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IgG4-Related Disease

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Preface

The past decade has witnessed the birth of a "new" multi-organ system, immune-mediated disease now known by consensus as IgG4-related disease (IgG4-RD). Excitement about this disease has stemmed both from the recognition of aspects of the disease that are truly new and from understanding certain features recognized in previous eras in a novel, broader context. IgG4-RD can be tracked readily back through every decade of the last century and easily into the 1800s, but there is little reason to believe that the condition is not far older.

In a chapter in this book, Drs. Kawa and Kawano liken this disease to "a crow flying through the dark night" of medical history. This is an apt metaphor. For well over a century of recorded medical history now, IgG4-RD has met one of three fates:

- It was labeled with another name—generally one emphasizing a disorder believed to affect only a single organ: "reactive lymphadenopathy," Riedel's thyroiditis, Ormond's disease, Küttner's tumor, and so on.
- It was grouped erroneously into established diagnostic categories (e.g., Sjögren's syndrome, tubulointerstitial nephritis, autoimmune pancreatitis, sclerosing cholangitis, and hypertrophic pachymeningitis).
- It was entirely unrecognized.

The process of identification IgG4-RD and stripping it away from diseases with which it was previously lumped or misclassified has enhanced our understanding of multiple other conditions, too. As examples, Sjögren's syndrome is not—as many of us once learned—associated with pancreatitis. Rather, patients with "Sjögren's syndrome" who have pancreatitis really have, in all likelihood, type 1 (IgG4-related) autoimmune pancreatitis and salivary gland enlargement secondary to IgG4-RD. Furthermore, IgG4-RD mimicking Sjögren's syndrome accounts for at least a portion (but not all) of the "Sjögren's syndrome" patients who do not have antibodies to the Ro or La antigens. Finally—but not the final example we could cite—IgG4-related sclerosing cholangitis accounts readily for the fact that a subset of patients with "primary sclerosing cholangitis" respond to glucocorticoids. This is because the true diagnosis for that subset of patients is in fact IgG4-related sclerosing cholangitis.

Over the last 10 years, IgG4-RD has been identified in every organ system and its clinical features have been outlined in broad strokes. Its pathology characteristics have been reported in a consensus document as well as hundreds of other papers devoted to the pathology features of individual organs. Nomenclature has been established and diagnostic criteria developed for both the overall condition and certain individual organ system manifestations. An effective therapy for this condition—glucocorticoids—has been identified. This treatment has been employed long enough now to realize that although patients often respond quickly and dramatically, the treatment is associated with high morbidity itself and often fails to induce lasting remissions. The need for the identification of effective steroid-sparing agents has been acknowledged.

Other important steps forward—without which none of the above would have been possible—have included multi-center collaborations on IgG4-RD, both within individual countries and across international boundaries. Such collaborations have been particularly productive in Japan, but more recently similar collaborations have developed in the United States and among specialists from many disciplines across multiple countries.

As the first decade of knowledge about IgG4-RD comes to a close, we are at the end of the beginning of our understanding of this condition. Now the next set of challenges—and perhaps the truly hard work—really begins. One illustrative example of where progress must come is in the area of pathophysiology. Although the general clinical boundaries of the disease have been mapped and the major and minor pathology features identified, our fundamental understanding of the condition at the mechanistic level remains primitive. Indeed, it is not yet clear whether IgG4 and IgG4-bearing plasma cells—which are such prominent findings in the serum and tissues of patients with this condition—have a central pathogenic role or whether they are merely "role players" in a larger symphony of inflammation that characterizes this disease.

A second area where more detailed knowledge is needed pertains to epidemiology. The epidemiologic features of IgG4-RD and its subsets of organ disease remain largely uncharted. Despite confirmations of IgG4-RD in every organ system and the rapidly expanding number of reports of this disease in the medical literature, even basic epidemiologic facts about this condition are not known with any level of certainty. This stems in part from the fact that the diagnosis of IgG4-RD remains challenging: many clinicians and pathologists remain unfamiliar with the disease, and one cannot diagnose what one does not know. The pathologic diagnosis of IgG4-RD requires considerable experience and a detailed understanding of how to integrate information from histopathology and immunostaining studies, and clinicians must recognize the possibility of IgG4-RD before a biopsy is even considered. All too often, we still back into the diagnosis after a patient is sent for a biopsy for the presumptive diagnosis of cancer. In short, significant challenges in diagnosis pose major issues in attempts to define the epidemiology of IgG4-RD.

Progress in IgG4-RD will require broad collaboration—among experts from many specialties, among clinical and basic investigators, and among the growing number of physicians worldwide who are driven to understand this remarkable disease. We suspect that the disease has much to tell us—about immune system pathways, to be sure, but also possibly much more: about the interplay between allergic and inflammatory disease; the connections between inflammation and malignancy; the interactions between cellular components of the immune system; potential environmental precipitants of disease; and more. Like any good mystery, the resolution of certain questions merely raises others, even as the field progresses, understanding deepens, and patient care is enhanced.

As the condition now known as IgG4-RD celebrates its tenth birthday, we are delighted to compile a current collection of knowledge pertaining to this disorder. We anticipate a second decade every bit as rich and exciting as the past 10 years have been, and look forward with eagerness as the journeys to understanding continue and merge.

Acknowledgments

Although limitations of space prevent us from thanking individually the many researchers and collaborators who have contributed in various ways to the IgG4-related disease field itself and also to making possible the completion of the English version of this book, we would like to gratefully acknowledge the work of all these persons in the aggregate here.

We would in addition like to make a special acknowledgment of the contribution made by the members of the all Japan IgG4 team, which was supported by the research program for the Study of Intractable Diseases provided by the Ministry of Health, Labor and Welfare of Japan. We are also very grateful to Mr. John Gelblum for his help with the translation and other aspects of this book.

Finally, we would like to dedicate this book to our patients whose experiences have taught us so much.

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An Overview

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Shigeyuki Kawa and Mitsuhiro Kawano

1.1 Introductory Remarks

In 2007, a small group of Japanese researchers held a meeting on type 1 autoimmune pancreatitis (AIP) and its types of extrapancreatic organ involvement. The meeting, held at a small hot-spring hotel in Ishikawa prefecture, generated great excitement and debate continued late into the night. Yoh Zen's Th2 cell and regulatory T cell dominant response theory [1] was introduced to a wide range of researchers on this occasion. This successful conference raised the field to a higher status and the attendees resolved to conduct annual meetings for the study of "IgG4-related disease (IgG4-RD)."

In 2010, the steering committee of this annual meeting published the first Japanese-language book in this area entitled "Invitation to IgG4-Related Disease." Two years later, however, the rapid growth of knowledge and increasing attention focused on IgG4-RD prompted us to publish a second book entitled "Atlas of IgG4-Related Disease." The goal of this book was to delineate the characteristic features of individual organs radiologically and histopathologically, with reference to many color photographs. After the publication of this book, Takayuki Sumida, the president of the Japanese Sjögren's Syndrome Society, noting that no English-language book on this disease was available, proposed that we publish an English version, so that physicians and researchers in countries other than Japan could read it, as well. In this way we undertook to translate into English and provide an update of current thinking about the spectrum of this disease. We very much hope that our international readers will find the results of our efforts of some interest and benefit.

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Until the concept of an overarching, systemic disorder was established at the beginning of the present century, IgG4-RD had eluded recognition despite tantalizing hints and flew like a crow on a dark night through the history of medicine [2, 3]. One reason why the recognition of this disease was so delayed is that its clinical picture is extremely diverse and highly dependent on the pattern of organ involvement. Most physicians limited their focus to lesions in organs in their own respective specialties, without making the leap of recognition required to understand the systemic nature of the process.

According to the organs most affected, patients present to various medical departments including those of ophthalmology, otolaryngology, pulmonology, gastroenterology, urology, neurology, nephrology, and rheumatology. Until the establishment of the larger disease concept of IgG4-RD, the need to share both patient information and clinical expertise among different fields was not apparent.

The second reason for delayed recognition is the tendency of IgG4-RD to cause only relatively mild clinical symptoms. The subtle presentation of this condition often belies the prominent imaging findings of the lesions within individual organs. Some lesions, notably salivary gland swelling, can be left untreated for prolonged periods without problems and without subjecting the patient to the adverse effects of glucocorticoids. Recognition of the unifying concept of IgG4-RD therefore had to await the historical discovery of markedly elevated serum IgG4 concentrations in AIP (once termed "sclerosing pancreatitis") [4].

Subsequent to the establishment of the relationship between AIP and elevated serum IgG4 concentrations, the broader context was identified over the next decade as one extrapancreatic manifestation after another was linked to both high concentrations of IgG4 in blood and striking similarities in the pathology findings across all affected organs. The systemic nature of this disease as a single systemic disorder with diverse clinical expression was thereby understood in a manner analogous to that in which one assembles a jigsaw puzzle [2, 3, 5, 6]. Sharing the accumulated

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experience of ophthalmologists, otolaryngologists, neurologists, gastroenterologists, pulmonologists, nephrologists, rheumatologists, urologists, radiologists, pathologists, dental surgeons, cardiovascular surgeons, and others has been indispensible in delineating the breadth of IgG4-RD. Moreover, the contributions of investigators from many parts of the world have been invaluable. In 2011, many such investigators gathered in Boston to hold the first international symposium on IgG4-related disease. At this gathering, a consensus was reached regarding the nomenclature and the pathological findings of lesions in individual organs [7, 8].

In this book, the history of the discovery of this disease, currently established therapies, and imaging and pathological characteristics of individual organs are described. In this chapter, we provide a short overview of IgG4-RD, including its clinical associations and future anticipated developments.

1.2 IgG4 as a Subclass of IgG

IgG consists of four subclasses: IgG1, IgG2, IgG3, and IgG4 [9]. In healthy persons, IgG4 is the least abundant subclass, accounting for only 3–6 % of the total IgG. Unlike IgG1, IgG2, and IgG3, IgG4 does not bind to C1q and is not believed to activate complement effectively [9]. In addition, its ability to bind Fc receptors is weak. On the other hand, in IgG4-RD, hypocomplementemia and elevated blood immune complexes levels are often found, with C3 and C4 levels decreased [4, 10–12]. Because there are cases in which immune complex levels are high when measured by the C1q method, as well, IgG, rather than IgG4 may be involved in immune complex formation [10]. (It is typical for serum IgG1 concentrations to be elevated in such cases, as well.) Patients with hypocomplementemia often manifest renal disease but given the profound degree of hypocomplementemia observed, the clinical symptoms in IgG4-RD are mild in contrast to those of systemic lupus erythematosus (SLE) [11, 12]. Deposition of immune complexes in IgG4-RD has been reported mainly in the renal tubular basement membrane [13–15]. Accordingly, no evidence to suggest that immune complexes are actively involved in the tissue injury of IgG4-RD is currently available.

Characteristics not found in immunoglobulins other than IgG4 include Fab-arm exchange [16] and rheumatoid factor-like activity [17, 18]. In general, the IgG molecule is formed by heavy (H) and light (L) chains that have the same amino acid sequence as their counterparts in the other half-molecule. IgG also has two same binding sites for the same antigen; i.e., it is bivalent. Because the disulfide bonds between the H chains are unstable in the IgG4 molecule and sometimes separate, combinations of H and L chains can form that have binding sites for two different antigens, thereby producing a novel molecule. This phenomenon, unique to IgG4 among all of the immunoglobulins, is referred to as the "Fab-arm exchange" property of IgG4 [16].

The theoretical upshot of Fab-arm exchange is that the IgG4 molecule is unable to cross-link the same antigen and its binding avidity is markedly decreased. This greatly decreases the likelihood that IgG4 will be associated with immune complexes and probably has a substantial impact on the anti-inflammatory action of IgG4.

IgG4 has also long been known to react with the Fc portion of IgG; in other words, to have rheumatoid factor activity. However, the reactivity of IgG4 to the Fc portion of IgG is not because of binding by the IgG4 Fab fragments but rather Fc to Fc binding (i.e., IgG4 Fc binding to IgG Fc) [17, 18]. Thus, this Fc binding is not rheumatoid factor activity in a strict sense. The physiological and etiopathological significance of this rheumatoid factor-like activity of IgG4 is presently unknown.

1.3 Conditions Causing Abnormal Elevations of IgG4 or Associated with IgG4

Diseases associated with abnormally elevated serum IgG4 concentrations include allergic disorders such as atopic eczema [19, 20]. Beekeepers who are hyposensitized to bee venom after years in their occupation have markedly elevated serum concentrations of IgG4. This observation is consistent with the concept that IgG4 is an antibody that serves a protective function in the setting of allergic disease [21]. However, opinions differ as to whether IgG4 alone plays the main role in desensitization therapy. In parasitic infestations such as filariasis [22] and schistosomiasis [23], serum parasite specific IgG4 concentrations are elevated.

Pathogenic IgG4 is implicated in a number of antibody-triggered bullous dermatoses [20]. Representative examples include pemphigus, bullous pemphigoid, and epidermolysis bullosa acquisita. Pathogenic IgG4 has similarly been implicated in other conditions such as myasthenia gravis [24], "idiopathic" membranous nephropathy [25], and thrombotic thrombocytopenic purpura [26]. However, these conditions have no relationship to IgG4-RD and are not encompassed by the spectrum of IgG4-RD.

1.4 Clinical Picture of IgG4-RD

IgG4-RD most commonly affects middle-aged and elderly men [2]. Onset below the age of 20 years is extremely rare. Allergic conditions such as bronchial asthma, allergic rhinitis, and chronic sinusitis are frequently associated with IgG4-RD, and peripheral blood eosinophilia and elevated serum IgE

concentrations are often found [2, 27]. Rheumatoid factor and low titers of antinuclear antibodies are present in many cases, but almost no patients have disease-specific antibodies. Coexistent autoimmune disease is rare [27].

Although involvement of the salivary and lacrimal glands is common, the disease is plainly distinct from primary Sjögren syndrome. If antibodies against either the Ro/SSA or the La/SSB antigens are detected, then this unusual combination is assumed to represent the chance occurrence of two unrelated conditions [27]. In cases with sialadenitis, xerostomia is found but is usually mild and typically less severe than that associated with primary Sjögren syndrome.

AIP and sclerosing cholangitis commonly present with obstructive jaundice and are sometimes diagnosed with and treated for pancreatic cancer, but in general other lesions show relatively mild clinical symptoms [28–30]. Affected organs show swelling, mass formation, nodule formation, and/or hypertrophy/thickening. Either single organs or various combinations of multiple organs can be affected [31]. Disease in multiple organs can be present simultaneously but often appears metachronously in serial organs over time.

Examinations of the peripheral blood generally reveal elevated serum IgG levels, and hypocomplementemia is also often present. Although the erythrocyte sedimentation rate can be markedly elevated as a function of hypergammaglobulinemia, serum C-reactive protein (CRP) concentrations are usually normal. The major exceptions to this rule regarding CRP are patients with vascular involvement, e.g., IgG4-related aortitis. The serum IL-6 concentration—an important driver of CRP—is also usually normal. This fact is useful in differentiating IgG4-RD from Castleman disease [32]. Soluble IL-2 receptor values are frequently elevated in IgG4-RD, a reflection of lymphocyte activation [33].

A characteristic feature of IgG4-RD is an elevated serum IgG4 concentration (to ≥135 mg/dL) or a serum IgG4/IgG ratio in the peripheral blood of ≥8 % [34]. The positive and negative predictive values of elevated serum IgG4 concentrations are not sufficiently high as to stand alone as diagnostic tests, however. IgG4 concentrations are normal in approximately 20 % of cases and conversely, as noted above, allergic diseases, parasitic infestations, and autoimmune blistering conditions can be associated with elevated serum IgG4 concentrations. Vasculitides such as Churg–Strauss syndrome and granulomatosis with polyangiitis (formerly Wegener's), some cases of rheumatoid arthritis, as well as Castleman disease, pancreatic cancer, and other conditions may also show elevated values [35]. Thus, excessive importance should not be attached to the presence or absence of an elevated serum IgG4 concentration.

More critical to the diagnosis is the finding of a prominent IgG4-positive plasma cell infiltrate in tissues. The typical histopathologic finding is a lymphoplasmacytic infiltrate, with ≥40 % of the plasma cells present staining positively for IgG4 (i.e., the IgG4/total IgG ratio in tissue is typically >0.4). Cutoff values for the absolute number of IgG4-positive plasma cells per high-power field within a given organ vary according to the specific organ [8]. This point was one of the major conclusions from a detailed consensus that emerged from the work of the international symposium held in Boston in 2011 [8]. Care must also be taken in the interpretation of the finding of IgG4-positive plasma cell infiltrates, because such infiltrates can be found in conditions other than IgG4-RD, including adjacent to neoplastic lesions [36, 37]. Organ-related histopathological features and diseases requiring differentiation in each organ are described in detail in the pathology chapters in this book.

1.5 Mechanisms Underlying the Development of IgG4-RD

Both the innate and adaptive immune systems are suspected of playing significant roles in disease pathogenesis. With regard to the innate immune system, microbial antigen stimuli have been shown to enhance IgG4 production by B cells. This is mediated through the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) or toll-like receptor (TLR) on monocytes or basophils, leading to the production of B cell-activating factor of the tumor necrosis family (BAFF) [38, 39]. Increased serum concentrations of both BAFF and a proliferation-inducing ligand (APRIL) have also been reported in IgG4-RD, but at this time verification of these reports is necessary [40].

Reports of the presence of various autoantibodies in IgG4-RD suggest potential contributions from adaptive immunity, albeit the etiopathogenetic significance of such antibodies has not been clarified [41]. According to one theory, when type 1 AIP patients develop *Helicobacter pylori* infection, antibodies against bacterial cell carbonic anhydrase II (CA-II) are produced and induce pancreatic injury through molecular mimicry by reacting with pancreatic CA-II [42]. The HLA DRB1*04:05 molecule, which is surmised to be related to the development of type 1 AIP [43], presents fragments of CA-II to T cells [42]. Moreover, AIP has been reported to be induced in mice when they are made to express HLA DRB1*04:05 [44].

In the background of these immunological abnormalities, cytokines produced by type 2 helper T cells (Th2 cells) and cytokines produced by regulatory T cells (Treg) may also contribute to the disease pathophysiology (Fig. 1.1) [1, 45]. Of Th2-type cytokines, IL-4, IL-5, and IL-13 are thought to be involved, and their focal overproduction at sites of disease activity has been demonstrated. IL-4 is believed to be an essential component in the class switch to IgE. The Treg cytokines IL-10 and TGF-β are also both overproduced in IgG4-RD lesions. IL-10 is an important cytokine in the class

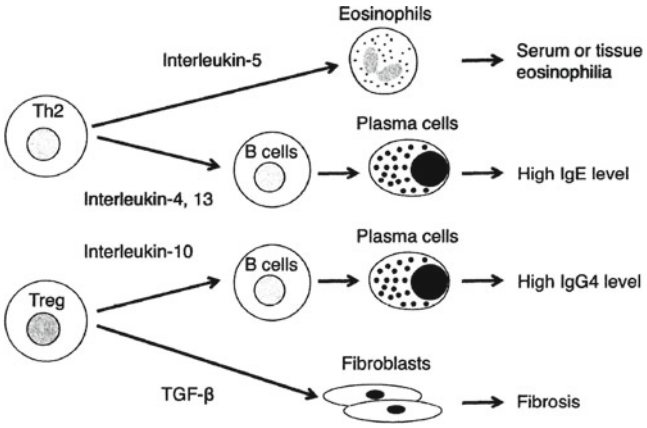

Fig. 1.1 Cytokine involvement in the pathogenesis of IgG4-related disease (modified and referred from Fig. 3 in [3])

switch to IgG4, while TGF-β is implicated in fibrosis. Some reports have also suggested that IL-21 produced from Th2 cells during the formation of lymph follicles plays an important role [46].

1.6 Concluding Remarks

IgG4-RD is a systemic disease that encompasses almost all medical disciplines. Its clinical spectrum ranges from cases that require no active treatment but only conservative follow-up to severe cases that, if neglected, may progress to renal failure or other serious organ dysfunction. The potential association between IgG4-RD and malignant tumors in some cases requires further scrutiny [47]. Most of the events in the etiopathogenesis of IgG4-RD require further definition. In order to sustain and enhance progress in all of these areas, physicians and scientists with broad collective expertise will be needed to continue the excellent tradition of collaboration established early on in the setting of IgG4-RD.

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Some Recollections of the History of Research on IgG4-RD

2

Establishment of the Concept of Lymphoplasmacytic Sclerosing Pancreatitis (LPSP)

Kenji Kawaguchi

2.1 Introductory Remarks

More than 20 years have passed since a paper describing cases of pancreatitis associated with cholangitis and showing a distinct clinicopathological picture was brought to the medical world's attention [1]. That paper described the histopathological findings of two cases in detail and speculated about the possibility of an association with systemic disease. The subsequent decade produced few additional insights about this condition. However, entering the 2000s, Hamano, Kawa, and colleagues in the Department of Gastroenterology of Shinshu University noted elevated serum IgG4 concentrations in patients with "sclerosing pancreatitis" and recognized the novelty of this finding. Since then there has been an explosion of clinical and pathological investigations focusing not only on the pancreatic and bile duct lesions but also increasingly on other associated lesions that have by now been detected in virtually all organs of the body [2]. Within the past several years, it has been suggested that lymphoplasmacytic sclerosing pancreatitis (LPSP) is one manifestation of the systemic disease now known as IgG4-related disease (IgG4-RD), and as such it has also attracted the attention of numerous clinicians and pathologists.

A favorite saying of my mentor and former chief of the pathology section of Komagome Hospital, Morio Koike, was that "Surgical pathology is a clinical discipline that provides the final diagnostic judgment and at the same time raises diverse new issues." He also used to emphasize that the essence of pathology is a process of playing catchball with the clinical disciplines.

I am very pleased that in response to the issues raised by the discovery of "IgG4"—the shorthand name for this condition now confirmed to be a systemic disease—the ball was thrown back to us pathologists. In this chapter, I rely on reminiscence to describe those two early cases and issues that were of major significance in unravelling the nature of IgG4-RD.

2.2 Two Coincidentally Overlapping Cases

In my younger days there was an atmosphere of great intellectual curiosity and excitement in the Department of Pathology of Komagome Hospital. Anyone was welcome to observe autopsy cases and surgical specimens of interest and was encouraged to offer his own opinions without hesitation regardless of experience or specialty. At that time at Komagome Hospital, numerous well-known clinicians worked and actively sought pathology consultations on their cases. Relationships between the Department of Pathology and the clinical services characterized by respect and mutually beneficial tension were established and maintained.

In December, 1988, a regional hospital that had no pathologists requested a pathology review of surgical materials by Dr. Koike. As luck would have it, Dr. Koike instructed me, who just happened to be on hand, to undertake this review. By a stroke of good fortune for me, the first case of LPSP was from that hospital. A 74-year-old man had presented with obstructive jaundice. He was diagnosed based on the imaging and laboratory findings with cancer of the pancreatic head and underwent pancreatoduodenectomy. The macroscopic appearance of the pancreas was of a swollen, grey-white, and firm organ with little residual lobular structure. The histopathological picture was extremely distinctive, with the pancreas showing an unclear remnant of lobulation and diffuse, dense intralobular and interlobular infiltrates that consisted of mature plasma cells and lymphocytes. There was also obliteration of veins caused by fibrosis that demonstrated a distinctive pattern and extension of the infiltration from the interlobular interstitium to the peripancreatic connective tissue. In sum, these parenchymal findings suggested the presence of an inflammatory pancreatic mass.

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The pancreatic ductal morphology was relatively well preserved, and epithelial cell injury was slight. The common bile duct and gallbladder wall, both of which were markedly thickened, showed histological findings that were similar to those of the pancreas. Regional lymph nodes showed lymphoid follicle formation, dense plasma cell infiltration, and marked swelling. Atypia was not observed in the pancreatic duct epithelium, nor were there any findings of pancreas cancer. My final report could conclude only that these histological findings differed entirely from those of chronic pancreatitis, which inevitably show dilatation of the pancreatic duct associated with pancreatic stone formation—characteristic, for example, of the type of pancreatic injury incurred as the result of alcohol abuse.

Then, through remarkable coincidence, I came across a similar case only 1 month later. The second patient, a 69-year-old man referred because of obstructive jaundice, had also undergone pancreaticoduodenectomy for a diagnosis of cancer of the pancreatic head. The macroscopic and histopathological findings were similar to those of the first case and although I was convinced that it represented the same disease process, I was unable to identify the name of any corresponding disease within any textbook of surgical or pancreatic pathology available at that time. In contrast to the current era, when the computer has made searching the medical literature so easy by comparison, I had to wade through the enormous Index Medicus. Despite many hours and enormous effort, I was unable to pinpoint an appropriate diagnostic name for these two patients' condition. I signed out the final pathology report on the two cases in the following manner: "Specific chronic pancreatitis enveloping the biliary tract."

In leafing through a file in which I keep interesting references and case reports, I subsequently found a clinicopathologic conference (CPC) from the New England Journal of Medicine (NEJM), published in 1982 [3]. That CPC reported a 55-year-old man with obstructive jaundice. The descriptions of pathology findings in the resected gallbladder, bile duct, and pancreatic biopsy tissues closely resembled those of the two cases I had evaluated. The pathology diagnosis in the NEJM CPC was primary sclerosing cholangitis (PSC). Reading the case reported in the NEJM prompted me to begin a reference search focusing on the differential diagnosis of such cases. And although this published case was not my own, it became a very valuable third one, motivating me to prepare a paper stressing the rarity and ambiguity of this disease entity.

2.3 Could This Be "Autoimmunity"?

At that time in Komagome Hospital, no cases of PSC were available for a histopathological comparison with the features of my cases. Furthermore—and somewhat surprisingly, perhaps—almost no textbooks or reference papers reported the histopathological findings of PSC in sufficient detail for me to decide if these cases truly represented PSC. Because we were not able to exclude PSC pathologically and to avoid criticism from Western reviewers, we added PSC to the subtitle to the title of our manuscript.

I considered it important to also differentiate these two pancreas cases from conditions showing a similar histopathological picture—for example, chronic sclerosing sialadenitis (Küttner tumor), chronic thyroiditis, and inflammatory pseudotumor. However, this was difficult solely on the basis of histopathological findings on H&E stains. In considering the possibility of autoimmune disease as a factor in these two cases, we investigated whether associations existed with any already recognized diseases such as Sjögren's syndrome, by performing salivary gland biopsies and searching for serum autoantibodies. In a minor salivary gland biopsy from one patient of these two pancreas cases, the sialadenitis demonstrated had features similar to those of "Sjögren's syndrome." We also noted that antinuclear antibodies were slightly positive in the sera of these patients and demonstrated other immunological abnormalities, as well, including positive LE preparations, anti-mitochondrial antibodies, and hypocomplementemia.

We considered the possibility that the patients had mounted autoimmune responses against their pancreas and bile duct tissues and used immunofluorescence assays to search for autoantibodies to these organs. We were unable to detect any antibodies to either the bile duct or pancreatic duct epithelium or the pancreatic acinar cells. We therefore decided not to use "autoimmune pancreatitis" in the title of our manuscript, despite the catchy sound of that term, but rather employed a descriptive diagnostic title instead. Even today I feel that there is still some resistance to referring to this form of pancreatitis as "autoimmune."

2.4 Further Indications of a Systemic Disease

In 1984, I assessed another case that had a major impact on my thinking. This was an autopsy case of a 70-year-old man who was the subject of a CPC at the Komagome Hospital in October of that year. The clinical diagnosis was pulmonary fibrosis and retroperitoneal fibrosis, with death attributed to lung abscess and hemothorax. Dr. Takizawa was the pathologist in charge of the CPC, and I still remember the pathology findings. A summary of these is shown below.

1. Circumferential, fibrous thickening of the aorta and the tunica adventitia of the main trunks of its primary arterial branches
2. Segmental, circumferential, fibrous thickening of the ureters at the site of their crossing of the common iliac artery

3. Extensive fibrosis of the pancreas
4. Circumferential, fibrous thickening of the bile ducts in the porta hepatis, enveloping both the intra- and extrahepatic bile ducts
5. Encasement of the bronchovascular bundles within both lungs in fibrotic sheaths, extending to interlobular interstitial fibrosis

Based on both the macroscopic and microscopic findings of the fibrotic lesions within the pancreas and bile ducts of that case, I had no doubt that this patient also had longstanding LPSP. More intriguing still was the observation—upon further exploration of the details of this patient's case—that the tissue obtained at the time of a transurethral resection of the prostate 4 years prior to death also demonstrated a lymphoplasmacytic cell infiltrate and fibrosis that resembled the morphology detected in the pancreas. This curious systemic fibrosclerosing disease was therefore understood to affect the prostate in a fashion strikingly similar to the manner in which the pancreas was shown to be involved. These pathological findings of the prostate were considered to be the same as those reported by Uehara, at present in the Central Laboratory Section of Shinshu University Hospital [4]. Although the details of this autopsy case were unfortunately never published, they remain in my mind even now as an example of how IgG4-RD can affect many organs either simultaneously or metachronously.

Recollections of other cases serve only to solidify this concept further, even if confirmation of the biopsy in retrospect is not always possible. A reexamination now of a case of coronary arteritis associated with a striking form of aortitis, first reported in 1988 by Tanaka et al. from Komagome Hospital, raises the possibility that these lesions represented one type of arterial involvement of a systemic disorder related to this kind of pancreatitis [5]. In addition, a case with systemic "Castleman's disease" admitted to the Hematology Service was characterized by extensive pancreatic swelling on diagnostic imaging. The requested pancreatic biopsy could not be performed, and no definitive conclusion could be reached in that case. The morphological specificity of these cases could be speculated about in papers but not proven. These cases were viewed as true rarities at the time in the absence of any larger context, and the path forward on additional investigations was not clear.

2.5 Curious Evolution of Our Understanding of an Unusual Type of Pancreatitis

After publishing the LPSP paper, I started to work at the 1st Department of Pathology of Shinshu University. The gastroenterology group of the 2nd Department of Medicine of this university was actively accumulating and clinically analyzing cases of "autoimmune pancreatitis" at that time. In addition, the groundbreaking paper of Hamano et al., which suggested a strong association between serum IgG4 concentration, sclerosing pancreatitis, and retroperitoneal fibrosis, was published. This paper was based on three cases, one of which was from Shinonoi General Hospital, where I am presently employed [6].

Drs. Hamano, Kawa, and their colleagues at Shinshu University are universally recognized as major leaders of research on IgG4-RD not only in Japan but also internationally. In addition, Dr. Kamisawa, presently at Komagome Hospital, became extremely interested in the pancreatic manifestations of the disease and proposed the term "IgG4-related sclerosing disease" for the underlying condition, based on his conviction that they represented similar manifestations of a single systemic disease [7]. Kamisawa actively follows The Department of Pathology of Komagome Hospital's approach to surgical pathology, by paying much attention to autopsy cases while also considering carefully the systemic background. This approach has led to further studies that have extended the findings of my own paper and has facilitated innovative research on diverse topics, being a source of great pride to all former and present members of the Department of Pathology of Komagome Hospital.

2.6 Concluding Remarks

As I initially imagined, thanks to the revolutionary concept of "IgG4," the histopathological picture shown by such pancreatic and bile duct lesions was eventually proved to be LPSP, and the likelihood of it being one manifestation of a systemic disease has become very strong. Although my paper has been excessively praised as ushering in the era of IgG4-RD research, it must be clearly stated that it and all subsequent studies have only been possible because of the recognition by Hamano and colleagues of the clinical significance of "IgG4." And if my observations are indeed useful, the most that I can claim is a refusal to pass off interesting findings as mere coincidence, as well as a strict adherence to one of the fundamental tenets of surgical pathology, namely, remaining unafraid to speculate and welcoming the raising of new issues.

In any event, although IgG4-RD is now understood to encompass a wide spectrum of conditions, much remains uncertain. In the near future, on a foundation of basic research, case analysis studies conducted on a national scale will be needed to clarify their etiopathogenesis and devise optimal diagnostic and therapeutic strategies for all IgG4-related manifestations.

However, I suspect that the IgG4 molecule itself is not the master key that will unlock the door to the answers to many of the issues that remain to be resolved. I suggest that the

importance of serum IgG4 concentrations and the results of IgG4 immunostaining studies not be overemphasized. Instead, I would hope that all investigators in this field will take a comprehensive look at the systemic and histopathological findings before making any final judgments regarding this complex disease.

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History: Pancreas

3

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3.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a systemic disorder characterized by high serum IgG4 concentrations and abundant IgG4-positive plasma cell infiltration in affected organs. Autoimmune pancreatitis (AIP) and Mikulicz's disease are two major manifestations of this condition; lesions associated with IgG4-RD have been reported in the respiratory system, bile ducts, retroperitoneum, kidney, prostate, thyroid gland, and others. Many of the characteristic imaging and pathologic findings of these lesions in the respective organs have been documented in the literature, and in this book these findings are outlined and discussed in greater detail. In this chapter, we describe how the concept of IgG4-RD was elaborated, focusing on AIP and other pancreatic lesions, and consider separately events that occurred prior to and after recognition of the fact that IgG4 plays an important role in this condition [1].

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3.2 Prior to Recognition of the Involvement of IgG4

3.2.1 Pancreatitis in Which Autoimmune Mechanisms Are Suspected

A specific type of pancreatitis associated with autoimmune phenomena has long been suspected. In 1961, Sarles et al. in France noted hypergammaglobulinemia and local lymphoplasmacytic cell infiltrates in pancreatic lesions and implicated autoimmune mechanisms in the pathogenesis of pancreatitis [2]. In 1978, Nakano et al. reported for the first time the efficacy of glucocorticoid therapy in a disorder we now term AIP [3]. Nakano and colleagues observed the concomitant occurrence of Mikulicz's disease and hilar lymphadenopathy in their patient.

3.2.2 Lymphoplasmacytic Sclerosing Pancreatitis and Multifocal Idiopathic Fibrosclerosis

In 1991, Kawaguchi et al. outlined the characteristic pathologic findings of a pancreatic disorder they termed lymphoplasmacytic sclerosing pancreatitis (LPSP) [4]. These investigators reported widespread lymphoplasmacytic cell infiltrates, fibrosis, and obliterative phlebitis. Moreover, they observed that since the same histological findings could also be detected within lesions of the bile ducts and salivary glands in some of the same patients, there existed the possibility that this disorder was identical to the systemic disorder known as multifocal idiopathic fibrosclerosis (MIF), first proposed by Comings et al. in the 1960s [5].

MIF is known to be associated with conditions such as sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, Riedel's thyroiditis, sicca complex, and orbital pseudotumor. Many patients with these conditions are now recognized to have IgG4-RD. Although it is clear that IgG4-RD does not account

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for all cases of retroperitoneal fibrosis or mediastinal fibrosis, when one or more of these lesions occur in the same patient the probability of IgG4-RD as a unifying diagnosis is high.

3.2.3 Proposal of Chronic Pancreatitis with Diffuse Irregular Narrowing of the Main Pancreatic Duct

In 1992, Toki et al. drew attention to the narrowing of the main pancreatic duct that is now viewed as a cardinal feature of AIP. Toki and colleagues regarded their cases as having a new condition: "chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct" [6]. Today we identify the features of these four patients as being highly consistent with type 1 (IgG4-related) AIP: advanced age; male/female ratio of 3:1; mild abdominal pain and signs of obstructive jaundice, including serum elevations of biliary enzymes; diffuse pancreatic swelling on imaging; and histological findings of lymphoplasmacytic infiltrates and fibrosis. Gastroenterologists started to pay attention to these characteristic pancreatic duct and clinical findings, and many such cases were reported from Japan.

3.2.4 Proposal of Autoimmune Pancreatitis

In 1995, Yoshida, Toki, and colleagues summarized the clinical characteristics of chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct in a total of 11 cases derived from their own series, as well as cases reported by Nakano, Kawaguchi, and colleagues, and other reported cases in Japan (Table 3.1) [7]. The features they considered characteristic of "autoimmune pancreatitis" were hypergammaglobulinemia, the presence of various autoantibodies, lymphocytic infiltrates in the pancreatic parenchyma, any other coexistent "autoimmune diseases" (e.g., "Sjögren's syndrome"), and a favorable response to glucocorticoid therapy. These clinical characteristics have since been used by many clinicians as diagnostic guidelines [8], and many cases of AIP have subsequently been reported from Japan.

This report of Yoshida et al. became the basis for the preparation of "Diagnostic Criteria for Autoimmune Pancreatitis by the Japan Pancreas Society (2002)." The currently recognized clinical features of AIP are summarized in Table 3.2.

Table 3.1 Clinical characteristics of chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct (cited from [1])

1	Hypergammaglobulinemia (elevated blood IgG)
2	Presence of autoantibodies in serum
3	Diffuse pancreatic swelling
4	Diffuse irregular narrowing of main pancreatic duct
5	Pancreatic fibrosis associated with lymphocytic infiltrates
6	No or only mild abdominal symptoms (epigastralgia)
7	Constricting stenosis (jaundice) of the lower bile duct (intrapancreatic bile duct)
8	Not associated with pancreatic calcification
9	Not associated with pancreatic cysts
10	Associated with other autoimmune disorders
11	Steroid therapy very effective

Table 3.2 Characteristic clinical features of autoimmune pancreatitis (cited from [1])

1	Advanced age, male predominance
2	Often presents with obstructive jaundice; unlike usual pancreatitis seldom shows severe epigastralgia
3	Bilirubin and biliary enzymes are frequently elevated
4	IgG and IgG4 are frequently elevated. Especially IgG4 is useful in diagnosis and evaluation of disease activity
5	Abdominal US, CT, and MRI demonstrate pancreatic swelling
6	Pancreatic duct irregular narrowing and intrapancreatic bile duct stenosis are found
7	Gallium and FDG accumulation are seen in lesions focally
8	In pancreatic lesions focal marked lymphoplasmacytic infiltrates, fibrosis, obliterative phlebitis, and IgG4-positive plasma cell infiltrates are found
9	Steroid therapy is markedly effective, with clinical symptoms and signs and blood test and imaging findings all showing improvement
10	Repeated relapses promote pancreatic calcification

3.3 After Recognition of IgG4 Involvement

3.3.1 AIP and IgG4

Human IgG is composed of four subclasses numbered, in their order of identification, as IgG1 through IgG4. IgG4 comprises the smallest subclass under normal circumstances, usually accounting for no more than 7 % of the overall total IgG concentration and often even less. Elevated serum concentrations of IgG4 are reported in a number of conditions but are especially recognized to occur in allergic diseases, parasitic infections, and pemphigus.

Why and how, then, was the connection between elevated serum IgG4 concentrations and AIP recognized? The clue came from an observation pertaining to serum protein electrophoresis evaluations in these patients, namely, the finding of a slowly migrating "β–γ bridge" between the β-globulin and γ-globulin peaks. Immunofixation of this region revealed an elevated IgG4 fraction (Fig. 3.1) [9].

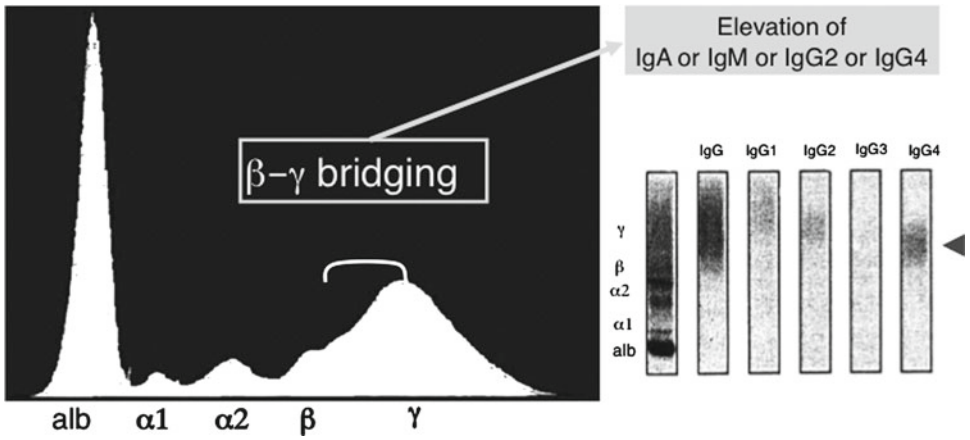

Fig. 3.1 Electrophoresis of the serum protein from a patient with autoimmune pancreatitis showing β–γ bridging and immunofixation study showing elevated IgG4 fraction

Subsequent analyses led to the realization that when serum IgG4 concentrations were compared between AIP patients and healthy persons, the values for the former group exceeded those of normal individuals by tenfold or more and that up to 90 % of AIP patients had elevated serum IgG4 concentrations. In contrast, elevated serum IgG4 concentrations of this magnitude were extremely rare among patients with conditions that often mimic AIP, to wit, pancreatic cancer, chronic pancreatitis of other etiologies, primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren's syndrome. In short, serum IgG4 concentrations were a useful factor in distinguishing AIP from these other conditions [9].

The finding of marked IgG4-positive plasma cell infiltrates within pancreatic lesions also proved in short order to be extremely helpful in establishing the histopathological diagnosis [10]. Moreover, these same IgG4-positive plasma cell infiltrates were also detected upon the histological examination of extrapancreatic lesions. It was therefore surmised that such pancreatic and extrapancreatic lesions share a common pathophysiology, and the underlying condition has come to be known as a systemic disorder related to IgG4, namely, "IgG4-related disease" [10–12].

3.3.2 Proposal of AIP from Countries Other than Japan (AIP Unrelated to IgG4)

Since 1995, AIP has been reported from countries other than Japan, as well. However, interesting differences have been observed in the nature of the AIP cases reported from Western countries, particularly from Europe, in comparison to the cases from Japan. The extent and explanation for these differences are the subject of ongoing investigations.

In 2002, discussions were held among researchers from the United States (Mayo Clinic), Italy, and Japan to clarify similarities and differences in AIP in the respective countries [13]. In the cases of AIP reported from Italy, the male/female ratio was approximately equal and the mean age at onset relatively young (42 years). However, the range in age of the patients affected was broad, and some patients presented with severe epigastric pain. No cases had elevated serum IgG4, and there was a frequent association with inflammatory bowel disease. All of these features differed substantially from the LPSP now known as type 1 (IgG4-related) AIP that is diagnosed most commonly in Japan, which is characterized by a male predominance, a tendency to affect older patients, mild abdominal symptoms, and generally striking elevations of the serum IgG4 concentration.

The cases of AIP reported from the Mayo Clinic differed histologically from LPSP in that destruction of the pancreatic duct epithelium associated with neutrophilic infiltrates was found and the existence of a histological subtype in which obliterative phlebitis is almost never present was reported. This variant, later named "idiopathic duct-centric chronic pancreatitis" (IDCP) by Notohara et al., is now regarded as being most compatible with type 2 AIP [14].

In 2004, Zamboni et al. reported a similar disease process from Italy that they termed "AIP with granulocytic epithelial lesions (GEL)" [15]. The clinicopathological pictures of IDCP and AIP with GEL, which are characterized by elevations in neither serum IgG4 concentration nor IgG4-positive plasma cell infiltrates within tissue, are identical. In summary, then, the LPSP variant of AIP that tends to predominate in Japan is recognized as being synonymous with type 1 (IgG4-related) AIP, and the IDCP/AIP with GEL variant—which has no relation to IgG4—is synonymous with type 2 AIP [16]. The frequency and clinical features of type 2 AIP in Japan remain largely obscure, because this entity is allegedly so rare in that country.

3.3.3 Diagnostic Criteria for AIP

In 2002, "Diagnostic Criteria for Autoimmune Pancreatitis by the Japan Pancreas Society (2002)" were presented. These included [1, 13, 17]:

- Narrowing of the main pancreatic duct that involves one third or more of the length of the pancreas, accompanied by pancreatic swelling.
- Hypergammaglobulinemia and/or positive autoantibodies such as antinuclear antibody and rheumatoid factor are noted.
- Pancreatic inflammation that consists primarily of a lymphoplasmacytic infiltrate and fibrosis.

AIP is diagnosed only if at least two of the items above are present, one of which must be the first item—narrowing of the main pancreatic duct and pancreatic swelling.

These diagnostic criteria were revised in 2006, with the essential changes being a discontinuation of the requirement that the pancreatic duct narrowing must affect ≥1/3 of the pancreatic duct length and the addition of serum IgG4 concentrations to the list of required blood test items [18].

With the generation of formal diagnostic criteria, AIP came to be internationally recognized as an independent disease entity. In 2006, investigators at the Mayo Clinic and South Korea proposed their own respective diagnostic criteria, and serum IgG4 was adopted as a diagnostic criterion [19, 20]. In order to unify the diagnostic criteria adopted in Japan and South Korea, researchers from the two countries held several meetings and in 2008 published a consensus statement on Asian diagnostic criteria for AIP [21]. In 2011, international consensus diagnostic criteria (ICDC) for AIP (both types 1 and 2) were proposed [22].

3.3.4 Extrapancreatic Lesions and IgG4

AIP can be complicated by diverse extrapancreatic lesions, most of which manifest the same histological features as those of pancreatic lesions, show marked IgG4-positive plasma cell infiltrates, and are responsive to glucocorticoid therapy [1, 23]. The realization that AIP and extrapancreatic lesions show the same underlying pathophysiology led to proposals that these entities be considered as part of a single systemic disorder related to IgG4 [11].

The lacrimal and salivary gland lesions of Mikulicz's disease were among the first to be linked to AIP and an underlying systemic disorder [24–26]. In 2010, the research group of the Japanese Ministry of Health reached a consensus on classifying these disorders together as a single disease entity to be called "IgG4-related disease" [11, 27]. An international symposium on IgG4-RD held in Boston in 2011 led to a consensus agreement on nomenclature for the diverse organ system manifestations of IgG4-RD and contributed further to the worldwide recognition of this disease [28, 29].

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History: Lacrimal and Salivary Glands

4

Susumu Sugai

4.1 Mikulicz's Disease

Mikulicz's disease [1, 2] and a case later regarded as the first described case of Sjögren's syndrome [3] were reported in the same year, 1888. Mikulicz's disease was presented at a medical meeting [4], while Sjögren's syndrome received first notice in an English journal. After Mikulicz's first report, confusion about the nature of this disease reigned for more than 60 years until the paper of Morgan and Castleman in 1953 [5], which appeared to settle the confusion by proposing that Mikulicz's disease, in fact, was a subset of Sjögren's syndrome. More than half a century later, however, Japanese investigators established Mikulicz's disease as a subset of IgG4-related disease [6].

Jan Mikulicz-Radecki, a Polish surgeon who lived in what was then Prussia, pioneered several surgical interventions and tools that had a lasting impact on his field. He is regarded rightly as one of the fathers of modern surgery. Ironically, this pioneer of gastric resection for cancer who had performed 183 gastrectomies during the course of his career died himself of gastric cancer at the age of 55 [7, 8].

Mikulicz was born in 1850 in Chernovcy (Czernowitz), the capital of a Polish–Austrian province. He was the son of a Polish nobleman. After finishing medical studies in Vienna, he worked by the side of the great professor and surgeon, Theodor Billroth, for 8 years as an assistant. Mikulicz designed the first endoscope for examining the esophagus and stomach and thereby became the first surgeon to observe cancer of the esophagus and stomach endoscopically before operation in a living patient. Mikulicz was appointed head of the surgical department in Wroclaw and was visited by outstanding surgeons from all over the world. He also traveled to Europe, Russia, and the United States, where he performed surgical demonstrations [7, 8].

While working at Königsberg, Mikulicz [4] reported before the *Verein für Wissenschaftliche Heilkunde* ("Association for Scientific Healing") a case of chronic, bilateral, painless enlargement of the lacrimal and salivary glands. He published this case in Billroth's *Festschrift für die Beiträge zur Chirurgie* ("Festschrift for Contributions in Surgery") in 1892 [1, 2]. The patient was a 42-year-old farmer who first experienced swelling of the lacrimal glands and then of the submandibular and parotid glands over a 7-month period (Fig. 4.1). He had difficulty in seeing, eating, and speaking. After obtaining no improvement with the medicine prescribed by his local physician, he consulted Mikulicz. Mikulicz described the findings of his examination as follows. "A small nodulated, firm tumor was palpable under the eyelid skin and the eyeballs were displaced inward and forward. Under each angle of the jaw projected a tumor about the size of a hen's egg covered by normal skin. Inside the mouth swellings of sublingual glands were so remarkable that these occupied the floor of the oral cavity on both sides of the frenulum. The palate on both sides was occupied by a sharply delineated swelling almost the size of a chestnut. Under the buccal mucous membrane there were movable nodules, about the size of a pea on each side of the excretory opening of Stensen's duct. A copious secretion of saliva took place during the examination [1]".

Mikulicz removed two thirds of the patient's lacrimal tumors bilaterally in an attempt to ameliorate the patient's visual impairment. By the time of the first postoperative visit 2 months later, however, the lacrimal gland swelling had reappeared and the submandibular tumors had increased in size. Pilocarpine injections were performed in the hope of promoting secretion as a means of reducing the size of the salivary glands but despite profuse salivation, the result was not satisfactory. These passages are noteworthy not only for their historical interest and insights into the medical thinking of Mikulicz' day, but also because they demonstrate clearly that the patient did not suffer from xerostomia.

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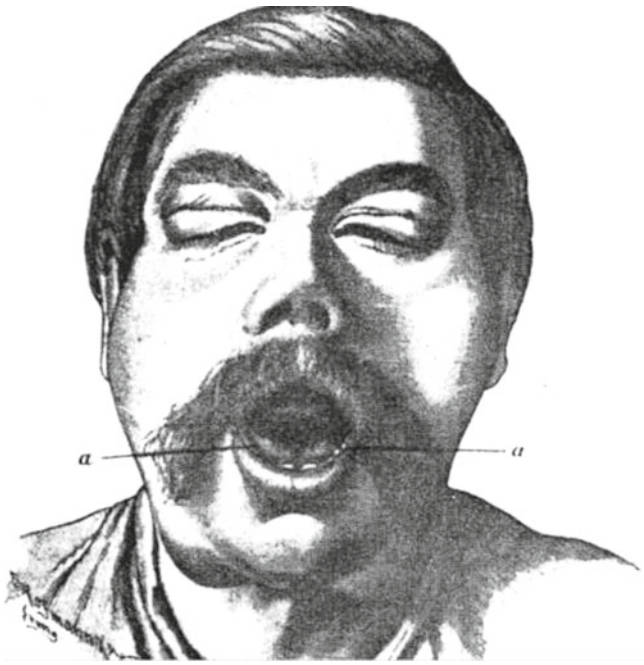

Fig. 4.1 Original patient described by Mikulicz, a 42-year-old male

Further excision of the remaining portions of the lacrimal and submandibular glands resulted in improvement, although swelling of the parotid glands persisted. The patient wrote to Mikulicz after discharge that he did not have trouble in the use of his eyes and was very satisfied with his condition, although the swelling of the parotid glands seemed to have increased. Unfortunately, 14 months after the onset of his glandular enlargement, the patient developed signs of peritonitis of unclear etiology and uncertain relationship (if any) to his glandular disease and died of probable perityphlitis over the period of a week. The swellings in the parotid glands and mouth were reported to have regressed markedly within a few days during the patient's terminal illness and had nearly disappeared before his death.

Descriptions of the resected tumors are instructive. Each was about the size of a child's fist, and the transverse section showed the normal structure of the gland. In places, it had a more homogeneous, pale reddish yellow, amyloid mass of lesser transparency. Microscopic examination of the excised salivary and lacrimal glands disclosed uniformly arranged tissue consisting of small round cells. In some places the cells laid compactly together, and in other places a fine reticulum was seen between them. Imbedded within these small-celled main masses were normal-appearing clusters of salivary gland acini, separated from one another in varying distances by the round cell tissue [1].

Mikulicz scoured the medical literature for similar cases. He noted four cases reported by Fuchs [9], Haltenhoff [10], Reymond [11], and Adler [12]. He also found descriptions of three cases in which enlargement of the lacrimal glands alone was reported by Arnold [13], Korn [14], and Power [15]. Mikulicz found no cases in which only the salivary glands were affected.

Mikulicz summarized this condition as follows: "The disease process exhibits itself clinically as a slowly arising, huge enlargement of all the salivary and lacrimal glands, without inflammatory signs and without demonstrable systemic manifestations. The process remains sharply confined to the region of these glands and involves neither the neighboring structures nor other organs or tissues. The microscopic examination reveals that the true parenchyma of the glands plays an entirely passive role. The increase in size is entirely brought about by a massive small-cell infiltration in the interstitial connective tissue." [1]

Mikulicz considered this disease to be a chronic process, first occurring in the lacrimal glands and under certain circumstances remaining localized but also with the potential for extension to the salivary glands. He strongly denied the possibility of malignancy such as sarcoma, lymphoma, or leukemia, as neither his case nor any of the others have features of cancer. He also rejected the notion of an infectious etiology such as mumps or tuberculosis.

Mikulicz remained stymied at the end of his examination of this disease with regard to the question of etiology. He wrote at the end of his paper, "Hoffentlich gelingt es künftigen Beobachtern, die Rätsel zu lösen, die uns diese merkwürdige Krankheit stellt (I hope that future observers will succeed in solving the riddle that this remarkable disease presents to us)" [1].

4.2 Confusion and Changes of the Concept of Mikulicz's Disease

According to Howard [16], four authors before Mikulicz had reported a total of five cases that were considered to be similar to the case of Mikulicz (Berlin [17]: two cases, Power [15], Haltenhoff [10], and Fuchs [9]). Although Mikulicz found no cases of isolated salivary gland swelling, in 1896 Küttner reported two cases of chronic inflammatory swelling of the submandibular glands [18]. For more than 100 years after Küttner's publication, the term "Küttner's tumor" was used loosely to refer to submandibular gland enlargement of a variety of causes. After the 2009 report of Kitagawa et al. [19], many cases of "Küttner's tumor" are now recognized to be a common manifestation of IgG4-related disease.

Within less than 10 years, despite Mikulicz's published description and concept of the disease, many reports appeared in the literature of patients with bilateral chronic enlargement of the lacrimal and/or salivary glands, classified as Mikulicz's disease. Von Brunn [20] argued in 1905 that the condition described by Mikulicz is a symptom complex,

rather than a disease entity, and that it is closely related to pseudoleukemia and leukemia. In 1907, Napp [21] reported that this condition may be produced by any one of several causes, including leukemia, malignant lymphoma, atypical lymphomatosis, sarcoidosis, and tuberculosis. In 1909, Howard [16] reviewed 81 cases collected from the literature and it became evident that, although all of these patients had the one common feature of symmetrical enlargement of the lacrimal or salivary glands, they differed widely in many other important aspects, leading to substantial confusion in the definition of "Mikulicz's disease." In many patients, the clinical course of this disease was that of a benign, self-limited condition, whereas in others it was rapidly fatal. Moreover, the pathological material obtained at biopsy or autopsy differed widely. It therefore became obvious that "Mikulicz's disease" was not one single pathologic entity but rather a syndrome that had any number of causes. Howard grouped them under three headings: [1] Mikulicz's disease proper, [2] pseudoleukemia, and [3] leukemia.

When referring to Mikulicz's disease proper, some authors looked beyond the diffuse lymphocytic infiltration and fibrosis present and focused attention instead on the unique pathological findings observed in that condition, particularly the lymphoid follicles and "conglutination cells" that originated from gland-epithelial cells [22, 23]. In 1914, Thursfield [24] first attempted to classify the syndrome on an etiologic basis. He divided all patients into eight groups: a congenital, familial, and hereditary condition; Mikulicz's disease proper; Mikulicz's disease with involvement of the lymphatic apparatus; leukemia; tuberculosis; syphilis; gout; and sialodochitis fibrinosa. In 1927, Schaffer and Jacobsen [25] reduced Thursfield's grouping into two groups: Mikulicz's disease proper and Mikulicz's syndrome caused by leukemia, lymphosarcoma, or tuberculosis. This classification was sensible and proper because they stressed the existence of Mikulicz's disease of unknown etiology. However, the basic histopathological features of Mikulicz's disease proper remained undefined.

In 1933, Sjögren [26] published a monograph on 19 patients entitled "Zur Kenntnis der Keratoconjunctivitis sicca" ("On the Identification of Keratoconjunctivitis sicca"). Sjögren correctly described many of the clinical components and histopathological changes, including those of the lacrimal and salivary glands and of the syndrome that later bore his name, Sjögren's syndrome. From the time of that description onwards, Sjögren's syndrome became one of the most important diseases to be differentiated from Mikulicz's disease.

In contrast, attempts to codify an understanding of Mikulicz's disease became even more muddled. Godwin [27] studied 11 cases of parotid tumors that showed unique and common microscopic features. For these patients with a good prognosis, several different pathological diagnoses might have been made based on previous understanding such as adenolymphoma, chronic infiltration, lymphoepithelioma, lymphocytic tumor, or Mikulicz's disease. The lesions microscopically consisted of a mass of lymphoid tissue consisting of either scattered foci of metaplastic epithelial cells or solid foci of closely packed cells. Some of those cases had findings closely resembling the epimyoepithelial islands reported by Morgan and Castleman 1 year later. To resolve the widespread confusion about Mikulicz's disease due to the impossibility of determining its characteristics from the unclear histological drawings in Mikulicz's paper, Godwin proposed in 1952 that the terms "Mikulicz's disease" and "Mikulicz's syndrome" be deleted and replaced by the term, "benign lymphoepithelial lesion."

Based on the understanding that an adequate histopathologic study of Mikulicz's disease was not available and that it was necessary to differentiate Mikulicz's disease from similar diseases on a histological basis, Morgan and Castleman in 1953 [5] studied 18 patients with clinically and pathologically defined Mikulicz's disease. The authors had had experience with the uncertainty of differentiating Mikulicz's disease from malignant lymphomas arising in the lacrimal or salivary glands. Despite the fact that six of their patients had been diagnosed as having malignant lymphoma, all had remained free of disease recurrences 9–16 years after surgical removal of their tumors. Histological examination of these six patients disclosed a characteristic alteration in the duct epithelium, in addition to diffuse lymphoid infiltration in the gland substance. Twelve additional patients were collected from either their own files (eight cases) or affiliated hospitals (four cases). The clinical and pathological aspects of these 18 patients were regarded as best fitting the original description of Mikulicz [28]. These patients had had diagnoses of chronic inflammation, Mikulicz's disease, metastatic carcinoma, atypical adenocystoma lymphomatosum, mixed tumor, lymphocytic leukemia, and malignant lymphoma, with many of them thought to have malignant diseases.

The data on 18 patients in these two papers [5, 28] are summarized in Table 4.1. Clinical review revealed that most of these patients had a history of a non-tender, progressively enlarging mass in the region of one or more salivary or lacrimal glands. In nine of them, swellings were confined to one parotid gland; in one patient, swelling was in a single submandibular gland; and in two patients, ipsilateral parotid and submandibular glands. Bilateral swelling was observed in three patients in parotid and submandibular glands; in two patients, parotid glands. Only one patient showed lacrimal gland swelling. Three patients died of apparently unrelated diseases. Autopsies done in these patients showed no evidence of malignant lymphoma. The age of the 18 patients ranged from 15 to 70 years. Fifteen patients were female, 12 of whom were between 37 and 59 years of age. The ages of the males were 15, 39, and 70 years. Two patients had

Table 4.1 Date in 18 patients (formed from papers 5 and 28)

Pt. no.	Sex	Age (years)	Affected glands	Clinical history	Follow-up (years)
1	F	35	P, P, SM, SM	Conjunctivitis	7
2	F	61	P, P, SM, SM	Dry M	7
3	F	62	P, P, SM, SM	Dry M, degenerative arthritis	7
4	F	39	L, L	KCS	3.7
5	F	47	P, P	KCS, Dry M, disseminated LE	Autopsy
6	F	55	P, P	Dry M, rheumatoid arthritis	Autopsy (Inf Hp)
7	M	70	P, SM	Arthritis	7
8	F	59	P, SM	–	Autopsy (post-op)
9	F	37	P	–	0.1
10	M	39	P	–	18
11	F	48	P	–	20
12	F	47	P	–	5.7
13	F	50	P	–	4
14	F	56	P	Dry M	18
15	F	37	P	Dry M, rheumatoid arthritis	15
16	F	40	P	Retinal arteritis	17
17	F	69	P	Dry M, degenerative arthritis	10
18	M	15	SM	Rheumatic fever	5.3
	F 15, M 3 (number)	F 48.4, M 41.3 (average age)			

P parotid gland, *Dry M* dry mouth, *Inf Hp* infectious hepatitis, *SM* submaxillary gland, *KCS* keratoconjunctivitis sicca, *Post-op* postoperation, *L* lacrimal gland, *LE* lupus erythematosus

keratoconjunctivitis sicca, one had diminished tear production (cheesy eye discharge), and one had recurrent bilateral conjunctivitis. Five patients had arthritis, including three with rheumatoid arthritis. One patient died of disseminated lupus erythematosus, and the 15-year-old boy had rheumatic fever.

On pathological examination, the cut surface of the tumor showed preservation of the lobular architecture and marked enlargement of the individual lobules. There were two fundamental changes in their findings: [1] a gradual lymphoid infiltration and proliferation within the lobule, with subsequent atrophy and loss of acinar tissue, and [2] an alteration of the ducts, characterized by a typical intraductal cellular proliferation and gradual narrowing of the ductal lumen leading to the formation of a compact cellular island lying in a stroma of lymphoid tissue. Morgan and Castleman thought that the microscopic features of these cases were so similar as to leave no room for doubt that a single disease process was common to all.

The tissue was characterized by lymphocytic infiltration, which replaced the glandular parenchyma concomitantly with intraductal proliferation of epithelial and myoepithelial cells. The latter change resulted in the obliteration of the ductal lumens and the formation of solid cell masses, which they called "epimyoepithelial islands" (Figs. 4.2 and 4.3) scattered throughout the lymphomatoid stroma (Fig. 4.4).

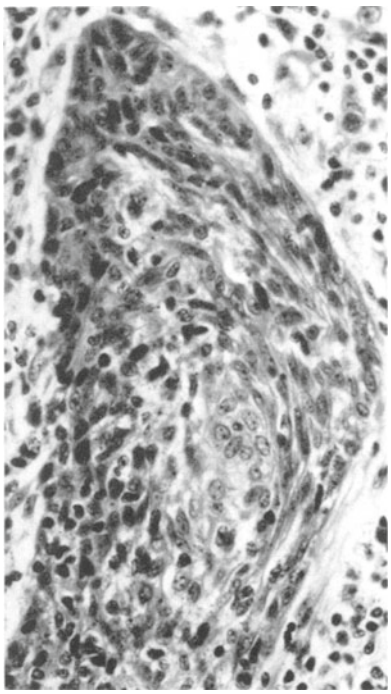

Fig. 4.2 An epimyoepithelial island named by Morgan and Castleman, the formation of a compact cellular island in a stroma of lymphoid tissue

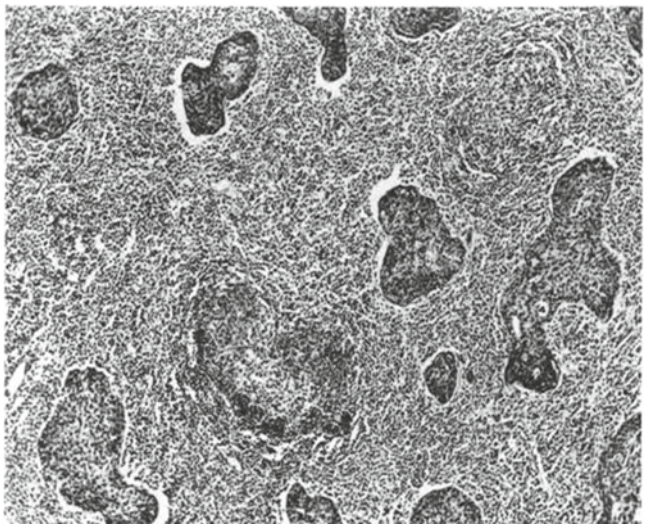

Fig. 4.3 Epimyoepithelial islands in a lymphoid stroma shown by Morgan and Castleman

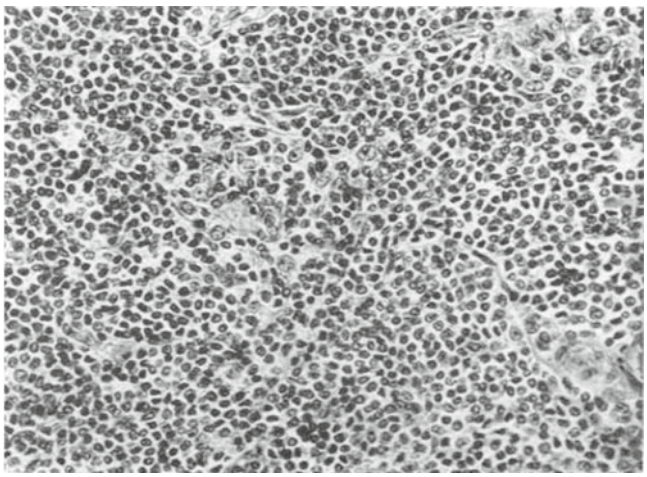

Fig. 4.4 Massive lymphocytic infiltration shown by Morgan and Castleman

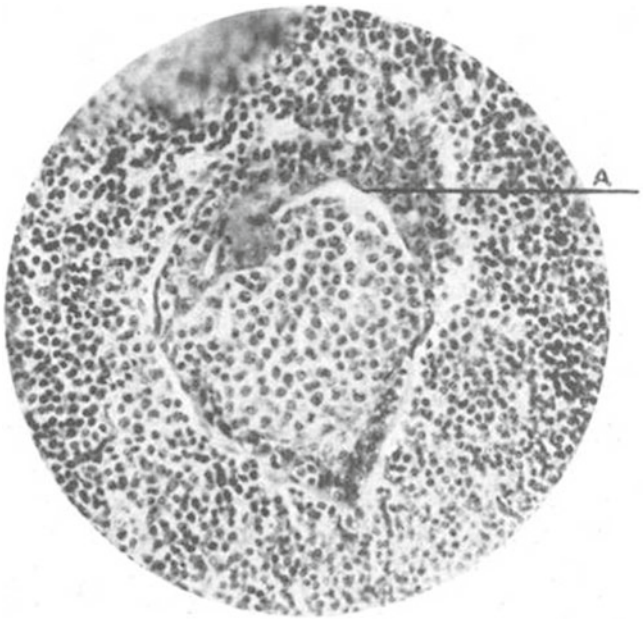

Fig. 4.5 A patient reported by Smith, a 62-year-old female. Microscopic findings of lymphocyte infiltration with proliferation of ductal cells

Figure 4.4 appears to me to show mucosa-associated lymphoid tissue (MALT) lymphoma judging from the modern understanding of lymphoma. In differentiating Mikulicz's disease from malignant lymphoma, Morgan and Castleman stressed that the presence of these epimyoepithelial islands was the most dependable diagnostic feature, with the formation of these epimyoepithelial islands probably being pathognomonic of Mikulicz's disease. They understood that the primary lesion in Mikulicz's disease was in the duct system, with involvement of lymphoid tissue being a secondary response. In a search of the literature they found a case reported previously by Smith and Bump [29], who drew attention to the unique microscopic finding, an island of cells composed of metaplastic ductal cells. Their pictures were similar to the epimyoepithelial islands named by Morgan and Castleman (Fig. 4.5). This picture, too, might be that of MALT lymphoma. They did not mention the important paper published 1 year before them by Godwin [27].

Morgan and Castleman finally concluded that "on the basis of certain clinical and pathologic similarities to Sjögren's syndrome, it seems likely that Mikulicz's disease is not a distinct clinical and pathologic disease entity as previously believed, but merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome."

In another paper, Morgan [28] reported that Sjögren's original microscopic slides of salivary glands showed all the features previously reported in the 18 patients with Mikulicz's disease described by Morgan and Castleman. He described that Mikulicz's disease and Sjögren's syndrome were similar in their clinical nature and course; their tendency to occur in middle age; their preponderance in women; their identical histological findings in the salivary and lacrimal glands; and the coexistence in both groups of similar associated lesions, in addition to disease in the salivary glands, such as keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis. Of these 18 patients, nine had one or more of the features of Sjögren's syndrome in addition to the diseases of the salivary glands (Table 4.1). He thought that this degree of similarity suggests that the two conditions are related, if not actually the same pathologic process. Morgan argued that, in contrast to Mikulicz's contention that the disease always involved the lacrimal glands, the disorder described in his own cases was

more commonly confined to the salivary glands. At variance with the long-held belief that the glandular involvement in Mikulicz's disease is always bilateral, 12 of their 18 patients had only unilateral enlargement.

As only one of the 18 patients had enlarged lacrimal glands, Morgan described that lacrimal glands were less frequently enlarged in Mikulicz's disease than previous authors had believed and the presence or absence of one physical finding, such as enlargement of lacrimal glands, should not be used as a basis for dividing such cases into two entities. Then, he concluded that the condition characterized by chronic enlargement of the salivary or lacrimal glands, which in the past had been called Mikulicz's disease, may be a less highly developed variant of a larger symptom complex, Sjögren's syndrome.

The conclusion drawn by Morgan and Castleman that Mikulicz's disease is a subset of Sjögren's syndrome was so rapidly and widely accepted among researchers at that time in the USA and Europe that subsequently the number of English-language reports on Mikulicz's disease decreased significantly.

In retrospect, however, it is appreciated that these papers obfuscated rather than clarified the concept of Mikulicz's disease. By focusing on 18 patients, many of whom were very different from the original patient described by Mikulicz, Morgan and Castleman derived a different disease picture from that originally proposed, namely one manifestation of Sjögren's syndrome. In contrast to Mikulicz's contention that the disease is bilateral and involves the lacrimal glands, the authors reported bilateral involvement in only six of 18 patients. Ten patients had swelling of a single parotid or submandibular gland and only one involvement of both lacrimal glands. Most of their patients were women, in the fifth and sixth decades, and nine of these 18 patients had one or more of the features of Sjögren's syndrome. It is important to note that Mikulicz's original patient showed copious salivation.

The most problematic issue in their paper was that the selection criteria that Morgan and Castleman used for recruiting patients were not fully described, except for one: "a characteristic alteration in the duct epithelium in addition to diffuse lymphoid infiltration of the gland substance." The important histological finding described as "epimyoepithelial islands," which was thought to differentiate Mikulicz's disease from other diseases, is now called lymphoepithelial lesions or lymphoepithelial sialadenitis and is considered to be a typical feature of the active and more advanced cases of Sjögren's syndrome.

I paid attention to the presence of the lymphoepithelial lesion in Sjögren's syndrome because intraductal infiltration of lymphocytes and proliferation of ductal cells leading to the lymphoepithelial lesion are distinctive microscopic features of Sjögren's syndrome, but not of Mikulicz's disease. Our group think that the lymphoepithelial lesion might be a locus of lymphoma development in Sjögren's syndrome [30] and that the mucosal epithelial cell presents antigens to lymphocytes in Sjögren's syndrome. In relation to this, Moutsopoulos had proposed autoimmune epithelitis as a key feature of Sjögren's syndrome [31]. Accordingly, we regard the lack of the lymphoepithelial lesion as one of the microscopic features of Mikulicz's disease in addition to the presence of lymphocytes, IgG4-bearing plasma cells, lymph follicles, and fibrosis in affected tissues.

4.3 Mikulicz's Disease and IgG4-Related Disease in Japan

Since the appearance of the papers by Morgan and Castleman, more than 20 patients with Mikulicz's disease have been reported in Japan mainly in Japanese, and discussion has continued on the similarities and differences between Mikulicz's disease and Sjögren's syndrome. Konno [32] reported that Mikulicz's disease differs from Sjögren's syndrome in three aspects: (1) no gender difference is evident in Mikulicz's disease, (2) the function of the salivary and lacrimal glands in Mikulicz's disease recovers to normal after disappearance of gland swelling, and (3) sialography in patients with Mikulicz's disease shows only mild damage and is quite different from that of Sjögren's syndrome.

Konno argued that the pathological findings described by Morgan and Castleman, including epimyoepithelial islands, were not confined to Mikulicz's disease or Sjögren's syndrome, but could be observed in other conditions, such as chronic inflammation, in circumstances in which the salivary glands were severely damaged. In 1993, Suzuki et al [33] described a 73-year-old man with Sjögren's syndrome who showed huge swelling of the bilateral lacrimal and submandibular glands and a serum IgG4 concentration of 5,800 mg/dL. After treatment with 30 mg prednisolone for 1 month, the swelling of the glands and serum abnormality disappeared almost completely. This case is no doubt considered to be the first report of a high level of IgG4 in a patient with Mikulicz's disease. Tsubota et al. [34] reported in 2000 that, compared to patients with Sjögren's syndrome, patients with Mikulicz's disease showed an almost normal state of the corneal surface with rose bengal and fluorescent staining. They had microscopically fewer APO2.7-positive apoptotic acinar cells in the lacrimal glands and lower expression of Fas and Fas-ligand in lymphocytes. They understood that this was the reason why the function of the lacrimal glands was only slightly, if at all, impaired in patients with Mikulicz's disease despite massive lymphocytic infiltration into the affected

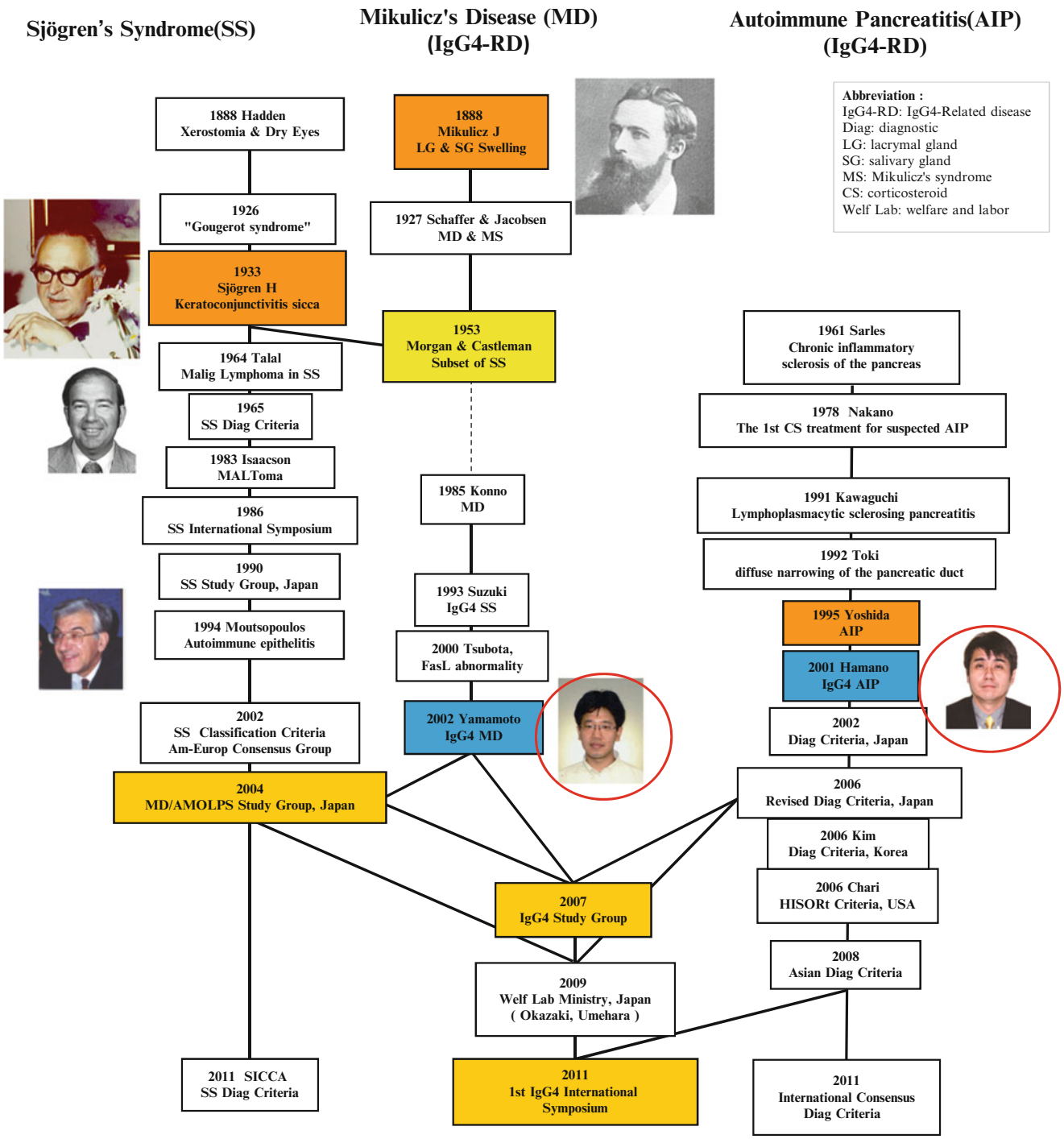

Fig. 4.6 Historic events in Sjögren's syndrome (SS), Mikulicz's disease (MD), and autoimmune pancreatitis (AIP) (Sugai S & Kawa S)

glands. They [35] later found a point mutation in the promoter region of the Fas-ligand gene in one patient with Mikulicz's disease.

Yamamoto et al. [36] reported in 2002 that Mikulicz's disease differed from Sjögren's syndrome in that six patients with Mikulicz's disease showed high serum concentrations of IgG4 and low numbers of Fas-positive cells and apoptotic cells in the salivary glands. This report was the first to convincingly show elevated serum IgG4 values in Mikulicz's disease and appeared only 1 year after the report of Hamano et al. [37], who first showed a high serum IgG4 concentration in patients with sclerosing pancreatitis, which is now

known as type 1 (IgG4-related) autoimmune pancreatitis disease is different from SS. Yamamoto et al. [40, 41] described comprehensively the clinical and laboratory features of Mikulicz's disease. In 2004, the Japanese Medical Society for Sjögren's Syndrome established a study group of Mikulicz's disease/IgG4 + AMOPLS and began to collect records of patients with Mikulicz's disease. Analyses of 64 patients with Mikulicz's disease resulted in the elaboration of a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome (IgG4 + MOLPS), by Masaki et al. [42].

The new disease concept, autoimmune pancreatitis with elevated IgG4, originated from Japan and has been accepted globally, especially after the finding of the high concentration of IgG4 in sera and plasma cells in affected tissues by Hamano et al. [37]. Great efforts have been made to establish and revise the diagnostic criteria for autoimmune pancreatitis in Japan, in other parts of Asia and in the USA. During this process, it became understood that some patients with autoimmune pancreatitis have features of Sjögren's syndrome as an extra-pancreatic manifestation, while in some cases Mikulicz's disease also complicates autoimmune pancreatitis. Then, in 2007 clinicians in the field of gastrointestinal and autoimmune disease and pathologists cooperated to establish an IgG4 study group in Japan. Since then, they have accelerated their research activity to better define the whole picture of this disease. In 2009 the Japanese Welfare and Labor Ministry launched three groups, namely IgG4-related systemic sclerosing disease (Okazaki group), IgG4-related multi-organ lymphoproliferative disease (Umehara group), and Mikulicz's disease and IgG4-related disease (Naeshiro group). By thoroughly discussing the clinical and pathological features of this disease, they were able to settle on an appropriate name for it, namely IgG4-related disease, and in establishing clinically useful diagnostic criteria [6]. Comprehensive reviews by outstanding researchers in each field of IgG4-related disease were published in 2011 [43]. Finally, the 1st international symposium on IgG4-related disease was held in Boston, in 2011, organized by Dr. John Stone, the results of which have already been published [44] (Fig. 4.6).

The riddle left by Mikulicz in 1892 is now, 120 years later, being finally solved aided by the recognition of this disease as an IgG4-related disease. We Japanese researchers are proud to have been able to make a significant contribution to this process of scientific discovery. However, neither the pathologic role of IgG4 nor the etiopathogenesis of this disease is yet well understood, and thus, much more work will be required to define and untangle the many riddles remaining and more importantly to use the new knowledge gained to help the patients inflicted with IgG4-related disease in all its manifestations.

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Salivary Gland Lesions in Mikulicz's Disease and Küttner's Tumor

5

Toshio Yoshihara and Mariko Miyamoto

5.1 Introductory Remarks

Since the 1888 report of Johann von Mikulicz-Radecki [1] of a case of bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands, the term Mikulicz's disease has been used to denote a group of diseases showing similar clinical findings. Because a variety of other diseases described subsequently—including leukemia, lymphoma, sarcoidosis, and Kimura's disease—have sometimes been labeled "Mikulicz's disease." Schaffer et al. [2] classified cases with an obvious underlying disease as having Mikulicz's syndrome and those without such a disease as having Mikulicz's disease.

In 1933, Henrik Sjögren [3] reported cases of Sjögren's syndrome associated with dry eye and keratoconjunctivitis. In two of these cases, major salivary gland swelling was also present. Twenty years later, Morgan and Castleman [4] concluded that the condition hitherto reported as Mikulicz's disease was in fact a subtype of Sjögren's syndrome, and for more than the next half-century, Mikulicz's disease was regarded by most physicians as a variant of Sjögren's syndrome. However, Yamamoto et al. [5] proposed that Mikulicz's disease should be regarded as an independent disease entity differing from Sjögren's syndrome because it shows elevated serum IgG4 values and only mild gland secretory impairment and is markedly responsive to steroid therapy. Moreover, Yamamoto and colleagues indicated that Mikulicz's disease should be considered part of the IgG4-related disease (IgG4-RD) spectrum.

Küttner's tumor, also known as chronic sclerosing submandibular sialadenitis, was reported in 1896 by Küttner [6] as a hard swelling of the submandibular gland. Kitagawa et al. [7] recognized recently, however, that some cases diagnosed with Küttner's tumor are actually characterized by an infiltrate of IgG4-positive plasma cells and share other features frequently observed in Mikulicz's disease patients, namely, similar patterns of extra-glandular involvement, elevations in serum IgG4 concentrations, and unifying histopathological features such as a lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. In this chapter, we present some of our own cases so as to clarify the similarities and differences between these two diseases [8].

5.2 Laboratory and Clinical Findings in Mikulicz's Disease and Küttner's Tumor

Of the 31 cases of Mikulicz's disease evaluated in our department between the years 1994 and 2011, 13 were men and 18 were women. The range in age for these patients was 35–81 years (mean 53.8 ± 11.6 years) (all values in this chapter are given as the average ± standard deviation, unless otherwise indicated). Of the 20 cases of Küttner's tumor evaluated during this same period, 12 were men and 8 were women, ranging in age from 47 to 78 years (63.4 ± 9.0 years). Figures 5.1 and 5.2 show submandibular gland swelling in Mikulicz's disease and Küttner's tumor, respectively, illustrating that the clinical appearances of these conditions, both characterized by hard, painless swellings of the submandibular gland, are indistinguishable. The serological and histopathological findings and the comorbidities of these diseases are described below.

5.2.1 Serological Findings

Mikulicz's disease and Küttner's tumor patients were compared to a group of five controls, comprised of patients with pleomorphic adenomas of salivary glands. At presentation, the total IgG concentration in the control group was

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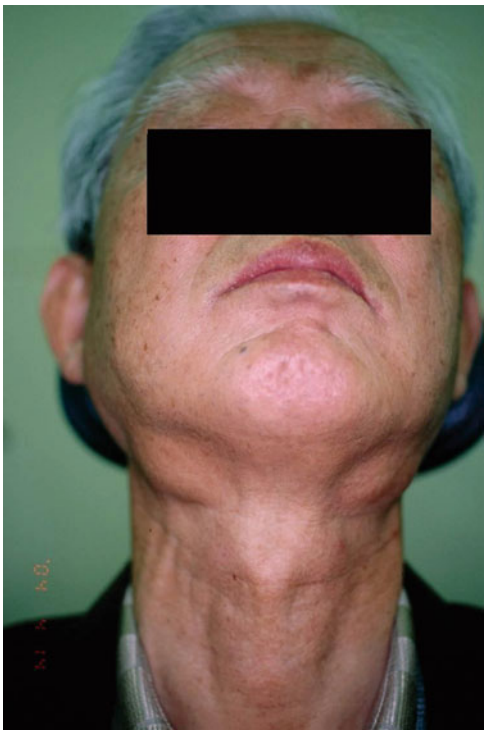

Fig. 5.1 Mikulicz's disease. Bilateral submandibular gland swelling

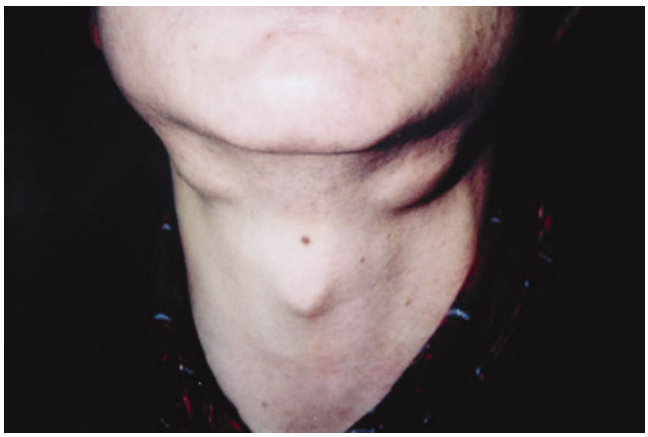

Fig. 5.2 Küttner's tumor. Bilateral submandibular gland swelling

1,257.4 ± 632.0 mg/dL, compared with 2,233.8 ± 905.9 mg/dL in Mikulicz's disease group and 1,632.9 ± 434.4 mg/dL in Küttner's tumor group ($p = 0.013$ and $p = 0.025$ versus control group, respectively).

The contrasts between Mikulicz's disease and Küttner's tumor patients on one hand and the control group on the other were even more marked when it came to serum IgG4 concentrations. The serum IgG4 concentration was only 23.8 ± 18.2 mg/dL in the control group, but 816.9 ± 712.4 mg/dL among Mikulicz's disease patients ($p = 0.0002$) and 390.7 ± 178.2 mg/dL among Küttner's tumor patients

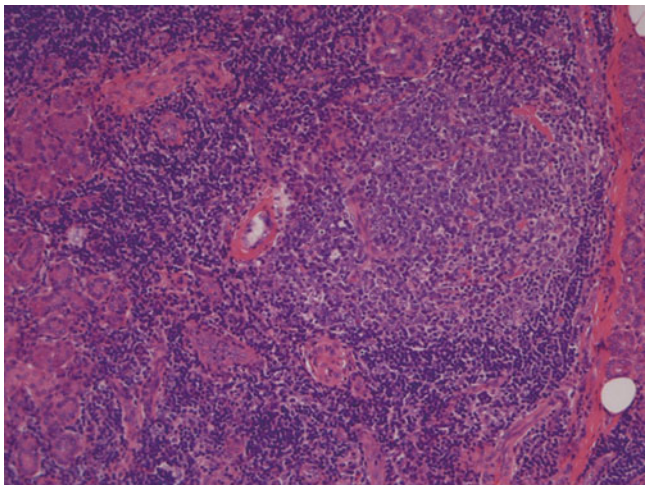

Fig. 5.3 Submandibular gland tissue findings in Mikulicz's disease: H&E staining ×100

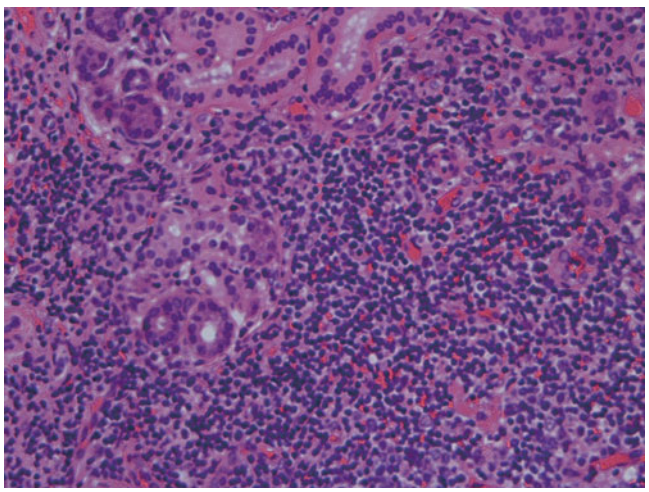

Fig. 5.4 Submandibular gland tissue findings in Mikulicz's disease: H&E staining ×100

($p = 0.0002$). The proportion of total IgG occupied by IgG4 was calculated to be 2.4 ± 1.5 % in the control group, compared with 23.9 ± 10.2 % in Mikulicz's disease and 19.3 ± 5.9 % in Küttner's tumor group ($p = 0.0004$ and $p < 0.0001$, respectively, versus controls).

5.2.2 Histopathological Findings

The results of hematoxylin and eosin (H&E) and immunostains on the submandibular gland tissue are shown in Figs. 5.3, 5.4, 5.5, 5.6, 5.7, and 5.8. When the two diseases were compared at magnifications ×100 and ×200, no differences were evident between Mikulicz's disease and Küttner's tumor patients with regard to the degree of such chronic

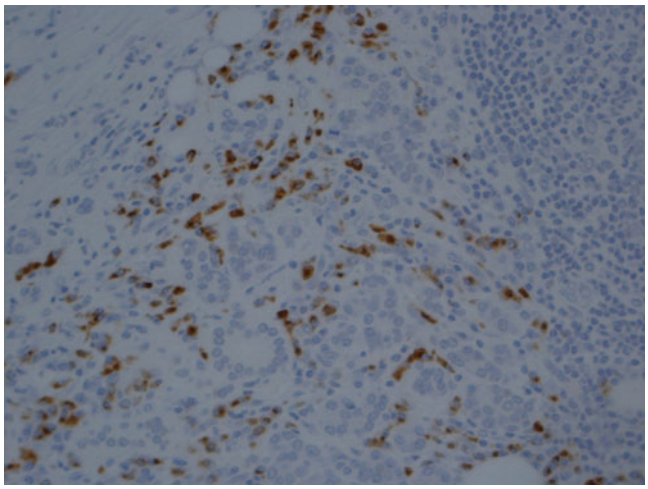

Fig. 5.5 Submandibular gland in Mikulicz's disease: IgG4-immunostaining ×200

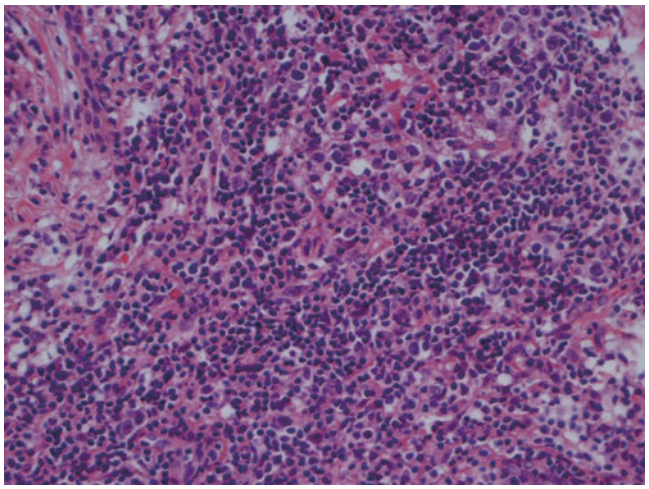

Fig. 5.7 Submandibular gland histological findings in Küttner's tumor: H&E ×200

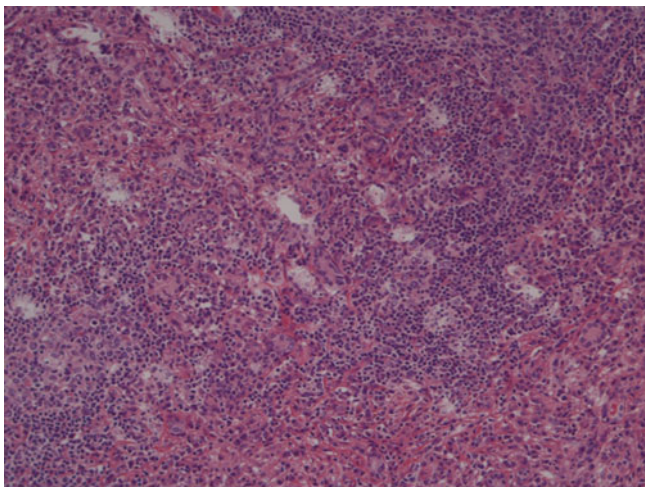

Fig. 5.6 Submandibular gland histological findings in Küttner's tumor: H&E ×100

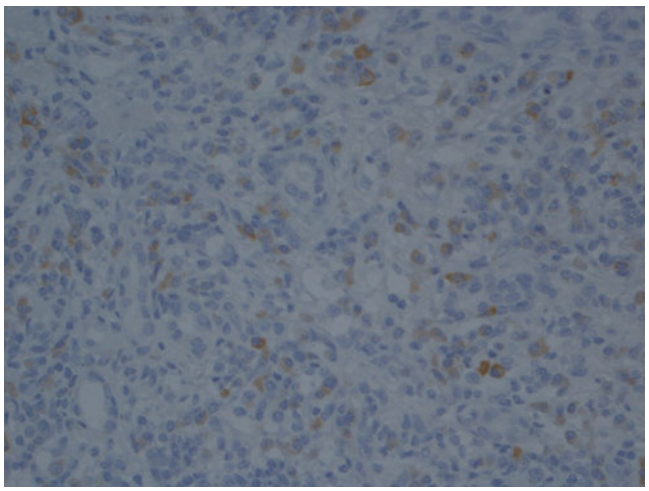

Fig. 5.8 Küttner's tumor. Submandibular gland IgG4-immunostaining ×200

inflammatory findings as perilobular fibrosis, lymphocyte infiltration, and acinar cell atrophy.

IgG4-positive plasma cells were not detected in any of the salivary glands examined from 12 control patients. In contrast, the IgG4/total IgG ratios for Mikulicz's disease and Küttner's tumor patients were 50.3 ± 25.4 % and 27.8 ± 31.4 %, respectively.

5.2.3 Comorbidities

Six of the thirty one cases of Mikulicz's disease had autoimmune pancreatitis. In addition, bronchial asthma and allergic rhinitis were noted in seven cases each, interstitial pneumonia in two cases, and diabetes mellitus in three. There were 16 other potentially relevant comorbidities in Mikulicz's disease patients (Table 5.1). Six of the 20 Küttner's tumor patients also had autoimmune pancreatitis and seven had allergic rhinitis. Two had bronchial asthma, and autoimmune hypophysitis, interstitial pneumonia, interstitial nephritis, and retroperitoneal fibrosis were observed in one patient each (Table 5.2).

5.3 Historical Background and Discussion

Morgan and Castleman [4] reviewed the histopathological findings of 18 cases considered to have "Mikulicz's disease" and concluded that Mikulicz's disease is a subtype of Sjögren's syndrome. For some 50 years thereafter, the

Table 5.1 Complications of the patients with Mikulicz's disease

	Age	Gender	Complications
1	52	F	Asthma, hypertension
2	68	M	Hypertension, gout
3	64	F	Interstitial pneumonia
4	61	M	Asthma, myocardial infarction, iatrogenic adrenal failure
5	50	F	Allergic rhinitis
6	35	F	Autoimmune hepatitis, primary biliary cirrhosis
7	47	F	Asthma, depression
8	38	F	Asthma, depression
9	54	F	Autoimmune pancreatitis, interstitial nephritis
10	35	F	Allergic rhinitis
11	47	F	Asthma, allergic rhinitis
12	68	M	Autoimmune pancreatitis, olfactory dysfunction
13	47	M	Allergic rhinitis
14	62	M	Myocardial infarction, allergic rhinitis
15	53	M	Unknown
16	61	M	Myelodysplastic syndrome, asthma, gout
17	45	M	Gout
18	48	F	Depression, interstitial nephritis, sclerosing cholangitis
19	51	F	Retroperitoneal fibrosis
20	57	F	Autoimmune pancreatitis, hypertension, diabetes mellitus
21	61	M	Cerebral infarction, prostate cancer
22	75	M	Autoimmune pancreatitis
23	64	F	Hypertension, diabetes mellitus, breast cancer
24	51	M	Autoimmune pancreatitis, allergic rhinitis
25	46	F	Autoimmune pancreatitis
26	50	F	Allergic rhinitis
27	36	M	Allergic rhinitis
28	81	M	Hypertension, diabetes mellitus, angina pectoris, lung cancer
29	65	F	Diabetes mellitus
30	35	F	Keratoconjunctivitis

Table 5.2 Complications of the patients with chronic sclerosing submandibular gland disease

	Age	Gender	Complications
1	61	M	Depression
2	71	F	Allergic rhinitis, gout, hypertension, focal glomerulonephritis
3	63	M	Allergic rhinitis, renal cell carcinoma
4	48	M	Keratoconjunctivitis
5	47	M	Allergic rhinitis
6	76	M	Autoimmune pancreatitis, diabetes mellitus Retroperitoneal fibrosis, myelodysplastic syndrome
7	74	F	Autoimmune pancreatitis, interstitial pneumonia
8	69	M	Autoimmune pancreatitis, diabetes mellitus
9	65	M	Autoimmune pancreatitis, diabetes mellitus Retroperitoneal fibrosis, myelodysplastic syndrome
10	56	M	Autoimmune pancreatitis, autoimmune hypophysitis Allergic rhinitis
11	73	M	Allergic rhinitis, eosinophilia, diabetes mellitus
12	68	M	None
13	69	F	Autoimmune pancreatitis, diabetes mellitus x Retroperitoneal fibrosis, myelodysplastic syndrome
14	72	F	None
15	59	F	Hypertension
16	69	M	Asthma, diabetes mellitus
17	43	F	Asthma, allergic rhinitis
18	59	M	None
19	78	F	Interstitial nephritis, Hashimoto's thyroiditis

prevailing view was that Mikulicz's disease was a subtype of Sjögren's syndrome. Even the term "Mikulicz's disease" disappeared almost completely from the Western medical literature during this time. Even in Japan, opinions such as those of Konno et al. [9], who called attention to differences between the two diseases in the 1980s, were consumed by the consensus opinion that still embraced the concept put forth by Morgan and Castleman [4]. In retrospect, with the more complete knowledge of IgG4-RD available at the present time, the differences between Mikulicz's disease and Sjögren's syndrome seem self-evident: salivary gland swelling and function respond to glucocorticoid therapy in Mikulicz's disease but not in Sjögren's syndrome; patients with Sjögren's syndrome are anti-SS-A antibody and anti-SS-B-antibody positive, whereas those with Mikulicz's disease are not; and so on. But these are the benefits of hindsight, often much more clear than views of the present.

Recognition of chronic sclerosing submandibular sialadenitis began with the 1896 report of Küttner [6], who reported four patients with hard, bilateral submandibular gland masses that suggested malignant tumors. Seifert and Donath [10] adopting a broad definition of this disease discussed its etiology as including chronic inflammation induced by salivary gland stone. There remains considerable confusion in the literature on this point. Japanese otolaryngologists generally use the term Küttner's tumor to refer to conditions in which salivary gland stone, chronic inflammation, duct occlusion, and other findings have been excluded. Painless, hard submandibular gland swelling (unilateral or bilateral) is often encountered in daily practice and may often correspond to Küttner's tumors or the "immune sialadenitis" discussed by Seifert and Donath [10].

Küttner's tumors demonstrate marked lymphoplasmacytic cell infiltration, frequent rheumatoid factor positivity, elevated serum IgG values, and an elevated blood sedimentation rate, all of which implicate an underlying set of immunological abnormalities [11]. The pathological features of Küttner's tumors include infiltration of small round

cells—the lymphoplasmacytic infiltrate—associated with lymphoid follicle formation, and acinar cell degeneration and disappearance. Salivary gland fibrosis at sites of vigorous cell proliferation in the interlobular connective tissue is also characteristic. In this feature, Küttner's tumor again bears a striking similarity to the salivary gland histopathology associated with Mikulicz's disease. Because Mikulicz's disease also frequently begins with submandibular gland lesions, one possibility is that chronic sclerosing submandibular sialadenitis is a localized form of Mikulicz's disease. Sialodocholithiasis can be associated with some degree of inflammatory cell inflammation in the glandular parenchyma, but IgG4-bearing plasma cells are not typical in that setting.

