rheumatism Inflammatory condition associated with fever, Raynaud's, and polyarthritis
β2-microglobulin amyloidosis Most commonly affects the shoulders, volar wrists, and tongue. Amyloid deposited in tissue
Superficial fibromatosis (Dupuytren's, Ledderhose, and Peyronie's diseases) Localized fibrotic cord of the hand, feet, or penis causing secondary tissue retraction
Porphyria cutanea tarda Blistering lesions in sun-exposed areas that can cause scarring after repeated injury

References: [107, 108, 114]

List of conditions that may resemble gadolinium-induced fibrosis (GIF) and their distinguishing features

15.6 Prevention, Treatment, and Prognosis

In 2010, the American College of Radiology published guidelines restricting the use of GBCAs in patients with compromised renal function, which subsequently have been updated [115]. These recommend that alternative imaging studies, which do

Table 15.4 Therapies attempted for gadolinium-induced fibrosis

Ineffective
Topical corticosteroids
Oral corticosteroids
Histamine-2 receptor antagonists
Thalidomide
Cyclosporine
Variable effectiveness
Plasmapheresis
Ultraviolet-A phototherapy
Extracorporeal photopheresis
Sirolimus
Sodium thiosulfate
Renal transplantation
Promising effectiveness
Imatinib mesylate

From Bernstein et al. [104]

not require GBCA, be considered for patients with renal disease. Administration of high-risk GBCAs, especially in double and triple doses, should be avoided. When a medium- or low-risk GBCA is used, the patient should be given the lowest dose necessary to obtain the desired clinical information. Immediately after GBCA exposure, HD should be considered for patients with severe renal dysfunction, although it has been shown that HD following GBCA administration does not completely prevent GIF [15]. Following the introduction of these guidelines, very few new cases of GIF have appeared.

Treatment of established GIF remains challenging (Table 15.4). Shortly after the first cases of GIF appeared, a variety of treatments were attempted, but none was effective. These included potent topical steroids, selective H2 blockers, immunosuppressive agents such as prednisone and cyclosporine, and plasmapheresis. Treatment with other medications, such as pentoxifylline and sodium thiosulfate, were reported to result in qualitative improvement in individual patients. Improvement in skin "tightness" and in mobility was described in several patients who underwent extracorporeal photopheresis with UV-A, but others who received this treatment did not respond.

Imatinib mesylate, an inhibitor of the bcr-abl tyrosine kinase, inhibits the translation and transcription of type I collagen and fibronectin by dermal fibroblasts [116]. Prompted by this finding, one of us (JK) treated two GIF patients with imatinib mesylate. Each patient exhibited a rapid reduction in his modified Rodnan skin score, reflecting improvement in skin tethering. Knee joint range of motion also increased in one patient with joint contractures. On histological examination of skin, after 4 months of imatinib mesylate treatment, dermal collagen deposition was less dense, and immunohistochemical staining for type I procollagen was decreased. Clinical improvement regressed when imatinib mesylate was discontinued, and the patients again improved when therapy was resumed [92]. Subsequently, others have confirmed that imatinib mesylate brought about similar improvement in other

patients with GIF [117, 118]. Furthermore, gadolinium-induced dermal lesions were less severe in rats treated with imatinib mesylate, compared to untreated controls [119]. Consequently, imatinib mesylate became a standard treatment for GIF. However, because not all changes of GIF are reversible late into the disease course, it is best to initiate medical therapy as early as possible to prevent progression of fibrosis and development of joint contractures.

Because joint contractures and cutaneous fibrosis can be very painful, especially when fluid retained in the legs cannot expand because of fibrosis of the overlying skin, many GIF patients required chronic treatment with narcotic analgesics to control their symptoms. Thus, many became dependent upon narcotics and required dose escalation over time.

Non-pharmacological treatments are also very important for patients with GIF. Physical therapy should be initiated, with splinting of joints to maintain and improve range of motion and reduce fixed contractures. Hand therapy may be useful to improve hand function and provide devices to assist in the performance of activities of daily living. When significant knee joint flexion contractures prevent independent ambulation, wheelchairs and other appliances to assist patients with mobility may be required.

15.7 Future Directions and Conclusions

Exposure of individuals with renal dysfunction to GBCAs, which once were believed to be safe to use in patients with underlying renal disease, has been strongly associated with the subsequent development of a chronic, often systemic, fibrosing disease. The term "nephrogenic systemic fibrosis" mischaracterizes that which has been learned about the etiopathogenesis of this condition, since it neither originates in the kidney nor produces kidney tissue. The term "gadolinium-induced fibrosis" more accurately reflects the totality of our understanding of this condition. In patients with renal dysfunction, every effort should be made to avoid using the high-risk GBCAs: formulated gadodiamide, gadopentetate dimeglumine, and gadoversetamide. Eliminating the use of these agents in patients with underlying kidney disease, according to restrictive guidelines, has largely eradicated new cases of this disabling and potentially fatal condition. Emerging anti-fibrotic therapies, such as imatinib mesylate, may reduce the extent of disease and alleviate suffering among those patients who already have developed GIF.

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Index

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