In 2005 Kitagawa et al. [7] described Küttner's tumor as a fibrotic lesion of the salivary gland that is associated with elevated serum IgG4 values and the infiltration of IgG4-positive plasma cells. The Japan Sjögren's Syndrome Study Group proposed diagnostic criteria for Mikulicz's disease in 2007, but when applying these criteria to Küttner's tumor (chronic sclerosing submandibular sialadenitis), the criterion of a IgG4-positive cell ratio of ≥50 % cannot be satisfied in all patients because severe fibrosis is present in some long-term cases. Some of these cases are perhaps described more aptly as "probable" or "possible" cases, depending on the rest of the evidence that suggests a process associated with IgG4-RD.

In our series of 31 Mikulicz's disease cases, we measured serum IgG and IgG4 concentrations in 25 and performed biopsies in 27. Twenty-two of the 25 patients whose sera were assayed had elevated serum IgG4 concentrations. Of the 27 cases biopsied, 25 demonstrated IgG4-positive cell infiltration. No IgG4-positive plasma cells were found in the tissues of two patients who underwent biopsies, and their serum IgG4 values were also within normal limits. However, one of those patients had a history of autoimmune pancreatitis and the lacrimal and salivary gland swelling was therefore also classified as being a consequence of IgG4-RD. In markedly fibrotic tissue, the number of IgG4-positive cells is decreased, and during the course serum IgG4 values fluctuate in many cases, and so it was surmised that IgG4 values may have been measured when in a decreased state.

Similarly, in 16 of the 20 cases with Küttner's tumor undergoing biopsy, elevated serum IgG4 values were often noted, while in (some) cases with marked progression of submandibular gland fibrosis, neither IgG4-positive plasma cells nor a significant lymphoplasmacytic cells infiltrate was found. Such cases in which IgG4-positive cells are not found in tissue should be considered as advanced cases, and with reference to the diagnostic criteria investigated with similar care.

In general, lacrimal gland and salivary gland swelling in Mikulicz's disease is usually rubbery to hard and not associated with tenderness. Only mild secretory function impairment is the rule for most patients [5]. In Küttner's tumor, submandibular gland sclerosis and tenderness are not found either, and salivary gland secretory function is only slightly impaired in most cases. Keratoconjunctivitis sicca is not usually found in either disease, and even when found is mild in most cases, with lacrimal gland secretory function normal or only slightly impaired.

In summary, Mikulicz's disease and Küttner's tumor share many features and in most instances it seems appropriate to assign them to the same category of underlying disease, namely, IgG4-RD. Further studies on these patients will clarify their relationships further and lead to broader understanding of the relationships between these two entities, previously regarded as separate diagnoses.

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Comprehensive Diagnostic Criteria for IgG4-Related Disease

6

Hisanori Umehara and Kazuichi Okazaki

6.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a new disease concept first recognized in the twenty-first century [1, 2]. The condition is characterized by elevated serum IgG4 values and marked IgG4-positive plasma cell infiltration of affected lesions [1, 2]. The initial clue to its detection was contributed by Hamano et al. [3], who reported elevated serum IgG4 concentrations in patients with sclerosing pancreatitis. Following this observation, many additional reports on this disease, pertaining to clinical, pathology, radiological, and therapeutic aspects, have been supplied by investigators from Japan and beyond. IgG4-RD now attracts worldwide attention, and the formulation of a carefully considered disease concept and diagnostic criteria are both awaited eagerly.

Under the auspices of the Japanese Ministry of Health, Labor and Welfare, two research groups focusing on IgG4-RD have been organized. One is a group for research on the new disease entity of IgG4-related multiorgan lymphoproliferative syndrome (IgG4+MOLPS) (group leader: Hisanori Umehara, Department of Hematology & Immunology, Kanazawa Medical University, 66 members). The other is charged with establishing diagnostic and therapeutic approaches for IgG4-related systemic sclerosing diseases (group leader: Kazuichi Okazaki, Third Depatment of Internal Medicine, Kansai Medical University; 55 members).

Because IgG4-RD is a disease process that afflicts multiple organs, both groups are comprised of a versatile membership with representation of specialists from various clinical fields, pathologists, and basic investigators. These two cooperative groups have accomplished much in the field to date, including the achievement of a broad consensus on the disease name (IgG4-RD) and publication of a comprehensive set of diagnostic criteria. In this chapter, we outline these comprehensive diagnostic criteria for IgG4-RD [4].

6.2 Comprehensive Diagnostic Criteria for IgG4-RD

The establishment of diagnostic criteria for IgG4-RD was complicated by the fact that IgG4-RD is a truly multifaceted disorder that encompasses many conditions once considered to be separate but now recognized to overlap broadly. These conditions include autoimmune pancreatitis [5–8], Mikulicz's disease [9, 10], Riedel's thyroiditis [11], Küttner's tumor [11, 12], retroperitoneal fibrosis [13, 14], inflammatory pseudotumor [15], interstitial nephritis [16, 17], interstitial pneumonia [18, 19], and others [1] (Fig. 6.1). In addition, accurate pathology characterization is essential to the diagnosis, as IgG4-RD is often difficult to differentiate from immune-mediated conditions such as Sjögren's syndrome and granulomatosis with angiitis (formerly Wegener's) and from hematological conditions such as Castleman's disease and malignant lymphoma. These facts posed daunting challenges to the formulation of diagnostic criteria that are applicable potentially to all cases.

In approaching the task, an "All Japan IgG4 Team" comprised of representatives from both the Umehara and Okazaki groups was created to draft diagnostic criteria. The aims of this effort included:

1. Formulating criteria that would be useful not only to specialist clinicians devoted to the study of their respective organs but also to nonspecialist clinicians

The two authors contributed equally to this work.

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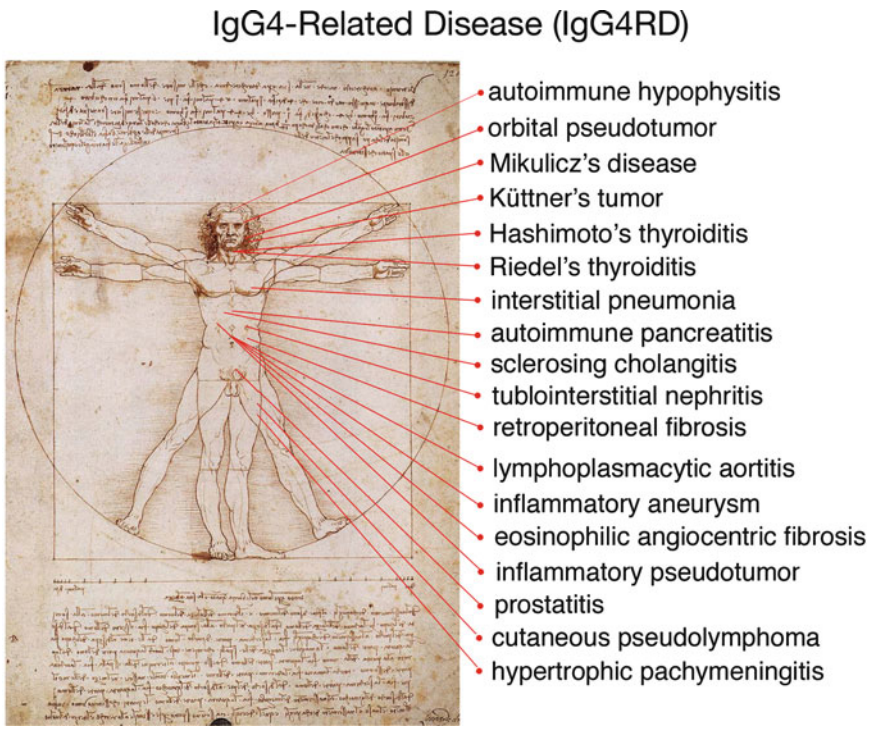

Fig. 6.1 IgG4-related disease (IgG4RD)

2. Devising diagnostic criteria that would be consistent for all organs
3. Succinctness
4. Sufficient emphasis on the need to exclude malignancy
5. Rationale for not recommending trials of glucocorticoid therapy for diagnostic purposes in possible IgG4-RD

We therefore proposed the first "comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011," attempting to encompass these concepts (Table 6.1) [4].

These criteria are comprised of three major items:

1. Single or multiple organs involved by diffuse or localized swelling, masses, nodules, and/or hypertrophic lesions
2. Elevated serum IgG4 levels(≥135 mg/dL)
3. Histopathological features that include
   - marked lymphocytic and plasma cell infiltration and fibrosis,
   - IgG4-positive plasma cell infiltration: IgG4/IgG-positive cell ratio ≥40 % and IgG4-positive plasma cells exceed 10/HPF

Patients can be classified into categories of definite, probable, or possible IgG4-RD, depending on how many of these diagnostic items are present.

The evaluation and diagnosis of patients with possible IgG4-RD requires the punctilious assessment of lesions in multiple organs, the interpretation of blood test findings, review of the pathology features (histopathology and immunostaining) and diagnostic imaging findings, judgment of the responsiveness to glucocorticoids, and exclusion of a lengthy list of potential mimickers (Table 6.1).

A variety of clues can be present in the blood. An elevated IgG4/IgG ratio (>8 %) in the blood may aid in the diagnosis in some cases even if the serum IgG4 concentration is <135 mg/dL, as is often the case – particularly in patients with single-organ disease. Patients with IgG4-RD typically demonstrate a polyclonal hypergammaglobulinemia with elevations of the total IgG concentration – IgG1 as well as IgG4 – though the IgG4 elevation is more impressive. The serum IgE concentration is also often elevated, and despite the putatively limited ability of IgG4 to fix complement and form immune complexes, hypocomplementemia is sometimes present, especially in those patients with renal disease.

The true role of IgG4 in the etiology and pathophysiology of IgG4 remains obscure. Elevations in serum IgG4 concentrations are by no means specific for IgG4-RD because the serum values can be elevated in a host of other diseases, as well, e.g., atopic dermatitis, pemphigus, bronchial asthma, and multicentric Castleman's disease. Increased serum IgG4 values are also reported in some patients with malignant tumors. The likelihood of pancreatic cancer, however, is low when IgG4 values are less than twice the upper limit of normal.

Histopathology is the key to the diagnosis of IgG4-RD. Characteristic histopathological findings include a swirling, "storiform" fibrosis and obliterative phlebitis. Neutrophilic infiltrates are not typical but can be observed occasionally in some organs such as the lung, where the biopsy may be taken from tissue bordering on mucosal surfaces.

Pancreatic cancer and other malignancies are sometimes associated with a reactive IgG4-positive plasma cell infiltration

Table 6.1 Comprehensive diagnostic criteria for IgG4-related disease, 2011 [4]

I. Concept

IgG4-related disease (IgG4-RD) shows organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously, due to marked infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis of unknown etiology. IgG4-RD affects various organs, including the pancreas, bile duct, lacrimal gland, salivary gland, central nervous system, thyroid, lung, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, others show involvement of a single organ. Clinical symptoms vary depending on the affected organ, and some patients may experience serious complications, such as obstruction or compression symptoms due to organomegaly or hypertrophy and organ dysfunction caused by cellular infiltration or fibrosis. Steroid therapy is often effective

II. Comprehensive clinical diagnostic criteria for IgG4-RD

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL)
3. Histopathologic examination shows:
   (1) Marked lymphocyte and plasmacyte infiltration and fibrosis
   (2) Infiltration of IgG4 + plasma cells: ratio of IgG4+/IgG+ cells >40 % and >10 IgG4+ plasma cells/HPF
   Definite: 1) +2) +3)
   Probable: 1) +3)
   Possible: 1) +2)

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g., cancer, lymphoma) and similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination

Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4RD

III. Explanatory notes

(1) The comprehensive diagnostic criteria are the minimal consensus, to aid specialists and non-specialist physicians in the clinical diagnosis of IgG4-RD. For each affected organ, organ-specific diagnostic criteria, established for IgG4-related Mikulicz's disease, IgG4-related autoimmune pancreatitis, and IgG4-related kidney disease, should be used concurrently

(2) Concept: The difference from multifocal fibrosclerosis is unclear although these diseases may be IgG4-RD. Many patients show multiple organ involvement and are characterized as having systemic disease, whereas other patients show involvement of a single organ

1. Autoimmune pancreatitis, Type I (IgG4-related autoimmune pancreatitis)

This disease is synonymous with IgG4-related sclerosing pancreatitis/lymphoplasmacytic sclerosing pancreatitis (LPSP). It can be diagnosed using the clinical diagnostic criteria for autoimmune pancreatitis established by the Ministry of Health, Labor and Welfare, Japan Pancreas Society in 2006 [26]

2. IgG4-related sclerosing cholangitis

This disease is characterized by sclerotic changes with diffuse or localized stenosis in the intrahepatic/extrahepatic bile duct and gallbladder. Circumferential wall thickening is observed at the site of stenosis, with similar changes in areas without stenosis. Obstructive jaundice often develops, making it important to differentiate this condition from tumors, such as cholangiocarcinoma and pancreatic cancer, and from primary sclerosing cholangitis. It is also necessary to exclude secondary sclerosing cholangitis as an apparent cause

3. IgG4-related lacrimal, orbital, and salivary gland lesions

This condition includes IgG4-related Mikulicz's disease, characterized by symmetrical (sometimes unilateral) swelling of any of the lacrimal, parotid, submandibular, and sublingual glands, and some minor salivary glands. Nodular/infiltrative lesions may also occur in orbital tissue other than the lacrimal glands. IgG4-related Mikulicz's disease can be diagnosed by the organ-specific diagnostic criteria for IgG4-related Mikulicz's disease established by the Sjögren's syndrome Study Group of Japan in 2008 [25]

4. IgG4-related central nervous system lesions

These lesions include infundibular hypophysitis, hypertrophic pachymeningitis, and intracerebral inflammatory pseudotumor

5. IgG4-related respiratory lesions

These lesions occur primarily in the interstitium, such as the bronchovascular bundles, interlobular septum, alveolar septum, and pleura. They are frequently accompanied by mediastinal and hilar lymphadenopathy, along with X-ray evidence of a mass or infiltration of the lung. Some patients have asthma-like symptoms. It is important to differentiate these lesions from malignant tumors, sarcoidosis, collagen diseases of the lung, and infection

6. IgG4-related renal lesions

Abnormal imaging findings include diffuse renal enlargement, multifocal contrast defects of the renal parenchyma, renal mass lesions, and pelvic wall thickening. Renal histology shows mainly interstitial nephritis, but glomerular lesions (e.g., membranous nephropathy) may also be present. IgG4-related tubulointerstitial nephritis can be diagnosed using the organ-specific diagnostic criteria for IgG4-related kidney disease [27]

7. IgG4-related retroperitoneal fibrosis/periarterial lesions

This disease is characterized by thickening of the abdominal aortic adventitia and periuretheral soft tissue, often accompanied by hydronephrosis or mass lesions. Periarteritis may occur around the aorta or relatively large branches and is evident as arterial wall thickening on radiological imaging. MRI and PET have been shown to be helpful for making diagnosis of retroperitoneal fibrosis in addition to CT. Biopsy is often not possible, making it difficult to differentiate this condition from secondary retroperitoneal fibrosis due to malignant tumors or infectious diseases

8. Other tumefactive lesions

Proliferation of IgG4-positive plasma cells and lymphocytes may accompany fibrosis. Including some conventional inflammatory pseudotumors, these lesions have been reported in the brain, orbit, lung, breast, liver, pancreas, retroperitoneum, kidney, and lymph nodes

(continued)

Table 6.1 (continued)

IV. Blood test findings
1. Polyclonal serum γ-globulin, IgG, and IgE are often elevated, and hypocomplementemia may occur 2. Elevated IgG4 can also be seen in other diseases (e.g., atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease) and is therefore not specific to IgG4-RD 3. On rare occasions, serum IgG4 concentration may be elevated in patients with malignant tumors. However, patients with >270 mg/dL IgG4 are unlikely to have pancreatic cancer 4. In patients with single-organ involvement and serum IgG4 concentration less than 135 mg/dL, the IgG4/IgG ratio may be helpful in making a diagnosis 5. At present, the significance of elevated IgG4 in the pathogenesis/pathophysiology of IgG4-RD is unknown
V. Histopathological findings
1. Storiform or swirling fibrosis or obliterative phlebitis is characteristic of IgG4-RD and may be important in its diagnosis 2. Eosinophilic infiltration often occurs, along with infiltration of IgG4- positive cells 3. Reactive infiltration of IgG4- positive cells and fibrosis may also occur, such as at the periphery of pancreatic cancers
VI. Imaging studies
IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney, and retroperitoneum. MRI and FDG -PET (fluorodeoxyglucose positron emission tomography) have been shown to be helpful for detecting multi-organ involvements
VII Steroids
1. Patients with malignant lymphoma or paraneoplastic lesions can sometimes be improved by steroid administration. Therefore, steroid trials should be strictly avoided 2. Efforts should be made to collect tissue samples for diagnosis. However, patients having disease in organs difficult to biopsy, such as the pancreas, retroperitoneum, and pituitary, and respond to steroids may possibly have IgG4-RD 3. In accordance with the guidelines for treatment of autoimmune pancreatitis, patients should be started on 0.5–-0.6 mg/kg/day/ prednisolone. If patients do not respond to the initial steroid therapy, the diagnosis should be reviewed
VIII Diseases to be excluded or differentiated
1. To exclude malignancies (e.g., cancer, lymphoma) in the involved organs, it is essential to determine whether malignant cells are present histopathologically 2. Similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, idiopathic retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg-Strauss syndrome) are diagnosed using the diagnostic criteria for each disease 3. Multicentric Castleman's disease is a hyper IL-6 syndrome and is not included among the IgG4-related diseases even if the diagnostic criteria for IgG4-RD are fulfilled

and fibrosis in the peritumoral tissues. These findings represent a nonspecific, reactive phenomenon. High on the differential diagnosis of IgG4-RD, though, is malignancy, and thus it is essential to exclude malignant cells by careful histopathological evaluation and special marker studies as appropriate.

Nonmalignant conditions can also bear strong resemblance to IgG4-RD. These include Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease [20], idiopathic retroperitoneal fibrosis, granulomatosis with polyangiitis (formerly Wegener's), sarcoidosis, and the Churg–Strauss syndrome [21]. Multicentric Castleman's disease occasionally manifests elevated serum IgG4 concentrations and IgG4-positive cell proliferation in tissues and can be difficult to distinguish from IgG4-RD. However, multicentric Castleman's disease is recognized to be a different disease.

Responses to glucocorticoids can be useful but imperfect indicators of IgG4-RD in cases in which it may be difficult to obtain diagnostic tissue, e.g., the pancreas, retroperitoneum, and pituitary gland. However, lymphoma and paraneoplastic lesions can also improve following glucocorticoid therapy, and so empiric steroid trials must not be undertaken lightly. For this reason, the response to glucocorticoid administration for diagnostic purposes has not been adopted in comprehensive diagnostic criteria for IgG4-RD, and the greatest possible effort must be made to obtain tissue samples to permit a histopathological diagnosis.

6.3 Algorithm for IgG4-RD Diagnosis

The diagnostic sensitivity of the comprehensive diagnostic criteria outlined above is not known for patients with lesions that are difficult to biopsy. To compensate for these limitations when applying these criteria in clinical practice, the use of detailed IgG4-RD organ-specific diagnostic criteria is helpful (Fig. 6.2). Diagnostic criteria for IgG4-related Mikulicz's disease and type 1 (IgG4-related) autoimmune pancreatitis have already been announced [22, 23]. Diagnostic criteria for IgG4-related kidney disease have also been created in collaboration with the Japan Kidney Society [24].

6.4 Concluding Remarks

Researchers in a variety of different fields from across the world have contributed to the acquisition and distribution of knowledge regarding IgG4-RD. With enhanced recognition of this entity, interest in IgG4-RD continues to grow. An IgG4-RD International Symposium was held in the context of the 20th Annual Meeting of the Japanese Society for Sjögren's syndrome (September 2011, Kanazawa, Japan), and an International Symposium for IgG4-RD was also held

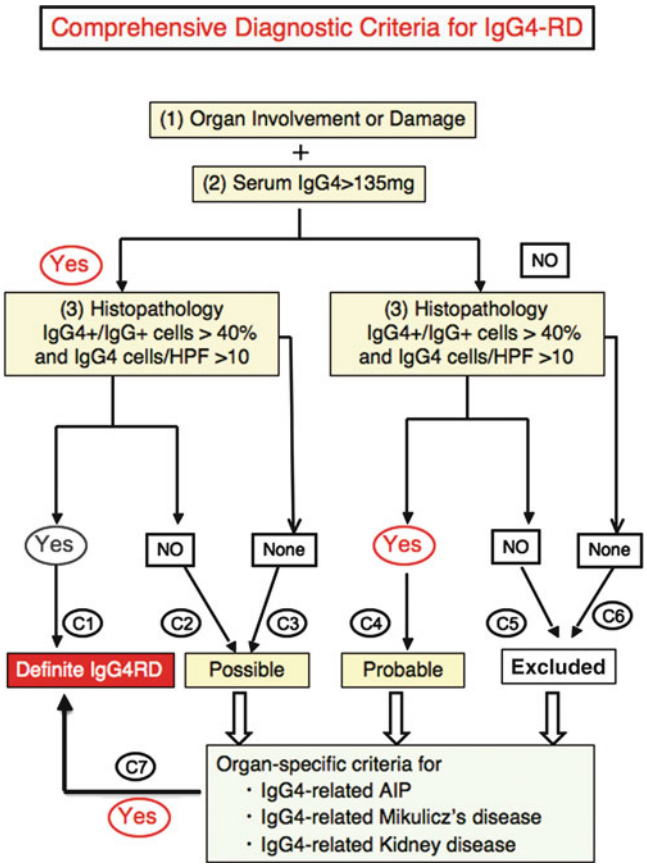

Fig. 6.2 Comprehensive diagnostic criteria for IgG4-RD

in the United States (October 2011, Boston). International consensus about nomenclature in each organ and pathology of IgG4-RD has been reached [25, 26]. As a next step, we must aim for broader recognition of IgG4-RD in daily clinical practice and promote the participation of larger numbers of physicians and other researchers in the investigation of this field.

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7 Autoimmune Pancreatitis with Normal Serum IgG4 Concentrations: What Is the Correct Classification for Such Patients?

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7.1 Introductory Remarks

Autoimmune pancreatitis (AIP), which was introduced from Japan to the rest of the world, is a distinctive type of pancreatitis. In 1995, a case was reported that showed pancreatic duct narrowing, pancreatic swelling, hypergammaglobulinemia, and positive autoantibodies, as well as marked responsiveness to steroids [1]. It subsequently became clear that in the condition now known as type 1 AIP, an elevated serum IgG4 concentration is observed in a high proportion of cases [2].

Extrapancreatic lesions are common in patients with type 1 AIP and may affect a wide range of organs with pathological features that are strikingly similar to those of the pancreas and tend to respond well to steroids. These pathological features include a marked lymphoplasmacytic infiltrate with an increased number of IgG4-positive plasma cells and a distinctive form of fibrosis that often assumes a storiform pattern. These multi-organ features are now recognized to comprise one systemic disease with the capability of affecting multiple organs in either a simultaneous fashion or, more commonly, in a metachronous manner. Thus, lymphoplasmacytic sclerosing pancreatitis (LPSP), as type 1 AIP is commonly known in the medical literature, is now regarded as the pancreatic lesion of IgG4-related disease (IgG4-RD) [3–5].

Broader experience with AIP led to the recognition of a form of this condition that is associated with normal IgG4 concentrations in the blood. In this chapter, we outline the clinical features of such cases, focusing on our own experience.

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7.2 Autoimmune Pancreatitis: Types 1 and 2

Before the clear emergence of a second type of AIP and recognition of the need to designate the two currently recognized forms of AIP as types 1 and 2, the most common form of AIP in Japan came to be known as LPSP [6]. LPSP is characterized by extensive cellular infiltrates consisting of IgG4-positive plasma cells, T lymphocytes, fibrosis, and obliterative phlebitis. Neutrophils are typically absent in LPSP, and the inflammatory cell infiltrate tends to spare the pancreatic duct epithelium. The typical patient is an elderly man who presents with painless jaundice, i.e., minimal to no signs of acute pancreatitis. Other sclerosing extrapancreatic lesions are often present, such as in the biliary tree (IgG4-related sclerosing cholangitis) or salivary glands (IgG4-related sialadenitis, with submandibular or parotid gland involvement). In contrast to type 2 AIP, inflammatory bowel disease is almost never seen in LPSP [4, 5].

A European histopathological study detected neutrophil infiltration of the pancreatic duct epithelium (granulocytic epithelial lesion: GEL) in 24 of 53 AIP cases [7]. In these cases the mean age at onset was young compared to that of LPSP patients, the sexes were affected in equal proportions, and inflammatory bowel disease was frequently present. The patients in that European series whose pancreatic biopsies did not show GEL had clinical and pathological features similar to the type of AIP described consistently in Japan. In a recent international study, AIP patients in Italy showed similar features with regard to age at onset—approximately 20 years younger than that in Japan and no tendency to affect one sex more frequently than the other [8]. In addition, symptoms of acute pancreatitis and inflammatory bowel disease were reported in 32 % and 30 %, respectively, of the Italian patients. The contrasting experiences between Japan and Europe indicate clearly that there are at least two different conditions grouped under the common heading of "AIP."

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Histopathological studies from the Mayo Clinic of resected cases of idiopathic chronic pancreatitis with heavy inflammatory cell infiltration revealed cases with copious neutrophil infiltration, particularly in the pancreatic lobule [9]. These cases, readily separated from the pathology of LPSP, were termed "idiopathic duct-centric chronic pancreatitis" (IDCP). In IDCP, neutrophil infiltration within the pancreatic duct epithelium is a hallmark of the condition but in contrast to LPSP (type 1 AIP), but there is little inflammatory cell infiltration in the fibrotic layer, obliterative phlebitis is rare, and IgG4-positive plasma cell infiltrates are considerably less prominent than in LPSP. In these cases a clinical picture almost identical to that of the GEL-positive cases is present [9]. Some cases of juvenile-onset AIP have demonstrated similar clinical and pathological pictures [10].

Substantial clarity has been brought to the field in recent years [11, 12]. LPSP and IDCP are now recognized as type 1 and type 2 AIP, respectively [11]. In the recently proposed international consensus diagnostic criteria for AIP [13], the diagnostic criteria for types 1 and 2 AIP are listed separately. The criteria emphasize that the two types of AIP share the same pancreatic imaging findings and responsiveness to steroids, but elevated serum IgG4 values and the presence of IgG4-related extrapancreatic lesions are limited to type 1, and inflammatory bowel disease is limited to type 2. Moreover, marked periductal lymphocyte and IgG4-positive plasma cell infiltration (>10/HPF), obliterative phlebitis, and storiform fibrosis are noted in type 1 and neutrophil infiltration of the pancreatic duct wall in type 2.

7.3 Clinicopathologic Features of AIP with Normal Serum IgG4 Concentrations in Our Own Cases

Fifty-eight AIP patients diagnosed in our department were divided into two groups according to their serum IgG4 concentrations: a normal serum IgG4 AIP group (≦135 mg/dL; $n=13$) and an elevated serum IgG4 positive group positive group (>135 mg/dL; $n=45$). We then compared their clinicopathologic features [14].

7.3.1 Age and Sex Distribution

The proportion of women tended to be higher among the group of patients with normal serum IgG4 concentrations, although this comparison fell just short of statistical significance. The male/female ratio in the normal serum IgG4 group was 7/6, compared with 36/9 among those patients with elevated serum IgG4 concentrations ($p=0.07$). There was no difference in the mean age at diagnosis between the two groups: 61.5 years (normal serum IgG4) versus 63.7 years (elevated serum IgG4).

7.3.2 Presenting Symptoms

Obstructive jaundice was substantially less common among the patients with normal serum IgG4 concentrations (31 % versus 78 %, $p<0.01$), but abdominal symptoms suggestive of acute pancreatitis were markedly more common (38 % versus 7 %, $p=0.01$).

7.3.3 Pancreatic Swelling

Segmental pancreatic swelling was noted more frequently in the group of patients with normal serum IgG4 concentrations (46 % versus 13 %, $p<0.05$).

7.3.4 Extrapancreatic Lesions

Extrapancreatic lesions such as sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, and retroperitoneal fibrosis were more frequently found among the group of patients whose serum IgG4 concentration was elevated (51 % versus 8 %, $p<0.01$), but acute pancreatitis was more common in the group with normal serum IgG4 values (23 % versus 4 %, $p<0.05$). Ulcerative colitis was seen in one case each in both groups.

7.3.5 Salivary Gland and Lacrimal Gland Function

Salivary gland function determined by biochemical analysis of saliva and lacrimal gland function by Schirmer's test. Salivary Na^+ and β2-microglobulin concentrations were increased significantly in both groups as compared to the control, but they were significantly higher in the group with elevated serum IgG4 concentrations (Na^+: a mean 32.6 mEq/L vs. 21.7 mEq/L, $p<0.05$, and β2-microglobulin: 2.7 mg/dL vs. 1.5 mg/dL, $p<0.05$).

Data of Schirmer's test were significantly lower in the group with elevated serum IgG4 concentrations (a mean 5.4 mm vs. 11.9 mm, $p<0.05$).

7.3.6 Responsiveness to Steroids

Both groups were initially responsive to steroids. No patients with normal serum IgG4 concentrations relapsed

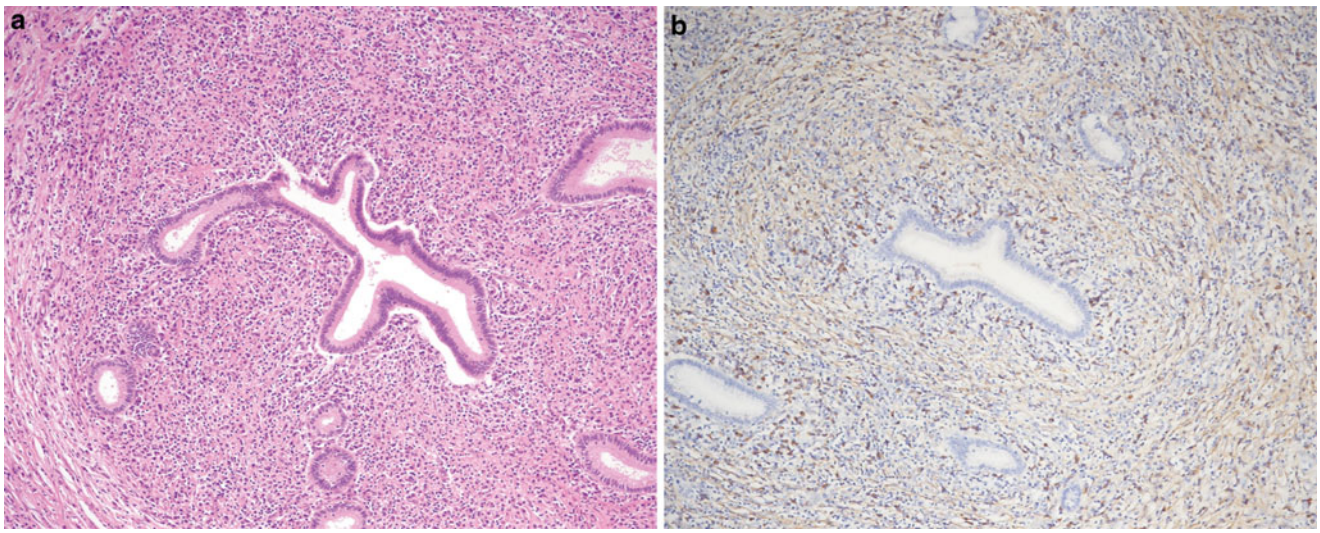

Fig. 7.1 Histopathological features of the pancreas in autoimmune pancreatitis cases with elevated serum IgG4 values. (**a**): Around the pancreatic duct marked inflammatory cell infiltration and fibrosis are seen (H&E staining ×100). (**b**): Numerous IgG4-positive plasma cell infiltrates are found around the pancreatic duct (IgG4 staining ×40)

during a mean 57.3 (8–140) months, while five patients with elevated serum IgG4 concentrations relapsed during 50.2 (6–173) months.

7.3.7 Histopathological Findings of the Pancreas

The five resected and the five biopsied pancreatic specimens of patients with elevated serum IgG4 concentrations revealed LPSP in ten cases, and EUS-FNA of three patients could not confirm the diagnosis. Two resected, one biopsied, and 1 EUS-FNA pancreatic specimen of patients with normal serum IgG4 concentrations revealed LPSP, two fine needle aspirates yielded tissue that was insufficient for diagnosis, and two other biopsies showed B cell infiltrates and fibrosis. One patient whose fine needle aspirate was non-diagnostic had a high pretest likelihood of IDCP (type 2 AIP), as he presented with acute pancreatitis and had a history of inflammatory bowel disease.

In the specimens from patients with elevated serum IgG4 concentrations, dense lymphocyte and IgG4-positive plasma cell infiltrates were noted. The lymphoplasmacytic infiltrates were particularly concentrated in the pancreatic interlobular interstitium and around the pancreatic duct (Fig. 7.1a, b). In contrast, the specimens from the patients with normal IgG4 concentrations were characterized by comparatively little inflammatory cell infiltration (Fig. 7.2a, b).

7.3.8 Number of IgG4-Positive Plasma Cells in the Biopsied Gastric Tissues

The IgG4-positive plasma cells infiltrating gastric mucosal tissues obtained by biopsy numbered a mean 7.0 (0–20)/HPF in the positive group ($n=17$) as compared to only 1.4 (0–3)/HPF in the negative group ($n=7$, $p<0.01$).

7.3.9 Subsets of AIP Among Patients with Normal Serum IgG4 Levels

The AIP patients with normal serum IgG4 concentrations could be divided into three groups: (a) type 1 AIP; (b) fibrosis associated with dense B lymphocyte infiltration; and (c) an undiagnosable category. The specimens from patients with type 1 AIP but normal serum IgG4 concentrations had relatively little IgG4-positive plasma cell infiltration in the pancreas, and in some cases lesions were limited to the pancreas. The histopathologically undiagnosable cases were thought to possibly include some type 2 cases. It is possible that cases exist with a histological picture that differs from either type 1 or type 2 AIP.

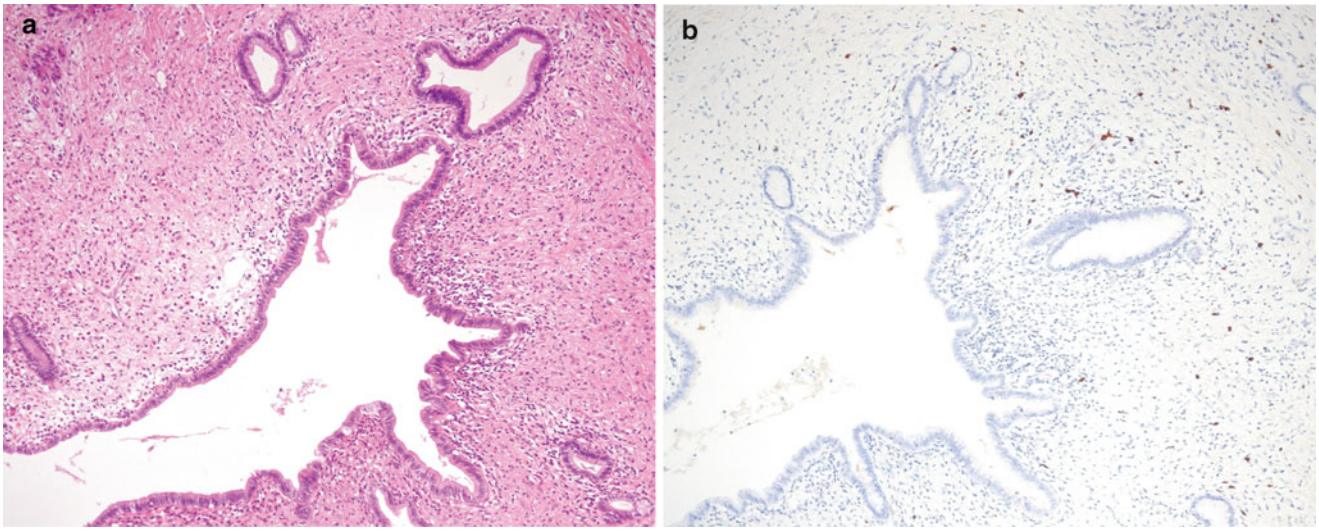

Fig. 7.2 Histopathological features of the pancreas in autoimmune pancreatitis cases with low serum IgG4 values. (**a**): Inflammatory cell infiltration and fibrosis are seen around the pancreatic duct, but the degree of cell infiltration is less than that seen in Fig. 7.1 (H&E staining ×100). (**b**): IgG4-positive plasma cell infiltration is also markedly less conspicuous as compared to that in Fig. 7.1 (IgG4 staining ×40)

7.4 Concluding Remarks

Patients with AIP and normal IgG4 concentrations in the serum appear to have three possible diagnoses: (a) type 1 AIP that is characterized histopathologically be relatively sparse IgG4-positive plasma cell infiltration with fibrosis; (b) type 2 AIP, a condition that is not part of the IgG4-RD spectrum; and (c) other pathology not classifiable at present as either type 1 or type 2 AIP, suggesting that the spectrum of AIP may extend beyond these two currently recognized entities.

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Pharmacotherapy of IgG4-Related Disease

8

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8.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a systemic disorder encompassing a very diverse clinical spectrum and pathophysiological features [1]. Therapeutic approaches for the individual components comprising this disease have not yet been adequately established, and for the most part have been devised with reference to the experience obtained with the treatment of type 1 autoimmune pancreatitis (AIP), the pathophysiology of which was the first to be investigated in detail. The most suitable therapeutic strategies still need to be established for each IgG4-related condition based on the pathophysiological and clinical features specific to each type of organ involvement. With this in mind, in this chapter we outline the pharmacotherapy for type 1 AIP and also introduce reported therapies for other IgG4-RD. The definitions of terms are provided according to Chari's definitions with slight modification (Table 8.1) [2].

The efficacy of glucocorticoid therapy for type 1 AIP has been widely documented since the first report of this intervention, published in 1978 by Nakano et al., even before the concept of AIP had been formed fully [3]. Despite the use of glucocorticoids for several decades now, however, no consensus has been reached about precisely how these medications should be employed. There is no widely accepted, uniform protocol for administration, and each institution or individual practitioner has devised its or his/her own. Furthermore, because some patients with AIP achieve spontaneous remissions, there is no consensus regarding even the indications for initiating glucocorticoid therapy.

Some investigators have attempted to use patients' responses to glucocorticoid trials to differentiate benign conditions such as type 1 AIP from malignant disorders. In an attempt to gain a handle on such approaches, the research group on intractable pancreatic diseases (Ohtsuki group) established by the Japanese Ministry of Health surveyed the therapeutic methods adopted at individual institutions in Japan and formulated a consensus document in 2007 based on their analysis of the data (Table 8.2) [4]. Based on this effort, glucocorticoid therapy-centered pharmacotherapy has become widely accepted and applied [5].

8.2 Glucocorticoid Therapy for Type 1 AIP

The ability to predict at the time of diagnosis which patients with type 1 AIP will achieve spontaneous remission without glucocorticoid therapy is decidedly poor. In addition, delays in the initiation of treatment can be associated with substantial consequences for pancreatic function and overall health. Extensive experience with glucocorticoids has demonstrated that the great majority of patients achieve remission with this therapy and that maintenance of sufficient doses of prednisone leads to a reduction in disease recurrences (albeit at the cost of glucocorticoid-related morbidity in many patients) [6, 7]. Because of the efficacy of glucocorticoids, oral administration of these agents remains the cornerstone of therapy for type 1 AIP [4].

No consensus has yet been reached on the issues of whether or not all patients with type 1 AIP should be treated with glucocorticoids. Published guidelines for the therapy of this condition indicate that glucocorticoid administration should be employed for patients who are symptomatic with issues such as obstructive jaundice, abdominal pain, and back pain, as well as symptomatic extrapancreatic lesions [5, 8, 9].

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Table 8.1 Definitions of remission and relapse

Clinical (symptomatic) remission: resolution of clinical symptoms
Serologic remission: normalization of serum IgG4 and hypergammaglobulinemia
Radiologic remission: resolution of diffuse or localized swelling, masses, nodules, and/or hypertrophic lesions
Clinical (symptomatic) relapse: recurrence of disease-related symptoms such as obstructive jaundice, cough, dry mouth, and so on
Serologic relapse: re-elevation of serum IgG or IgG4 levels, or elevation of biliary enzymes in type 1 AIP, or elevation of serum Cr levels

Table 8.2 Consensus on the treatment for patients with type 1 AIP in Japan (cited from [3], Table 4)

1. Administration of an oral glucocorticoid should be the standard therapy for AIP
2. Consider performing biliary drainage for patients with jaundice
3. Blood glucose concentrations should be controlled to the extent possible in patients with diabetes mellitus and monitored in all patients
4. For patients with jaundice or bile duct stricture, or cases in which the clinical manifestations do not improve, e.g., abdominal pain, consider administration of an oral steroid. However, if the patient has not been diagnosed as having AIP, glucocorticoid therapy should be used with extreme caution. In addition, if a course of glucocorticoid therapy does not achieve the desired result, carry out a reevaluation focusing on the possibility of pancreatic carcinoma
5. Start the administration of a glucocorticoid orally with a dose of 30–40 mg/day as the initial dose
6. Maintain the initial dose of glucocorticoid for 2–4 weeks, while carefully monitoring the patient's clinical manifestations, laboratory data, and imaging findings. Then gradually reduce the amount of glucocorticoid to a maintenance dose over a period of 2–3 months
7. In principle, continue glucocorticoid maintenance treatment (2.5–5 mg/day) after remission is achieved.
8. The length of time that maintenance treatment should be continued is not yet clear, but it can probably be stopped after a predetermined period (about 6–12 months) as long as the improvement in the clinical manifestations is sustained. In addition, the patient should be followed indefinitely to detect any late recurrence

8.2.1 Initial Remission Induction Therapy [4, 5]

Before the initiation of glucocorticoids, malignancy must be excluded by a thorough evaluation [7]. Biliary decompression and antidiabetic therapies should be implemented in the setting of obstructive jaundice and glucose intolerance. One approach to the induction of remission is the administration of prednisolone (0.6 mg/kg body weight/day) for a period of 2–4 weeks. In practice, 30 or 40 mg/day of prednisolone is often prescribed. Most patients treated with such a regimen demonstrate clinical, laboratory, and imaging evidence of improvement within 2 weeks and achieve a clinical remission on therapy within 1 month. Following this initial segment of the remission induction period, the prednisolone dose is reduced gradually until a target glucocorticoid maintenance dose is reached. This is generally on the order of 5–10 mg/day of prednisolone [7].

8.2.2 Glucocorticoid Taper

One widely accepted approach to glucocorticoid tapers in AIP is to reduce the prednisolone by 5 mg every 1–2 weeks so as to reach a maintenance dose approximately 2–3 months after the initiation of treatment (Fig. 8.1) [4, 5]. Minor variations on this approach are common. During the prednisolone taper, the clinician must monitor the patient's clinical symptoms, blood biochemical examinations, serum γ-globulin, IgG and IgG4 values, and imaging findings. The issues of whether or not prednisolone should be discontinued entirely and, if so, when this discontinuation should occur remain unresolved.

Glucocorticoid therapy often leads to improvement in both the exocrine and endocrine function of the pancreas in AIP. An improvement of approximately 40 % on the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (BT-PABA) test—a measure of exocrine function—has been reported [10]. Endocrine function has been reported to improve in 47 % and worsen in 17 % of cases. These inconsistent results may be attributable to differences in the disease stage at the start of glucocorticoid administration and will require further study [4, 11].

8.2.3 Maintenance Therapy

Recurrence rates of AIP are lower in patients who are maintained on a low daily dose of glucocorticoid. Continuation of prednisolone at a dose of 5–7.5 mg/day for at least 3 years is considered desirable by many experienced clinicians [4, 5]. On the other hand, in cases in which disease activity is believed to be low, namely, those without extrapancreatic

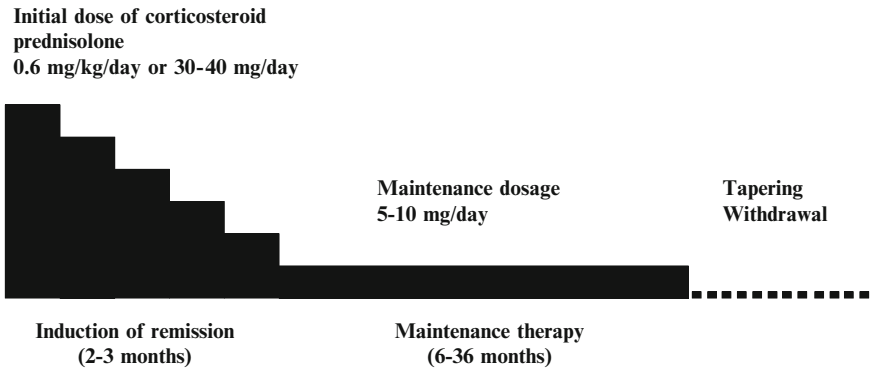

Fig. 8.1 Corticosteroid therapy for Type 1 AIP (cited from [4])

lesions such as dacryoadenitis/sialadenitis, extensive lymph node swelling, intrahepatic bile duct sclerosing lesions, or retroperitoneal fibrosis, further dose reduction or even cessation may be appropriate. The serum IgG4 concentration is useful in many but not all patients as a guide to when further reductions in the glucocorticoid dose or discontinuation of this treatment modality altogether is appropriate. Sustained clinical remissions with normal serum IgG4 concentrations have been reported following a course of glucocorticoid treatment (without maintenance) for more than 10 years in a minority of patients [12]. Thus, maintenance therapy with glucocorticoids is not required in all patients. In contrast, in cases with persistently elevated serum IgG4 levels or high disease activity as manifested by the presence of extrapancreatic lesions, long-term continuation of glucocorticoid use or the use of a steroid-sparing agent may be appropriate. Some AIP patients develop alterations in the pancreatic ductal system that culminate in the formation of pancreatic stones, caused by fluid stasis [13, 14]. The aims of long-term maintenance therapy include not only the prevention of recurrences but also the preservation and recovery of pancreatic function. Longitudinal studies are required to determine the effectiveness of therapies in achieving these goals.

8.2.4 Criteria for Cessation of Maintenance Therapy

Recurrence most frequently occurs within 3 years of continuous maintenance therapy, and in cases showing high disease activity it is considered desirable to continue maintenance therapy for a minimum of 3 years [4, 5]. Since this patient population is elderly, there is concern about the well-known adverse effects of glucocorticoids. Bone mineral density must be assessed in patients treated with long-term glucocorticoid therapy or in patients otherwise judged to be at risk for osteoporosis. The administration of calcium, vitamin D, and bisphosphonate therapies may be appropriate to prevent sequelae of glucocorticoid treatment on bones. One reasonable option is to cease their administration for a given period if the activity index is decreased and resume maintenance therapy indefinitely only in those patients who demonstrate a propensity to recurrence.

8.3 Examination Methods and Timing in the Outpatient Clinic

8.3.1 Activity Index

The activity of AIP is assessed on the basis of:

1. Obstructive jaundice
2. Various blood findings including biliary enzymes, pancreatic enzymes, antinuclear antibody, rheumatoid factor, IgG, IgG4, immune complexes, soluble IL2 receptor, elevated β2-microglobulin, and hypocomplementemia
3. Pancreatic swelling on imaging examinations
4. Extrapancreatic manifestations such as dacryoadenitis, sialadenitis, lymphadenopathy, sclerosing cholangitis, retroperitoneal fibrosis, and others

Biochemical and serological abnormalities in the blood can be useful indicators of impending disease flares on longitudinal follow-up [5]. When IgG4 and immune complexes are measured serially in cases with multiple recurrences, elevations in serum concentrations can be detected several months prior to clinical disease flares [15]. Hypocomplementemia of C3 and C4 is observed in approximately one third of patients with active disease, suggesting that complement levels are another useful clinical indicator in this disease [16].

8.3.2 Follow-Up Protocol in the Outpatient Clinic

During the period of maintenance therapy, patients should be evaluated every 1–2 months in the outpatient clinic, with the performance of blood examinations at each visit.

Measurements of IgG and IgG4 are useful but imperfect biomarkers of disease activity predicting clinical recurrences [5]. Biliary and pancreatic enzymes, concentrations of glycosylated hemoglobin (HbA1c), and serum complement levels should be assessed on a serial basis. Imaging examinations such as abdominal US, CT, and MRI should be performed at regular intervals according to the patient's degree of disease severity and clinical activity. An interval of 1 year is appropriate for patients who are stable, and it is helpful to have consistency in the type of study performed (i.e., when possible, it is desirable to compare CT studies with previous CT studies rather than with US examinations).

When a disease recurrence is suspected, serum measurements of IgG4, immune complexes, and soluble interleukin-2 receptor concentrations should be performed. Gallium scintigraphy or FDG-PET, which can screen comprehensively for both pancreatic and extrapancreatic lesions, should also be considered to facilitate a complete understanding of the extent of disease involvement.

8.3.3 Recurrent Cases

The duration of maintenance therapy for patients who have demonstrated a propensity to disease exacerbations following glucocorticoid tapers must be decided on an individual patient basis. Factors such as the extent of organ damage from previously active disease, the importance of preventing subsequent flares, and patient comorbidities all figure prominently in these decisions. When recurrences occur during maintenance therapy, a higher maintenance dose than the initial one should be set and then gradually reduced. A steroid-sparing medication may also be considered in such circumstances.

8.4 Glucocorticoid and Minipulse Therapy for Type 1 AIP

When an adequate effect is not obtained with oral glucocorticoid administration, or its use is not feasible because of planned surgery or patient refusal, the combination of glucocorticoids and minipulse therapy may be effective in some cases. Inadequate initial glucocorticoid doses can lead to improvement in pancreatic swelling but persistence of severe lower bile duct stenosis. In such cases, a "minipulse" of high-dose glucocorticoid treatment, e.g., methylprednisolone 500 mg/day for 3 days, can lead to marked improvement [14]. This is often an effective option even for cases in which an adequate effect is not obtained with oral glucocorticoids. In cases with bile duct stenosis in which malignancy cannot be excluded and surgery must be considered, the adverse influence of minipulse therapy on surgery is thought to be minimal, and cases in which surgery could be avoided altogether have been reported [17]. Also, minipulse therapy exerts more potent anti-inflammatory and immunosuppressive actions than does oral glucocorticoid therapy, and so the use of minipulse therapy as the initial intervention may achieve a more effective state of remission than conventional steroid administration. In the future it will also be necessary to consider expanding the types of cases for which its use may be indicated.

8.5 Nonsteroidal Therapy for Type 1 AIP

In intractable cases with repeated recurrences the combined use of glucocorticoids with other immunosuppressants such as azathioprine, mycophenolate mofetil, or rituximab has been reported in western countries [18–23]. Because azathioprine administration is associated with a risk of acute pancreatitis, caution must be employed when using this agent [17]. However, there are cases with persistent high activity that experience repeated recurrences despite fine-tuning of the oral prednisolone administration protocol. For this kind of intractable case the combined use of immunosuppressants will have to be evaluated, and rituximab therapy is one of the most promising therapies (see Stone's chapter).

8.6 Therapy for IgG4-Related Disease Other than Type 1 AIP

8.6.1 Indications

Oral glucocorticoid administration is the first-line pharmacotherapeutic choice for most organ system manifestations of IgG4-RD, as it is for type 1 AIP. Glucocorticoids are not indicated in all cases, but should be considered strongly when the disease involves major organs. In the absence of symptoms, careful observation without therapy can be considered in some cases. No broadly applicable treatment guidelines exist currently, and therefore decisions about whether and how to treat patients remain individual ones, based upon the type and extent of lesions present [1].

8.6.2 Therapy for IgG4-Related Dacryoadenitis and Sialadenitis

Glucocorticoid therapy is almost always employed in dacryoadenitis because of issues of cosmetic concern to the

patient such as eyelid swelling and troubling symptoms such as double vision. In contrast, glucocorticoids are seldom administered early in the course of sialadenitis and many patients with this type of organ involvement are never treated with systemic therapy. Exceptions to this are patients with severe xerostomia, dramatic enlargement of the glands that is troubling for the patient for cosmetic reasons, or significant pain associated with glandular swelling.

If the decision is made not to employ glucocorticoid treatment, periodic surveillance is required for the development of lesions at new sites beyond the salivary gland and to assess whether or not the xerostomia has been progressive. The possibility of lymphoma must be excluded before glucocorticoids are begun for lesions of the lacrimal and salivary glands. In addition, if glucocorticoid therapy is less effective than anticipated, the pathological specimen should be reexamined (or a new biopsy performed) to ensure that lymphoma has not been overlooked.

The efficacy of glucocorticoid therapy for lacrimal and salivary gland lesions has been investigated in only small numbers of cases. Masaki et al. retrospectively reviewed 64 such cases in a multi-institutional collaborative study [24]. Glucocorticoids were administered to 38 cases—59 % of the group overall. Prednisolone was used in all cases. Twenty-five patients received starting doses of prednisolone between 10 and 30 mg/day, and thirteen patients started therapy between 40 and 60 mg/day. The glucocorticoid dose was based on the presence of lesions at sites other than the lacrimal and salivary glands. Recurrences occurred in 39 %—many while patients remained on glucocorticoid treatment—and up to 10 mg/day of prednisolone was required as maintenance therapy for many patients.

Yamamoto et al. treated eight cases of dacryoadenitis and sialadenitis (Mikulicz's disease) with prednisolone at doses between 30 and 40 mg/day [25]. This resulted in an increase in the saliva volume from the pre-therapy value of 1.98 g/2 min to 15.70 g/2 min by the Saxon test and in the tear secretion volume from 6.9 mm/5 min to 15.7 mm/5 min by the Schirmer test.

The above findings suggest that in cases with lacrimal or salivary gland lesions in which active therapy is considered necessary, the selection of the initial prednisolone dose and maintenance therapy should be guided by recommendations issued for the treatment of type 1 (IgG4-related) AIP [5, 7].

8.6.3 Therapy of IgG4-Related Kidney Disease

Unlike Type 1 AIP, no large, definitive clinical studies have focused on therapy for IgG4-related kidney disease (IgG4-RKD). The evidence base on which to predicate treatment decisions stems exclusively from case reports and case series. The aims of therapy in IgG4-RKD are to prevent the deterioration of renal function and to normalize renal function to the full extent possible.

In a review of 18 previously published case reports, six patients were treated with an initial prednisolone dose of ≥50 mg/day with three patients receiving additional glucocorticoid pulses [26]. Eleven patients were treated with 30–40 mg of PSL and the remaining one patient with 20 mg. In two cases, azathioprine or cyclosporine was used in combination with a glucocorticoid. All patients showed a good response to corticosteroid, and rapid improvement of serum creatinine (Cr) levels was obtained in patients with elevated serum Cr levels. On the other hand, cases with normal serum Cr levels with typical radiologic findings showed dramatic improvement of the radiologic findings.

In a study of 23 cases by Saeki et al., glucocorticoid pulse therapy was administered to two cases, and therapy started with prednisolone alone in 19 of the remaining 21 cases at doses ranging between 10 and 60 mg/day [27]. The initial dose of prednisolone was unrelated to the pre-therapy renal function, and at the 1-month follow-up 18 of the 19 cases showed a decrease in serum Cr levels and improvement in the imaging findings. However, the remaining case progressed to renal failure requiring hemodialysis. Results similar to those of this series were reported by Raissian et al., who described the outcomes of 27 patients with renal disease, 21 of whom received glucocorticoids (dose not specified) and two of whom also received mycophenolate mofetil [28].

These results suggest that for renal involvement in IgG4-RD, the same therapy as used for pancreas involvement can be effective. However, Mizushima et al. compared the contrast-enhanced CT findings before and after therapy and observed that even when glucocorticoid therapy was initiated from an early stage in patients with essentially normal renal function, a significant number of patients manifested renal atrophy on follow-up [29]. Thus, we recommend that glucocorticoid therapy be started if there is evidence of renal disease, even if renal function at presentation is normal. Serum complement concentrations may be useful in monitoring disease activity in some patients with renal disease. Therefore, both C3 and C4 levels as well as serum creatinine concentrations should be monitored longitudinally.

8.7 Therapy of Other IgG4-Related Conditions

Other lesions requiring therapy include IgG4-related ophthalmic disease, retroperitoneal fibrosis, cholangitis, hepatitis, pulmonary lesions, hypophysitis, hypertrophic pachymeningitis, and skin lesions. In the case of IgG4-related periaortitis, some reports have described increased vascular wall fragility and rupture associated with glucocorticoid therapy. Some investigators recommend, therefore, that the glucocorticoid dose be limited accordingly to ≤20 mg/day. If the aneurysmal diameter increases in size, preparations should be made for surgical intervention.

A retrospective study from France on therapy for 25 cases of a variety of IgG4-RD described the use of prednisolone as a treatment agent at a mean dose of 0.67 mg/kg (range, 0.12–1). This regimen was effective at least initially in 90 % of cases [30]. However, 12 cases required other therapy in conjunction with or instead of steroids because of glucocorticoid tapering and cessation, side effects, or an insufficient response (two cases). The other agents used were azathioprine in six cases (effective in 3/4 for long-term follow-up cases), rituximab three cases (effective in 2/3), cyclophosphamide three cases, and methotrexate two cases. These results indicate that basically the same therapeutic protocol as used for pancreatic involvement is effective for extrapancreatic lesions as well. In the future large-scale investigations using a unified protocol will be needed to establish optimal therapeutic strategies including maintenance therapy for the various manifestations of IgG4-RD.

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B Cell Depletion in IgG4-Related Disease

9

John H. Stone

9.1 Introduction

As IgG4-related disease (IgG4-RD) emerged and then began to come into sharper clinical focus during the first decade of the new century, those who have studied the disease have been privileged to appreciate many "Eureka" moments. One such moment was the observation of the substantial effect of B cell depletion on the clinical features and laboratory manifestations on IgG4-RD. Investigations of the use of this treatment strategy and studies of its mechanistic effects have led to important observations and are likely to yield important additional information about the nature of this disease.

The optimal treatment approach to IgG4-RD remains uncertain. Data on treatment are derived primarily from experience with autoimmune pancreatitis. Serum IgG4 concentrations decline in most patients after treatment with glucocorticoids but often remain above normal despite decreasing substantially. Reports of the experience with disease-modifying antirheumatic drugs (DMARDs) as steroid-sparing agents are limited in both number and detail.

9.2 Shortcomings and Dearth of Data for IgG4-RD Therapies

Most patients with IgG4-RD respond briskly to glucocorticoids with improvements in both the clinical picture and laboratory abnormalities. More often than not, however, patients flare during glucocorticoid tapers or, if followed for a sufficient period of time, after the cessation of these drugs.

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Glucocorticoids carry with them the potential for causing substantial treatment-associated morbidity. This potential is enhanced by several factors. First, IgG4-RD has a tendency to affect middle-aged to elderly individuals (men>women), a population already at risk for some of the worst glucocorticoid effects such as osteoporosis, glucose intolerance, hypertension, infection, easy bruisability, insomnia, depression, and others. Second, IgG4-RD often targets the pancreas, leading to clinical diabetes in a significant number of patients even before treatment with glucocorticoid therapy. Finally, IgG4-RD has a tendency to recur. A retrospective study of AIP in Japan revealed that 56 % of patients had experienced a disease flare by 1 year and more than 90 % had relapsed [1]. The need for recurrent courses of treatment with glucocorticoids heightens the risk of morbidity related to this therapy.

9.3 Overview of the RTX Molecule and the Cellular Infiltrate of IgG4-RD

RTX is a chimeric monoclonal antibody directed against the B-lymphocyte-specific antigen CD20. CD20 is first expressed on cells of the B-lymphocyte lineage in the bone marrow, at the pre-B stage, and continues to be expressed through the memory B cell stage. The CD20 antigen is lost following maturation of fully developed B lymphocytes into plasma cells. Thus, within 2 weeks of administration in most individuals, RTX depletes all components of the B-lymphocyte lineage from the pre-B stage through the mature B-lymphocyte stage.

For the discussion below, it is crucial to observe that plasma cells, a major constituent of the cellular infiltrate in IgG4-RD, do not express CD20 and therefore are not expected to be affected directly by anti-CD20 strategies. In addition to IgG4-positive plasma cells, CD4+ T lymphocytes are also quite numerous in IgG4-RD lesions and are located through the involved tissue. In contrast, the direct targets of B cell depletion—CD20-positive lymphocytes—tend to be concentrated within germinal centers [2].

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9.4 Original Rationale for the Use of RTX in IgG4-RD

B-lymphocyte depletion with RTX is now employed in a growing number of conditions associated with autoimmunity. In many cases, the initial rationale for RTX treatment was to blunt the effects of disease-associated autoantibodies. However, the precise mechanisms through which RTX achieves its effects appear more complex than simply the elimination of autoantibodies. Indeed, strong indications of clinical efficacy exist in many diseases despite the persistence, albeit usually at lower titers, of disease-associated autoantibodies [3, 4].

Part of the reason for believing that RTX might be effective in IgG4-RD was an extrapolation from the efficacy of B cell depletion in pemphigus vulgaris, a disorder in which the primary autoantibody is an IgG4 molecule and in which RTX constitutes a highly effective therapy [5]. Other examples of the participation of IgG4 molecules in autoantibody responses also exist, e.g., membranous glomerulonephritis and pemphigus vulgaris [6, 7]. Certain important differences exist between these models of disease, however, particularly the fact the IgG4-RD is not associated with a well-defined, target-specific autoantigen per se but rather is characterized by the infiltration of IgG4-bearing plasmablasts and other distinctive histopathology and immunohistochemical findings.

9.5 Success of B Cell Depletion in Other Diseases

RTX (RTX) is approved by the US Food and Drug Administration for the treatment of lymphoma in 1997. The medication has become part of standard therapeutic regimens for several variants of B cell lymphoma and is typically used in combination with chemotherapies, e.g., in the treatment of diffuse large cell lymphomas. About the same time that IgG4-RD was recognized as a distinct clinical condition with the capability of affecting multiple organ systems [8], the beneficial effects of this B cell depletion strategy began to be reported in immune-mediated conditions. RTX is approved in many countries for the treatment of rheumatoid arthritis and ANCA-associated vasculitis and is widely used in a number of immune-mediated disorders on an "off-label" basis, including pemphigus vulgaris, mucous membrane pemphigoid, dermatomyositis, immune thrombocytopenic purpura, and many others.

9.6 Early Experience with B Cell Depletion in IgG4-RD

The following case description pertains to one of the first patients with IgG4-RD ever treated with RTX [9]:

A 53-year-old man with a history of asthma developed left eye proptosis, caused by lacrimal gland and extraocular muscle enlargement, 8 years before presentation. Magnetic resonance imaging demonstrated swelling of the left fifth cranial nerve and abnormal soft tissue extending from his left orbit through the left greater palatine foramen into the pterygomaxillary cistern. A biopsy of the periorbital region was non-diagnostic, and the patient was diagnosed with "idiopathic orbital pseudotumor." Prednisone (60 mg/day) led to substantial improvement initially, but tapering of the dose led to recurrent, bilateral periorbital disease and parotid enlargement (Fig. 9.1a). Biopsy of his parotid gland led to an initial diagnosis of "chronic sialadenitis." Mediastinal lymphadenopathy was detected on a chest radiograph 6 years before presentation, and on physical examination a large lymph node was noted in the left axilla. Biopsy of the axillary node revealed "lymphoid hyperplasia."

Four years before presentation, the patient remained on prednisone (20 mg/day) and had experienced numerous

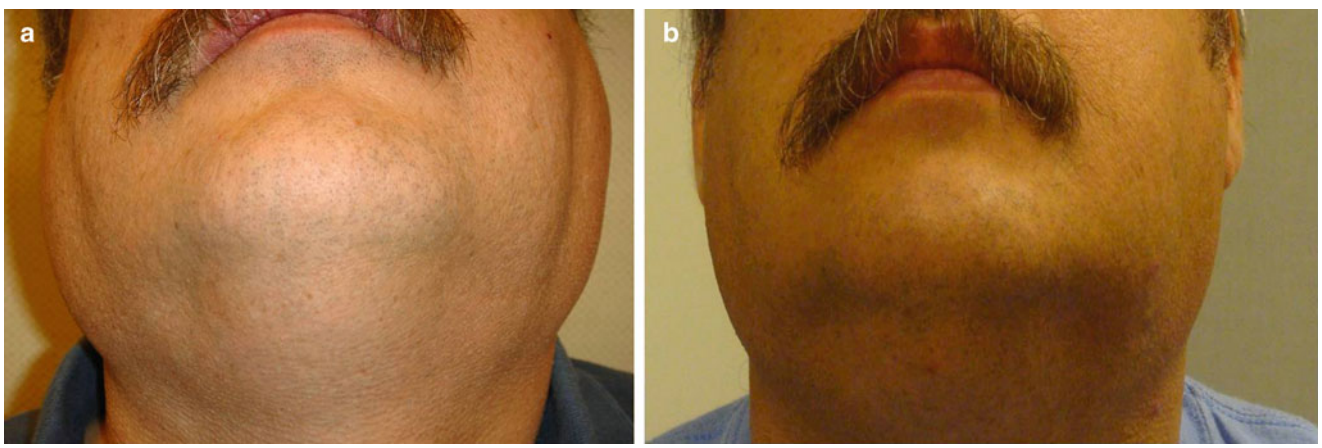

Fig. 9.1 (**a**–**b**) Parotid swelling before and after treatment with rituximab

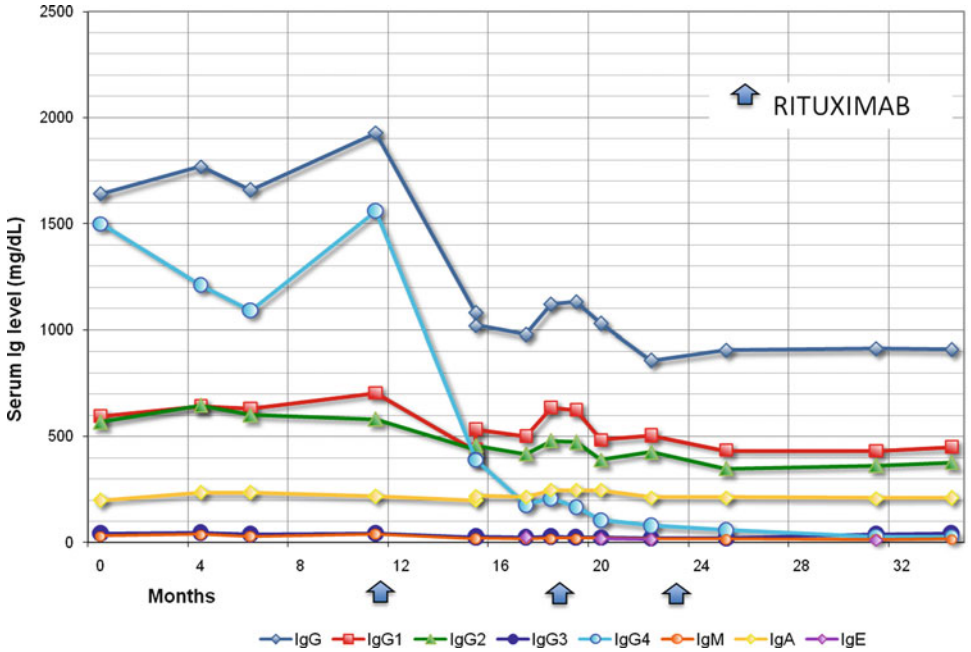

Fig. 9.2 Targeted effect of B cell depletion on the IgG4 subclass. The decline in total IgG is accounted for entirely by the decrease in serum IgG4 concentration. The concentrations of other immunoglobulin classes and IgG subclasses remain stable

glucocorticoid-associated side effects. Attempts to taper his prednisone had been accompanied by worsening periorbital and parotid gland disease. Methotrexate injections (25 mg) were added in a glucocorticoid-sparing effort. The development of persistent sinusitis prompted the measurement of serum IgG subclass concentrations to exclude immunodeficiency. The serum IgG4 concentration was 1,500 mg/dL (normal 8–140 mg/dL). Reevaluation of the parotid gland biopsy revealed a lymphoplasmacytic infiltrate with intense IgG4 staining (120 IgG4+ plasma cells/high power field (hpf); ratio of IgG4-to-IgG-positive plasma cells = 0.8). The correct diagnosis of IgG4-RD was finally evident.

The patient was treated empirically with RTX (1 g intravenously times two doses) because he had tolerated methotrexate poorly (nausea) and had become hypertensive, hyperglycemic, and obese on prednisone, yet still had active IgG4-RD. Within 1 month of completing RTX, the ocular and salivary gland swelling had improved dramatically (Fig. 9.1b). CT imaging confirmed substantial decreases in size of the left extraocular muscles, the left lacrimal gland, and the left parotid soft tissue lesion. His serum immunoglobulin subclasses demonstrated an equally impressive response: 6 months after his RTX infusion, his serum IgG4 concentration had declined from 1,560 mg/dL at baseline to 178 mg/dL. Most remarkably, perhaps, the decline in serum IgG was targeted on the IgG4 subclass. The decline in total IgG was accounted for entirely by the decrease in total serum IgG (Fig. 9.2).

The patient's B cells began to return 6 months after his initial course of RTX and his serum showed an elevation of his IgG4 concentration to 206 mg/dL. He was given a second course of RTX using the same infusion protocol. Three weeks after his second RTX course, his serum IgG4 concentration had normalized for the first time known in his disease course, to a concentration of 104 mg/dL (1,400 mg/dL lower than his pretreatment peak concentration). He has now remained off prednisone for several years, receiving RTX on an intermittent basis.

The experience with RTX in cases of prednisone-refractory IgG4-RD was repeated with several other patients at our hospital. These early cases were reported in 2010 [9].

9.7 Targeted Effect of B Cell Depletion: Reduction of the Plasma Cell Mass?

These initial observations with B cell depletion in IgG4-RD suggested that RTX achieved the effects by disrupting the normal differentiation of IgG4-bearing B lymphocytes into plasma cells. This hypothesis was supported by the rapid decrease in serum IgG4 concentrations relative to those of other IgG subclasses and total IgG, implying that the IgG4-bearing plasma cells in IgG4-RD are inherently shorter-lived than are those that express other IgG subclasses. In fact, one specific effect of RTX is to interfere with the repletion of the short-lived IgG4+ plasmablasts within blood and IgG4+ plasma cells within tissue. When such short-lived cells undergo their programmed fate, they are not replaced because the administration of RTX has depleted the pool of CD20-positive precursors.

The dramatic shrinkage of the parotid glands following RTX shown in Fig. 9.1b is consistent with effects achieved in other conditions by the removal of cells, leading to relief of tumefactive enlargement and/or mechanical obstruction. One explanation is that the striking improvement observed in many patients' mass lesions in IgG4-RD is that the plasma cell mass within the affected organ has been attenuated sharply by a reduction in the plasma cell mass.

9.8 Another Instructive Case: Indirect Effect on T Cells?

The case of another patient early in the experience of using a B cell depletion strategy in IgG4-RD led to the identification of another potential mechanism [10]. This case is described below:

A 72-year-old woman developed a nodular rash on her face that was accompanied by bilateral parotid gland enlargement and periorbital swelling. A magnetic resonance imaging study demonstrated marked lacrimal, parotid, and submandibular gland swelling. Biopsy of the lacrimal gland was interpreted as showing reactive lymphoid hyperplasia with an abundance of IgG4+ plasma cells. Flow cytometry studies of peripheral blood were not consistent with a hematopoietic malignancy. A skin biopsy of the patient's nodular, erythematous rash revealed perivascular and interstitial lymphohistiocytic infiltrates, with an abundance of IgG4+ plasma cells. Although no firm diagnosis has been made, it was decided to treat the patient for a reactive process.

She began therapy with prednisone (40 mg/day). Her lacrimal, parotid, and submandibular glands decreased markedly in size within 2 weeks, but the parotid swelling worsened when her prednisone taper reached 10 mg/day, necessitating a return to a higher dose. Her nodular skin rash persisted (although improved) despite continuation of prednisone 20 mg/day. The total IgG was 1,170 mg/dL (normal 600–1,500 mg/dL), but the IgG4 concentration was 429 mg/dL (8–140 mg/dL).

Review of the patient's skin biopsy revealed a dense, deep dermal infiltrate with focal involvement of the subcutaneous fat (Fig. 9.3a). The infiltrate was composed predominantly of lymphocytes, plasma cells, and a few eosinophils. There were 210 IgG4-positive plasma cells/hpf, and the IgG4 to IgG ratio was 0.95 (Fig. 9.3b). Review of the lacrimal gland biopsy showed a dense lymphoplasmacytic infiltrate with rare eosinophils within adipose tissue. Multiple reactive germinal centers were noted. There were 126 IgG4-positive plasma cells/hpf, and the IgG4 to IgG ratio was 0.9. Immunohistochemical stains for kappa and lambda light chains performed on both the orbital and cutaneous biopsies showed a polyclonal plasma cell population. These pathologic findings confirmed the diagnosis of IgG4-RD.

The patient tolerated her prednisone therapy poorly, suffering many of the anticipated adverse effects, including weight gain and the development of a cushingoid facies. Moreover, her lacrimal and parotid enlargement increased and the rash worsened as the prednisone was tapered. She discontinued glucocorticoid therapy and the total IgG and IgG4 serum concentrations rose to 1,790 mg/dL (600–1,500 mg/dL) and 1,140 mg/dL (8–140 mg/dL), respectively. She was then treated with rituximab 1,000 mg intravenously times two doses. One month after completing her second rituximab dose, her serum IgG4 concentration had declined to 31 mg/dL, but the total IgG and other IgG subclasses remained stable (Table. 9.1). Two months after her first rituximab infusion, her nodular skin rash had resolved. Re-biopsy of the site of an earlier facial nodule revealed dramatic resolution of the intradermal inflammatory infiltrate (Fig. 9.3c). Immunostaining studies performed on the skin biopsies performed both before and after RTX revealed substantial resolution of the CD3+ (T lymphocyte) population following this targeted B cell therapy (Fig. 9.3d).

9.9 Implications for Pathophysiology

Our experience with B cell depletion thus far in the treatment of IgG4-RD suggests that this treatment strategy achieves its effects through more than one mechanism. First, by depletion of the circulating population of CD20-positive B cells, RTX disrupts the process whereby short-lived plasma cells are repleted. Plasma cells do not have CD20 on their surface and are therefore not affected directly by B cell depletion, but short-lived plasma cells are reliant upon continuous repletion from the B cell pool. Disruption leads to the swift decline of serum IgG4 concentrations, but the other immunoglobulin concentrations remain generally stable because, for reasons that remain obscure, IgG4-RD is characterized by an abundance of short-lived plasma cells that manufacture IgG4. Other immunoglobulin subclasses are more likely to be made by longer-lived plasma cells that reside in the bone marrow rather than in peripheral tissue. These cells, which secrete the preponderance of other immunoglobulins, are little affected by B cell depletion because they do not rely upon continuous regeneration from the CD20 pool.

Second, an alternative and complementary mechanism is suggested by the case of the patient with cutaneous involvement. Resolution of the CD3+ cellular infiltrate following CD20 depletion suggests that T cells within the inflammatory lesion are dependent upon B cells—perhaps through continuous antigen presentation of B cells to T cells—for maintenance. This in situ observation is consistent with the concept that the maintenance of CD4+ T cell memory cells is reliant upon interaction with B cells and that in IgG4-RD

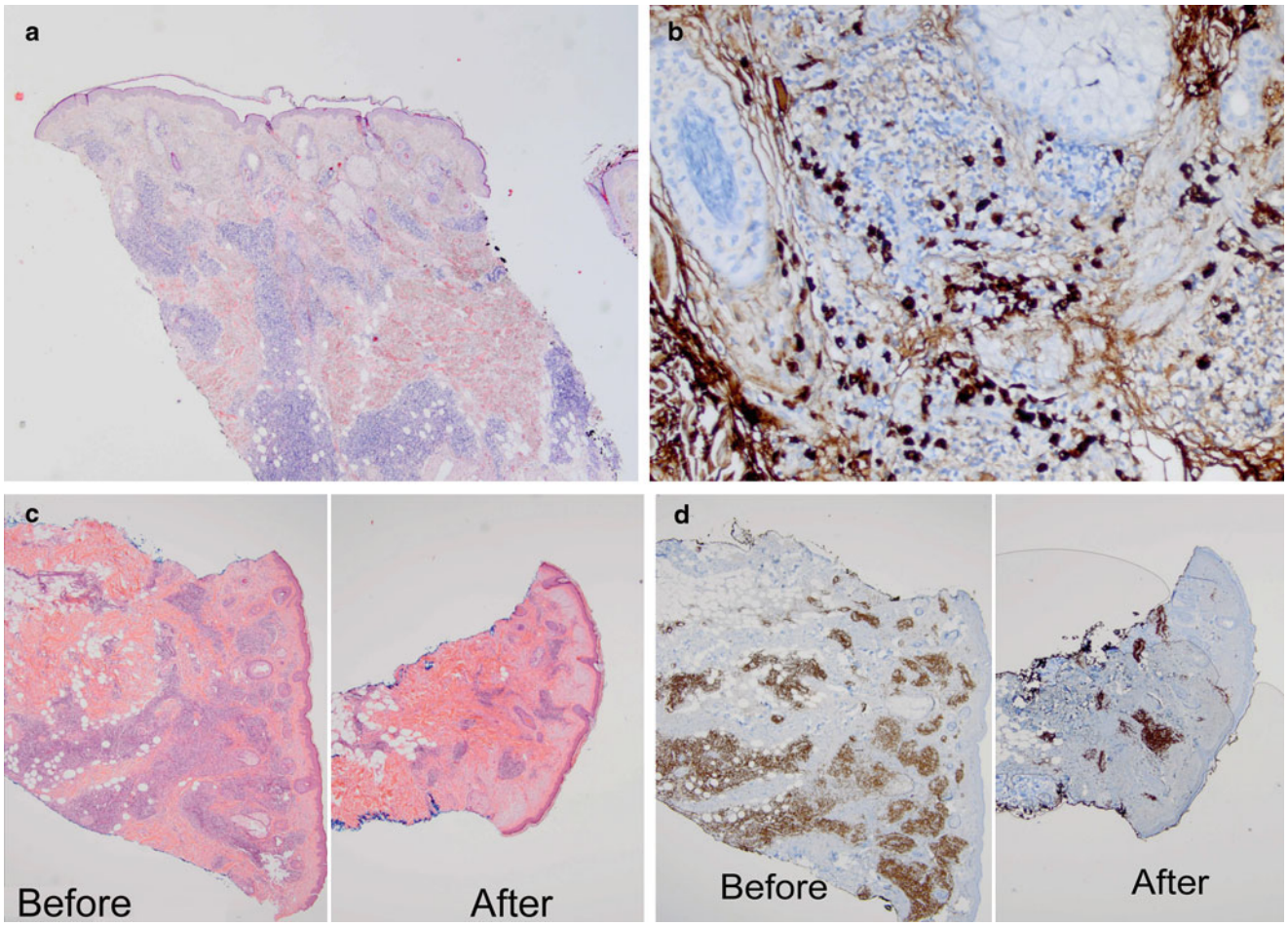

Fig. 9.3 (**a**–**d**) Histopathology and immunostaining of IgG4-related skin lesions before and after treatment with rituximab. (**a**) Before treatment. Dense, deep dermal infiltrate with focal involvement of the subcutaneous fat. The infiltrate is composed predominantly of lymphocytes, plasma cells, and a few eosinophils. (**b**) Before treatment. Immunostaining studies reveal 210 IgG4-positive plasma cells/high power field, with an IgG4 to IgG ratio of 0.95. (**c**) After treatment. Re-biopsy of the site of an earlier facial nodule reveals dramatic resolution of the intradermal inflammatory infiltrate. (**d**) After treatment. CD3+ (T lymphocyte) population has largely resolved following targeted B cell therapy

Table 9.1 Serum IgG subclasses before and after rituximab. One month after the patient had completed her second rituximab dose, her serum IgG4 concentration had declined to 31 mg/dL, but the total IgG and other IgG subclasses remained stable

Total IgG and subclasses	6/9/2010 (Pred 20)	9/28/2010 (Pred 0)	11/8/2010 (1 month after RTX)
Total IgG (767–1,590)	1,170	1,790	1,690
IgG1 (341–894)	645	803	848
IgG2 (171–632)	336	482	640
IgG3 (18–106)	143	197	285

(as, presumably, in other conditions) complex, mutually dependent relationships between B and T cells exist. B cell depletion as a therapeutic strategy offers the advantage of affecting both lineages directly (CD20-positive cell depletion) and indirectly (failure to replete or sustain short-lived IgG4+ plasma cells and CD4+ effector T cells, respectively).

9.10 Additional Experience with B Cell Depletion

We continue to investigate the effects of B cell depletion in patients whose disease was refractory to glucocorticoid treatment or whose disease flared followed glucocorticoid tapers. In an expanded series, we reported the clinical and serologic responses to B-lymphocyte depletion therapy in ten consecutive patients with steroid- and DMARD-refractory IgG4-RD [11].

Ten patients with IgG4-RD were treated with two doses of RTX (1,000 mg each), administered 15 days apart. Clinical improvement was assessed by monitoring patients' ability to taper prednisone to discontinuation and to stop any concurrent DMARD. We employed an IgG4-RD Responder Index (IgG4-RD RI) to the assessment of these patients' courses [12]. The organs affected by IgG4-RD in this series were

Table 9.2 Treatment responses

Patient	Treatment before rituximab	Prednisone dose at entry	Disease activity score before RTX	Courses of RTX	Disease activity score after RTX
1	Prednisone (3 years) Azathioprine (2 months) Mycophenolate mofetil (18 months) 6-mercaptopurine (1 month)	10 mg	14	4	1
2	Prednisone (4 years) Methotrexate (4 years)	10 mg	5	3	0
3	Prednisone (1 year)	10 mg	6	3	2
4	Prednisone (1 year)	0	6	1	1
5	Prednisone (2 months)	0	3	1	0
6	Prednisone (20 years) Methotrexate (1 year) Mycophenolate mofetil (1 month)	0	3	1	1
7	Prednisone (1 month)	60 mg	4	1	0
8	Prednisone (4 months) Tamoxifen (2 years)	0	6	1	3
9	Prednisone (18 months) Methotrexate (1 year)	10 mg	2	3	0

quite disparate, including the pancreas, biliary tree, aorta, salivary glands (submandibular and parotid), lacrimal glands, lymph nodes, thyroid gland, and retroperitoneum.

A summary of clinical outcomes is shown in Table 9.2. All ten patients discontinued prednisone and DMARDs entirely following RTX therapy. One patient with advanced thyroid fibrosis associated with Riedel's thyroiditis and a history of disease in multiple other organ systems did not have improvement in her thyroid gland, but her disease did not progress to involve new organs. Nine of the ten patients demonstrated striking clinical improvement within 1 month of starting RTX.

This expanded experience confirmed the targeted effect of B cell depletion on the IgG4 subclass. Four patients were re-treated with RTX after 6 months because of either symptom recurrence and increasing IgG4 concentration at the time of peripheral B cell reconstitution ($n=2$) or because of physician discretion ($n=2$). Repeated courses of RTX maintained their effectiveness, and serial RTX courses led to steadily lower IgG4 concentrations. X of the ten patients had normal serum IgG4 concentrations, a finding consistent with other reports in the literature on IgG4-RD. However, if the patients' serum IgG4 concentrations were elevated at baseline, this measure appeared to be a reliable surrogate of disease activity.

The effects of B cell depletion in IgG4-RD are now being evaluated in a prospective 30-patient trial, with patients enrolled at both the Massachusetts General Hospital and Mayo Clinic. This trial completed enrollment in June, 2013. The results will be reported at future scientific meetings.

9.11 Conclusion

B cell depletion appears to have an important role in the treatment of IgG4-RD. Careful studies of patients before and after treatment with this medication have much to inform us about the pathophysiology of IgG4-RD, the mechanism of B cell depletion, and the nature of immune system pathways overall.

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Part II

Radiology

Autoimmune Pancreatitis

10

Kazuichi Okazaki

10.1 Introductory Remarks

The disease concept of autoimmune pancreatitis (AIP) was proposed in 1995 by Yoshida et al. [1], and subsequently a subset of patients with this condition have been recognized to have the pancreatic manifestation of IgG4-related disease (IgG4-RD) [2]. The concept of AIP has undergone changes through the years and is now recognized internationally as being classified into two distinct types that in fact represent different diseases altogether [3, 4]. The history of the understanding of AIP over the past two decades is described in the chapter by Notohara (Chap. 21). AIP is subclassified according to the International Consensus of Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis as either type 1 (IgG4-related) or type 2 (granulocytic epithelial lesions). Both types of AIP present with pancreatic swelling, mass formation, or complicating bile duct lesions, often leading to obstructive jaundice. These features can be difficult or impossible to separate from adenocarcinoma of the pancreas or cholangiocarcinoma on the basis of the clinical and radiologic findings alone.

Type 1 (IgG4-related) AIP accounts for the great majority of cases in Japan. This condition, once termed lymphoplasmacytic sclerosing pancreatitis, is characterized histopathologically by lymphocytic and IgG4-positive plasmacytic cell infiltration, obliterative phlebitis, and fibrosis [3, 5, 6]. Type 2 AIP, once termed idiopathic duct-centric chronic pancreatitis (IDCP) [7], appears to be more common in Western countries than in Japan, but type 1 AIP still accounts for the majority of cases outside of Japan, as well. Type 2 AIP is characterized by granulocytic epithelial lesions (GEL) [5, 8], but its etiopathogenesis and pathophysiology are obscure. Revised diagnostic criteria focusing on type 1 AIP have recently been prepared by the Japan Pancreas Society and a research group of the Japanese Ministry of Health [5]. In this chapter, I outline pancreatic imaging against the background of these new diagnostic criteria.

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10.2 Autoimmune Pancreatitis Diagnostic Criteria 2011 in Japan [9]

The 2011 Japanese diagnostic criteria are listed in the Table 10.1. A variety of changes from previous criteria were adopted: (1) classification of the extent of ICDC lesion involvement (diffuse, localized) on pancreatic parenchyma imaging; (2) simplification of the classification of ICDC diagnostic items into levels 1 and 2; (3) blood test findings limited to IgG4; (4) pathological findings limited to type 1 (IgG4-related) AIP; and (5) other organ involvement. In addition, the response to glucocorticoids was adopted as an optional criterion. With regard to the diagnosis, to avoid discrepancies with ICDC, various combinations of the diagnostic items are adopted to provide definite, probable, and possible diagnoses. In cases with normal serum IgG4 values, even those showing typical pancreatic imaging features and glucocorticoid responsiveness, only a possible diagnosis is appropriate in the absence of histopathological confirmation because of the possibility of type 2 AIP.

ERP has long been considered essential in Japan for potential AIP cases marked by localized pancreatic swelling [1]. However, in another departure from the ICDC, under the 2011 criteria a possible diagnosis of AIP can be rendered without ERP if a fine-needle aspiration under endoscopic ultrasonography excludes malignancy, and a probable diagnosis is appropriate if the patient responds to a trial of glucocorticoids.

Abdominal US, CT, and MR imaging assumes a particularly important role in the evaluation of AIP because the number of institutions capable of performing endoscopic US is limited, routine biopsy is difficult to perform, and the pathological diagnostic rate based on biopsy materials is only about 20 % [8].

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Table 10.1 Autoimmune pancreatitis clinical diagnostic criteria 2011 [7] (Japan Pancreas Society and Japanese Ministry of Health Research Group on Intractable Pancreatic Disease)

Disease concept
Autoimmune mechanisms have been implicated in the onset of the autoimmune pancreatitis frequently reported in Japan, but the possibility that this is in fact a pancreatic manifestation of IgG4-related systemic disease is high. Since elderly and middle-aged men are most frequently affected, and sometimes obstructive jaundice develops associated with pancreatic swelling and mass formation, differentiation from conditions such as pancreatic cancer and bile duct cancer is required. Hypogammaglobulinemia, elevated serum IgG values, elevated serum IgG4 values, and positive autoantibodies are frequently found, and sometimes other organ involvement such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis is associated. Lymphoplasmacytic sclerosing pancreatitis (LPSP) is characterized histopathologically by marked lymphocyte and IgG4-positive plasmacytic cell infiltration, storiform fibrosis, and obliterative phlebitis. The response to glucocorticoids is good, but the long-term prognosis is unclear, and recurrences are common. Cases complicated by pancreatolithiasis have also been described
On the other hand, in Western countries, distinct from IgG4-related pancreatitis, idiopathic duct-centric chronic pancreatitis (IDCP) has also been reported as autoimmune pancreatitis, in which despite similar clinical signs and pancreatic imaging findings, abnormal hematoimmunological findings are few. In IDCP, more commonly known now as type 2 AIP, the histopathological hallmark is granulocytic epithelial lesion (GEL). There is no sex predilection, relatively young persons are also affected, and inflammatory bowel disease can be associated with this condition. Glucocorticoids are also highly effective in type 2 AIP, and recurrences appear to be rare by comparison to type 1 AIP. Type 2 AIP is substantially less common in Japan compared to Western countries
Diagnostic criteria
A. Diagnostic items
I. Pancreatic swelling: (a). diffuse swelling; (b). localized swelling (segmental/focal)
II. Irregular narrowing of the main pancreatic duct: ERP
III. Serological findings: elevated serum IgG4 values (≥135 mg/dL)
IV. Pathological findings: among the (1)–(4) findings listed below, (a) three or more are observed; (b) two are observed.
① Marked lymphoplasmacytic cell infiltration and fibrosis
② IgG4-positive plasma cell infiltration exceeding ten cells per one high power field
③ Storiform fibrosis
④ Obliterative phlebitis
V. Other organ involvement: sclerosing cholangitis, sclerosing dacryoadenitis, and sialadenitis, retroperitoneal fibrosis
a. Clinical lesions: in the clinical and imaging findings, extrapancreatic bile duct sclerosing cholangitis, sclerosing dacryoadenitis and sialadenitis (Mikulicz's disease), or retroperitoneal fibrosis can be diagnosed.
b. Pathological lesions: characteristic pathological findings of sclerosing cholangitis, sclerosing dacryoadenitis and sialadenitis, or retroperitoneal fibrosis are found.
<optional criterion> response to glucocorticoid therapy
In specialist institutions, after excluding pancreatic cancer and bile duct cancer, it is possible to include the therapeutic effect of glucocorticoids in the diagnostic items. In cases in which the differentiation from malignant bile duct disease is difficult, an EUS-FNA and cytological examination should be performed. If malignancy has not been excluded by a histopathological examination, the diagnosis of an IgG4-RD lesion should be regarded with caution, even in the setting of an apparent glucocorticoid response.
B. Diagnosis
I. Definite
① Diffuse type: Ia + <III/IVb/V(a/b)>
② Localized type: Ib + II + more than two of < III/IVb/V(a/b) > or Ib + II + < III/IVb/V(a/b) > + option
③ Histopathological definite: IVa
II. Probable
Localized type (segmental/focal): Ib + II + < III/IVb/V(a/b)>
III. Possible diagnosis*
Diffuse type: Ia + II + option localized type: Ib + II + option

In cases with localized pancreatic swelling suggestive of AIP, when ERP findings are not obtained, pancreatic cancer is excluded by EUS-FNA, one or more of < III/IVb/V(a/b) > are met; a possible diagnosis is made. If the optional criterion is also met, a probable diagnosis is made
Possible diagnosis *: the possibility of the in Japan extremely rare type 2 also exists. +: and, /: or

10.3 Pancreatic Imaging [5, 11]

Abdominal US, CT, and MR imaging is useful in the morphological diagnosis of the pancreatic parenchyma. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are useful in the morphological diagnosis of the pancreatic duct. In addition, positron emission tomography (PET) studies may be useful in gauging the response to therapy and the extent of extrapancreatic involvement.

10.3.1 Pancreatic Parenchyma Imaging

Diffuse swelling of the pancreas, leading to a sausage-like appearance of the organ, is highly specific for AIP. This feature can be demonstrated readily by US, CT, or MRI. However,

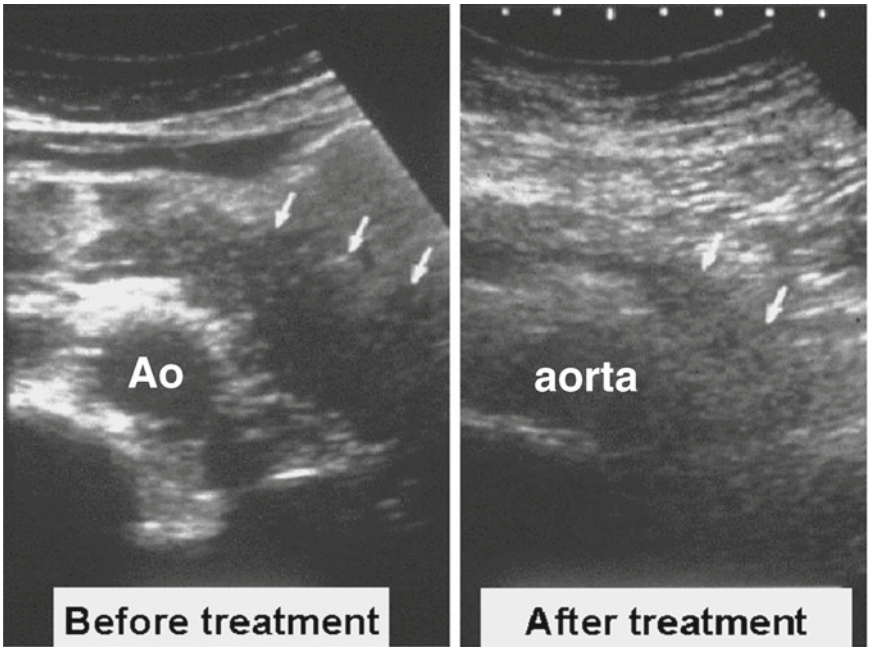

Fig. 10.1 Abdominal ultrasonographic image of autoimmune pancreatitis

localized (segmental/focal) swelling requires differentiation from pancreatic cancer. Concerning the definition of pancreatic swelling, many institutions use the Haaga Criteria (pancreatic head: ≥1 vertebral body, pancreatic body and tail ≥2/3 vertebral body defined as pancreatic swelling, corresponding to roughly head 3 cm, and body and tail 2 cm) [12]. As the pancreas typically becomes atrophic in the elderly, a strict definition is difficult to achieve, but these criteria make it possible to recognize pancreatic swelling also in cases with shrinkage of the pancreas due to steroid administration. "Diffuse" and "localized" are not strictly defined, but the ERP findings in the majority of cases with chronic pancreatitis are consistent with the Cambridge Classification (2/3 < diffuse, 1/3 < segmental < 2/3, focal < 1/3) [13].

10.3.1.1 Abdominal Ultrasonography Imaging [5, 11]

Figure 10.1 demonstrates the typical US appearance of the pancreas in AIP: a diffusely swollen organ that resembles a sausage. The swollen portion is hypoechoic with scattered hyperechoic spots. In cases with localized swelling, the differential diagnosis between pancreatic cancer and mass-forming pancreatitis is problematic. Dilatation of the main pancreatic duct (MPD) is frequently not detected by US, but delineation of the MPD within the mass—known as the "duct penetration sign"—is helpful in differentiating AIP from pancreatic cancer [14]. However, the findings of only mild ductal dilatation or multiple hypoechoic masses within the pancreatic parenchyma make differentiation between AIP and metastatic pancreatic tumors or lymphoma difficult (Fig. 10.2).

10.3.1.2 Abdominal CT Imaging [5, 11]

The CT findings in AIP are diverse. Classic CT features are pancreatic swelling, a pattern of delayed contrast enhancement, and (on dynamic CT) a capsule-like rim surrounding the pancreas [15, 16]. Most AIP patients are elderly and therefore tend to have atrophic pancreata before the onset of AIP. This can obscure the presence of pancreatic swelling in the early stages of the disease. On the other hand, there are also cases in which pancreatic swelling can be judged to have been present at onset based on a decrease in the size of the pancreas following glucocorticoid therapy. Other cases are characterized by atypical findings of mild diffuse swelling alone of the pancreas and/or partial dilatation of the MPD, cystic lesions, or calcification of the pancreatic parenchyma.

Pancreatic Swelling and Delayed Enhancement (Fig. 10.3a)

Delayed enhancement is characteristic on the portal phase of dynamic CT, but the specific findings vary according to disease stage and activity. The enhancement effect can be altered by the degree of fibrosis. If the extent of fibrosis is only mild, the amount of enhancement may be difficult to distinguish from normal pancreas. Thus, the absence of delayed enhancement does not exclude AIP in the early stages of the condition, when extensive fibrosis is unlikely.

Capsule-Like Low-Density Rim (Fig. 10.3b)

The finding of a low-density, capsule-like rim around the edge of the pancreas is less common than delayed enhancement, but such a finding has a high specificity for AIP [15].

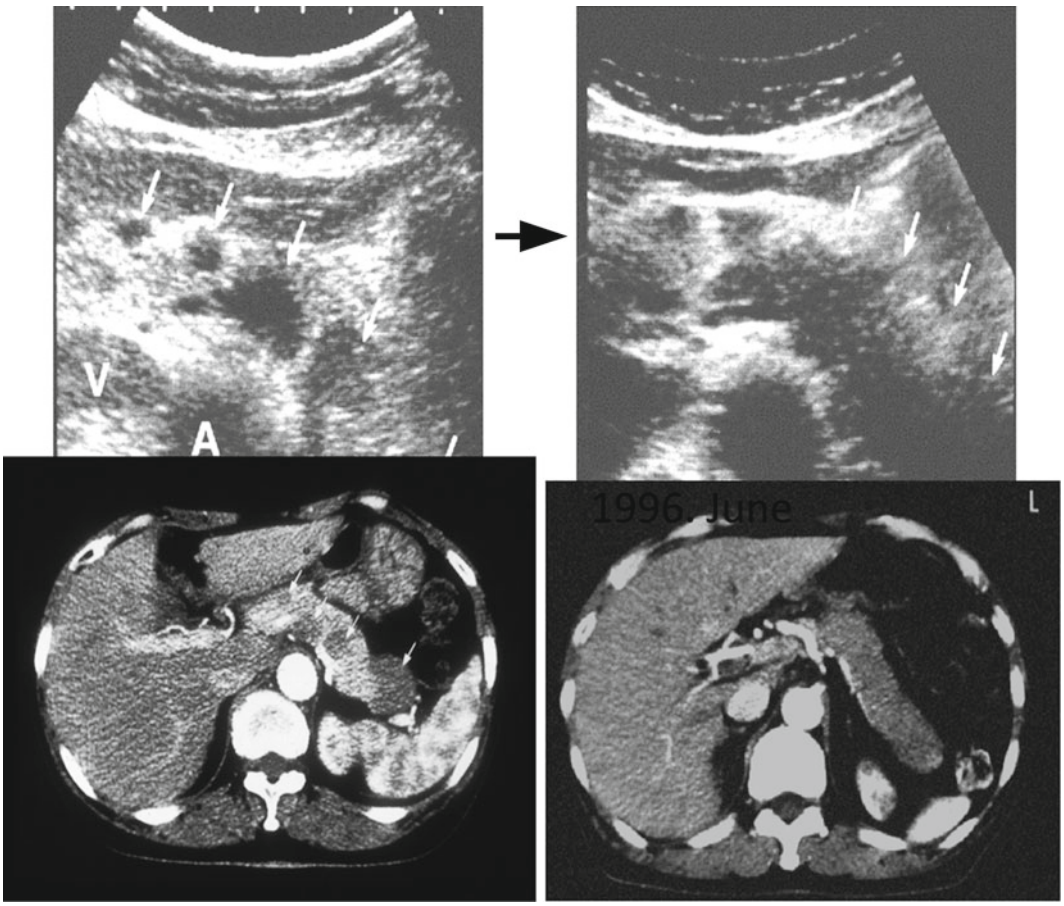

Fig. 10.2 Autoimmune pancreatitis associated with multiple masses within the pancreas. Lymphoma had been strongly suspected before a biopsy was obtained

The capsule-like rim is thought to reflect fibrosis at the edge of the lesion, corresponding to the delayed pattern of enhancement observed on dynamic CT. A capsule-like rim is extremely helpful in differentiating AIP from pancreatic cancer. The absence of such a rim, however, by no means excludes AIP. However, pancreas imaging alone cannot distinguish type 1 from type 2 AIP due to the similarity of their findings.

10.3.1.3 Abdominal MR Imaging [5, 11]

Pancreatic Swelling and T1/T2-Weighted Pancreatic Parenchyma Findings (Fig. 10.4)

Hypointensity on T1-weighted MR images and delayed enhancement on the portal phase of dynamic MRI are characteristic of AIP—in addition, of course, to diffuse swelling. Because the normal pancreas is hyperintense relative to the liver on T1-weighted images, any relative hypointensity detected must be considered abnormal. However, hypointensity on MR is also found in both pancreatic cancer and chronic pancreatitis from other causes and therefore does not distinguish AIP among these entities. Similar to the situation with CT, differentiation of the normal pancreas from cases of only mildly fibrotic AIP is challenging. Conversely, severe fibrosis can be associated with only slight hypointensity on T2-weighted images, because of the limited inflammation present at that point.

Capsule-Like Rim

Both a capsule-like rim and a delayed enhancement pattern can be detected by MRI. Both of these findings reflect fibrosis and are highly specific for AIP. The capsule-like rim is visualized as a hypointense region on T2-weighted images. Dynamic MRI is the most effective means of demonstrating delayed enhancement.

10.3.1.4 Nuclear Medicine Examinations

Gallium citrate (Ga-67) scintigraphy and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) [5, 11] (Fig. 10.5)

Ga-67 and FDG accumulate in pancreatic lesions, making the differentiation from lymphoma difficult. Ga-67 and FDG accumulation is not limited to pancreatic lesions alone,

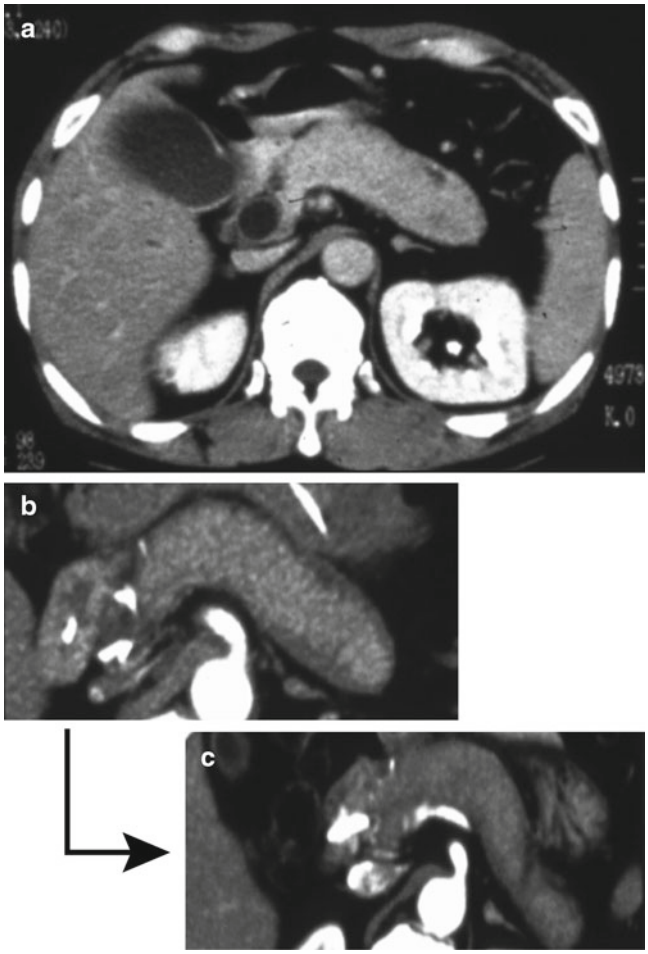

Fig. 10.3 Abdominal CT images of autoimmune pancreatitis (diffuse swelling). (**a**) Pancreatic swelling and delayed enhancement (sausage like). (**b**) Capsule-like low-density rim. (**c**) after steroid

but is also found at sites of extrapancreatic involvement, notably in the hilar lymph nodes of the chest, lacrimal glands, and salivary glands. Such lesions frequently disappear rapidly after glucocorticoid administration [16, 17]. However, the expense of these examinations further limits their clinical utility.

10.3.2 Pancreatic Duct Imaging [5, 11]

Diffuse and irregular narrowing can be found in the MPD [19]. Irregular narrowing of MPD refers to a situation in which the pancreatic duct diameter is thinner than usual and irregular. These lesions tend to affect greater lengths of the duct than do occlusive or stenotic lesions. In typical cases, irregular narrowing accounts for more than one third of the entire pancreatic duct length (~5 cm). Even in localized lesions, however, marked dilatation of the MPD upstream to the stenotic portion is frequently not seen. In cases with short irregular narrowing pancreatic duct (roughly <3 cm), the differentiation from pancreatic cancer is difficult. Side branches arising from the narrowed portion of the MPD and multiple MPD skip lesions are useful signs in the differentiation from pancreatic cancer [20].

When evaluating patients with possible AIP and other disorders that can mimic it, delineation of the morphological features of the pancreatic duct by ERP or another direct visualization method is essential. MRCP cannot yet evaluate irregular narrowing of the MPD with sufficient precision. Its ability to demonstrate non-continuity of the duct is helpful in making the diagnosis of AIP, but the specificity of this finding by itself is imperfect.

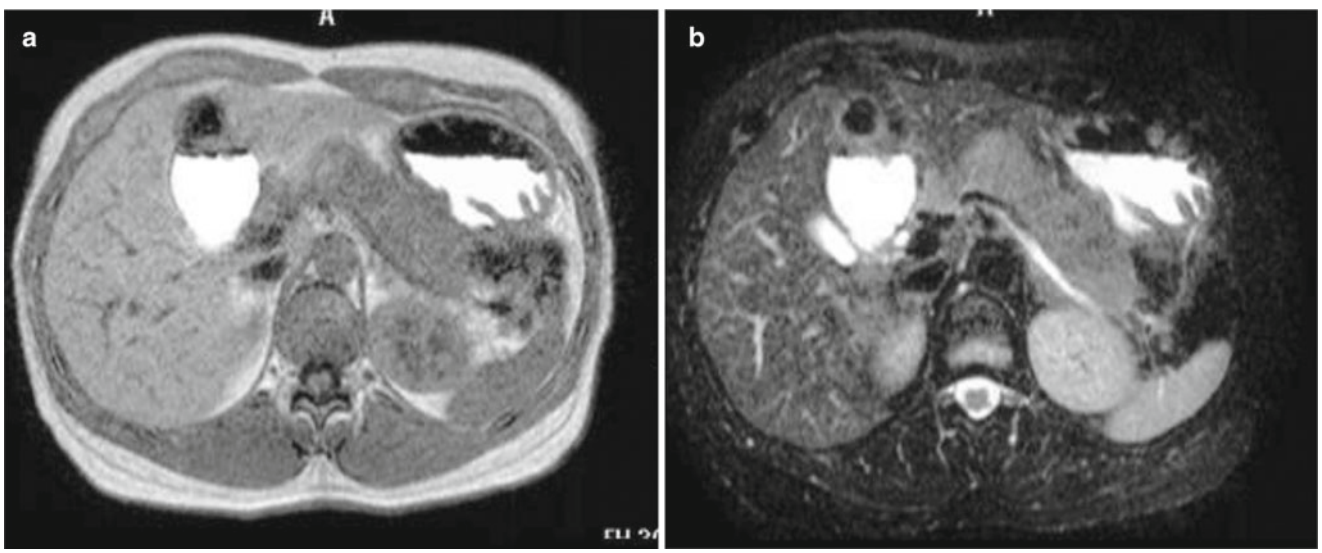

Fig. 10.4 Abdominal MRI of autoimmune pancreatitis. (**a**) T1-weighted image hypointensity relative to the liver is shown. (**b**) T2-enhanced image (from "Autoimmune Pancreatitis Atlas" edited by Makoto Ohtsuki and Kazuichi Okazaki, published by Arcmedia Tokyo, 2007)

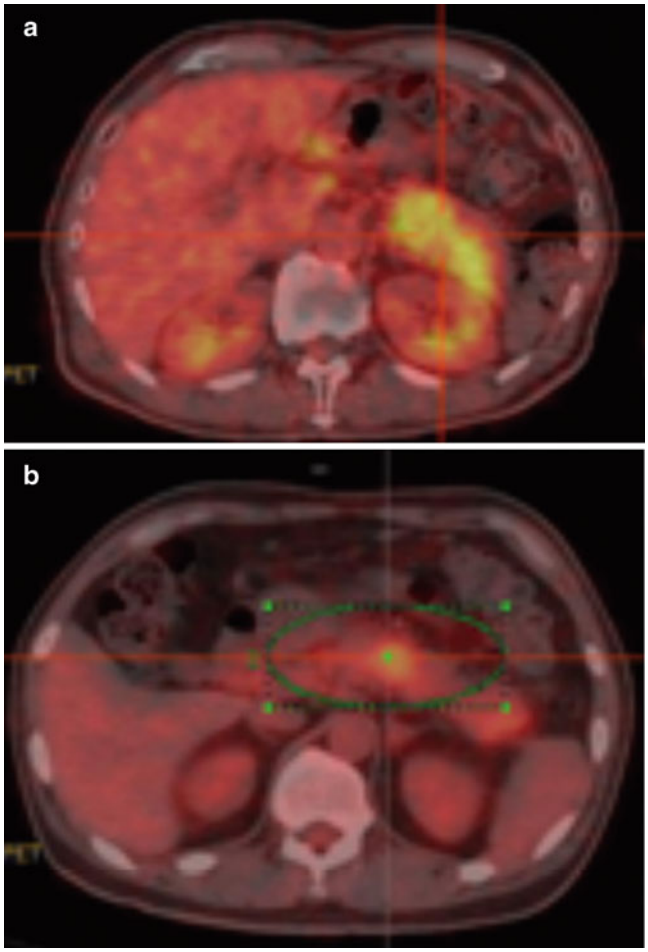

Fig. 10.5 PET images of autoimmune pancreatitis. (**a**) Diffuse accumulation of fluorodeoxyglucose (FDG) in the pancreas before the administration of glucocorticoids. (**b**) After glucocorticoid therapy, a decrease in FDG uptake

10.3.2.1 ERCP Findings [5, 11] (Fig. 10.6)

In AIP, characteristic irregular narrowing of the MPD constitutes strong evidence in favor of the diagnosis. Irregular narrowing of the MPD is defined as a lesion in which the pancreatic duct diameter is irregularly thinner than usual with more extensive lengths of the pancreatic duct affected as compared to lesions regarded as occlusions or stenoses. In the earlier diagnostic criteria for AIP put forth in Japan, the finding of characteristic irregular narrowing within the MPD was considered to be an essential piece of diagnostic evidence [5, 11]. This is no longer the case. In cases with focal irregular narrowing, the need to differentiate AIP from pancreatic cancer must be kept in mind. In AIP, bile duct stenosis is found in about 80 % of cases. Bile duct stenosis is most common in the inferior bile duct, but may also develop in the extrahepatic and intrahepatic bile ducts.

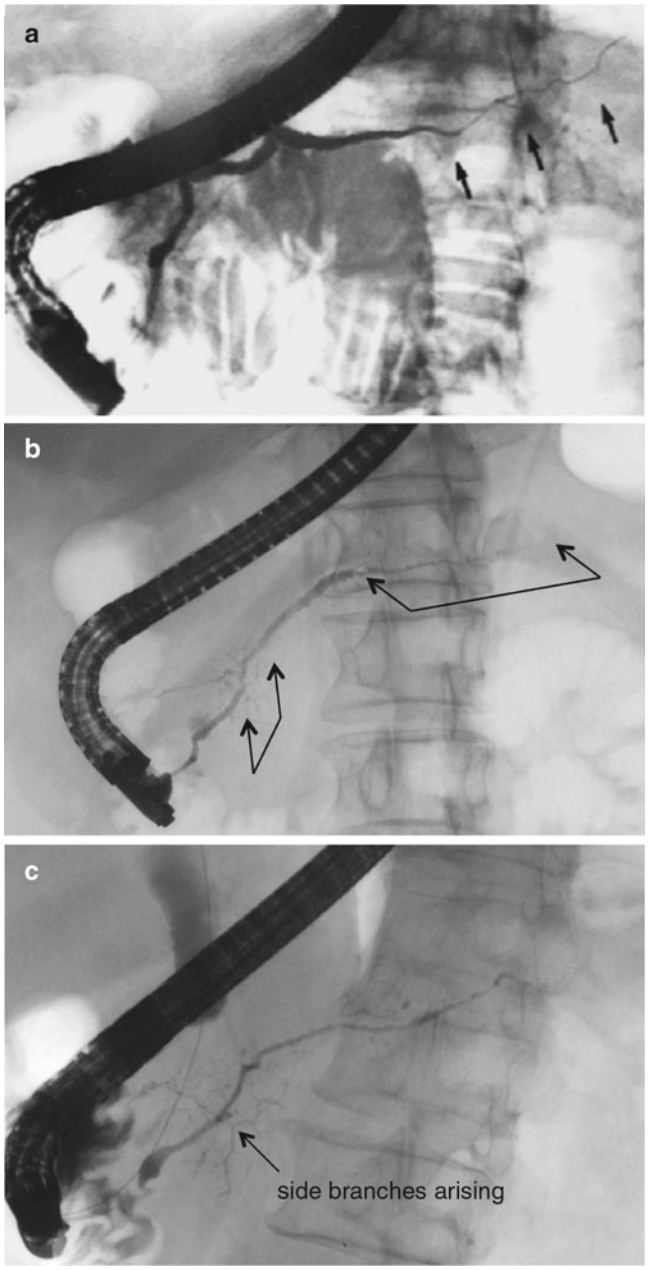

Fig. 10.6 ERP images of autoimmune pancreatitis. (**a**) Focal irregular narrowing (<1/3) is limited to the pancreatic tail. (**b**) Segmental (1/3–2/3): In this case, irregular narrowings are found in the pancreatic head and tail. (**c**) Diffuse (<2/3): diffuse irregular narrowings of the main pancreatic duct extend from the head to tail. Side branches arising from the stenotic portion of the main pancreatic duct can be observed

10.3.2.2 MRCP Findings [5, 11] (Fig. 10.7)

At present, MRCP does not delineate the pancreatic duct with sufficient accuracy for reliable diagnosis of AIP or the precise evaluation of irregular narrowing in the MPD. However, 3-dimensional MRCP can now detail the MPD within a normal pancreas, and failure to identify the main duct suggests the presence of irregular narrowing. With the

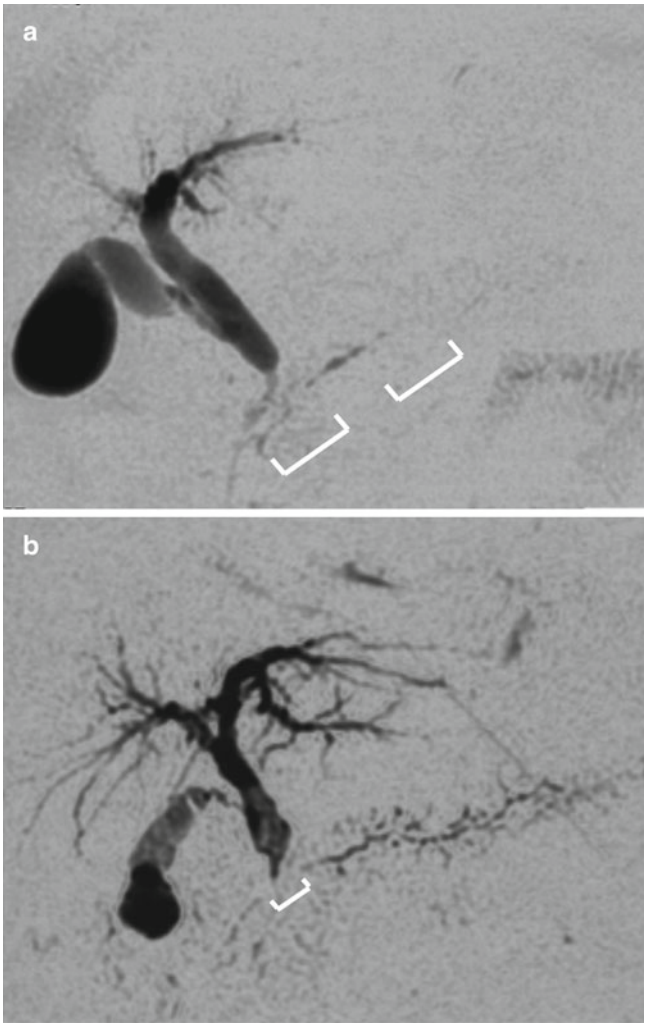

Fig. 10.7 MRCP findings of autoimmune pancreatitis. Pancreatic duct skip lesions extend from the body to tail. (**a**) Autoimmune pancreatitis. The main pancreatic duct appears segmented(skip lesions), suggesting the possibility of autoimmune pancreatitis. (**b**) Pancreatic head cancer. Pancreatic head, main pancreatic duct stenosis, and pancreatic tail duct dilatation

recently introduced 3.0 T MR imagers, further enhancement of the image quality of MRCP is anticipated, and MRCP may have roles to play in the assessment of the response of AIP to therapy and in follow-up observations.

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Bile Duct Lesions

11

Takashi Muraki, Hideaki Hamano, and Shigeyuki Kawa

11.1 Introductory Remarks

Autoimmune pancreatitis(AIP), the pancreatic manifestation of IgG4-RD, is frequently complicated by IgG4-related sclerosing cholangitis (IgG4-SC). On endoscopic retrograde cholangiography, stenosis of the extrapancreatic bile ducts is found in only 26 % of cases, but wall thickening on endoscopic ultrasonography and intraductal ultrasonography or sclerotic changes on endoscopic retrograde cholangiography have been noted in 73 % of cases [1].

AIP cases with swelling of the pancreatic head show a particularly high rate of stenosis of the intrapancreatic bile duct. IgG4-SC not associated with AIP also exists [2], and the diagnosis of IgG4-SC in the presence of bile duct stenosis is extremely important, because the therapeutic strategy and prognosis of other diseases differ so greatly.

In this chapter, we outline the diagnosis and therapy of the clinically important bile duct lesions, focusing on IgG4-SC.

11.2 Diagnosis of IgG4-SC

The mechanisms underlying the bile duct stenosis in IgG4-RD can be divided into two major categories. The first is a constricting stenosis of the intrapancreatic bile duct that is caused by pancreatic head swelling. This must be differentiated from pancreatic cancer and chronic pancreatitis. The second is the development of sclerotic changes within the bile duct itself. This lesion must be distinguished from cholangiocarcinoma and primary sclerosing cholangitis (PSC).

11.2.1 Cross-Sectional Imaging Studies

Fujinaga et al. reported extrapancreatic bile duct wall thickening in 78 % of a series of patients with AIP, using computed tomography (CT) and magnetic resonance imaging (MRI) [3]. Itoh et al. identified the characteristic findings of IgG4-CT findings as (1) wall thickening extending to the hilus; (2) smooth thickening; (3) a detectable lumen despite stenotic bile duct; (4) uniform staining in the delayed phase; and (5) no vessel infiltration (Fig. 11.1) [4]. MRI reveals similar findings to those of CT but is superior to CT in demonstrating wall thickening (Fig. 11.2). Despite the information provided by these imaging modalities, the differentiation of IgG4-SC from bile duct cancer and PSC by imaging alone remains problematic [3]. Attempts at a histopathological diagnosis are generally required.

11.2.2 Ultrasound Findings

Thickening of the bile duct wall can be demonstrated on external abdominal ultrasonography, even at sites that do not appear to be stenotic on cross-sectional imaging. When the bile duct is abnormal in the manner of IgG4-SC, the ductal wall is usually visualized by either endoscopic ultrasonography or intraductal ultrasonography as a structure three layers thick:

- The hyperechoic first layer corresponds to the borderline echo of the duct luminal side, including the mucosal layer.
- The hypoechoic second layer corresponds to the fibrous muscle layer and subserosal layer (fibrous layer).
- The hyperechoic third layer corresponds to the subserosal layer, including the serosa (adipose layer).

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H. Umehara et al. (eds.), *IgG4-Related Disease*, DOI 10.1007/978-4-431-54228-5_11,

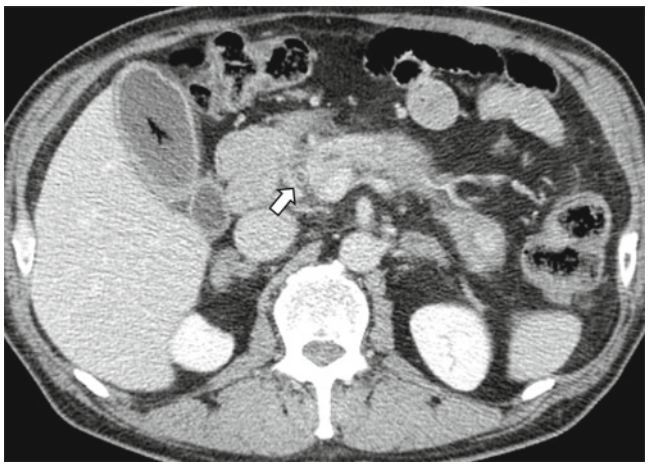

Fig. 11.1 CT findings of IgG4-related sclerosing cholangitis (enhanced portal phase). The gallbladder wall is circumferentially and uniformly thickened, and the density of the surrounding adipose tissue is increased. A similarly thickened bile duct wall shows concentric delayed staining (*arrow*)

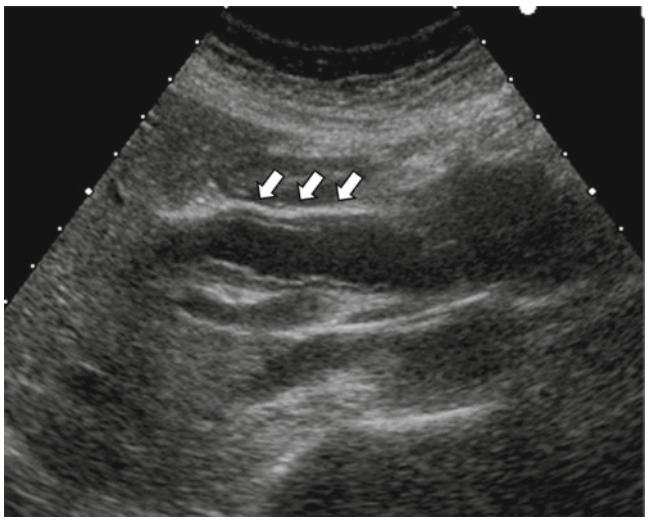

Fig. 11.3 External abdominal US findings of IgG4-related sclerosing cholangitis. The bile duct is dilated, and the bile duct wall shows from the medial side a hyper-hypo-hyperechoic 3-layer structure (*arrows*)

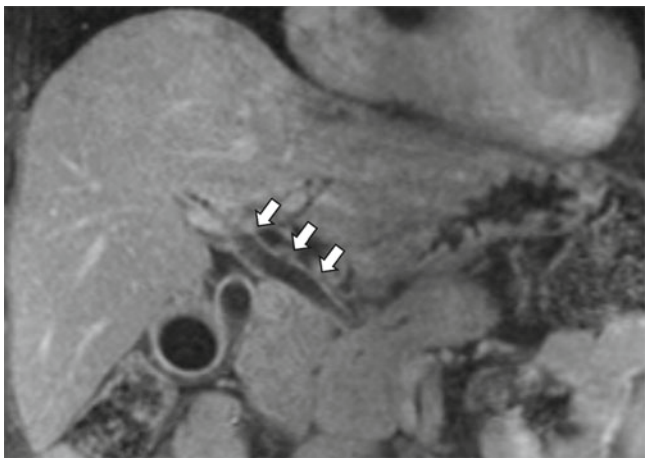

Fig. 11.2 MRI findings of IgG4-related sclerosing cholangitis (fat-suppressed T1-weighted findings, enhanced portal phase). Like on CT, the extrapancreatic bile duct wall is uniformly thickened and stained (*arrows*)

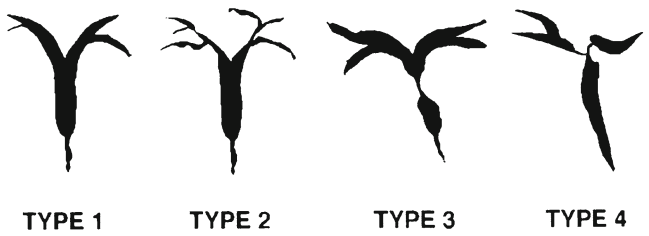

Fig. 11.4 Classification of the bile duct findings of IgG4-related sclerosing cholangitis (cited from [8])

In normal, unthickened bile duct walls, only one or two of these layers are discernible [5]. In bile duct cancer, the wall is depicted as a hypo-hyperechoic 2-layer structure. In IgG4-SC, the three-layered wall has the hyper-hypo-hyper echoic structure described above (Fig. 11.3). The hyperechoic appearance of the innermost layer is not a feature limited to IgG4-SC. Rather, this finding is observed frequently in all types of inflammatory thickening and should be interpreted as a reference finding.

Naitoh et al. note that as an aid to differentiating IgG4-SC from cholangiocarcinoma, IgG4-SC typically shows concentric, uniform thickening and a smooth wall on intraductal ultrasonography. In addition, on endoscopic retrograde cholangiography, bile duct thickening without stenosis is observed [6]. Although these findings favor IgG4-SC, in practice cholangiocarcinoma can also present with non-stenotic bile duct wall thickening. As a rule, therefore, definitive statements regarding the cause of biliary tract abnormalities are not possible on the basis of radiologic findings alone. Histopathology remains the gold standard for diagnosis in this body region.

11.2.3 Endoscopic Retrograde Cholangiography Findings

11.2.3.1 Classification

Nakazawa et al. have classified the endoscopic retrograde cholangiography findings of IgG4-SC into four types (Fig. 11.4) [7, 8]. The characteristic bile duct findings, diseases requiring differentiation from IgG4-RD in the biliary tree, and hints about distinguishing these conditions are provided below.

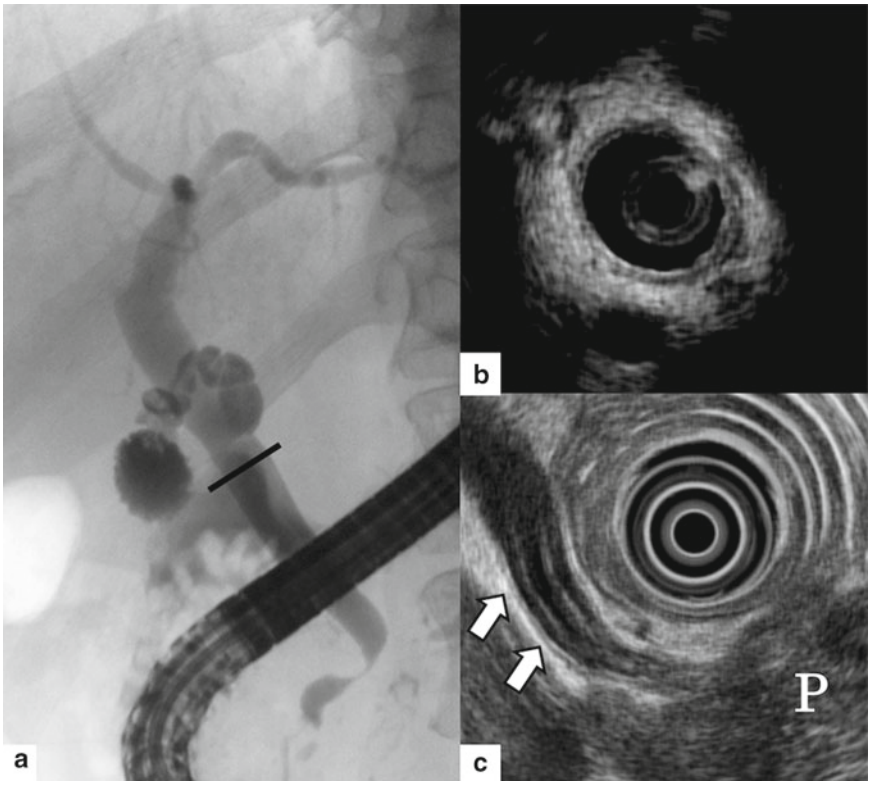

Fig. 11.5 IgG4-related sclerosing cholangitis type 1. (**a**) Endoscopic retrograde cholangiography findings of IgG4-related sclerosing cholangitis. The intrapancreatic bile duct deviates to the left and shows a smooth, one-sided stenosis. Pancreatic constricting stenosis is thought to be the main lesion. (**b**) Intraductal ultrasonography findings (seen at the *line* in 5**a**). The bile duct wall shows a hyper-hypo-hyperechoic 3-layer structure from the medial side. (**c**) Endoscopic ultrasonography examination findings. The extrapancreatic bile duct wall shows a 3-layer structure (*arrows*). *P* pancreatic head

11.2.3.2 Type 1 Endoscopic Retrograde Cholangiography Findings

Focal stenosis is found in the intrapancreatic bile duct. In many cases, the bile duct deviates to the left, and the intrapancreatic bile duct shows a smooth stenosis (Fig. 11.5a). The possibility that this is a constricting stenosis due to fibrosis of the pancreatic parenchyma as seen in chronic pancreatitis and pancreatic head cancer is high. Because the findings on endoscopic retrograde cholangiography alone do not differentiate readily between IgG4-SC and conditions such as chronic pancreatitis and adenocarcinoma of the pancreatic head, other imaging modalities such as endoscopic retrograde pancreatography, CT, and MRI are an important part of the work-up.

11.2.3.3 Type 2 Endoscopic Retrograde Cholangiography Findings

Type 2 endoscopic retrograde cholangiography findings are typified by both intrahepatic and extrahepatic stenoses. Many cases are also characterized by intrapancreatic bile duct stenosis.

Two subtypes of type 2 endoscopic retrograde cholangiography have also been formulated. Type 2a is characterized by intrahepatic bile duct and intrapancreatic bile duct stenosis associated with distal bile duct dilatation (Fig. 11.6a). Type 2b, in contrast, is defined by intrahepatic bile duct and intrapancreatic bile duct stenosis without distal bile duct dilatation (Fig. 11.6b) [7].

PSC, secondary causes of SC other than IgG4-SC, and diffusely advanced bile duct cancer must be distinguished from IgG4-SC that is associated with type 2 endoscopic retrograde cholangiographic changes. Nakazawa et al. have clarified the points of differentiation between IgG4-SC and PSC based on a detailed endoscopic retrograde cholangiography study (Fig. 11.7) [9].

11.2.3.4 Type 3 Endoscopic Retrograde Cholangiography Findings

Type 3 endoscopic retrograde cholangiographic changes with stenosis of the hilar and intrapancreatic bile ducts (Fig. 11.8). Hilar bile duct cancer is the major disease requiring differentiation, which is often not easy [10]. IgG4-SC can be suspected in cases complicated by typical AIP, but particular care is necessary because cases with bile duct cancer complicated by AIP may also exist [11].

11.2.3.5 Type 4 Endoscopic Retrograde Cholangiography Findings

Focal stenosis of the hilar bile duct is characteristic of a type 4 lesion (Fig. 11.9). Intrapancreatic bile duct lesions are not associated with this type, and of all the categories of endoscopic retrograde cholangiographic changes this one is the

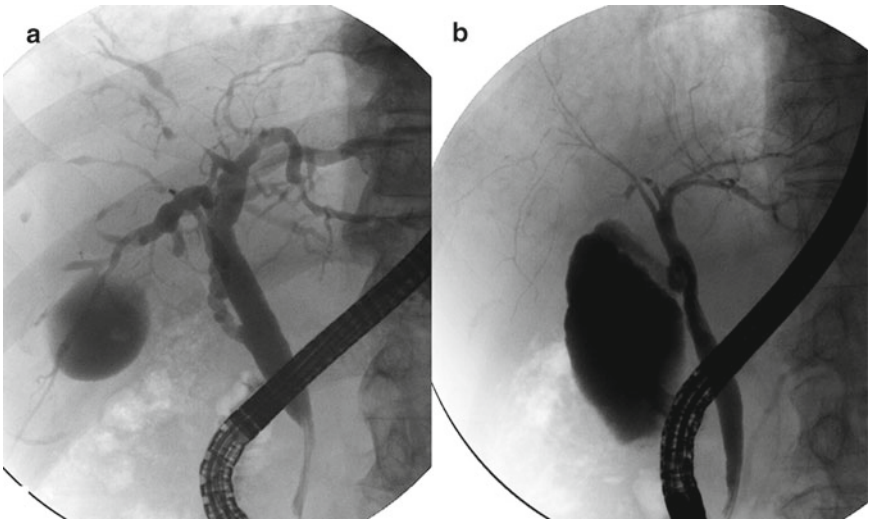

Fig. 11.6 IgG4-related sclerosing cholangitis type 2 endoscopic retrograde cholangiography findings. (**a**) Type 2a. Mainly at the right anterior segmental branches there is smooth narrowing, while the distal bile duct is dilated. (**b**) Type 2b. Adequate injection pressure must be applied during cholangiography. When examining in detail the intrahepatic bile duct branches, sclerotic changes are found in the right anterior segmental branches. No distal dilatation is associated

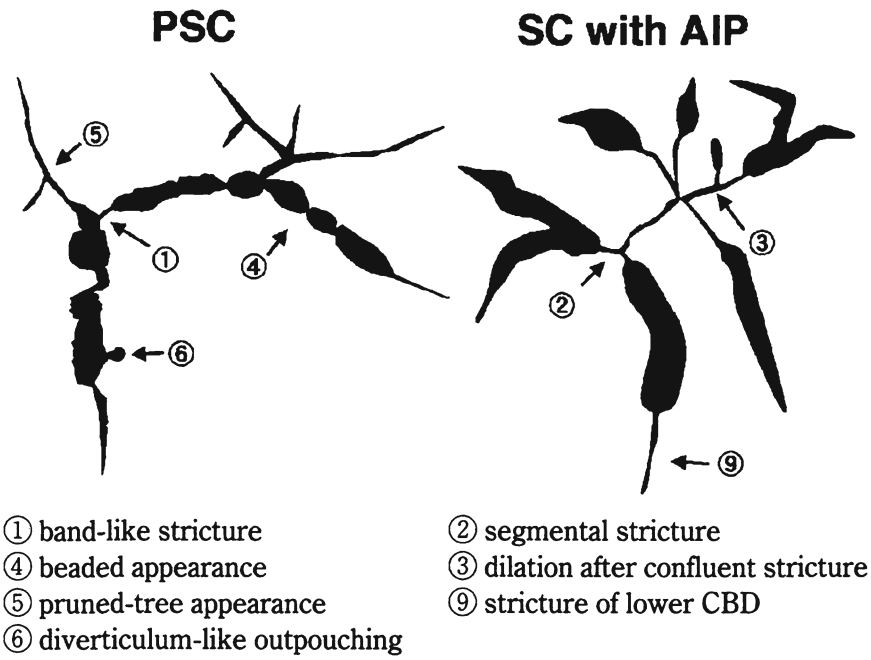

Fig. 11.7 IgG4-related sclerosing cholangitis and primary sclerosing cholangitis. Points of differentiation in the bile duct findings of cholangitis (cited from [8])

most difficult to differentiate from hilar bile duct cancer (Fig. 11.10). Histopathological study of the bile duct is critical to making this distinction.

11.2.3.6 Stenosis of the Middle Common Bile Duct

Stenosis of the middle common bile duct is an unusual complication of IgG4-SC and is not a component of any of the types 1–4 changes outlined above. Cholangiocarcinoma is far more likely than IgG4-SC to cause such a picture on endoscopic retrograde cholangiography (Fig. 11.11).

11.2.4 Serological Characteristics

Determination of the serum IgG4 value is useful in the diagnosis of IgG4-SC [12]. However, it must be emphasized that serum IgG4 assays can never differentiate absolutely between

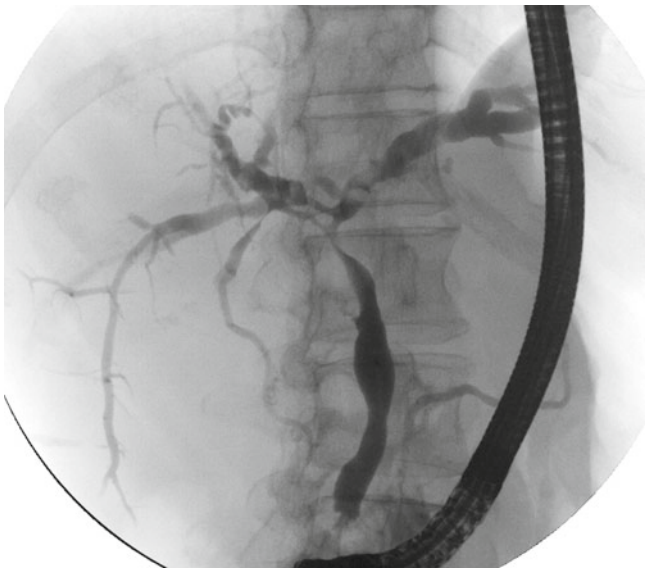

Fig. 11.8 IgG4-related sclerosing cholangitis type 3 endoscopic retrograde cholangiography findings

IgG4-SC and conditions such as bile duct cancer, pancreatic cancer, and PSC. Cases without IgG4-RD but showing elevated serum IgG4 values exist, while the reverse pattern is also encountered.

11.2.5 Pathological Characteristics

Inflammation extending to all layers of the bile duct and periductal tissue and IgG4-positive plasmacytic cell infiltration are characteristic. In contrast to PSC, the bile duct epithelium is preserved, the degree of fibrosis is mild, and obliterative phlebitis is present [13–15].

Differentiation of IgG4-SC from bile duct cancer, pancreatic cancer, and PSC is frequently difficult on the basis of imaging and serological findings alone. In this situation, pathological examination becomes the most important modality to distinguish other diseases. Unfortunately, the sensitivity of transpapillary bile duct biopsy is suboptimal in both IgG4-SC and cholangiocarcinoma [16, 17]. One study estimated a sensitivity of only 52 % [16] for finding ≥10 IgG4-positive plasma cells/HPF at the most heavily infiltrated sites in cases of IgG4-SC [16]. The yield of transpapillary bile duct biopsy for cancer tissue collection in bile duct cancer was similarly low in another study at 56 % [17].

Although neither of these sample collection rates is at all satisfactory, obtaining an adequate tissue sample is thought to be vital. Given the relatively low yield of initial biopsies, repeat procedures should be considered if IgG4-SC appears likely, because the management of this condition differs so dramatically from that of its mimickers.

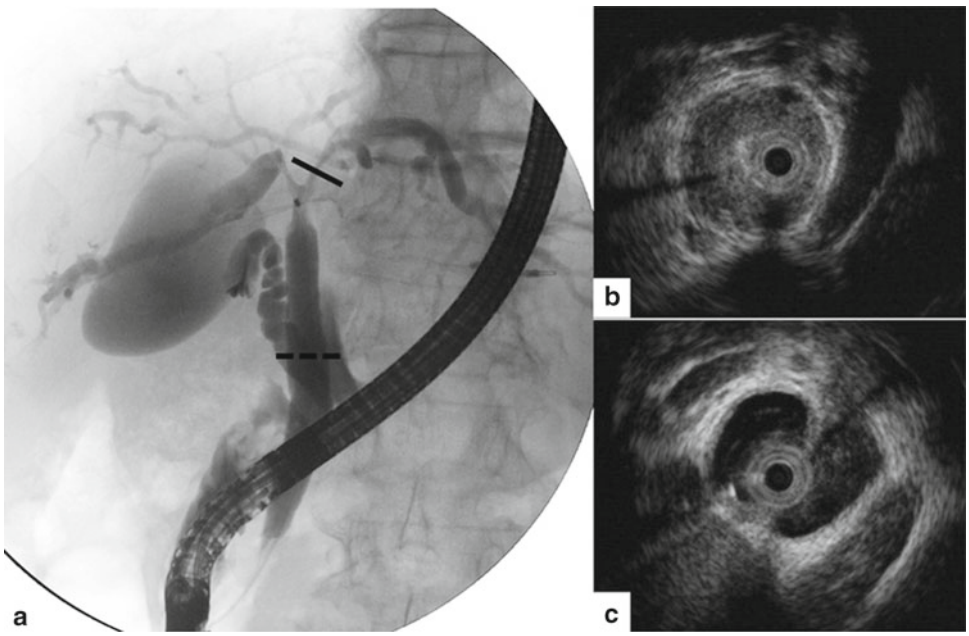

Fig. 11.9 IgG4-related sclerosing cholangitis type 4. (**a**) Endoscopic retrograde cholangiography findings. Smooth stenosis is found in the hilus. (**b**) Intraductal ultrasonography findings at the left hepatic bile duct (seen at the *underline* in 9a). Thickened bile duct wall is depicted as relatively uniformly hypoechoic. There is little extension to the outermost hyperechoic layer and surrounding vessels. (**c**) Intraductal ultrasonography findings at the *dotted line* (junction between cystic duct and common bile duct). Uniform circumferential wall thickening is found

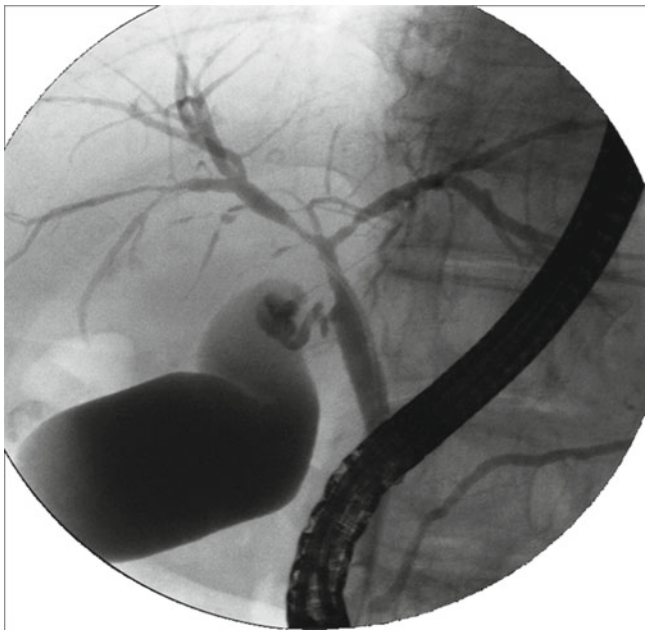

Fig. 11.10 Bile duct findings of hilus bile duct cancer. Relatively smooth stenosis is found in the hilus. Stenosis is also present in the right intrahepatic bile duct. Skip lesions are seemingly present, and sclerosing cholangitis was suspected, but transpapillary bile duct biopsy revealed an adenocarcinoma. It was a widely advanced bile duct cancer

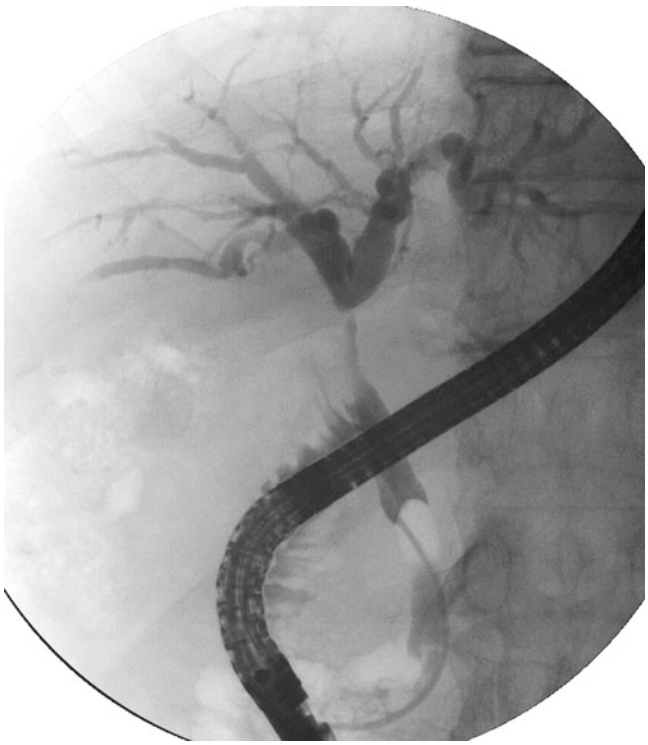

Fig. 11.11 IgG4-related sclerosing cholangitis. Unclassifiable middle bile duct stenosis cases

11.2.6 Lesions in Other Organs

IgG4-SC is associated not only with AIP in a high proportion of cases but also with a wide variety of other conditions including retroperitoneal fibrosis, lacrimal gland and salivary gland lesions, hilar lymph node swelling, and tubulointerstitial nephritis. Accordingly, when IgG4-SC is suspected, surveys of other organs should also be implemented. Furthermore, for cases in which the possibility of PSC exists, it is important to exclude inflammatory bowel disease by appropriate examinations.

11.3 Therapy of IgG4-SC

As in other disease manifestations of IgG4-RD, glucocorticoid therapy is effective in IgG4-SC. In almost all cases, the bile duct stenosis shows improvement and the need for bile duct drainage is obviated by steroid treatment. Rare exceptions to this rule exist [18]. Both bile duct drainage and steroid therapy are indicated in IgG4-SC cases in which jaundice is associated with bile duct stenosis.

11.4 Prognosis of IgG4-SC

Although the long-term prognosis has not been clarified, the lesion recurrence rate of hilar and intrahepatic bile duct stenosis has been reported to be higher than that of intrapancreatic bile duct stenosis [19], and the former requires especially meticulous follow-up observation. In cases not treated with steroids, progression to cirrhosis and portal hypertension has been described [20]. Future studies will be needed to better define the long-term prognosis.

11.5 Papillary Lesions

Papillary swelling is found in 41 % of AIP cases [21], and IgG4-positive plasmacytic cell infiltrates (≥10 cells/HPF at the most heavily infiltrated sites) are found in between 50 % and 80 % of endoscopic papillary biopsies in such cases [22–24]. Papillary cancer must be excluded by biopsy.

11.6 Gallbladder Lesions

Thickening of the gallbladder wall is found in a high proportion of AIP cases [25]. The CT, MRI, and US features of the gallbladder wall resemble those of bile duct lesions in AIP, with circumferential uniform wall thickening (Figs. 11.1 and 11.2).

11.7 Concluding Remarks

IgG4-SC is an important cause of secondary SC that has been recognized only relatively recently and much remains to be discovered about this entity. Serum IgG4 concentrations should be measured whenever PSC is suspected [26].

The diagnosis of IgG4-SC based on imaging examinations alone is not easy. The other diseases requiring differentiation, notably bile duct cancer and PSC, require a completely different therapeutic approach from that of IgG4-SC often encompassing liver transplantation, hepatic lobectomy, or pancreaticoduodenectomy. Their prognoses also differ from that of IgG4-SC. However, the differentiation of IgG4-SC from cholangiocarcinoma can be difficult even on meticulously conducted endoscopic retrograde cholangiography examinations. If IgG4-SC is suspected because of the presence of other IgG4-RD such as AIP, chronic sclerosing sialadenitis, or retroperitoneal fibrosis, the most important next step is to obtain a pathological diagnosis based on adequate bile duct biopsy materials.

As a cause of bile duct stenosis, the frequency of IgG4-SC is low compared to that of cholangiocarcinoma. Steroid trials in the absence of clear evidence for the diagnosis of IgG4-SC should be avoided. Expert consultation is often required in the setting of cases in which the diagnosis is not straightforward.

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Ophthalmology

12

Masayuki Takahira and Atsushi Azumi

12.1 Introductory Remarks

Mikulicz's disease, which is characterized by symmetrical swelling of the lacrimal and salivary glands, is a representative IgG4-related disease (IgG4-RD), for which the initial patient sketched in the "portrait of a farmer" by Mikulicz in his original publication has subsequently served as a virtual advertising poster for this disease. Because lacrimal glands are relatively easy to biopsy, basic research and pathological and clinical studies on IgG4-RD in the ophthalmic region have focused to a large extent on lesions in these organs. Recently, however, a growing understanding has developed of the frequency with which IgG4-RD involves not only the lacrimal gland but also other ocular adnexa such as the extraocular muscles and orbital nerves. Lacrimal gland lesions are described in detail in other chapters of this book. We therefore concentrate on orbital lesions other than the lacrimal gland.

Manifestations of IgG4-RD in the ophthalmic region are recognized with a frequency that is now surprising, given that IgG4-RD was identified as a distinct disease entity only within the past decade. In our collective experience, IgG4-RD appears to account for approximately 25 % of cases in which patients present with proptosis, eyelid swelling, and other features of orbital inflammation.

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12.2 IgG4-RD in Orbital Inflammatory Disease

The most prominent pathological feature in IgG4-RD is lymphoplasmacytic cell infiltration. The differential diagnosis of orbital inflammatory and lymphoproliferative lesions includes malignant lymphoma, "reactive lymphoid hyperplasia," "idiopathic orbital inflammation," and "orbital pseudotumor." Inflammatory and lymphoproliferative conditions comprise the largest group of mass-forming diseases in the orbit and account for more than 40 % of such lesions in Japan [1, 2]. Data available from the United States suggest a somewhat lower percentage, but the figure is still on the order of 20 % [3–5].

The most common lymphomas among the lymphoproliferative disorders that affect the orbit are MALT lymphomas (i.e., extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue), diffuse large B-cell lymphomas (DLBCL), and follicular lymphomas [4]. These low- and medium-grade tumors originate in the ophthalmic region and tend to preserve the shape of the eyeball and orbital bones, demonstrating a predilection for infiltrating the gaps between them (Fig. 12.1d, e).

Computed tomographic (CT) and magnetic resonance imaging (MRI) studies in orbital lymphoma typically demonstrate an absence of globe compression and bone destruction. The absence of destructive lesions facilitates differentiation of lymphomas from the other common orbital tumors such as pleomorphic adenoma (Fig. 12.1a), lacrimal gland cancer (Fig. 12.1b), and hemangioma (Fig. 12.1c). In contrast, the differentiation between lymphomas and nontumorous lesions diagnostic imaging is sometimes difficult (Fig. 12.1d–f), and histopathological confirmation of the diagnosis, often aided by gene rearrangement studies, is essential.

A breakdown of the orbital inflammatory and lymphoproliferative disorders seen at the authors' institutions is shown in Fig. 12.2. IgG4-RD accounts for approximately

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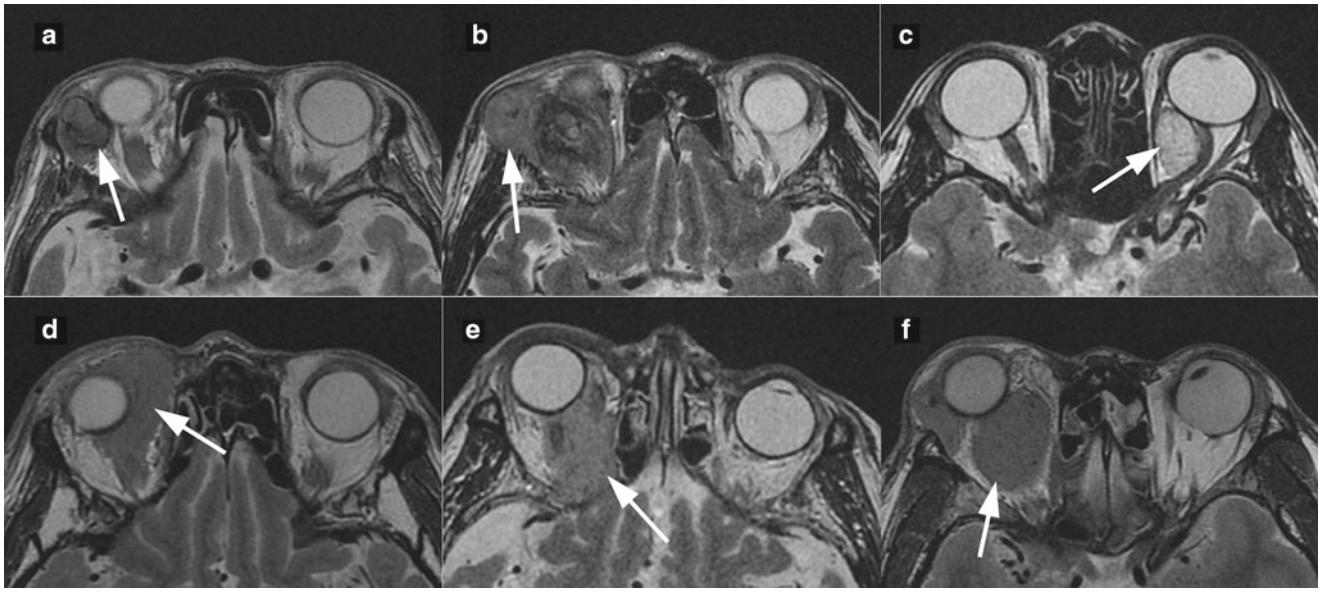

Fig. 12.1 Representative orbital tumor and lymphoproliferative disorders. (**a**) Right lacrimal gland pleomorphic adenoma (81-year-old man). The tumor is clearly demarcated and spherical and strongly compresses the eyeball. (**b**) Right lacrimal gland adenoid cystic carcinoma (60-year-old man). Destruction of the lateral wall of the orbit (zygomatic bone) is seen. (**c**) Cavernous hemangioma (38-year-old woman). The tumor is spherical and occurs preferentially in the muscle cone. The diagnosis is relatively easy to establish from the pattern of enhancement. (**d**) Right orbital MALT lymphoma (77-year-old man). The tumor infiltrates the eyeball as if encircling it. (**e**) Right DLBCL (85-year-old man). The tumor infiltrates up to the orbital apex in the muscle cone. (**f**) IgG4-related orbital lesions (44-year-old man). Right lacrimal gland swelling and a mass in the muscle cone are seen

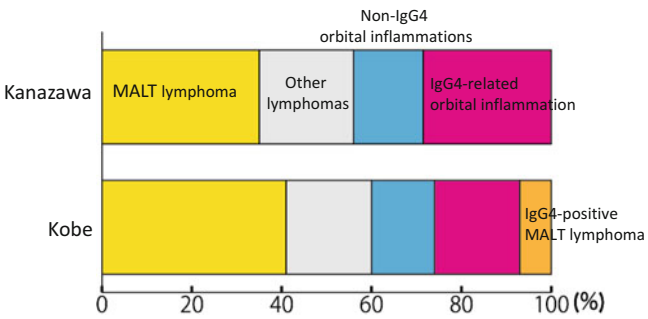

Fig. 12.2 IgG4-related disease as a percentage of orbital inflammatory and lymphoproliferative disorders. Breakdown of pathologically diagnosed orbital lymphoproliferative disorders cases at the authors' institutions. At Kanazawa University, there were 71 cases from November 2005 to November 2011, and at Kobe University and Kobe Kaisei Hospital, 58 cases from March 2008 to June 2011

one quarter of the total. In general, serum IgG4 values are low and tissue immunostaining for IgG4 is negative in MALT lymphoma. However, prominent IgG4 staining has been reported in some cases of MALT lymphoma (Fig. 12.2). In addition, both the development of malignant lymphoma against a background of IgG4-related dacryoadenitis [6–8] and IgG4-producing MALT lymphomas [9] have also been described.

12.3 Diversity of IgG4-Related Lesions in the Ophthalmic Region

A pivotal event in the elaboration of the IgG4-RD concept was the discovery that serum IgG4 values are elevated in autoimmune pancreatitis. Subsequently, Mikulicz's disease was reported to be IgG4-related [10, 11], prompting attention to be focused on systemic IgG4-related lesions in other organs. We focus the majority of our attention on IgG4-related involvement of orbital structures other than the lacrimal gland.

12.3.1 Extraocular Myositis

Extraocular muscle swelling is one of the most common IgG4-related orbital lesions after dacryoadenitis [12, 13]. Figure 12.3 illustrates representative cases of IgG4-related extraocular myositis. Swelling is seen in the superior, inferior, medial, and lateral rectus muscles and in the inferior oblique muscle (Fig. 12.3a–d). The pathology findings in the extraocular muscle are similar to those of IgG4-related dacryoadenitis, i.e., an IgG4-positive lymphoplasmacytic infiltrate associated with follicle formation and fibrosclerosis (Fig. 12.3e, f). The frequency of IgG4 extraocular

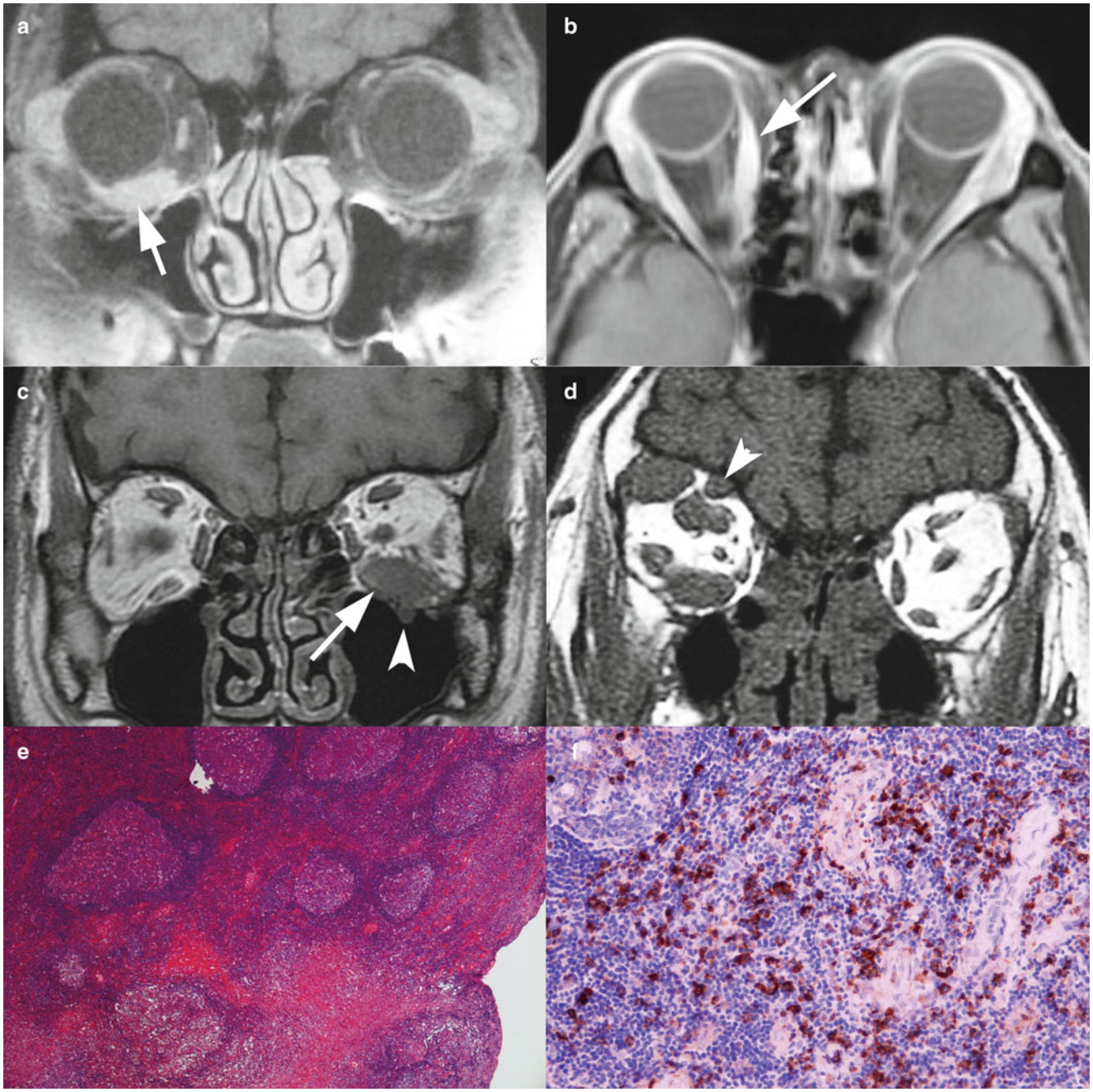

Fig. 12.3 MRI and pathological findings of IgG4-related extraocular myositis. (**a**) A 46-year-old woman. Serum IgG4 value 209 mg/dL. In addition to bilateral lacrimal gland swelling, right inferior oblique muscle swelling (*arrow*) is seen. (**b**) A 45-year-old man. Serum IgG4 value 914 mg/dL. In addition to bilateral lacrimal gland swelling, right medial rectus muscle swelling (*arrow*) is seen. (**c**) A 65-year-old man. Serum IgG4 value 404 mg/dL. Left inferior rectus muscle swelling (*arrow*) and lesions around the infraorbital nerve (*arrowhead*) are seen. (**d**) A 74-year-old woman. Serum IgG4 was not measured, (**e**, **f**) but IgG4-related lesions were diagnosed pathologically. Right lacrimal gland and right superior and inferior lateral rectus muscle swelling and right supraorbital nerve enlargement (*arrowhead*) are seen. (**e**) Pathological picture of H-E staining in case (**d**). Lymphoplasmacytic infiltration with follicle formation and fibrosis is seen. (**f**) IgG4 staining picture in case (**d**). Numerous IgG4-positive cells are seen

myositis among patients with IgG4-related ophthalmic disease requires further investigation of larger numbers of patients. Biopsy of the extraocular muscles is seldom performed.

Graves' ophthalmopathy, which can also affect multiple extraocular muscles, must be distinguished from IgG4-RD in this setting. Kubota et al. have reported a case in which IgG4-related orbital inflammation and thyroid

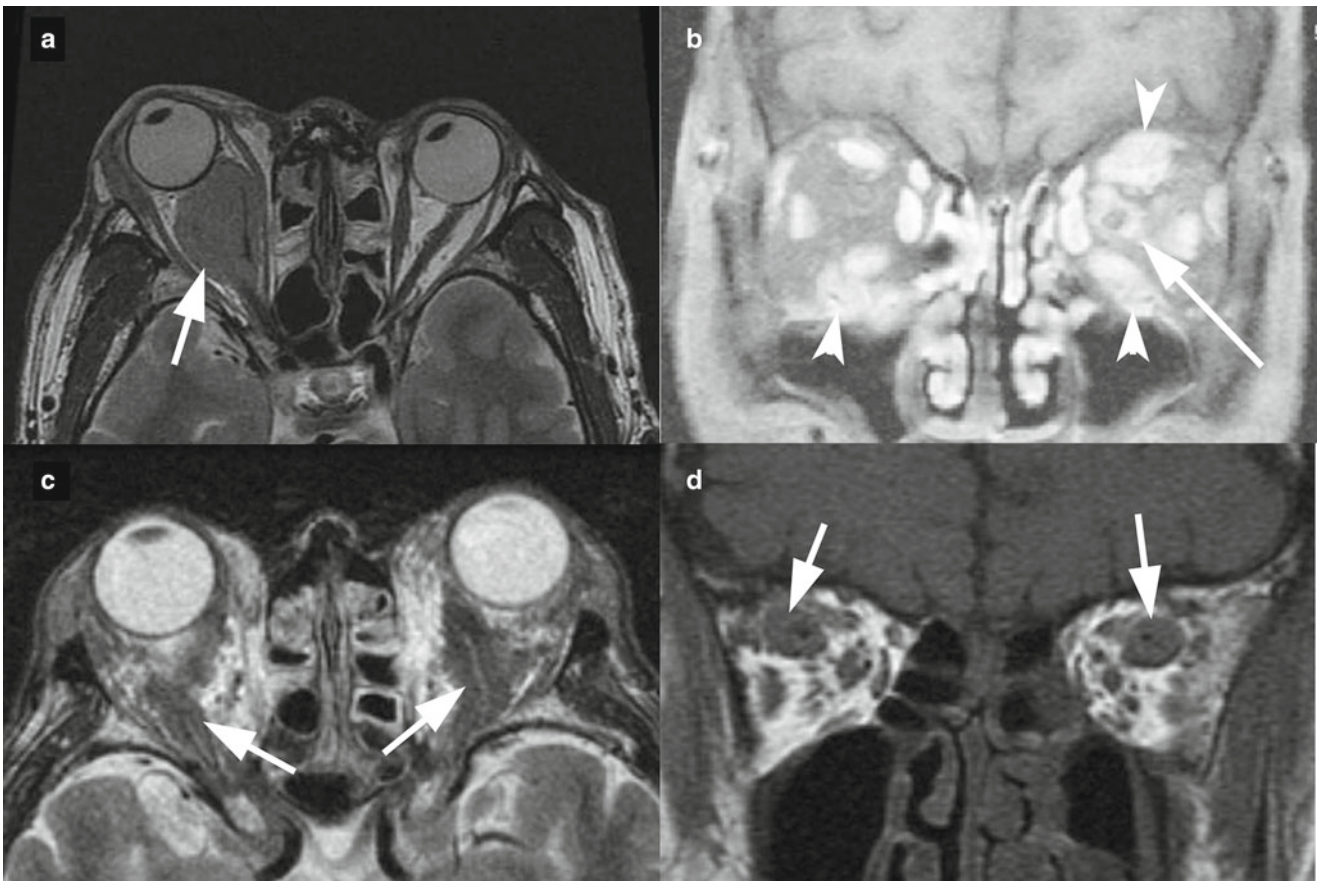

Fig. 12.4 IgG4-related orbital lesions extending into the muscle cone. (**a**) A 44-year-old man. Serum IgG4 value 599 mg/dL. A tumor is seen around the right optic nerve (*arrow*). (**b**) A 60-year-old man. Serum IgG4 value 463 mg/dL. In addition to mild swelling of the left extraocular muscle, lesions (*arrowhead*) are present around the optic nerve (*arrow*), supraorbital nerve, and infraorbital nerve. (**c**) A 54-year-old man. Serum IgG4 value 1,950 mg/dL. Bilateral lacrimal gland swelling and lesions (*arrow*) along the bilateral superior ophthalmic veins are seen. (**d**) Coronal plane findings in case (**c**). In this case, the perivascular lesions (*arrow*) are more prominent than the extraocular muscle swelling

ophthalmopathy occurred concomitantly [14], but this occurrence is considered to be coincidental.

12.3.2 Supraorbital and Infraorbital Nerve Swelling

In IgG4-RD, enlargement of the infraorbital nerve as well as of the infraorbital canal has recently been reported [13, 15, 16]. Lesions around the infraorbital nerve (Figs. 12.3c and 12.4b) and supraorbital nerve are seen in some cases (Figs. 12.3d and 12.4b). Although nerve tissue for pathological examination is difficult to obtain, Katsura et al. reported a perineural lymphoplasmacytic infiltration with foci of IgG4-positive plasma cells and fibrosis [16]. Numbness of the affected nerve appears to be common, but most patients are asymptomatic.

12.3.3 Lesions in the Muscle Cone

IgG4-RD lesions are sometimes seen in the muscle cone (the portion surrounded by the four rectus muscles) and around the optic nerve (Fig. 12.4a, b). Patients with such lesions are prone to exophthalmos (Fig. 12.4a). These lesions have been interpreted both as inflammation of the tissues surrounding the optic nerve (i.e., the optic nerve sheath) and as inflammation of the adipose tissues [13]. Perivascular lesions also form in the muscle cone in some patients (Fig. 12.4c, d).

12.3.4 IgG4-Related Optic Neuropathy

When lesions of IgG4-RD form near the optic canal, visual acuity and/or visual field impairment due to optic neuropathy may occur. Although this is attributed to compression near

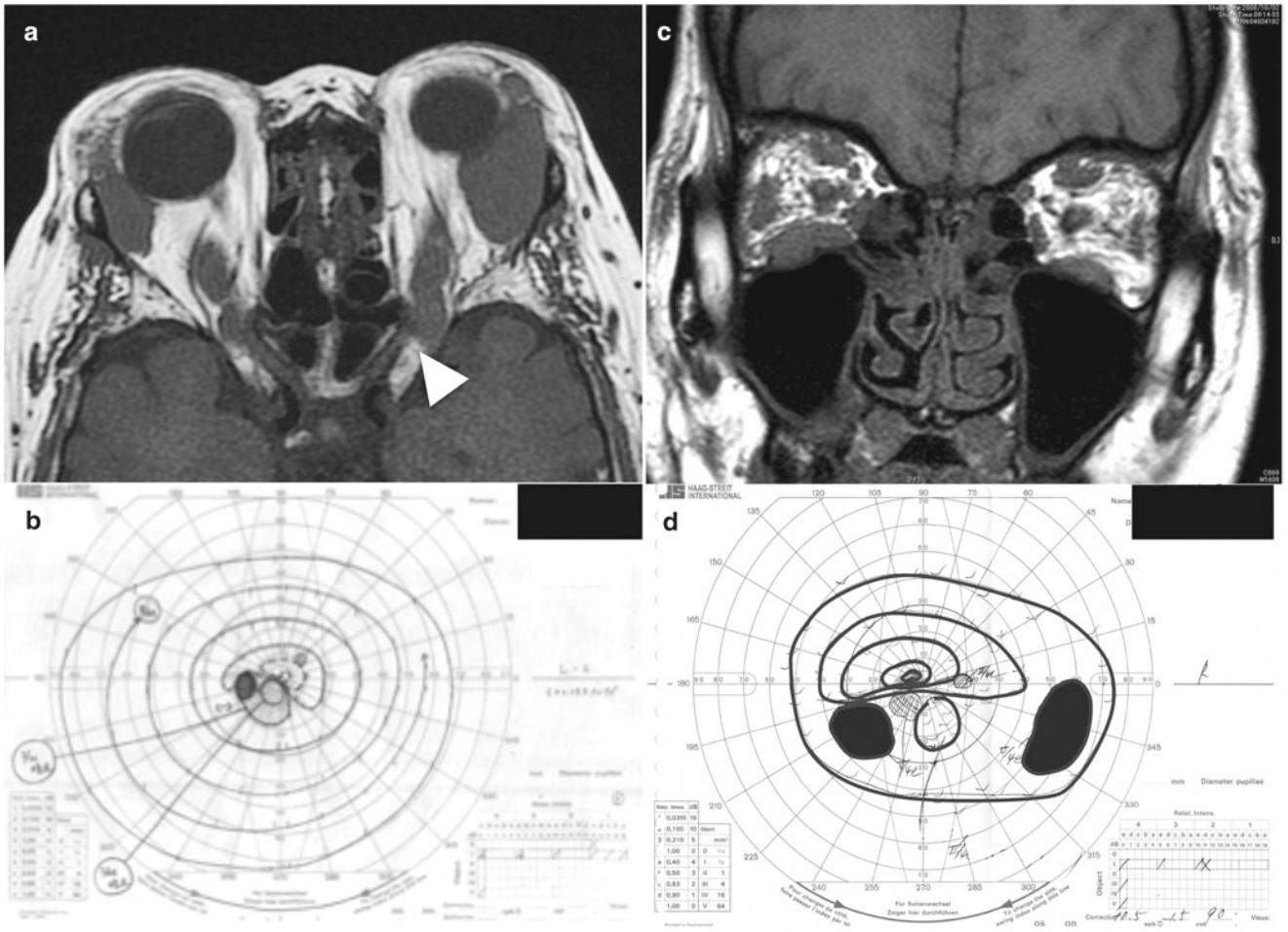

Fig. 12.5 IgG4-related optic neuropathy. Two cases complicated by optic neuropathy. (**a**) A 60-year-old woman. In addition to bilateral lacrimal gland involvement, supraorbital nerve enlargement is also seen bilaterally. The *arrowhead* indicates the site where the left optic nerve is compressed from above. (**b**) Goldmann kinetic perimetry reveals lower altitudinal hemianopia. Left corrected visual acuity was 0.1. (**c**) A 53-year-old woman. Enlargement of the right infraorbital nerve is seen. A cord-like shadow is seen in the muscle cone, but no masses are identified. (**d**) Altitudinal (horizontally) visual field impairment is seen. Corrected visual acuity of the right eye was 1.0

the optic canal (Fig. 12.5a, b), cases without masses are also encountered (Fig. 12.5c, d). Multiple mechanisms may contribute to this type of optic neuropathy.

12.4 Gray Zone of IgG4-Related Lesions in the Ophthalmic Region

The diagnosis of IgG4-RD requires the synthesis of clinical, serological, radiologic, and pathology data from a variety of potential organs that can be involved. As described elsewhere in this book, the pathology of IgG4-RD consists of foci of marked lymphoplasmacytic infiltration associated with fibrosclerosis, and a high percentage of plasma cells stain for IgG4. The serum IgG4 concentration is elevated in the majority of patients, but not all. It must be emphasized, however, that elevations neither in tissue nor in serum are diagnostic of IgG4-RD in and of themselves. For example, typical lacrimal gland cyst cases (Fig. 12.6a–d) can be associated with inflammatory cell infiltration by numerous IgG4-positive cells. This tissue specimen contains none of the other histopathological features of IgG4-RD, however, and it would therefore be erroneous (and dangerous) to render the diagnosis of IgG4-RD in this setting.

The majority of cases diagnosed with IgG4-related Mikulicz's disease or IgG4-related dacryoadenitis are straightforward, demonstrating both serological and pathology characteristics that are strongly suggestive or diagnostic of IgG4-RD. In some patients, however, the diagnosis of IgG4-related dacryoadenitis is predicated upon pathological findings on biopsy in the setting of normal serum IgG4 concentrations (Fig. 12.6e, f).

The case shown in Fig. 12.6g, h illustrates the clinical variability of IgG4-RD. This 65-year-old diabetic man

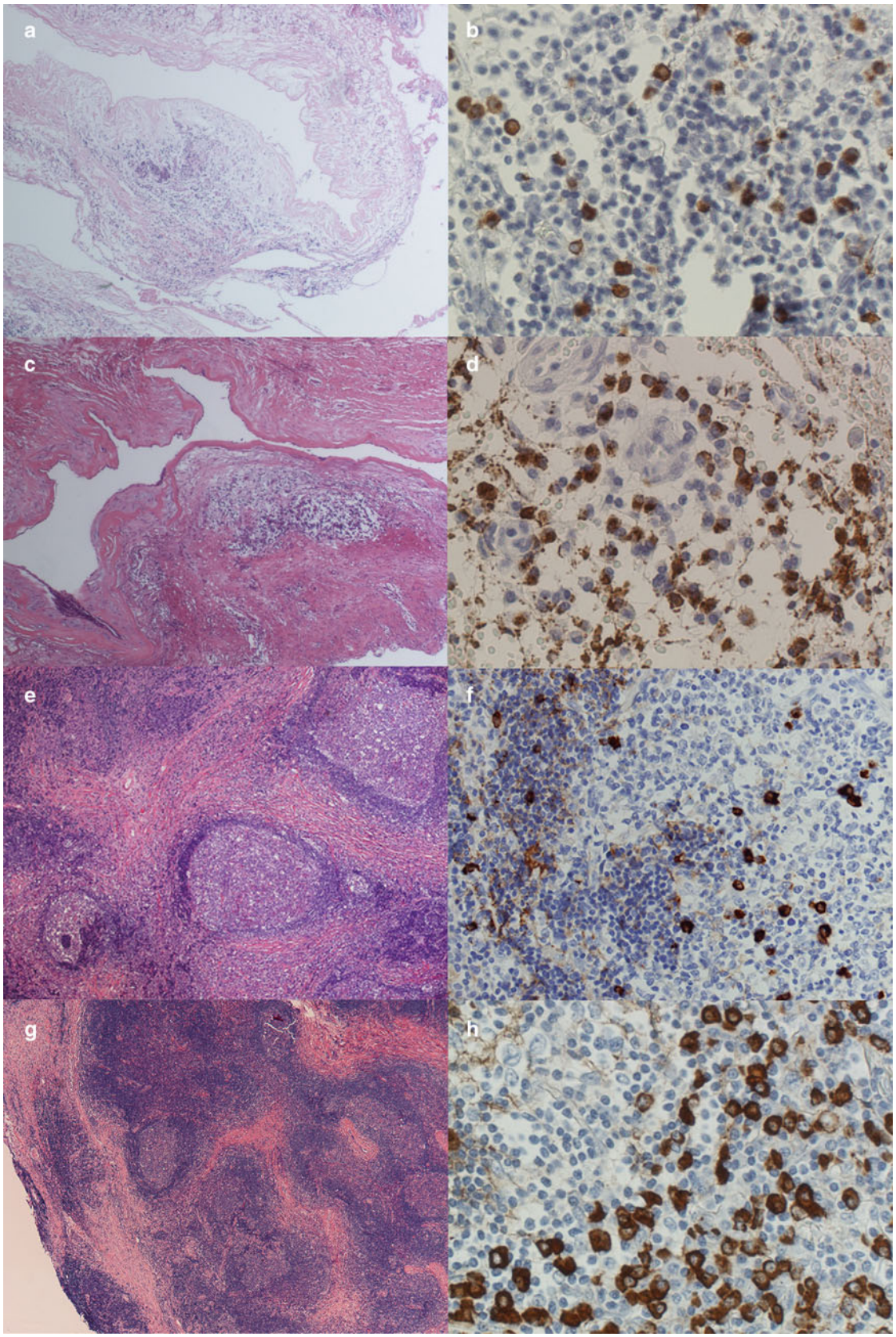

Fig. 12.6 Pathological and IgG4 staining findings of various orbital lesions. (**a**, **b**) A 51-year-old woman with a left lacrimal gland retention cyst. IgG4 staining-positive cells are seen at sites of lymphocyte infiltration. (**c**, **d**) A 53-year-old man with left conjunctival cyst. Similar IgG4-positive staining sites are seen. (**e**, **f**) A 62-year-old woman with serum IgG4 of 29 mg/dL. In this case with right lacrimal gland swelling, lymphoplasmacytic cell infiltration associated with follicle formation and fibrosis is seen. IgG4-positive cells exceed 30/HPF, and so this patient could be diagnosed with IgG4-RD histologically. (**g**, **h**) A 65-year-old man. IgG4-positive lymphoplasmacytic infiltration associated with follicle formation and fibrosis was seen. Initially, serum IgG4 was 164 mg/dL, and typical IgG4-related Mikulicz's disease was diagnosed, but 5 years later in the untreated state serum IgG4 normalized to 55 mg/dL

was diagnosed with IgG4-related dacryoadenitis on the basis of histopathological and immunostaining features of a lacrimal gland biopsy. At the time of diagnosis, his serum IgG4 concentration was 164 mg/dL (normal <121 mg/dL). Glucocorticoid treatment was withheld because of concern about its effects on his glucose metabolism, and he was followed with expectant management. Five years later, his serum IgG4 concentration had normalized (55 mg/dL) and the bilateral lacrimal gland swelling also decreased. This case demonstrates the variable natural history of IgG4-RD, its prolonged course, and its potential for spontaneous improvement in some patients. It also indicates that the diagnosis of IgG4-RD should be considered in the appropriate clinical setting despite normal serum IgG4 concentrations.

At the First Boston International Symposium on IgG4-RD, Cheuk et al. reported cases of chronic dacryoadenitis in which the serum IgG4 values were normal and IgG4-immunostaining was negative, but hematoxylin and eosin studies revealed a pathological picture of fibrosclerosis and lymphocyte infiltration with follicle formation (Cheuk et al., unpublished observation). We have also observed such cases. Cheuk et al. have referred to such cases as "IgG4-negative IgG4-RD." Further investigation is required to understand the relationship of such cases, if any, to IgG4-RD.

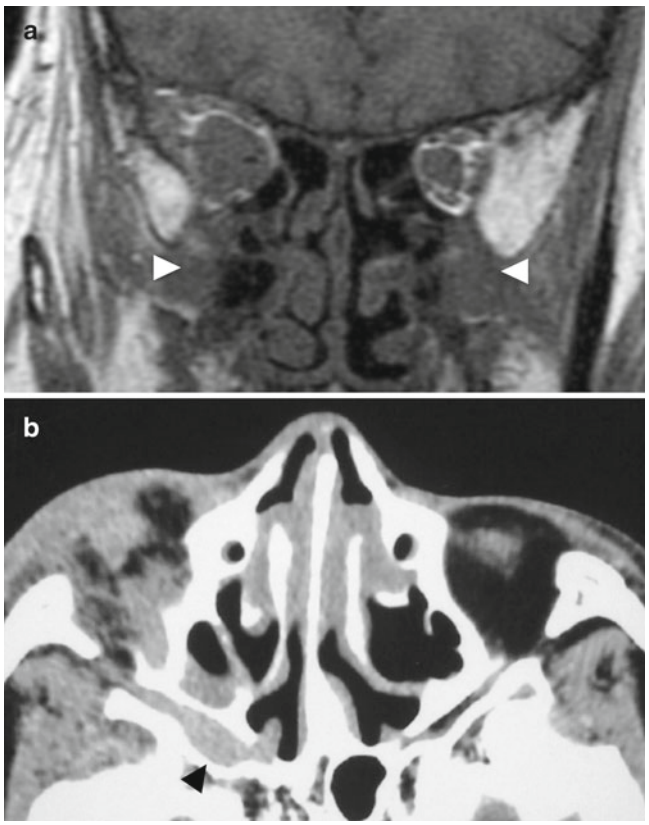

Fig. 12.7 Lesions from the orbital apex to adjacent structures of the orbit. (**a**) A 64-year-old man. Serum IgG4 value 816 mg/dL. Lesions are seen around the bilateral optic nerves and also extend to the lateral paranasal sinus (*white arrowhead*). (**b**) A 63-year-old man. Serum IgG4 value 860 mg/dL. Lesions are seen near the right inferior orbital fissure and right pterygopalatine fossa (*black arrowhead*)

12.4.1 Dacryocystitis and Lacrimal Ducts

Recently, cases of IgG4-related lacrimal duct lesions [17] and IgG4-related dacryocystitis [18] have been reported. Perhaps because lacrimal duct occlusive disease is not usually subjected to pathological examination, we have not encountered such cases at our institutions. More scrutiny needs to be devoted to these potential lesions in the future. Some cases of IgG4-RD are known to be complicated by sinusitis, and lacrimal duct lesions may develop in some of these cases similar to the manner observed in granulomatosis with polyangiitis (formerly Wegener's).

12.4.2 Eyeball Lesions

In posterior scleritis, extreme inflammatory thickening of the sclera is sometimes seen. The pathophysiology of this lesion has not been adequately explained. Recently, a case with a prominent intraocular protrusive lesion that was subjected to enucleation because of a suspicion of malignant tumor was reported at a Japanese meeting (unpublished observation by Tsuji). Marked scleral thickening and IgG4-positive plasma cell infiltration were demonstrated on the enucleated eye, and a serum IgG4 concentration >130 mg/dL was documented. The fact that this patient had a history of retroperitoneal fibrosis was also consistent with the diagnosis of IgG4-RD. Another case with IgG4-related intraocular lesion was also reported [19]. In this case, enucleation of the eyeball was performed for the preliminary diagnosis of choroidal tumor.

12.4.3 Lesions of the Orbital Apex and Adjacent Structures of the Orbit

Cases are encountered in which extension of the disease to the orbital apex or other adjacent structures of the orbit occurs (Fig. 12.7a, b). When no superficial orbital lesions are present, histopathological diagnosis is extremely difficult to achieve. In this sense, these cases must be considered to have "gray zone" lesions. Depending on the degree of inflammatory cell infiltration into these tight spaces, marked visual impairment can result. Anecdotal reports have described cases in which excessive therapy such as enucleation of the eyeball or orbital exenteration was performed because of a suspicion of malignancy. Determination of the serum IgG4

value can be extremely important in such cases, but even a normal serum IgG4 concentration does not necessarily rule out IgG4-RD.

12.5 Nomenclature Encompassing All Lesions in the Ophthalmic Region: IgG4-Related Ophthalmic Disease

Bilateral lacrimal gland swelling is indisputably a typical manifestation of IgG4-RD in the ophthalmic region. However, it has become apparent that IgG4-related lesions exhibit diverse infiltrative patterns and can also involve the extraocular muscles, nerves, and other structures. Although the assignment of names to each of these lesions would be possible—e.g., "IgG4-related extraocular muscle lesions" or "IgG4-related orbital nerve lesions"—the proliferation of names would merely complicate issues of nomenclature, to little purpose. An international consensus document on the nomenclature of IgG4-RD recently recommended "IgG4-related ophthalmic disease" as the broader name for all complications of this disease occurring in this region [20]. However, this summary term does not preclude the use of more precise terminology, e.g., IgG4-related dacryoadenitis, when such anatomic specificity is required.

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Salivary Glands in Mikulicz's Disease

13

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13.1 Introductory Remarks

Mikulicz's disease (MD) is a unique condition characterized by enlargement of the lacrimal and salivary glands caused by infiltration of lymphocytes. MD has been considered a subtype of SS because of certain histopathological similarities, particularly lymphocytic infiltration [1]. However, MD patients show elevated levels of serum IgG4 and infiltrating IgG4-positive plasma cells in the gland tissues [2], and these findings have also been identified in other diseases such as autoimmune pancreatitis (AIP) [3], interstitial pneumonia [4], retroperitoneal fibrosis [5], sclerosing cholangitis (SC) [6], bronchial asthma, and atopic dermatitis. These diseases are now called "IgG4-related disease (IgG4-RD)" [7, 8].

In this study, we outline the salivary gland lesions of MD, with reference to patients evaluated at our own institution.

13.2 Patients

Twenty patients with MD (14 women and 6 men, mean age 60.1 ± 12.1 years) and 18 patients with SS (16 women and 2 men, mean age 54.6 ± 12.8 years), referred to the Department of Oral and Maxillofacial Surgery, Kyushu University Hospital between April 1993 and December 2010, were included in the study. MD was diagnosed according to the diagnostic criteria of the Japan Sjögren's Syndrome Society [9]. SS was diagnosed according to both the Research Committee on SS of the Ministry of Health and Welfare of the Japanese Government (1999) [10] and the American–European Consensus Group criteria for SS [11]. The degree of lymphocytic infiltration in the specimens was graded from 0 to 4 using the scale reported by Chisholm and Mason [12]. All MD and SS patients in this study had strong lymphocytic infiltration (Chisholm and Mason scale: Grade 4).

13.3 Clinical Findings

The clinical and serological findings of MD patients are listed in Table 13.1. All cases showed bilateral swelling of the lacrimal or salivary glands over the course of at least 3 months (mean disease duration: 28.3 ± 54.2 months). Frequent complications of MD included AIP (seven cases), SC (four cases), asthma (three cases), and diabetes mellitus (three cases). As shown in Table 13.2, only 50 % of patients showed an objective decrease of saliva flow in both gum and Saxon tests. The mean value of the gum test from MD patients was 9.51 ± 4.86 mL/10 min (normal > 10 mL/10 min). These results suggest that the decrease of saliva flow was relatively mild in MD.

13.4 Serological Findings

As shown in Table 13.2, hypergammaglobulinemia was found in 18 of 19 MD cases (94.7 %). The serum IgG4 concentration was elevated in all 13 of the cases in which it was measured and the elevations were marked: a mean concentration of 1,091.5 ± 643.5 mg/dL (range: 380–2,290 mg/dL; normal < 105 mg/dL). In contrast, all cases were negative for anti-SS-A and anti-SS-B antibodies. Serum IgA and IgM levels were within normal limits. The serological findings in SS patients included high serum IgG concentration, 68.8 %; positive rate of ANA, 100.0 %; anti-SS-A antibodies, 88.9 %; and anti-SS-B antibodies, 50.0 %.

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Table 13.1 Clinical characteristics of MD patients

					Swollen glands						Complaint				Serological test							
No.	Age	Sex	Disease duration	Complications	LG	PG	SMG	SLG	PLG	LSG	Dry mouth	Dry eyes	Gum test (g/10 min)	Schirmer's test (Right side/Left side) (mm/5 min)	RF (IU/mL)	ANA	IgG (mg/dL)	IgG4 (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	Anti-SS-A	Anti-SS-B
1	70	M	6 months	Asthma	–	○	○	–	–	–	○	○	1	1/1	20>	–	2,010[a]	ND	390	222	–	–
2	48	F	3 months	Asthma	○	–	–	–	–	○	○	○	4	4/8	20>	1+[a]	2,401[a]	ND	161	85	–	–
3	31	F	1 years 6 months	AIP, DM	○	○	–	○	–	–	○	–	8	ND	20>	1+[a]	2,055[a]	ND	184	36	–	–
4	68	F	3 months	AIP, DM	○	–	○	○	–	–	○	–	13	ND	20>	–	2,827[a]	ND	290	91	–	–
5	52	F	3 years	Breast cancer	○	–	○	○	○	○	○	–	7.8	ND	20>	2+[a]	3,191[a]	ND	197	142	–	–
6	37	F	20 years	–	○	○	○	–	–	–	○	○	14	9/4	65[a]	3+[a]	1,443	ND	285	111	–	–
7	66	M	2 years	Prostate hypertrophy	–	–	○	○	–	–	–	–	16	ND	ND	ND	ND	ND	ND	ND	–	–
8	65	M	5 months	Hydronephrosis	–	–	○	–	–	○	–	–	12	ND	20>	–	3,142[a]	1,700[a]	138	59	–	–
9	57	F	6 months	AIP, SC	○	–	○	–	–	–	–	–	9.8	3/3	20>	–	1,842[a]	748[a]	187	63	–	–
10	61	F	3 months	AIP, SC	–	–	○	–	–	○	○	○	6.3	1/3	ND	–	2,891[a]	1,080[a]	187	63	–	–
11	64	F	1 years	AIP	–	○	○	–	–	–	○	○	ND	ND	61[a]	2+[a]	2,585[a]	456[a]	305	53	–	–
12	79	F	10 years	AIP, SC	–	○	○	–	–	–	○	○	ND	ND	20>	–	2,430[a]	896[a]	182	53	–	–
13	60	F	1 years	AIP, SC	–	–	○	–	–	–	○	○	11.6	ND	20>	–	2,087[a]	490[a]	276	74	–	–
14	70	F	5 years	–	–	○	–	○	○	○	○	○	11.1	ND	20>	–	5,408[a]	1,930[a]	148	89	–	–
15	76	F	4 months	DM	–	○	○	–	–	–	○	○	5.3	9/4	ND	–	2,381[a]	823[a]	187	52	–	–
16	79	F	3 months	–	–	○	○	–	–	–	–	–	ND	ND	20>	–	2,608[a]	896[a]	132	68	–	–
17	46	F	6 months	Chronic thyroiditis	○	–	○	○	○	○	○	–	8.1	ND	20>	–	2,200[a]	769[a]	244	78	–	–
18	66	M	5 years	–	○	–	○	–	–	–	–	–	17.2	3/3	20>	–	2,121[a]	344[a]	167	45	–	–
19	61	M	3 years	Pulmonary nodules	○	○	○	○	–	–	–	–	6.8	1/3	20>	–	7,603[a]	2,290[a]	121	62	–	–
20	61	M	2 years	Asthma	○	–	–	○	–	–	–	–	12.5	ND	20>	–	2,728[a]	590[a]	233	54	–	–

AIP autoimmune pancreatitis, *SC* sclerosing cholangitis, *DM* diabetes mellitus, *LG* lacrimal gland, *PG* parotid gland, *SMG* submandibular gland, *SLG* sublingual gland, *PLG* palatal gland, *LSG* labial salivary gland, *ND* not done

– Negative

[a]Higher than normal values

○Presence of Swelling

Table 13.2 Comparison of clinical and laboratory findings between MD and SS

	SS	MD
Decreased salivary flow by gum test	100.0 % (18/18)*	52.9 % (9/17)
<mean ± S.D; mL/10 min>	<4.9 ± 2.5>	<9.7 ± 4.3**>
Glandular swelling	11.1 % (2/18)	100.0 % (20/20)*
Sialography (Rubin and Holt)		
Stage 0	0.0 % (0/18)	100.0 % (20/20)
Stage I	5.6 % (1/18)	0.0 % (0/20)
Stage II	44.4 % (8/18)	0.0 % (0/20)
Stage III	50.0 % (9/18)	0.0 % (0/20)
Infiltration of IgG4 + plasma cells[a]	0.0 % (0/18)	100.0 % (20/20)*
Elevation of serum IgG	68.8 % (11/16)	94.7 % (18/19)
Detection of IgG4	ND	100.0 % (13/13)
ANA	100.0 % (16/16)*	26.3 % (5/19)
Anti-SS-A	88.9 % (16/18)*	0.0 % (0/20)
Anti-SS-B	50.0 % (9/18)*	0.0 % (0/20)

*$p < 0.05$ (Fisher's test)
**$p < 0.05$ (Student's t-test)
[a]IgG4+ plasma cells/IgG + plasma cells >50 %

13.5 Imaging Findings of Salivary Glands

Nineteen of the 20 MD cases showed normal parotid gland sialograms (Fig. 13.1), with the exception being one case with ductal dilation. No MD patients showed punctate or globular patterns (Table 13.2). In addition, sialography of the submandibular glands with swelling did not show the "apple-tree sign," which is characteristic of SS, although parenchymal defects in glandular images were observed in accordance with the nodal areas (Fig. 13.1, SMG).

On US, the nodal area in the submandibular glands of patients with MD showed hypoechoic areas with relatively high vascularization (Fig. 13.2). The adjacent submandibular gland parenchyma, however, showed a normal echo intensity level and homogeneity. In contrast, SS showed multiple hyperechoic lines and/or spots, with advanced cases showing a netlike pattern.

On CT, swollen salivary glands in MD showed features of chronic inflammation, namely, marked vascularization and enhancement with contrast (Fig. 13.3). By comparison, a salt and pepper pattern caused by fatty degeneration was frequently seen in SS.

Our previous reports suggest that sonography could be used to distinguish MD from SS [13, 14]. In addition, sialography and CT are also important in both the differentiation from SS and evaluation of individual lesions (identification of the swollen site, serial changes). PET has been reported to be useful in the evaluation of the systemic distribution of lesions [15]. The use of this imaging modality in IgG4-RD is reviewed elsewhere in this book.

13.6 Histopathological Findings of Salivary Glands

MD showed lymphocytic infiltration that was not confined to the periductal regions, hyperplastic germinal centers (GCs), and mild destruction of the acini. In contrast, SS was characterized by periductal lymphocytic infiltration with atrophy or severe destruction of the acini (Fig. 13.4). In the immunohistochemical findings, MD showed selective infiltration of IgG4+ plasma cells around GCs enriched with B cells (Fig. 13.5).

Our previous immunological analyses of MD patients focused on helper T (Th)-cell infiltration into the salivary glands. We previously reported that peripheral CD4+ T cells from IgG4-RD patients revealed deviation of Th1/Th2 balance to Th2 and elevated expression of Th2-type cytokines [16], suggesting that IgG4-RD has a Th2-predominant phenotype [17]. We also demonstrated a close association between the expression of IL-4 and IL-10 and IgG4 production in the labial salivary glands (LSGs) in IgG4-RD [18–20].

13.7 Therapeutic Effects

Oral glucocorticoid administration is typically the first line of therapy for MD. The starting dose of prednisolone was 0.6 mg/kg/day for 1 month and decreased to 5–10 mg/day every 2 weeks. However, no consensus approach to MD has been established, and further studies are thus required. As noted by others [21], glucocorticoid treatment resulted in a rapid decrease or disappearance of gland swelling, and both total IgG and IgG4 levels declined significantly (Fig. 13.6). Salivary function was either improved or normal after glucocorticoid therapy (Fig. 13.7).

A variety of mechanisms may account for the clinical improvement in MD following glucocorticoid treatment. First, lymphocyte infiltration into the salivary glands and lymphocyte function are suppressed by glucocorticoids. Second, in the setting of glucocorticoid treatment, the ability of stem cells in the ductal epithelium to promote acinar cell regeneration may be augmented. And third, probably as a result of the other two processes, salivary secretion by the acini is increased substantially. The ability of the salivary glands to respond to glucocorticoid treatment may decrease with time. Periods of longer disease duration are often associated with greater salivary gland fibrosis and the loss of acinar cells' ability to regenerate.

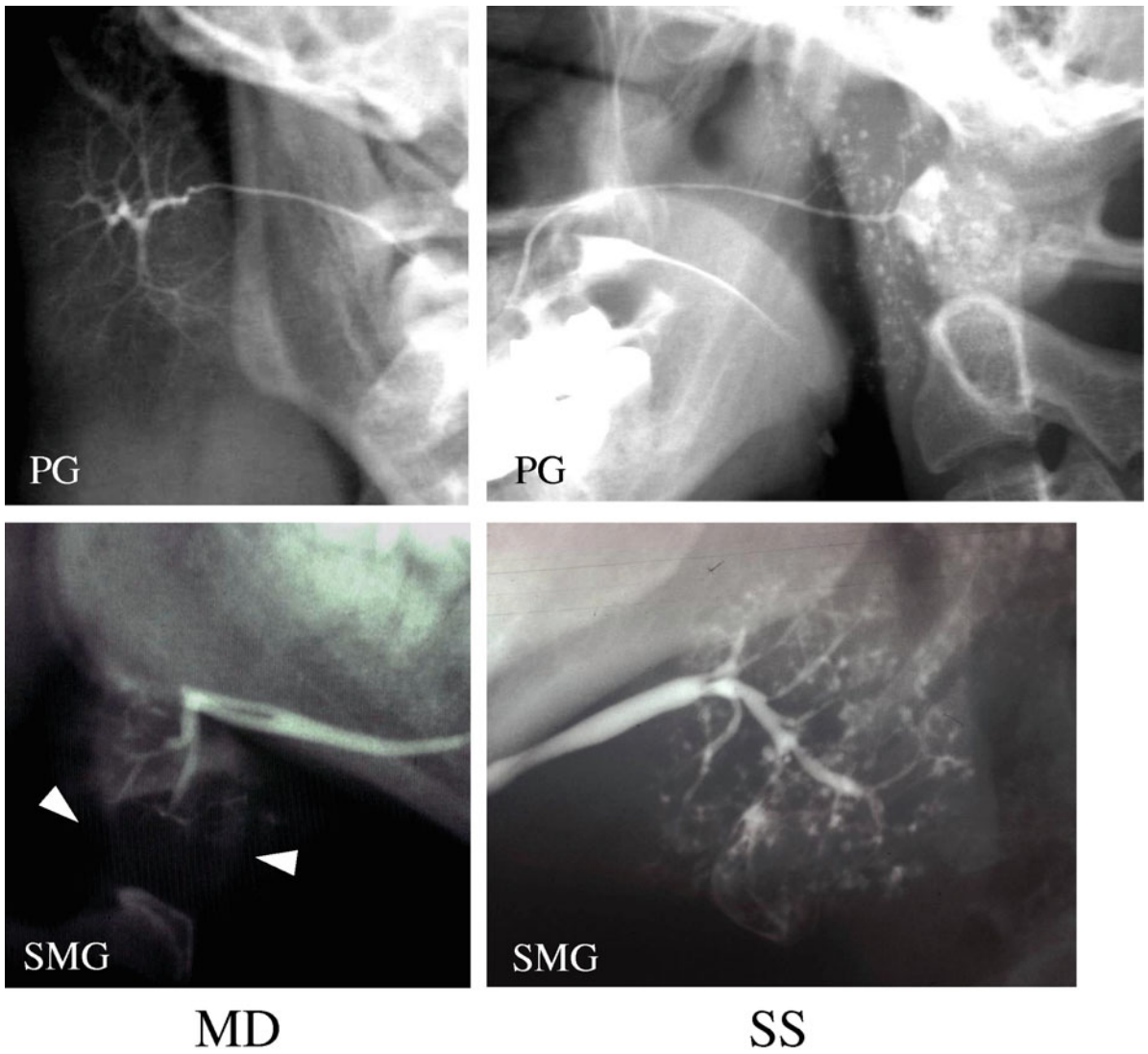


Fig. 13.1 Sialographic findings of MD and SS

13.8 Concluding Remarks

MD, a part of the spectrum IgG4-RD, can be distinguished readily from SS [6, 8, 22]. The results of the present study are consistent with the report of Yamamoto et al. [2, 21] and further clarify the differences between the two diseases.

MD can be diagnosed quickly with the aid of clinical data such as serum IgG4 concentrations and the immunohistochemical finding of substantial numbers of IgG4-positive cells in the salivary glands (combined with the requisite histology; see other chapters). Imaging studies such as sialography, sonography, and CT can also be helpful in distinguishing MD from other conditions. Early diagnosis and treatment of MD are important for the recovery of salivary secretion function.

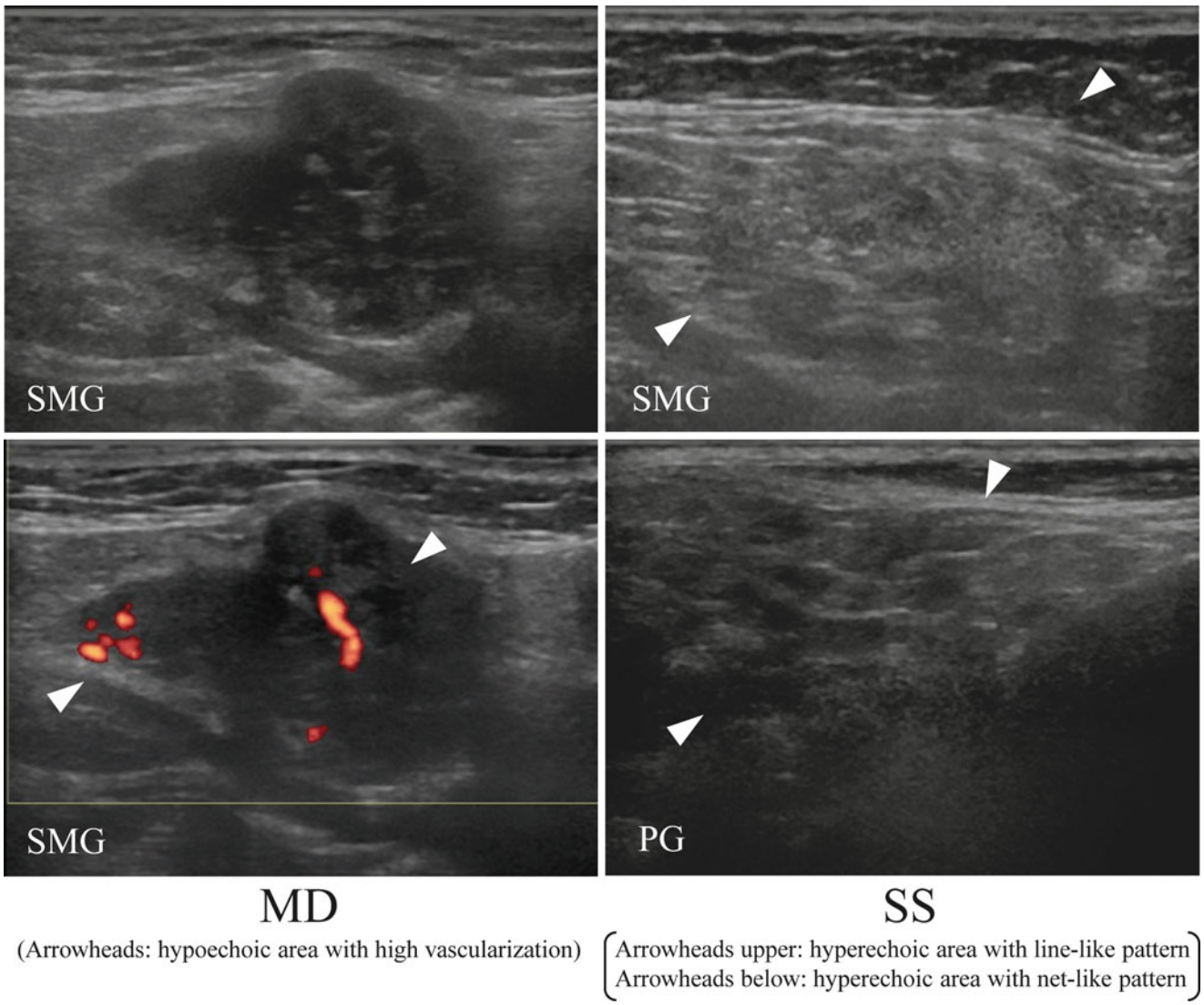


Fig. 13.2 Sonographic findings of MD and SS

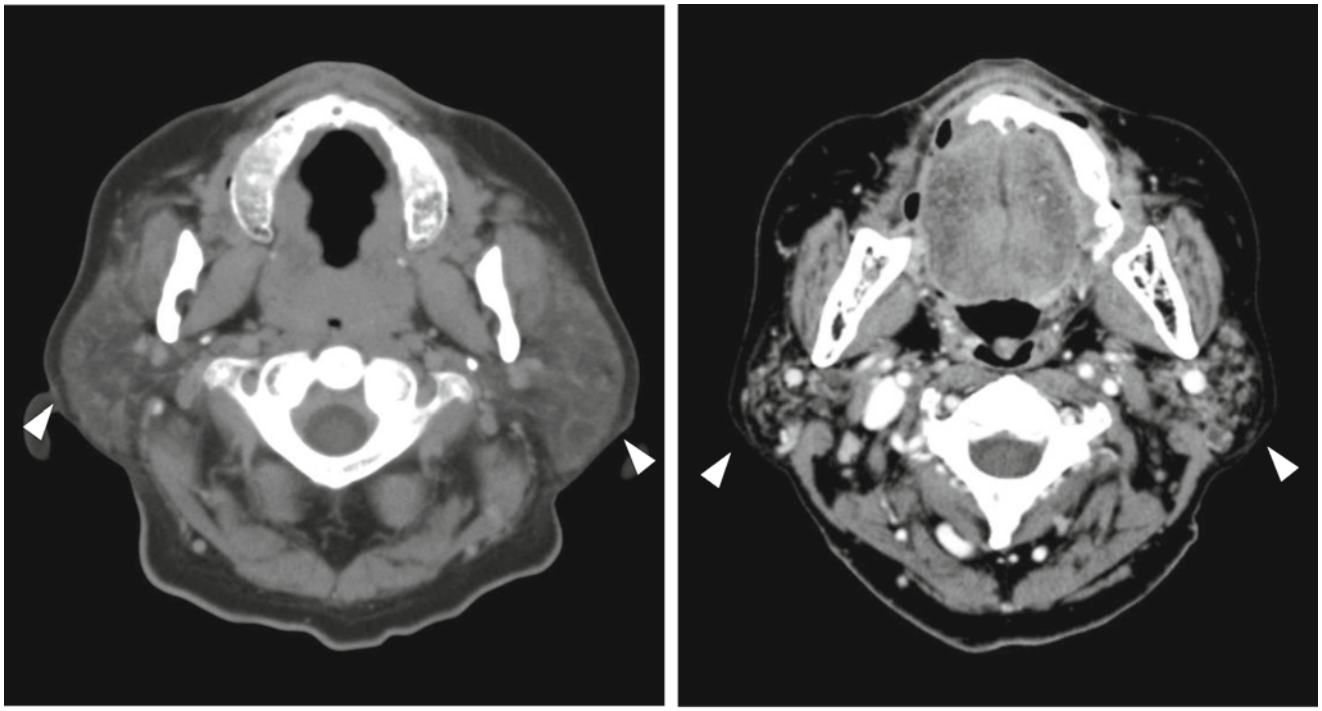


Fig. 13.3 CT findings of MD and SS

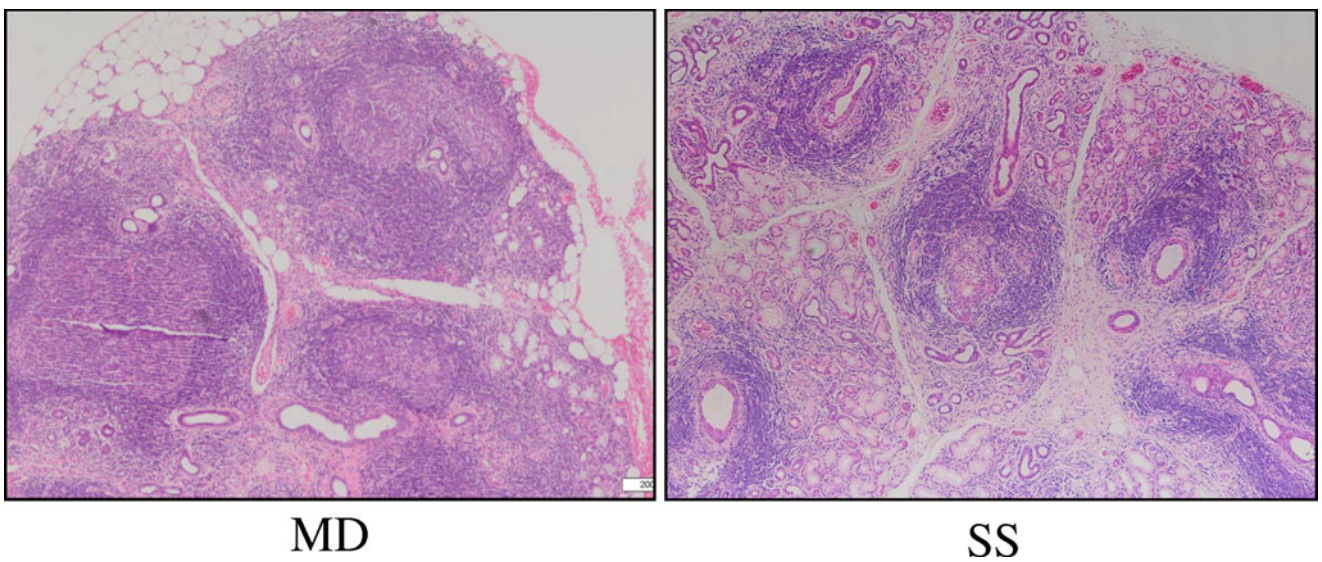


Fig. 13.4 Histological findings in the labial salivary glands of MD and SS

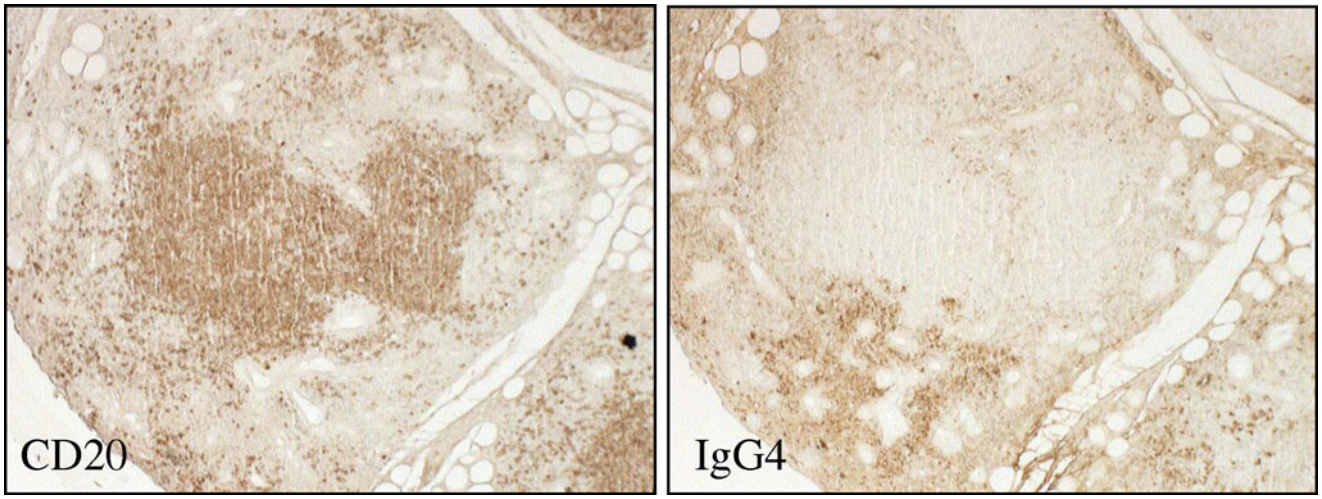
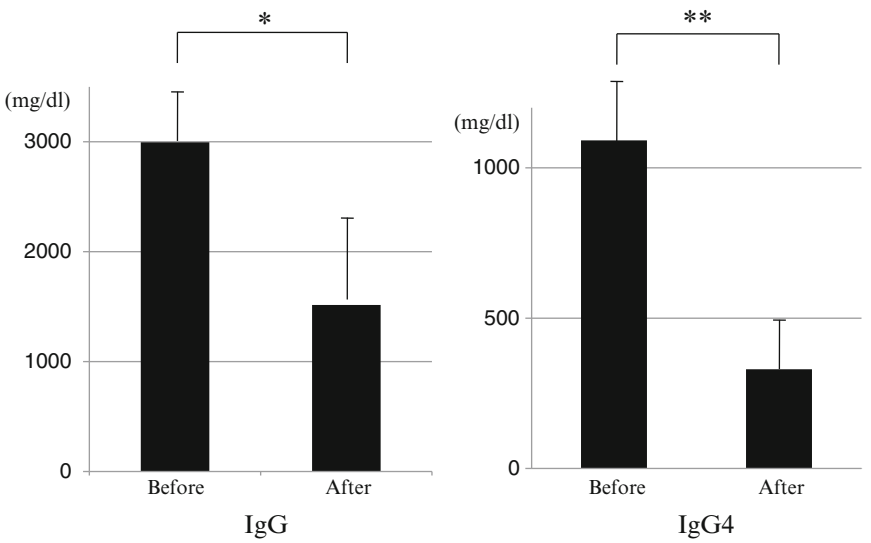
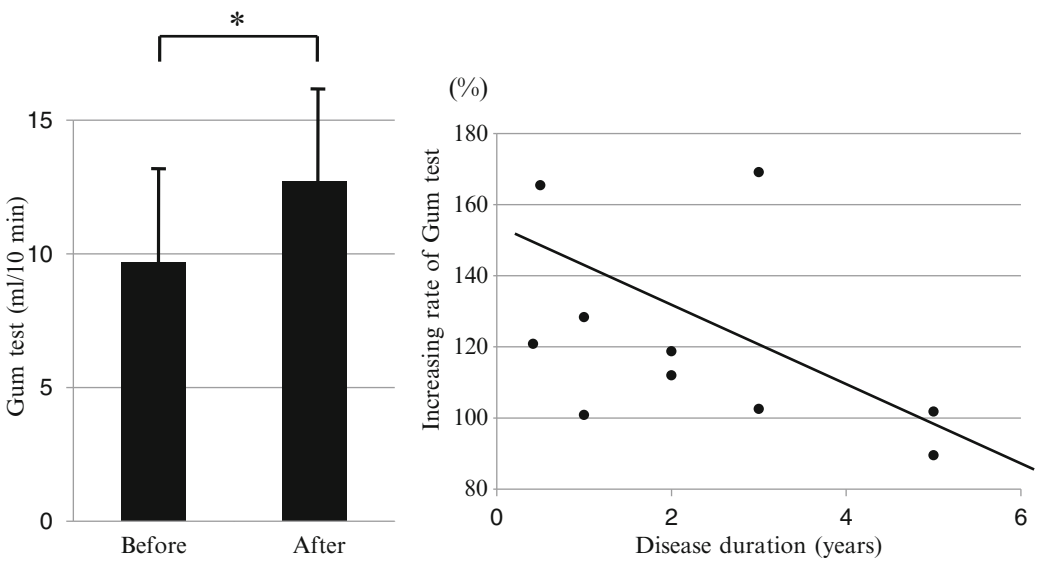


Fig. 13.5 Expression of B cells and IgG4-positive plasma cells in the labial salivary glands in MD

Fig. 13.6 Changes in total serum IgG and IgG4 after glucocorticoid treatment in MD



Student's *t* test : * $p<0.05$, ** $p<0.01$



Pearson's product-moment correlation: $p<0.05$, r = 0.64

Fig. 13.7 Changes in salivary function after glucocorticoid treatment in MD

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Lung Lesions

14

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14.1 Introductory Remarks

A variety of pulmonary lesions have been reported in IgG4-RD in the past several years, but many uncertainties remain regarding their pathophysiology and diagnosis. Such lung lesions had originally been reconized as interstinal pneumonia and inflammatory pseudotumor in patients with autoimmune pancreatitis or "Mikulicz's disease" [1–7]. Knowledge of the wide spectrum of the pulmonary phenotype in IgG4-RD continues to expand [8]. The radiologic features of IgG4-related lung disease rival the clinical findings in their diversity.

At least two factors contributed to the delay in recognition of IgG4-related lung disease in the past. First, mucosal lesions in the lung appear to be uncommon. And second, approaches to the diagnosis based upon transbronchial lung biopsy (TBLB) have a low yield. Histopathological diagnosis from lung tissue is essential when no other organ involvement is evident. In some cases, a definite diagnosis can be obtained only via a video-assisted thoracoscopy (VATS) procedure.

IgG4-RD occurs principally in middle-aged and elderly men across the full spectrum of organ involvement. Most cases are associated with elevated serum IgG4 concentrations and good responses to glucocorticoid therapy. Lesions show lymphoplasmacytic cell infiltration and fibrosis, and the infiltrating plasma cells demonstrate disproportionate staining for IgG4. Clinicians from every specialty must become familiar with the clinical and imaging findings specific not only to their individual organ of interest but also of the features that are common to the broader disease as a whole. In this chapter, we outline the lung lesions of IgG4-RD. Our focus is primarily on the imaging findings of IgG4-related lung disease, but where appropriate we also indicate other conditions in the differential diagnosis that must be excluded before settling upon the diagnosis of IgG4-RD.

14.2 What Lesions Occur Where?

Following careful radiopathologic correlation of surgical biopsies, we observed that four major types of IgG4-related lung disease are readily apparent. These types include (1) solid, nodular lesions; (2) rounded ground-glass opacities (GGO); (3) alveolar-interstitial infiltrates; and (4) a bronchovascular pattern [9]. We also have observed that the inflammatory cell infiltration and fibrosis occur mainly within the connective tissues of the lung—i.e., the interstitium—namely, the bronchovascular bundle, interlobular septa, and the alveolar interstitium [9, 10].

The distribution of disease along the bronchovascular bundle coincides generally with the intrapulmonary distribution of the lymphatic system. The bronchial mucosal surface is typically spared, despite the fact that severe lesions can develop within the bronchovascular bundle interstitium, bronchus-associated glands, interlobular septa, and alveolar

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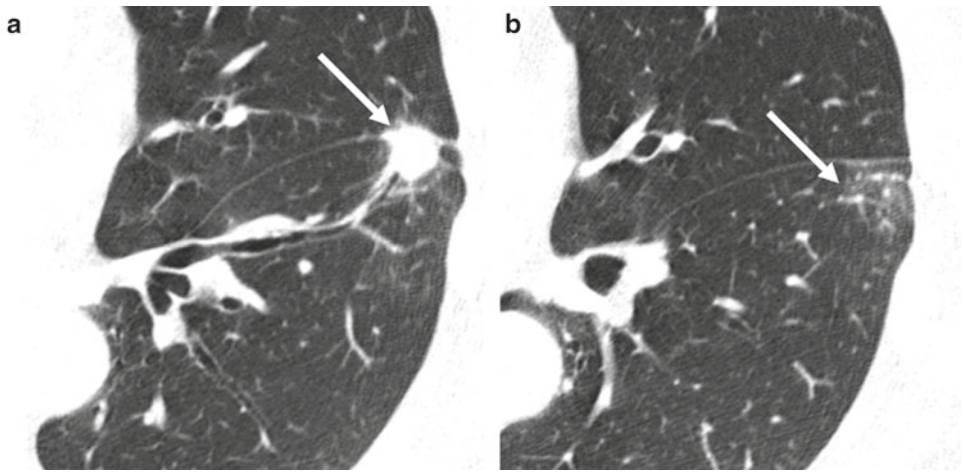

Fig. 14.1 In the left lower lobe, a spiculated nodule is demonstrated (**a**: *arrow*). Perinodularly patchy ground-glass opacities are seen (**b**: *arrow*)

interstitium. The CT correlates of this pathology are ground-glass opacities and thickening of the bronchovascular bundles and interlobular septa. Lesions occurring around the distal bronchi are sometimes recognized as small, centrilobular nodules.

The alveolar lumen can also be affected by the characteristic inflammatory cell infiltrates and fibrosis, and mass lesions develop in some cases. Lesions extending into the alveolar lumen are recognized on CT as a mass or infiltrative shadow. In about one half of cases, mediastinal lymph node swelling is observed, but central necrosis and fusion of lymph nodes are both atypical of IgG4-RD.

Most patients with pulmonary IgG4-RD present with a mixture of these findings, but it is possible to classify them according to the most prominent of these into one of these four major types. Below, we outline the clinical and radiologic features of each type and also discuss the differential diagnosis of each category.

14.2.1 Solid Nodular Type

Solid, nodular lesions are not limited to the lung interstitium, and when marked cell infiltration and fibrosis occur in the alveolar lumen, a large nodule or mass is recognized on CT. This corresponds to the "inflammatory pseudotumor" often reported in the literature. In some cases, these nodules are accompanied by inflammatory cell infiltration and fibrosis along the edge of the alveolar interstitium. On CT, these appear spicule-like and require differentiation from primary lung cancer (Figs.14.1a and 14.7a). In the surrounding tissues, bronchovascular bundle swelling and patchy ground-glass opacities are sometimes observed, marking features that are atypical of lung cancer (Fig. 14.1b). Although the presence of bronchovascular bundle thickening and ground-glass opacities is helpful in raising the possibility of IgG4-RD, cases generally require histopathological confirmation.

14.2.2 Rounded GGO Type

Ground-glass opacities are a common CT finding in IgG4-RD. These are typically focal and have a rounded shape (Fig. 14.2). Distinction of this lesion from well-differentiated adenocarcinoma and bronchial alveolar epithelial cancer by diagnostic imaging alone is not possible with certainty, and histological diagnosis via a VATS procedure is usually required.

14.2.3 Alveolar-Interstitial Type

"Interstitial pneumonia" was once recognized as an extrapancreatic complication of autoimmune pancreatitis [1]. In fact, such lesions were simply the pulmonary manifestations of IgG4-RD that is now referred to as the alveolar-interstitial type. Such lesions are characterized by ground-glass opacities on CT, but these lesions differ radiologically from the rounded ground-glass opacities described above and may be distributed widely. Fibrotic changes that ensue can lead to cyst-like dilatation of the alveolar lumen. These cysts are recognized on imaging as thick, ringlike structures that resemble honeycomb lung, but the lesions generally comprise a less severe form of honeycombing than that which accompanies usual interstitial pneumonia/idiopathic pulmonary fibrosis. Some cases show bronchovascular bundle thickening and bronchial dilatation due to tractive changes. On CT, findings of nonspecific interstitial pneumonia are frequently shown (Fig. 14.3).

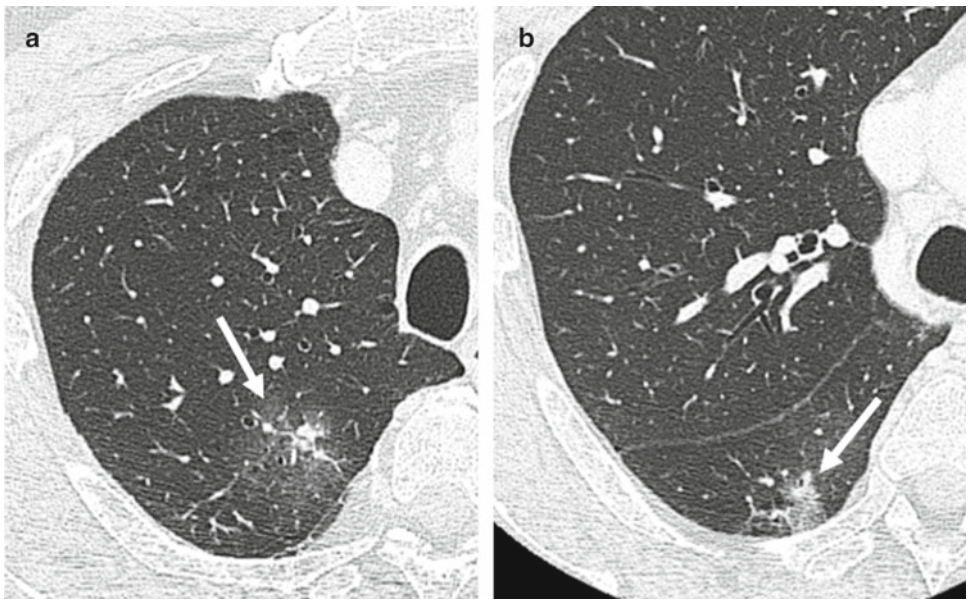

Fig. 14.2 In the right lung field, multiple round, localized ground-glass opacities are present (**a**, **b**: *arrow*)

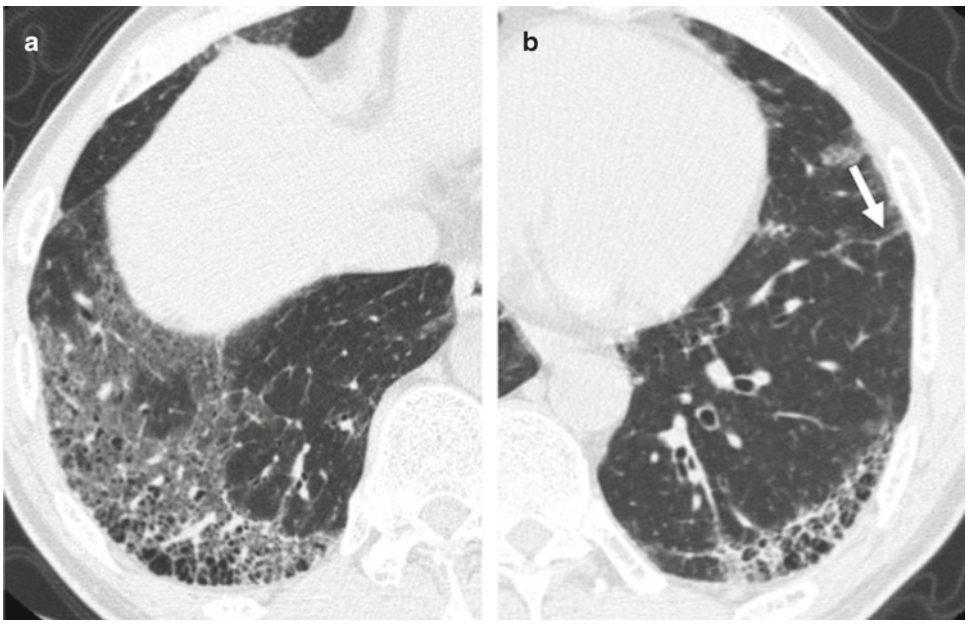

Fig. 14.3 In the bilateral lower lobe subpleura, a cluster of ringlike shadows is found. Also in the right lung field, patchy ground-glass opacities are seen. The interlobular septal wall is also thickened in parts (**b**: *arrow*)

14.2.4 Bronchovascular Type

The most typical picture of IgG4-related lung disease is perhaps the bronchovascular type. Its major CT findings are thickening of the bronchovascular bundle and interlobular septa, which reflects cellular infiltration and fibrosis (Figs. 14.4 and 14.5). Ground-glass opacities and small nodules are sometimes intermingled with these changes to varying degrees. The presence of small nodules reflects inflammatory cell infiltration around the distal bronchioles. These nodules usually have a centrilobular distribution. Cyst formation and pleural effusions are rare.

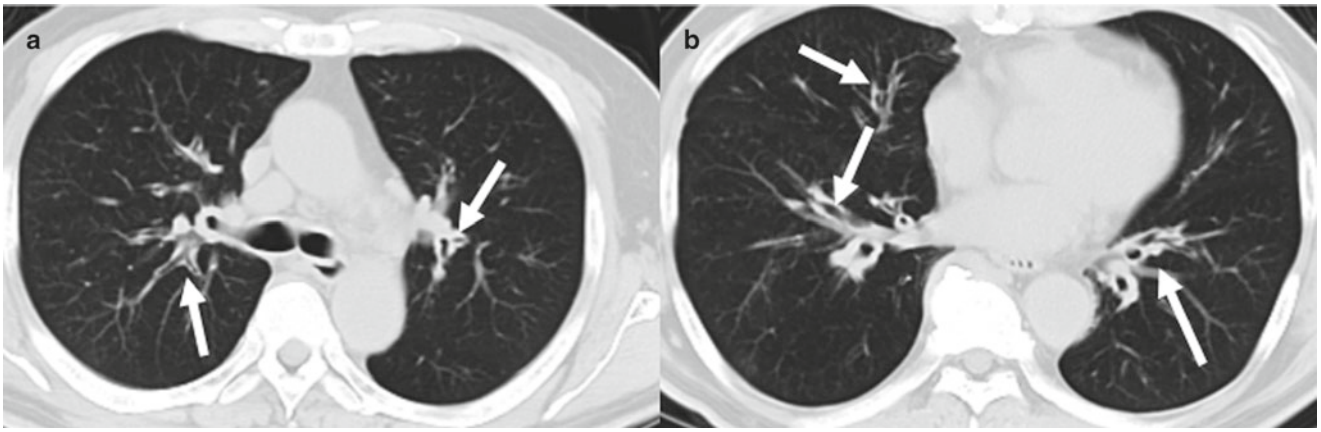

Fig. 14.4 Bilateral bronchovascular bundle swelling is found

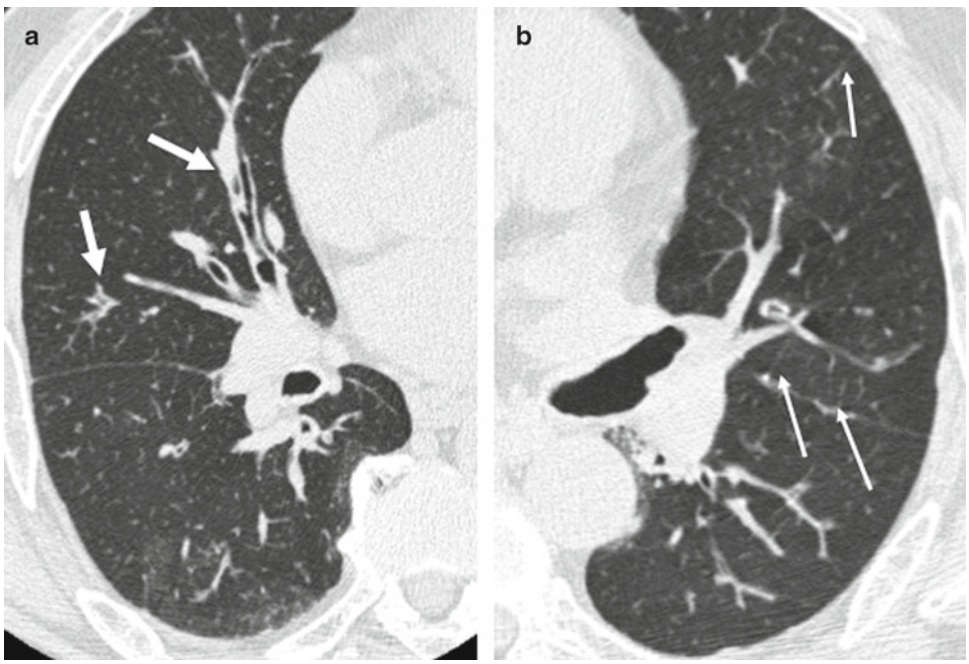

Fig. 14.5 Bronchovascular bundle swelling is found (**a**: *arrows*). Interlobular septal thickening is also seen (**b**: *arrows*)

The bronchovascular type of IgG4-related pulmonary disease must be distinguished from multicentric Castleman disease (MCD), lymphomatoid granulomatosis, lymphangiosis carcinomatosa, and sarcoidosis.

14.3 What Other Lesions Occur?

Cases with radiologic findings that suggest organizing pneumonia have been reported [6, 7]. These consist of dense, relatively well-defined shadows associated with ground-glass opacities (Fig. 14.6). In these lesions, a marked inflammatory cell infiltrate affects not only the lung interstitium but also extends to the alveolar lumen. These lesions have also been reported to form in the pleura [10]. Clinicians must be aware that this may be reflected as pleural thickening on imaging (Fig. 14.7).

14.4 Diagnosing IgG4-Related Lung Lesions

We have outlined the imaging findings of IgG4-related lung lesions in this chapter, but in clinical practice these lesions are frequently more difficult to diagnose than those in other organs. We surmise that the main reasons for this are:

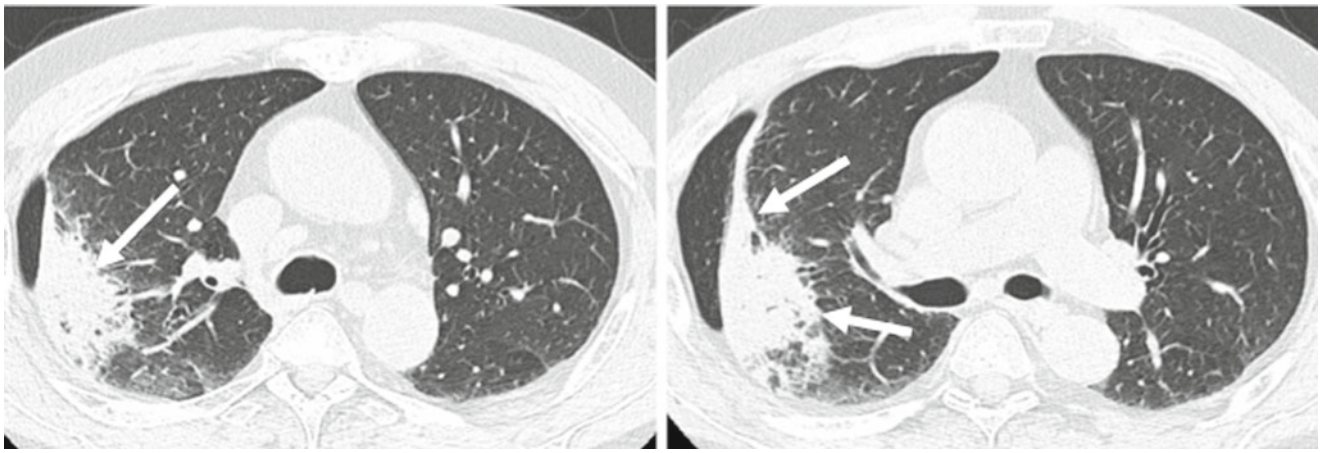

Fig. 14.6 A dense shadow is found in the right upper lobe around which patchy ground-glass opacities are seen

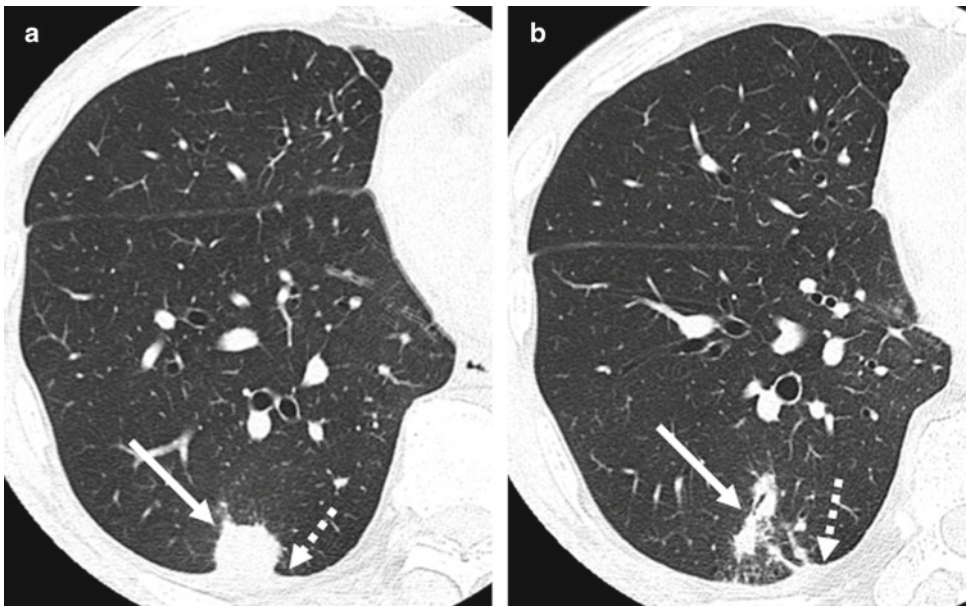

Fig. 14.7 A spiculated nodule is noted in the right lower lobe (**a**: *arrow*). Bronchovascular bundle swelling is also seen (**b**: *arrow*), associated with bilateral pleural thickening (**a**: *broken line*)

(1) the clinical spectrum is wide, with signs of respiratory distress like cough and breathlessness prominent in some cases, while others are asymptomatic when detected; (2) the imaging findings are similarly diverse; and (3) adequate amounts of tissue are difficult to procure by TBLB.

In cases associated with IgG4-RD in other organs, one can reasonably suspect IgG4-RD on the basis of guilt by association, and to diagnose lung disease it is important that appropriate investigations be undertaken to determine the presence/absence of multiorgan lesions. The majority of cases of IgG4-related lung disease have extra-pulmonary lesions. In cases with pathology limited to the lung, most of the lesions are of the solid nodular type and are diagnosed incidentally following a diagnostic evaluation for suspected cancer. Further refinement of the diagnostic approach to cases with lung lesions alone is required.

At present, it is thought possible to suspect alveolar-interstitial-type and bronchovascular-type lesions from the imaging findings, but in these cases as well, as already noted, some other diseases require differentiation, and a

comprehensive diagnosis must be made taking into consideration current serum IgG4 concentration, determination retrospectively of the presence/absence of other organ involvement, and histology.

To facilitate collection of adequate samples for a tissue diagnosis, multiple biopsies from the same sites by TBLB or biopsy by VATS is frequently necessary. In the setting of solid nodular lesions and rounded ground-glass opacities, IgG4-RD should not be diagnosed hastily even when the presence of lesions can be confirmed in other organs, and it is absolutely necessary to exclude malignancy by histological diagnosis beforehand. Other investigators and we have encountered cases in which autoimmune pancreatitis or IgG4-related lung lesions were complicated by lung cancer [10]. Whenever IgG4-RD is suspected, particular care must be given to the exclusion of cancer in the diagnostic process.

14.5 Concluding Remarks

We have outlined the lung lesions of IgG4-related disease, focusing mainly on their radiologic aspects. Recently IgG4-RD has attracted increasing interest, and conversely the number of cases difficult to diagnose has also been rising. We consider that IgG4-related lung lesions occur mainly along the distribution of the lung connective tissue (lymph tract). And even though the imaging findings of lung lesions are diverse, this does not mean that any lesion can be attributed to an IgG4-related cause.

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Kidney and Urinary Tract Lesions

15

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15.1 Introductory Remarks

The renal lesions of IgG4-RD are relatively easy to biopsy and therefore lend themselves well to histological examination. As a result, their clinical [1–6] and pathological characteristics [4–7] and imaging findings [8, 9] have been clarified with some thoroughness compared to other organs affected by IgG4-RD, and diagnostic strategies have been devised in both Japan and Western countries [10, 11].

Renal parenchymal lesions are characterized by tubulointerstitial nephritis (TIN) accompanied by lymphoplasmacytic cell infiltration and fibrosis in the peritubular interstitium. The infiltrating plasmacytic cells show a high rate of IgG4 positivity, and this is a key component of the diagnosis. Lesions also occur in the ureteropelvic wall and many cases in the past have been categorized as part of the spectrum of retroperitoneal fibrosis. However, because of the difficulty in obtaining a biopsy from the retroperitoneum, the relationships between ureteropelvic lesions and retroperitoneal fibrosis have not been examined fully. The question of whether the hydronephrosis associated with ureteral involvement in periaortic lesions and retroperitoneal fibrosis should be included in the category of renal pelvis/ureter lesions at all also remains open to discussion. Thus, in contrast to the renal parenchymal disease, several issues pertaining to ureteropelvic involvement require elucidation.

At present, when specialists in various fields are preparing detailed diagnostic criteria and devising algorithms for the diagnosis of IgG4-related lesions in individual organs, the question of whether or not the renal and urinary tract lesions should be studied separately needs to be considered. The authors, based on our experience with IgG4-RD as nephrologists or diagnostic radiologists, consider that the lesions occurring within the renal parenchyma, the renal pelvis wall, and the ureter itself should be recognized as the renal and urinary tract lesions of IgG4-RD. In other words, the proximal and distal tubules, collecting ducts, renal pelvis and calices, and ureter should be regarded as one continuous luminal structure. Moreover, the lesions occurring within the walls of these structures and the interstitium that surrounds them should be considered the renal and urinary tract manifestations of IgG4-RD. Finally, these lesions should be categorized as distinct from hydronephrosis due to involvement of periarterial lesions and retroperitoneal fibrosis.

We believe that this classification of lesions in the abdomen and retroperitoneum leads to a straightforward understanding that the clinical signs and imaging findings of renal and urinary tract lesions differ according to the sites affected. In this chapter we outline the imaging findings and diseases that require differentiation from lesions that occur at various sites in the urinary tract.

15.1.1 Clinical Characteristics

Urinary tract lesions occur most frequently in middle-aged and elderly men as in other organ lesions. This disease epidemiology is highly consistent with the age and gender patterns observed across the clinical spectrum of organ involvement. Urinary tract lesions are usually associated with elevated serum IgG4 concentrations and marked responsiveness to glucocorticoids. Urinary β2-microglobulin (β2-MG) values are often elevated, reflecting the presence of tubular atrophy

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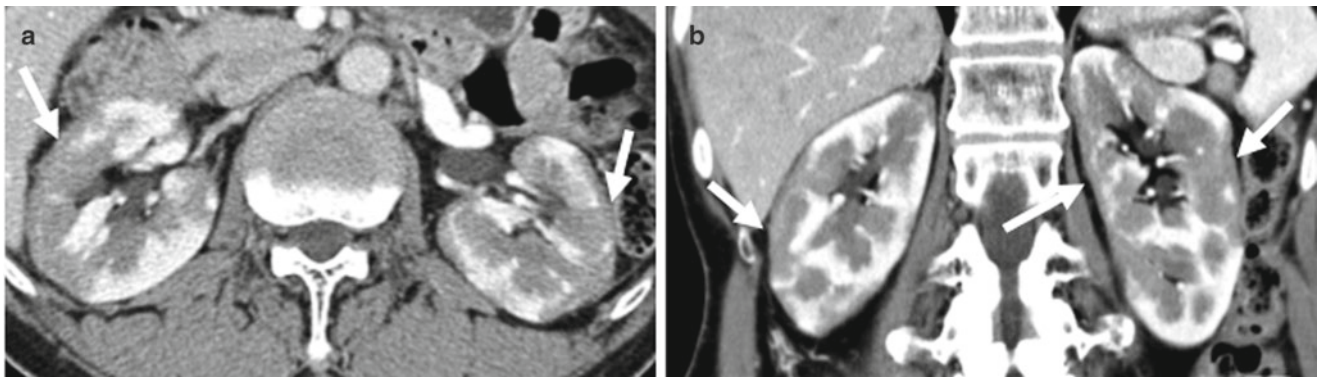

Fig. 15.1 Multiple poorly enhanced areas are seen mainly in the bilateral renal cortices (**a**, **b**: *arrows*)

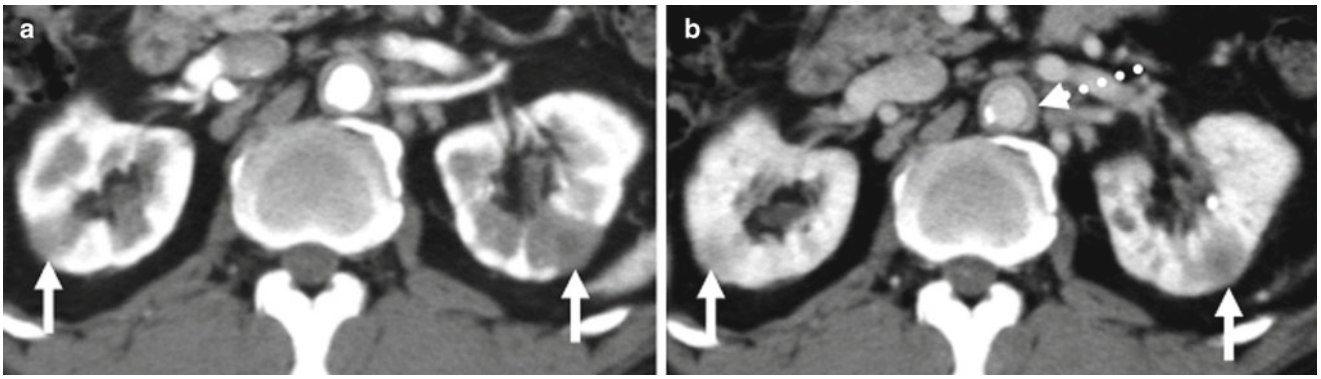

Fig. 15.2 Multiple poorly enhanced areas are seen in the bilateral kidneys. A few lesions are also noted in the medulla (**a**, **b**: *arrows*). Periaortic lesion is also demonstrated (**b**: *dashed arrow*)

and destruction of tubules by interstitial fibrosis. Since, almost all filtered β2-MG is usually reabsorbed at the proximal renal tubules, any dysfunction or destruction of the proximal renal tubules leads to elevation of urinary β2-MG. In fact, increased urinary β2-MG concentrations were noted in 83 % of patients with IgG4-related TIN in a previous small study [12].

Creatinine clearance is well preserved in many cases of IgG4-related renal disease, but severe renal dysfunction can ensue. The tendency of IgG4-RD to form lesions in multiple organs in a metachronous fashion is also observed in renal urinary tract lesions. Multi-organ involvement is the rule when renal lesions are present. In the setting of renal lesions that are consistent with IgG4-RD, all radiologic studies (including older ones) should be reviewed in order to detect or exclude extrarenal disease that might be relevant to the diagnosis and management of the patient.

15.1.2 Renal Parenchymal Lesions

Renal lesions that can be imaged radiologically with the current modalities correspond to lesions around the proximal and distal tubules and the collecting ducts. In the usual imaging protocol for contrast-enhanced CT of the kidney after plain CT, the cortical phase images are obtained 30–45 s after rapid injection of the contrast agent. The renal parenchymal phase images are obtained after 90–120 s and when necessary excretory phase images are obtained after 180–300 s.

Fibrosis with varying degrees of severity occurs in and around the inflammatory lesions of IgG4-related renal disease (and IgG4-RD, in general). Affected parts of the kidney are recognized as low-density areas in the cortical and parenchymal phases (Figs. 15.1 and 15.2). The inflammation can extend throughout the renal parenchyma to the capsule. On contrast-enhanced CT, inflammation is sometimes identified as a rim-like structure along the renal parenchyma, corresponding to the well-known capsule-like rim in autoimmune pancreatitis (Fig. 15.3).

The typical imaging findings in IgG4-related renal disease consist of multiple patchy, wedge- or round-shaped areas that are distributed predominantly in the renal cortices and enhance poorly [8, 9]. Renal parenchymal lesions involve the renal cortex most frequently. These lesions are identified as low-density areas in the cortical phase.

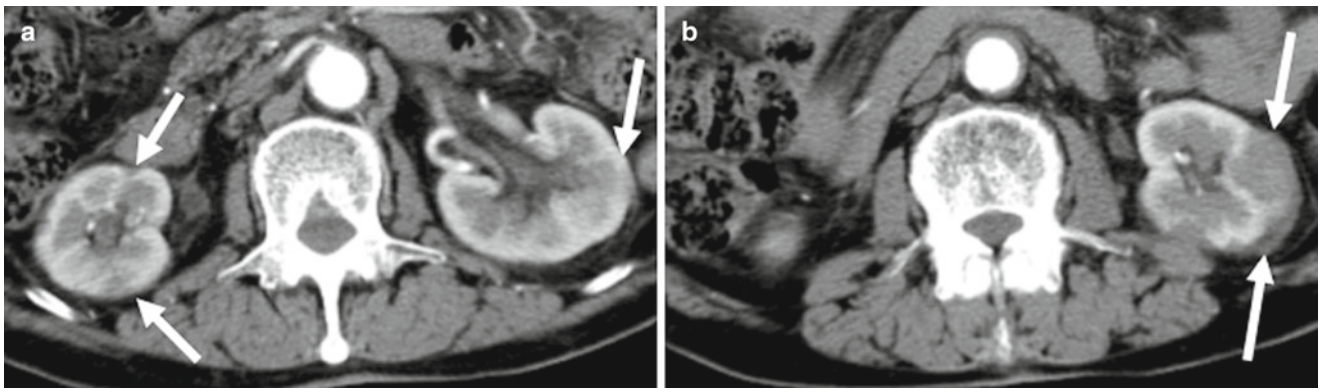

Fig. 15.3 Poorly enhanced areas are seen in the bilateral renal cortices (**a**: *arrows*). A rim-like lesion is also seen along part of the capsule (**b**: *arrows*)

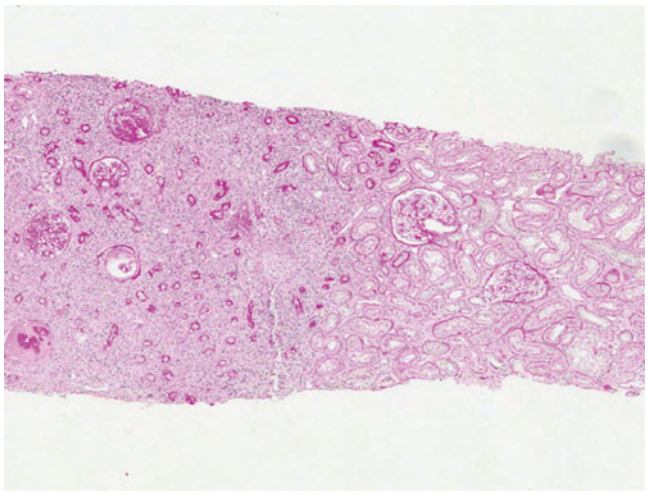

Fig. 15.4 Lesions are patchily distributed in the renal parenchyma. The border with unaffected portions is clearly demarcated

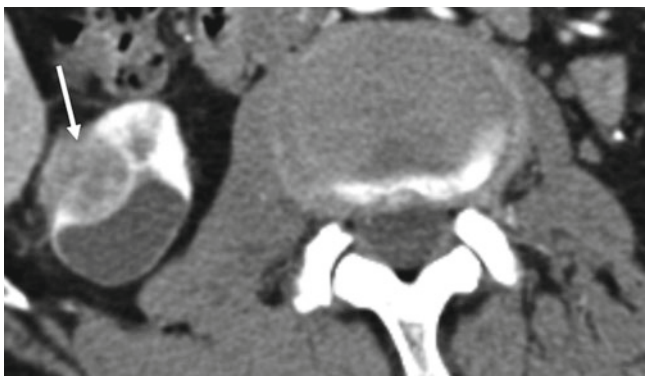

Fig. 15.5 A solitary mass is found in the right kidney (*arrow*). It was diagnosed by biopsy as an IgG4-related lesion

Lesions at the collecting duct level are identified in a similar fashion—as low-density areas in the renal parenchymal phase. Renal involvement in IgG4-RD is typically patchy, with clearly demarcated borders between affected and unaffected portions (Fig. 15.4). Accordingly, renal lesions on contrast CT are demonstrated to be well-demarcated, patchy, wedge- or round-shaped low-density areas. Small lesions are prone to the partial volume phenomenon, in which the lesion and the unaffected adjacent portion are included on the same slice of the actual image. When this occurs, both sites are depicted as intermediate density and the true lesion appears to be poorly demarcated.

The radiologic differential diagnosis of IgG4-related kidney disease includes pyelonephritis, renal infarction, and vasculitis. However, all of these conditions can usually be differentiated from IgG4-RD on the basis of patient demographics, clinical symptoms and signs, and the findings on urinalysis and other laboratory studies. Pyelonephritis is typically associated with wedge-shaped areas that peak in the renal calices and enhance poorly. Few cases of pyelonephritis have radiologic findings focused in the cortices. Renal infarction and vasculitis usually show low-density, wedge-shaped lesions that correspond to specific vascular territories. Thus, in practice, when the clinical and laboratory features are considered along with the radiologic findings, differentiation of these disorders is seldom difficult.

Two imaging findings exemplify the distinctive morphology of renal parenchymal lesions in IgG4-RD: (1) single focal lesions and (2) swelling and decreasing enhancement of the entire renal parenchyma. These are discussed separately.

15.1.2.1 Single Focal Lesions

Single focal lesions limited to one kidney are seen in some cases (Fig. 15.5). Cellular infiltration and fibrosis develop focally and because of associated swelling, this lesion is recognized on CT as a hypovascular renal mass. This finding is potentially difficult to distinguish from renal cancer, but because renal cancers tend to be hypervascular, the differentiation is not problematic in the presence of lesions typical of

IgG4-RD in other organs. Lymphoma, sarcoidosis, and granulomatosis with polyangiitis (formerly Wegener's) are also in the differential diagnosis of such single focal renal masses, and both serological examinations and biopsies may be required to exclude these conditions.

15.1.2.2 Swelling and Decreasing Enhancement of the Entire Renal Parenchyma

Some patients with IgG4-related renal disease have lesions that are not distributed patchily but rather involve the entire kidney. Severe renal dysfunction often develops in these cases, but in some, despite imaging findings that suggest the possibility of marked kidney injury, the creatinine clearance is well preserved. In such cases, the entire renal parenchyma is swollen, and there is decreased enhancement of the entire organ (Figs. 15.6 and 15.7).

15.1.2.3 Role of MRI

Contrast-enhanced CT is the most useful modality in the evaluation of renal parenchymal lesions, but in the setting of iodine allergy, renal dysfunction, or other contraindications to contrast agents, MRI may be the more appropriate study. MRI, with its high contrast resolution, can demonstrate renal lesions (with somewhat large size) without contrast agents.

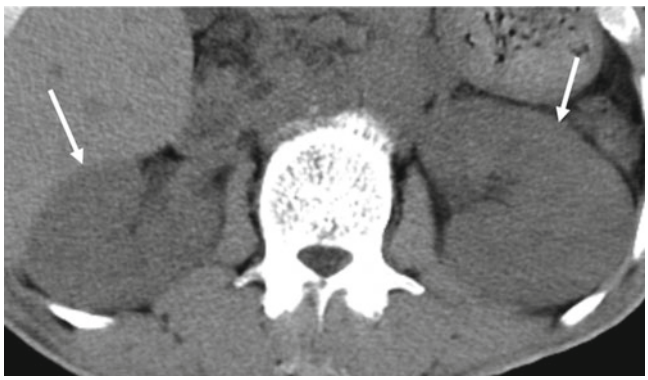

Fig. 15.6 Swelling is found in the bilateral renal parenchyma (*arrows*)

On T1-weighted images, the cortical hyperintensity expected in normal kidneys disappears in the setting of cortical lesions, and the lesional areas are recognized as being relatively hypointense [8]. On T2-weighted images, normal cortex and medulla cannot be distinguished, and lesions are depicted as hypointense as compared to normal parenchyma. Also on diffusion-weighted images, lesions are depicted as hyperintense (Fig. 15.8). The enhancement pattern is like that of CT, and renal parenchymal lesions are well demarcated from uninvolved areas. For cases in which contrast CT cannot be performed prior to biopsy, MRI is considered to be an essential imaging examination to evaluate the presence, absence, and distribution of lesions.

15.1.3 Ureteropelvic Lesions

IgG4-related lesions of the renal pelvis, calices, and ureter may occur with or without parenchymal renal disease. IgG4-RD that occurs in luminal structures in these areas—e.g., the ureters—is recognized on CT by their thickened walls on CT. Such findings can be demonstrated anywhere from the renal pelvis to the inferior ureter but are most common in the region between the renal pelvis and upper ureter. Hydronephrosis or hydroureter can occur upstream to such lesions, but the degree of dilatation itself is usually mild. Focal cases limited to the inferior ureter are rare [13]. Although circumferential wall thickening is typical of IgG4-RD that involves the ureter, the lesions do not have a predilection for infiltrating surrounding tissues.

The most important disease in the differential diagnosis is ureteropelvic cancer. Ureteropelvic cancers develop from the intimal epithelium. In contrast, IgG4-related ureteropelvic lesions usually show a normal intimal epithelium, with lesions forming laterally from the muscle layer. Delineating these differences on diagnostic imaging is essential to rendering the correct diagnosis. The ureteropelvic lesions of IgG4-RD show normal enhancement of the affected intima

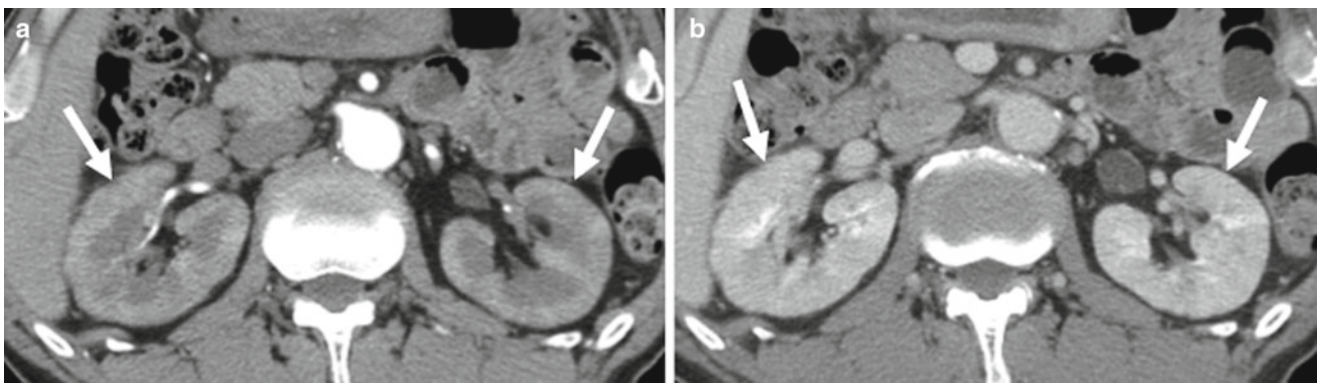

Fig. 15.7 The bilateral renal parenchyma shows decreased enhancement (*arrows*)

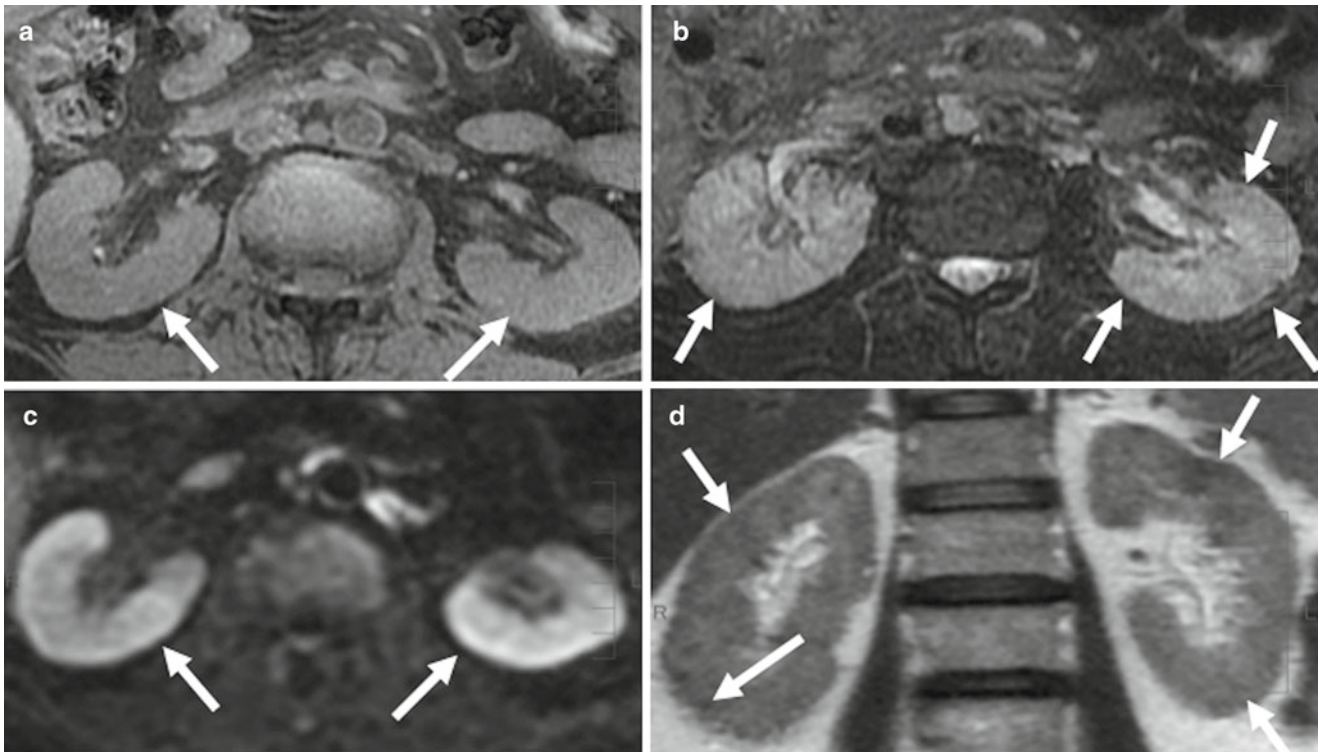

Fig. 15.8 On T1-weighted images, (**a**) the hyperintensity of the normal cortex has disappeared. On T2-weighted images, (**b**, **d**) lesions are depicted as hypointense areas. On diffusion-weighted images, (**c**) lesions are hyperintense (**a**–**d** *arrows*)

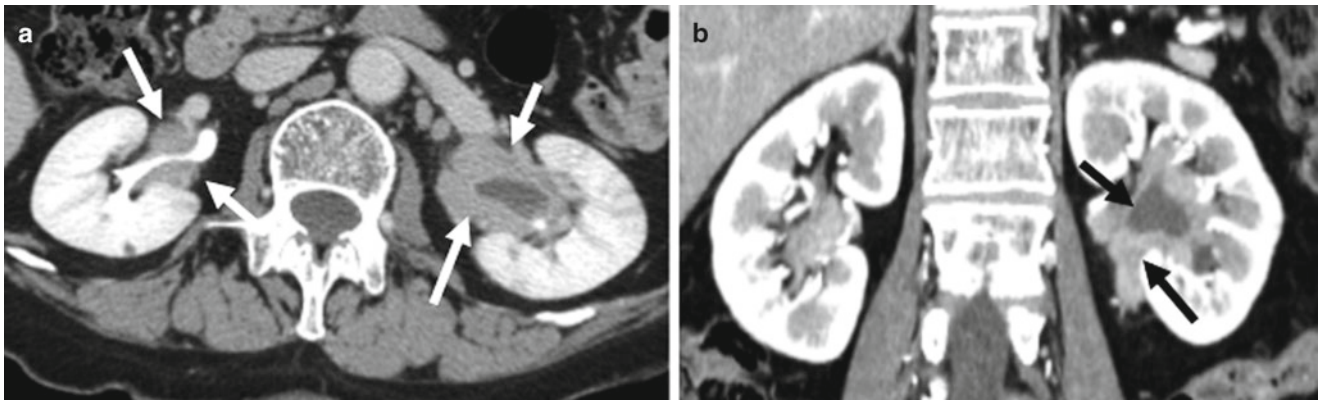

Fig. 15.9 Bilateral renal pelvis wall thickening is found. The luminal surface of the affected part is smooth (**a**, **b**: *arrows*)

on contrast-enhanced CT, and even when luminal stenosis is present, the luminal surface remains smooth (Figs. 15.9 and 15.10). This lack of tissue disruption stands in contradistinction to ureteropelvic cancer, which is marked by tearing of the normal intima in affected lesions, protrusion into the luminal surface, and a tendency to infiltrate surrounding tissues.

The properties of the ureteral wall are evaluated during the cortical and parenchymal phases of contrast-enhanced CT. The excretory phase permits an evaluation of the luminal surface for irregularities. Confirmation that the ureter lumen is normal during the excretory phase is an important imaging consideration. When dilatation of the upper ureter is seen due to delayed excretion on routine dynamic study, an adequate volume of contrast agent is sometimes not excreted into the ureter lumen. To compensate for this, the timing of the imaging should be slightly delayed.

The multidetector-row CT (MDCT)—new technology that is now increasingly available—allows the reconstruction of multiplanar images. This permits the assessment of lesions in a craniocaudal direction on the coronal plane as well as the entire ureteropelvic lumen. In renal ureteropelvic lesions, the drip infusion pyelography and retrograde pyelography can also be useful, particularly in differentiating ureteropelvic lesions from cancer (Fig. 15.10b).

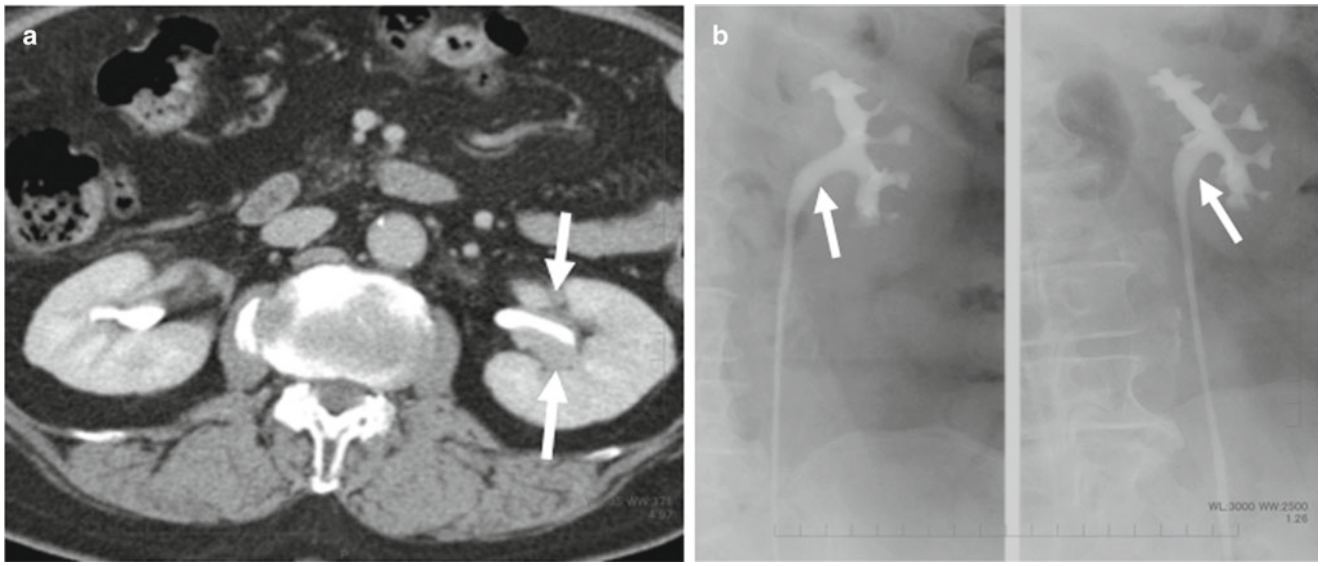

Fig. 15.10 Left renal pelvis wall thickening is found (**a**: *arrows*). On retrograde urography too, (**b**) the lumen is smooth (**b**: *arrows*)

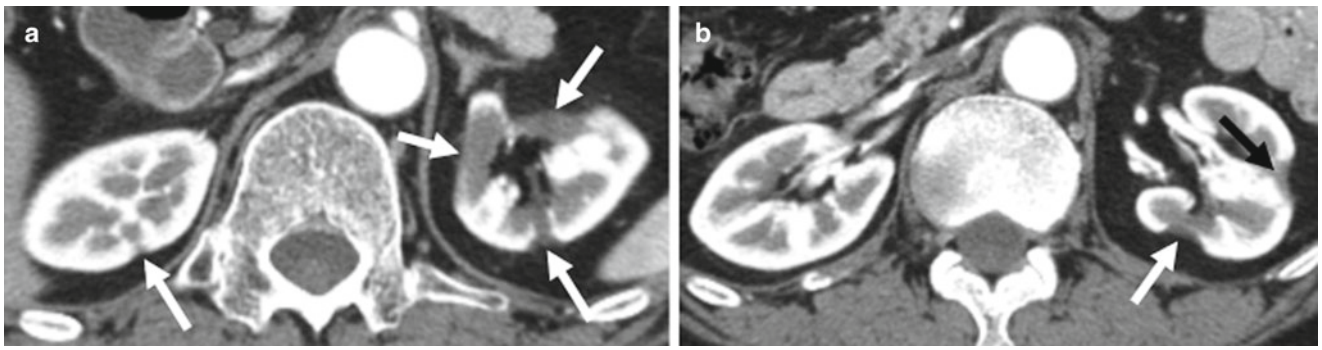

Fig. 15.11 Follow-up observation of untreated case. Lesions are depicted as atrophic low-density areas (**a**, **b**: *arrows*)

Diagnostic imaging must be supplemented by urinary cytological examination and, on occasion, ureteroscopic examination and biopsy.

15.1.4 Imaging Findings After Therapy/After Natural Course

No strict guidelines have been established with regard to the indications for glucocorticoid therapy for renal urinary tract lesions, but many such lesions respond well to these agents. On imaging, changes are frequently reversible, while in other cases fibrotic foci persist, and despite lesion shrinkage, atrophy shown as poorly enhanced areas may be permanent (Fig. 15.11). In the follow-up observation of cases left untreated, spontaneously remitting cases are seen, as are cases in which the lesions become atrophic as fibrosis progresses. Lesions detected in this state after the passage of years resemble those of scarring following infarction or pyelonephritis. At this stage, biopsy reveals only fibrosis, rendering any more specific diagnosis difficult. Ureteropelvic wall thickening is also reversible, and in cases followed in the untreated state for long periods, as in the case of renal parenchymal lesions, spontaneously remitting cases are encountered and so are cases showing almost no changes with the passage of time.

15.2 Concluding Remarks

In this chapter, the imaging findings of renal and urinary tract lesions in IgG4-RD were outlined, with particular focus on the CT findings. We hope that it will be of help in the precise diagnosis of IgG4-related renal and urinary tract lesions in the everyday clinical setting.

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Periarterial Lesions

16

Dai Inoue, Yoh Zen, Osamu Matsui,
and Toshifumi Gabata

16.1 Introductory Remarks

IgG4-RD is a systemic disease often associated with sclerosing lesions in the retroperitoneum and mediastinum [1–3]. These disease conditions are termed IgG4-related retroperitoneal fibrosis (RPF) and IgG4-related sclerosing mediastinitis, respectively.

One disease subset within the diagnostic entity of RPF falls within the spectrum of IgG4-RD. Another RPF disease subset, in contrast, is clearly a separate disorder in terms of the sex distribution of patients and both the histopathology and immunohistochemistry features [4]. In other words, not all cases of RPF are encompassed within the spectrum of IgG4-RD. At present, IgG4-related and non-related RPF cannot be distinguished by diagnostic imaging characteristics. In addition, no obvious differences between the sites of disease involvement, e.g., the perivascular regions, the periureteral areas, pelvic wall localization, and so forth, have been identified to date. Provided that the inflammatory process (regardless of its nature) has not progressed to an advanced fibrotic stage, however, both IgG4-related and non-IgG4-related RPF generally respond well to glucocorticoids.

IgG4-RD is implicated in some cases of inflammatory aortic aneurysms [5–7]. In such patients, the adventitia and periaortic tissues appear to be the major focus of disease. Some investigators have identified the occurrences of inflammatory aortic aneurysm, RPF, and combinations of both of these entities by the collective label of chronic periaortitis [8].

The principal IgG4-related lesions occurring in the retroperitoneum comprise the following three types:

1. Lesions occurring in the soft tissues around the ureteropelvis
2. Lesions occurring around the aorta and its major branches
3. Lesions occurring unrelated to any existing organs

As outlined in our chapter on renal urinary system involvement, the lesions developing around the ureteropelvis can be understood as lesions occurring in a series of luminal structures, namely tubules, renal pelvis, and ureters. In the same way, the artery is the target organ in the case of periarterial lesions. When IgG4-RD lesions occur without a direct relationship to any particular organ, it is speculated that the peritoneum itself may be the site of origin, but the occurrence of IgG4-RD in the peritoneum itself has not been documented to date.

Our experience of considering together the pathological features of RPF has facilitated a reinterpretation of the principal lesions of the artery, ureter, and other sites. We consider it important to apply this same approach to the process of elucidating the clinical, imaging, and pathological characteristics of lesions in the respective affected organs and apply it to mediastinal lesions as well. In this chapter, we focus mainly on the periarterial lesions and also outline the imaging findings of lesions occurring unrelated to any existing organs.

16.2 Periarterial Lesions

16.2.1 Clinical Characteristics

IgG4-related periarterial lesions are similar to those that involve other organs in that they tend to occur in middle-aged and elderly men, the serum IgG4 concentration is a useful (albeit imperfect) diagnostic marker, and glucocorticoids have an important therapeutic impact. These lesions are often detected

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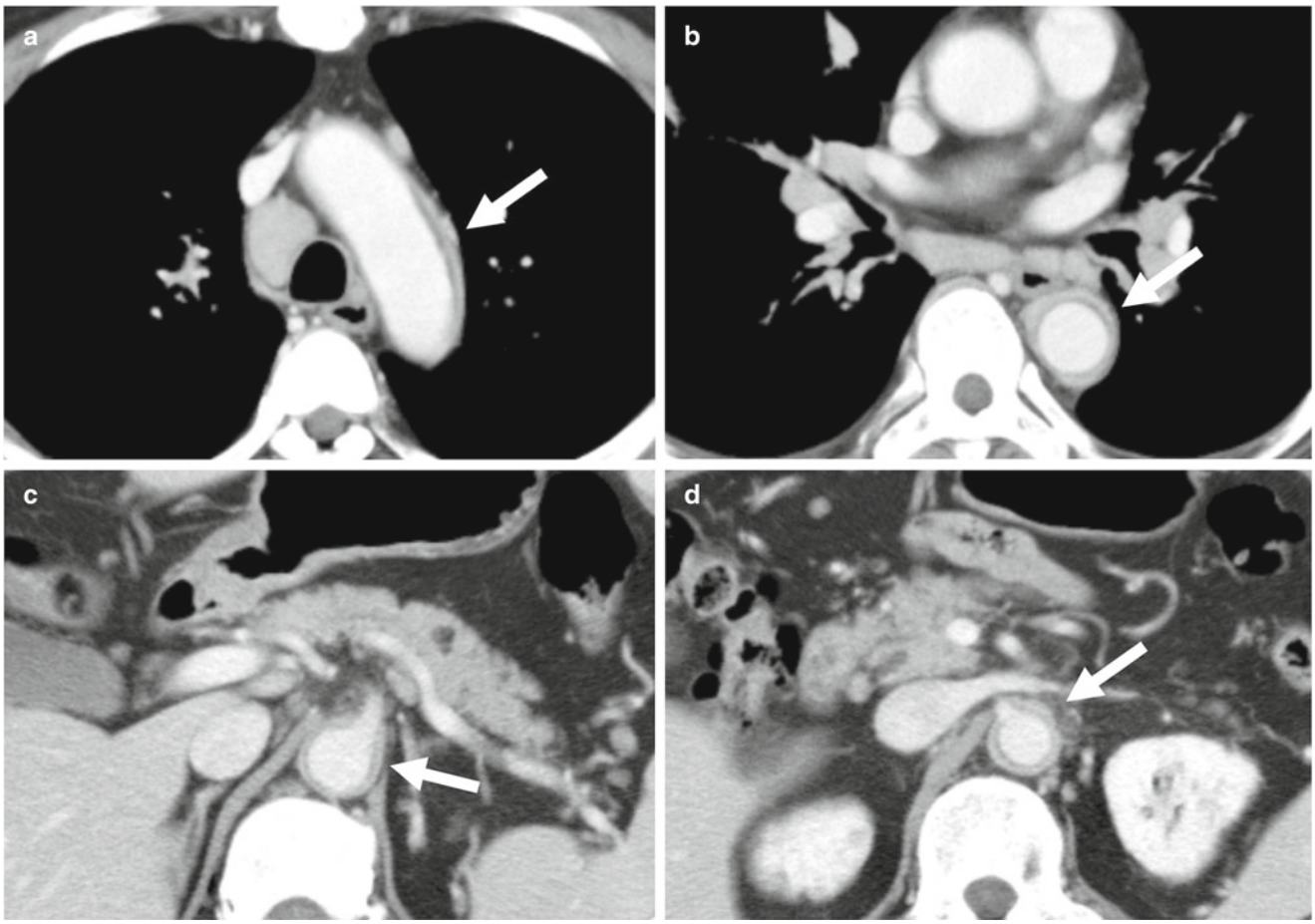

Fig. 16.1 Wall thickening is seen from the aortic arch to abdominal aorta (**a**–**d**: *arrow*)

incidentally during evaluations for back pain or other symptoms, many of which are unrelated to periaortitis and periarteritis.

16.2.2 Sites of Predilection

Lesions are formed around medium- to large-sized arteries. Periaortic lesions can occur anywhere in the ascending, arch, thoracic, and abdominal periaorta (Figs. 16.1, 16.2a, and 16.3), as well as around the iliac artery (Fig. 16.2b). The most common site of disease involves the infrarenal abdominal aorta to the iliac artery. In the thoracic aorta the arch is most commonly involved. Lesions have also been documented around the major branches originating from the aorta, including the superior and inferior mesenteric and splenic arteries (Figs. 16.4 and 16.5). Periarterial lesions of the coronary arteries have also been described (Fig. 16.6) [9].

16.2.3 Pathological Features on Imaging

The arterial adventitia is the principal site of inflammatory cell infiltration and fibrosis, and these pathological conditions are reflected in the imaging examinations [10]. Imaging of these lesions generally shows circumferential wall thickening (Figs. 16.1 and 16.3). In the arterial dominant phase of the contrast-enhanced computed tomography (CT), small vessels such as the intercostal, lumbar and inferior mesenteric arteries sometimes appear to penetrate the lesions (Fig. 16.3). In aortic lesions, the media and intima, present between the lesion area and the contrast-enhanced intravascular lumen, are shown to have a linear structure (Fig. 16.2). The border with the surrounding tissue (mostly adipose tissue) is demarcated clearly, and lesions are uniformly enhanced in the late phase. Calcification and necrosis within the lesion are rare.

Stenosis and occlusion seldom occur in the affected arteries (Figs. 16.4 and 16.5b), and in many cases the artery diameter shows no changes compared to unaffected portions. In cases of inflammatory aortic aneurysms, the adventitia is the main site of lesion formation but the inflammatory cell infiltrate can also extend into the media, with disruption of the elastic laminae. These cases are at risk for rupture and, if sufficiently large, generally require surgical repair. If instituted at an advanced stage of aneurysmal dilatation, glucocorticoid therapy may increase the risk of rupture [11].

Mural thrombus and arterial sclerotic changes such as intimal calcification can be prominent in affected portions of

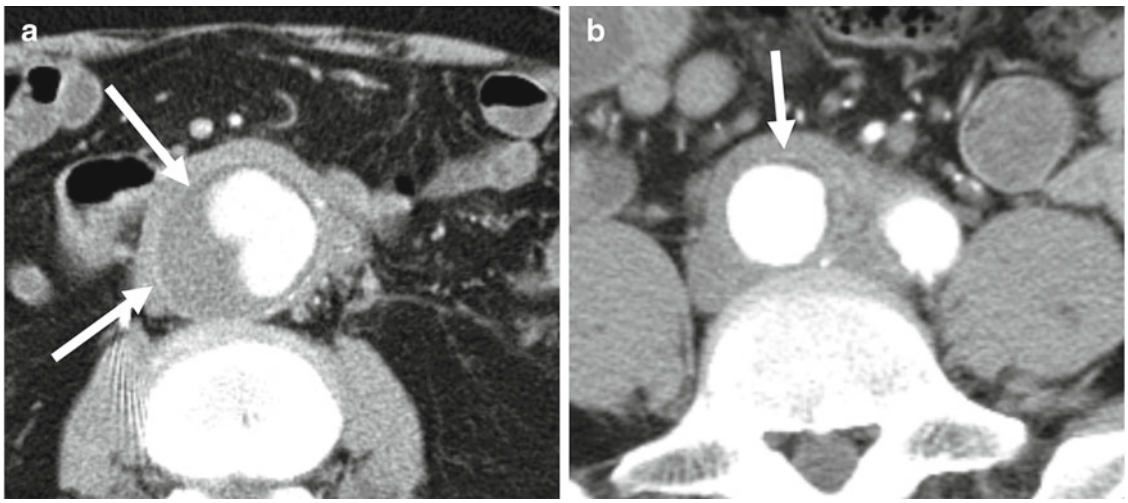

Fig. 16.2 (**a**) Thickening of the abdominal aorta wall and aneurysmal dilatation are found, associated with a mural thrombus. (**a**, **b**) A linear structure thought to be the intima/media between the lesion and mural thrombus can be identified (**a**: *arrow* **b**: *arrow*)

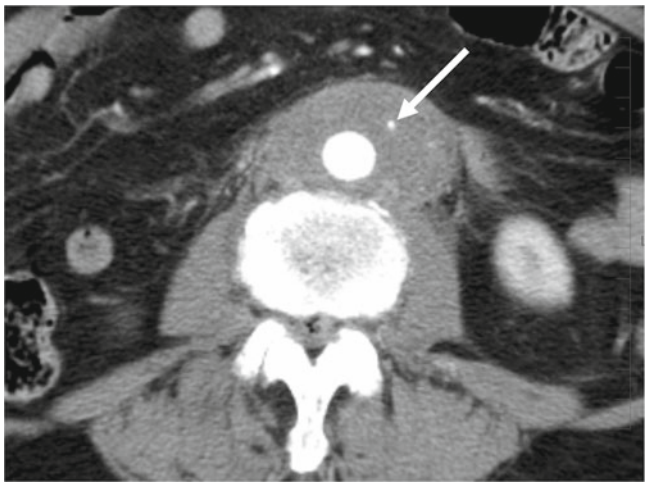

Fig. 16.3 Marked wall thickening of the abdominal aorta is found. The inferior mesenteric artery is penetrating the lesion without stenosis (*arrow*)

the artery (Figs. 16.2a and 16.5a). These lesions, which can be present even in lesions without aneurysm formation, have been attributed to compromised circulation within the intima associated with intralesional obliterative phlebitis. This theory, however, remains speculative.

16.2.4 Diagnosing Periarterial Lesions

The imaging findings described above provide important clues to the diagnosis of IgG4-related periarterial lesions, but in the clinical setting the diagnostic process must also encompass clinical information such as age, serum IgG4 concentration, and the presence or absence of other organ involvement. In 12 (71 %) of our own 17 cases, IgG4-related lesions were found in other organs [10]. Among the disorders that must be distinguished from IgG4-RD, the most important is lymphoma, the imaging findings of which can mimic IgG4-RD closely. We have observed several patients subjected to surgical biopsy for a presumed diagnosis of lymphoma. Large-vessel vasculitides such as Takayasu's arteritis must also be distinguished from IgG4-RPF and periarteritis. This distinction is facilitated by determining the degree of stenosis and occlusion of affected arterial segments on imaging, as well as a review of the clinical context, particularly the age and sex of the patient.

Inflammatory aortic aneurysms can be either IgG4-related or non-related. Since currently there are no adequate points of differentiation between the two on imaging examinations, a pathological diagnosis is required.

16.3 IgG4-Related Arteritis

Lesions develop not in the adventitia but in the media, and cases with arterial dissection have been reported by Stone et al. [12, 13]. Although we ourselves have not encountered such cases, we consider that their manifestations differ from those of cases hitherto described as having periarteritis.

To a large extent the incidence, pathophysiology, and imaging findings of IgG4-related arteritis itself are still unclear, but clinicians must be aware that such cases exist. For a different interpretation of these lesions, please refer to the paper of Stone et al. [12, 13].

16.4 Lesions Unrelated to Specific Organs

Although the incidence is lower than that of periarterial lesions, sheetlike lesions sometimes form mainly along the pelvic wall. As a reflection of this, contrast-enhanced CT imaging frequently shows a uniformly enhanced, sheetlike

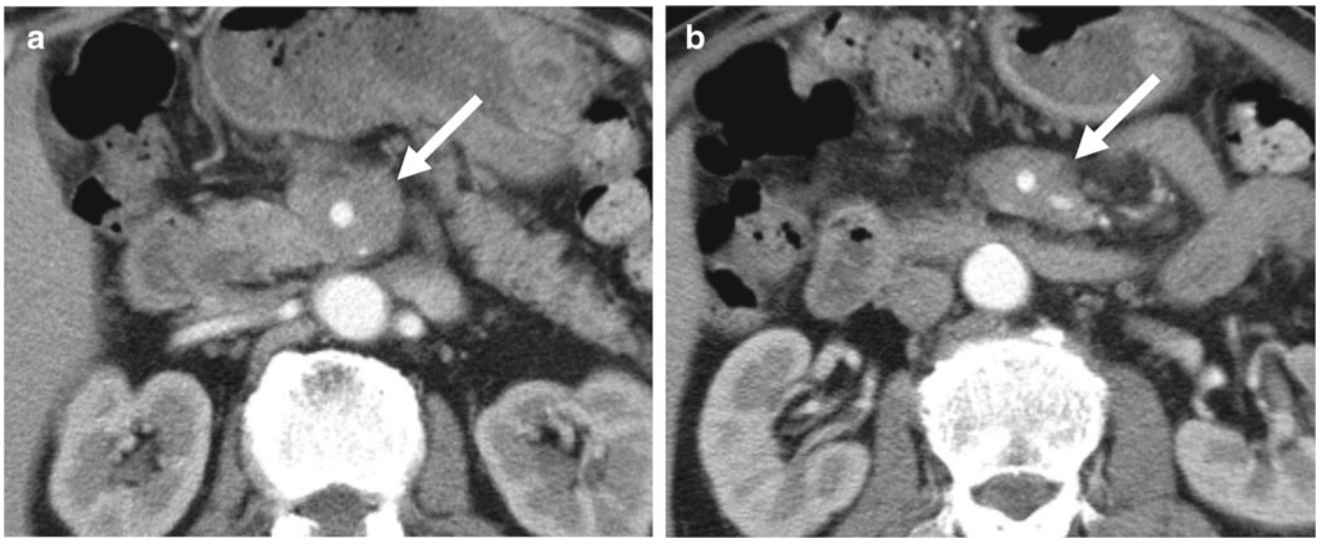

Fig. 16.4 (**a**) Superior mesenteric arterial wall thickening is found (*arrow*). (**b**) No stenosis is found in the affected vessel (*arrow*)

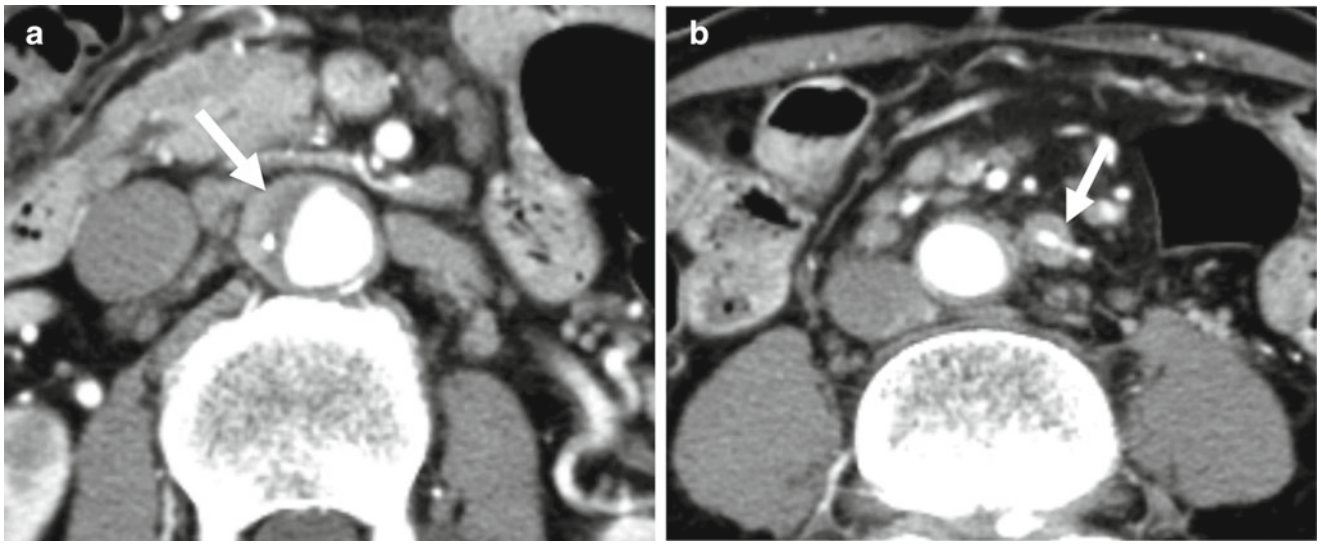

Fig. 16.5 (**a**) Wall thickening of the abdominal aorta is found, associated with a mural thrombus (*arrow*). (**b**) The inferior mesenteric arterial wall is also thickened (*arrow*)

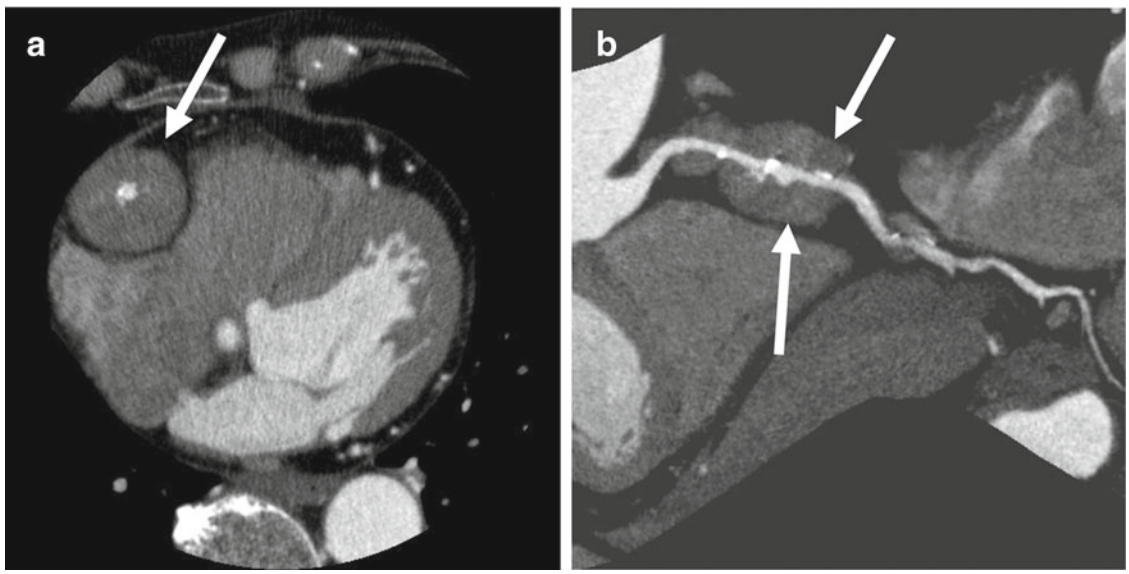

Fig. 16.6 (**a**, **b**) Marked wall thickening is found in the right coronary artery (*arrow*)

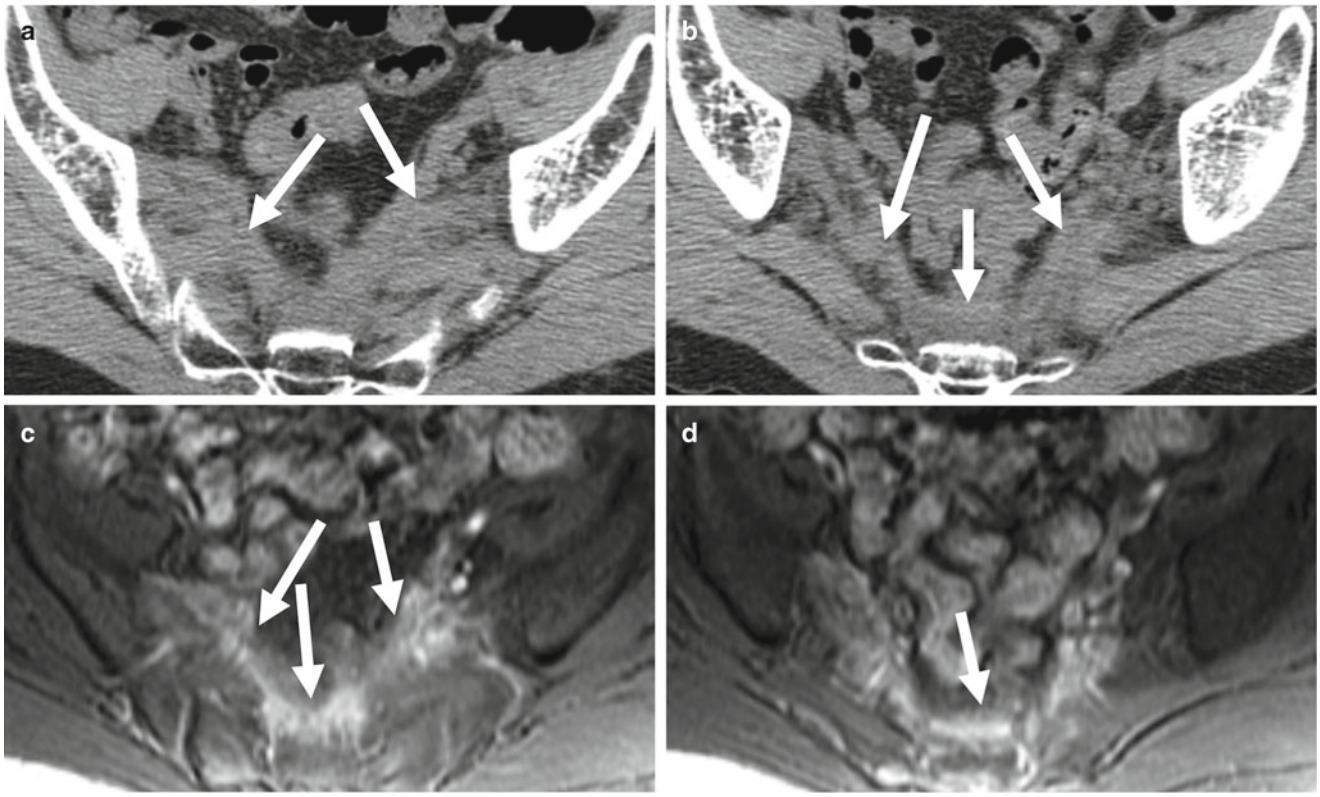

Fig. 16.7 (**a**, **b**) Platelike soft tissue density is found along the pelvic wall (*arrows*). (**c**, **d**) On post-contrast MRI the lesion is uniformly enhanced (*arrows*)

lesion along the anterior surface of the sacrum and/or medial ilium (Fig. 16.7). Hydronephrosis and lower extremity edema frequently occur in this setting because of involvement of the ureter and veins. In non-IgG4-related RPF, too, formation of similar lesions along the pelvic wall is seen. But since differentiation by imaging alone can be difficult, a comprehensive diagnosis considering the presence/absence of other organ involvement, serum IgG4 concentrations, biopsy, and other factors is frequently necessary.

16.5 Concluding Remarks

We outlined here the periarterial lesions associated with IgG4-RD focusing mainly on the imaging findings. The next task will be to define more precisely the imaging and clinical findings of the various lesions in the respective affected organs. By directing our attention to and readjusting the currently vague notions of RPF and sclerosing mediastinitis, the answers to questions such as "Where do the lesions of IgG4-RD occur?" and "What is the nature of these lesions?" may be forthcoming.

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Other Organs (Central Nervous System, Prostate)

17

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17.1 Central Nervous System Lesions

17.1.1 Hypertrophic Pachymeningitis

Hypertrophic pachymeningitis is a refractory inflammatory disease characterized by fibrous thickening of the dura mater. The causes of hypertrophic pachymeningitis include tuberculosis, fungal, and other infections; sarcoidosis; rheumatoid arthritis; vasculitides such as giant cell arteritis and granulomatosis with polyangiitis (formerly Wegener's); and malignancies. In a substantial percentage of cases, however, the cause cannot be determined and the etiology is regarded as "idiopathic." In recent years, an increasing number of the cases previously considered idiopathic have been attributed to IgG4-related disease (IgG4-RD).

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Hypertrophic pachymeningitis can occur in either the intracranial or spinal dura mater, leading to a variety of symptoms according to the site of disease. With involvement of the intracranial dura mater, headaches, cranial nerve dysfunction, optic nerve injury, and cerebellar damage may result. When the spinal dura mater is involved, nerve root and spinal cord compression cause sensory impairment and muscle weakness [1–8] (Figs. 17.1 and 17.2).

17.1.2 Hypophysitis

Nonspecific pituitary inflammation includes the long-recognized disease entity known as lymphocytic hypophysitis. Inflammation of the anterior pituitary gland is called lymphocytic adenohypophysitis, while inflammation extending from the posterior lobe to the pituitary stalk is called lymphocytic infundibuloneurohypophysitis. IgG4-RD has now been reported as a cause of lymphocytic hypophysitis leading to pituitary gland dysfunction, affecting either the anterior or posterior lobe of the gland (including the stalk) or both (Fig. 17.2) [9–16]. The frequency of IgG4-RD as a cause of adenohypophysitis and infundibuloneurohypophysitis compared to other causes, such as sarcoidosis or histiocytosis, is not clear at this time.

Diverse symptoms and signs can be associated with pituitary gland dysfunction, according to the specific hormone deficiency that results from hypophysitis. The most commonly affected hormones are adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone

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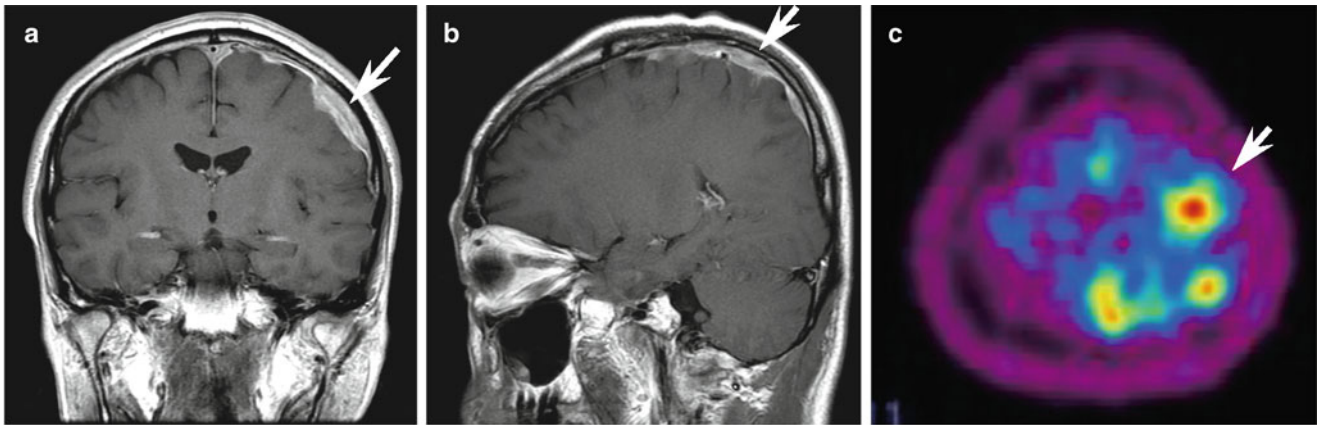

Fig. 17.1 Images of IgG4-related hypertrophic pachymeningitis. (**a**) Anterior section, (**b**) sagittal section of MRI, and (**c**) l-[methyl-^{11}C]-methionine (MET)—PET coronal section. On MRI, a thickened dura mater is confirmed (*right arrow*), and at the same site marked methionine accumulation is found. ^{18}FDG-PET is a common examination and marked accumulation of ^{18}FDG is usually observed in IgG4-RD lesions; however, since ^{18}FDG accumulates in the central nervous system itself, abnormal accumulation is difficult to discern. The usefulness of MET-PET in central nervous system lesions such as hypertrophic pachymeningitis has been reported [7]. However, at present the number of institutions at which such examinations can be performed is limited. (These images were supplied by Dr. Hiroaki Dobashi, Dr. Yuka Yamamoto and Prof. Yoshihiro Nishiyama, Kagawa University)

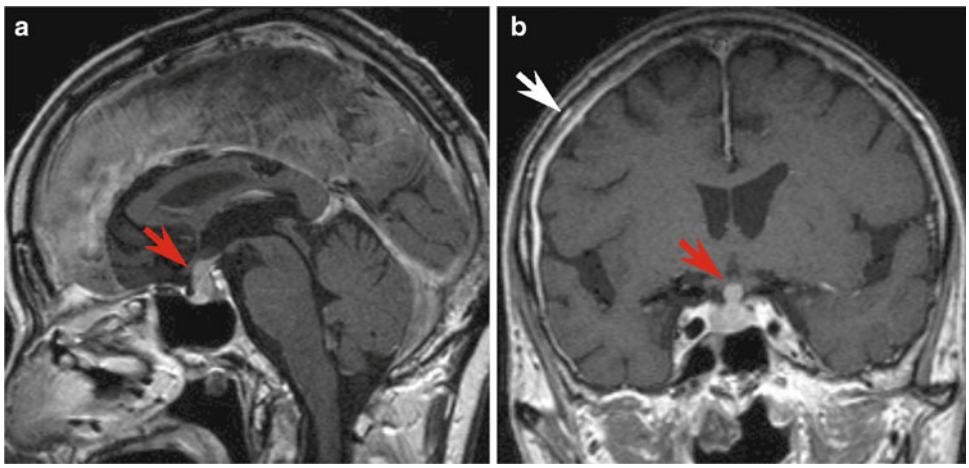

Fig. 17.2 MR images of IgG4-related hypophysitis and hypertrophic pachymeningitis. (**a**) Sagittal section and (**b**) anterior section. Swelling is found from the pituitary anterior lobe to the pituitary stalk. The entire lesion is enhanced by gadolinium. The optic chiasm is compressed slightly superiorly by a swollen pituitary stalk (*red right arrow*). In this case, hypertrophic pachymeningitis is also found (*white right arrow*)

(FSH), and prolactin. Pituitary dysfunction can result from injuries to the pituitary itself, but also from damage to the hypothalamus or the pituitary stalk. In practice, sites of injury often extend over multiple areas. The development of a deficiency of vasopressin, a posterior lobe hormone, causes central diabetes insipidus. Multiple hormone deficiencies result in some cases. Panhypopituitarism and partial anterior hypopituitarism can exist in varying degrees and combinations.

Hypopituitarism shows diverse symptoms, depending on the type of hormone that is insufficient and degree of the insufficiency. The diagnosis of hypopituitarism is often challenging, because symptoms are generally nonspecific,

at least at first. The list below catalogs diagnostic clues to deficiencies in particular hormones:

- ACTH: Hypoglycemia, hyponatremia, and eosinophilia, all indicators of adrenal insufficiency.
- TSH: Cold intolerance and bradycardia. These symptoms are frequently mild compared to those caused by primary hypothyroidism.
- GH: Few specific findings in adults.
- LH, FSH: Lack of secondary sex characteristics after puberty. Given that IgG4-RD tends to affect middle-aged to elderly males, however, alterations in these characteristics are sometimes difficult to discern.
- Prolactin: An elevated blood prolactin level can be a clue to the presence of an organic disease in either the hypothalamus or pituitary gland. A common symptom of prolactin excess is galactorrhea.

A variety of other symptoms also point to organic disease of the diencephalon and pituitary gland. As examples, chronic headache can be a manifestation of organic disease within the sella turcica; polydipsia and polyuria may complicate posterior lobe injury; and compression of the optic chiasm by expansile growth of an IgG4-RD lesion can affect visual acuity and lead to visual field defects.

Shimatsu et al. described 22 reported cases of IgG4-related hypopituitarism [12]. The sex and age characteristics of those patients were typical of IgG4-RD: 21(95 %) of the patients were men and the median age was 64 years. The number of cases reported increased with each decade of life: two patients were in their 40s, four in their 50s, eight in their 60s, and eight in their 70s. Symptoms included general malaise in 11 cases, headache (six cases), visual impairment including eye movement disorders (6), fever (5), polyuria (6), anorexia (4), weight loss (4), and decreased libido (3).

Varying degrees of anterior pituitary hormone deficiency were observed in 19 patients and central diabetes insipidus occurred in 12. Eleven patients (50 %) had features of both hypopituitarism and central diabetes insipidus. Subclinical diabetes insipidus was observed in three cases, and hypopituitarism preceded by diabetes insipidus in four. Isolated gonadal hormonal insufficiency was noted in two cases, and isolated central hypothyroidism and isolated ACTH insufficiency were found in one case each. Among the other 15 cases, complex pituitary anterior lobe hormone insufficiency was present. These cases included decreased levels of LH/FSH (all 15 cases), ACTH deficiency in 14 cases, TSH deficiency in 12 cases, and GH deficiency in 8 cases. Hyperprolactinemia was found in 3 cases.

Pituitary stalk thickening or mass formation was detected by MRI in 18 cases. The thickening replaced the proximal portion of the pituitary infundibulum and stalk. Pituitary swelling and mass formation were found in ten cases. Other IgG4-related complications were common in this cohort of patients: retroperitoneal fibrosis ($n=10$), "Mikulicz's disease" ($n=8$), pulmonary disease ($n=8$), type 1 autoimmune pancreatitis ($n=6$), lymphadenopathy ($n=5$), hypertrophic pachymeningitis ($n=5$), sinusitis ($n=3$), and orbital pseudotumor ($n=2$) [12].

Recently, Leporati et al. proposed diagnostic criteria for IgG4-related hypophysitis [15] and reported that GH and proopiomelanocortin constitute autoantigens in this condition [16]. These proposals require validation in larger numbers of patients.

17.1.3 Intracerebral Inflammatory Pseudotumor

Inflammatory pseudotumor in IgG4-RD has been reported in various organs including the lung, breast, and liver and also the central nervous system [11]. The neurological symptoms and signs associated with pseudotumor are diverse and depend upon the site of involvement. Although only few such cases have been reported, some previously described intracerebral tumors associated with neurological symptoms that spontaneously remitted with steroid administration alone are likely to have been IgG4-related intracerebral inflammatory pseudotumors [17]. We surmise that many such cases are treated in the absence of a formal diagnosis, but the true frequency with which this occurs is unknown. When elevated serum IgG4 values are detected and lesions at other sites demonstrate unambiguous histopathological findings of IgG4-RD, it is reasonable to conclude in many cases that an intracerebral lesion represents a manifestation of IgG4-RD, as well.

The optimal approach to the diagnosis of intracerebral lesions has not been determined. Histopathological proof of the diagnosis of IgG4-RD and exclusion of other conditions through biopsy is desirable but often not easily obtained. Considering the invasiveness of many intracerebral surgical procedures, an empiric trial of glucocorticoids may be prudent before attempting biopsy. If the response to glucocorticoids is unsatisfactory, other conditions such as lymphoma, glioma, or meningioma must be considered further.

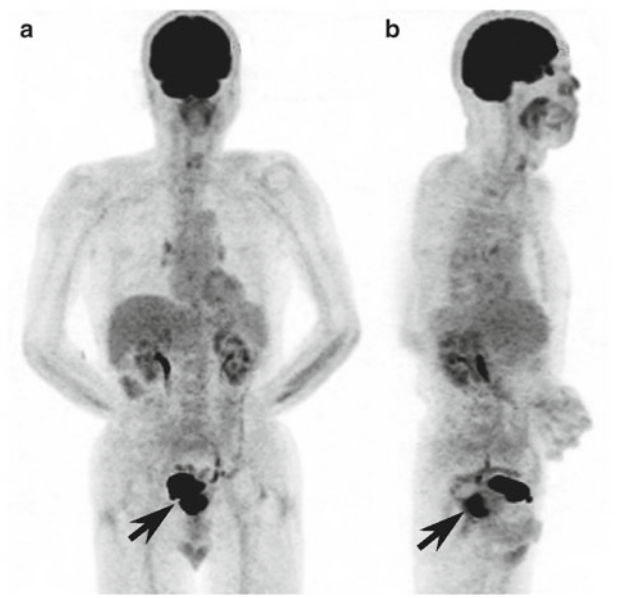

Fig. 17.3 ^{18}FDG-PET images of a case with isolated IgG4-related prostate lesions ((**a**) frontal view, (**b**) lateral view). In the lesion-bearing prostate gland, marked ^{18}FDG accumulation is found (*right arrow*). This case did not satisfy the criterion of an elevated serum IgG4 (≥135 mg/dL), and according to the comprehensive diagnostic criteria for IgG4-related disease [21] is assigned to the probable group

17.2 Prostate Lesions

The frequency of IgG4-RD as a cause of "benign prostate hypertrophy" is unclear. Prostate lesions are usually detected incidentally during a systemic examination for other IgG4-RD involvement [18–20]. Prostate involvement is typically suspected in the setting of symptoms of prostatism in a patient with known IgG4-RD—particularly in a man who presents with these symptoms at a young age—or when an ^{18}F-fluorodeoxy glucose (^{18}FDG)-positron emission tomography (PET) or ^{67}Ga-scintigraphy scan demonstrates uptake in the prostate. IgG4-related prostatitis must be differentiated from prostate cancer, of course, given that the classic IgG4-RD patient is a middle-aged to elderly male. Thus, determination of serum prostate-specific antigen (PSA) concentrations and a histopathological diagnosis are important. Prostatic involvement by IgG4-RD typically responds dramatically to glucocorticoids, with relief of dysuria and other symptoms of prostatic obstruction within days (Figs. 17.3, 17.4, and 17.5).

17.3 Concluding Remarks

We have outlined the relatively rare IgG4-RD entities of the central nervous system and prostate involvement. The diagnosis of IgG4-RD at these sites is challenging when

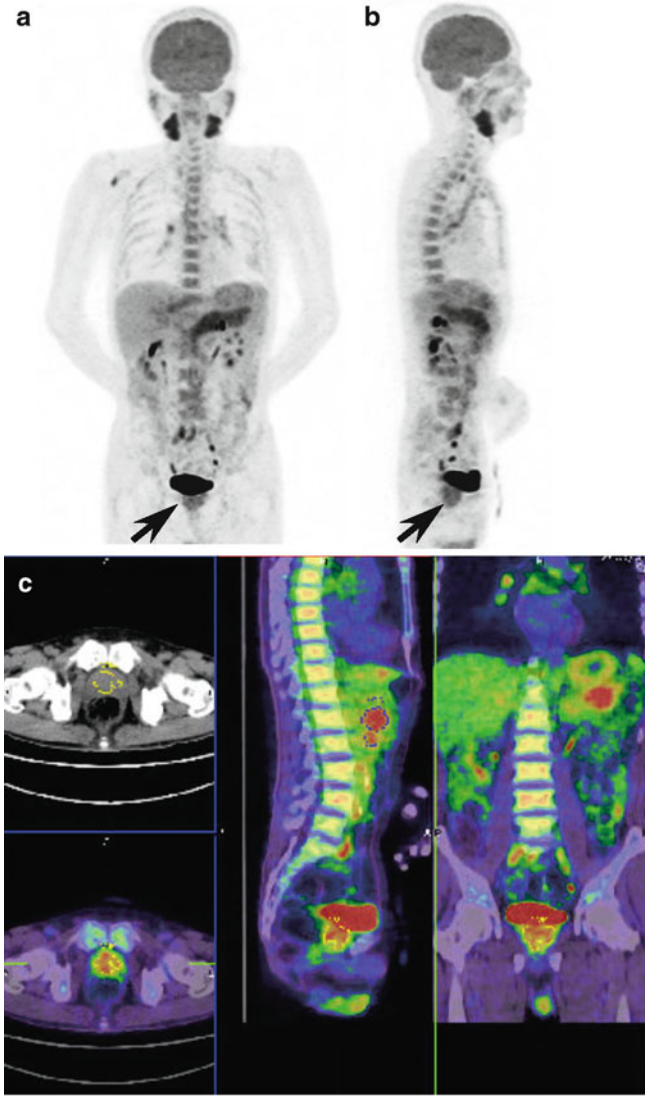

Fig. 17.4 ^{18}FDG-PET images of a case with IgG4-related prostate lesions as a part of systemic IgG4-RD ((**a**) frontal view, (**b**) lateral view, (**c**) color images). In the lesion-bearing prostate gland, marked ^{18}FDG accumulation is found (*right arrow*), in addition to which accumulation was also noted in the bilateral submandibular glands, parotid glands, pancreas, right axilla, and pulmonary hilum lymph nodes

no other foci of disease are evident but facilitated greatly when the serum IgG4 concentration is elevated substantially and findings typical of IgG4-RD are also evident in other organs. Because the differential diagnosis in both the central nervous system and prostate includes malignancy, appropriate imaging examinations and tissue biopsies must be undertaken whenever possible. The comprehensive diagnostic criteria for IgG4-RD [21] may be useful in making the diagnosis.

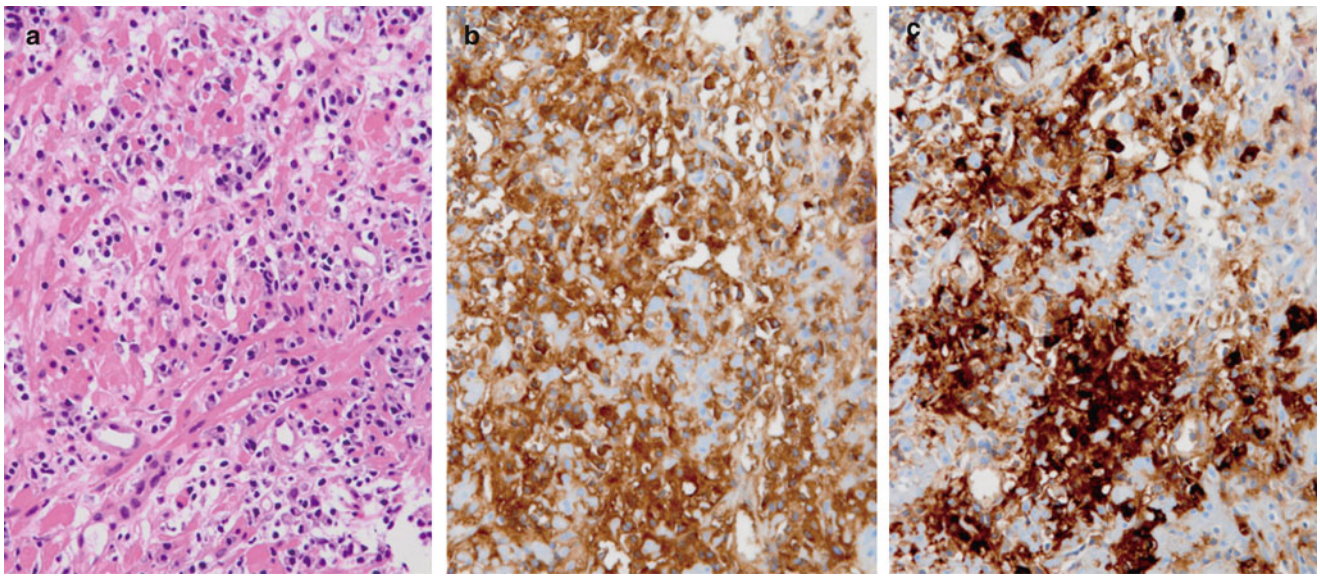

Fig. 17.5 Biopsy findings of a case with prostate lesions ((**a**) H&E staining, (**b**) IgG immunostaining, (**c**) IgG4 immunostaining). Lymphoplasmacytic cells proliferate as if replacing normal prostate gland cells. The majority of these cells are IgG4-positive

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Nerve Lesions

18

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18.1 Introductory Remarks

Type 1 autoimmune pancreatitis (AIP), which pathologically corresponds to lymphoplasmacytic sclerosing pancreatitis (LPSP), is a distinctive disorder of the pancreas characterized pathologically by a lymphoplasmacytic infiltrate, fibrosis, and obliterative phlebitis. Its cause has not been fully elucidated, but since the report of Hamano et al. [1], serum IgG4 has been believed to play an important role in the pathophysiology of this condition.

By accumulating larger numbers of cases, it has become evident that AIP is associated with lesions in multiple organs, some of the most frequently affected being the lacrimal gland, salivary gland, pulmonary hilar lymph nodes, lung, bile duct, kidney, retroperitoneum, and prostate. These lesions have previously been referred to collectively by a variety of names: IgG4-related sclerosing disease [2], systemic IgG4-related plasmatic disease (SIPS) [3], and IgG4-positive multiorgan lymphoproliferative syndrome (IgG4+MOLPS) [4]. However, in recent years, the name has been unified as IgG4-related disease (IgG4-RD).

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18.2 Experience at Our Institution

We encountered lesions of the infraorbital nerve (first branch of the maxillary nerve, which is the second branch [V2] of the trigeminal nerve) associated with AIP and investigated whether these lesions are increased in frequency in this condition. Of 71 AIP cases, MRI of the head and neck was performed in 11 patients. Twenty patients undergoing head and neck MRI during the same period served as the control group [5]. The control group did not include any patients with a history of head and neck malignant tumors, lymph node swelling, pain, hoarseness, radiotherapy, or osteomyelitis, nor did it include patients with maxillary sinus hypoplasia or maxillary sinus tumors.

All images were obtained on a 1.5 T MR unit, and the infraorbital nerves were observed on an image viewer on T1-weighted images, T2-weighted images, or short T1 inversion recovery (STIR) coronal sections. The nerve diameter was measured in a total of 62 right and left eyes in the AIP and control groups combined, and the mean widths of the nerve diameters were compared between the two groups. In the glucocorticoid-treated patients, changes in the nerve diameter before and after therapy were investigated. The MRI studies were also examined for other nerve lesions in the head and neck region.

In AIP group, serum IgG4 values were determined, and the presence/absence of pain and abnormal paresthesia was also investigated.

Measured values of the infraorbital nerve diameters are illustrated in Fig. 18.1 The mean diameter was significantly greater in AIP group, in which a bimodal distribution was shown. When the threshold for nerve swelling was set at 5 mm, swelling was detected in 5/11 cases (8/22 nerves) (Fig. 18.2).

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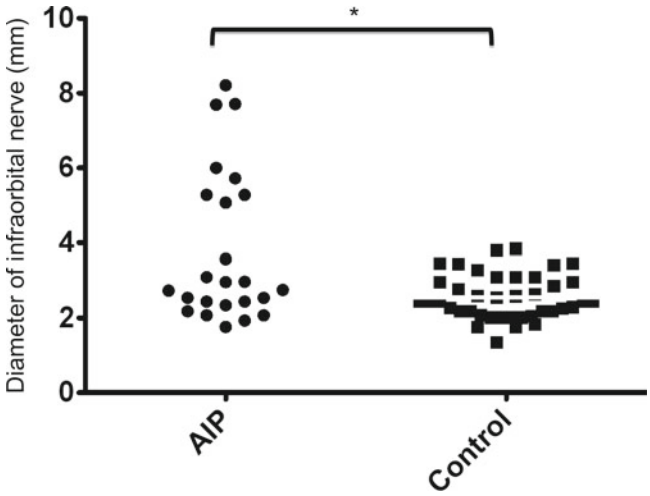

Fig. 18.1 Comparison of infraorbital nerve diameter in the AIP and control groups

In contrast, in the control group no cases showed nerve swelling. Among the five AIP patients who had infraorbital nerve swelling, the abnormality was bilateral in three cases and unilateral in two. Among the five swollen nerves that could be evaluated with follow-up MRI studies, significant shrinkage following therapy was observed in all five nerves.

Table 18.1 catalogs the other head and neck lesions detected in the AIP group. Bilateral lacrimal gland swelling was found in eight cases, submandibular gland swelling in seven (bilateral in six cases, unilateral in one), parotid gland swelling (one case), unilateral extraocular muscle swelling (1), bilateral frontal nerve swelling (2), and unilateral inferior alveolar nerve swelling (2). Considering only the five patients with infraorbital nerve swelling, 4 (80 %) showed lacrimal gland swelling and 2 (40 %) submandibular gland swelling. All of the head and neck lesions improved following glucocorticoid treatment.

In the AIP group, serum IgG4 values exceeded 135 mg/dL in all patients (mean, 1,626; range 305–3,660 mg/dL). In both the AIP and control groups, all of the patients were asymptomatic with regard to nerve lesions.

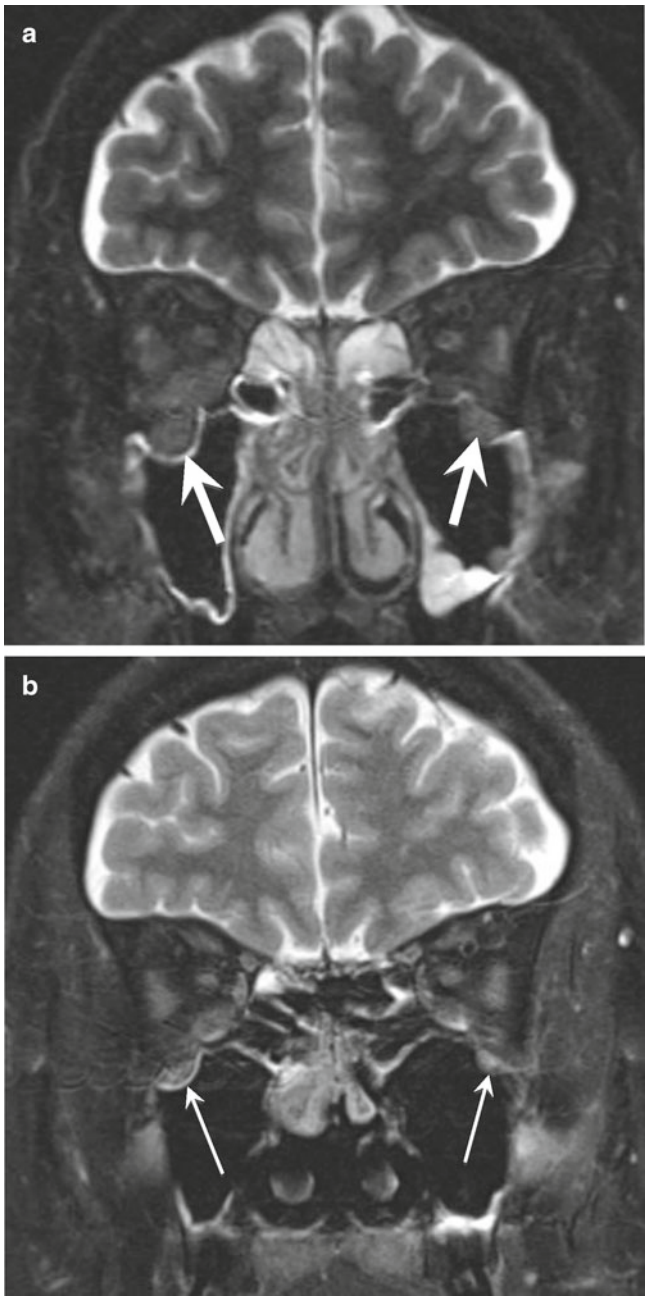

Fig. 18.2 A 50-year-old man with infraorbital nerve swelling. (**a**) On STIR coronal section infraorbital nerve swelling is found (*arrows*). (**b**) The nerve swelling improved after steroid therapy (*arrows*)

18.3 Discussion

In the present study, ≥5 mm infraorbital nerve swelling was found in 5 of 11 cases (45 %) in AIP group, representing a significantly higher frequency than that exhibited by the control group ($P<0.05$). In these patients, diverse lesions were associated at the same time at various sites including the lacrimal gland, submandibular gland, extraocular muscles, and frontal and inferior alveolar nerves.

Our study clarifies the fact that infraorbital nerve lesion swelling is associated with type 1 AIP and, by extension, with IgG4-RD. Until recently, such nerve lesions in the head and neck region were unknown. A few cases in which infraorbital nerve lesions were subjected to biopsy have been reported lately [6–8]. The imaging findings in these cases were the same as in the cases experienced by us, and histologically the lesions showed lymphocyte and IgG4-positive plasmacytic

Table 18.1 Head and neck lesions in autoimmune pancreatitis patients (quoted from [5])

Patient number	Age/sex	Frontal nerve	Infraorbital nerve	Inferior alveolar nerve	Lacrimal gland	Submandibular gland	Parotid gland	Extraocular muscle
1	55/M	+	+	–	+	+	–	–
2	74/M	–	+	+L	–	–	OS	–
3	50/M	–	+	OS	+	OS	OS	+
4	66/M	–	+L	–	+	+	–	–
5	51/M	–	+L	OS	+	OS	OS	–
6	68/M	OS	–	–	OS	+	–	–
7	69/M	–	–	–	+	+	+	–
8	65/M	–	–	–	–	+	–	–
9	63/M	–	–	OS	+	OS	OS	–
10	63/F	+	–	+R	+	+L[a]	–	–
11	50/M	–	–	–	+	+	–	–

M male; *F* female; – negative finding; + positive finding such as swelling of nerve, gland, or muscle; *L* left side only; *R* right side only; *OS* out of scan range

cell infiltration and fibrosis. These findings lead us to conclude that infraorbital nerve lesions are one component of IgG4-RD.

In some patients in whom infraorbital nerve swelling is found, head CT has been performed, and despite the fact that the infraorbital canal where swollen nerves run is enlarged, no osteoclastic changes are detected (Fig. 18.3). This suggests that infraorbital nerve swelling does not occur rapidly, but rather gradually over a long period. Many aspects of the natural history of IgG4-RD, including those of AIP, remain unclear. Elucidation of these will be an important focus for future studies.

When nerve swelling is detected on head and neck imaging, conditions requiring differentiation include malignant lymphoma, nerve infiltration by cancer, nerve sheath tumor, chronic inflammatory demyelinating polyneuropathy (CIDP), inflammatory pseudotumor, and neurofibromatosis. Many but not all patients with these other conditions in the differential diagnosis have symptoms from their peripheral nerve involvement when abnormalities of these nerves are detectable by radiology. In contrast, in IgG4-RD, even the nerves that showed marked swelling were not associated with symptoms, making them unsuspected clinically. When present, infraorbital nerve swelling in IgG4-RD is usually bilateral and is often associated with other more classic organ manifestations of the underlying systemic condition, particularly enlargement of the lacrimal and salivary glands.

Infiltration of nerves by malignant tumors is asymptomatic in some cases, but the presence of bilateral lesions is rare in the setting of malignancy. This point aids in the differentiation of IgG4-RD associated with nerve swelling from cancer. Neurotropic lymphoma and neurofibromatosis are difficult to differentiate by imaging, but serum IgG4 determinations and the presence/absence of lesions in multiple organs provide useful information in this regard.

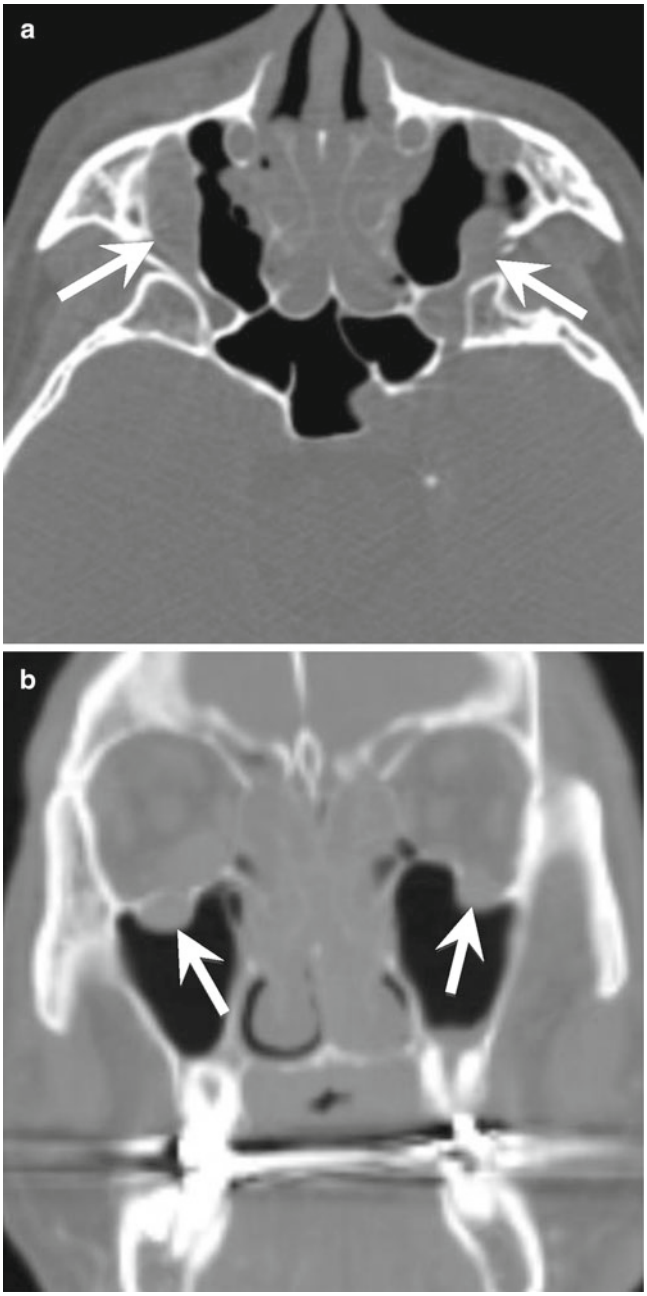

Fig. 18.3 Same case as in Fig. 18.2. (**a**) CT axial section and (**b**) coronal section. Enlargement of the bilateral infraorbital canals is found, but no osteoclastic changes are evident

18.4 Concluding Remarks

Infraorbital nerve lesions complicate AIP at a high frequency and should be considered to be a component of IgG4-RD. Many aspects of IgG4-RD, including its cause(s), underlying mechanisms, and natural history, remain unclear, but it can be anticipated that various studies now in process will shed light on these and other issues in the near future.

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Scintigraphy and Single-Photon Emission Computed Tomography

19

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19.1 Whole-Body Evaluation with ^{67}Ga Scintigraphy

^{67}Ga is a metal ion that belongs to the third group of the periodic table. This ion is transported to target organs after binding with transferrin in the blood. ^{67}Ga is a classic agent in the field of nuclear medicine and has been employed widely in the investigation of malignant and inflammatory processes. SPECT scanning is particularly useful in lymphoma, undifferentiated cancer, and malignant melanoma, but also accumulates avidly in nonmalignant inflammatory conditions such as sarcoidosis, infections, and abscesses.

^{67}Ga shows diffuse accumulation in interstitial diseases of the lung and kidney when the process is active. With the recent widespread availability of ^{18}F-fluorodeoxyglucose/positron emission tomography (FDG-PET), the use of ^{67}Ga to diagnose cancer and metastases has declined. ^{67}Ga is still used frequently to search for systemic involvement, however, because its accumulation correlates well with parenchymal or interstitial inflammatory changes.

^{67}Ga accumulates physiologically in the nasopharynx, lacrimal gland, parotid gland, bowel excretion, and liver. When evaluating the degree of accumulation at these sites, the first step of interpretation is to judge whether it is physiological or pathologic. In addition, the degrees of accumulation in the bone marrow, pulmonary hila (usually symmetric), and breasts show individual variations, which must be taken into consideration.

In general, abnormalities related to autoimmune dysfunction include systemic lymph node involvement, interstitial pneumonia, pleuritis, pericarditis, pancreatitis, inflammatory changes of the hepatobiliary tree, retroperitoneal fibrosis, sialadenitis, interstitial nephritis, arthritis, and thyroiditis. All of these organs and tissues are known to be affected by IgG4-related disease (IgG4-RD). An advantage of whole-body ^{67}Ga imaging is that this imaging approach can identify abnormal regions throughout the body with just one study. ^{67}Ga scintigraphy is also performed sometimes to monitor changes in the degree of accumulation as an index of the effect of therapy. The usefulness of whole-body ^{67}Ga scintigraphy or SPECT has been reported not only in the pancreas as related to autoimmune pancreatitis (AIP) but also in extrapancreatic lesions including those in the lung, lymph nodes, and kidney [1–7]. In Mikulicz's disease, abnormal accumulations have also been detected in the lacrimal gland, salivary gland, and kidney [8].

19.1.1 Case 1: ^{67}Ga Accumulation in the Salivary Glands and Kidneys

A woman in her late 70s sought medical attention because of bilateral submandibular gland swelling. The etiology of her complaint remained unclear despite a salivary gland biopsy. During the work-up of another condition, however, the presence of renal dysfunction became clear when an elevated serum creatinine value, proteinuria, and hematuria were detected. Hypocomplementemia, hypergammaglobulinemia, and elevated IgG4 concentration (486 mg/dL) were also noted. On renal biopsy, a marked inflammatory infiltrate within the interstitium was found, and the diagnosis of IgG4-RD was proposed.

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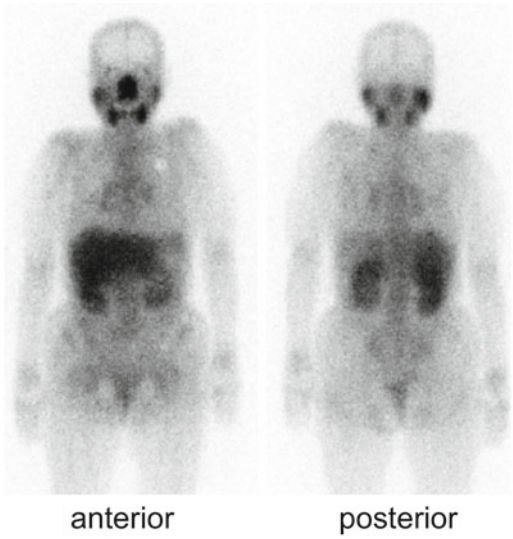

Fig. 19.1 Accumulation in the salivary glands and kidneys on whole-body ^{67}Ga scintigraphy (anterior and posterior views)

On ^{67}Ga scintigraphy, high accumulation was found in the bilateral parotid and submandibular glands. Symmetrical high accumulation was observed in the bilateral kidneys (Fig. 19.1).

19.1.2 Case 2: IgG4-RD Lesions of the Pancreas, Lung, and Periaortic Tissues

A man in his early 60s presented with abdominal pain and was diagnosed with type 1 AIP. He subsequently became aware of diplopia and a magnetic resonance imaging (MRI) study revealed pituitary gland swelling. On biopsy, a lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells was found, and IgG4-RD was diagnosed.

Whole-body SPECT scanning was performed. Abnormal ^{67}Ga accumulation was observed in the mediastinum (including the pulmonary hila), the right lower lung field, and the midline of the abdomen on both the whole-body image (a) and the abdominal SPECT coronal section (b). Based on the CT coronal sections (c), SPECT-CT software-generated fusion images were created (d). A soft tissue density shadow was found extending from the abdominal aorta to the common iliac artery (Fig. 19.2).

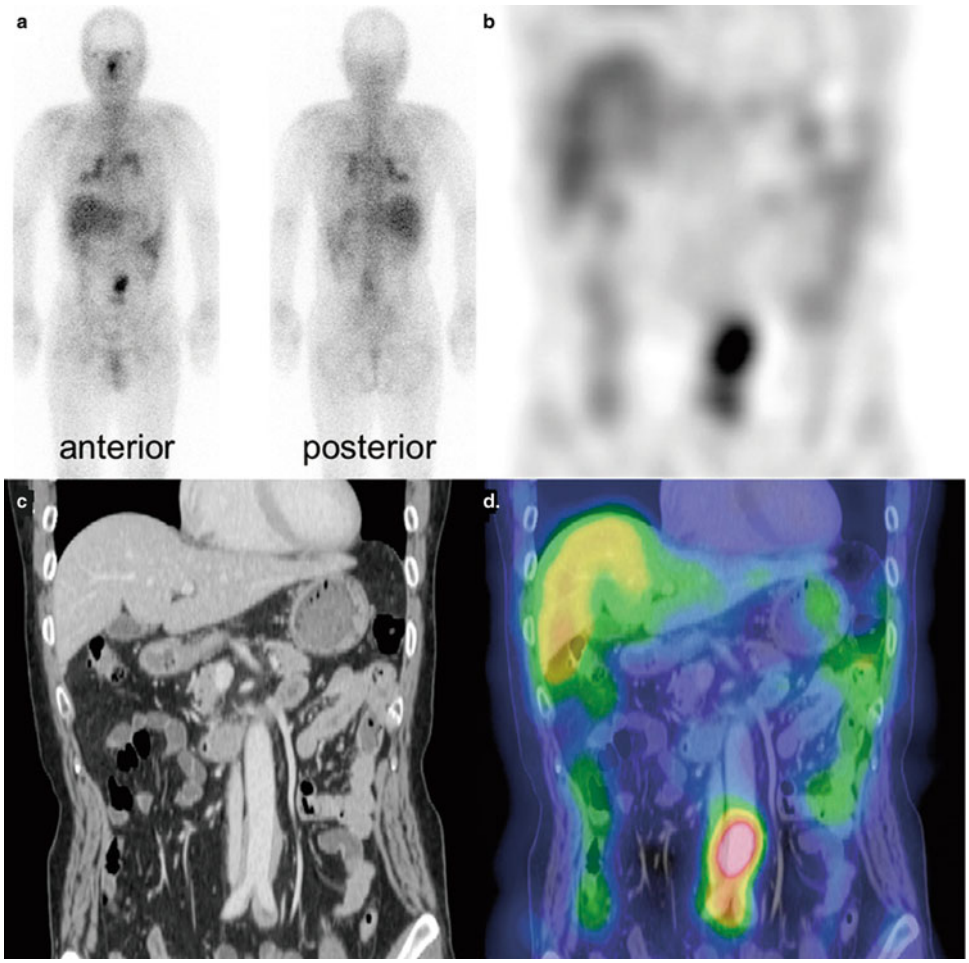

Fig. 19.2 Detection of pancreatic, pulmonary, and periaortic lesions by whole-body ^{67}Ga scintigraphy (**a**) and SPECT (**b**–**d**)

19.1.3 Case 3: IgG4-Related Lesions of the Pancreas

A man in his late 70s presented with intermittent left abdominal pain. On abdominal US and CT, pancreatic swelling and irregular stenosis of the main pancreatic duct were noted, and laboratory examinations showed an elevated serum IgG4 value. On pancreatic biopsy, IgG4-positive lymphoplasmacytic infiltrate was found and IgG4-RD diagnosed.

On whole-body SPECT imaging, ^{67}Ga accumulation was noted at multiple sites within the abdomen (a), but differentiation from accumulation in the digestive tract was difficult. The abdominal SPECT coronal and CT coronal sections (b and c, respectively) were also indeterminate. However, on the SPECT-CT fusion image, the accumulation in the midline was consistent with the marked accumulation seen in the pancreas (d). There was also a horizontal, band-like collection in the transverse colon felt to represent physiological accumulation. However, the area indicated by the thick arrow shows abnormal accumulation in the pancreas (a) (Fig. 19.3).

19.2 Salivary Gland Scintigraphy

Salivary gland scintigraphy is usually performed as a dynamic image data acquisition for 20–45 min after an intravenous injection of ^{99m}Tc pertechnetate. Accumulation in the parotid and submandibular glands and excretory function into the oral cavity after vitamin C administration are evaluated together. As a quantitative analysis, regions of interest are set on four salivary glands and background areas, and time-activity curves are created. Quantitative parameters include degree of accumulation in each gland and washout rate after stimulation by vitamin C. The aims of the examination are to assess salivary gland dysfunction related to IgG4-RD and to evaluate the impact of therapy.

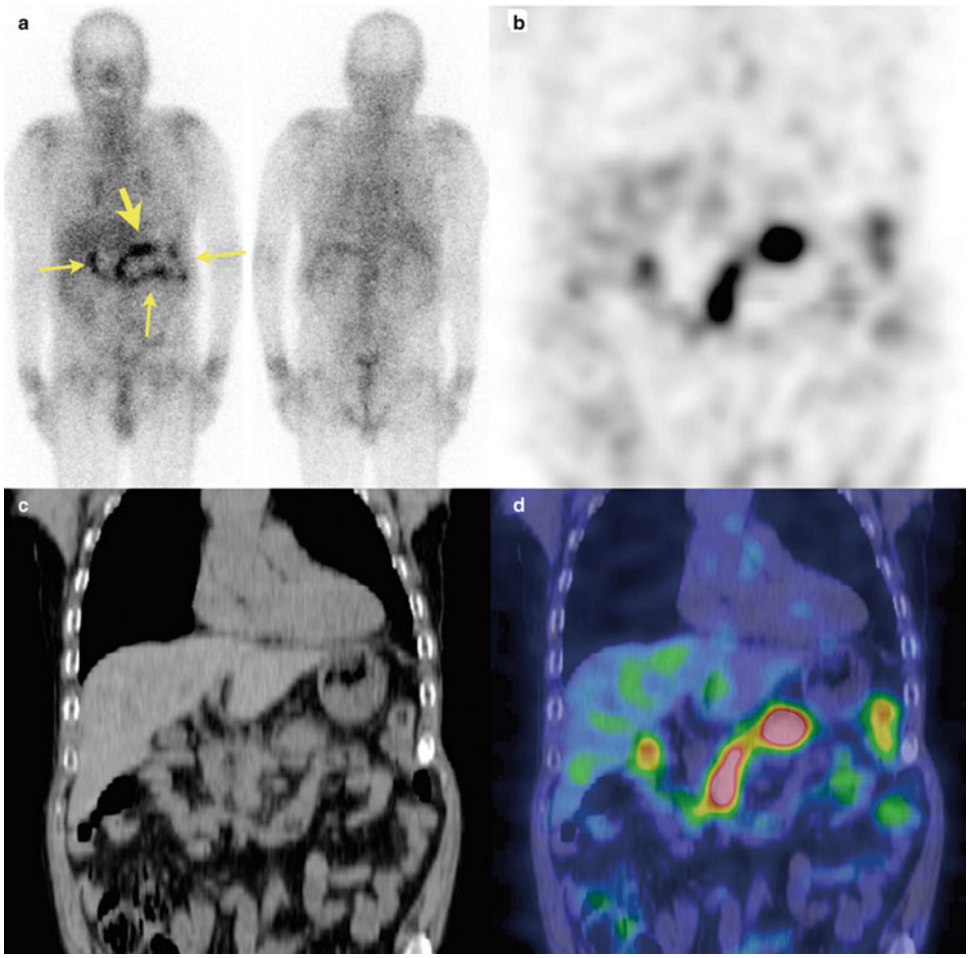

Fig. 19.3 Detection of pancreatic lesions by whole-body ^{67}Ga scintigraphy (**a**) and SPECT (**b–d**). On coronal section fusion image (**d**), clear accumulation in the pancreas is seen

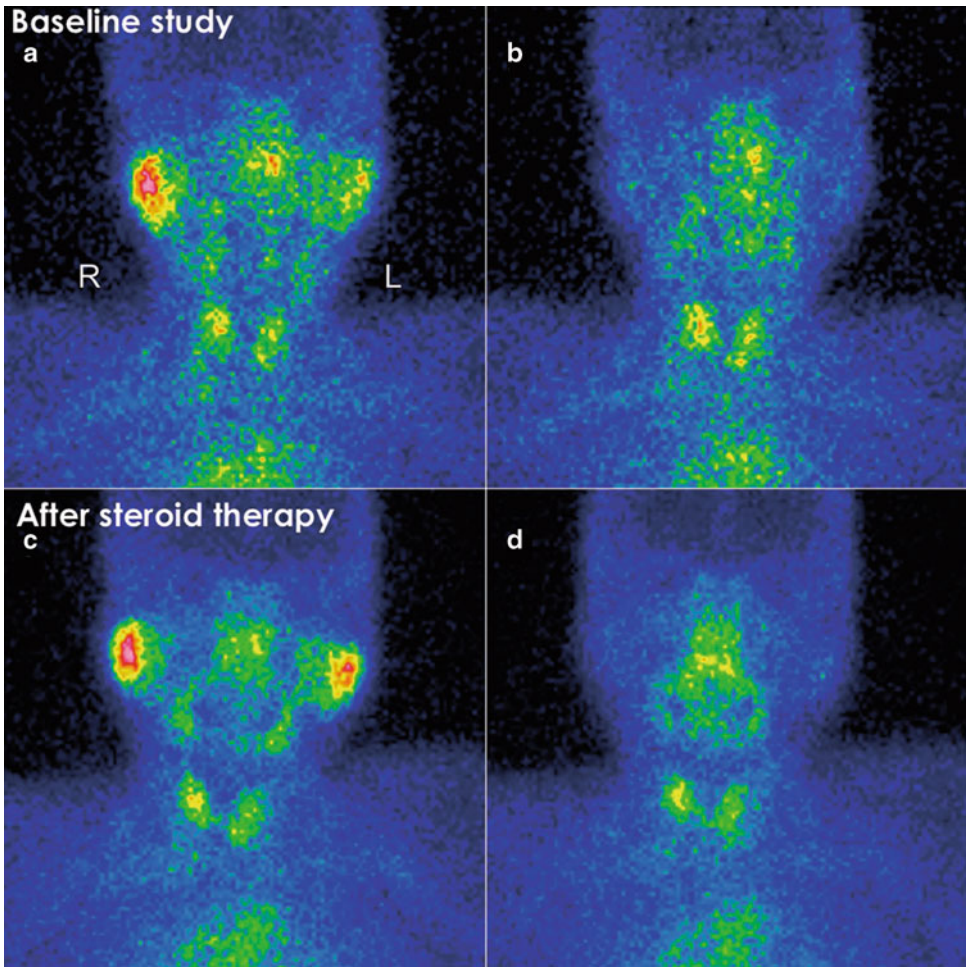

Fig. 19.4 Changes in salivary gland function before and after therapy (**a**, **b**) pre-therapy; (**c**, **d**) post-therapy

Table 19.1 Changes in salivary gland function before and after therapy in case 4

	Submandibular glands	Parotid glands	Submandibular/parotid uptake ratio
Salivary gland uptake/background ratio			
Before therapy	4.05	5.72	0.71
After therapy	5.17	5.95	0.87
Washout rate (%)			
Before therapy	1.9 %	56.3 %	0.03
After therapy	21.7 %	61.9 %	0.35

19.2.1 Case 4: Changes in Salivary Gland Function Before and After Therapy

A woman in her late 70s (the same patient described in Case 1, above) had submandibular gland swelling for 20 years. Two years before presentation an MRI study had shown symmetrical swelling of the lacrimal, parotid, and submandibular glands, and a minor salivary gland biopsy of the lower lip had revealed a lymphoplasmacytic infiltrate that stained positively for IgG4-bearing plasma cells. The serum IgG4 concentration was 696 mg/dL, and anti-SS-A/B antibodies were negative.

The patient was treated with glucocorticoids and scintigraphy was performed before and after this intervention. The upper images in Fig. 19.4 show the findings before therapy, and the lower ones illustrate those following treatment. Before therapy accumulation in the bilateral parotid glands was relatively well preserved, whereas that in the submandibular glands was markedly and heterogeneously decreased (a). Washout after vitamin C administration was also decreased (b). On post-therapy scintigraphy, accumulation in the submandibular glands became clearer (c), and washout was also improved (d) (Fig. 19.4). In a semiquantitative evaluation using the accumulation count, both the washout rate after vitamin C administration and the accumulation in the submandibular glands as compared with the parotid showed clear improvement (Table 19.1).

19.3 Renal Scintigraphy

For the evaluation of renal function, renal dynamic imaging is performed using ^{99m}Tc-diethylene-triamine-pentaacetic acid (DTPA). Renograms are created for each kidney and split glomerular filtration rate is calculated. Renal cortex imaging using ^{99m}Tc-dimercaptosuccin acid (DMSA) is also utilized. Because of limited resolution in ^{99m}Tc-DTPA examination, minor functional abnormalities cannot be detected, but areas with major functional decreases in each kidney can be identified. ^{99m}Tc-DMSA static scintigraphy and SPECT are used to detect renal cortical fibrosis. With regard to renal lesions, ^{67}Ga scintigraphy is performed to assess the inflammatory response [3, 8], while DTPA and DMSA scintigraphies are indicated for the evaluation of function and fibrosis.

19.3.1 Case 5: Renal Cortical Lesions

A man in his early 60s presented 1 year earlier after noticing bilateral submandibular swelling. Bilateral submandibular gland swelling, pancreatic tail lesions, bilateral renal lesions, and lesions around the aorta and right internal iliac artery were demonstrated by contrast-enhanced CT. A renal biopsy was consistent with IgG4-RD. The serum IgG4 concentration was 350 mg/dL.

On DMSA scintigraphy, localized sites of decreased accumulation were found in the upper part of the left kidney and both the upper and lower poles of the right kidney (a, arrows). In the arterial phase of contrast-enhanced dynamic CT, heterogeneous enhancement of the cortex was noted mainly at the same sites (b) (Fig. 19.5).

19.4 Concluding Remarks

In this chapter we presented a number of IgG4-RD cases to outline the various examination methods using single-photon radionuclides that are useful in this context. ^{67}Ga inflammation scintigraphy has frequently been used for whole-body screening for lesions, but the diagnostic accuracy of IgG4-RD as compared with FDG-PET will require additional study. For other functional and static evaluations, a number of other scintigraphic examinations can be also used (Table 19.2). In any case, although scintigraphic evaluation was not specific for IgG4-RD, it provides information on organ function and an index for diagnosis and therapeutic effects. Combined use of SPECT-CT is recommended to confirm functional-anatomical correspondence.

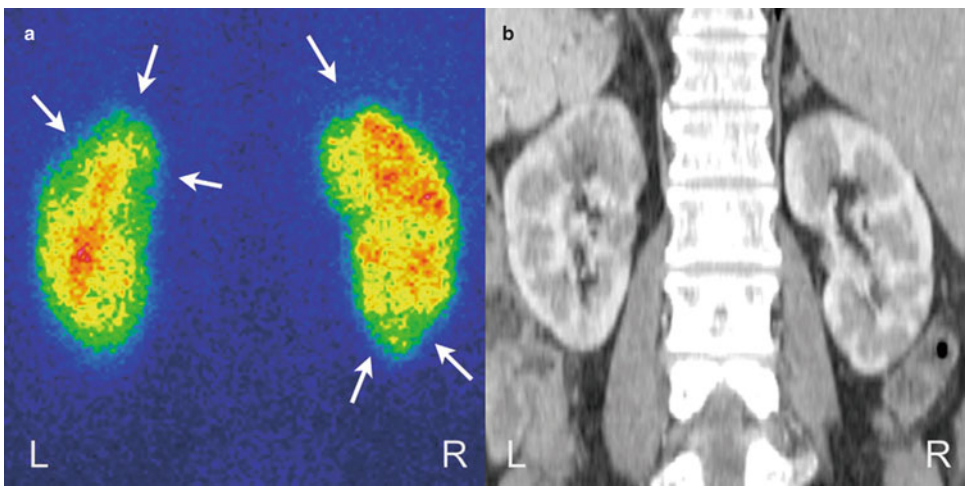

Fig. 19.5 Evaluation of lesions by renal cortex scintigraphy (**a**). To compare the anterior CT images with the posterior images on scintigraphy, left-right inversion of the former was performed (**b**)

Table 19.2 Functional evaluation using single-photon radiopharmaceuticals of organs with possible IgG4 disease involvement

Organ	Scintigraphy	Radiopharmaceutical	Application
Whole body	^{67}Ga scintigraphy, SPECT	^{67}Ga-citrate	Detection of inflammatory lesions and severity (lacrimal glands, salivary glands, lungs, pancreas, kidneys, retroperitoneum, mediastinum, pleura, pericardium, great vessels, intraorbital tissues)
Salivary glands	Salivary gland scintigraphy	^{99m}Tc-pertechnetate	Impaired accumulation and excretion
Liver and bile ducts	Hepatobiliary scintigraphy	^{99m}Tc-PMT	Abnormal excretion due to cholangitis
Kidney	Renal cortical perfusion scintigraphy, renal dynamic study	^{99m}Tc-DMSA, ^{99m}Tc-DTPA	Cortical perfusion defect, abnormality in blood flow and excretion

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Positron Emission Tomography with F-18 Fluorodeoxyglucose

20

Kenichi Nakajima, Anri Inaki, Takafumi Mochizuki, Seigo Kinuya, and Mitsuhiro Kawano

20.1 Basic Properties of ^{18}F-Fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (FDG) is a unique glucose analog that reflects glucose metabolism in various organs and diseases. In this molecule, the positron-emitting radioactive isotope fluorine-18 is substituted for the normal hydroxyl group at the **2′** position of the glucose molecule. The labeled molecule is absorbed into cells via a glucose transporter, becomes phosphorylated, and then accumulates within the cell. Regions of high glucose metabolism, as found in malignant tumors and inflammatory conditions, can be detected. The technique is also useful for assessing glucose metabolism within the heart and brain for myocardial viability, epilepsy, and dementia.

20.2 Physiological Distribution of FDG

The judgment as to whether or not FDG accumulation is abnormal in a given case must be informed by knowledge of this molecule's physiological distribution. FDG normally accumulates in the brain due to its vigorous glucose metabolism and to varying degrees in the heart, an organ in which glucose metabolism accounts for a part of the total energy expenditure. Slight to moderate accumulation is also observed in the palatine tonsil, digestive tract, and liver and also usually along its route of excretion, namely, the urinary tract including the kidneys, ureters, and bladder. High accumulation is sometimes seen in brown adipose tissue from the neck to supraclavicular regions and around the vertebral bodies. Positive accumulation is also sometimes found in large vessels with atheroma. When FDG accumulation is considered as a reflection of glucose metabolism activity, it should be kept in mind that FDG accumulation is observed in both normal and abnormal metabolic conditions.

20.3 Interpretation and Processing of FDG-PET

A dose of 4.0 MBq/kg of ^{18}F-FDG is administered in the fasting condition after confirmation of the blood glucose level. Early images are interpreted 60 min thereafter, and when necessary late images are added 120 min after injection. In our institution, the PET images are obtained using PET-CT Discovery ST Elite or Discovery PET-CT690 (GE) that has a capability of time-of-flight reconstruction. The degree of FDG accumulation is expressed as the widely used Standardized Uptake Value (SUV), and its maximum value (SUVmax) within the region of interest is used. SUV is defined as radioactivity (Bq/g)/(administered dose (Bq)/weight (g)) and is an index indicating how many folds of accumulation are present compared with FDG distributed uniformly throughout the body.

20.4 Application of FDG-PET to IgG4-Related Disease

Of the various diseases now classified as part of the IgG4-RD spectrum, type 1 AIP has been the focus of greatest study. Ultrasonography (US), computed tomography (CT), and FDG-PET have all been employed in the evaluation of type 1 AIP [1–6]. Although reports on the use of PET in extrapancreatic IgG4-RD have been relatively few, it has been found helpful in

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Table 20.1 Possibly useful indications for FDG-PET in IgG4-RD

Purposes	Organs
Whole body survey for IgG4-related diseases	
Useful	Lacrimal glands, salivary glands, lymph nodes, pancreas, mediastinum, retroperitoneum, great vessels
Possibly useful	Intraorbital tissues other than lacrimal glands, lung, pleura, pericardium, hepatobiliary ducts, kidneys, nerve plexus, pseudotumor, pituitary gland, dura mater, thyroid, breasts, prostate
Evaluation of severity based on accumulated activity	All organs
Therapeutic effects	All organs

cholangitis [7, 8], retroperitoneal fibrosis [3, 4, 9], Mikulicz's disease [10], sialadenitis/dacryoadenitis [3, 5], and renal IgG4 lesions [3, 11], and we anticipate that this imaging modality has an important role to play in the assessment of IgG4-RD. Table 20.1 lists the roles of FDG-PET in individual organs.

FDG accumulates in the pancreas in both autoimmune pancreatitis and pancreatic cancer. Thus, differentiation of the two is not possible based on the presence and absence of accumulation or some SUVmax cutoff value. Whereas FDG accumulation is limited to the tumor in pancreatic cancer; however, in autoimmune pancreatitis FDG tends to accumulate diffusely throughout a swollen pancreas or heterogeneously at multiple sites. These findings are thought to reflect activity corresponding to cell infiltration consisting mainly of lymphocytes and plasmacytic cells and fibrotic lesions in the pancreas.

When extrapancreatic lesions are detected, particularly in organs or regions classically involved by IgG4-RD such as the salivary gland, lacrimal gland, kidney, aorta, pseudotumor, hepatic bile duct, pleura, pericardium, mediastinum, or retroperitoneum, IgG4-RD can be diagnosed tentatively (Table 20.1). FDG-PET has been widely used to search for metastases from cancer and is also useful in the detection of IgG4-related lymph node lesions. Accordingly, FDG-PET has advantages as a whole-body screening method for organs bearing IgG4-related lesions.

In cases in which a diagnostic biopsy is required in lymph nodes or renal lesions, suitable sites to biopsy can be chosen by referring to the sites of the highest FDG accumulation [11, 12]. Improvement in the degree of FDG accumulation has been documented following the administration of glucocorticoids or other agents [2, 3, 5, 13].

Below, we describe the FDG-PET findings in several patients with IgG4-RD.

20.4.1 Case 1: Sialadenitis

A woman in her 70s with sialadenitis is shown in Fig. 20.1. She had had submandibular gland swelling for 20 years. On an MRI examination performed 2 years before presentation, symmetrical swelling of the lacrimal, parotid, and submandibular glands was noted. On a lower lip minor salivary gland biopsy, IgG4-positive plasma cells were found, and the serum IgG4 concentration was 696 mg/dL. Anti-SS-A/B antibodies were negative.

On FDG-PET maximum-intensity projection images, marked accumulation was found in the parotid and submandibular glands, most prominently in the latter. The site of maximum accumulation of FDG showed an SUVmax of 7.4. PET-CT fusion images of the parotid gland (upper right panel) and submandibular gland (lower left panel) showed high accumulation of FDG. A PET-CT fusion image of the pancreas is shown in the lower right panel. An FDG maximum-intensity projection image showed slight diffuse accumulation around the pancreas, while PET-CT showed localized accumulation within the pancreas. These salivary gland and pancreas findings were consistent with those of IgG4-RD.

20.4.2 Case 2: Type 1 AIP and Inflammatory Abdominal Aortic Aneurysm

A man in his 70s was found to have both pancreatic lesions and an abdominal aortic aneurysm by CT (Fig. 20.2). The examination revealed a periaortic soft tissue shadow, inflammatory changes of the pancreatic bile duct, a left common iliac artery aneurysm with mural thrombus, and a right common iliac artery aneurysm. The serum IgG4 concentration was 1,420 mg/dL.

An FDG-PET study was performed. High FDG accumulation was found within the swollen pancreas, and the SUVmax was 5.3. FDG accumulation was found from the abdominal aorta to the bilateral common iliac artery wall, with SUVmax slightly elevated at 3.5.

20.4.3 Case 3: Interstitial Nephritis and Hepatic Pseudotumor [11]

Figure 20.3 illustrates the case of a man in his late 50s in whom both renal and hepatic lesions had been demonstrated by other imaging modalities. Mass lesions were first demonstrated in the liver by abdominal ultrasound. A contrast-enhanced CT scan of the abdomen revealed non-enhancing lesions in both the liver and kidneys. Tissue biopsies demonstrated

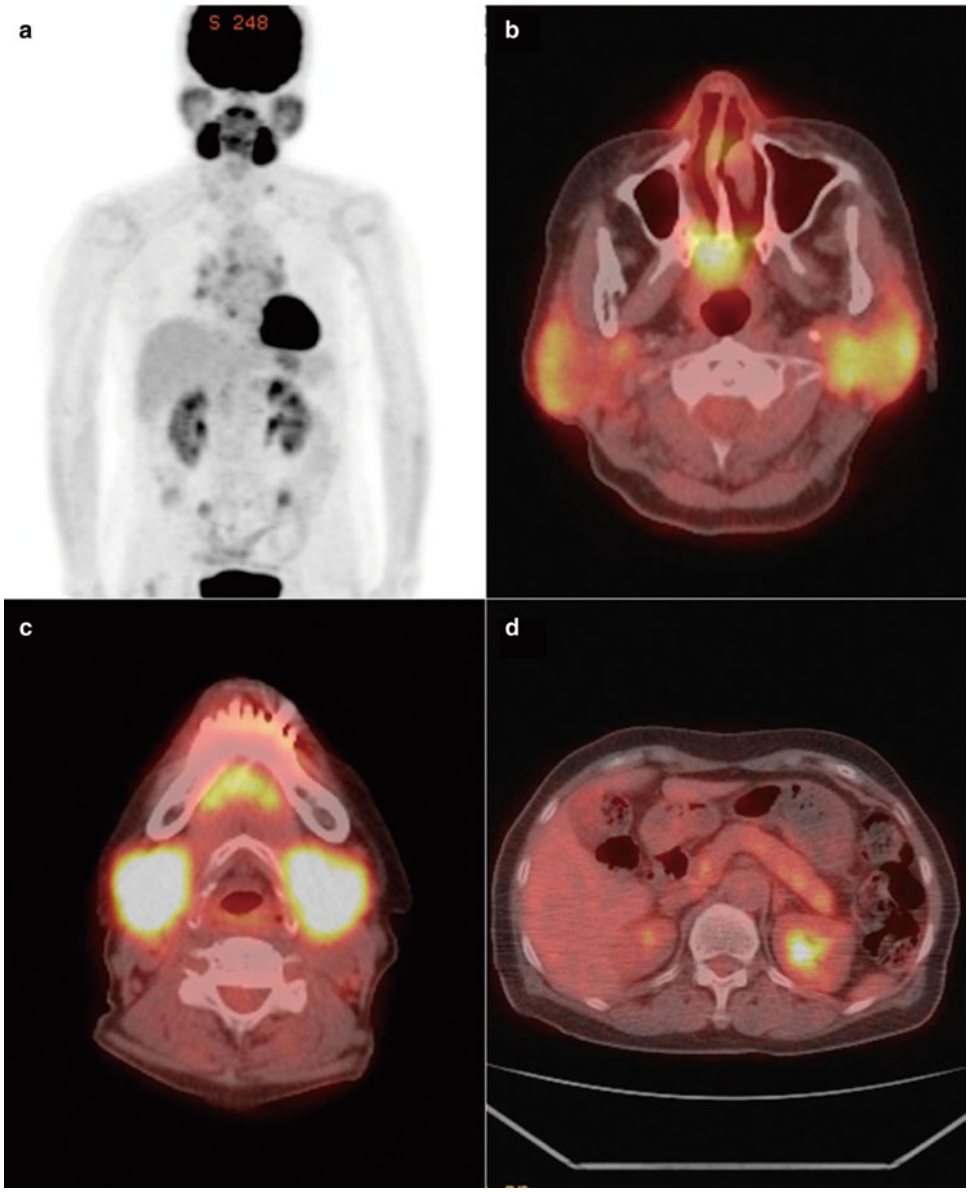

Fig. 20.1 FDG accumulation is found in the bilateral lacrimal, parotid, and submandibular glands. (**a**) Maximum-intensity projection image; (**b**–**d**) PET-CT fusion image

histopathology consistent with IgG4-RD in both organs, and IgG4-related liver pseudotumor and interstitial nephritis were diagnosed. The serum IgG4 concentration was 1,470 mg/dL.

A maximum-intensity projection image from an FDG-PET study is shown in the upper left panel of Fig. 20.3. Both hepatic and renal lesions are demonstrated, with an SUVmax of 5.8. The upper right panel shows a coronal section of an abdominal PET-CT fusion image, and the lower left an axial section of a hepatic PET-CT fusion image. The lower right shows a coronal section of a PET-CT fusion image of a brachial nerve plexus from C6. Extension of inflammation consistent with the nerve plexus was suspected, and this was thought to originate from IgG4-RD lesions at the same site.

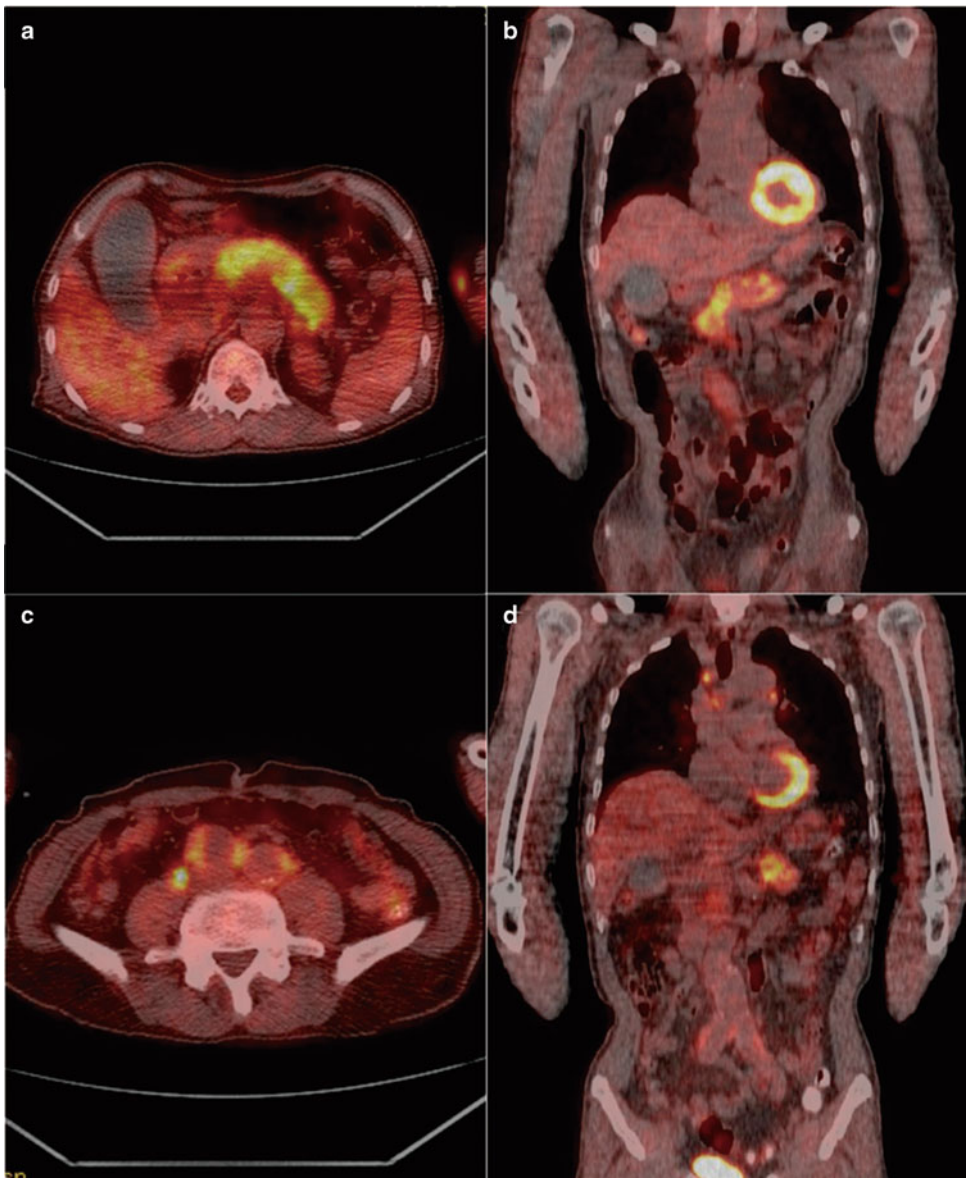

Fig. 20.2 FDG accumulation in the pancreas, abdominal aorta, and large vessels on transaxial (**a**, **c**) and coronal (**b**, **d**) PET-CT fusion images

20.4.4 Case 4: Dacryoadenitis

A woman in her late 50s with dacryoadenitis is shown in Fig. 20.4. She presented because of an abrupt decrease in the visual acuity of her right eye. Bilateral lacrimal gland swelling was observed at this time. The serum IgG4 concentration was 606 mg/dL and assays for antibodies to the Ro/SS-A and La/SS-B antigens were negative.

An FDG-PET study was performed. The upper left shows the lateral view of a maximum-intensity projection image, confirming FDG accumulation in the lacrimal glands. No significant accumulation was found in the pancreas, periaortic

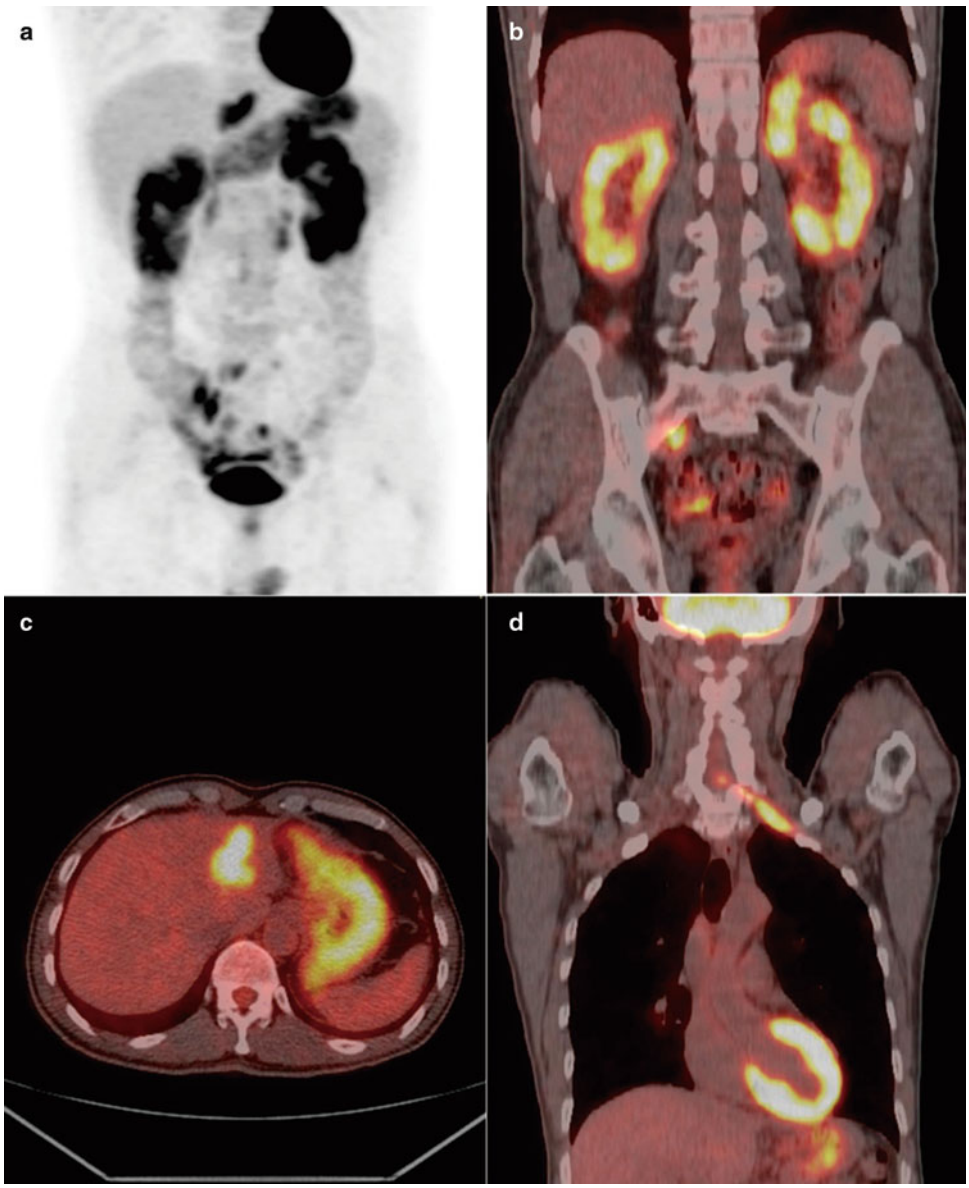

Fig. 20.3 FDG accumulation in interstitial nephritis (**a**, **b**) and liver pseudotumor (**c**). FDG accumulated clearly in the nerve plexus (**d**). (**a**) Maximum-intensity projection image, (**b**–**d**) PET-CT fusion images

tissues, or salivary glands. The upper right panel, showing a transaxial CT image, indicated bilateral swelling of the lacrimal glands. The FDG PET (lower left panel) demonstrated accumulation consistent with the bilateral lacrimal gland involvement, and SUVmax was 6.5. The lower right shows the corresponding PET-CT fusion image.

20.5 Concluding Remarks

In this chapter we presented some cases in which FDG accumulation was useful in the localization and evaluation of the activity of various IgG4-related lesions and discussed the areas in which its use is of particular value. FDG accumulation

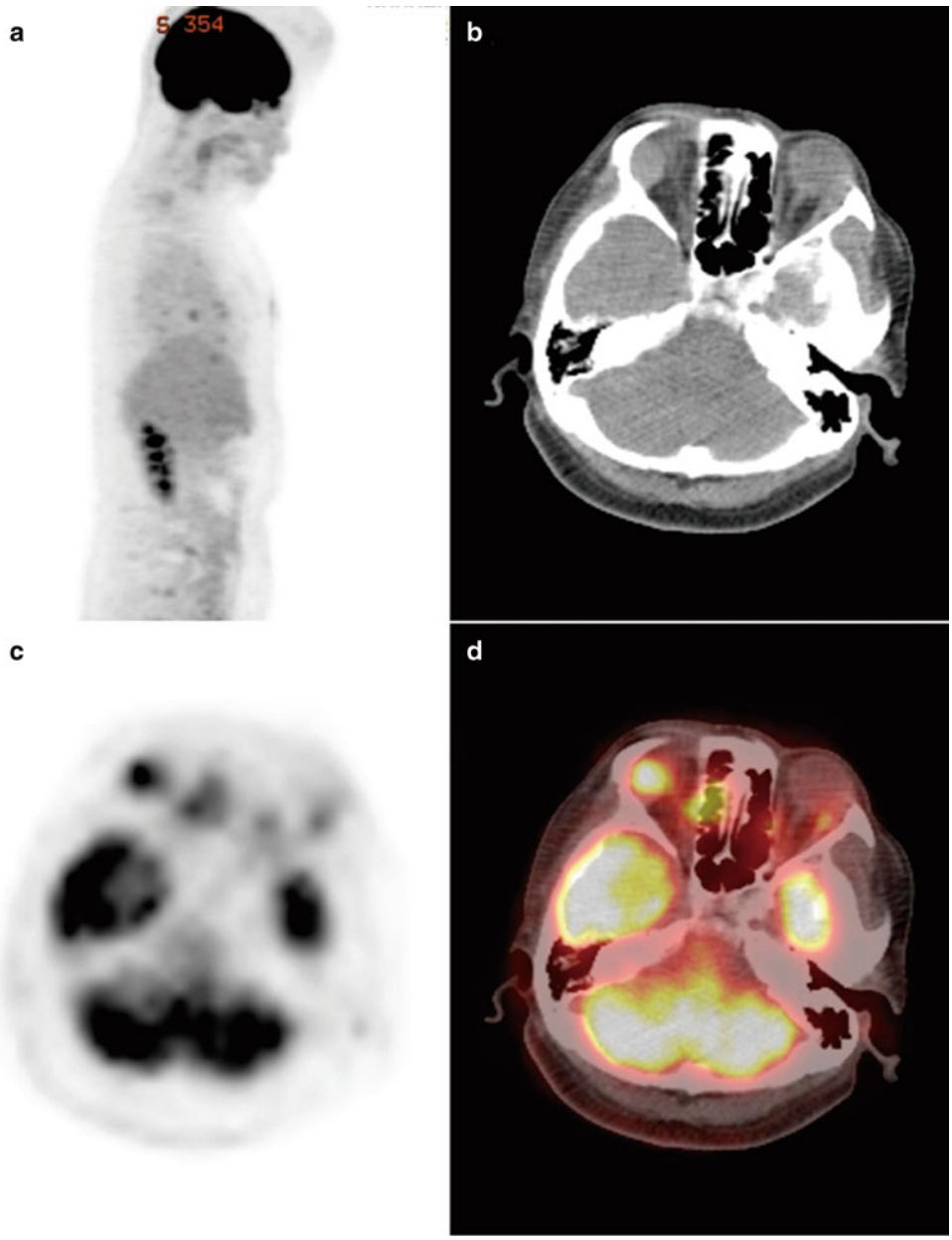

Fig. 20.4 FDG accumulation consistent with lacrimal gland swelling. (**a**) Maximum-intensity projection lateral view; (**b**) CT axial section; (**c**) FDG-PET image; (**d**) PET-CT fusion image

is not specific for IgG4-RD. However, when high abnormal accumulation of FDG is detected, one should suspect active glucose metabolism related to an inflammatory response associated with cell infiltration or active fibrosis. In cases requiring diagnostic biopsy, sites showing the highest FDG accumulation can be preferentially considered as candidate biopsy sites. Further studies will be required to determine the full potential for FDG-PET in the initial evaluation and longitudinal management of patients with IgG4-RD.

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Part III

Pathology

Pancreas

21

Kenji Notohara

21.1 Introduction

The IgG4-related lesion in the pancreas, now termed type 1 autoimmune pancreatitis (AIP), was first reported in 1991 under the descriptive moniker of lymphoplasmacytic sclerosing pancreatitis (LPSP) [1]. Kawaguchi and colleagues focused upon only two cases in their report but in doing so accounted for nearly all of the pathological characteristics of type 1 AIP recognized today. The authors demonstrated remarkable foresight in observing that the disease delineated by their cases must have a systemic distribution (see Chap. 2).

A similar report published by a European group in 1997 proposed the concept of nonalcoholic duct destructive chronic pancreatitis (NDCP) [2]. In retrospect, some of the cases seem to fall into the category of type 1 AIP/LPSP with an association of "Sjögren's syndrome" or "primary sclerosing cholangitis" or histological identification of numerous obliterated veins (this was detected only in one of twelve cases). However, cases with the pancreatic duct epithelium infiltrated by neutrophils and destroyed—a process highly reminiscent of type 2 AIP—are also included. The authors concluded that all of these histological features are a process of continual change, and neutrophilic inflammation seen in the duct causes the extensive fibrosis.

Other trends in the AIP literature confirmed the existence of a subset of patients with discordant features such as neutrophil infiltration into the pancreatic duct epithelium, similar (or identical) to that observed in NDCP. This entity, known for several years as idiopathic duct-centric chronic pancreatitis (IDCP) [3], or AIP with granulocytic epithelial lesion (GEL) [4], is now considered to be an entity distinct from LPSP.

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The confusing tale describing nomenclature changes within the two entities now considered to comprise AIP stems from the fact that the literature surrounding these entities was conceived, developed, and debated without the benefit of the immunostaining of tissues for IgG4. Subsequent to much of the discussion about LPSP, NDCP, and IDCP, Hamano et al. demonstrated that serum IgG4 values are elevated in AIP patients [5] and that tissue lesions are infiltrated by numerous IgG4-positive plasma cells [6]. The number of IgG4-positive plasma cells was then noted to be significantly higher in LPSP than in IDCP [7], leading to the realization that LPSP and IDCP are in fact different diseases and that LPSP is the IgG4-related condition.

The existence of various clinical differences between the two also became apparent [8]. At present, LPSP and IDCP are called type 1 and type 2 AIP, respectively [9], and in the International Consensus Diagnostic Criteria for AIP, separate diagnosis criteria for the two types have been proposed [10].

LPSP and IDCP are now recognized as related conditions that demonstrate the pathological features of type 1 and type 2 AIP, respectively. Yoshida et al. announced the concept of AIP in 1995 [11] and in that single case reported a clinical picture now regarded as classic for type 1 AIP.

Few inflammatory diseases of the pancreas other than AIP show major lymphoplasmacytic infiltration. For this reason, the attention of pathologists became focused upon this glaring anomaly within the spectrum of pancreatic disease. Indeed, the author considers it inevitable that the first IgG4-related lesion to be identified was that of the pancreas as opposed to any other organ. The highly specific nature of type 1 (IgG4-related) AIP, formerly known as LPSP, can be appreciated by reading the original report of Kawaguchi et al [1]. In describing the history of AIP, the importance of those initial observations pertaining to the histological features of this condition must be emphasized.

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21.2 Pathological Characteristics of Type 1 AIP

21.2.1 Fibrotic Lesions

The basic pathological findings of type 1 (IgG4-related) AIP are marked lymphoplasmacytic infiltration and fibrosis that involve the exocrine tissues, including pancreatic ducts and lobules, peripancreatic adipose tissue, and blood vessels, resulting in the formation of characteristic lesions. Lymphoid follicle formation is also often present. Within these lesions eosinophilic infiltration is occasionally seen, while copious eosinophilic infiltrates are observed only rarely and neutrophil infiltrates almost never.

The storiform type of fibrosis seen in type 1 AIP is characterized by bands of fibrosis that radiate in various directions from the center, sometimes forming a characteristic swirling pattern. Despite its fibrotic nature, it is typically accompanied by a copious inflammatory cell infiltrate. These findings are fundamentally different from those of the forms of fibrosis seen in other types of chronic inflammation. Storiform fibrosis shows a range of changes varying from lesions with a cell-rich component to others that consist mainly of collagen. Within a single case, a mixture of lesions may be found. Lesions with a cell-rich component are comprised of small spindle cells, lymphocytes, and plasma cells, with little collagen content (cell-rich type; Fig. 21.1a). Over time, collagen formation progresses, with a gradual reduction in the cellular component of the inflammation (transitional type; Fig. 21.1b). The final stage of this process is the fibrotic stage, at which time fibrotic foci develop that consist mostly of collagen with a scanty cellular component (fibrotic type; Fig. 21.1c). Cell-rich and transitional types of storiform fibrosis are of the greatest diagnostic significance, because the diagnosis of type 1 AIP and IgG4-RD is difficult to render with conviction at the fibrotic stage.

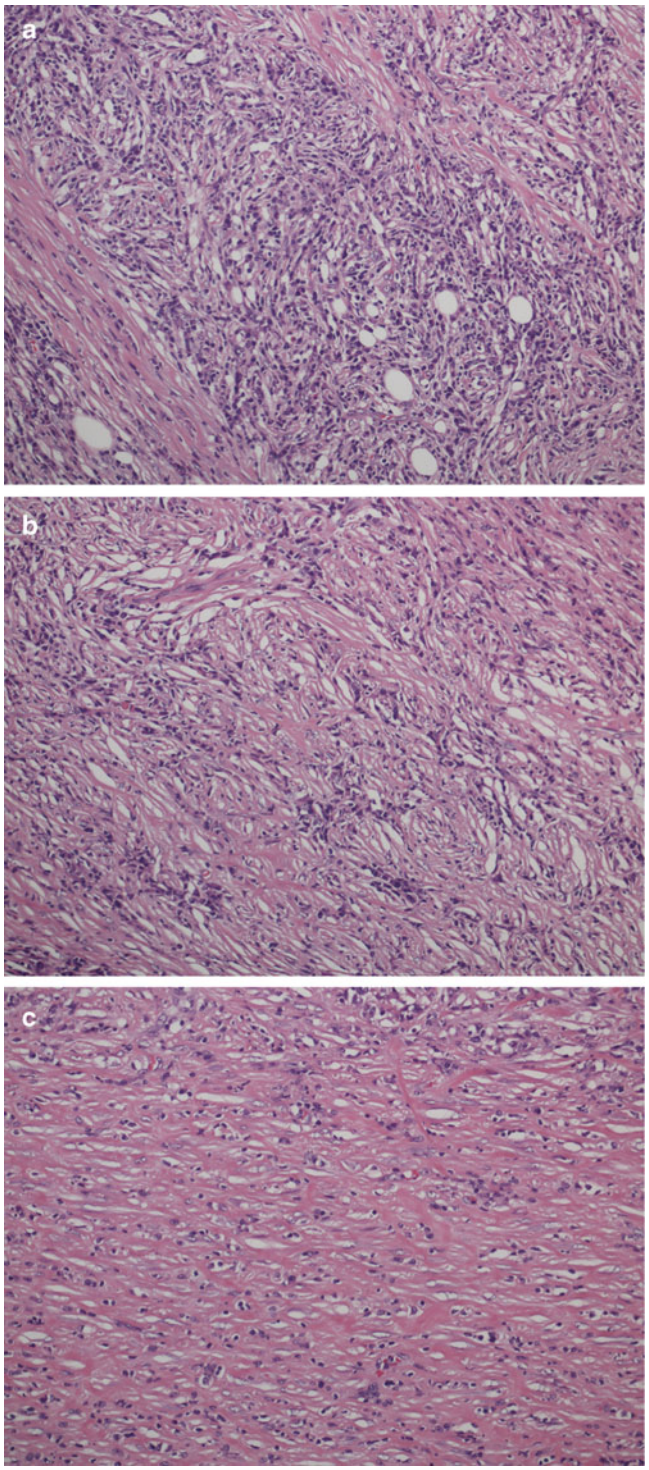

Fig. 21.1 Storiform fibrosis seen in type 1 AIP. (**a**) Cell-rich type; (**b**) transitional type; (**c**) fibrotic type

21.2.2 Pancreatic Duct Lesions

Lesions composed of lymphoplasmacytic infiltration and fibrosis form and surround the ductal epithelium of the pancreas. Inflammatory cell infiltration of the pancreatic duct epithelium, regressive epithelial changes, and regenerative findings are typically not seen in type 1 (IgG4-related) AIP, but rather are characteristic of type 2 AIP. Typical pancreatic duct lesions are easy to identify in the interlobular pancreatic ducts, and lesions are also often observed in the intralobular pancreatic ducts. Occasionally, a thin layer with a simple infiltration of lymphocytes and plasma cells just beneath the epithelium is surrounded by fibrosis. In others, a thick inflammatory band with storiform fibrosis surrounds the epithelium, creating the impression of a thickened pancreatic duct wall (Fig. 21.2) [12].

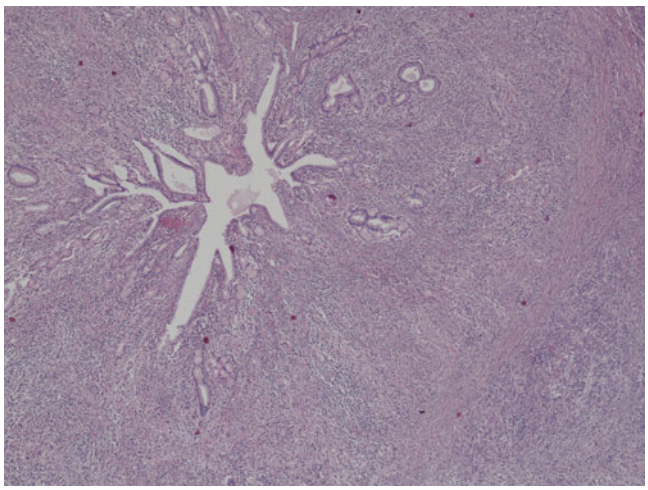

Fig. 21.2 Pancreatic duct lesions of type 1 AIP. Around the epithelium a thick inflammatory lesion associated with storiform fibrosis has formed, giving the appearance of a thickened pancreatic duct wall

21.2.3 Lobular Lesions

Lymphoplasmacytic infiltration of the lobules is frequently seen, with the development of interlobular fibrosis. Lymphoplasmacytic infiltration may be also present in interlobular fibrotic foci. Lobular atrophy generally ensues with pancreatitis of other causes, but in type 1 AIP, the inflamed lobules usually do not become atrophic and their borders remain well preserved (Fig. 21.3a) [12, 13]. On the other hand, acinar cell loss does occur (Fig. 21.3b). This is thought to reflect injury to the pancreatic parenchyma. The lobules also occasionally become edematous. When the lobular structure has been largely destroyed, the lobule and surrounding fibrosis merge, sometimes showing storiform fibrosis. This phenomenon is particularly common at the border between the pancreas and surrounding adipose tissue. In the absence of such findings, obvious storiform fibrosis is difficult to detect in the lobules.

21.2.4 Peripancreatic Adipose Tissue Lesions

Peripancreatic adipose tissue inflammation, virtually a sine qua non for the diagnosis of type 1 AIP, is the site where storiform fibrosis and obliterative phlebitis are most commonly observed. Inflammation involves the fat lobules and spreads by enclosing individual adipocytes, until they are gradually replaced by inflammatory foci (Fig. 21.4). At the pancreatic border, parenchymal injury is often severe, and the border between the pancreatic parenchyma and adipose tissue becomes indistinct.

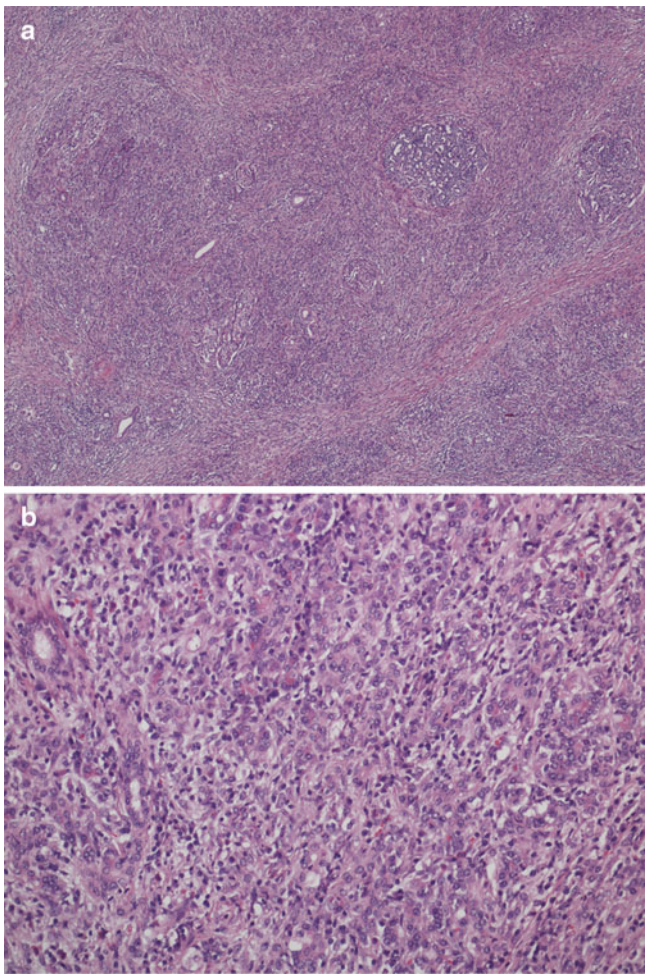

Fig. 21.3 Lobular lesions of type 1 AIP. (**a**) Lobular atrophy is absent, and the borders are preserved. (**b**) In the lobules there is loss of acinar cells, and lymphoplasmacytic infiltration is seen

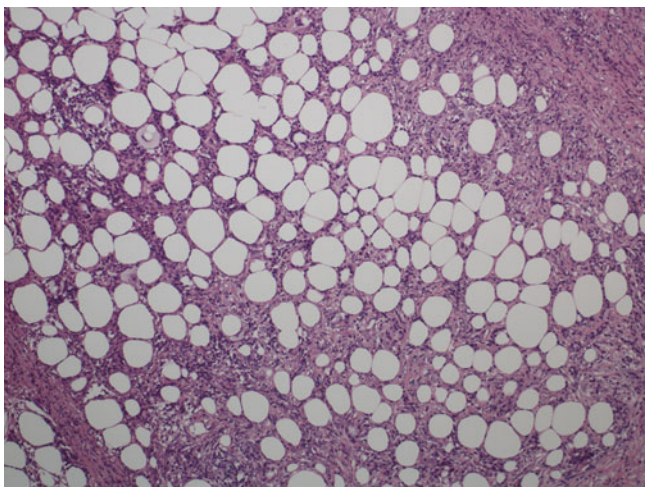

Fig. 21.4 Peripancreatic adipose tissue lesions of type 1 AIP. Inflammatory cell infiltrates spread between adipocytes, and in areas in which inflammation has advanced, adipocytes have become unclear

21.2.5 Vascular Lesions

Phlebitis is an essentially universal finding in type 1 AIP. Inflammation of the venules is the major finding, with lymphocytes and plasma cells infiltrating from the venous wall into the lumen, culminating in venous obliteration. For this reason, this condition is called "obliterative phlebitis." Phlebitis may also be found in large veins such as the splenic and portal veins, but in these instances the inflammation is limited to only a portion of the wall and rarely results in obliteration.

Obliterative phlebitis is usually easy to recognize on sections stained by hematoxylin and eosin and should be suspected when no vein is evident adjacent to an artery, because under normal circumstances in the pancreas, arteries and veins run in parallel (Fig. 21.5a). Staining of elastic fibers using a stain like elastica van Gieson also facilitates the identification of obliterated veins (Fig. 21.5b), but venous occlusion such as may be caused by an organizing thrombus in the setting of either chronic pancreatitis or pancreatic cancer must be differentiated carefully. The histological picture of obliterative phlebitis is identical to that of the surrounding inflammatory changes. Thus, obliterative phlebitis may blend into the inflammatory background of the surrounding tissue. Storiform fibrosis may also be found in involved veins.

Small arteries are also occasionally inflamed (arteriolitis) with type 1 AIP [3]. Arterial lesions frequently form by extension from the adventitia to the outer layer of the media (Fig. 21.5c). These arterial lesions are similar in morphology to those of the IgG4-related periarteritis detected in the aorta and its larger branches, with lumen occlusion observed rarely. Marked inflammation is present in the surrounding tissue in early lesions, making it difficult to judge whether the inflammation in the portion of the vessel corresponding to the arteriolar adventitia represents a true arteritis or not. For this reason, only few reports are yet available on the characteristics and frequency of such arterial lesions.

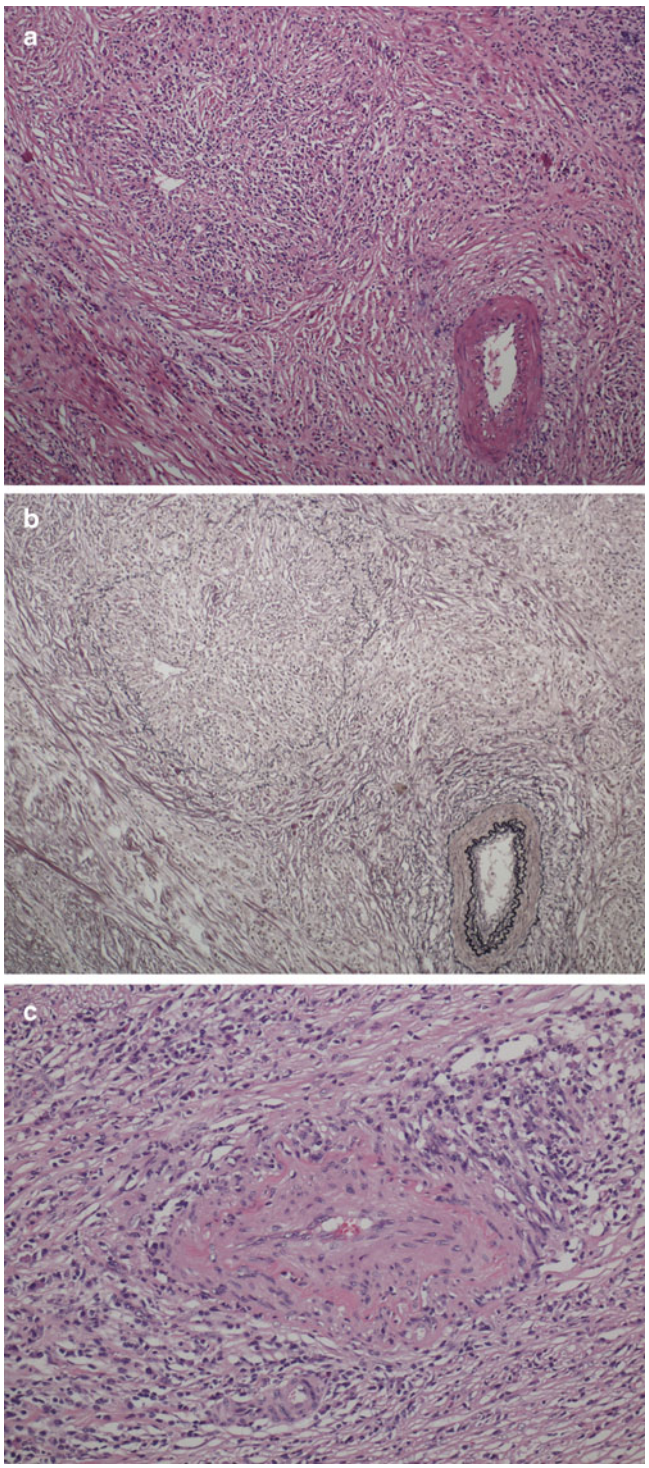

Fig. 21.5 Vascular lesions of type 1 AIP. (**a**) Obliterative phlebitis. A vein running in parallel with the artery cannot be identified, and at the site where the vein would be expected to be present, a nodule-like inflammatory focus has formed. (**b**) Obliterative phlebitis (elastica van Gieson stain). At the same site as (**a**) elastic fibers are stained, an obliterated vein is clearly observed. (**c**) Arteriolitis. Inflammation extends from the adventitia to media, and the medial smooth muscle layer has become obscured

21.2.6 IgG4-Positive Plasma Cells

Abundant IgG4-positive plasmacytic infiltration is present in type 1 AIP (Fig. 21.6). In resected materials, usually >50 positive cells per high-power field (HPF) are noted [14]. However, because this criterion is only rarely satisfied in biopsy materials, the number of IgG4-positive plasma cells has been set at >10/HPF in some proposed diagnostic criteria [10]. Setting the cutoff point at only 10 IgG4-positive plasma cells per HPF in the pancreas lowers the diagnostic specificity

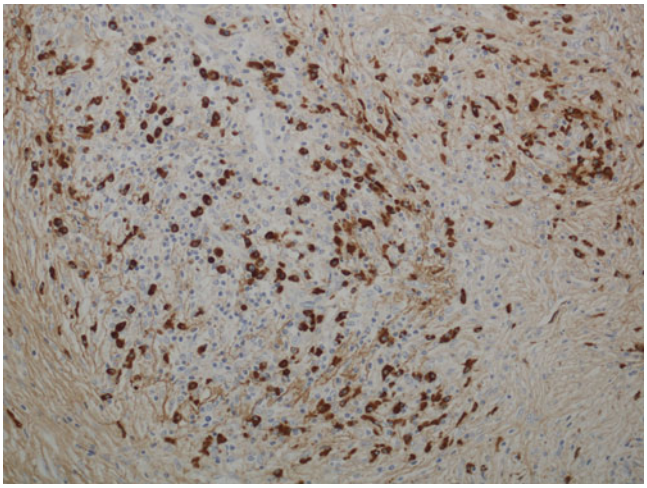

Fig. 21.6 Abundant IgG4-positive plasmacytic infiltration seen in type 1 AIP

of this finding, because such tissue concentrations of IgG4-positive cells are also observed occasionally in conditions other than type 1 AIP (e.g., in the inflammation associated with pancreatic cancer [7]). Thus, this tissue finding alone is not diagnostic of type 1 AIP.

In the pancreas as well as other organs, determination of the IgG4/IgG ratio within tissue is a useful diagnostic indicator, sometimes more useful than the simple count of IgG4-positive plasma cells per HPF. The IgG4/total IgG ratio may be conceptualized to be more useful than the count of IgG4-positive plasma cells as the degree of fibrosis within a tissue waxes and the cellular inflammatory component wanes. In type 1 AIP, the IgG4/total IgG ratio is usually >0.40, though exceptions to this guideline certainly exist.

In the International Consensus Diagnostic Criteria for AIP, a diagnosis of type 1 autoimmune (IgG4-related) pancreatitis can be established when ≥3 of the following histological items are satisfied: (1) periductal lymphoplasmacytic infiltration without granulocytes; (2) storiform fibrosis; (3) obliterative phlebitis; and (4) numerous (>10/HPF) infiltrating IgG4-positive cells [10]. These criteria emphasize the importance of the histological picture in the diagnosis of type 1 AIP. For example, even if the number of infiltrating IgG4-positive plasma cells exceeds 10/HPF, the diagnosis of type 1 AIP cannot be rendered if neither storiform fibrosis nor obliterative phlebitis is present. The strict requirement for the characteristic histopathological findings of storiform fibrosis and obliterative phlebitis compensates to some degree for the relatively low diagnostic hurdle of only >10 IgG4-positive plasma cells per HPF.

21.3 Pathological Characteristics of Type 2 AIP

The lesions of type 2 AIP extend from the pancreatic ducts to within the lobules, involving mainly the exocrine tissue. It is clearly an epithelium-centric inflammation, with the lumen and/or epithelium of the pancreatic ducts infiltrated by neutrophils—the so-called GEL—resulting in epithelial degeneration and loss and the finding of regenerative changes (Fig. 21.7a, b). Lymphoplasmacytic infiltration surrounds the epithelium but there is not a predominance of IgG4 staining among the plasma cells present. Pathological evaluation is essential to making the diagnosis of type 2 AIP, and the presence of GEL in the interlobular pancreatic duct establishes this diagnosis. This epithelium-centric inflammation further extends from the peripheral intralobular pancreatic duct to the acinar cells (Fig. 21.7c, d), and lymphoplasmacytic infiltration is seen within the intralobular stroma. Fibrosis is seen in the interlobular regions, but this differs from the interlobular inflammation seen in type 1 AIP because the inflammatory cell infiltration in this area is sparse by comparison to type 2 AIP. Storiform fibrosis and obliterative phlebitis, so characteristic in type 1 AIP, are absent in the type 2 subset. Finally, the degree of peripancreatic adipose tissue inflammation is substantially less in type 2 AIP than in type 1 AIP.

In the diagnosis of type 2 AIP, GEL is emphasized as a specific finding. In the opinion of this author, this emphasis is misguided. Although the finding of GEL is useful in differentiating type 2 AIP from type 1, the epithelium-centric inflammation observed in type 2 AIP is not specific for this disease and cannot be differentiated from similar or identical lesions detected in *Helicobacter pylori* gastritis and ulcerative colitis. (In ulcerative colitis, the finding that corresponds to GEL is called "crypt abscess.") In contrast, the histological picture of type 1 AIP is unique, with similar features found in no other diseases.

21.4 Similarity to Other IgG4-Related Lesions

Compared with the pathological features of IgG4-related lesions in other organs, the marked inflammation that occurs in both the exocrine pancreas and the adjacent adipose tissue marks a relatively distinct phenomenon within IgG4-RD. In contrast, for example, salivary gland lesions in IgG4-RD (IgG4-related sialadenitis involving the submandibular glands, parotid glands, or both) show inflammation that primarily affects the lobules, with inflammation of adipose

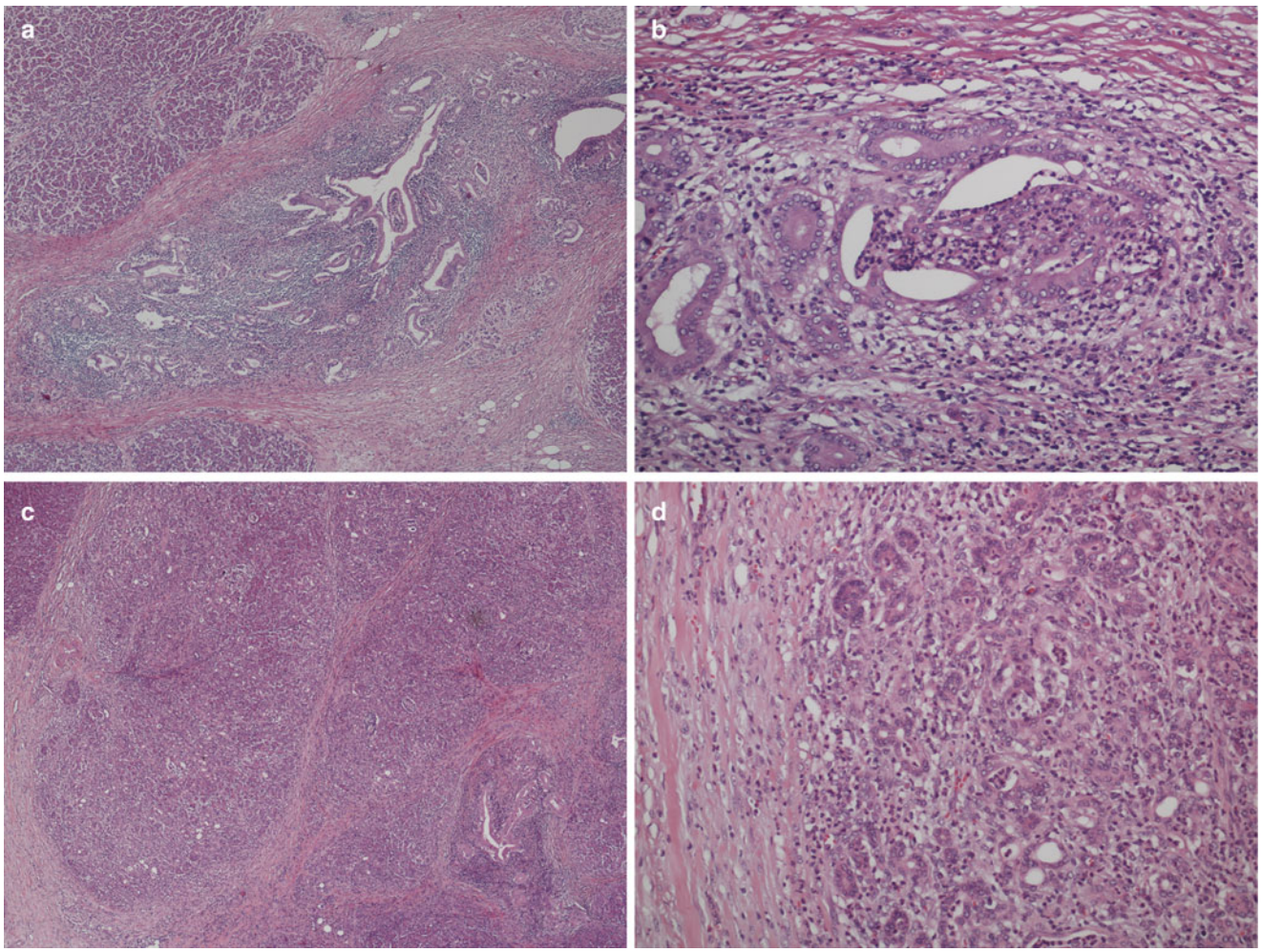

Fig. 21.7 Type 2 AIP. (**a**, **b**) Interlobular pancreatic duct lesions. Marked lymphoplasmacytic infiltration is seen surrounding the epithelium (**a**), and in the lumen, neutrophil infiltration (GEL) is found (**b**). Nuclear swelling in the pancreatic duct epithelium is seen and is interpreted as a regenerative change. (**c**, **d**) Lobular lesions. In the lobule, infiltrates consisting of neutrophils, lymphocytes, and plasma cells are seen, and neutrophils also infiltrate the lumen of the intralobular pancreatic ducts. In the fibrotic foci seen in the interlobular space (**d**: *left-hand side*) there is only scanty inflammatory cell infiltration

tissue rare. In bile duct lesions, adipose tissue inflammation is mild in the absence of pseudotumor formation. The lesion of the peripancreatic adipose tissue resembles that of retroperitoneal fibrosis, and it is appealing to believe that the marked inflammation of adipose tissue associated with type 1 AIP relates in some fashion to the location of the pancreas in the retroperitoneum.

21.5 Concluding Remarks

I reviewed type 1 AIP focusing on its pathological characteristics. The histological picture of type 1 AIP is unique, and its histological findings are essential to the pathological diagnosis.

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Sclerosing Cholangitis

22

Kenichi Harada and Yasuni Nakanuma

22.1 Introductory Remarks

In 2001, the report of Hamano et al. from Shinshu University [1] drew widespread attention to the relationship between elevated serum concentrations of IgG4 and sclerosing pancreatitis, now known as type 1 (IgG4-related) autoimmune pancreatitis. In little more than a decade since that time, IgG4-RD has been described in essentially every organ system in the body. Bile duct lesions in the setting of IgG4-related sclerosing cholangitis are known to occur in isolation, in association (very commonly) with type 1 autoimmune pancreatitis, and often with other organ manifestations of IgG4-RD.

IgG4-related sclerosing cholangitis, primary sclerosing cholangitis, and cholangiocarcinoma are unique clinicopathological entities that bear vastly different implications for treatment and prognosis, but differentiation among these three disorders is not always easy. In this chapter, we focus on the clinicopathological features of IgG4-RD in the hepatobiliary system and address as appropriate the conditions that must be distinguished from IgG4-related sclerosing cholangitis.

22.2 IgG4-Related Sclerosing Cholangitis Within the Larger Cholangitis Context

IgG4-related sclerosing cholangitis demonstrates a lymphoplasmacytic infiltrate enriched by IgG4-positive plasma cells and biliary sclerosis caused by progressive fibrosis within the bile duct wall. This inflammation leads to bile duct stenosis. Other forms of inflammatory and sclerotic biliary tract disease are shown in Table 22.1. These include primary sclerosing cholangitis in adults and biliary atresia in children, as well as conditions of sclerosing cholangitis that result from biliary infection and biliary tract surgery.

Bile duct sclerosis differs in its localization and pattern according to the underlying disease or cause and is sometimes accompanied by a characteristic inflammatory cell infiltrate, type of bile duct injury, or ductopenia. Both primary sclerosing cholangitis—the prototype of sclerosing cholangitis—and IgG4-related sclerosing cholangitis are characterized by nonspecific chronic inflammation and fibrosis of the bile duct wall and periductal area. Multifocal lesions extend from the large bile ducts in the hepatic hilus to the extrahepatic bile ducts in a localized, diffuse, or segmental manner. Stenosis and occlusion develop as a consequence of wall sclerosis, leading to clinical signs such as jaundice.

22.3 IgG4-Related Sclerosing Cholangitis

IgG4-related sclerosing cholangitis describes the bile duct lesions of IgG4-RD. Diffuse or localized sclerotic and stenotic lesions are found within the large bile ducts of the hepatic hilus, the extrahepatic bile ducts, and gallbladder. Circumferential wall thickening is noted at stenotic sites, and similar changes are also often seen at non-stenotic sites. Isolated biliary tract disease without evidence of other organ involvement is rare. Type 1 (IgG4-related) autoimmune pancreatitis is the most common type of extrahepaticbiliary disease, and lesions are typically found within intrapancreatic bile ducts. Serum IgG4 concentrations are usually elevated to ≥135 mg/dL, and the lesions are reversible and responsive to glucocorticoid therapy, at least in their early stage.

The extrahepatic bile ducts (including the gallbladder but excluding the intrapancreatic bile duct) form a three-layered structure consisting of the mucosa, muscularis propria, and subserosa. In contrast, the pancreatic duct lacks a layered structure. However, both the bile ducts and pancreatic ducts are covered by a single layer of their own epithelium, and both also have the proper glands (peribiliary gland and pancreatic duct gland). Thus, the histologies of

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bile duct lesions in IgG4-related sclerosing cholangitis resemble those of the pancreatic duct in autoimmune pancreatitis in many respects:

- Similar to autoimmune pancreatitis, the inflammation mainly affects the collagen tissue of the bile duct wall, with a predilection for the area around the peribiliary glands. In contrast, the biliary epithelium is relatively well preserved.
- Chronic cholangitis with marked lymphoplasmacytic cell infiltration, fibrosis, and luminal stenosis are typical of both IgG4-related sclerosing cholangitis and autoimmune pancreatitis.
- Storiform fibrosis is found in IgG4-related sclerosing cholangitis, just as in autoimmune pancreatitis.

Table 22.1 Classification of sclerosing cholangitis

1. Primary sclerosing cholangitis
2. IgG4-related sclerosing cholangitis
3. Biliary atresia (in children)
4. Secondary sclerosing cholangitis
- Infectious sclerosing cholangitis
- History of biliary tract trauma or surgery
- Eosinophilic cholangitis
- Xanthogranulomatous cholangitis
- Ischemic cholangitis
- Hepatobiliary lithiasis
- AIDS-related cholangitis
- Bile duct injury due to transcatheter arterial chemoembolization (TACE)

- Immunohistochemical staining reveals numerous IgG4-positive plasma cells in both disorders.
- Obliterative phlebitis and perineural infiltration of IgG4-positive cells are detected common to both conditions.
- When the biliary tract becomes inflamed from the hepatic hilus to intrahepatic bile duct, a tumorlike lesion may form, thereby forming an inflammatory pseudotumor. This resembles the lesions observed in some cases of autoimmune pancreatitis, when mass lesions result from the inflammatory process and may lead to misdiagnoses as pancreatic malignancies.

The present proposed classification of this group of diseases is as illustrated in Fig. 22.1 [2]. This figure takes into consideration the presence, absence, and combination of pancreatic and bile duct lesions; findings of mass-forming pancreatitis; and inflammatory pseudotumor in the hepatobiliary area.

IgG4-related sclerosing cholangitis is usually associated with type 1 autoimmune pancreatitis. Only rare cases without involvement in other organs have been encountered and, indeed, some experts question whether it truly exists. The characteristics of IgG4-related sclerosing cholangitis not associated with pancreatic lesions include [3]:

- Disease that mainly affects middle-aged to elderly men.
- Normal or only slightly elevated serum IgG4 concentration.
- Serum IgE and soluble IL-2 receptor elevations.
- Antinuclear antibody positivity.

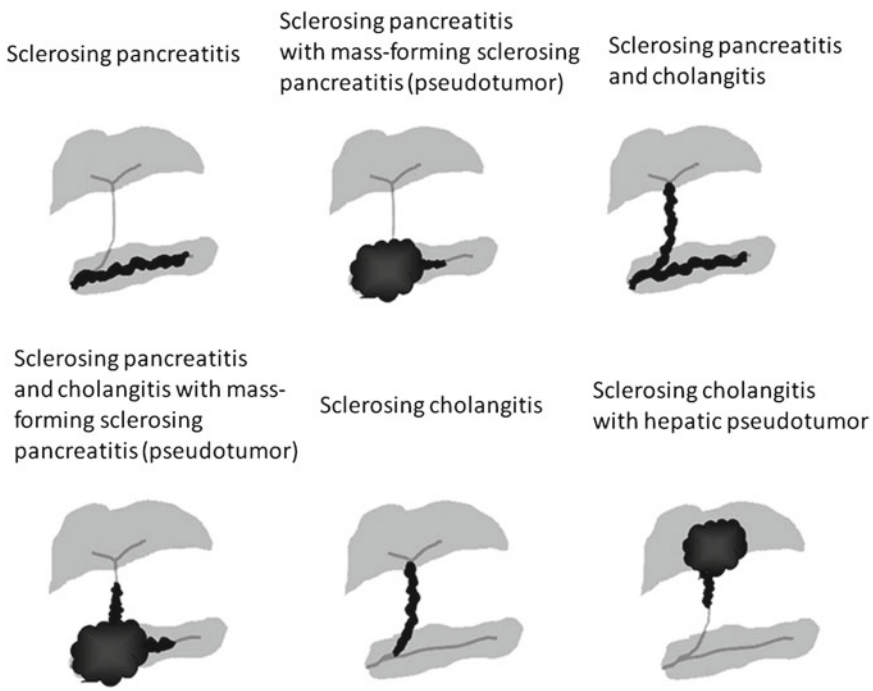

Fig. 22.1 Type of IgG4-related sclerosing cholangitis and autoimmune pancreatitis [2]

- Affected bile ducts show relatively long and flat narrowing, but peripheral bile duct stenosis is mild.
- Affected bile ducts show marked IgG4-positive plasma cell infiltration.

The diagnosis of IgG4-related sclerosing cholangitis is relatively easy when type 1 autoimmune pancreatitis is present. However, in cases without clinically obvious pancreatic involvement, differentiation of IgG4-related sclerosing cholangitis from primary sclerosing cholangitis and cholangiocarcinoma becomes especially important.

At this time, no criteria defining what degrees of serum IgG4 concentration elevation or tissue IgG4 infiltration are "diagnostic" of IgG4-related disease have been established. Diagnostically useful histological findings of bile duct tissue specimens include:

- IgG4-positive plasma cell infiltration (≥10/HPF and IgG4-/IgG-positive plasma cell ratio ≥40 %) (Fig. 22.2)
- Marked lymphoplasmacytic cell infiltration and fibrosis, without neutrophil infiltration (Fig. 22.2)
- Obliterative phlebitis or swirling fibrosis
- Storiform fibrosis (Fig. 22.2)

Unfortunately, it is often difficult to identify such characteristic histological features in small biopsy specimens obtained from the face of the bile duct.

In the diagnostic criteria for AIP (the HISORt criteria) [4] proposed by the Mayo Clinic and in their application to IgG4-related sclerosing cholangitis [5], IgG4-positive plasma cell infiltration is emphasized. However, even a marked IgG4-positive cellular infiltrate does not constitute adequate pathological evidence for the diagnosis of IgG4-RD. Conversely, because of similarities in the clinical and histological findings, some cases considered to have IgG4-RD have in fact no marked IgG4-positive cell infiltrate within affected organs. Thus, one must not be influenced to an excessive degree by diagnostic criteria that overemphasize IgG4-positive cell infiltration in affected organs.

22.4 Papillitis of IgG4-Related Sclerosing Cholangitis

Inflammation of the papilla of Vater (papillitis), also called duodenitis, is frequently detected in a number of pancreatobiliary diseases, including malignant tumors. In many settings, this papillitis appears as a nonspecific inflammatory cell infiltrate and is attributed to a consequence of aging. In contrast, in IgG4-related sclerosing cholangitis and type 1 autoimmune pancreatitis, IgG4-positive plasma cell infiltrates accompany the papillitis. The IgG4-positive cell infiltration seen in the ampulla of Vater in IgG4-related sclerosing cholangitis and autoimmune pancreatitis is comparatively more severe than that of primary sclerosing cholangitis, pancreatic cancer, and bile duct cancer, providing an aid to the diagnosis of IgG4-RD (Fig. 22.3). However, the degree of papillary swelling does not correlate with the magnitude of IgG4-positive cell infiltration [6], and it is therefore difficult to predict the presence of IgG4-positive cell infiltration from the endoscopic findings.

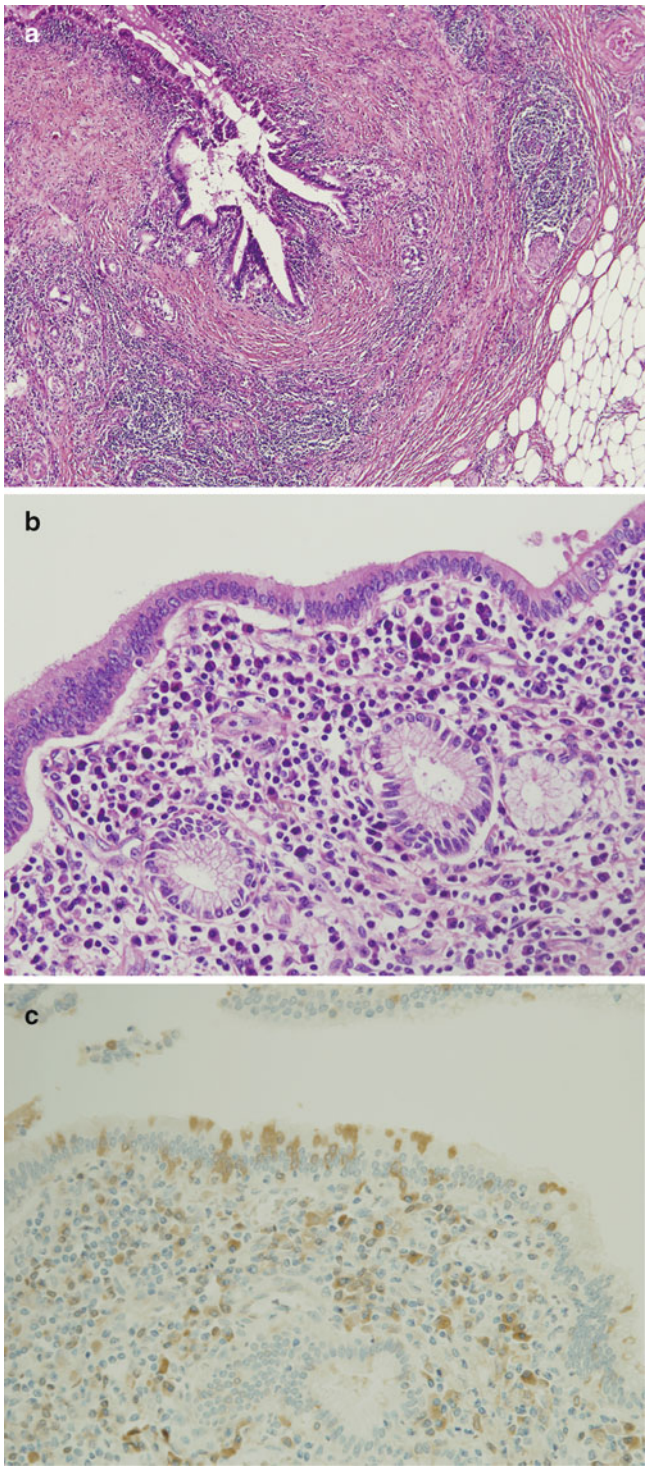

Fig. 22.2 Characteristic histological findings of IgG4 sclerosing cholangitis. (**a**) Periductal inflammation and fibrosis (storiform fibrosis) in a large bile duct in the hepatic hilus. (**b**) Chronic inflammation with prominent plasmacytic cell infiltration. (**c**) Abundant IgG4-positive cell infiltration (immunohistochemical staining for IgG4)

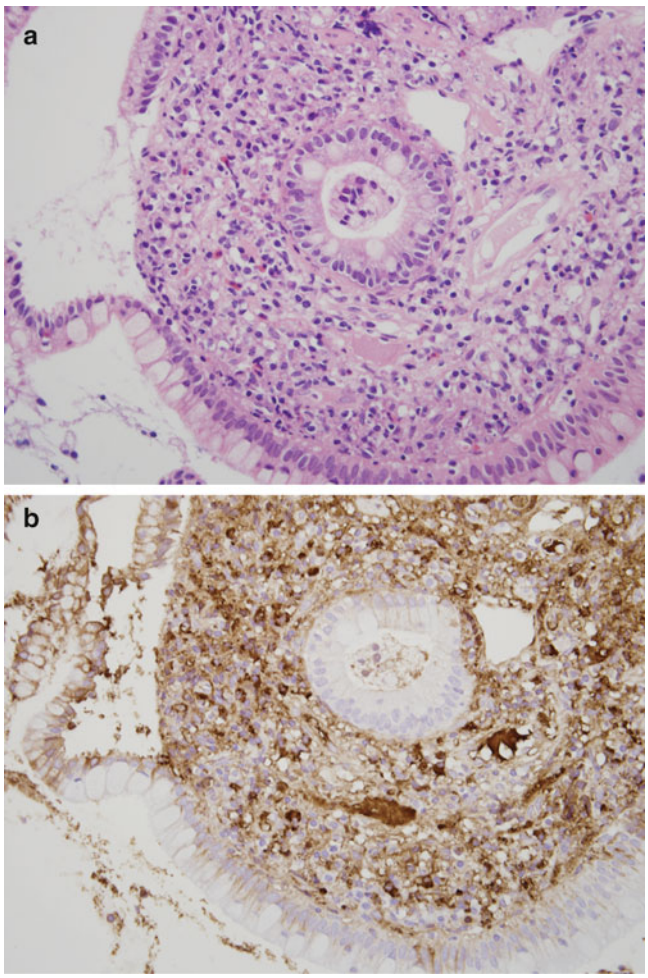

Fig. 22.3 Biopsy specimen of the ampulla of Vater from a patient with IgG4-related cholangitis and type 1 autoimmune pancreatitis. (**a**) Although inflammation is mild, plasma cells are scattered. (**b**) IgG4-positive cells are seen (immunohistochemical staining for IgG4)

22.5 IgG4-Related Hepatic Lesions (IgG4-Hepatopathy)

Liver dysfunction is found in 50–70 % of IgG4-related AIP patients [7, 8]. In addition, liver biopsies in many patients with type 1 autoimmune pancreatitis reveal marked IgG4-positive inflammatory cell infiltration in the portal tract [9, 10]. Umemura et al. investigated the liver biopsy findings of AIP patients to clarify the pathogenesis of their liver injury. They identified five main intrahepatic histological findings: portal inflammation, large bile duct injury, portal sclerosis, parenchymal inflammation, and cholestasis [7]. All of these findings, however, are nonspecific. Clinicopathological study revealed intrahepatic IgG4-positive cell infiltration of ≥5/HPF in approximately one half of the cases, which was correlated with the serum IgG4 levels. Moreover, correlations were noted between parenchymal inflammation and serum bilirubin/AST values, as well as between cholestasis and serum bilirubin values. Both the parenchymal inflammation and IgG4-positive plasmacytic cell infiltration improved following steroid therapy. Such hepatic lesions as seen in IgG4-related autoimmune pancreatitis are presently called IgG4-hepatopathy and are important findings not only for the diagnosis of IgG4-RD but also for elucidating its etiopathogenesis.

22.6 Autoimmune Hepatitis Associated with Elevations of IgG4 in Serum and Tissue

Cases showing elevated serum IgG4 levels have been reported in patients diagnosed with autoimmune hepatitis [11]. In a report surveying 60 cases of autoimmune hepatitis, approximately 3 % showed features suggestive of IgG4-RD with elevated serum IgG4 values (≥135 mg/dL) and ≥10/HPF IgG4-positive cells in the portal tracts. The histopathological findings in those patients, however, showed chronic active hepatitis accompanying liver cell rosetta formation, quite typical of ordinary autoimmune hepatitis. It is probable that many of these cases represent autoimmune hepatitis with an IgG4 component to the inflammation that is more robust than usual, rather than another hepatic manifestation of IgG4-RD.

Patients with autoimmune hepatitis associated with elevations of IgG4 in serum and tissue demonstrate good responses to glucocorticoids, with improvements in serum IgG4 values, liver function data, and histological findings. A small number of such cases have developed IgG4-related sclerosing cholangitis or marked IgG4-positive plasma cell infiltration of the liver and gallbladder (resected gallbladder specimens) during follow-up [11]. The scoring system of the International Autoimmune Hepatitis Group has been widely used to diagnose autoimmune hepatitis, but simplified criteria were revised in 2008 [12] to include items such as autoantibodies, serum IgG values, evidence of viral infection, and liver tissue findings (lymphoplasmacytic cell infiltration in the portal tracts and interface hepatitis, hepatic cell rosetta formation, and emperipolesis). Although the treatment approaches to IgG4-RD and autoimmune hepatitis are similar, additional investigations are required to elucidate the true relationship (if any) between these conditions, which at the present time should be regarded as separate entities.

22.7 Differential Diagnosis

22.7.1 Primary Sclerosing Cholangitis

The disease concept of primary sclerosing cholangitis as the prototype of sclerosing disease within the biliary tree is well established, but its cause remains unclear. Its main pathological

findings are bile duct injury extending from the large bile ducts in the hepatic hilus to the extrahepatic bile ducts and periductal fibrosis. Chronic progressive cholestasis results from ductopenia and bile duct obstruction, leading finally to biliary cirrhosis. Primary sclerosing cholangitis affects patients across a broad range of ages, from children to adults. This contrasts with IgG4-related sclerosing cholangitis, which tends to affect middle-aged to elderly individuals. In further contrast to IgG4-RD, immunosuppressive medications are ineffective in primary sclerosing cholangitis, leaving liver transplantation as the sole effective therapy.

Inflammatory bowel disease, particularly ulcerative colitis, complicates primary sclerosing cholangitis in a high percentage of cases in both Western countries and Japan, while the frequency is different between Western countries (about 70 %) and Japan (about 37 %) [13]. It is almost certain that some cases of IgG4-related sclerosing cholangitis have been included in epidemiologic studies designed to target primary sclerosing cholangitis. As an example, in the Japanese study mentioned above, 7.2 % of the cases of "primary sclerosing cholangitis" were observed to have autoimmune pancreatitis, as well. The existence of an atypical primary sclerosing cholangitis that responded to glucocorticoids and was associated with a favorable prognosis was known before the concept of IgG4-RD was established. These cases are thought now to correspond to IgG4-related sclerosing cholangitis that lacks pancreatic involvement [14].

The cholangiographic characteristics [15] and clinicopathological characteristics of PSC and IgG4-related sclerosing cholangitis are listed in Fig. 22.4 and Table 22.2, respectively.

22.7.2 Cholangiocarcinoma

The differentiation of IgG4-related sclerosing cholangitis from cholangiocarcinoma is a pressing clinical issue. We have observed cases of cholangiocarcinoma in which an inflammatory reaction is characterized by large numbers of IgG4-positive plasma cells within or around the tumorous area [16, 17]. Some cases of cholangiocarcinoma and precancerous lesion (BilIN) preceded by IgG4-related sclerosing cholangitis have been reported. Therefore, in practice, it is impossible to completely exclude the presence of cholangiocarcinoma in the diagnosis of IgG4-related sclerosing cholangitis. Elevated

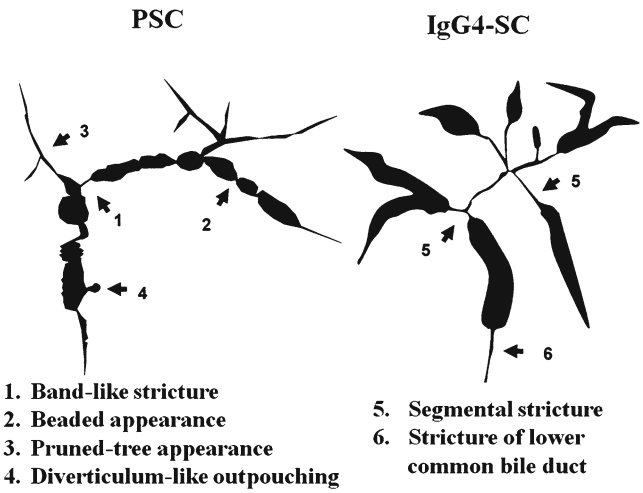

Fig. 22.4 Cholangiography findings of primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis (PSC-SC) (cited from [18], with some modification)

Table 22.2 Clinicopathological characteristics of primary sclerosing cholangitis and IgG4-related sclerosing cholangitis

	Primary sclerosing cholangitis	IgG4-related sclerosing cholangitis
Clinical items		
Age	Bimodal (elderly and children)	Elderly
Sex distribution	Men > women	Men > women
Associated IBD	Yes	No
Associated autoimmune pancreatitis	Rare	Yes
Sclerotic lesions in other organs	No	Yes
Serum IgG4 values	Normal values	High values (>135 mg/dL)
Associated cholangiocarcinoma	4 % (Japan)	Occasional case reports
Pathology items		
Distribution	Diffuse	Localized
Localization of inflammation	Mostly mucosa	Transmural
IgG4-positive cell infiltration	No–mild	Marked
Obliterative phlebitis	Rare	Frequent
Bile duct mucosa	Erosive–ulcerative	Well preserved
Pseudotumor formation	No	Yes

serum IgG4 levels are an important finding when diagnosing autoimmune pancreatitis and IgG4-related sclerosing cholangitis, but are not sufficient to diagnose IgG4-RD definitively. Rather, a danger lurks that IgG4-RD may be diagnosed or excluded too quickly on the basis of serum IgG4 concentrations alone. Serum IgG4 levels should not be regarded as more than an adjuvant diagnostic clue.

IgG4-related sclerosing cholangitis complicating autoimmune pancreatitis can be differentiated, relying on the same diagnostic criteria used for type 1 autoimmune pancreatitis such as serum IgG4 levels and lesion distribution. In cases of IgG4-related sclerosing cholangitis without pancreatic lesions, however, the differentiation from conditions such as primary sclerosing cholangitis and cholangiocarcinoma is more challenging. Bile duct biopsy and cytological examination are particularly important in the exclusion of malignancies. Accordingly, to diagnose or exclude cancer, adequate biopsy or cytology specimens are required. Multiple biopsies as well as multiple specimens from the same site may be needed in order to obtain cancerous or atypical cells.

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Lacrimal Gland and Salivary Gland Lesions

23

Motohisa Yamamoto, Hiroki Takahashi, and Yasuhisa Shinomura

23.1 Concept of Mikulicz's Disease and Related Disorders

IgG4-related disease (IgG4-RD) is a chronic inflammatory disease characterized by swollen and thickened lesions of the affected organ(s), elevated serum concentrations of serum IgG4, and marked IgG4-positive plasma cell infiltration of affected tissues. During long-term follow-up, cases in which inflammation extends to multiple organs may be seen. IgG4-RD is therefore regarded as a systemic disorder [1, 2]. In the head and neck region alone, lesions have been reported in the dura mater [3], pituitary gland [4], orbit [5], lacrimal gland [6, 7], paranasal sinuses [8], salivary gland [6, 9], and thyroid gland [10, 11], among others. Disease involving the combination of lacrimal and major salivary gland involvement has often been termed "Mikulicz's disease" or "Mikulicz's syndrome" in the past.

Mikulicz's disease is named after a surgeon, Johann von Mikulicz-Radecki, who in 1888 reported a 42-year-old farmer with bilateral, symmetrical, and painless swelling of the lacrimal, parotid, and submandibular glands [12]. Tuberculosis, sarcoidosis, lymphoma, conditions diagnosed as "syphilis," and a number of other disorders were subsequently shown to demonstrate similar signs. Disorders whose etiology was unclear came to be referred to as Mikulicz's syndrome [13].

In the 1930s the ophthalmologist Henrik Sjögren analyzed patients with keratoconjunctivitis sicca and noted some with salivary gland swelling. Later this observation was related to the establishment of the concept of Sjögren's syndrome [14]. In 1953, based on histopathological studies of archived tissue specimens from patients with "Mikulicz's disease," it was asserted erroneously that this condition was a variant of Sjögren's syndrome [15]. The entity of Mikulicz's disease then largely disappeared from the medical literature for more than 50 years before investigators in Japan began to reconsider the differences between Mikulicz's disease and Sjögren's syndrome [16–18]. The marked IgG4-positive plasma cell infiltration of the lacrimal, parotid, and submandibular glands in Mikulicz's disease clearly differentiates this disorder from Sjögren's syndrome. Other differences in clinical manifestations, extra-glandular involvement, serological markers, and treatment responses also characterize these two conditions.

Mikulicz's syndrome is characterized by bilateral lacrimal gland and major salivary gland (submandibular gland and parotid gland) swelling. Cases with proven IgG4 involvement are diagnosed as having IgG4-related Mikulicz's disease [19, 20]. The full spectrum of glandular disease need not be present for the diagnosis of IgG4-RD: cases with only unilateral swelling, with swelling of the lacrimal gland(s) alone [7], or of the salivary gland(s) alone [9] have been described. Such cases were formerly termed "chronic dacryoadenitis of unknown origin" or "Küttner's tumor" (chronic sclerotic submandibular gland sialadenitis) [21]. Because of their common clinical and histopathological features [22], however, these conditions should now be regarded and referred to as IgG4-related dacryoadenitis and sialadenitis. In this chapter, we outline the pathological features of IgG4-related dacryoadenitis and sialadenitis and related topics.

23.2 Anatomy of the Lacrimal Gland

The lacrimal gland, which secretes tears containing lysozymes, is located in the superolateral part of the orbit. The gland is comprised of several independent lobes, and the acini and superior conjunctival fornix are connected by 6–12 excretory ducts (Fig. 23.1). The lacrimal gland is a

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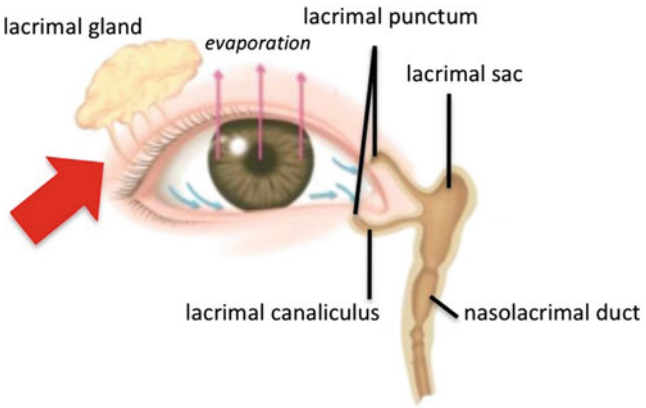

Fig. 23.1 Lacrimal gland anatomy. The gland is comprised of several independent lobes, and the acini and superior conjunctival fornix are connected by 6–12 excretory ducts

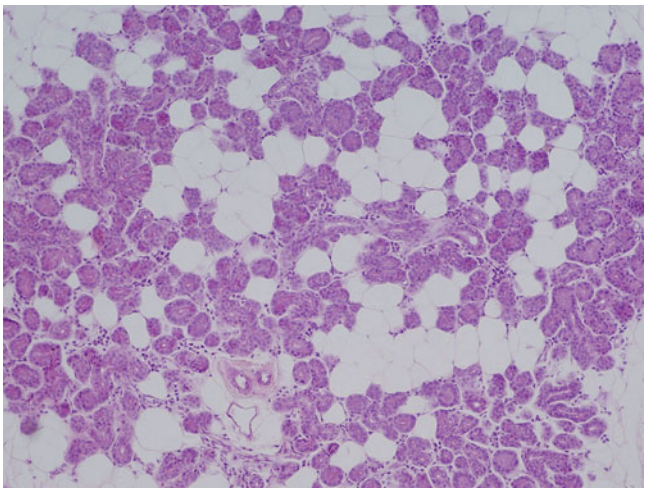

Fig. 23.2 Normal lacrimal gland H&E stain, ×100. It is made up of serous acinar cells

tubuloalveolar gland whose lumen is usually open, and is made up of serous cylindrical cells. The glandular cells have clear secretory granules and are separated from the surrounding connective tissue by basement membrane (Fig. 23.2).

23.3 Pathology of IgG4-Related Dacryoadenitis

Numerous lymphocytes and plasmacytic cells forming small clusters are found within the cell-rich interstitial connective tissue even in healthy persons. In IgG4-related dacryoadenitis, however, a marked lymphoplasmacytic cell infiltration extends to the areas surrounding acinar cells and ducts. Within the lacrimal gland tissues, lymph follicles frequently form, and the interstitium shows fibrosclerosis (Fig. 23.3a–c) [7]. The degree of fibrosis differs in individual cases, tending to be somewhat more marked than in salivary gland lesions. The obliterative phlebitis that is observed universally in type 1 (IgG4-related) autoimmune pancreatitis is not prominent in lacrimal gland tissue. Immunostaining shows lymphocytes to consist of B cells (CD20 and CD79a-positive) and T cells (CD3-positive). Stains for the immunoglobulin light chains κ and λ show no restriction. On anti-IgG4 monoclonal antibody staining, IgG4-positive cell infiltration affects mainly the areas around acinar cells and follicles (Fig. 23.3d, e). These are plasmacytes, of which IgG-positive cells amount to ≥40 % of the total.

Histopathological analyses reveal that despite massive inflammatory cell infiltration, almost no acinar cell or duct apoptosis is present until tissue fibrosis is very advanced [23]. The lymphocytes and plasma cells infiltrate in the lacrimal gland in Sjögren's syndrome, which is the major differential diagnosis for IgG4-RD, but the main are lymphocytes, and the degree of fibrosis is often mild.

23.4 Anatomy of the Salivary Glands

The salivary glands include three major salivary glands, namely, the parotid, submandibular, and sublingual glands, as well as the minor salivary glands. Capsules made up of collagen fiber-rich connective tissue envelop the major salivary glands. Glandular parenchyma is made up of a secretory terminal portion and ductal system branching from it and shows small lobular structures separated by connective tissue septa originating from the capsule. In the secretory terminal portion, two types of secretory cells, serous and mucinous, in addition to muscle epithelial and other cells are present. The secretory portion is connected to the ductal system, where the composition of the saliva is adjusted, and the saliva then conveyed to the oral cavity.

The parotid gland is a branched acinous gland, and its secretory (terminal) portion is a pure serous gland made up of only serous cells. Serous cells have protein-rich secretory granules and show high amylase activity. Since the intercalated ducts and strial portions are relatively long, they are easily detected within the lobules. Numerous plasma cells and lymphocytes are found in the connective tissue of these glands, even in healthy persons. IgA is secreted from plasmacytes as part of an immunoprotective mechanism against pathogens in the oral cavity (Fig. 23.4).

The submandibular gland is a branched acinous gland, whose secretory portion is a seromucous gland containing both mucosal and serous cells. Serous cells comprise the major component of the submandibular gland, are made up of round nuclei and basophil cytoplasm, and are easily differentiated from mucosal cells, which are faintly stained. Ninety percent of the terminal portions of the submandibular glands are comprised of serous acini, and ten percent of mucinous

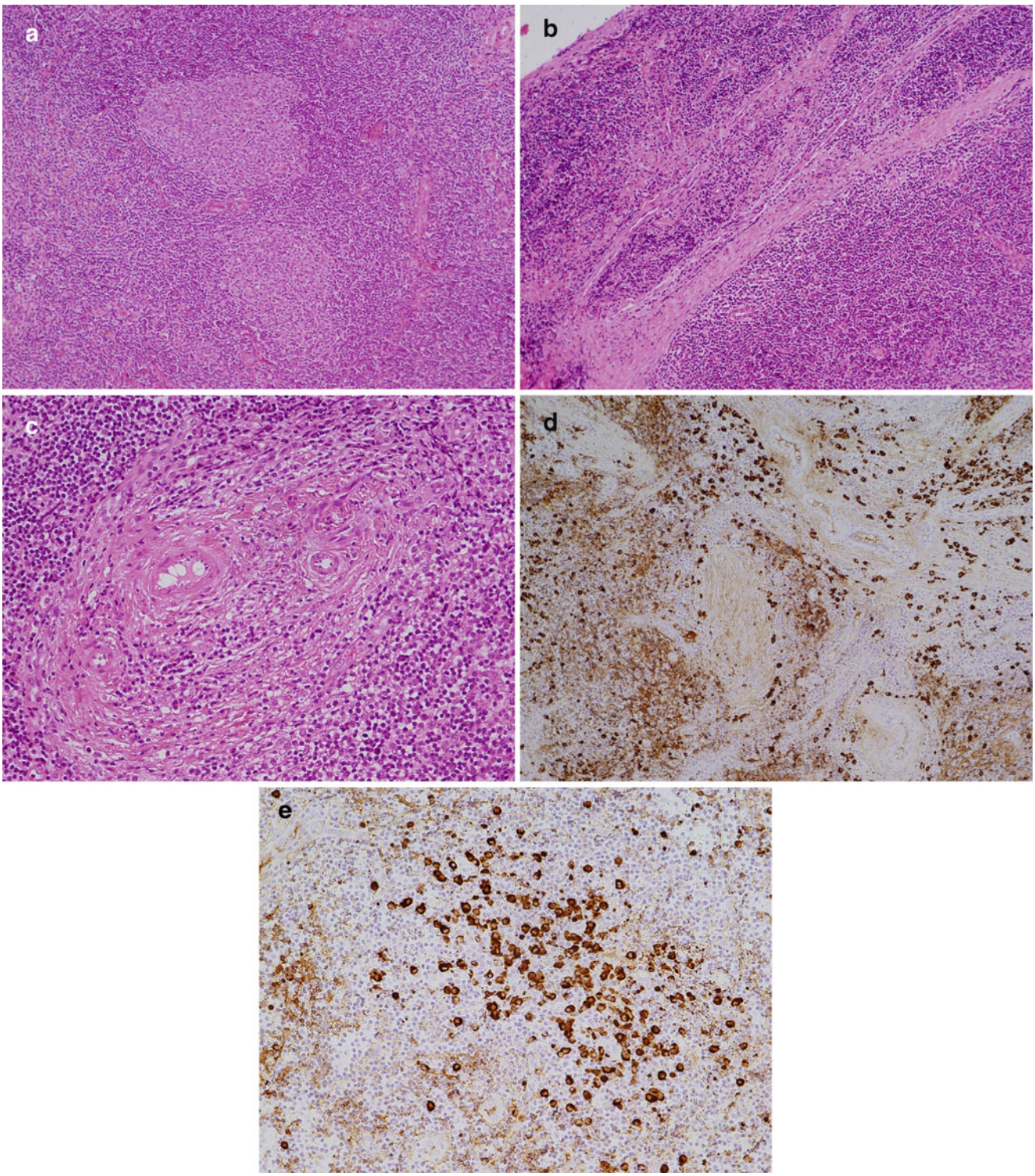

Fig. 23.3 IgG4-related dacryoadenitis (**a**) H&E stain, ×100. (**b**) H&E stain, ×100. (**c**) H&E stain, ×200. Lymph follicles form in lacrimal gland tissue, and fibrosclerosis is found in the interstitium. (**d**) Anti-IgG4 monoclonal antibody stain, ×100. (**e**) Anti-IgG4 monoclonal antibody stain, ×200. IgG4-positive cell infiltration around acinar cells and follicles is found

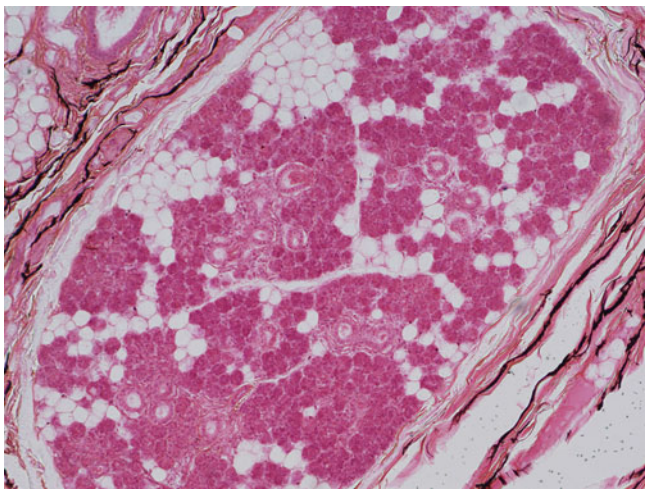

Fig. 23.4 Normal parotid gland H&E stain, ×100. The parotid gland is a pure serous structure made up of only serous cells

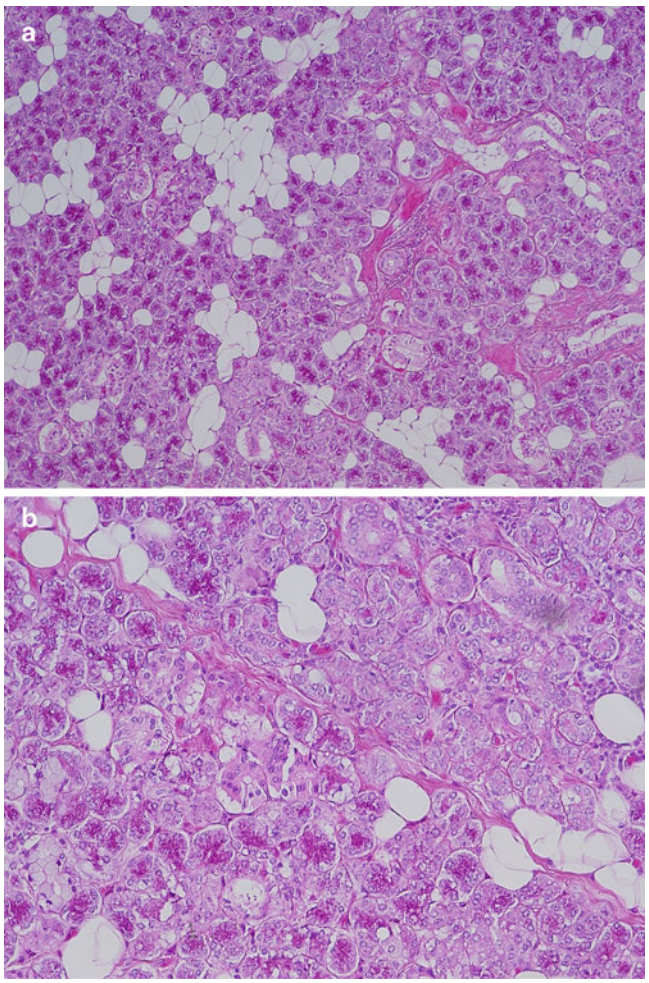

Fig. 23.5 Normal submandibular gland (**a**) H&E stain, ×100. (**b**) H&E stain, ×200. The submandibular gland is a branched acinous gland, whose secretory portion is a seromucous gland containing both mucosal and serous cells. The mucosal cell cytoplasm is faintly stained

ductule portions with serous lunulae. The submandibular gland serous cells also show amylase activity, albeit weak. In the submandibular gland, the serous cells that form the lunulae secrete lysozymes and play a role in immunoprotection. Epithelial cells of the acini and striated ducts of the major salivary glands also secrete lactoferrin that binds with the iron that is essential for bacterial growth. The ducts of the submandibular gland strial portion are easily detected, while the intercalated ducts are extremely short (Fig. 23.5a, b).

The sublingual gland, like the submandibular gland, is a branched acinous gland and is a mixed gland made up of serous and mucosal cells. In the sublingual gland, mucosal cells are the most numerous cell type, while the majority of serous and mucinous cells are present only in the ductal portion of the lunulae. Like the submandibular gland, the serous cells of the lunulae of the sublingual gland secrete lysozymes. The intralobular ducts unlike those in the other major salivary glands are not well developed.

The minor salivary glands, which are not encapsulated, are present in the mucosal and submucosal tissues throughout the oral cavity. Saliva, produced by small groups of secretory units, is delivered via ducts to the oral cavity. Almost all minor salivary glands are mucous glands. Von Ebner's gland, present in the posterior portion of the tongue, is exceptional in that it is a serous gland and secretes lipase. Clusters of lymphocytes involved in IgA secretion are usually found within the minor salivary glands.

23.5 Pathology of IgG4-Related Sialadenitis

IgG4-related sialadenitis, like type 1 (IgG4-related) autoimmune pancreatitis, is a core disease in the spectrum of IgG4-RD [1, 2]. Because computed tomography (CT) and positron emission tomography (PET) demonstrate the same imaging findings in all of the major salivary glands, IgG4 involvement in them is surmised to be pathologically similar as well. Generous biopsies of the parotid gland are seldom obtained because of concern about causing injury to the facial nerve. Sublingual glands are also rarely biopsied (and may be affected less frequently in IgG4-RD; this is not clear). In contrast, the submandibular gland is often prominently involved in IgG4-RD and is readily accessible. When large biopsies are required, surgeons often find it prudent from the standpoint of wound healing to remove the entire submandibular gland rather than to perform wedge biopsies. For these reasons, we focus our remarks on the submandibular glands.

Submandibular glands developing IgG4-related inflammation show marked, firm swelling. Upon macroscopic examination, the inner portion is a milky white color. Some cases have lobular nodules measuring up to 1 cm in diameter

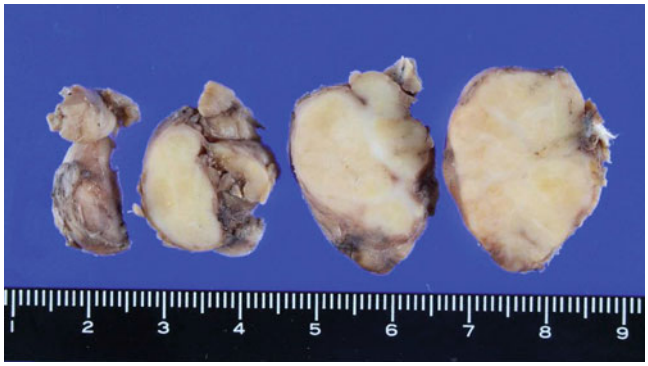

Fig. 23.6 Macroscopic findings of IgG4-related sialadenitis (submandibular gland). The inner portion is a *milky white color*, and lobular nodules measuring 5–10 mm can be seen

(Fig. 23.6). The histopathological features include a marked peri-lobular lymphoplasmacytic cell infiltrate, and lymph follicle formation is also noted occasionally (Fig. 23.7a). At the same time, marked fibrosis that appears to surround the lobules from the periductal areas is observed (Fig. 23.7b). Storiform fibrosis or fibroblast and collagen fiber proliferation with apparent intercellular spaces are also frequently found (Fig. 23.7c). However, as compared to the pancreas and kidney, storiform fibrosis is found somewhat less often in the salivary gland (approximately 70 % of cases) [24]. Few infiltrating lymphocytes show atypia, and lymphoepithelial lesions (a hallmark of Sjögren's syndrome) are not evident (Fig.23.7d).

T cells (Fig. 23.8a) and B cells are intermingled (Fig. 23.8b), and plasmacytes are also found. IgG4-positive plasma cells are often noted at lymph follicle margins and

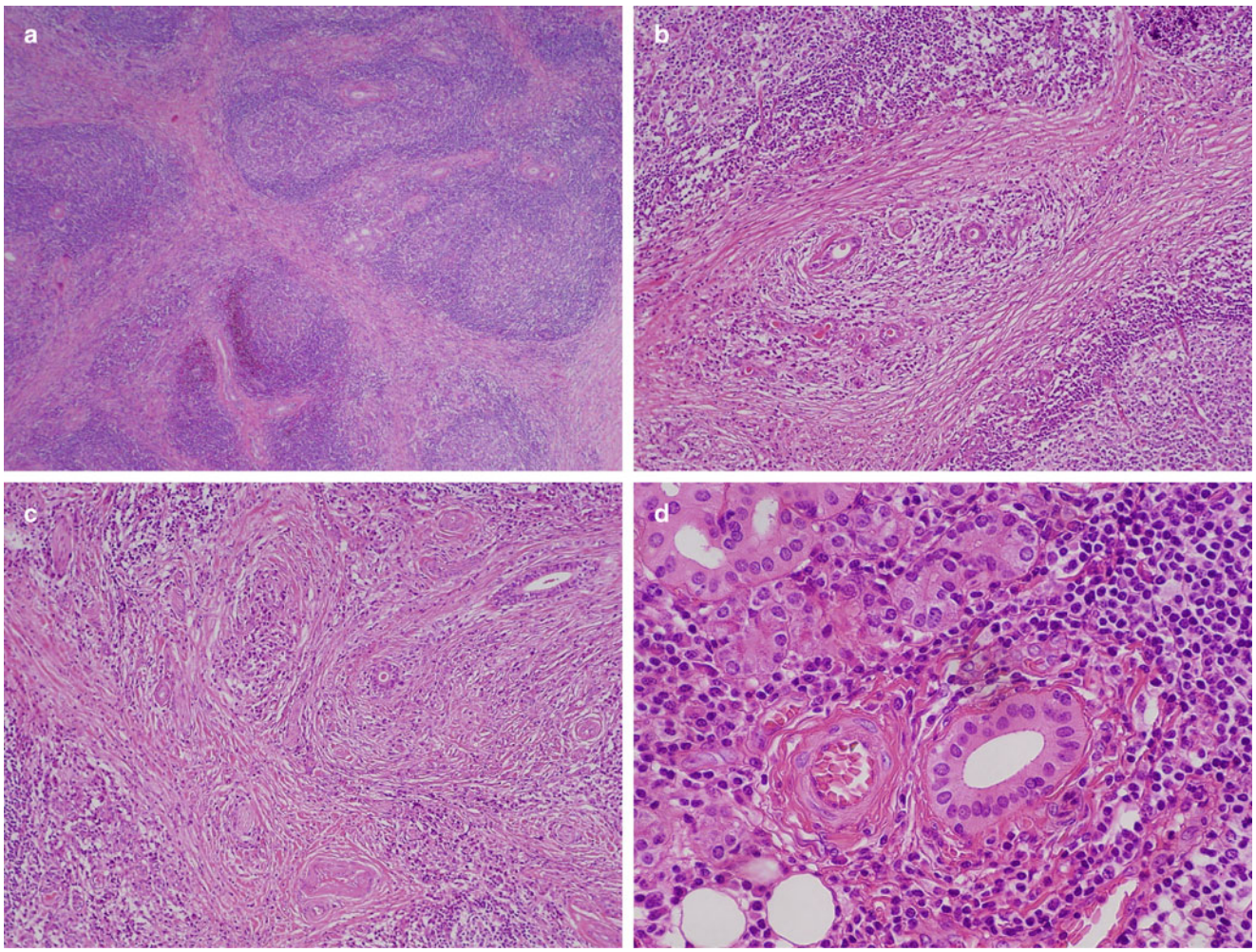

Fig. 23.7 IgG4-related sialadenitis (submandibular gland) (**a**) H&E stain, ×40. Marked lymphoplasmacytic cell infiltration is seen around the lobules, and occasionally, lymph follicles form. (**b**) H&E stain, ×100. At the same time marked fibrosis appearing to surround the lobules from the periductal areas is observed. (**c**) H&E stain, ×100. Storiform fibrosis or intercellular spaces infiltrated by fibroblasts and collagen fiber proliferation are also frequently found. (**d**) H&E stain, ×400. Lymph epithelial lesions are not evident

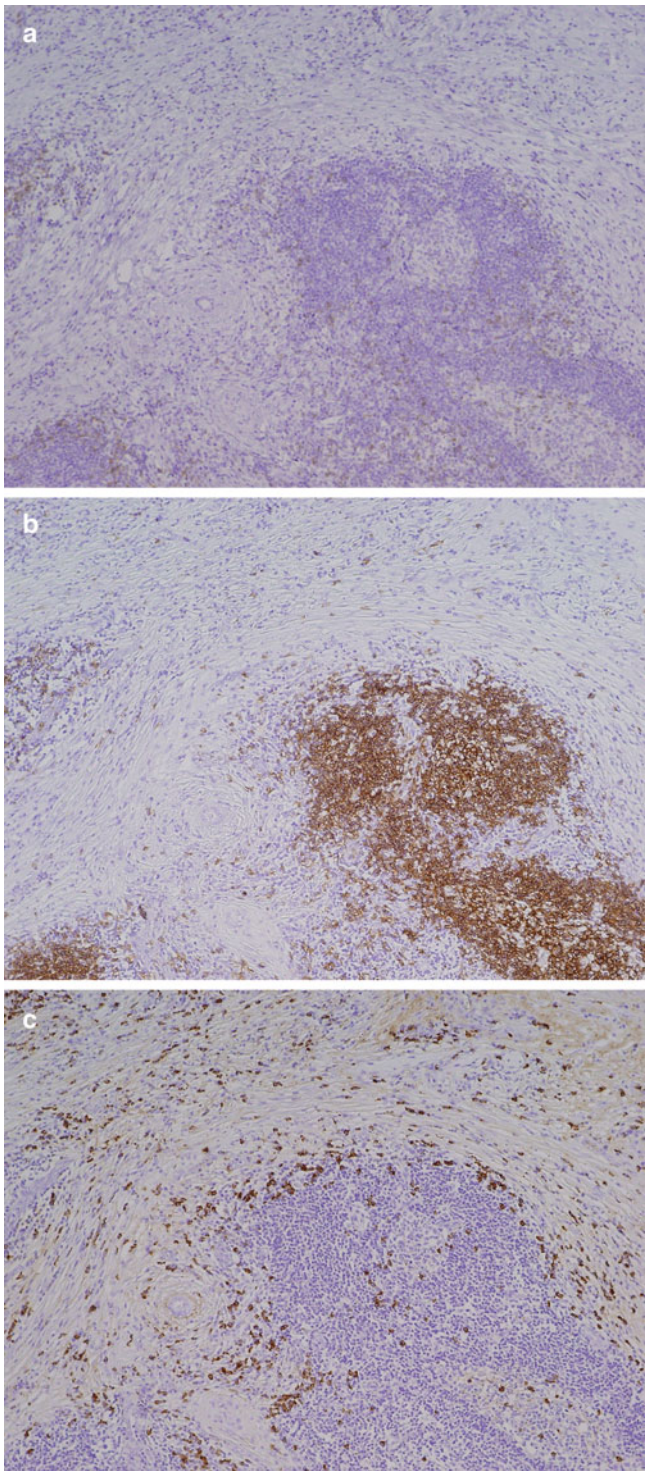

Fig. 23.8 IgG4-related sialadenitis (submandibular gland). (**a**) Anti-CD3 antibody stain, ×100. (**b**) Anti-CD20 antibody stain, ×100. (**c**) Anti-IgG4 antibody stain, ×100. T cells (Fig. 23.8a) and B cells are intermingled (Fig. 23.8b), and plasmacytes are also found. IgG4-positive plasma cells are often noted at lymph follicle margins and fibrotic portions

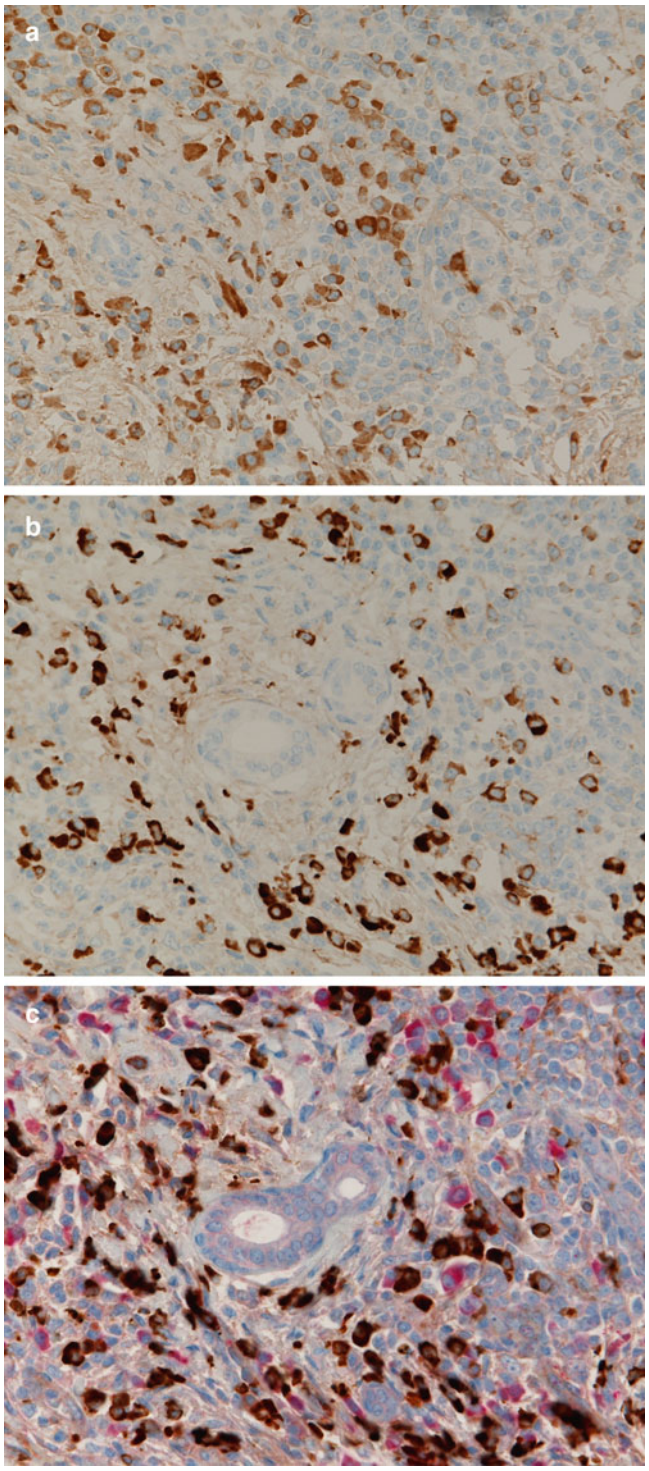

Fig. 23.9 IgG4-related sialadenitis (submandibular gland). (**a**) Anti-IgG antibody stain, ×400. (**b**) Anti-IgG4 antibody stain, ×400. (**c**) Anti-IgG antibody and anti-IgG4 antibody double stain, ×400. Rabbit anti-IgG antibody (Roche) and anti-IgG4 antibody (The Binding Site Co.) were used. IgG was stained red using an UltraView AP Red ISH Detection Kit, and IgG4 stained brown using the labeled streptavidin biotinylated antibody method (LSAB). The IgG4-/IgG-positive cell ratio was ≥40 %

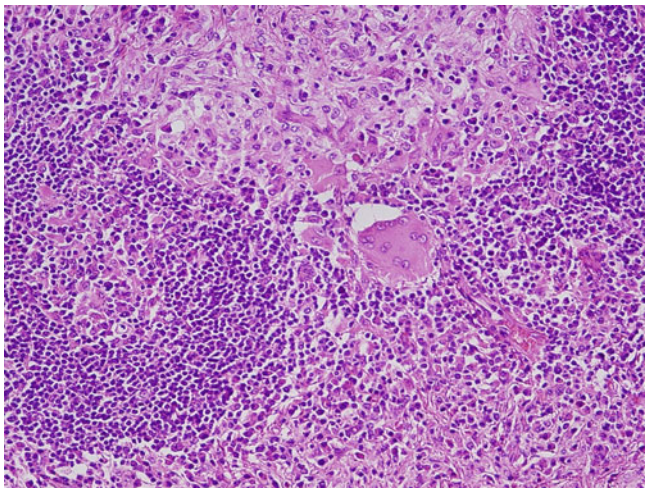

Fig. 23.10 In IgG4-related sialadenitis giant cells are seen. H&E stain, ×200. In the inflammatory cell infiltrate(s) rare giant cells are found

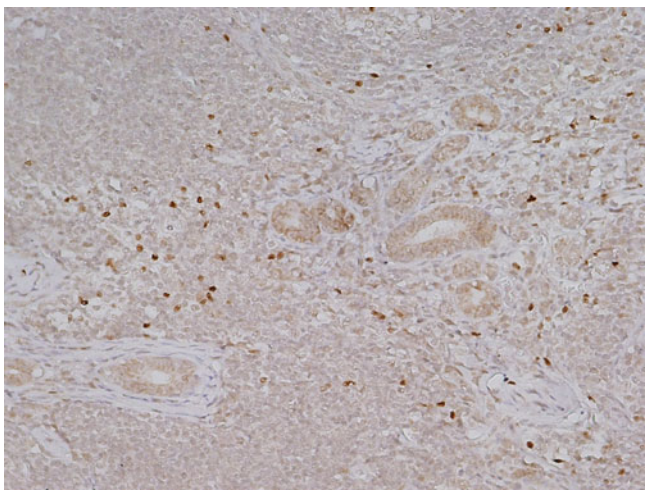

Fig. 23.11 IgG4-related sialadenitis (submandibular gland). Anti-FoxP3 antibody stain, ×200. Numerous FoxP3-positive regulatory T cells are found in submandibular gland tissue

fibrotic portions (Fig. 23.8c). Light chain restriction is not seen. The intermingling of eosinophils in the inflamed areas is characteristic of IgG4-related sialadenitis. Obliterative phlebitis is unusual in salivary glands, in contrast to the situation with type 1 (IgG4-related) autoimmune pancreatitis. When anti-IgG and anti-IgG4 antibody immunostaining is performed, the IgG4-/IgG-positive cell ratio is ≥40 % (Fig. 23.9a–c). Giant cells are seen rarely (Fig. 23.10) and their significance is unclear. Recently, a relationship between IgG4-RD and regulatory T cells has been described [25]. FoxP3-positive regulatory T cells are frequently found in salivary gland tissue (Fig. 23.11).

Sialadenitis of the minor salivary glands generally shows findings similar to those of the submandibular gland, but lymph follicles and severe fibrosis are observed less frequently. In the differential diagnosis with Sjögren's syndrome, the frequency of infiltrating plasma cells and admixture of eosinophils are major points (Fig. 23.12a, b). Numerous IgG4-positive cell infiltrates are found on immunostains of tissue from patients with IgG4-related sialadenitis of the minor glands (Fig. 23.12c, d). In IgG4-related sialadenitis, as in lacrimal gland tissue, the frequency of acinar and ductal cell apoptosis is low despite massive inflammatory cell infiltration (Fig. 23.13a, b) [26].

23.6 Anatomy of Nasal Mucosa and Pathology of Rhinitis

In some cases of IgG4-related dacryoadenitis and sialadenitis, an impaired sense of smell is also present [27]. Olfactory chemoreceptors are present in the olfactory epithelium, located in the uppermost portion of the nasal cavity in a special region of the superior nasal turbinate mucosa. The olfactory mucosa is composed of three cell types, namely, supporting cells, olfactory cells, and basal cells, and also Bowman's glands, which secrete mucus and cover the olfactory mucosa. Olfactory cells, which are present between basal cells and supporting cells in the uppermost portion of the nose, contain 6–8 cilia per cell. Cilia, which are extremely long and immobile, generate a receptor potential when they react to an odorous substance. This electric signal is transmitted by afferent neurons to the brain's olfactory bulb. Takano et al. analyzed the results of a histopathological study of the nasal mucosa in cases of IgG4-related dacryoadenitis and sialadenitis with an impaired sense of smell, and reported marked IgG4-positive plasma cell infiltration in the nasal mucosa as well as the salivary glands (Fig. 23.14a). Differentiation of this entity from allergic rhinitis is difficult (Fig.23.14b). The overall relationships between IgG4-RD, allergic rhinitis, and disturbances of olfaction require more extensive investigation [27].

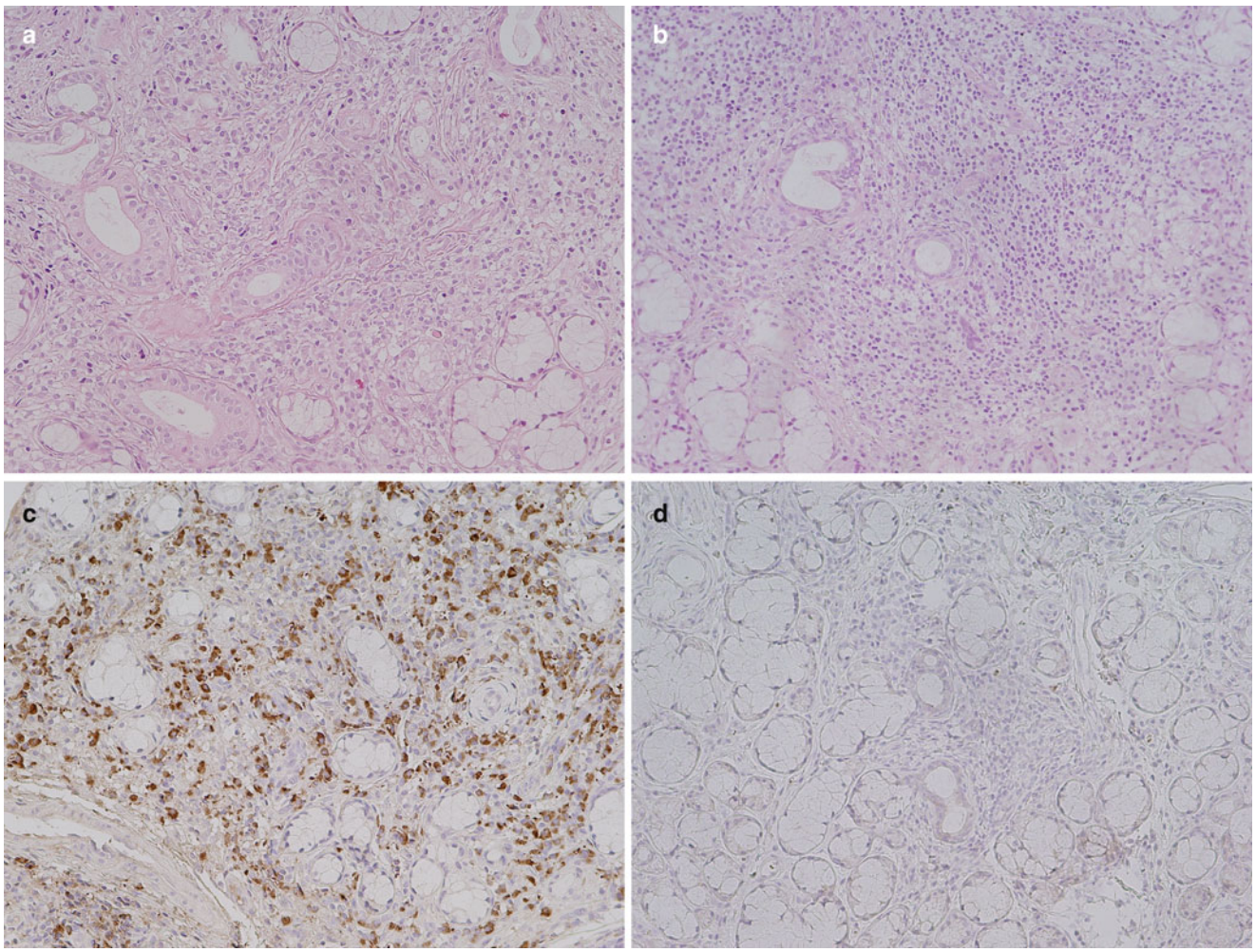

Fig. 23.12 IgG4-related sialadenitis (minor salivary gland) and sialadenitis in Sjögren's syndrome. (**a**) IgG4-related sialadenitis (minor salivary gland). H&E stain, ×200. (**b**) Sjögren's syndrome. H&E stain, ×200. Both IgG4-related sialadenitis (minor salivary gland) and Sjögren's syndrome show periductal lymphoplasmacytic cell infiltration. A tendency to more marked fibrosis is noted in IgG4-related sialadenitis (minor salivary gland). (**c**) Anti-IgG4 antibody staining of IgG4-related sialadenitis (minor salivary gland), ×200. (**d**) Anti-IgG4 antibody staining of Sjögren's syndrome, ×200. Only in IgG4-related sialadenitis (minor salivary gland) are numerous IgG4-positive cell infiltrates found

23.7 Concluding Remarks

The histopathological characteristics of IgG4-related dacryoadenitis, sialadenitis, and rhinitis were outlined. Common characteristics of IgG4-RD include marked IgG4-positive plasma cell infiltration of tissues (IgG4-/IgG-positive cell ratio ≥40 %), intermingling of eosinophils, and storiform fibrosis [28]. Obliterative phlebitis, observed nearly always in autoimmune pancreatitis, is a highly specific diagnostic finding, but is not often seen in IgG4-related dacryoadenitis or sialadenitis.

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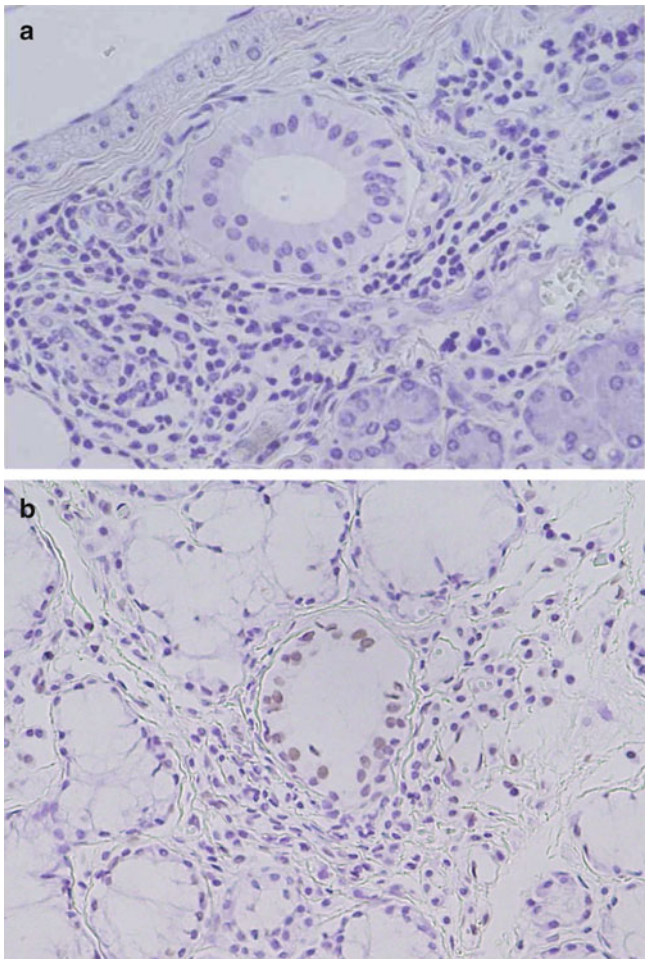

Fig. 23.13 Apoptosis of minor salivary gland cells. (**a**) IgG4-related sialadenitis (minor salivary gland) (TUNEL method), ×400. (**b**) Sjögren's syndrome (TUNEL method), ×400. In IgG4-related sialadenitis, the frequency of acinar and ductal cell apoptosis is low. In contrast, in Sjögren's syndrome, the presence of ductal cells undergoing apoptosis is confirmed (nuclei are stained brown)

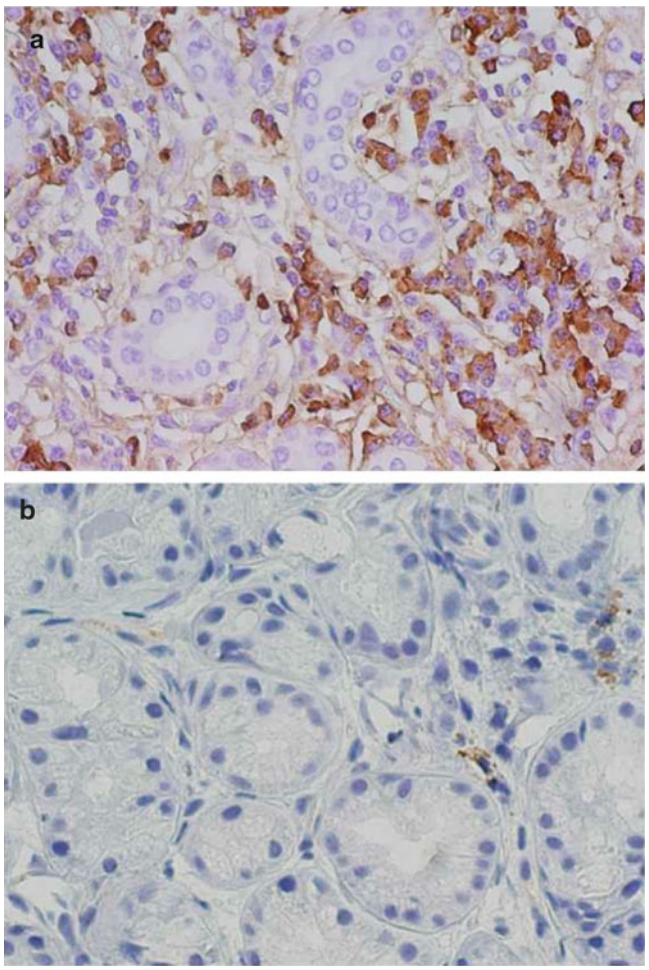

Fig. 23.14 Nasal mucosa in IgG4-RD cases. (**a**) Nasal mucosa in cases with impaired sense of smell (anti-IgG4 antibody stain), ×400. (**b**) Nasal mucosa in cases without impaired sense of smell (anti-IgG4 antibody stain), ×400. Cases of IgG4-related dacryoadenitis and sialadenitis with impaired sense of smell show marked IgG4-positive plasma cell infiltration in the nasal mucosa, whereas such cases without an impaired sense of smell do not show IgG4-positive plasma cell infiltration

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Pathological Findings of IgG4-Related Lung Disease

24

Shoko Matsui, Kenji Notohara, and Yuko Waseda

24.1 Introductory Remarks

IgG4RD is known to cause tumefactive lesions in almost all organs of the body including the pituitary gland, lacrimal gland, submandibular gland, pancreas, bile duct, kidney, retroperitoneum, aorta, and prostate. In the respiratory organs, too, diverse lesions are now known to develop at numerous sites including the mediastinal lymph nodes, bronchi, peribronchovascular sheath, alveolar septa, and pleura. However, in contrast to type 1 autoimmune pancreatitis (AIP), characteristic histopathological findings in the lung are few, and the diagnosis of IgG4-related lung disease (IgG4-RLD) can be difficult to render with certainty. In this chapter, we outline the lesions seen in IgG4-RLD, focusing on their histopathological features.

24.2 Clinical Characteristics of IgG4-RLD

IgG4-RLD occurs most commonly in middle-aged and elderly men. It is estimated to be present in about 10 % of all cases of IgG4-RD, although its frequency has not yet been accurately determined. Because respiratory organ lesions often produce few subjective symptoms, they are frequently detected during a workup for other organ lesions or an abnormal chest shadow. They may also present with asthmatic symptoms such as cough or wheezing and are therefore susceptible to misdiagnosis as bronchial asthma.

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Laboratory abnormalities in IgG4-RLD include extremely elevated serum IgG and IgG4 values. Serum IgG4 values >135 mg/dL raise a suspicion of IgG4-RD. Among the 13 cases with IgG4-RLD evaluated in our combined experience, the mean serum IgG concentration was 3,930 mg/dL (normal: 863–1,589 mg/dL) and the mean serum IgG4 concentration was 1,347 mg/dL (normal: 4–108 mg/dL). These values represent substantial elevations over the values observed in patients with IgG4-RD whose lesions are limited to the lacrimal or salivary glands [1]. Autoantibodies such as rheumatoid factor and antinuclear antibodies are present in 30–40 % of patients with IgG4-RLD, but to date no autoantibody specific to IgG4-RD has been identified. Serum complement protein concentrations (i.e., the CH50, C3, and C4) tend to be low. The erythrocyte sedimentation rate is often elevated from modest to high levels—probably as a consequence of the excessive concentrations of immunoglobulins—but the C-reactive protein is typically within normal limits or elevated to only a mild degree.

The reader is referred to another chapter in this book (Imaging: Lung lesions) for an outline of the chest CT findings of IgG4-RLD, which reflect the lesions being formed at various sites. The radiology of IgG4-RLD is complex because diverse findings can be intermingled in a single case.

24.3 Histological Variations of IgG4-RLD

IgG4-RLD is an inflammatory disease that primarily affects the interstitial tissues of the lung, including the peribronchovascular sheath, interlobular septa, parenchymal interstitium, and visceral pleura. The imaging findings vary according to the lesion site(s) and severity of the inflammation. Obtaining tissue from the lesion is essential to make the diagnosis, but since the lung has only sparse parenchyma a sufficiently large tissue sample is frequently difficult to collect. In particular, biopsies of lesions frequently noted on imaging such as mediastinal lymph node swelling and central bronchial wall thickening are often either difficult to interpret or

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difficult even to obtain. For this reason, in this chapter, we focus on distal lesions from which adequate pathological tissue can be obtained by thoracoscopic lung biopsy.

24.3.1 Tumefactive Lesions

In 2005, it was reported that IgG4-RD was included in cases previously diagnosed with inflammatory pseudotumor of the lung [2]. Inflammatory pseudotumor is classified into three subtypes according to its pathological characteristics. These three subtypes are:

- Fibrohistiocytic type with predominant histiocyte infiltration
- Inflammatory myofibroblastic tumor (IMT) with predominant spindle cell proliferation
- Plasma cell granuloma (lymphoplasmacytic type) with predominant plasmacytic infiltration [3]

Of these three subtypes, the lymphoplasmacytic type characterized by abundant lymphoplasmacytic infiltration and little spindle cell proliferation has been reported to correspond to IgG4-RD. This lesion consists histologically of diffuse lymphoplasmacytic infiltrates and fibrosis. A characteristic fibrosis called storiform fibrosis is found in the lesion (Fig. 24.1) [4], with occasional eosinophils also seen. In some cases, the inflammation extends to surround the bronchovascular bundles in and around lesions, as well as along the alveolar septa. Obliterative phlebitis typical of that observed in type 1 AIP can also be found (Fig. 24.2), and abundant IgG4-positive plasmacytic infiltration is detected by immunostaining (Fig. 24.3). These histological findings are highly concordant with the pathological findings with other organs involved by IgG4-RD and greatly facilitate the diagnosis. One distinctive feature of the histology of IgG4-RLD, however, is the finding of obliterative features not only involving veins ("obliterative phlebitis") but the arteries ("obliterative arteritis") as well (Fig. 24.4). The finding of obliterative arteritis is specific to lung lesions [4].

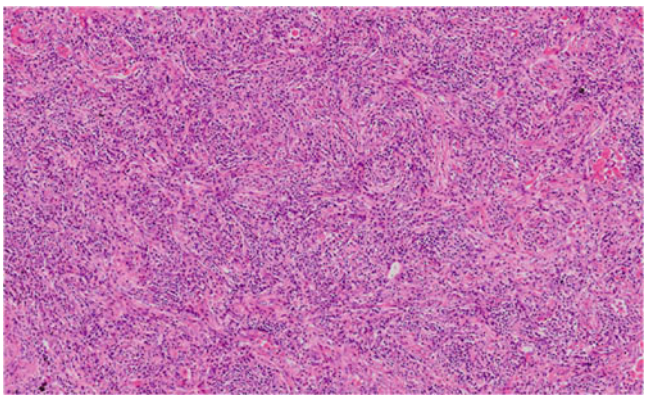

Fig. 24.1 Fibrosis showing lymphocyte infiltration and storiform pattern (H&E stain)

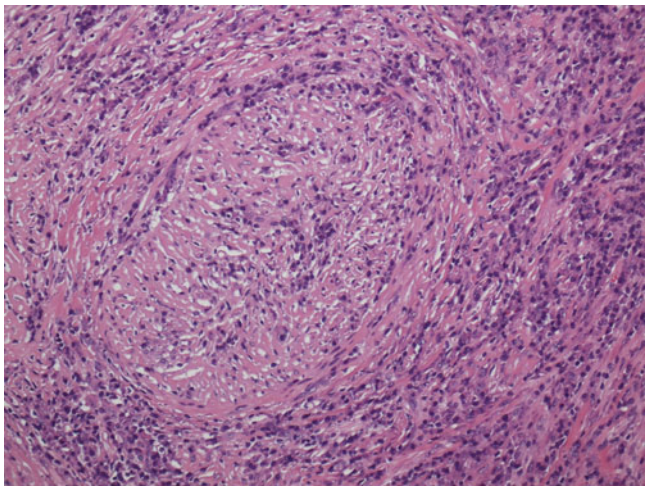

Fig. 24.2 Obliterative phlebitis (H&E stain)

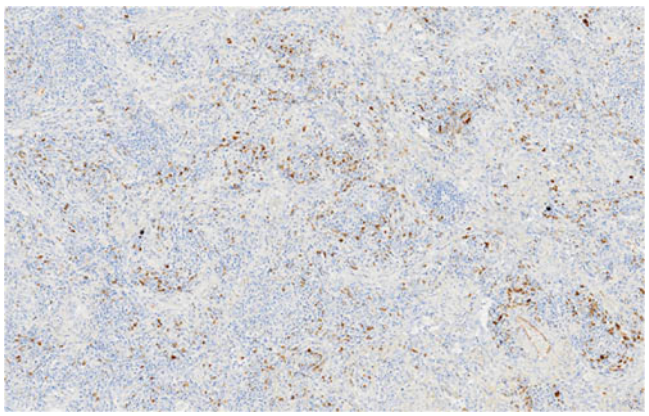

Fig. 24.3 IgG4-positive cells within storiform fibrosis (IgG4 stain)

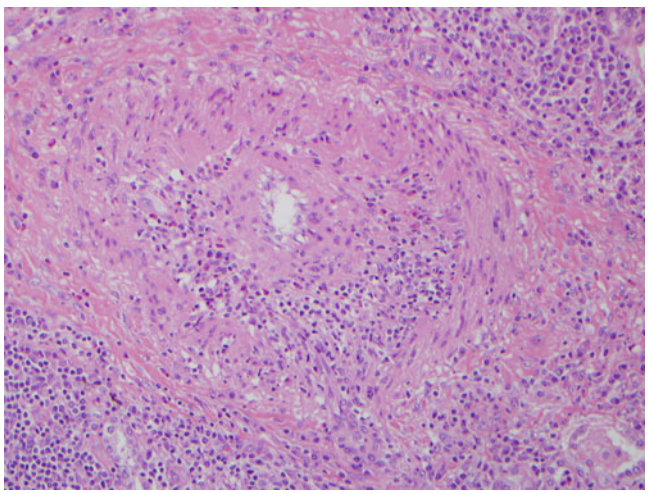

Fig. 24.4 Obliterative arteritis (H&E stain) (courtesy of Dr. Joanne E Yi at Mayo Clinic)

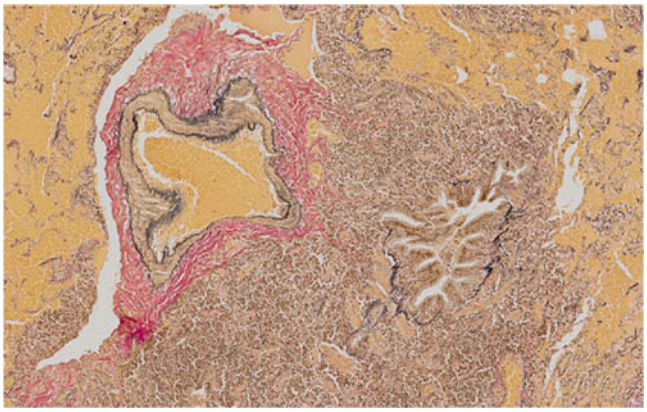

Fig. 24.5 Respiratory bronchioles and pulmonary artery surrounded by numerous inflammatory cells (EVG stain)

24.3.2 Bronchial Lesions

In IgG4-RLD, diagnostic imaging reveals a high frequency of mediastinal lymph node swelling and less frequently bronchial wall thickening. On bronchial mucosal biopsy, infiltration by IgG4-positive plasma cells and eosinophils is observed within the lamina propria [5]. Furthermore, tumefactive lesions associated with fibrosis in the bronchial lumen have been reported in some cases [6]. As noted above, however, the amount of tissue obtainable by biopsy at this site is limited. This largely precludes a definite diagnosis based on the histopathology alone in most cases.

24.3.3 Infiltrative Lesions Along Bronchovascular Bundles and Pleural Lesions

On imaging, dense shadows extend in some cases from central bronchial lesions continuously along the bronchovascular bundles. Such lesions sometimes extend to the pleura, which also occasionally become thickened at focal areas. Numerous lymphocytes and plasma cells infiltrate these lesion sites (Fig. 24.5), and scattered eosinophils are also seen. On immunostaining, IgG- and IgG4-positive plasma cell infiltration is found. In these infiltrative lesions, in contrast to the tumefactive lesions observed at other sites (including elsewhere in the lung), findings such as storiform fibrosis and obliterative phlebitis are scarce. This renders the likelihood of a definitive diagnosis from this site low.

24.3.4 Interstitial Pneumonia

Most interstitial lesions reported in IgG4-RD to date have been characterized by a nonspecific interstitial pneumonia (NSIP) pattern associated with elevated KL-6. Lesions showing an organizing pneumonia pattern have also been reported occasionally [7, 8]. The Mayo Group reviewed in detail the histopathological findings of pulmonary lesions seen in six patients with AIP. In three cases, which included two with findings of organizing pneumonia, a cellular type of NSIP was observed [9]. Five of the six cases also had peribronchial inflammation, suggesting that the interstitial lesions are formed in contiguity with the bronchiolar lesions. Because the differential diagnosis of interstitial lesions is broad, the diagnosis of IgG4-RLD must be made cautiously in the setting of NSIP (see below).

24.4 Differential Diagnosis of IgG4-RLD and Associated Problems

24.4.1 Inflammatory Myofibroblastic Tumor

The concept of inflammatory pseudotumor of the lung generally includes reactive inflammatory conditions. One of its subgroups, IMT, is characterized by myofibroblast proliferation and various proportions of inflammatory cells such as lymphocytes, plasma cells, eosinophils, and histiocytes [10]. At least some IMT are considered neoplastic (Fig. 24.6a). Evidence for this is the existence of cases showing translocation of the anaplastic lymphoma kinase (ALK) gene region of chromosome 2p23 and ALK protein-positive immunostaining [11], as seen in anaplastic large cell lymphoma (Fig. 24.6b).

IMT forms a solitary mass, which requires differentiation from the tumefactive lesions of IgG4-RLD. IMT may occur at any age, but is especially frequent in children and young adults. In contrast, IgG4-RLD occurs in middle age and later and is rare in children and young adults. In addition, the proliferation of swollen myofibroblasts that characterize IMT is usually not prominent in IgG4-RLD. Moreover, the obliterative phlebitis and lymphoid follicle formation with germinal centers are typical of IgG4-RLD but rare in IMT [12]. Although IgG4-positive plasma cell infiltration may be found in IMT, the IgG4-/IgG-positive cell ratio remains low: on the order of 10–15 %. Finally, immunostaining for the ALK protein followed by genetic studies on the tissues of positive cases can lead to clear differentiation of IMT from IgG4-RLD.

24.4.2 Lymphomatoid Granulomatosis

IgG4-RLD and lymphomatoid granulomatosis resemble each other histologically. Deshpande et al. reported two cases of IgG4-RLD initially diagnosed with lymphomatoid granulomatosis [13]. Yamashita et al. reported three cases of

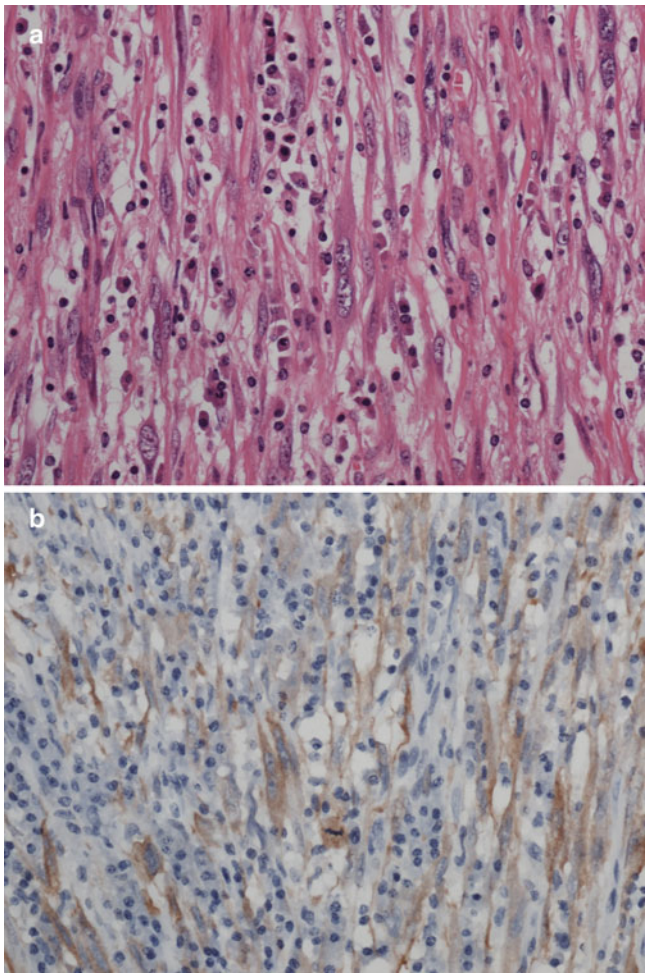

Fig. 24.6 (**a**) Inflammatory myofibroblastic tumor (H&E stain) (courtesy of Dr. Yasumasa Monobe at Kawasaki Hospital). (**b**) Inflammatory myofibroblastic tumor (ALK stain) (courtesy of Dr. Yasumasa Monobe)

IgG4-RLD associated with severe inflammatory cell infiltration around the bronchovascular bundles, pulmonary arteries, alveolar septa, and pleura, as well as fibrosis, confirming that the pathological findings of grade 1 lymphomatoid granulomatosis are difficult to distinguish from those of IgG4-RLD [14].

Lymphomatoid granulomatosis is considered to be an angiocentric lymphoproliferative disorder predominantly composed of atypical Epstein–Barr virus (EBV)-positive B cells, around which numerous nonmalignant small T lymphocytes infiltrate [15]. Plasma cells, immunoblasts, and histiocytes intermingle in these lesions. Malignant B lymphocytes are sometimes difficult to identify morphologically but can be identified by immunostaining of lymphocyte markers and in situ hybridization of EBV-encoded small RNA (EBER). Some of the lung lesions previously diagnosed as EBER-negative lymphomatoid granulomatosis probably in fact represent cases of IgG4-RLD.

24.4.3 Pulmonary Hyalinizing Granuloma

Pulmonary hyalinizing granulomas are seen as solitary or multiple masses, associated with hypergammaglobulinemia. These lesions are characterized histopathologically by laminar, hyalinized fibrotic tissue. With the exception of inflammatory cell infiltrates that are often seen on the rim of these lesions, the cellular component is extremely sparse. This feature facilitates the differentiation of pulmonary hyalinizing granuloma from IgG4-RLD.

A condition termed "sclerosed inflammatory pseudotumor" of the lung, considered in the past to be a borderline condition resembling both pulmonary hyalinizing granuloma and inflammatory pseudotumor, is characterized by incomplete hyalinization. Some of these cases of sclerosed inflammatory pseudotumor of the lung probably represent IgG4-RLD [16]. Cases in which sclerosing mediastinitis [17] or systemic idiopathic sclerosis [18] was associated have also been reported, and these cases too require reevaluation in the context of information emerging about IgG4-RD.

24.4.4 Interstitial Pneumonia

The majority of cases with IgG4-RLD are reported to show the nonspecific interstitial pneumonia (NSIP) pattern. However, based on the histomorphological findings alone, it is difficult to differentiate IgG4-RLD from other types of interstitial pneumonia that show the NSIP pattern. Shrestha et al. investigated the presence/absence of IgG4-positive plasma cells in various lung diseases and reported that usual interstitial pneumonia and NSIP often demonstrated mild to moderate (11–30/high-power field) IgG4-positive plasmacytic infiltrates [7]. Therefore, the pathological differentiation of IgG4-RLD showing an interstitial pneumonia pattern from idiopathic interstitial lung disease or secondary interstitial lung disease associated with other conditions such as collagen vascular disease is difficult. For the present, the diagnosis must be made with reference to other findings such as the presence/absence of other organ involvement.

24.4.5 Multicentric Castleman's Disease

Lung lesions often complicate multicentric Castleman's disease, which is characterized by diffuse lymph node swelling. Numerous IgG4-positive plasma cells and a high IgG4-/IgG-positive cell ratio have been described, and it is difficult to differentiate this entity pathologically from IgG4-RD [19]. If characteristic findings of IgG4-RD such as storiform fibrosis and obliterative phlebitis are absent, this distinction between these two entities on the basis of histology alone is not possible. In Castleman's disease, serum IL-6 is often

extremely elevated, in contrast to the normal or only slightly elevated values seen in IgG4-RD. This point is useful in distinguishing between these two conditions.

24.4.6 Diseases Showing Numerous IgG4-Positive Cells

Numerous IgG4-positive cells may also be found around malignant tumors [4] and in collagen vascular disease-related conditions such as granulomatosis with polyangiitis (formerly Wegener's granulomatosis) [20]. It is a fundamental rule that IgG4-RLD should not be diagnosed based on immunostaining alone [21].

24.5 Concluding Remarks

The pathological findings occupy an important place in the diagnosis of IgG4-RD. The consideration of IgG4-RD as a possible diagnosis leads to the correct diagnostic label in some (but not all) patients with previously undiagnosed conditions. On the other hand, with the increasingly widespread use of IgG4 immunostaining, the problem of discrepant clinical and pathological findings is now encountered with growing frequency. The clinicopathological characteristics of IgG4-RLD have not yet been clarified in their entirety, and the diagnosis of lung disease must always be made with painstaking attention to detail and careful clinicopathological correlation.

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IgG4-Related Kidney Disease

25

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Mitsuhiro Ueno, Michio Nagata, and Yutaka Yamaguchi

25.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a systemic disease characterized by a wide spectrum of clinical signs depending on the combination of organs involved [1]. The lesions in the respective organs are diagnosed based on the common pathological findings of marked infiltration of IgG4-positive plasma cells and characteristic fibrosis. In IgG4-related kidney disease (IgG4-RKD), several additional pathological findings can occur in the kidney [1–5]. Because of the critical role that both immunofluorescence and electron microscopy have played routinely in the evaluation of many types of renal lesions for the past several decades, understanding of the important contributions of immune complex formation to disease pathophysiology has been appreciated most clearly in the kidney.

In this chapter, we focus on the renal lesions associated with IgG4-RD, outlining separately the tubulointerstitial lesions and glomerular lesions based mainly on the findings of light microscopy, immunofluorescence microscopy, and electron microscopy.

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25.2 Clinical Features of IgG4-Related Kidney Disease

IgG4-RKD occurs most commonly in men in their sixties. High serum IgG concentrations are noted in more than 80 % of patients, and more than 50 % have hypocomplementemia [1–3]. Serum IgE levels are also elevated in more than 70 % of patients [1, 3]. Serum IgG4 levels are extremely high, sometimes exceeding 1,000 mg/dL [1–4]. About 30 % of patients have antinuclear antibodies (ANA), but most show only weakly positive results [1, 6]. Nearly half of all patients with IgG4-RKD have proteinuria that is mild in the majority of cases. Nephrotic range proteinuria is rarely detected, except when glomerular lesions such as membranous nephropathy are also present [3]. Hematuria is also sometimes detected, but the most typical renal manifestation in IgG4-RD is mild proteinuria.

More than 80 % of patients have extrarenal IgG4-RD. The pancreas, salivary gland, lacrimal gland, and lymph nodes are frequently affected [1–3]. In one study, renal lesions were detected by chance for the first time in the course of systemic radiologic evaluation of IgG4-RD in approximately half of all patients with IgG4-RKD [3]. The remaining patients were suspected of having IgG4-RKD because of decreased renal function, urinary abnormalities, or incidental radiologic abnormalities detected on imaging studies performed for other indications. A full appreciation of the spectrum of IgG4-RKD continues to evolve, however, and cases of decreased renal function without obvious radiologic findings have been reported with greater frequency.

Radiologic features are very important for the diagnosis (refer to radiology chapter). The development of renal dysfunction is acute in some cases, with deterioration over a few months, and chronically progressive in others, with

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decline over a period of 1 year or more [7]. Comorbidity of diabetes mellitus sometimes makes it difficult to evaluate the time course of IgG4-RKD because of possible overlapping diabetic nephropathy. Approximately half of patients with IgG4-RD and renal involvement have normal renal function at diagnosis [3].

25.3 Tubulointerstitial Lesions

The main renal pathological characteristics of IgG4-RD are tubulointerstitial nephritis (TIN) associated with a marked IgG4-positive plasma cell infiltration and fibrosis [1–5]. As described in other chapters, these findings are common to those seen in extrarenal organ involvement in IgG4-RD. Severe TIN results in marked tubular atrophy and the disappearance of tubules. In addition to these features, clear borders between affected and unaffected areas (i.e., a well-defined, regional distribution of lesions), the extension of lesions into the renal capsule (Fig. 25.1), and eosinophil infiltration are findings useful in the distinction between IgG4-related TIN and non-IgG4-related TIN. Lymphoid follicles are sometimes detected in IgG4-related TIN. However, obliterative phlebitis, which is detected commonly in the pancreas and certain other organs typically affected in IgG4-RD, is rarely seen in the kidney [8]. In contrast, neutrophil infiltration, (necrotizing) angiitis, granulomatous lesion, and advanced tubulitis are very rare findings in IgG4-related TIN, and their presence points to non-IgG4-related TIN [5].

25.3.1 Components of Infiltrating Cells

The inflammatory infiltrate in IgG4-related TIN is comprised primarily of lymphocytes and plasma cells (Fig. 25.2). Eosinophil infiltration is also sometimes seen (Fig. 25.3). These components are the same as those in other affected organs. However, IgG4-positive plasma cell infiltrates are dominant in some non-IgG4-related TIN as well; thus, the presence of IgG4-positive plasma cells is not pathognomonic (refer to section 25.3.7 IgG4-positive plasma cell infiltration). In drug-induced TIN, lymphoplasmacytic infiltration with eosinophils is also shown frequently and IgG4-positive plasma cell infiltrates are dominant in some drug-induced plasma cell-rich TIN (unpublished observation). However, since tubulitis is usually absent or mild in IgG4-related TIN, advanced tubulitis suggests drug-induced TIN or other non-IgG4-related TIN (Fig. 25.4). In addition, moderate neutrophil infiltration, which is relatively frequently seen in infection or vasculitis, is usually absent in IgG4-related TIN. Distinct neutrophil infiltration suggests non-IgG4-related TIN.

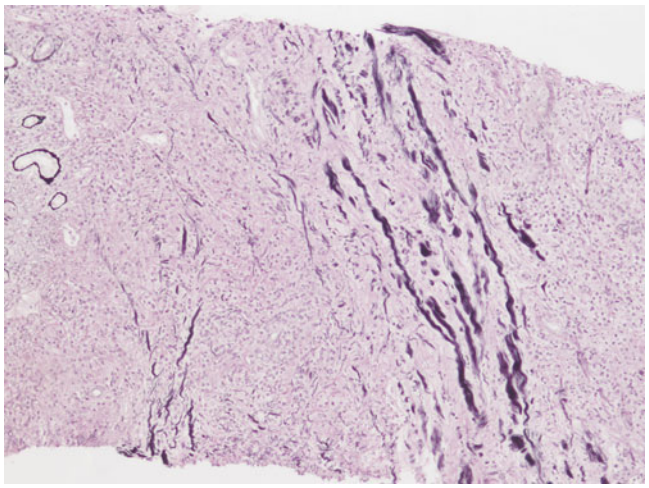

Fig. 25.1 Lymphoplasmacytic cells infiltrate into and beyond the renal capsule (PAM-staining ×100)

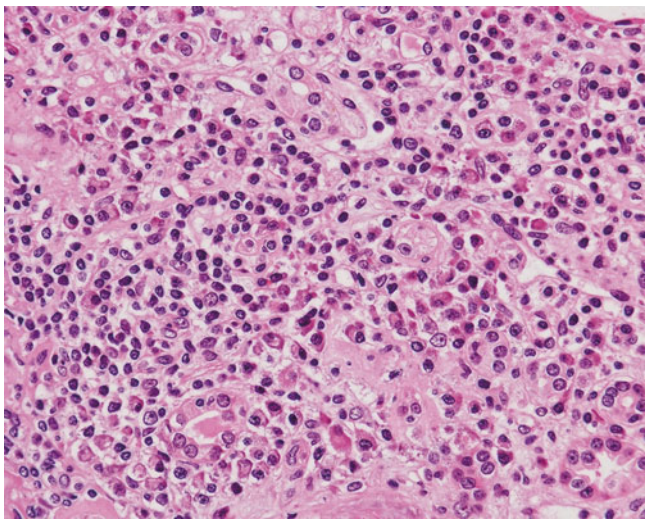

Fig. 25.2 Lymphoplasmacytic cell infiltration of the interstitium (HE-staining ×400)

25.3.2 Distribution of the Lesions

The characteristic distribution of the lesions is sometimes helpful in making a diagnosis of IgG4-related TIN. A regional lesion distribution is characteristic in IgG4-related TIN [1–5]. Affected and unaffected areas are clearly demarcated (Fig. 25.5). This correlates with the radiologic finding of multiple low-density lesions on enhanced computed tomography (CT). We have evaluated cases in which only a single biopsy sample had severe TIN, while the others all showed normal or nearly normal histology. Therefore, careful selection of the biopsy site through contrast-enhanced CT or other imaging modalities is important.

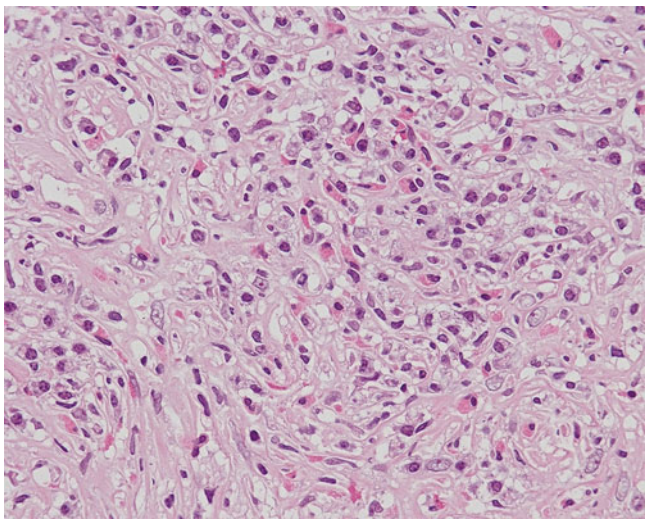

Fig. 25.3 Prominent eosinophil infiltration of the interstitium (HE-staining)

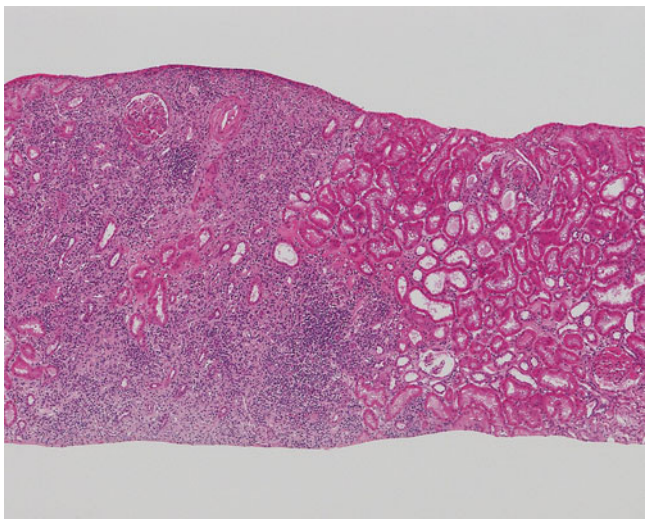

Fig. 25.5 Affected portion (*left*) and non-affected portion (*right*) are well demarcated. HE-staining × 50

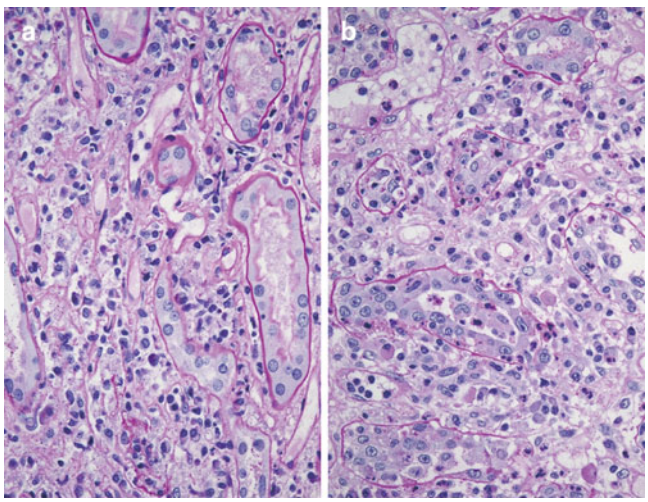

Fig. 25.4 Tubulitis is mild in IgG4-related kidney disease (**a**) as compared to idiopathic acute TIN (**b**) (×400)

Although most other types of TIN show a homogeneous distribution of lesions, two important potential exceptions exist. The renal lesions in TIN associated with Sjögren's syndrome—an important IgG4-RD mimicker—can be patchy [9], and chronic pyelonephritis also sometimes shows a patchy distribution of gross scars and an abrupt transition from normal cortex to a damaged area. Thus, distinguishing among IgG4-RD, Sjögren's syndrome, and chronic pyelonephritis requires careful scrutiny and close clinicopathologic correlation.

Another characteristic of IgG4-related TIN is the tendency of this lesion to infiltrate into and beyond the renal capsule (Fig. 25.1). Such a finding is highly unusual in non-IgG4-related TIN.

25.3.3 Fibrosis

Fibrosis is a very important feature of Ig4-RD, and storiform fibrosis is a useful finding to differentiate IgG4-related TIN from other non-IgG4-related TIN (Fig. 25.6) [5]. Storiform fibrosis is comprised of inflammatory cell infiltrates and irregular fibers, shows storiform disarray, and leads to various degrees of fibrosis. This fibrosis is a common pathological finding of most sites of IgG4-RD involvement. Small nests of plasma cells or lymphocytes are encased by the irregular fibrosis, which Yamaguchi et al. named "bird's-eye" fibrosis [4]. This finding is clearly shown by periodic acid methenamine silver stain (PAM stain). Accordingly, reports of "bird's-eye" fibrosis are accumulating only in IgG4-RKD.

When the stages of the fibrosis are defined according to the degree of fibrosis in IgG4-related TIN, a lack of uniformity is observed within different areas of the same case. Substantial differences exist according to site within the lesion, and there is an intermingling of different stages of fibrosis (Fig. 25.7) [5]. The degree of fibrosis found in the TIN of IgG4-RKD is significantly more severe than that of other types of TIN [5]. Therefore, the finding of distinct and mixed degrees of fibrosis should also raise suspicion of IgG4-related TIN, even in the absence of any typical storiform fibrosis or bird's-eye fibrosis.

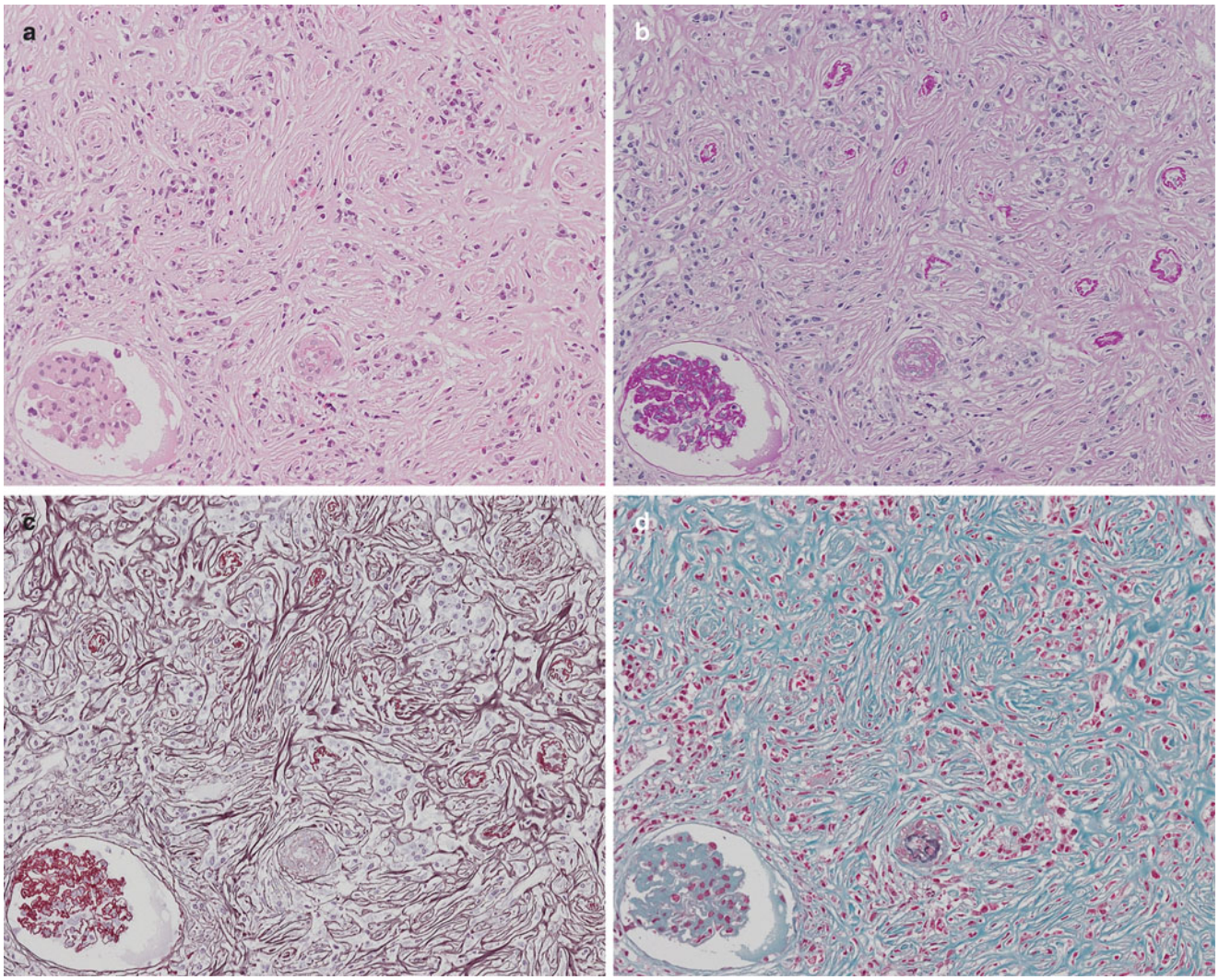

Fig. 25.6 Storiform fibrosis. (**a**) HE-staining, (**b**) PAS-staining, (**c**) PAM-staining, and (**d**) Elastica–Masson trichrome-staining (modification of Goldner method) (×200)

Raissian et al. report that fibrosis is not evident in some IgG4-RD cases in which the development of TIN is particularly acute [2]. Consequently, in the absence of fibrosis, other clinical features such as hypergammaglobulinemia, hypocomplementemia, or other typical organ involvement are helpful in supporting the diagnosis of IgG4-RKD.

25.3.4 Necrotizing Angiitis

In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, reports or studies of predominant plasma cell infiltration with IgG4-positive plasma cells, which fulfill the criteria of the number and the ratio of IgG4-positive plasma cells, have been accumulated [10–12]. In patients with Churg–Strauss syndrome, elevated serum IgG4 levels have also been reported [10]. Therefore, the existence of vasculitis and clinical features including ANCA positivity and elevated serum CRP levels must be carefully evaluated to avoid misdiagnosing vasculitis as IgG4-RKD. In particular, since only TIN without glomerular lesions or vasculitis is sporadically reported in ANCA-associated glomerulonephritis (perhaps because of sampling error), the presence of RBC casts suggestive of upstream crescentic glomerulonephritis or neutrophil-rich infiltrates are important findings to differentiate these two diseases [13].

25.3.5 Granulomatous Lesions

Granulomatous lesions are rarely seen in IgG4-related TIN. Accordingly, drug-induced TIN, Churg–Strauss syndrome,

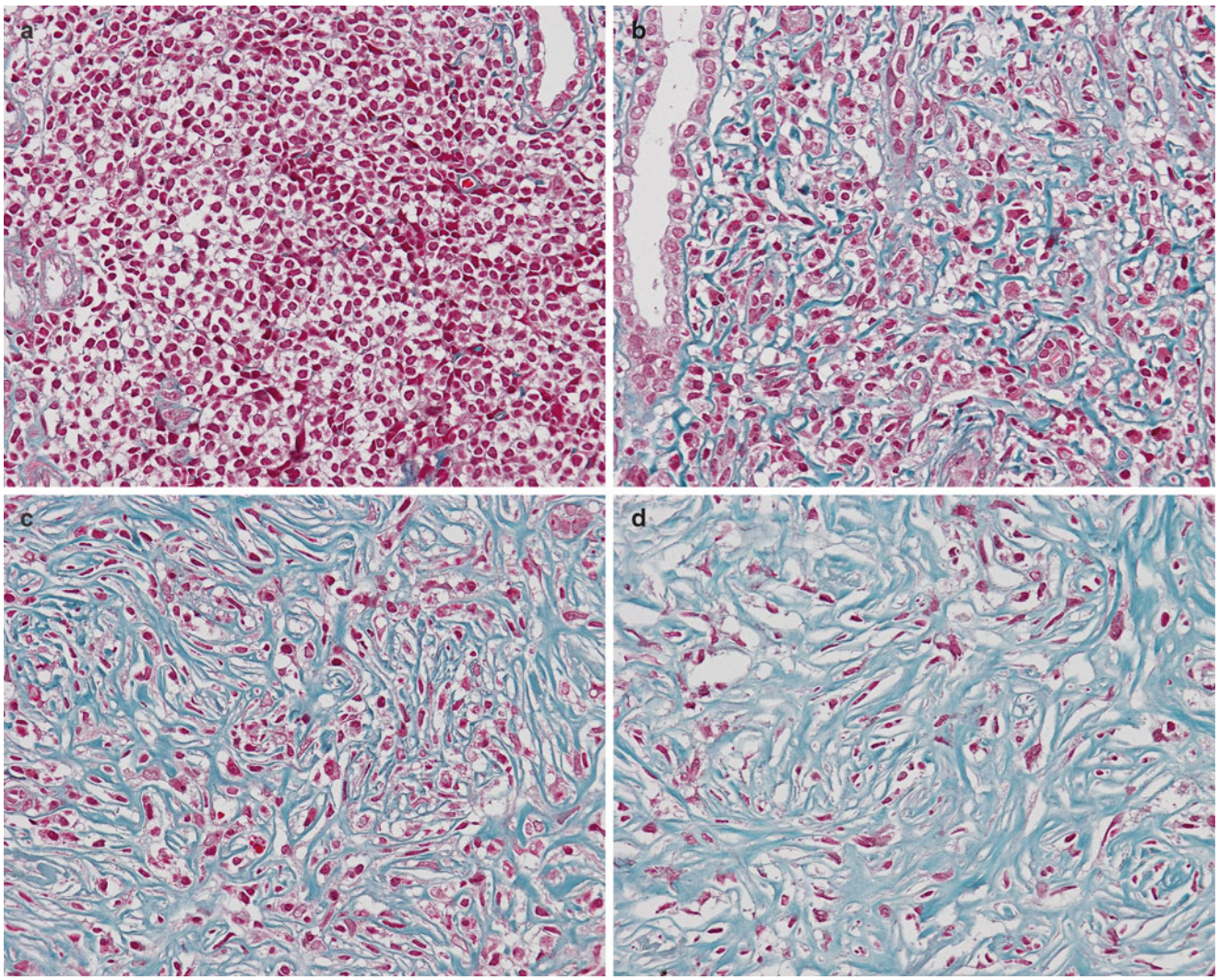

Fig. 25.7 Stages of interstitial fibrosis. (**a**) Stage 0 (fibrosis absent), (**b**) stage 1 (fibrosis mild), (**c**) stage 2 (moderate fibrosis), and (**d**) stage 3 (severe fibrosis) Elastica–Masson trichrome-staining (modification of Goldner method) (×400)

granulomatosis with polyangiitis (Wegener's), sarcoidosis, or uncommon infections such as tuberculosis should be considered in the differential diagnosis when apparent granulomatous lesions are associated.

25.3.6 Inflammatory Pseudotumor

Solitary mass lesions limited to a single kidney are very rare but have been sporadically described in IgG4-RD [14, 15]. This lesion shows a hypovascular mass on contrast-enhanced CT. In such cases, suspicion for a malignant tumor is high and often leads to nephrectomy. Histological examination shows a mass-like nodular pattern of inflammation with abundant IgG4-positive plasma cells and fibrosis, surrounded by normal kidney tissue.

25.3.7 IgG4-Positive Plasma Cell Infiltration

IgG4 immunostaining is indispensable for the diagnosis of IgG4-RD (Fig. 25.8). The degree of IgG4-positive plasma cell infiltration is influenced by the organ biopsied and the type of biopsy procedure. Because needle biopsies are typically performed on the kidney, the number of IgG4-positive plasma cells sufficient for the diagnosis is small, with a threshold of >10/high-power field (HPF) selected in two proposed sets of diagnostic criteria [2, 3]. In addition, determination of the IgG4+/IgG+plasma cell ratio is also mandatory, with >40 % commonly adopted as the threshold in every affected organ [8]. However, since some cases with Churg–Strauss syndrome, granulomatosis with polyangiitis (Wegener's), and other ANCA-associated vasculitis fulfill this item of the pathological criteria [10–12], other clinical

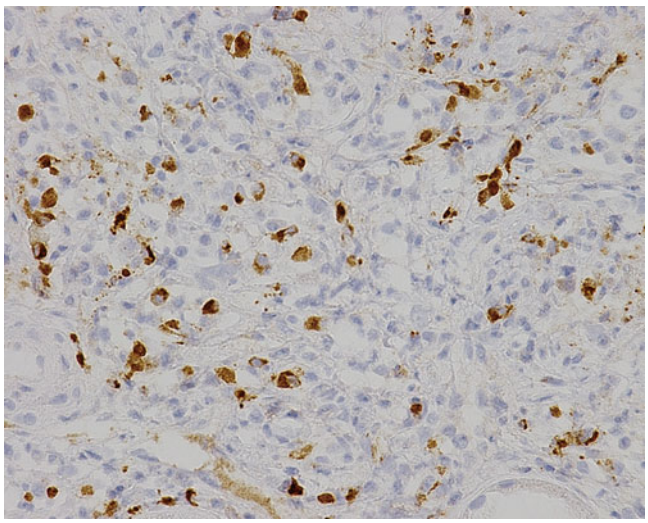

Fig. 25.8 Findings of immunostaining with anti-IgG4 antibody. Most of the plasma cells infiltrating the interstitium are IgG4-positive (×400)

and pathological features should be referred to as well so as to avoid a misdiagnosis. Moreover, many IgG4-positive plasma cell infiltrates are reported in some cases of lupus nephritis and idiopathic TIN, suggesting that infiltration of many IgG4-positive plasma cells is not necessarily specific for IgG4-RKD (IgG4-positive plasma cell infiltration) [16]. In surgical specimens of the kidney, a threshold of >30/HPF (high-power field) is proposed as a suitable item of diagnostic criteria [8].

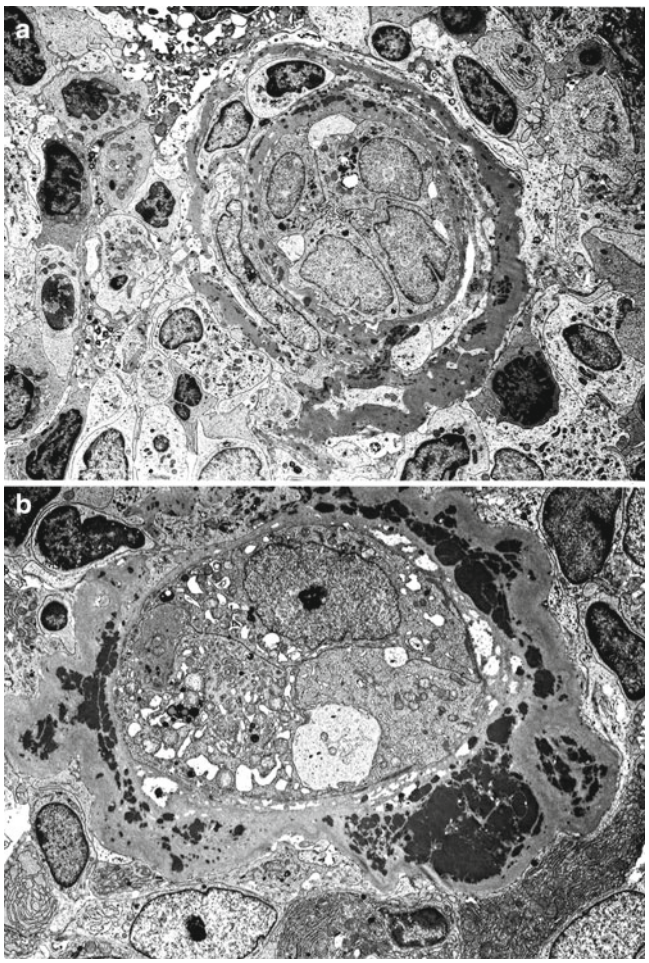

Fig. 25.9 (**a**) Tubular basement membrane thickening and slight deposition of electron-dense material in the basement membrane are found. (**b**) Tubular basement membrane thickening and marked deposition of electron-dense material on the basement membrane are found

25.3.8 Immune Complex Deposits in the Tubular Basement Membrane and Interstitium

In IgG4-RKD, immunoglobulin and complement deposition in the tubular basement membrane (TBM) (Fig. 25.9), interstitium (Fig. 25.10), and vascular wall has been documented [2, 4]. Raissian et al. reported immune complex deposition in the TBM in ≥80 % of IgG4-RD patients with TIN diagnosed at the Mayo Clinic [2]. By immunofluorescence microscopy, IgG is found as somewhat coarse, granular deposits of IgG4 and C3 (Fig. 25.11a), with occasional C1q deposits also seen (Fig. 25.11b). Both κ and λ light chains are positive with no restriction, suggesting that the immunoglobulins deposited are polyclonal. Deposits of IgG subclasses other than IgG4, namely IgG1, IgG2, and IgG3, are also found (Fig. 25.12)—rather weak in the case of IgG2—suggesting that IgG4 forms complexes with other immunoglobulins. Major tubulointerstitial deposits are limited to the area with interstitial inflammation, and the degrees of IgG4-positive plasma cell infiltration and fibrosis correlate. For these reasons, some researchers consider that immune complexes are unlikely to be the cause of the tubulointerstitial lesions, but rather result from excessive local production within the kidney. Moreover, these deposits are not limited to the tubulointerstitium, but are found in the Bowman's capsule wall as well (Fig. 25.13). An electron microscopy study demonstrated mosaic-like electron-dense deposits in the interstitium and in and around the vascular wall [4].

Other diseases in which this kind of TBM immune complex deposition is found include systemic lupus erythematosus (SLE) and Sjögren's syndrome. However, in SLE, immune complex deposits involve unaffected areas as well as the affected areas of the interstitium. Immune complex deposition in the TBM has been described in Sjögren's syndrome patients with TIN, but the deposition is mild in degree and easily differentiated from IgG4-RD with close clinicopathologic correlation.

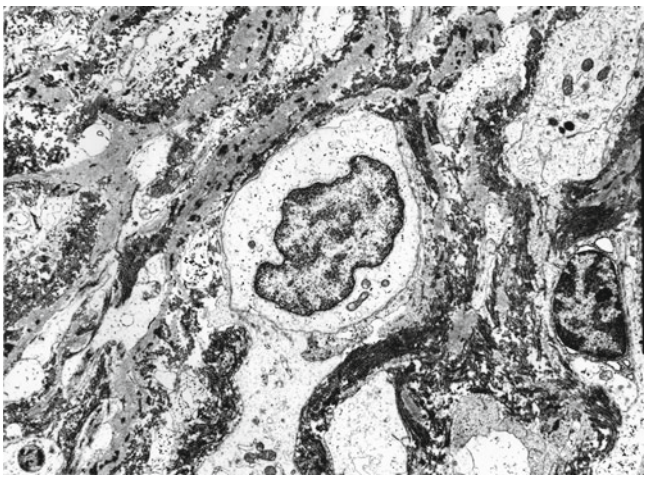

Fig. 25.10 Electron-dense deposits in the interstitium

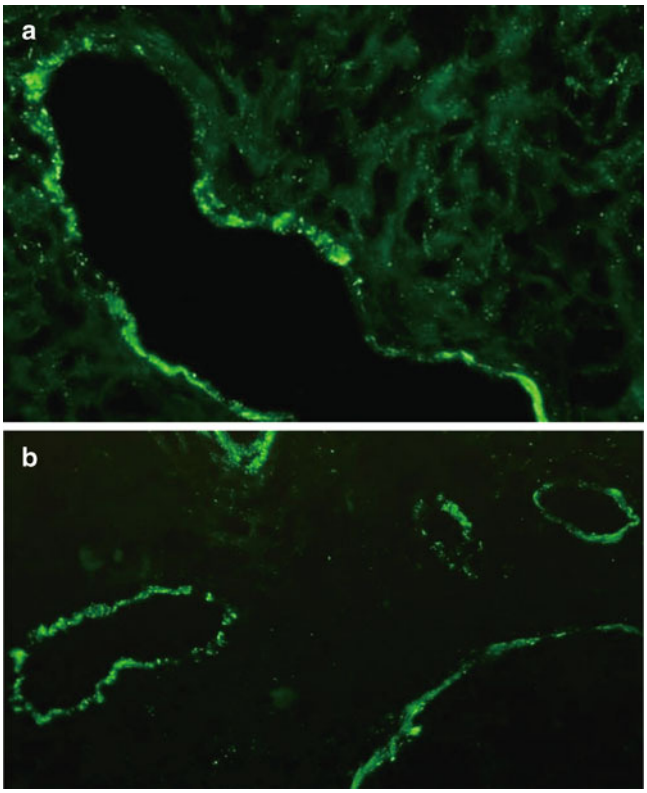

Fig. 25.11 (**a**) IgG-staining. (**b**) C1q-staining

25.3.9 Pathological Changes After Corticosteroid Therapy

Mizushima et al. showed that patchy marked fibrosis persisted among the normal renal tissue after successful steroid therapy. This finding was interpreted as being consistent with the mixture of recovering and atrophic lesions detected by contrast-enhanced CT during maintenance steroid therapy [17]. In addition, they showed rapid disappearance of IgG4-positive plasma cells and Foxp3-positive regulatory T cells after successful steroid therapy. Accordingly, evaluation of the number and ratio of IgG4-positive plasma cells during corticosteroid administration should be carefully interpreted for the diagnosis of IgG4-RKD.

25.4 Glomerular Lesions

In IgG4-RKD, glomerular lesions concurrent with TIN have been reported [18–26]. Membranous nephropathy is particularly common in this setting [18, 19, 23, 24].

25.4.1 Membranous Nephropathy in Cases Associated with TIN

Most cases of membranous nephropathy in IgG4-RD reported to date have shown TIN associated with IgG4-positive plasmacytic cell infiltration [18, 19, 23, 24] (Fig. 25.14). In the first case reported by Uchiyama-Tanaka et al. [18], proteinuria rapidly disappeared and subepithelial electron-dense deposits were also found to disappear in parallel with improvement of the TIN with steroid therapy. In contrast, in the 2nd case reported by Watson et al. [19], despite the fact that steroid therapy was effective in controlling the TIN, proteinuria persisted for 7 months. In subsequently reported cases of Saeki et al. [23], IgG1 and IgG4 were deposited mainly in the glomeruli, while in those of Fervenza et al. [24], both IgG2 and IgG4 deposits were found, with IgG2 dominant. In the latter report, anti-M-type phospholipase A2 receptor (PLA2R) antibodies were negative. Anti-PLA2R antibodies are said to be present in about 70 % of idiopathic membranous nephropathy cases, in which IgG4 is also dominant on the glomerular capillary walls. These receptors are present on the glomerular epithelial cell membrane, and determination of the presence/absence of receptor antibodies may possibly aid in the differentiation of idiopathic membranous nephropathy and IgG4-RD-associated membranous nephropathy.

25.4.2 Membranous Nephropathy in Cases Not Associated with TIN

A small number of cases of IgG4-RD in which membranous nephropathy is the sole kidney lesion have been reported [27, 28], although they are not defined as IgG4-related kidney disease [3, 29]. The first report of this renal lesion demonstrated the development of proteinuria during the course of IgG4-related chronic periaortitis [27]. In these

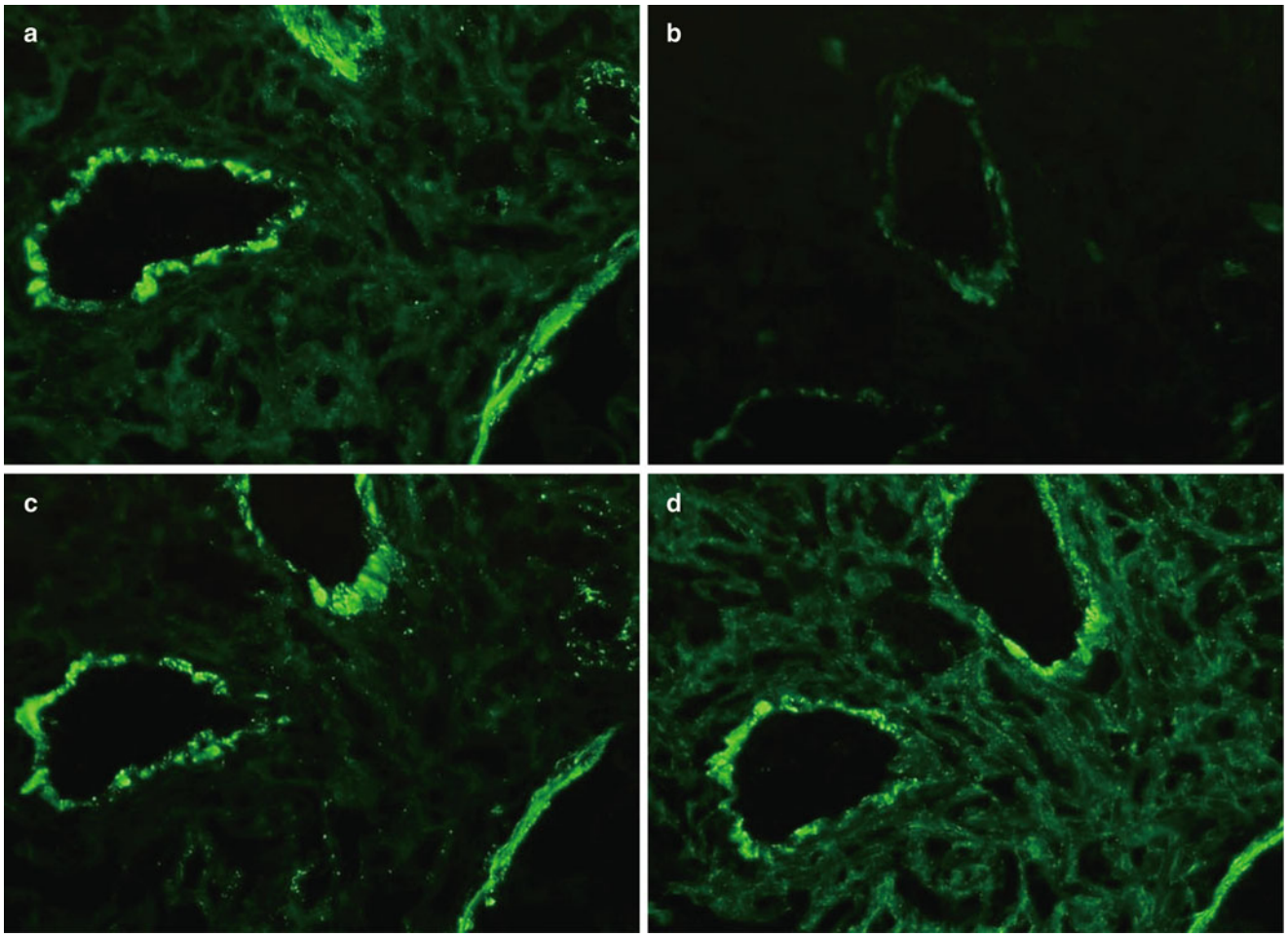

Fig. 25.12 IgG subclass deposits. (**a**) IgG1, (**b**) IgG2, (**c**) IgG3, and (**d**) IgG4

cases, IgG4 deposition was dominant in both the glomerular capillary loop wall and tubular basement membrane, but no cellular infiltration into the interstitium was found. On the other hand, the report of Cravedi et al. [28] described a case in which serum IgG4 concentrations rose and new-onset proteinuria appeared over the course of treatment for autoimmune pancreatitis and Mikulicz's disease. The IgG deposits in the glomeruli were IgG3-dominant, followed by slight IgG4 deposits. Almost no C3 deposition was found, while C1q deposition was marked in the capillary loop wall. No deposits were noted in the TBM. No cellular infiltration into the interstitium was noted in these cases either. Anti-PLA2R antibodies were negative. A recent study by Khosroshahi et al. demonstrated that none of 28 patients in a series of IgG4-RD had circulating anti-PLA2R antibodies, consistent with the absence of any involvement of these antibodies in the pathophysiology of IgG4-RD [6]. Studies of additional cases of membranous nephropathy in the setting of IgG4-RD are important to identify any common developmental mechanism(s) shared by these two disorders.

25.4.3 Henoch–Schönlein Purpura

A case of IgG4-RD with concurrent Henoch–Schönlein purpura nephritis was first reported by Tamai et al [25]. Purpura was also associated in some of the earlier reported cases with IgG4-related renal involvement. Additional cases with coexistent Henoch–Schönlein purpura nephritis have subsequently been described [26], and Henoch–Schönlein purpura has long been known to complicate type 1 autoimmune pancreatitis in occasional cases. Accordingly, we consider that Henoch–Schönlein purpura may not be a mere coincidental association, but rather may be related

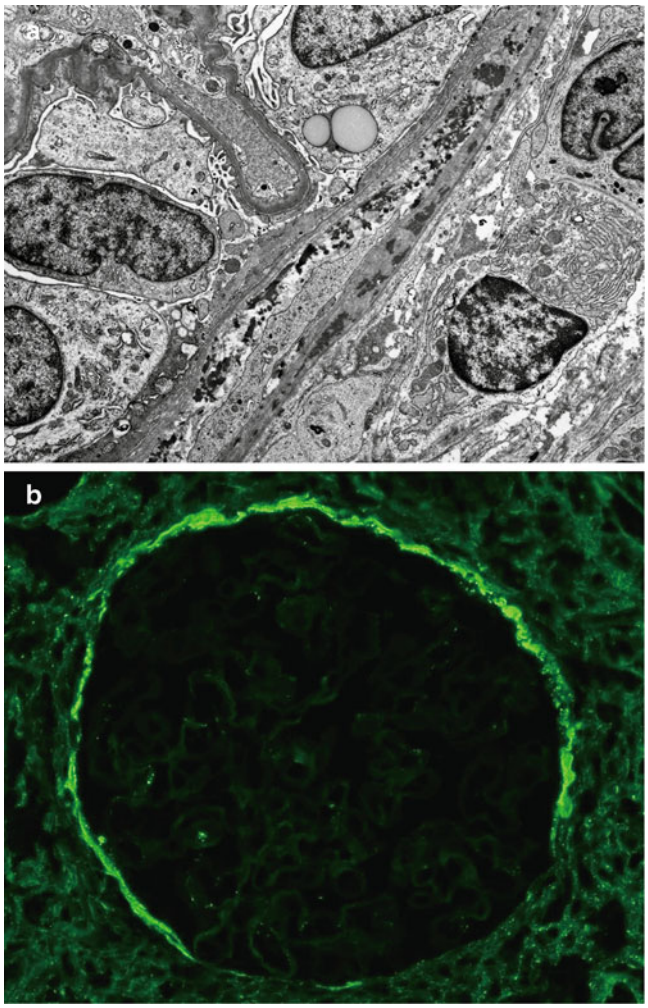

Fig. 25.13 Deposition of electron-dense material in Bowman's capsule wall. (**a**) Electron microscopic findings. (**b**) Immunofluorescence microscopic findings

etiopathologically in some way to IgG4-RD. Figure 25.15 shows one of our own cases [26]. The nature of the association between purpura and IgG4-RD will have to be resolved in future by conducting detailed studies of larger numbers of cases.

25.4.4 Other Glomerular Lesions

In addition, cases of IgG4-RD with concomitant IgA nephropathy, endocapillary glomerulonephritis, and membranoproliferative glomerulonephritis have been reported. Whether such cases represent merely a coincidental

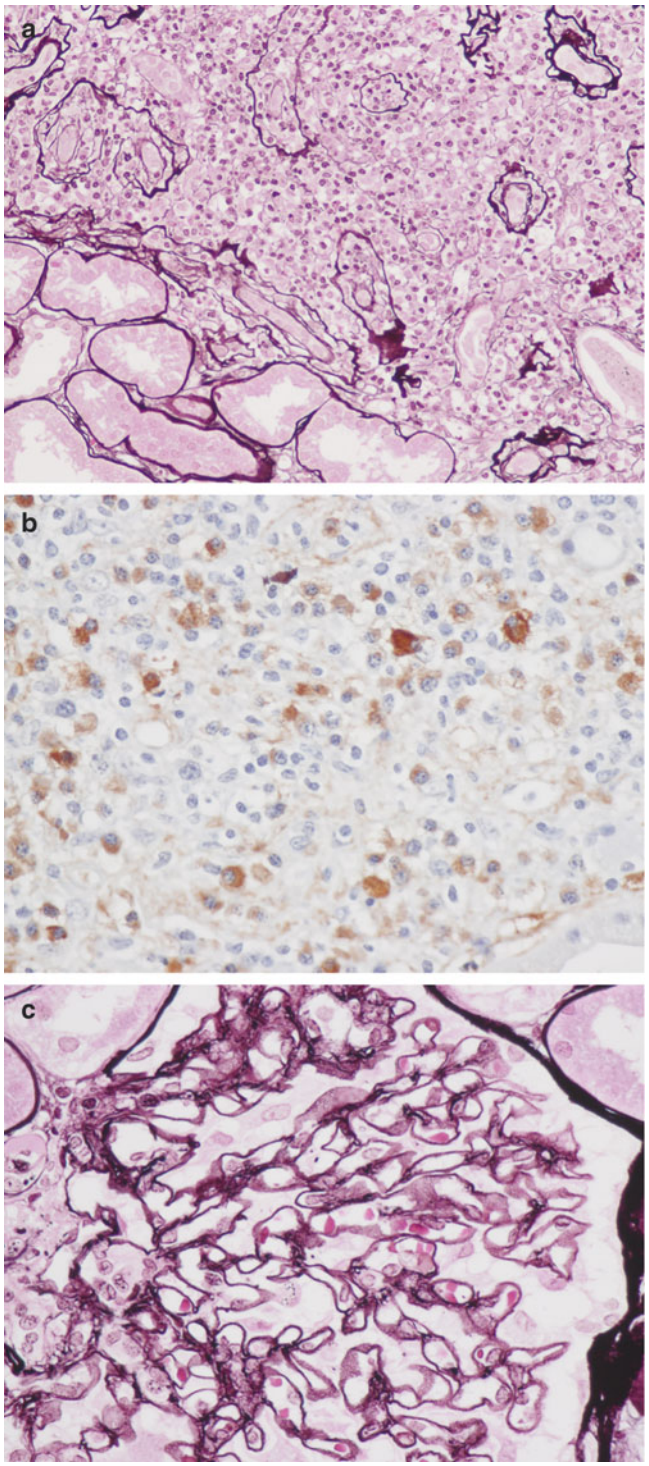

Fig. 25.14 IgG4-related TIN associated with membranous nephropathy. (**a**) TIN with clearly demarcated normal and involved portions. PAM-staining. (**b**) Most infiltrating plasmacytic cells are IgG4-positive. IgG4 immunostaining. (**c**) Prominent vacuolated appearance is found. PAM-staining (fluorescent antibody method showed IgG granular deposits in basal membrane)

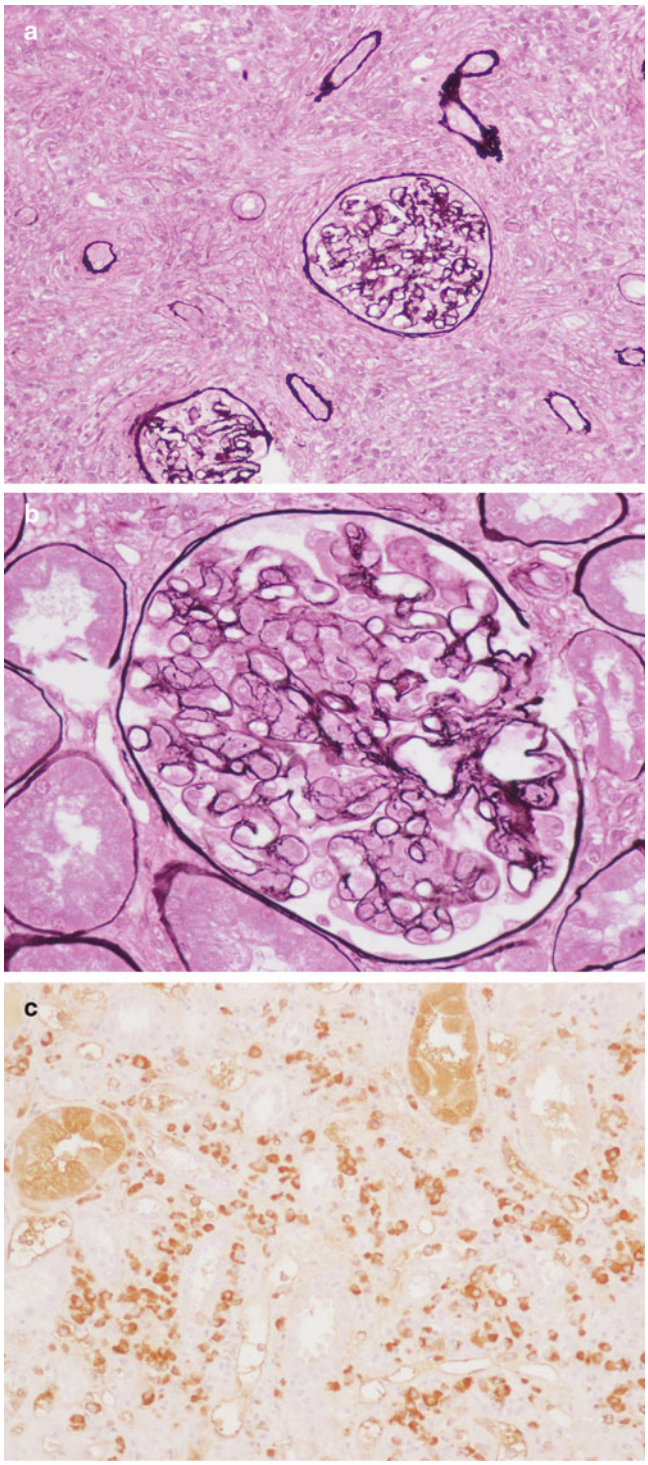

Fig. 25.15 IgG4-related TIN associated with purpura nephritis. (**a**) Marked interstitial nephritis associated with fibrosis is found. PAM-staining. (**b**) Mesangioproliferative glomerulonephritis with marked endocapillary proliferation. PAM-staining. (**c**) Most plasmacytic cells infiltrating the interstitium are IgG4-positive. IgG4-staining

occurrence or are significant from an etiopathological standpoint will have to be determined by accumulating and carefully studying larger series of cases.

25.4.5 Conclusion

IgG4 immunostaining has led to the discovery of a new disease entity known as IgG4-related RKD. However, overreliance on IgG4 immunostaining has introduced the new risk of misdiagnosing lupus nephritis with plasma cell-rich TIN or ANCA-associated vasculitis as IgG4-related TIN. Therefore, the specificity of IgG4-staining requires evaluation in a large-scale study including wide varieties of TIN.

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Retroperitoneal Fibrosis and Arterial Lesions

26

Kenji Notohara

26.1 Retroperitoneal Fibrosis

26.1.1 Historical Background

The 1905 report of Albarran [1] is considered to be the first mention of retroperitoneal fibrosis (RPF) in the medical literature. In 1948, Ormond [2] rediscovered the entity and RPF became known more widely, such that it is now sometimes termed "Ormond's disease" even today. Because urography was the main imaging modality described in the initial reports of this condition, RPF was characterized as a disease in which fibrotic lesions form around the ureter leading to ureteral stenosis and hydronephrosis. Mitchinson [3] later clarified in a pathological study of autopsied cases that the main lesions were located in the abdominal aorta immediately above the bifurcation, where they tended to envelop both ureters and lead eventually to bilateral ureteral stenosis. Computed tomographic examinations have confirmed this thinking in recent years [4] and the term "periaortitis" has come to be used synonymously with RPF. However, involvement limited to the area around a single ureter—namely, unilateral RPF—is also recognized [5].

In reports on RPF from the 1960s to 1970s, hints of an association between this disease and IgG4-RD can already be discerned. The common development of hypergammaglobulinemia (not otherwise specified) was observed [6] and the histological finding of obliterative phlebitis was noted [7]. Glucocorticoid therapy was recognized to be effective—sometimes strikingly so—in many cases [8]. And finally, the simultaneous occurrence of diseases that affected diverse organs under the single rubric of "multifocal fibrosclerosis," e.g., sclerosing cholangitis, "sclerosing pancreatitis," Riedel's thyroiditis, and orbital pseudotumor, was reported [3, 4, 7–9].

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On the other hand, it was recognized that similar lesions could be induced by certain infections [10, 11] or medications (e.g., ergot alkaloids) [12] and that tumors such as malignant lymphoma and carcinoid could also lead to this presentation [13, 14]. Similar lesions for which no cause was evident were referred to as idiopathic RPF.

26.1.2 The Current and Evolving Concept of RPF

In 1995, the concept of autoimmune pancreatitis (AIP) was established [15]. RPF is now known to occur concurrently with AIP in approximately 10 % of AIP cases [16, 17]. Shortly after the report of Hamano et al. [18, 19] that identified abnormalities of serum IgG4 concentrations and the numbers of IgG4-positive plasma cells in the affected tissues among patients with "sclerosing pancreatitis" (AIP) and that of Kamisawa et al. [20] that proposed the concept of IgG4-related sclerosing disease, RPF was confirmed to be part of the spectrum of IgG4-RD.

In retrospect, many cases diagnosed as "idiopathic" RPF in the past were almost certainly examples of IgG4-related RPF. However, the etiology of RPF is clearly diverse, and at least two major categories of RPF are now established: those associated with IgG4-RD (whatever its ultimate cause(s)) and those linked to other putative triggers or etiologies, including infections, medications, and tumors [21, 22]. At the present time, the only well-established clinicopathological concept under the umbrella of RPF is the IgG4-related lesion. It is appropriate to call this lesion IgG4-related RPF and to distinguish it from other non-IgG4-related lesions. In addition, cases of RPF associated with malignancies should also be distinguished from IgG4-related RPF and those cases of RPF that are truly idiopathic.

IgG4-related RPF most commonly involves the areas around the abdominal aorta and ureters. This presentation, once termed periaortitis, is regarded as the classic RPF presentation. However, this type of perivascular lesion has long been reported to develop sporadically in the thoracic aorta

H. Umehara et al. (eds.), *IgG4-Related Disease*, DOI 10.1007/978-4-431-54228-5_26,

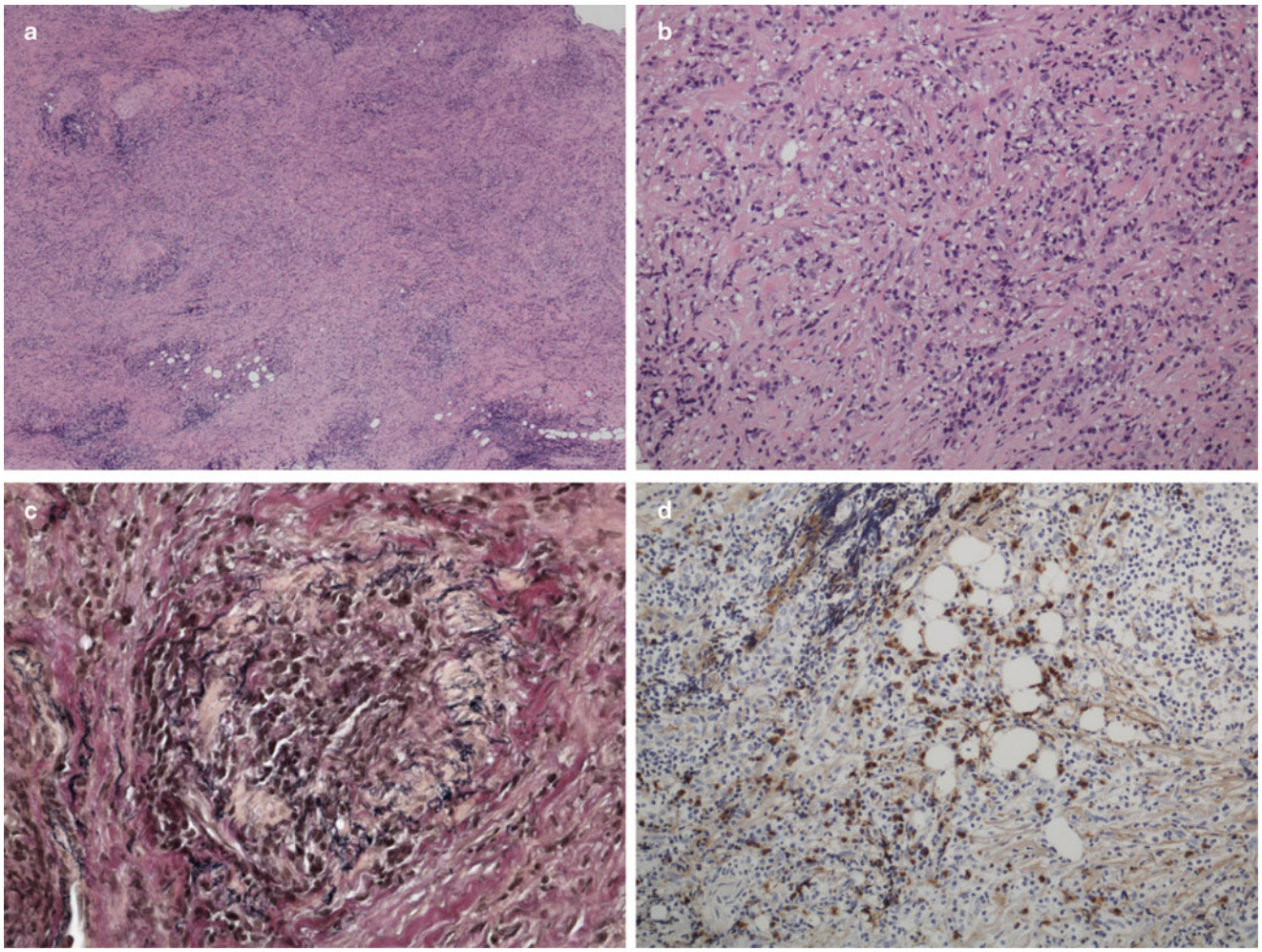

Fig. 26.1 IgG4-related RPF (periaortitis). (**a**) Lymphoplasmacytic infiltration and fibrosis are seen throughout the lesion. (**b**) Storiform fibrosis with fibers extending in various directions is characteristic, and within this, lymphoplasmacytic infiltration is seen. Because of adipose tissue degeneration, numerous fatty vacuoles are found. (**c**) Obliterative phlebitis. Elastica van Gieson stain. (**d**) On IgG4 immunostaining, numerous positive plasma cells are found

and its primary branches, as well [3, 23]. With the wider recognition of IgG4-RD [24–26], the concept of RPF as a disease localized to the area of the abdominal aortic bifurcation and tending to entrap one or both ureters must change. The current understanding of this disorder includes histopathologically identical vascular lesions that may involve portions of the thoracic aorta and its branches, as well. The concept of an IgG4-related periarteritis or arteritis is now emerging.

On the other hand, there is a minor group called "unilateral RPF," in which the lesions are confined to one periureteral or perirenal pelvic area without involving major vessels.

26.1.3 Pathological Characteristics of IgG4-Related RPF

The basic histological picture of IgG4-related RPF comprises adipose tissue destruction, marked lymphoplasmacytic infiltration, and fibrosis (Fig. 26.1a). Lymph follicle formation and eosinophil infiltration are both frequently seen, whereas neutrophil infiltration is rare. These are common features of IgG4-RD regardless of the site of organ involvement and their presence is strongly suggestive of, though not specific for, this diagnosis. In fibrotic foci, storiform fibrosis (Fig. 26.1b) is found, but compared with type 1 (IgG4-related) AIP, the tissue in many cases has an overwhelming fibrosis with only a scanty cellular component(see Chap. 21). Moreover, in others, the features of storiform fibrosis are difficult to recognize. In studies of resected materials, obliterative phlebitis has been reported significantly more frequently than in non-IgG4-related RPF (Fig. 26.1c) [22]. On immunostaining, numerous IgG4-positive plasma cells are identified (Fig. 26.1d). In typical examples, >50 infiltrating IgG4-positive plasma cells per high-power field (HPF) are seen, while the number of inflammatory cells themselves is low in many cases, on

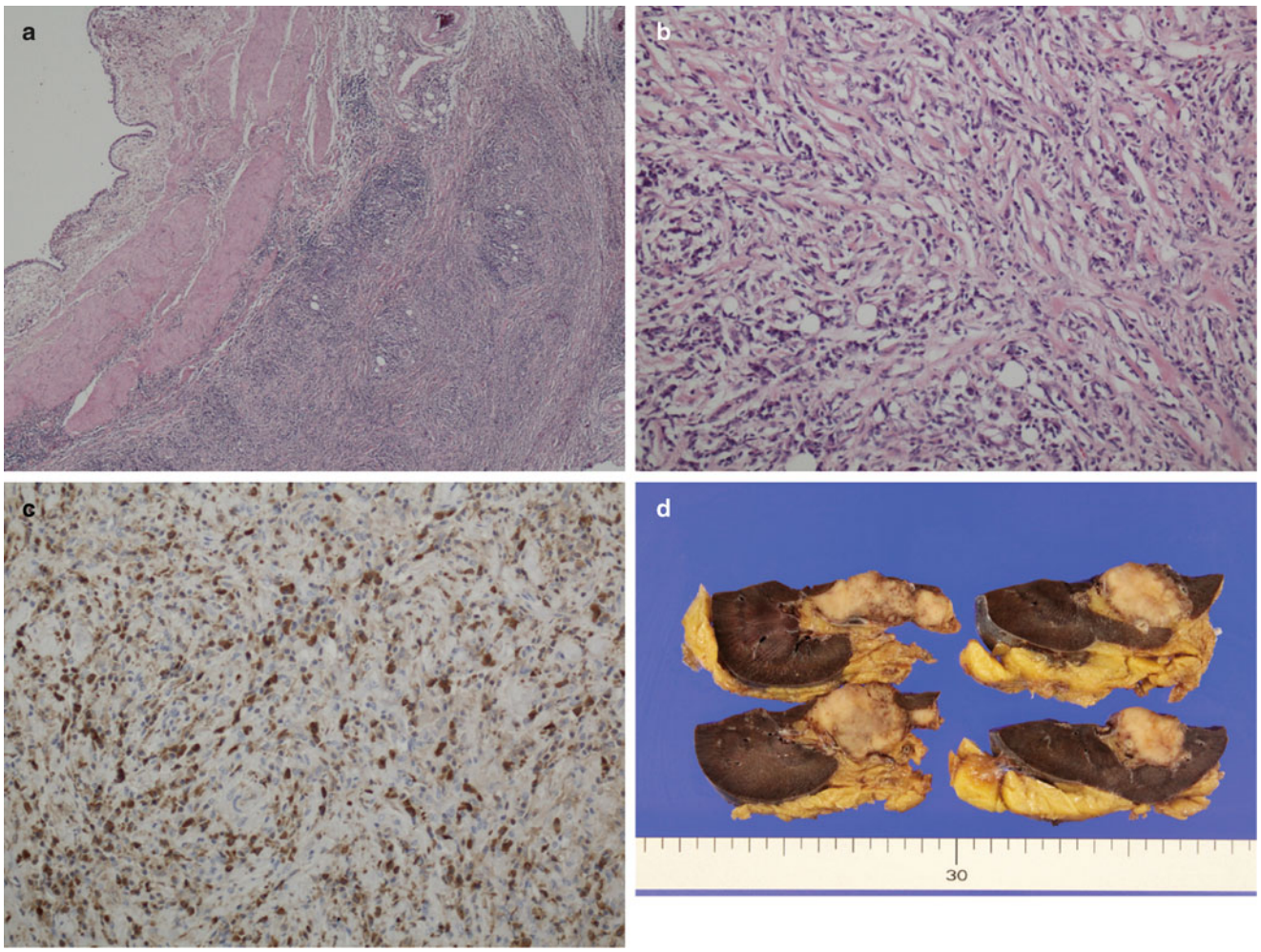

Fig. 26.2 IgG4-related RPF (periureteral and renal hilum lesions) (**a**–**c**): A periureteral lesion. Inflammation is seen around the muscularis propria (**a**). The inflammation involves a portion of the muscularis propria, but the mucosa (*left*) is normal. In fibrotic foci, storiform fibrosis (**b**) and on immunostaining numerous IgG4-positive plasma cells (**c**) are seen. (**d**) A renal hilar lesion. The lesion develops around the renal pelvis and pelvoureteral junction

occasion <50/HPF. In addition, the IgG4/IgG-positive plasma cell ratio (usually >40 %) is essential to consider when weighing the possibility of this diagnosis [27, 28]. The pathological "cutoffs" of an IgG4-/IgG-positive plasmacytic cell ratio >40 % and IgG4-positive plasmacytic cells >10/HPF [27] must be regarded as guidelines rather than rigid, unassailable rules in diagnosis, and the diagnosis can only be ascertained with any degree of certainty through careful correlation of the immunostaining findings with the histopathologic features of the case, as well as the patient's clinical manifestations in the organ under examination and beyond.

The periureteral lesions are most prominent around the muscularis propria (Fig. 26.2a–c). The inflammation extends to the muscularis propria of the ureter in many cases, while inflammation in the epithelium is absent or extremely mild in most cases. For this reason, it is considered unlikely that this lesion represents an extension of the mucosal inflammatory process. As mentioned above, similar lesions are also seen around the renal pelvis (Fig. 26.2d).

26.1.4 Non-IgG4-Related RPF

The differential diagnosis of IgG4-related RPF includes non-IgG4-related RPF, but this condition has yet to be subjected to sufficient pathological analysis. As noted above, infection and various medications have been proposed as causes of RPF, but with regard to the histological picture, no comprehensive reports are available, making it difficult to speculate about the etiology based on this. Moreover, it cannot be excluded that at least some cases were concluded to have non-IgG4-related RPF, when in fact regression of the IgG4-related inflammation may have occurred.

Tissue findings that are present in this subset but unlikely to be seen in IgG4-related lesions include (1) infiltration in

which lymphocytes are the predominant cell type and plasmacytic infiltration is scanty; (2) prominent neutrophil infiltration; and (3) a histological picture representative of granuloma or xanthogranuloma formation. Furthermore, since IgG4-RD most often affects the elderly, one must be skeptical about making this diagnosis in patients less than 30 years of age. Cases in which it is impossible to distinguish IgG4-related RPF based on the tissue morphology alone and which do not stain for IgG4 on immunostaining have also been reported [22], making IgG4 immunostaining important in the diagnosis of RPF.

The most important condition requiring differentiation from IgG4-related RPF is malignant lymphoma. Of these, Hodgkin's lymphoma and follicular lymphoma are sometimes associated with severe fibrosis, and at a glance it may sometimes be difficult to appreciate their tumorous nature. Pathologists are required to make a differential diagnosis of RPF and malignant lymphoma with biopsy tissue, but the harvested tissue is often too crushed to grasp the morphological features, complicating the diagnosis. At such times, a meticulous differential diagnosis including immunostaining is necessary.

In lymphomas, lymphocytes are usually the main cellular component with scarce or no plasma cells present, and the density of lymphocytes is in general higher than that of IgG4-related RPF. When encountering this kind of retroperitoneal lesion, the differentiation must be made with caution. Confirmation of the presence/absence of monoclonality by κ and λ immunostaining is also useful in the differentiation of lymphoma and inflammation. For cases in which differentiation is especially difficult, chromosomal and gene rearrangement studies are also of help.

In the ureter, an inflammatory lesion of unknown cause called idiopathic segmental ureteritis can occur and occasionally requires differentiation from tumors [29]. Transmural inflammation is said to be seen in the ureter, differing in this point from IgG4-related RPF. A case developing obliterative phlebitis has also been described [29], making a painstaking differential diagnosis, including immunostaining for IgG4, necessary.

26.2 Arterial Lesions (Periarteritis and Arteritis)

26.2.1 Disease Concept

As mentioned above, the formation of lesions around the abdominal aorta in RPF is also referred to as periaortitis, and the nature of the association between aortic atherosclerosis and inflammatory disease has long been debated. In some cases, these lesions form in sections of the aorta consistent with those affected by severe atherosclerosis, and it was hypothesized and widely accepted at the time that ceroid present in atheromatous plaque might leak into the adventitia and thereby provoke an immune reaction leading to the development of periaortitis [30, 31]. This also spurred wide recognition of the theory that RPF is a lesion related to the aorta.

Recently, similar lesions have been recognized to develop in the thoracic aorta (especially in the arch), superior and inferior mesenteric arteries, splenic artery, and coronary arteries [24–26]. Some lesions previously considered to be inflammatory abdominal aortic aneurysms are now recognized to be IgG4-related periaortitis [32].

26.2.2 Pathological Characteristics

Regardless of the artery affected, formation of thick fibrotic inflammatory foci chiefly in the adventitia and extreme thickening of the vascular wall are characteristic (Fig. 26.3a). The histological characteristics of these inflammatory foci are the same as those of IgG4-related RPF, showing marked lymphoplasmacytic infiltration and fibrosis, with lymph follicle formation and eosinophil infiltration. Findings of storiform fibrosis (Fig. 26.3b) and obliterative phlebitis (Fig. 26.3c) should heighten suspicion of this disease. Inflammation of the adventitia often extends to the media as well, and for this reason, this arterial lesion is sometimes reported as "periarteritis/arteritis." However, whether cases with arteritis actually exist in the absence of periarteritis is not yet clear. Infiltration by numerous IgG4-positive plasma cells (Fig. 26.3d), usually exceeding 50/HPF, and an IgG4/IgG-positive plasmacytic ratio >40 % are seen in most cases.

A difficult-to-classify type of arteritis limited to the thoracic aorta (isolated aortitis) has been reported, and at least a portion of lesions with the lymphoplasmacytic variant in which lymphoplasmacytic infiltration is a prominent feature may in fact be IgG4-related lesions [33, 34]. In reported cases, not only the adventitia but also the media has been described to show severe changes, suggesting the interesting possibility that IgG4-RD may induce true arteritis. More studies are needed to characterize this entity.

Complications of IgG4-related arterial lesions have been reported to include rupture [35], inflammatory abdominal aortic aneurysm [32], and aortic dissection [36].

26.2.3 Diagnostic Problems

The inflammatory lesions seen in the aorta and its branches are diverse, and as noted in the section on RPF, it is important to make a diagnosis while paying careful attention to the differential points. Because IgG4-related arterial lesions are prone to involve the major arteries, including the aorta and

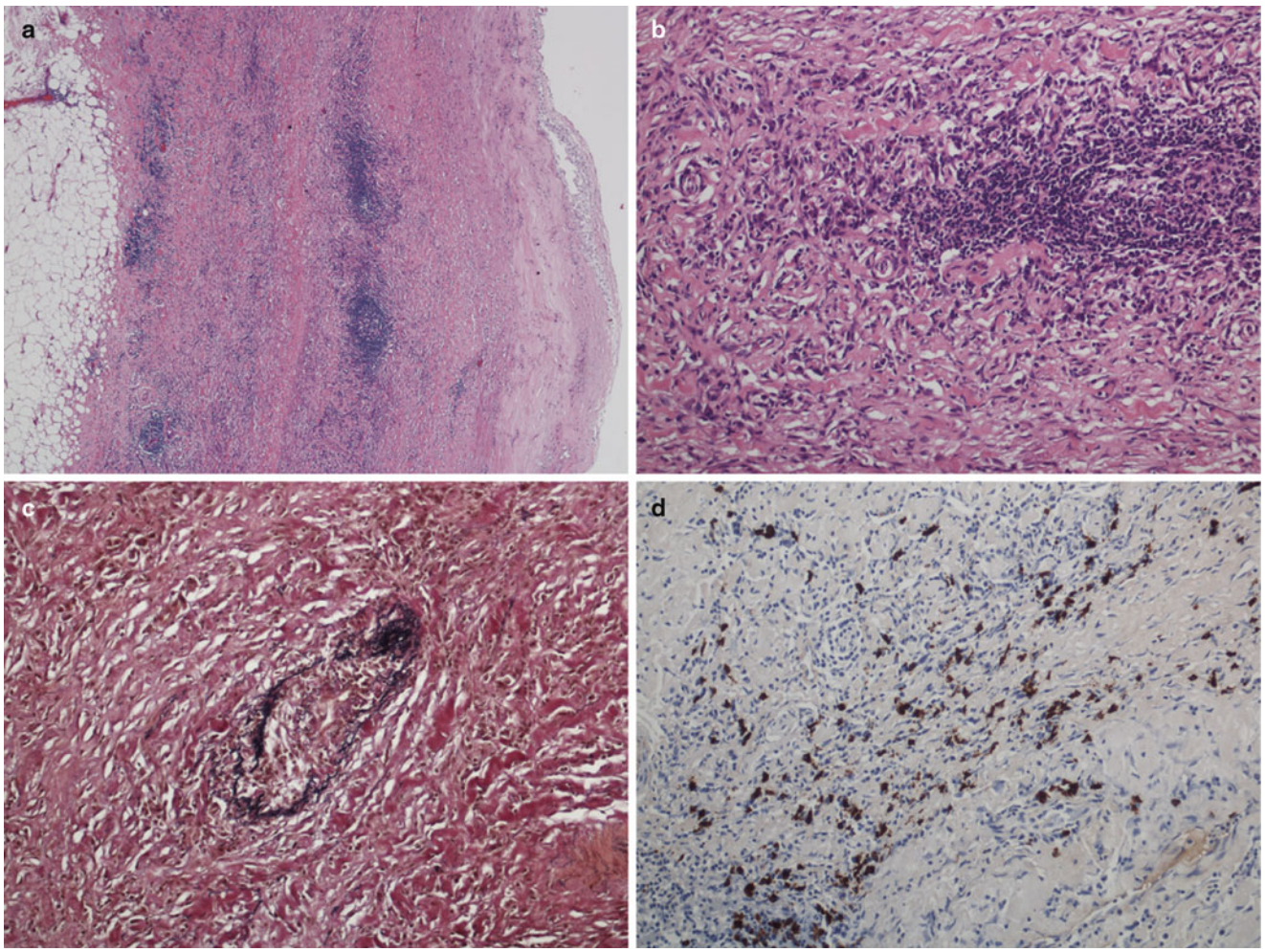

Fig. 26.3 IgG4-related periaortitis (**a**) A lesion is formed in the adventitia (*left*) and causes severe thickening of the vascular wall. Severe atherosclerosis is found from the intima (*right*) to media. (**b**) This lesion characteristically shows storiform fibrosis, with abundant lymphoplasmacytic infiltration also seen. (**c**) Elastica van Gieson stain. Obliterative phlebitis. (**d**) Immunostain(IgG4). Numerous positive plasma cells are found

its branches, Takayasu arteritis and giant cell arteritis, in which lesions form in the same vessels, are important in the differential diagnosis [37, 38]. In particular, Takayasu arteritis typically shows severe fibrosis of the adventitia, making differentiation from IgG4-related periarteritis problematic, but in Takayasu arteritis, severe inflammation is also seen in the media, granulomas and necrotic foci often form, and even after the resolution of the inflammatory process severe fibrosis may persist, with these points all useful in the differential diagnosis. In Takayasu arteritis, IgG4-positive plasma cells have not been reported to be increased [25]. Furthermore, on occasion, severe inflammation extending from the adventitia to adjacent connective tissue is associated with infectious arterial aneurysm, but differs from IgG4-related periarteritis in that neutrophil infiltration is severe. Atherosclerosis is also associated with inflammation, but is rarely of such severity as to make the differentiation from IgG4-related arterial lesions difficult.

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Lymph Node Lesions

27

Yasuharu Sato and Tadashi Yoshino

27.1 Introductory Remarks

IgG4-RD is often accompanied by lymph node swelling and in some patients lymphadenopathy is the presenting sign [1–3]. Malignant lymphoma and other lymphoproliferative disorders are frequently suspected clinically [2]. Two hallmarks of IgG4-RD in most organs affected by this disease are fibrosclerosis and obliterative phlebitis. In IgG4-related lymphadenopathy, however, these features are almost never noted. Moreover, the histological spectrum of lymph node lesions is extremely wide, precluding an easy diagnosis [1, 2].

Of the pathological diagnostic criteria for IgG4-RD, in addition to $IgG4^+$ cell infiltration, an $IgG4^+/IgG^+$ cell ratio >40 % is important diagnostically [2, 4]. Despite this, the lymph node lesions of numerous cases in non-IgG4-RD conditions, such as multicentric Castleman's disease, rheumatoid lymphadenopathy, and other immune-mediated conditions, easily satisfy these histological diagnostic criteria [5–8]. And since these non-IgG4-RD, like IgG4-RD, show a high frequency of lymph node involvement, their differentiation from IgG4-related lymphadenopathy is always problematic.

At least five histological types of IgG4-related lymphadenopathy are thought to exist [1] (Table 27.1). In this section, we outline the pathological tissue findings and essential points in the differential diagnosis of IgG4-related lymphadenopathy.

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27.2 Histopathological Characteristics of IgG4-Related Lymphadenopathy

Below we outline the histopathological characteristics and differential diagnosis of each histological subtype of IgG4-related lymphadenopathy.

27.2.1 Type I: Multicentric Castleman's Disease-Like

Systemic lymph node swelling develops at an early stage of disease in many cases. One histological feature of the lymph node is interfollicular expansion with normal to hyperplastic germinal centers. The germinal centers are penetrated by blood vessels. Abundant mature plasma cells and scattered eosinophils are apparent in the interfollicular zone. The majority of the infiltrating plasma cells are IgG4-positive (Fig. 27.1). These histological features strongly resemble those of multicentric Castleman's disease (MCD) [1, 2]. Certain important differences between MCD and IgG4-related lymphadenopathy exist: the germinal centers in MCD are often small or atrophic, and eosinophils are not prominent [5]. Differentiation between these two conditions can be challenging, however, because MCD sometimes fulfills the diagnostic criteria for IgG4-RD (i.e., $IgG4^+/IgG^+$ cell ratio >40 %) and elevated serum IgG4 levels [5]. For this reason, it is extremely dangerous to base the differential diagnosis of the two diseases solely on the immunostaining results. Rather, a comprehensive diagnosis that also takes into account the results of clinical tests and other data is necessary (refer below for details of the differential diagnosis).

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Table 27.1 Histological classification of IgG4-related lymphadenopathy

Type	Histological subtype	Distribution of IgG4+ cells	Lymph node swelling
I	Multicentric Castleman's disease-like	Interfollicular	Systemic
II	Reactive follicular hyperplasia-like	Interfollicular	Localized
III	Interfollicular expansion and immunoblastosis	Interfollicular	Systemic
IV	PTGC type	Intragerminal centers	Localized/systemic
V	Inflammatory pseudotumor (IPT)-like	Interfollicular	Localized

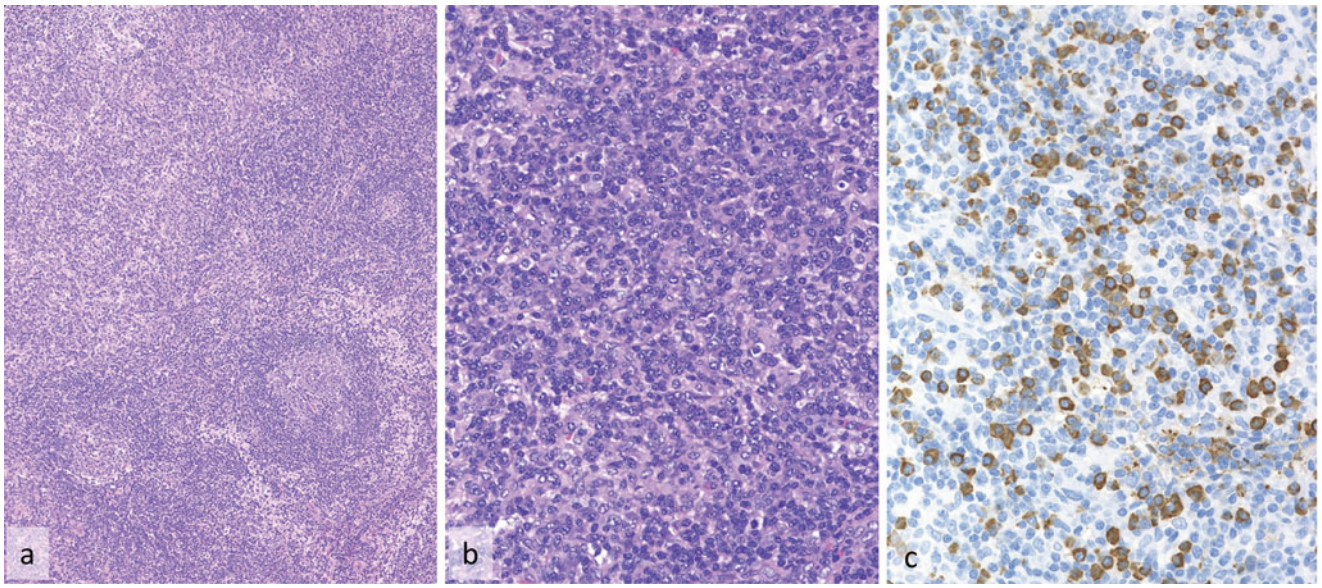

Fig. 27.1 IgG4-related lymphadenopathy (multicentric Castleman's disease-like; type I) (**a**): The lymph node shows interfollicular expansion with normal to hyperplastic germinal centers. (**b**) The germinal centers are penetrated by blood vessels. A large number of mature plasma cells with small lymphocytes are seen in the interfollicular zone. (**c**) On immunostaining, most infiltrating plasma cells are IgG4-positive

27.2.2 Type II: Reactive Follicular Hyperplasia-Like

Follicular hyperplasia reminiscent of a reactive process is frequently found in the regional lymph nodes in IgG4-RD. The basic structure of the lymph nodes is preserved in reactive processes and the lymphatic sinuses are generally patent; follicular hyperplasia is present. In the interfollicular zone, mild to moderate infiltration of mature plasma cells with small lymphocytes and eosinophils is found [1]. Most infiltrating plasma cells are IgG4 positive (Fig. 27.2).

27.2.3 Type III: Interfollicular Expansion and Immunoblastosis

Systemic lymph node swelling with interfollicular expansion and immunoblastosis is also a pattern observed in early stages of IgG4-RD. Marked vascular proliferation often accompanies the interfollicular expansion. The germinal centers demonstrate a normal to hyperplastic appearance, and partially atrophic germinal centers are also seen. In the interfollicular zone, numerous immunoblasts and both mature and immature plasma cells are found. Small lymphocytes and scattered eosinophils are also present [1, 2]. Both the mature and immature plasma cells are usually IgG4-positive (Fig. 27.3).

The histological picture shows a marked resemblance to that of angioimmunoblastic T-cell lymphoma, and the differentiation of these two diseases is always problematic. However, some features typically found in angioimmunoblastic T-cell lymphoma such as $CD10^+$ clear cell clusters with obvious cell atypia, $CD21^+$ follicular dendritic cell proliferation, and T-cell receptor gene rearrangements are not found in IgG4-related lymphadenopathy [1, 2].

27.2.4 Type IV: Progressively Transformed Germinal Centers Type

The pattern of lymphadenopathy known as "progressively transformed germinal centers (PTGC)" shows an extremely

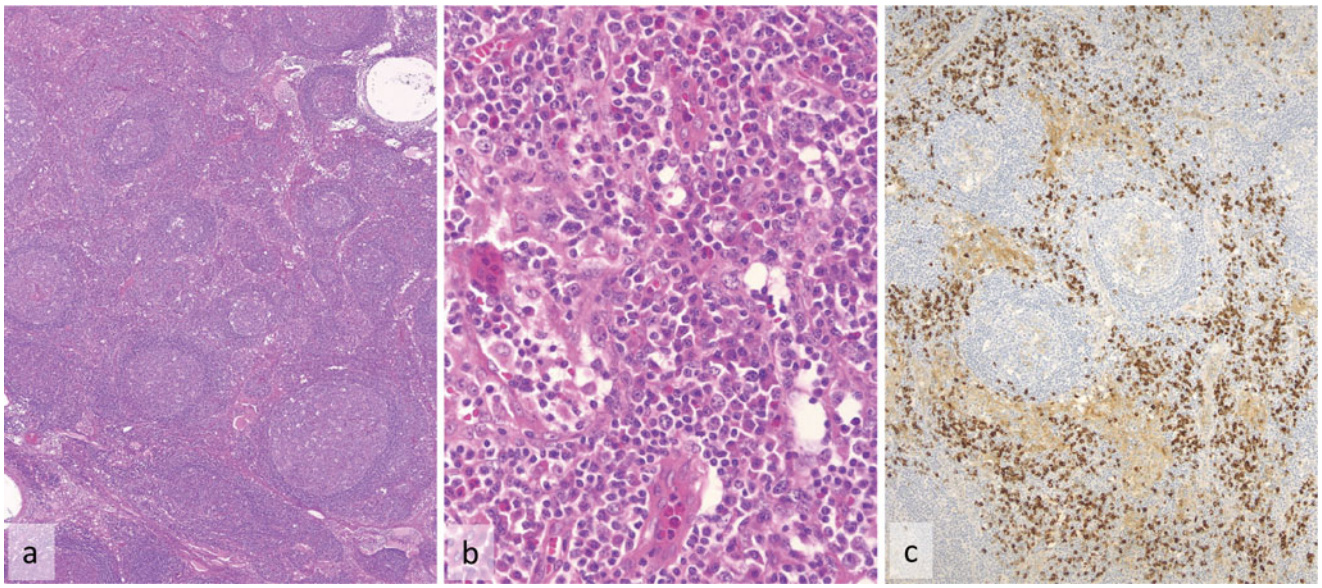

Fig. 27.2 IgG4-related lymphadenopathy (reactive follicular hyperplasia-like; type II) (**a**): Lymph nodes show a reactive follicular hyperplasia pattern, and the lymphatic sinuses are intact. (**b**) In the interfollicular zone, a small to moderate number of infiltrating plasma cells, small lymphocytes, and eosinophils are found. (**c**) Most infiltrating plasma cells are IgG4-positive

uniform clinical picture. The patients initially present with asymptomatic, localized submandibular lymphadenopathy. Approximately half of these patients demonstrate progression to extranodal IgG4-RD, systemic disease, or both during follow-up [9]. The lymph nodes demonstrate numerous lymphoid follicles with hyperplastic germinal centers and a distinct mantle zone, but no expansion of the interfollicular zone. PTGC are also apparent, appearing as round to oval structures with diameters two or three times the diameter of the other reactive follicles. In the interfollicular zone, plasma cell infiltration is not prominent, but abundant eosinophil infiltration is found. Characteristics of this type that differ from those of other types of IgG4-related lymphadenopathy are the presence of $IgG4^+$ cell infiltrates in the germinal centers [1, 2, 9] and the paucity of interfollicular $IgG4^+$ cell infiltration (Fig. 27.4). However, in a few cases of this type, $IgG4^+$ plasma cells are detected in both the germinal centers and interfollicular zone [9].

Differentiation of the PTGC-type IgG4-related lymphadenopathy from low-grade lymphoma may be difficult. Patients present with localized swelling of the submandibular lymph nodes but local relapse, the development of extranodal lesions, and progression to systemic disease can occur.

27.2.5 Type V: Inflammatory Pseudotumor-Like

The inflammatory pseudotumor (IPT)-like of IgG4-related lymphadenopathy is extremely rare. The authors themselves have evaluated thus far only two such cases, both of which presented with localized lymph node swelling. Most of the lymph node in the IPT type is occupied by hyalinized fibrous tissue. A few residual lymphoid follicles with hyperplastic germinal centers and a focally dense lymphoid infiltrate are observed in the lymph node. Small lymphocytes, plasma cells, and eosinophils infiltrate the dense sclerotic tissue (Fig. 27.5). This lesion strongly resembles the inflammatory pseudotumor of lymph nodes [10]. B symptoms that are clinically suggestive of malignant lymphoma are frequently found in inflammatory pseudotumor of the lymph nodes, but such symptoms are typically absent in IgG4-related lymphadenopathy [11, 12]. Another important difference is positive α-smooth muscle actin (α-SMA) staining within the sclerotic portion of inflammatory pseudotumors of lymph nodes. Such staining is absent in cases of IgG4-related lymphadenopathy [10].

27.3 Differential Diagnosis of IgG4-RD and Hyper-IL-6 Syndromes

Diseases to be considered in the differential diagnosis of IgG4-RD are those that commonly result from excessive interleukin (IL)-6 production [1, 13], including MCD, rheumatoid arthritis, and other immune-mediated conditions [14]. In hyper-IL-6 syndromes, prominent $IgG4^+$ cell infiltration can be evident within affected lesions and elevated serum IgG4 concentrations are often found. Cases sometimes fulfill the histological diagnostic criteria for IgG4-RD [5–8, 15]

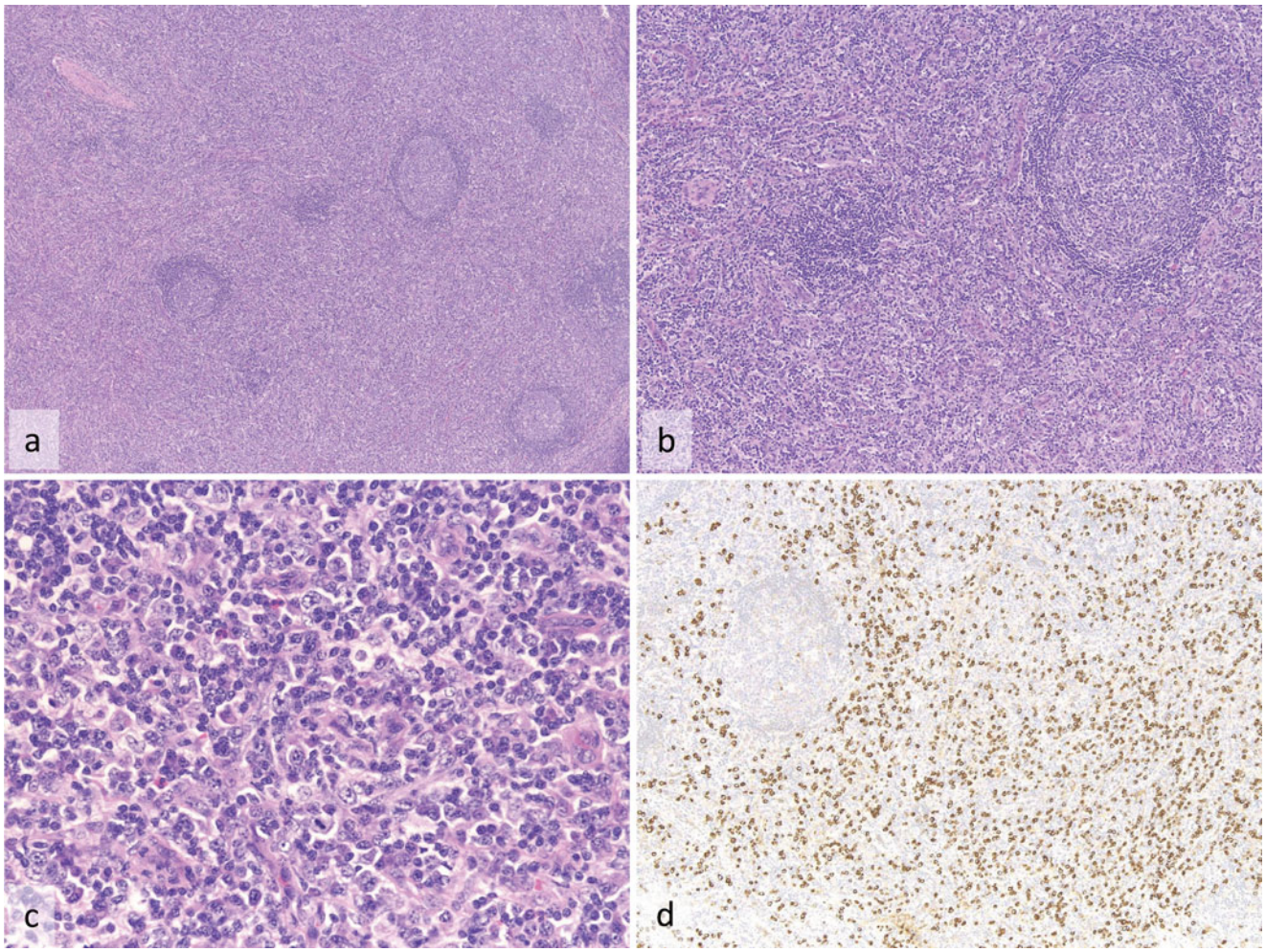

Fig. 27.3 IgG4-related lymphadenopathy (interfollicular expansion and immunoblastosis; type III) (**a**): Lymph nodes show marked interfollicular expansion with normal-sized to small germinal centers. (**b**) Hypervascular proliferation is seen in the interfollicular zone. (**c**) A mixed infiltrate of small lymphocytes, immunoblasts, immature plasma cells, mature plasma cells, and scattered eosinophils are seen. (**d**) Most infiltrating plasma cells are IgG4-positive

(Figs. 27.6 and 27.7). This is because IL-6 induces differentiation of B cells into plasma cells and promotes polyclonal production of immunoglobulins [5, 6, 8, 16, 17]. For this reason, not only IgG4 but also other IgG subclasses as well as IgA and IgM levels are elevated. Unlike IgG4-RD, hyper-IL-6 syndromes are characterized by elevated serum levels of IgG, IgA, IgM, and C-reactive protein (CRP); thrombocytosis; anemia; hypoalbuminemia; and hypocholesterolemia (Table 27.2). These abnormalities are closely related to high IL-6 levels. Accordingly, the diagnosis of IgG4-RD, especially IgG4-related lymphadenopathy, cannot be differentiated on the basis of the histological findings alone. The diagnosis of IgG4-RD needs to be based not only on the pathological findings but also on close correlation between those findings and the clinical and laboratory data. Elevated serum IgE concentrations are often observed in IgG4-RD, but these do not help differentiate IgG4-RD from syndromes associated with excessive production of IL-6 [5, 8].

27.4 Problems in the Pathological Diagnosis of IgG4-RD

The diagnosis of IgG4-RD is frequently based on pathological examination of biopsy or surgical materials. As a diagnostic criterion, an $IgG4^+/IgG^+$ cell ratio of >40 % on immunostaining is important. It facilitates to a certain extent the drawing of a demarcation line, but as noted above, some cases of non-IgG4-RD meeting this diagnostic criterion also exist. In addition to hyper-IL-6 syndromes, some cases of inflammatory granulomatous tissue and nasal polyps have also been described in which plasma cell infiltration was

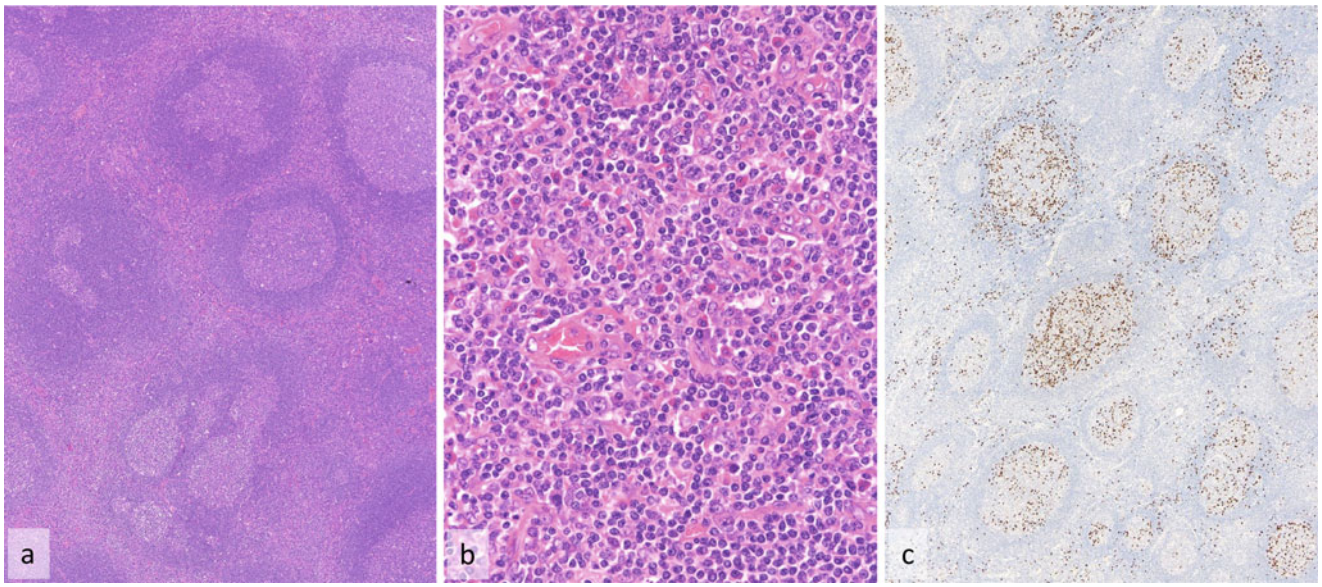

Fig. 27.4 IgG4-related lymphadenopathy (PTGC type; type IV) (**a**): Lymph nodes show marked follicular hyperplasia with PTGC. (**b**) Infiltration by numerous eosinophils in the interfollicular zone. (**c**) Most of the IgG4$^+$ cells are present within the germinal center and are not usually seen in the interfollicular zone

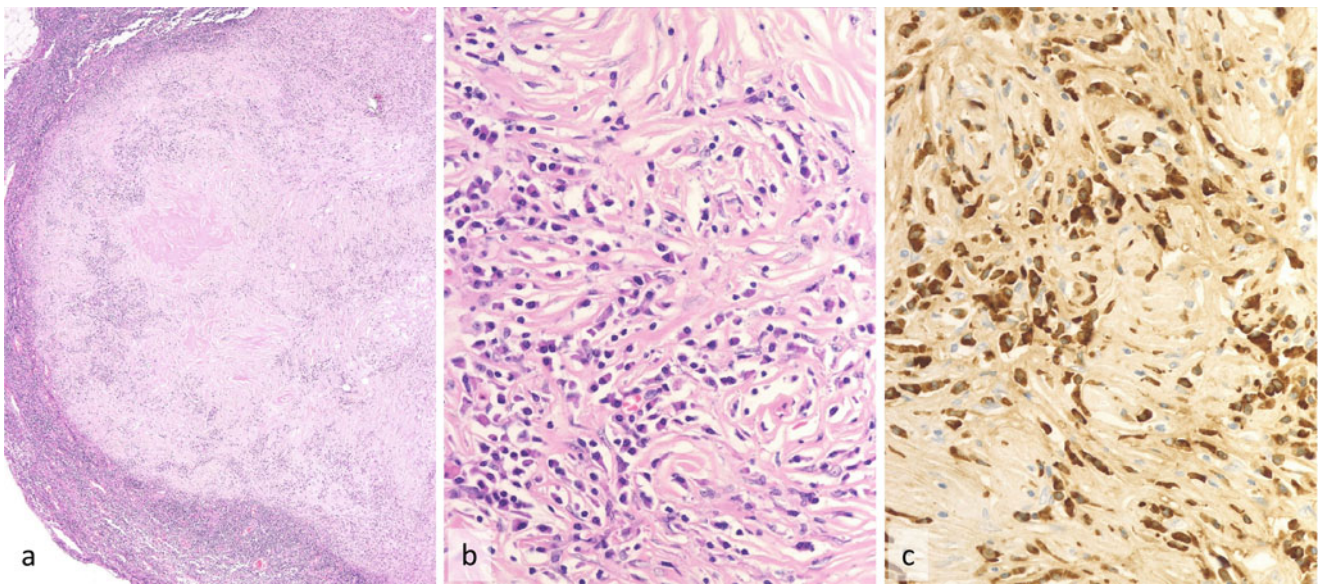

Fig. 27.5 IgG4-related lymphadenopathy (IPT-like; type V). Regional lymph node from a case with IgG4-related cholangitis. (**a**) The majority of the lymph node is replaced by hyalinized fibrous tissue. (**b**) Mature plasma cells infiltrate into the hyalinized fibrous tissue. (**c**) Most infiltrating plasma cells are IgG4-positive

prominent and the threshold of an IgG4$^+$/IgG$^+$ cell ratio of >40 % was exceeded.

In the case of organs such as lacrimal glands, salivary glands, and pancreas hitherto reported as being highly vulnerable to IgG4-RD, a pathological diagnosis alone including immunostaining can be considered acceptable, but in the case of organs with little known association with IgG4-RD or not yet reported in this context, the diagnosis must be confirmed with caution, painstaking detail, and close attention to the clinical picture and serologic data.

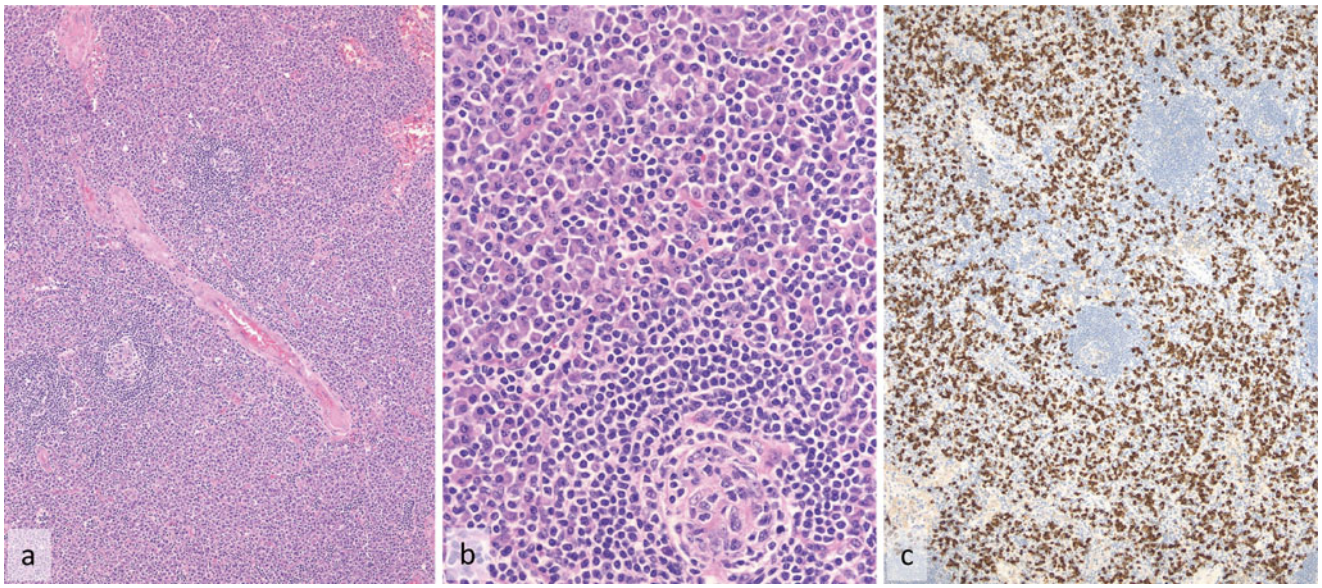

Fig. 27.6 Multicentric Castleman's disease fulfills the diagnostic criteria for IgG4-RD (**a**): Interfollicular expansion and atrophic germinal centers are seen. (**b**) Numerous mature plasma cells show sheet-like proliferation in the interfollicular zone. (**c**) The majority of infiltrating plasma cells are IgG4-positive ($IgG4^+/IgG^+$ cell ratio >70 %). In this case, serum IgG4 was also elevated

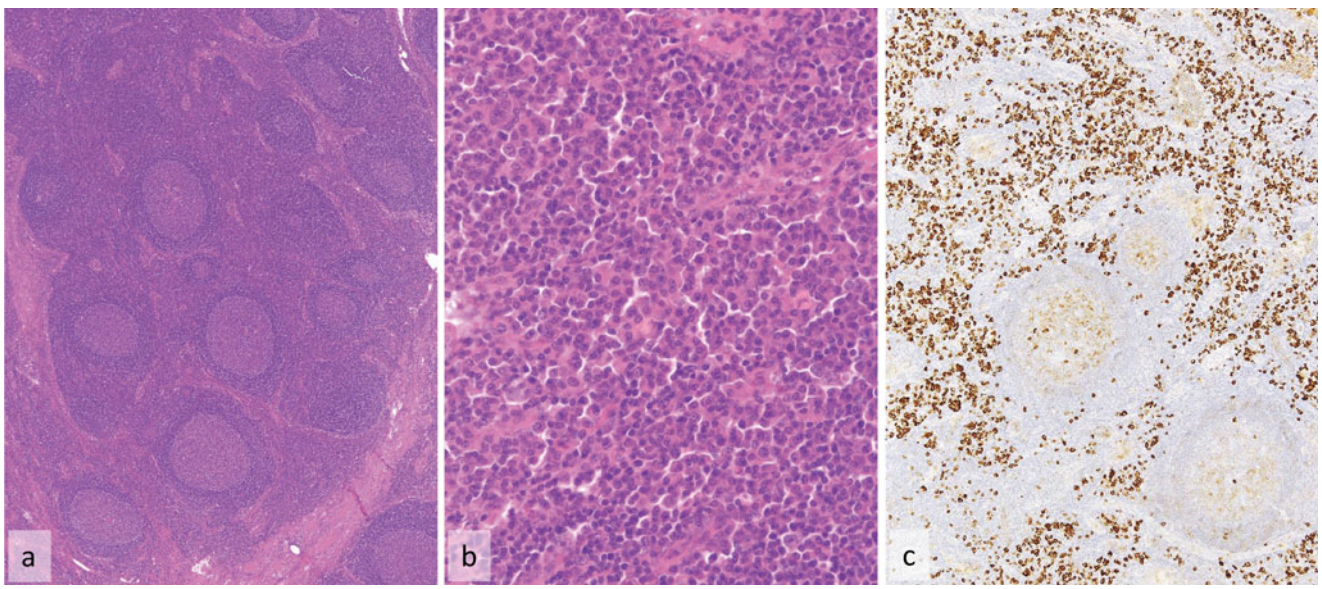

Fig. 27.7 Rheumatoid arthritis-related lymphadenopathy fulfills the diagnostic criteria for IgG4-RD (**a**): The lymph node shows marked follicular hyperplasia, but the basic structure is preserved. (**b**) Plasma cell and small lymphocyte infiltration is found, but no eosinophils in the interfollicular zone. (**c**) The majority of infiltrating plasma cells are IgG4-positive ($IgG4^+/IgG^+$ cell ratio >60 %)

27.5 Concluding Remarks

It has been only about 10 years since the concept of IgG4-RD was proposed, and many aspects of its pathophysiology remain obscure. In this era in which much remains unknown about this condition, pathologists and clinicians must guard against the wrongful inclusion of patients with non-IgG4-related conditions under the IgG4-RD diagnostic umbrella. The lymph nodes are particularly prone to modification by various disease processes, and further studies will be needed to shed more light on the pathophysiology of the disorders involving them and help establish definitive diagnostic criteria.

Table 27.2 Differential diagnosis of IgG4-related lymphadenopathy and hyper-IL-6 syndromes

	IgG4-related lymphadenopathy	Hyper-IL-6 syndromes
Serum immunoglobulin	IgG ↑(IgG4 ↑), IgE ↑	IgG ↑(IgG1-G4 ↑), IgA ↑, IgM–/ ↑, IgE ↑
Serum IgG4 /IgG ratio	Elevated (or markedly elevated)	Normal (or occasionally slightly elevated)
Serum IL-6	Normal (or occasionally slightly elevated)	Elevated
Serum CRP	Normal (or occasionally slightly elevated)	Elevated
Thrombocytosis	No	Yes
Anemia	No	Yes
Hypoalbuminemia	No	Yes
Hypocholesterolemia	No	Yes

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Skin Lesions

28

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28.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a recently proposed disease concept, whose lesions are found throughout the body, notably in organs like the lacrimal glands, salivary glands, pancreas, liver, kidney, retroperitoneum, and lymph nodes. IgG4-RD has been classified as an inflammatory disease. The cutaneous manifestations of IgG4-RD are now referred to as IgG4-related skin disease. The descriptions of IgG4-related skin disease have been limited to reports of only a few cases [1–3], amounting to a much smaller experience with this organ system compared to most other organs known to be affected by IgG4-RD. In every case reported to date in the literature, extracutaneous involvement has also been present.

In this chapter, we focus on the clinical and pathological features of five cases with IgG4-related skin disease and skin involvement seen at our institutions. We also review the other cases of IgG4-related skin disease reported to date in the medical literature, so as to weave together an outline of the current experience with the IgG4-related skin disease.

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28.2 Incidence

We pooled the experiences over a period of 8 years (2004–2011) in order to obtain a sense of the frequency of cutaneous disease compared to that of other features of IgG4-RD. Fifty cases of IgG4-RD were evaluated at Kanazawa University (Division of Rheumatology and Dermatology) during this time, and an additional thirty cases were evaluated at the Nagaoka Red Cross Hospital (Internal Medicine). Among these eighty cases, five (four from Kanazawa University and one from the Nagaoka Red Cross Hospital) demonstrated cutaneous lesions, representing 6.3 % of the patient group overall (Table 28.1). Age at onset was 53–78 years, and there were four men and one woman.

In other experience, Sato et al. found skin lesions in three of nine cases (33 %) with IgG4-related lymphadenopathy (45–81 years, all male) [2]. Cheuk et al. reported two cases, a 76-year-old man and 74-year-old woman [1], and Khosroshahi et al. described one case, a 72-year-old woman [3]. In these reports, as in our experience, the onset of skin lesions and IgG4-RD had its onset in middle-aged to elderly patients, and there was a male predominance. Although this limited experience reflects what is generally acknowledged about the demographic features of IgG4-RD – namely, a tendency to involve middle-aged to elderly males – more cases must be reported before a full experience can be claimed with confidence.

28.3 Clinical Picture

Our five cases showed the following skin manifestations: multiple erythematous papules (cases 1 [4] and 2 [5]) (Figs. 28.2a and 28.3a), subcutaneous nodule (case 3), erythematous nodule (case 4), and multiple brown papules like prurigo nodularis (case 5) (Fig. 28.6a–c). Another report has

H. Umehara et al. (eds.), *IgG4-Related Disease*, DOI 10.1007/978-4-431-54228-5_28,

Table 28.1 Clinical and laboratory characteristics of five patients with IgG4-related skin disease (cited and modified from [11])

Case	Age/sex	IgG (mg/dL)	IgG4 (mg/dL)	IgG4/ IgG (%)	IgE (IU/mL)	CH50 (U/mL)	ANA	Eo (%)	Affected organs	Onset of skin lesion (relative to the diagnosis of IgG4-RD)
1	66M	1,980	575	29	151	57	–	8.6	Lacrimal and salivary glands, lung, pancreas	2 years later
2	60M	1,570	463	29.5	4,554	NA	–	12.9	Lacrimal glands, pancreas	4 months earlier
3	69M	1,960	164	8.4	1,621	43	–	2.7	Lacrimal glands	5 years later
4	53F	1,983	896	45.2	447	50	–	17.8	Lacrimal and salivary glands, lung, liver	4.5 years earlier
5	78M	2,655	1,230	46.3	1,668	50	–	13	Salivary glands, kidney	9 years earlier

ANA antinuclear antibody, *Eo* Eosinophil, *IgG4-RD* IgG4-related disease, *NA* not available

described infiltrative red plaques [1] and subcutaneous induration with infiltration [1]. Cases with blisters, erosions, ulcers, or polymorphic skin atrophy have not been described. The protuberant lesions described in the skin thus far, i.e., papules and nodules, reflect the tendency of IgG4-RD in other organs to cause tumefactive lesions. Pruritus was present in our cases 2, 4, and 5 and in one of the patients reported by Cheuk et al. [1]. The most common distribution of the skin lesions in IgG4-RD appears to be in the head and neck region, particularly the cheek, neck, and retroauricular region. In one of our cases (case 3), however, subcutaneous nodules were found on the anterior chest. In another (case 5), multiple brown papules like prurigo nodularis was found on the four extremities and trunk.

In contrast, there have been no reports of IgG4-RD with involvement limited to the skin. This situation can be ascribed in part to the low level of recognition of this disease manifestation and to the fact that diagnostic criteria for IgG4-related skin disease have not yet been established. One publication described infiltration by IgG4-positive cells in three cases of cutaneous plasmacytoma [6] and it is possible that IgG4-RD was the true underlying diagnosis in those cases, but with all three patients described there was evidence of disease in organs beyond the skin, namely, the lymph nodes, bone marrow, or lung.

Thus, when IgG4-RD does affect the skin, other organ involvement is manifest in nearly all cases. The head and neck region, particularly the lacrimal, submandibular, and parotid glands, are affected commonly – but of course these very organs are also involved in many cases without known skin disease. Cases with lesions in the pancreas, liver, or kidney have also been reported.

28.4 Clinical Test Findings

In the five cases, serum IgG4 values were 164–1,230 mg/dL, and the serum IgG4/IgG ratio was 8.4–46.3 % (Table 28.1). Antinuclear antibodies were negative in all cases, and hypocomplementemia was not present. On the other hand, the serum eosinophil fraction was elevated in four of the five cases to 8.6–17.8 %.

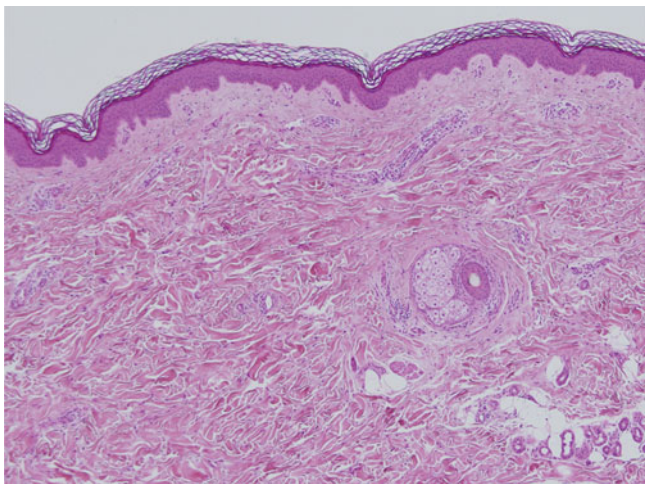

Fig. 28.1 Histological picture of normal skin (H&E stain, ×40)

28.5 Histological Findings

Characteristic histological findings of IgG4-RD include marked lymphoplasmacytic cell infiltration, lymphoid follicle formation, fibrosis, eosinophil infiltration, and obliterative phlebitis [7]. Among the solid and secretory organs affected, the distribution of inflammatory lesions is mainly periductal in many areas [8].

Normal skin is made up histologically of epidermis, dermis, and subcutaneous tissue (Fig. 28.1). The dermis con-

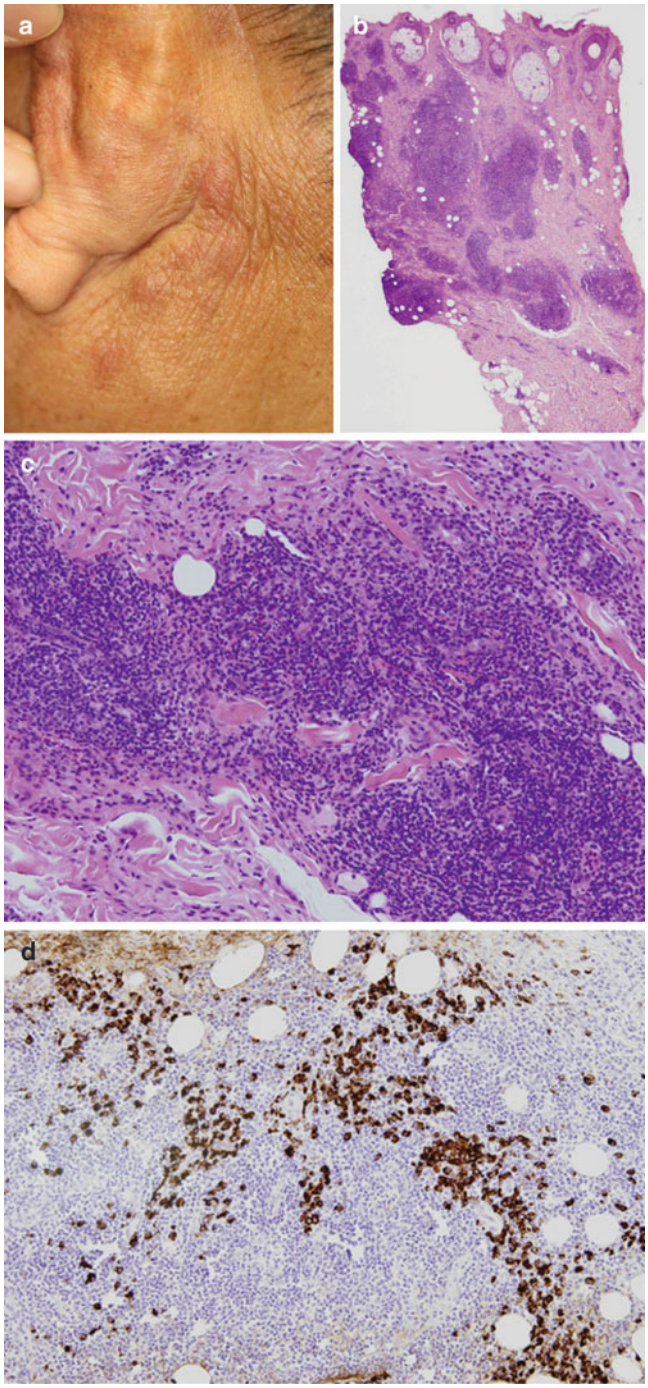

Fig. 28.2 Case 1: 66-year-old man. (**a**) IgG4-related dacryoadenitis and sialadenitis was diagnosed. After treatment with oral steroid for 2 years, non-pruritic red papules were found in the left retroauricular region. On skin biopsy, lymphoid follicle formation was seen from the dermis to subcutaneous tissue, associated with mild fibrosis. The infiltrating cells were mostly lymphocytes and IgG4-positive plasmacytic cells, with moderate eosinophil infiltration also present [(**b**, **c**) H&E stain, (**a**) ×20, (**b**) ×100, and (**d**) anti-IgG4 stain, ×100]

tains various components such as blood vessels, nerves, hair follicles, and sebaceous and sweat glands. The subcutaneous tissue is made up of fatty tissue and muscle layers.

In case 1, lymphoid follicle formation was noted from the dermis to subcutaneous adipose tissue, and perivascular infiltrates of lymphocytes, plasma cells, and eosinophils were present (Fig. 28.2b, c and Table 28.2). Similar histopathological features were observed in case 2 (Fig. 28.3b and Table 28.2). In case 3, lymph follicle formation was seen in the subcutaneous adipose tissue, with cell infiltration noted perivascularly and around accessory organs. Moderate fibrosis and obliterative phlebitis were also found (Fig. 28.4a–c and Table 28.2). The histological picture in case 4 was similar to that in cases 1 and 2; i.e., lymphoid follicle formation was noted from the dermis to subcutaneous adipose tissue, perivascular lymphoplasmacytic cell infiltration was present, and eosinophil infiltration was also found (Fig. 28.5a, b and Table 28.2). The histological picture of cases 1, 2, and 4 was similar to that of angiolymphoid hyperplasia with eosinophilia (see Differential diagnosis, below). No lymphoid follicle formation was observed in case 5, but perivascular lymphoplasmacytic cell infiltrates were evident (Fig. 28.6d, e and Table 28.2). Mild dermal fibrosis was present in cases 1, 2, 4, and 5, but obliterative phlebitis was evident only in case 3.

In both of the cases of Cheuk et al. [1], lymphoid follicle formation was found mostly in the subcutaneous adipose tissue, with the cell infiltration mostly perivascular in one case and perivascular and surrounding the accessory organs in the other. The infiltrating cells were mainly lymphocytes and plasmacytic cells with some intermingled histiocytes. Eosinophil infiltration was not found. In the cases of Khosroshahi et al. [3], lymphoid follicle formation was noted from the dermis to subcutaneous adipose tissue, and perivascular infiltrates consisting of lymphoplasmacytic cells with a few eosinophils were seen.

Immunostaining using anti-IgG4 monoclonal antibody revealed various degrees of IgG4-positive cell infiltration in all of the five cases (Figs. 28.2d, 28.3c, 28.4d, 28.5c, and 28.6f).

Like the lesions in other organs, IgG4-related skin disease was characterized by varying degrees of marked lymphoplasmacytic cell infiltration, lymphoid follicle formation, eosinophil infiltration, and fibrosis. The cellular infiltrates were marked by a principally perivascular distribution. The degree of periductal cell infiltration differed across cases, and the frequency of obliterative phlebitis was low.

Table 28.2 Rash and pathological findings of five cases of IgG4-related skin disease (cited and modified from [11])

Case	Type	Pruritus	Region	Distribution	Eosinophils infiltration	Follicular formation	Obliterative phlebitis	Fibrosis	IgG4+ cells (HPF)
1	Multiple erythematous papules	−	Left opisthotic region	Dermis to subcutaneous Perivascular	+	+	−	Mild	112.2
2	Multiple erythematous papules	+	Parietal scalp, neck	Dermis to subcutaneous Perivascular	+	+	−	Mild	47
3	Subcutaneous nodules	−	Anterior chest	Dermis Around accessory organs	+	+	+ (focal)	Moderate	128.6
4	Erythematous nodules	+	Nose	Dermis to subcutaneous tissue Perivascular	+	+	−	Mild	23
5	Multiple brown papules	+	Trunk, extremities	All layers of dermis Perivascular	+	−	−	Mild	25.8

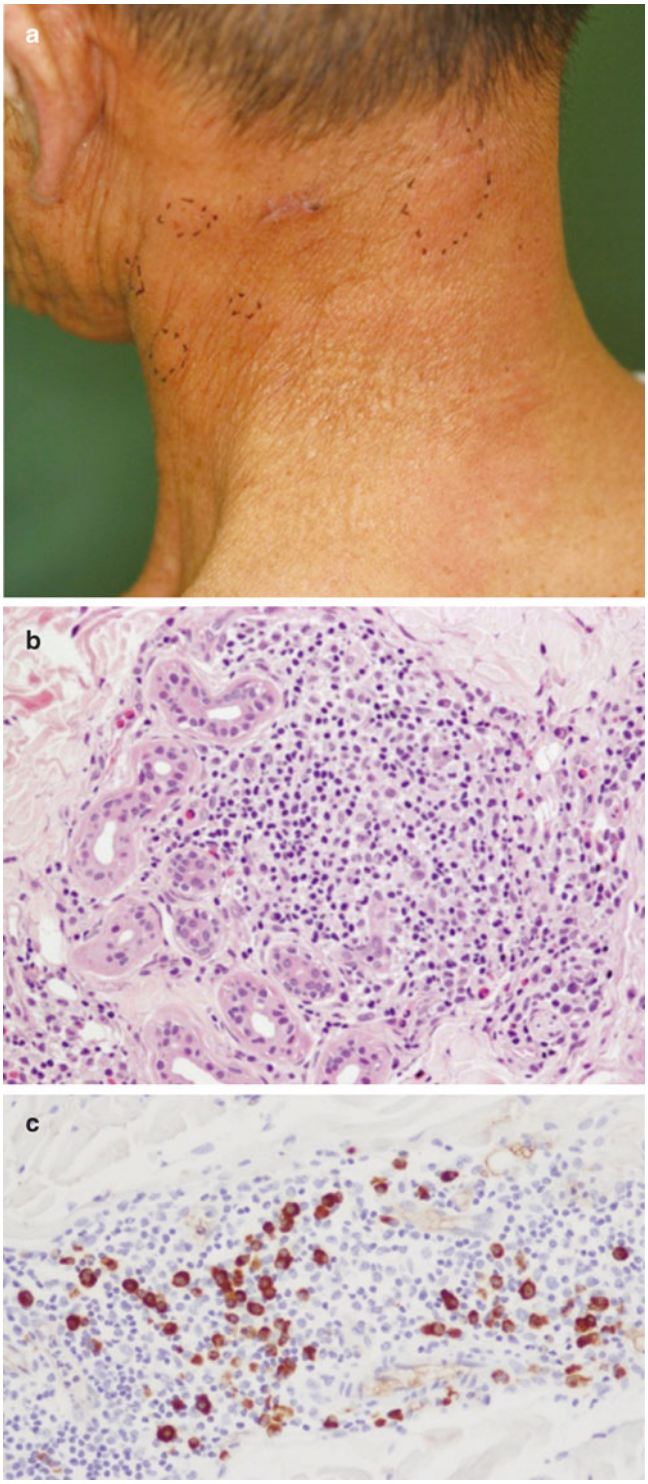

Fig. 28.3 Case 2: 60-year-old man. (**a**) Simultaneous with the onset of IgG4-related dacryoadenitis and sialadenitis, pruritic reddish nodules developed from the occiput to neck. On skin biopsy, cell infiltrates consisting mainly of IgG4-positive lymphoplasmacytic cells were seen to extend from the dermis to subcutaneous tissue, particularly in perivascular locations [(**b**) H&E stain, ×200 and (**c**) anti-IgG4 stain, ×400]

28.6 Differential Diagnosis

Diseases showing plasmacytic cell infiltration in the skin include cutaneous plasmacytoma, skin infiltration of multiple myeloma, and plasmacytoma involving body orifices. Diseases characteristically showing eosinophil infiltration and lymphoid follicle formation include Kimura disease and the above-mentioned angiolymphoid hyperplasia with eosinophilia (ALHE). The clinical features of ALHE often include papules. Thus, both its clinical and histopathological features resemble those of IgG4-RD strongly, and these conditions require careful differentiation [4].

28.7 Therapy and Prognosis

In general, IgG4-RD shows a good response to steroid therapy [9]. Regarding the therapy and effect on the skin lesions in these five cases, on follow-up observation of case 1 the symptoms were unchanged (with oral steroid continued for co-existent IgG4-related dacryoadenitis and sialadenitis). In case 2, when oral steroid was added, the rash promptly subsided, but recurred with steroid tapering. In case 3, there was only a single subcutaneous nodule for which an excisional biopsy was performed. In case 4, local steroid injection induced shrinkage, while in case 5 moderate improvement was achieved with topical steroid and oral anti-allergy agents.

In one of the two cases of Cheuk et al. [1], symptoms were unchanged with topical steroid application, while in the other case, oral steroid was successful in reducing the size of the rash. In the case of Khosroshahi et al. [3], anti-CD20 monoclonal antibody therapy with rituximab led to disappearance of the rash. The above findings suggest that skin lesions, like lesions at other sites, may show a good response to oral steroids, while being resistent to their topical application. In future, more cases will have to be accumulated to establish better therapeutic approaches for these skin lesions.

28.8 Concluding Remarks

In future, with wider recognition of IgG4-RD, it is expected that the number of reports on skin lesions will increase. On the other hand, IgG4-positive plasmacytic cell infiltration has also been reported as a nonspecific finding [10]. The preparation of diagnostic criteria for IgG4-related skin disease, clarification of its clinical and histological characteristics, and establishment of optimal therapeutic approaches are eagerly awaited.

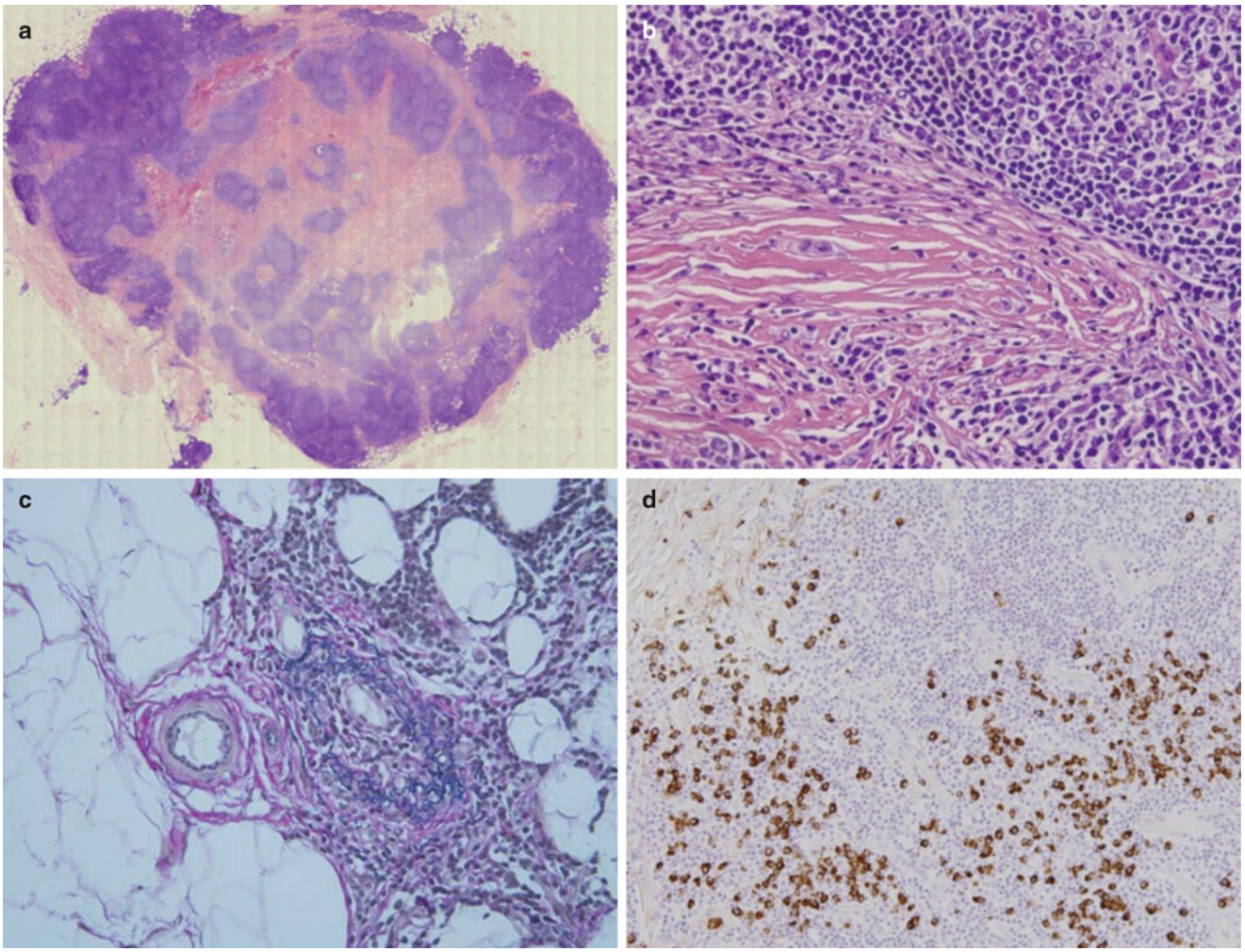

Fig. 28.4 Case 3: 69-year-old man. During follow-up of this patient with IgG4-related dacryoadenitis and sialadenitis, subcutaneous finger tip-sized nodules appeared on the anterior chest. The histological picture of a tissue specimen obtained by excisional biopsy showed lymphoid follicle formation, moderate fibrosis, obliterative phlebitis, and IgG4-positive plasmacytic cell infiltration [(**a**–**c**) H&E stain, (**a**) ×4, (**b**) ×400, (**c**) ×200, and (**d**) anti-IgG4 stain, ×200]

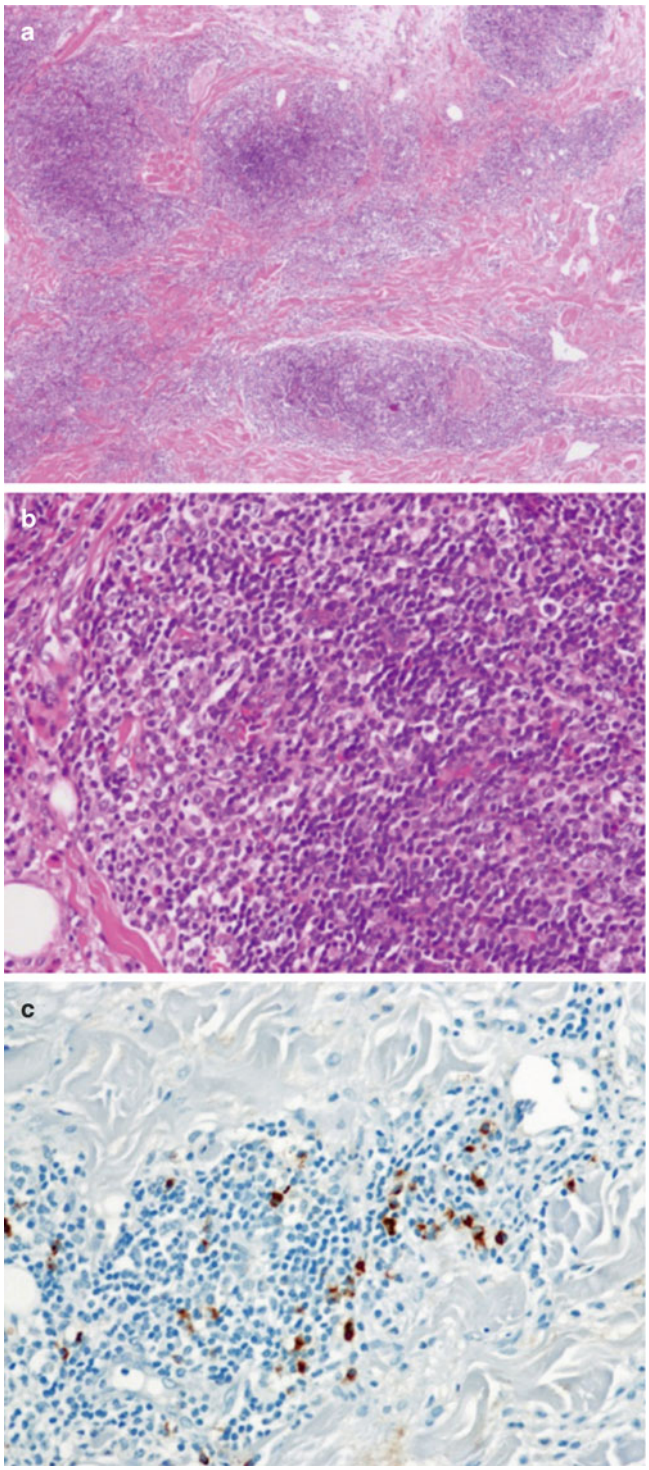

Fig. 28.5 Case 4: 53-year-old woman. (**a**, **b**) A biopsy of reddish nasal subcutaneous nodules that had appeared 6 months earlier revealed lymphoid follicle formation and lymphoplasmacytic cell infiltration. The nodules shrank after local steroid injection. Four years after the rash appeared on the nose, swelling of the bilateral lacrimal glands and submandibular gland, a liver mass, and infiltrative shadows in the lungs developed, and IgG4-RD was diagnosed from a salivary gland biopsy. When a tissue specimen from a previously biopsied subcutaneous nodule in the nose was stained with anti-IgG4 antibody, IgG4-positive plasmacytic cells were detected [(**c**) anti-IgG4 stain, ×200]

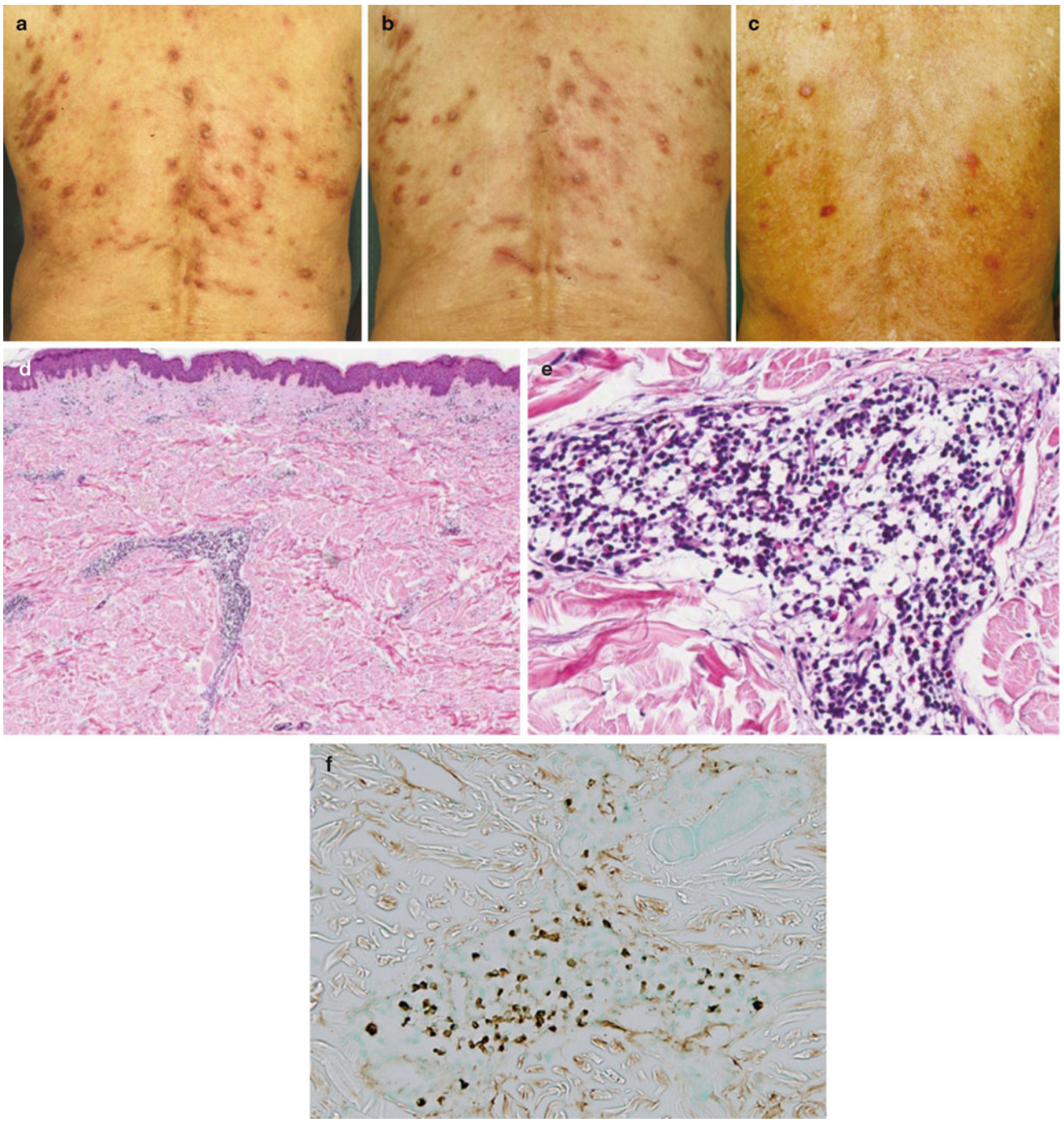

Fig. 28.6 Case 5: 78-year-old man. This man had a 30-year history of diabetes mellitus. From the age of 68 years topical steroid and anti-allergy agents were administered under a presumptive diagnosis of prurigo nodularis [(**a**) clinical findings at 68 years, (**b**) clinical findings at 70 years, and (**c**) clinical findings at 78 years]. At 78 years, he was admitted for workup of renal dysfunction. Serum creatinine was elevated (1.99 mg/mL), as was serum IgG4 (1,230 mg/mL). IgG4-related nephropathy was diagnosed by renal biopsy. Perivascular lymphoplasmacytic cell and eosinophil infiltration was found in skin biopsy tissue obtained at 70 years, and mild fibrosis was also associated [(**d**, **e**) H&E stain, (**d**) ×20, and (**e**) ×200]. On anti-IgG4 antibody immunostaining, IgG4-positive plasmacytic cell infiltrates were found [(**f**) ×400]

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IgG4-Related Hepatopathy

29

Takeji Umemura and Yoh Zen

29.1 Study of Hepatic Lesions in IgG4-Related Disease

In 2012, recommendations for the nomenclature of IgG4-related disease (IgG4-RD) in individual organs were published [1]. With regard to the liver, involvement of the liver itself—distinct from involvement of the biliary system—was referred to as IgG4-related hepatopathy. Numerous published studies have focused on the bile duct lesions associated with sclerosing cholangitis, and the concept of this clinicopathological entity has been well established. In contrast, few such histological studies on the liver have been reported, and so relatively little is known about how IgG4-RD affects this organ.

We previously conducted a detailed study on hepatic parenchyma biopsy specimens in autoimmune pancreatitis (AIP) and proposed the concept of "IgG4 hepatopathy," now termed IgG4-related hepatopathy [2]. In this chapter, we introduce the hepatic lesions of IgG4-RD based on our own work and that of other investigators. In addition, we observe that in some patients who meet diagnostic criteria for autoimmune hepatitis (AIH), abnormal serum concentrations of IgG4 are detected and copious numbers of IgG4-positive plasma cells are found within liver biopsy samples. We propose that some of these cases had a clinicopathological entity that is termed most appropriately "IgG4-related AIH." We introduce some cases presumed to have IgG4-related AIH in this chapter.

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29.2 Study of Hepatic Lesions in IgG4-Related Disease

It has long been recognized that the alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γGTP) values frequently become elevated in AIP [3]. This has typically been attributed to the high rate of "sclerosing cholangitis" believed to complicate AIP. In 2003, however, Hirano et al. investigated the hepatic biopsy findings in eight patients with AIP complicated by sclerosing cholangitis and described the presence of a marked lymphoplasmacytic infiltrate in the portal areas [4]. Kamisawa et al. simultaneously reported IgG4-positive plasma cells infiltrating a variety of organs, including the livers, of patients with AIP [5]. No detailed study of those hepatic lesions was undertaken at that time, however.

In 2007, we conducted a study on the changes in liver function tests and hepatic biopsy pathological findings in AIP [2]. In addition, we prospectively compared the pathological findings before and 4 weeks after prednisolone administration. Since our report, a number of additional studies on the liver biopsy findings in IgG4-related sclerosing cholangitis have been published. Some of these have included pathological examination of the hepatic parenchyma, including the reports of Nishino et al. [6], Deshpande et al. [7], and Naitoh et al. [8]. The investigators in these studies quantified the degree of IgG4-positive plasma cell infiltration. We will review these results below.

The liver histopathology in IgG4-related hepatopathy can be classified into five patterns (Fig. 29.1) [2]:

1. Portal inflammation pattern, with intense portal inflammation with or without interface hepatitis
2. Large bile duct damage pattern, characterized by bile ductular proliferation, neutrophil infiltration, and edematous change in the portal areas
3. Portal sclerosis pattern, exhibiting dense portal sclerosis with scarce portal inflammation

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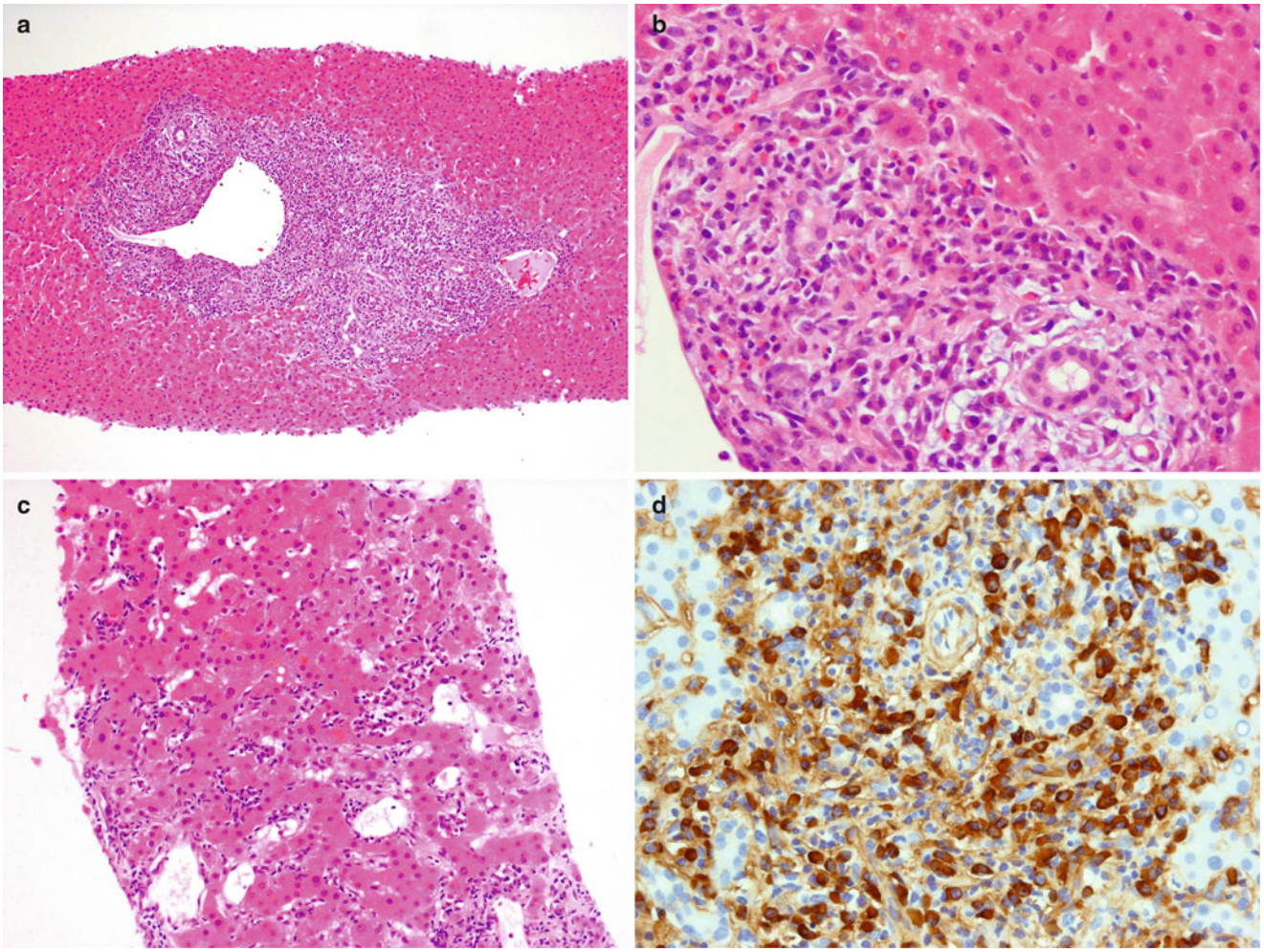

Fig. 29.1 Histological findings of liver biopsy specimens obtained from autoimmune pancreatitis patients. (**a**) The portal areas are markedly enlarged associated with dense inflammatory cell infiltration. H&E stain, ×100. (**b**) Inflammatory cells in the portal areas include numerous infiltrating plasma cells and eosinophils, associated with findings of bile duct injury. H&E stain, ×400. (**c**) In the parenchyma as well infiltrating lymphocytes and plasma cells are present and are associated with hepatocyte injury and necrosis. H&E stain, ×200. (**d**) In the portal areas numerous IgG4-positive plasma cells are included in the infiltrating inflammatory cells. IgG4 immunostain, ×400

4. Lobular hepatitis pattern, showing lobular inflammation with hepatocellular necrosis resembling viral hepatitis
5. Cholestatic pattern, with canalicular cholestasis predominantly in the centrilobular area

A wide range in the number of intrahepatic IgG4-positive plasma cells infiltrating the liver parenchyma has been reported, with mean values in the range of 2–60/high power fields (HPF). The proportion of cases showing ≥10 infiltrating IgG4-positive plasma cells per HPF similarly varies from 24 % to 60 % (Table 29.1).

The liver is relatively safe to biopsy, and since the amount of material that can be obtained is greater than is possible with bile duct biopsy, liver biopsy is an important diagnostic aid when histological study is deemed necessary. In our study, inflammatory cell infiltration in the portal areas, bile duct injury, hepatic fibrosis, and lobular hepatitis into the hepatic parenchyma were confirmed. Of particular interest was the confirmation of lobular hepatitis, establishing that changes caused by IgG4-RD do occur in the liver, notably in the hepatocytes and hepatic parenchyma. However, as compared with other organs, the degree of IgG4-positive plasma cell infiltration was not that striking and differed considerably in individual cases. This may be attributable in part to the fact that the degree of progression of sclerosing cholangitis correlates with the number of IgG4-positive plasma cells.

Our study [2] and that of Naitoh et al. [8] have clarified that in cases of IgG4-related hepatopathy complicated by IgG4-related sclerosing cholangitis, greater wall thickening and stenosis of the intrahepatic bile ducts is associated with a higher degree of intrahepatic IgG4-positive plasma cell infiltration. In the hepatic parenchyma, IgG4-positive plasma cells infiltrate the portal areas in almost all cases, but since

Table 29.1 Studies on hepatic parenchyma in IgG4-related disease

	Umemura [2] ($n=17$)	Nishino [6] ($n=8$)	Deshpande [7] ($n=10$)	Naitoh [8] ($n=19$)
Portal inflammation	6 (35)	8 (100)	7 (70)	7 (37)
Interface hepatitis	4 (24)	0 (0)	7 (70)	–
Lobular hepatitis	7 (41)	–	7 (70)	10 (53)
Plasma cells	6 (35)	–	9 (90)	5 (26)
Eosinophils	4 (24)	–	9 (90)	4 (21)
Ductal proliferation	10 (59)	8 (100)	–	–
Bile duct damage	10 (59)	–	–	6 (32)
Canalicular cholestasis	9 (53)	–	–	6 (32)
Fibrosis ≥3	7 (41)	0 (0)	1 (10)	–
IgG4-positive plasma cells (/HPF) mean (range)	9.5 (0–55)	2.2	60 (0–140)	7.2 (0–25)
IgG4-positive plasma cells (>10/HPF)	4 (24)	–	6 (60)	5 (26)

Data are number (%) unless indicated otherwise

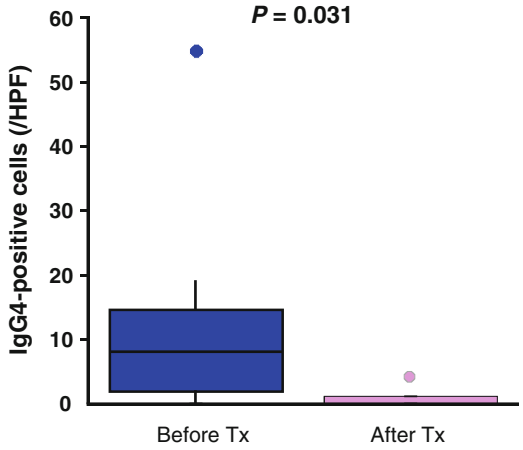

Fig. 29.3 Comparison of IgG4-positive plasma cell counts in hepatic parenchyma before and after therapy

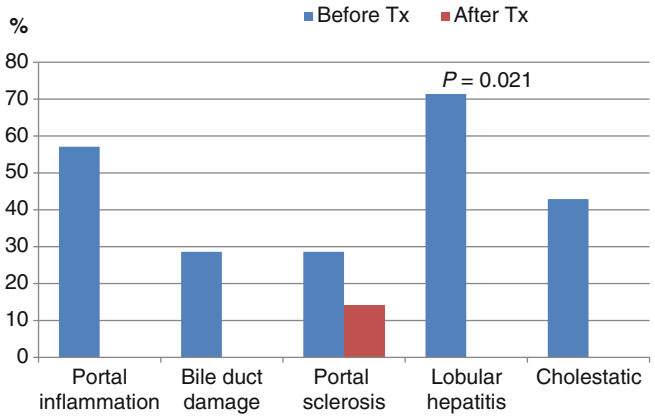

Fig. 29.2 Changes in hepatic parenchyma before and 4 weeks after the start of prednisolone therapy cited from ref. [2]

the degree of infiltration in the portal areas differs, evaluation based on adequate parenchyma samples is mandatory. In small samples, the possibility of sampling error must always be considered.

Considerable improvement in the liver histology after treatment was observed in our study, which examined liver biopsies before therapy and 4 weeks later. A statistically significant difference was noted only for the lobular hepatitis pattern, but the relatively small number of cases examined in this study may have precluded other statistically sound conclusions (Fig. 29.2). The number of IgG4-positive plasma cells within liver biopsies across all patterns of hepatic injury improved with therapy (Fig. 29.3). Improvements in liver function test abnormalities corresponded to the histological improvements observed. The efficacy in this context of prednisolone therapy, which is now being applied worldwide, was in this way documented for the first time not only by blood and imaging studies but also by pathological study.

29.3 IgG4-Related Hepatic Lesions in Autoimmune Hepatitis

We incidentally discovered an elevated IgG4 concentration ≥500 mg/dL in the stored serum of a patient with AIH who had not yet been treated. A liver biopsy specimen at diagnosis showed interface hepatitis, rosette formation, and syncytial multinucleated giant cell change of hepatocytes. The patient was diagnosed with definite AIH according to the diagnostic criteria of the International Autoimmune Hepatitis Group, and oral prednisolone therapy was started. However, on

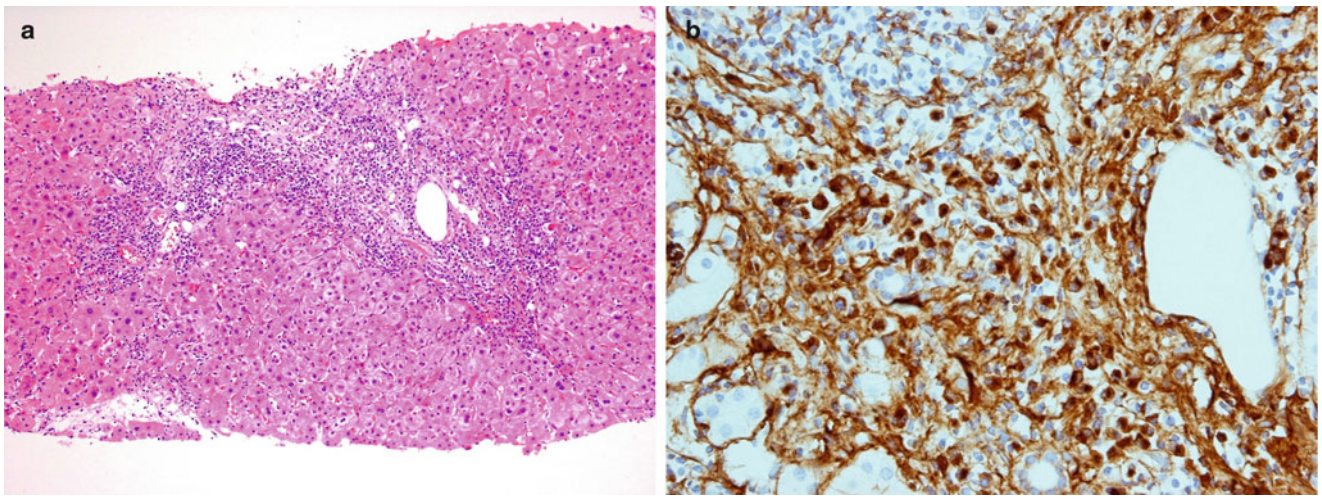

Fig. 29.4 IgG4-related hepatopathy seen in patients without autoimmune pancreatitis or sclerosing cholangitis. The histological findings are not inconsistent with those of autoimmune hepatitis. (**a**) A histological picture of chronic active hepatitis is seen, with dense inflammatory cell infiltration and interface hepatitis present in the portal areas. H&E stain, ×100. (**b**) In the portal areas numerous infiltrating IgG4-positive plasma cells are present. IgG4 immunostain, ×400

reevaluation, marked IgG4-positive plasma cell infiltration was found in the hepatic parenchyma (Fig. 29.4). No obvious abnormal findings in the extrahepatic bile ducts or pancreas were demonstrated by various diagnostic imaging examinations performed at the previous hospital. This case fulfilled the diagnostic criteria of AIH, but also had features characteristic of IgG4-related disease such as serum IgG4 concentration ≥135 mg/dL and an abundant IgG4-positive plasma cell infiltrate within the hepatic parenchyma. This prompted us to assign the name "IgG4-associated autoimmune hepatitis" to what we consider to be this new clinicopathological entity [9]. Now, it should be called "IgG4-related autoimmune hepatitis" to be consistent with other nomenclature.

To see if we could identify any other such similar cases, we determined the serum IgG4 values and intrahepatic IgG4-positive plasma cell counts in 60 patients with AIH. In this way, we were able to detect one additional such case with presumed IgG4-related AIH [10]. We then undertook an additional study of these two IgG4-related AIH cases as well as 58 cases with classic AIH [11]. Because there were only two cases of IgG4-related AIH, a statistical analysis was not performed, but IgG4-related AIH showed marked changes in the hepatic parenchyma, and the numbers of infiltrating IgG4-positive cells per HPF and ratios of IgG4/IgG positive cells were 24 and 29, and 0.282, and 0.528, respectively. The median numbers of IgG4-positive cells and the ratios of IgG4/total IgG positive cells in patients with classical AIH were 0 (range: 0–7) per HPF and 0.000 (range 0.000–0.102), respectively.

The first of the two patients with IgG4-related AIH developed hepatic dysfunction manifested mainly by biliary enzyme elevations as well as findings of sclerosing cholangitis on ERCP, despite continuing to receive oral prednisolone 2.5–5.0 mg/day 5 years after the start of therapy. Although the serum IgG4 concentration was normal, on bile duct biopsy an infiltration of IgG4-positive plasma cells was detected. IgG4-related sclerosing cholangitis thought to have intervened 5 years into the course.

29.4 Clinical Significance of Proposing the New Disease Concept of IgG4-Related Hepatopathy

From the study on the hepatic parenchyma findings of AIP, the existence of a new hepatopathy was demonstrated, with lesions consisting mainly of infiltrating IgG4-positive cells. This inflammation involves not only the biliary system but also extends to the hepatic parenchyma. To encompass these features, the new disease concept of IgG4-related hepatopathy was proposed. IgG4-related hepatopathy is thought to represent a combination of some of the features of sclerosing cholangitis and AIH. Additional investigations are required to understand the relationship between AIH and IgG4-related AIH. Should the long-term prognosis after corticosteroid therapy prove to be more favorable than that of AIH, it would be very important to firmly recognize this kind of disease entity and devise the most appropriate treatment for it.

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Part IV

Lesson from Cases

A Case of IgG4-Related Kidney Disease First Detected Because of Severe Renal Dysfunction

30

Ichiro Mizushima, Kazunori Yamada, Hiroshi Fujii, Masami Matsumura, Masakazu Yamagishi, and Mitsuhiro Kawano

30.1 Introductory Remarks

IgG4-related kidney disease (IgG4-RKD) is an inflammatory disease that most commonly affects middle-aged and elderly men. Its clinical spectrum is wide, with some cases showing a subclinical gradual course and others a rapidly decreasing renal function. Proteinuria is found in close to one half of cases, but urinary findings are frequently subtle and easily overlooked in the early phase of disease [1–3]. When seen in elderly persons, many of whom have comorbid conditions, these findings may be written off as nephrosclerosis in the absence of any serological, imaging, or histological evaluation. We report here the case of a patient with IgG4-RKD in which relatively rapidly progressive nephropathy developed during treatment for hypertension and glucose intolerance. Identification of the underlying cause and the institution of appropriate therapy were associated with a prompt response to glucocorticoids.

30.2 Case

A 68-year-old man was admitted to our hospital because of relatively rapidly progressive renal dysfunction. Twenty years previously he had been diagnosed with hypertension, for which he opted not to undertake treatment. Eight months prior to admission, nocturnal polyuria and thirst were noted, for which he consulted a local physician 2 months prior to admission. At that time, severe hypertension (204/114 mmHg), azotemia (serum creatinine 2.54 mg/dL), and glucose intolerance (hemoglobin A1c 6.1 %) were documented. Nephropathy associated with hypertension and diabetes mellitus was suspected, and an angiotensin receptor blocker and calcium channel blocker were administered. The blood pressure improved on these agents, but he developed general malaise and anorexia. Two weeks prior to admission, his serum creatinine had risen to Cr 4.88 mg/dL. A computed tomography scan of the kidneys performed without contrast showed no renal atrophy, but laboratory examination revealed a hypergammaglobulinemia(IgG 4,854 mg/dL; normal: 870–1,700 mg/dL) and hypocomplementemia (C3 10 mg/dL, normal: 65–135 mg/dL; C4 7 mg/dL, normal: 13–35 mg/dL). One week before admission, his serum creatinine rose yet further to 5.76 mg/dL.

On admission, the patient was alert and oriented, afebrile, and had a blood pressure of 126/88 mmHg and a pulse of 91/min. Conjunctival pallor was present. There were palpable, mobile, and painless lymph nodes in the cervical region bilaterally, and both submandibular glands were enlarged, firm, nodular, and mobile. The heart, lung, abdomen, musculoskeletal, skin, and nervous system examinations were unremarkable. Laboratory examinations on admission are shown in Table 30.1. Computed tomographic examinations of the neck, chest, and abdomen revealed bilateral swelling of the lacrimal and submandibular glands; cervical, supraclavicular, mediastinal, maxillary, paraaortic, and inguinal lymph node lymphadenopathy; reticular shadows in both lower lung fields; mild, diffuse swelling of the pancreas; bilateral renal swelling; and prostatic hypertrophy (Fig. 30.1). Lesions suggestive of IgG4-RD were observed in the salivary and lacrimal glands, lung, pancreas, kidney, prostate, and lymph nodes. A percutaneous renal biopsy under ultrasound guidance revealed diffuse, dense lymphoplasmacytic cell infiltrates within the renal interstitium and mild fibrosis surrounding the infiltrating cells (Fig. 30.2a, b, and d). The glomeruli showed intravascular proliferative lesions in addition to ischemic changes (Fig. 30.2c). On IgG4 immunostaining, the majority of the infiltrating plasmacytic cells were

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Table 30.1 Laboratory data of the present case on admission to our hospital

	Values	Normal range
Urinalysis		
Protein	2+	–
Occult blood	2+	–
Sugar	–	–
G. cats	2+	–
Blood count		
White blood cells (/μL)	7,110	3,300–8,800
Red blood cells (/μL)	384×10^4	430–550
Hemoglobin (g/dL)	11.2	13.5–17.0
Hematocrit (%)	34.5	39.7–51.0
Platelets (/μL)	17.5×10^4	13.0–35.0
Serum chemistry		
BUN (mg/dL)	67	8–22
Cr (mg/dL)	6.87	0.60–1.00
UA (mg/dL)	9.8	3.6–7.0
Na (mEq/L)	138	135–149
K (mEq/L)	4.2	3.5–4.9
Cl (mEq/L)	109	96–108
Ca (mg/dL)	8.9	8.0–10.5
IP (mg/dL)	4.5	2.5–4.5
ALP (IU/L)	133	115–359
γGTP (IU/L)	23	10–47
AST (IU/L)	14	13–33
ALT (IU/L)	11	8–42
LDH (IU/L)	177	119–229
Amy (IU/L)	87	40–113
TP (g/dL)	9.0	6.7–8.3
Alb (g/dL)	3.5	4.0–5.0
T-cho	129	128–219
HDL-cho	14	40–99
TG	166	30–149
Plasma glucose (mg/dL)	115	69–109
HbA1c (%)	6.5	4.3–5.8
Immunological findings		
CRP (mg/dL)	0.3	0.0–0.3
IgG (mg/dL)	4,661	870–1,700
IgG4 (mg/dL)	1,120	–
IgA (mg/dL)	149	110–410
IgM (mg/dL)	30	33–190
IgE (IU/mL)	335	<250
CH50 (U/mL)	5	32–47
C3 (mg/dL)	10	65–135
C4 (mg/dL)	7	13–35
ASO (IU/mL)	<70	<225
ASK	×80	<1,280
ANA	×320 (H)	–
RF (IU/mL)	<10	<20
Anti-Ro/SSA Ab (EU)	<10	<10.0
Anti-ds-DNA Ab (IU/mL)	<12	<12.0
Anti-Sm Ab	<7	<7.0
Anticardiolipin Ab (U/mL)	1.3	<3.5
MPO-ANCA (EU)	<10	<20
PR3-ANCA (EU)	<10	<10
Anti-GBM Ab (EU)	<10	<10
Cryoglobulin	–	–
ACE (IU/L)	9.2	8.3–21.4
sIL-2R (U/mL)	6,758	150–505

IgG4-positive (Fig. 30.2e, f). Taking these histological findings into consideration, IgG4-RKD was diagnosed [3]. Administration of prednisolone 30 mg/day was followed by improvement in the serum creatinine concentration from a peak of 7.26 mg/dL before treatment to 1.54 mg/dL 1 month later (Fig. 30.3). The renal swelling also showed marked improvement on follow-up CT (Fig. 30.4). A second renal biopsy performed on the 35th day after the initiation of therapy showed much less prominent IgG4-positive plasmacytic cell infiltrates, although a considerable number of cellular infiltrates persisted in the interstitium, with little progression of the extent of fibrosis. After glucocorticoid tapering was begun, there were no signs of recurrence, and the patient was discharged on a prednisolone dose of 20 mg/day. When the prednisolone dose was reduced to 5 mg/day 20 months after the start of glucocorticoid treatment, progressive azotemia and hypocomplementemia were observed, both of which improved again when the prednisolone dose was increased back to 20 mg/day (Fig. 30.3).

30.3 Discussion

We experienced a case of IgG4-RD in which multi-organ involvement affecting the kidneys, lungs, lymph nodes, and salivary, lacrimal, and prostate glands was detected. Although the extrarenal lesions were nearly asymptomatic and were discovered only incidentally during the course of evaluation for the renal dysfunction, the nephropathy was severe, with a pretreatment eGFR of 6.61 mL/min. Glucocorticoid therapy was nevertheless successful in restoring renal function. This case illustrates that IgG4-RKD must be considered in the setting of renal dysfunction of obscure etiology—even when potential causes such as hypertension and diabetes mellitus are present.

The elderly, the age group most frequently affected by IgG4-RD, are also the age group most prone to the development of comorbid conditions capable of causing renal injury. It is thus essential that physicians not automatically attribute renal dysfunction in such patients to these more common conditions, especially in the absence of other complications of hypertension or diabetes.

The central lesion in IgG4-RKD is IgG4-related tubulointerstitial nephritis (IgG4-related TIN). The amount of proteinuria in IgG4-related TIN is often not very striking, but since it may be associated with various glomerular lesions as well [1–5], diagnoses predicated on the finding of proteinuria may be misleading. However, symmetrical renal swelling, the hypergammaglobulinemia, and hypocomplementemia all provided important clues to the possibility of IgG4-RKD in our case. Accordingly, when renal insufficiency of unclear cause is detected for the first time in an elderly person, we recommend that the serum IgG concentration and complement titer be measured, and the renal size be determined regardless of the presence/absence of any underlying disease.

IgG4-RD is generally responsive to glucocorticoids [6, 7] and this rule also appears to apply to many patients with IgG4-RKD [1, 2]. However, we have observed histological

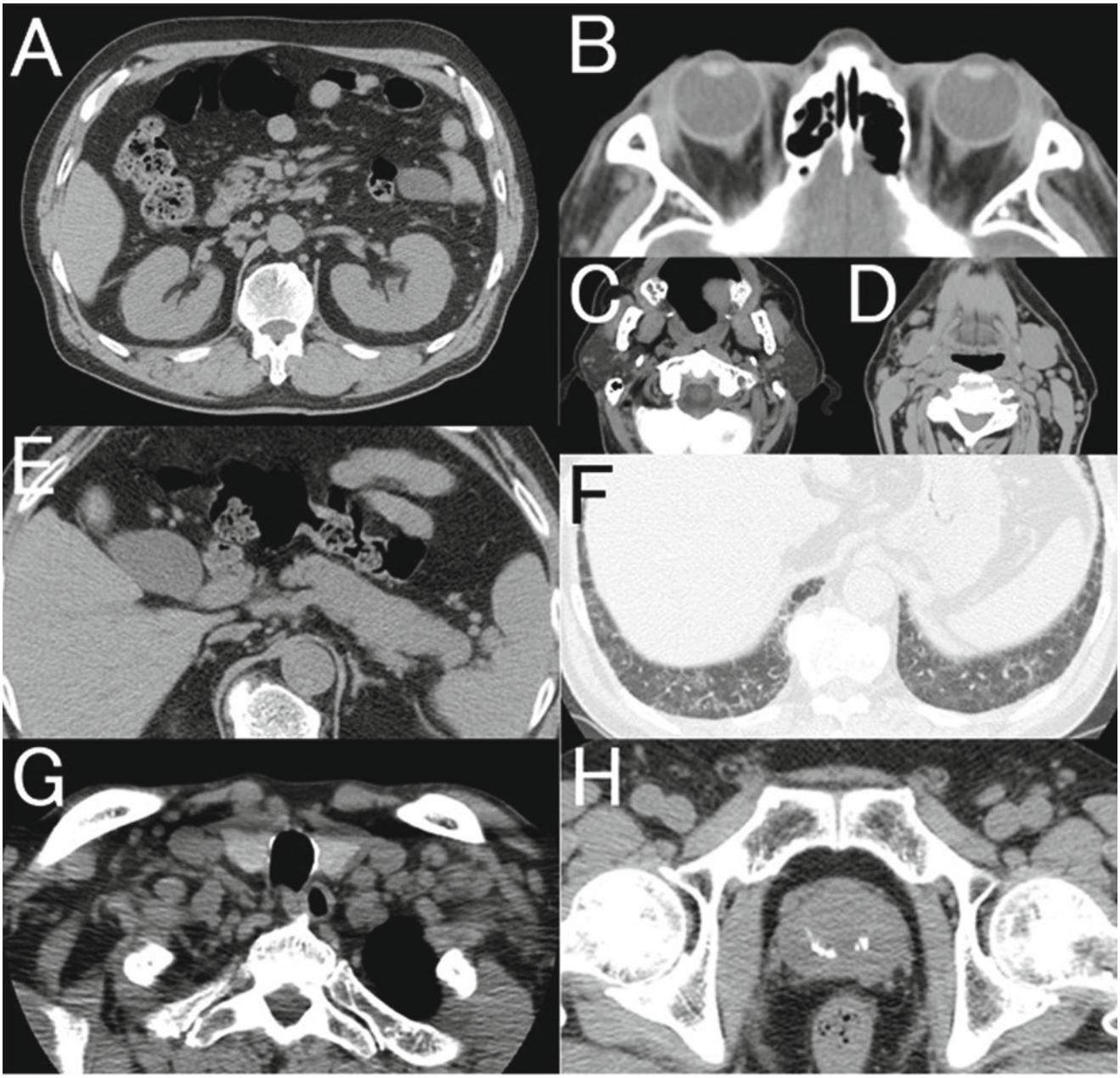

Fig. 30.1 Plain computed tomography (CT) findings of the present case. Diffuse bilateral renal swelling was observed before therapy (**a**). Bilateral lacrimal and parotid glands and left submandibular gland swelling (**b**–**d**, respectively), mild diffuse swelling of the pancreas (**e**), reticular shadows in the bilateral lung lower lobes (**f**), supraclavicular lymph node swelling (**g**), and prostatic hypertrophy (**h**) were noted

scarring and fibrosis and radiologic atrophy in some patients who appeared to have good clinical responses. In addition, renal function often does not return completely to normal in the majority of cases in which renal dysfunction was present before therapy. The point that early diagnosis and appropriate therapeutic intervention may help avoid permanent functional injury to the kidneys is suggested by the fact that among patients in whom treatment was begun at times of mild or clinically absent renal disease, renal function was preserved [8]. Additional studies on the long-term course of more such patients with IgG4-RKD are required to understand the optimal approach to therapy.

Several reports have already focused on the relationship between IgG4-RD activity and serum IgG4 concentration [9, 10]. Some investigators have concluded the existence of a significant relationship between the two based on the finding of a positive correlation between the number of affected organs and serum IgG4 concentration at diagnosis, a signifi-

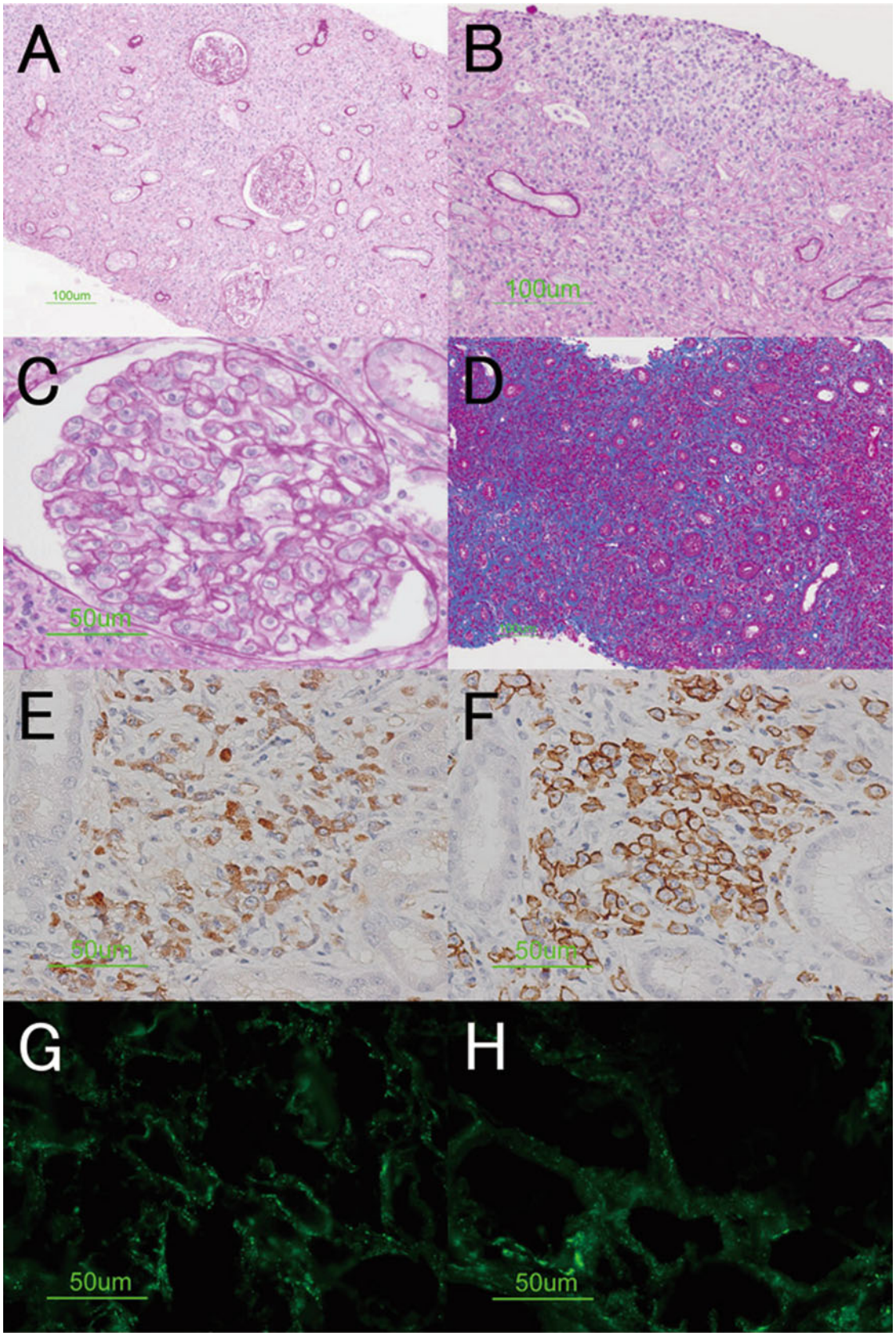

Fig. 30.2 Light microscopy, immunohistochemistry, and immunofluorescence findings of the renal specimens before corticosteroid therapy. Diffuse, dense lymphoplasmacytic cell infiltrates in the renal interstitium with mild fibrosis surrounding the infiltrating cells were observed (**a**, **d**). In addition, lymphoid follicle-like lesion was found (**b**). The glomeruli showed intravascular proliferative lesions in addition to ischemic changes (**c**). On IgG4 immunostaining, the majority of the infiltrating plasmacytic cells (**f**) were IgG4-positive (**e**). Immunofluorescence staining for C3 (**g**) and C1q (**h**) reveals granular deposits of C3 along the tubular basement membrane. [(**a**) Periodic acid Schiff (PAS) staining ×100, (**b**) PAS staining ×200, (**c**) PAS staining ×400, (**d**) Azan staining ×100, (**e**) IgG4 ×400, (**f**) CD138 ×400, and (**g**) C3 ×400, (**h**) C1q ×400]

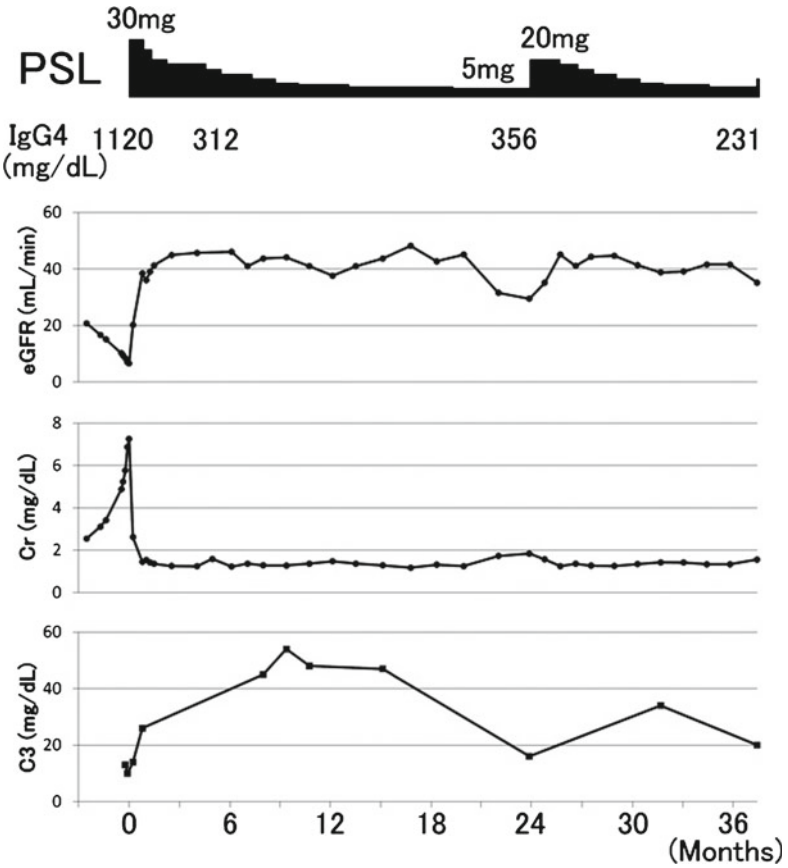

Fig. 30.3 Clinical course of the present case. Serum creatinine concentrations (Cr) and estimated glomerular filtration rate (eGFR) rapidly deteriorated before corticosteroid therapy. They promptly improved within 1 month after the initiation of prednisolone (PSL) 30 mg/day. After steroid tapering was begun, there were no signs of recurrence for a long time. Subsequently, however, decreased eGFR, increased serum Cr, and progressive hypocomplementemia were found when the PSL dose was reduced to 5 mg/day. All of them improved again when the PSL dose was increased

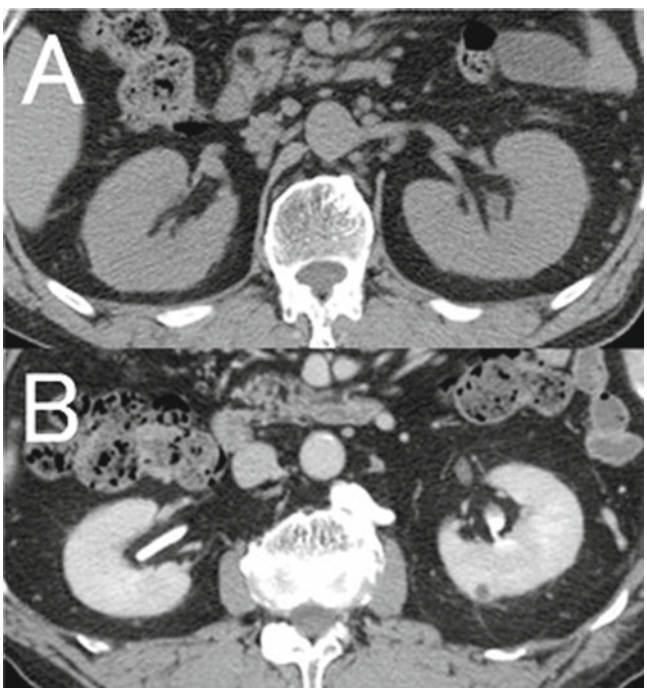

Fig. 30.4 Changes in computed tomography (CT) findings after corticosteroid therapy. Diffuse bilateral renal swelling before therapy (**a**) was improved with relatively uniform contrast enhancement 1 month after therapy (**b**)

cant decrease in serum IgG4 concentrations with therapy, and a re-elevation of serum IgG4 concentrations at the time of relapse. Hypocomplementemia is also a frequent finding in IgG4-RKD [1, 2], and immune complexes are often found within renal tissues at sites such as the tubular basement membrane [1, 2, 11]. Some connection between the activity of this disease and the complement system is therefore surmised to exist. In fact, in the present case, in addition to a modest rise in the serum IgG4 concentration at the time of relapse, worsening hypocomplementemia was seen, with complement concentrations rising again following the intensification of therapy. Prospective studies of serum complement concentration levels in patients with IgG4-RKD and subsets of organ involvement are required to understand the relationship between the complement system and IgG4-RD.

In this chapter we presented what we believe to be an instructive case with regard to the diagnosis and treatment of IgG4-RKD in daily medical practice. The importance of serological and diagnostic imaging screening to facilitate the earliest possible diagnosis and therapeutic intervention as well as the usefulness of follow-up of the complement titer as a therapeutic marker were suggested. To address these and other issues, studies on the long-term course of larger numbers of patients are awaited.

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IgG4-Related Disease and Malignant Tumor

31

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31.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is regarded as a benign disease that usually responds well to glucocorticoid therapy. However, an important proviso in approaching the diagnosis of IgG4-RD is careful differentiation of this condition from malignant tumors [1–3].

The diagnosis of IgG4-RD involves the interpretation of blood tests, imaging studies, and pathology findings, but it is well recognized that pancreatic cancer may mimic IgG4-RD closely, presenting with elevations of the serum IgG4 concentration, pancreatic masses on imaging, and IgG4-positive plasma cell infiltration of tissue [4]. Since the therapeutic strategies for type 1 (IgG4-related) autoimmune pancreatitis (AIP) and pancreatic cancer differ so greatly, distinction between these two conditions is essential.

The lines between these disorders are sometimes blurred in the clinical setting. As examples, cases of the occurrence of pancreatic cancer following the diagnosis of type 1 AIP have been reported [1]. In addition, malignant lymphoma has been known to supervene during the course of Mikulicz's disease [2]. With the growing number of reports of IgG4-RD, the number of cases in which this condition is found in association with malignant tumors has grown. The possibility of a true association between IgG4-RD and malignancy is an important question in this emerging field. Here, we present an autopsy case in which IgG4-RD developed during the course of mucinous cystadenocarcinoma of the appendix, discussed in the context of the pertinent medical literature.

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31.2 Case

A 73-year-old man was admitted to our hospital in December 2000 with abdominal pain, hepatobiliary enzyme elevation, pancreatic swelling, bile duct dilatation, and bile duct wall thickening. Four years before admission, a tumor of the appendix had been detected by colonoscopy and ileocecal resection had led to the diagnosis of a mucinous cystadenocarcinoma of the appendix with peritoneal dissemination (Stage IV).

Chemotherapy course using tegafur-uracil (300 mg daily) had been started and continued without any complication till 2000. During this period, he had been doing well. He was admitted to our hospital for the evaluation of weight loss of 5 kg yearly in December 2000. On admission, his blood pressure was 156/70 mmHg. Mild conjunctival pallor was present. He had slight bilateral submandibular gland swelling with slight oral mucosal dryness, but lymphadenopathy in the cervical, supraclavicular, and axillary regions was not detected. The heart, lung, and abdomen examinations were within normal limits. The results of the laboratory assessment upon admission are shown in Table 31.1. Marked elevations of the hepatic aminotransferases, the alkaline phosphatase, and the gamma glutaryl transferase were seen. The total serum IgG and IgE concentrations were also elevated, but hypocomplementemia was absent and an assay for antinuclear antibodies was negative.

Several Imaging Studies Were Performed

- A CT scan of the abdomen (Fig. 31.1) demonstrated diffuse swelling of the pancreas, most prominently of the pancreatic head. The pancreatic parenchyma enhanced weakly in the arterial phase. Gallbladder and bile duct dilatation and bile duct wall thickening were conspicuous, and wall thickening of the abdominal aorta was detected and corresponded to the initial manifestation of retroperitoneal fibrosis.

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Table 31.1 Laboratory data of the present case on admission to our hospital

	Values	Normal range
Urinalysis		
Protein (g/day)	0.07	0.0
Sugar	–	–
Erythrocytes (/HPF)	<1	<1
Leukocytes (/HPF)	<1	<1
Beta 2 microglobulin (μg/L)	4.9	<400
Blood count		
White blood cells (/μL)	3.600	3,300–8,800
Red blood cells (/μL)	396×10^4	430–550
Hemoglobin (g/dL)	12.6	13.5–17.0
Hematocrit (%)	37.8	39.7–51.0
Platelets (/μL)	18.5×10^4	13.0–35.0
Serum chemistry		
UN (mg/dL)	17.0	8–22
Cr (mg/dL)	1.0	0.60–1.00
UA (mg/dL)	4.4	3.6–7.0
Na (mEq/L)	143	135–149
K (mEq/L)	4.0	3.5–4.9
Cl (mEq/L)	107	96–108
ALP (IU/L)	1,776	115–359
γGTP (IU/L)	1,836	10–47
AST (IU/L)	91	13–33
ALT (IU/L)	92	8–42
LDH (IU/L)	209	119–229
Amy (IU/L)	76	40–113
T. Bil (mg/dL)	1.0	0.4–1.2
TP (g/dL)	7.7	6.7–8.3
Alb (g/dL)	3.1	4.0–5.0
Plasma glucose (mg/dL)	96	69–109
HbA1c (%)	4.5	4.3–5.8
Immunological findings		
CRP (mg/dL)	0.1	0.0–0.3
IgG (mg/dL)	2,240	870–1,700
IgG4 (mg/dL) (Nov. 2004)	1,490	
IgA (mg/dL)	207	110–410
IgM (mg/dL)	54	33–190
IgE (IU/mL)	466	<250
CH50 (U/mL)	45	32–47
C3 (mg/dL)	90	65–135
C4 (mg/dL)	18	13–35
ANA	–	
RF (IU/mL)	24	<10
Anti-Ro/SSA Ab (EU)	<10	<10.0
Anti-ds-DNA Ab (IU/mL)	<12	<12.0
Anti-Sm Ab	<7	<7.0
Anti-cardiolipin Ab (U/mL)	–	<3.5
MPO-ANCA (EU)	<10	<20
PR3-ANCA (EU)	<10	<10
Anti-GBM Ab (EU)	<10	<10
Cryoglobulin	–	
IL-6 (U/mL)	5.1	<4.0
Tumor markers		
CEA (μg/L)	2.6	<4.8
CA19-9 (U/mL)	72	<36
DUPAN-2 (U/mL)	930	<150
Span-1 (U/mL)	67	<30
Pancreas function		
PABA test (%)	34	>70

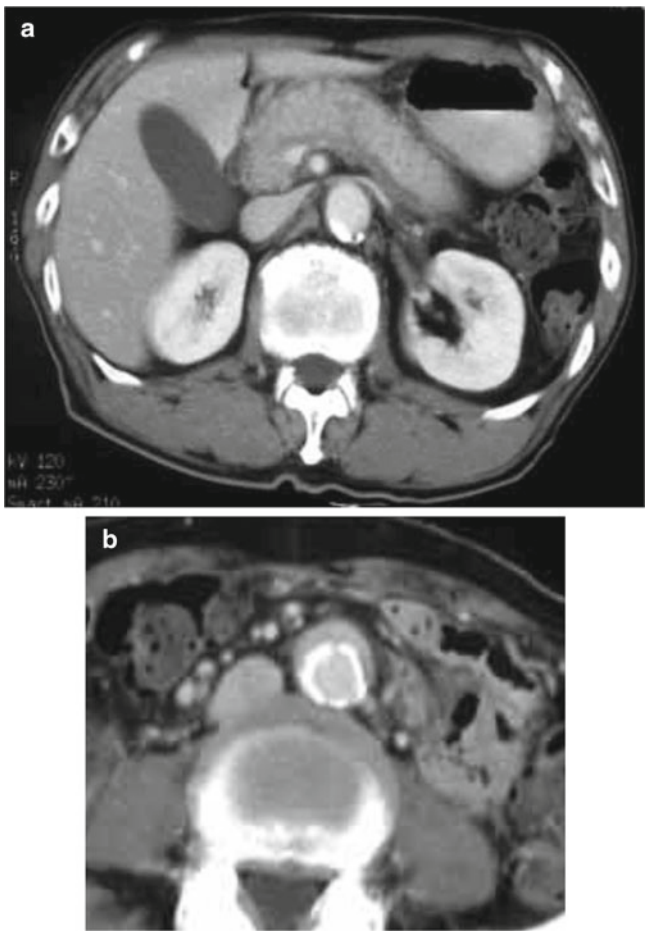

Fig. 31.1 Abdominal contrast-enhanced CT. (**a**) Diffuse swelling of the pancreas is found, especially of the pancreatic head. Gallbladder and bile duct dilatation and bile duct wall thickening are found. (**b**) A membrane-like structure is found around the aorta

- On abdominal MRI (MRCP) (Fig. 31.2), swollen pancreas showed a markedly decreased signal intensity on T1-weighted images compared to normal pancreas. In the rim of the pancreas a poorly enhanced membrane-like hypointense area was noted. The main pancreatic duct showed irregular slight dilatation. The common bile duct was stenotic in the pancreatic head portion, central to which dilatation of the common bile and intrahepatic bile ducts was found. The common bile duct wall showed circumferential thickening, most markedly in the pancreatic head. Narrowing of the splenic vein, superior mesenteric vein, and portal vein running near the pancreatic head was found.
- On ERCP, the main pancreatic duct was narrow with a withered branch appearance, with conspicuous unevenness and irregularity of the caliber. In the common bile

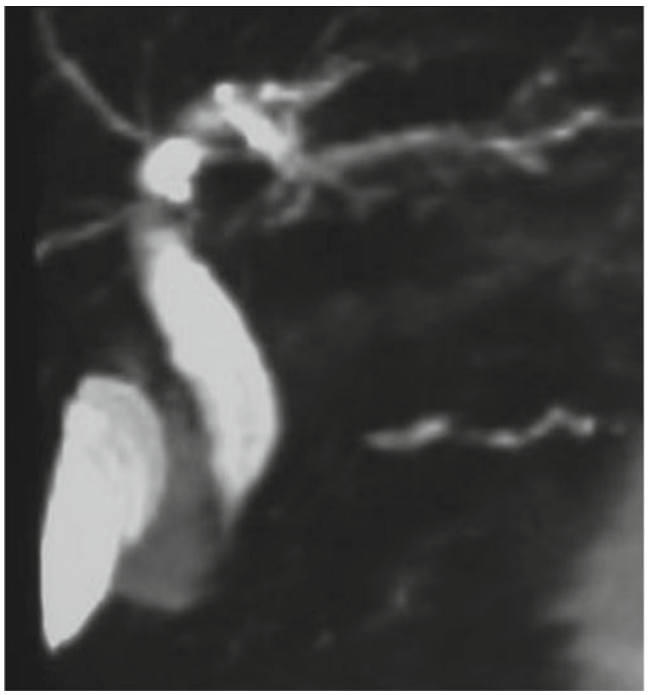

Fig. 31.2 MRCP The main pancreatic duct is uneven and its caliber is irregular, while the portion of the common bile duct within the pancreatic head is stenotic. Dilatation of the peripheral portion of the common bile duct and intrahepatic bile duct and circumferential thickening of the common bile duct wall are found

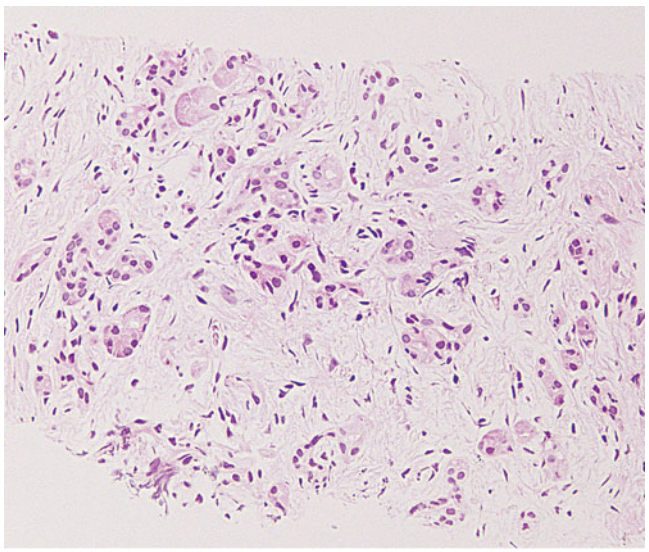

Fig. 31.3 Pancreas biopsy. Interstitial fibrosis associated with excretory duct hyperplasia and sparse lymphoplasmacytic cell infiltration was prominent

duct, severe stenosis was found in the lower bile duct, central to which slight dilatation and irregularity of the caliber were apparent.

- On salivary gland scintigraphy, both the bilateral parotid and submandibular glands showed decreased accumulation.

Biopsies of the pancreas and minor salivary glands were performed. On pancreas biopsy, almost of all the acini had desquamated, and interstitial edema associated with excretory duct hyperplasia and sparse lymphoplasmacytic cell infiltration was prominent, but no findings of malignancy were found (Fig. 31.3). On minor salivary gland biopsy, acini were replaced with fibrosis and were atrophic. In some places only the distal excretory ducts remained, and in the lobules occasional foci of sparse lymphoplasmacytic cell infiltration around the acini were seen.

Prednisolone (PSL) 30 mg/day was begun for the presumptive diagnoses of chronic pancreatitis associated with common bile duct stenosis and SSA/Ro-negative Sjogren's syndrome (Fig. 31.4). The hepatobiliary enzyme abnormalities and pancreas swelling improved markedly on this regimen, and the PSL was tapered to discontinuation in June 2001.

In September 2001, the carcinoembryonic antigen (CEA) level in the patient's blood began to increase. On an MR imaging study performed in January 2002, multiple nodular lesions were seen on the surface and the subdiaphragmatic areas of the right hepatic lobe. A subsequent biopsy confirmed peritoneal dissemination of mucinous cystadenocarcinoma of the appendix.

Chemotherapy using levofolinate 100 mg + 5-fluorouracil (FU) 500 mg daily was begun but the intraperitoneal mass gradually increased in size. The serum IgG concentration also increased gradually, reaching 2,430 mg/dL in November 2004. The serum IgG4 value was 1,490 mg/dL at that time. In November 2006, the patient's abdominal distension and respiratory distress gradually worsened, and he died. Autopsy was performed after informed consent was obtained.

The Autopsy Findings Were as Follows

Peritoneal dissemination developed from a mucinous cystadenocarcinoma of the appendix (Fig. 31.5), with the resulting peritoneal pseudomyxoma-like state causing digestive tract stenosis and bowel obstruction. Spleen infiltration (spleen: 120 g) was also seen. No hematogenous organ or lymph node metastases were found.

Lesions in Other Organs

(a) Pancreatic lesions: marked fibrosis around the pancreatic duct was the most notable finding, with lymphoplasmacytic cell infiltration only slight, the same as the pancreas biopsy findings (Fig. 31.6).

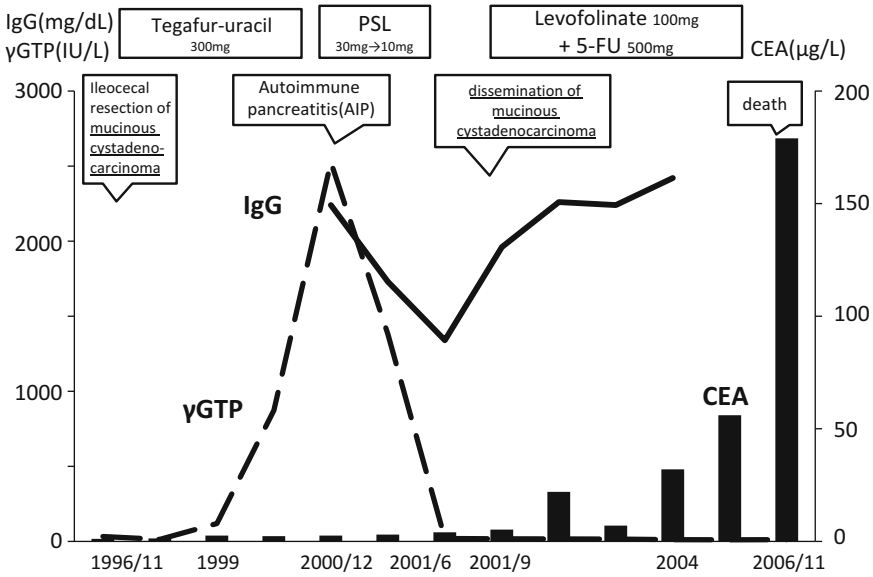

Fig. 31.4 Clinical course

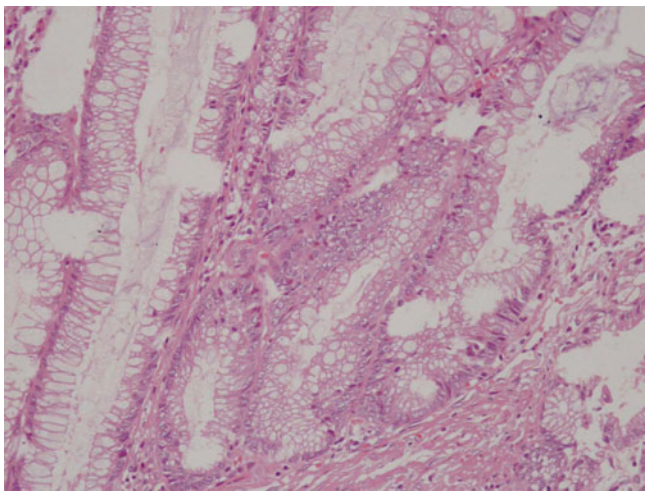

Fig. 31.5 Microscopy of well-differentiated mucinous cystadenocarcinoma of the appendix

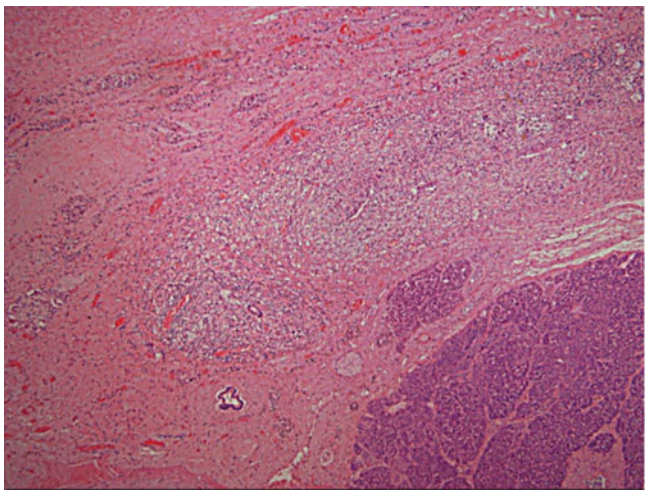

Fig. 31.6 Pancreas lesions

(b) Focal areas of fibrosis and marked lymphoplasmacytic cell infiltration were found in the submandibular and sublingual salivary glands, indicative of sialadenitis (Fig. 31.7).
(c) Fibrosis and marked lymphoplasmacytic cell infiltration were also found in the prostate.
(d) In the kidney, the main finding was localized marked lymphoplasmacytic cell infiltration in the tubular interstitium and perivascular area (Fig. 31.8a, b). In addition to lymphoplasmacytic cells, eosinophil infiltration was also prominent (Fig.31.8c). The plasmacytic cells were predominantly IgG4 positive (Fig. 31.8d). These changes were especially prominent around arterioles and veins.
(e) In the bone marrow a slight increase in the proportion of plasmacytic cells was found.

31.3 Discussion

This patient was diagnosed with chronic pancreatitis and SSA/Ro antibody-negative Sjogren's syndrome 4 years after being diagnosed with mucinous cystadenocarcinoma of the appendix. Although the clinical entity of IgG4-RD had not yet been established at the time the patient presented, the pancreatitis was consistent with the subsequently proposed clinical diagnostic criteria of type 1 AIP, and the sialadenitis was also considered retrospectively to be IgG4-related [5].

The potential relationships between IgG4-RD and malignant tumors have attracted growing attention recently [1, 2]. Zen et al. reported that during the course of IgG4-RD in 114 cases, 4 (3.5 %) had a history of malignant tumors at the time

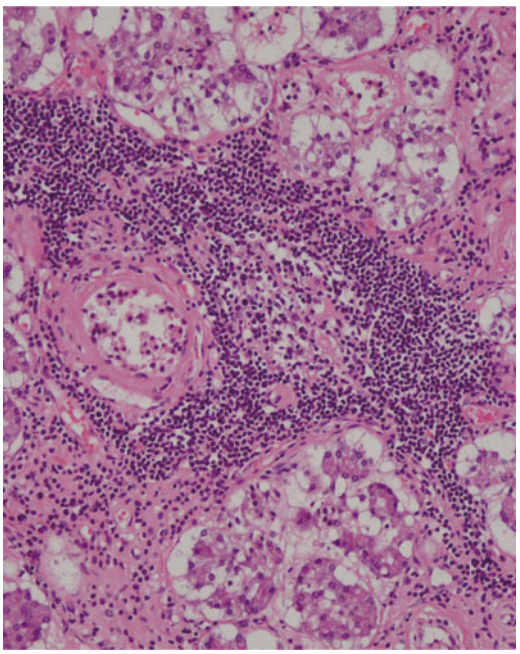

Fig. 31.7 Submandibular gland lesions

of diagnosis of IgG4-RD. These tumors included prostate cancer (1 case), endometrial adenocarcinoma (1), and adenocarcinoma of the lung (2). Three patients (2.6 %) in Zen's series were diagnosed with malignant tumors after the diagnosis of IgG4-RD [6].

Yamamoto et al. studied 106 with IgG4-RD with a mean observation period of 3.1 years. Malignancies developed in 10.4 % of the patients, amounting to a 3.5-fold increase as compared to healthy persons [7]. An array of malignancies was observed. Three patients developed lymphoma. Other types of cancer included colon (2), lung (2), and larynx, breast, ovarian, prostate, and kidney (1 each). Shiokawa et al. retrospectively analyzed 108 patients with type 1 AIP and found frequent complication of malignant tumor with a standard incidence ratio (SIR) of 2.7 (95 % confidence interval 1.4–3.9) [8]. Interestingly, they observed that tumors were apt to be found within the first year after the diagnosis of IgG4-RD and no recurrence of AIP was found after successful treatment of the cancer. With these findings, they speculated that AIP might develop as a paraneoplastic syndrome in some patients.

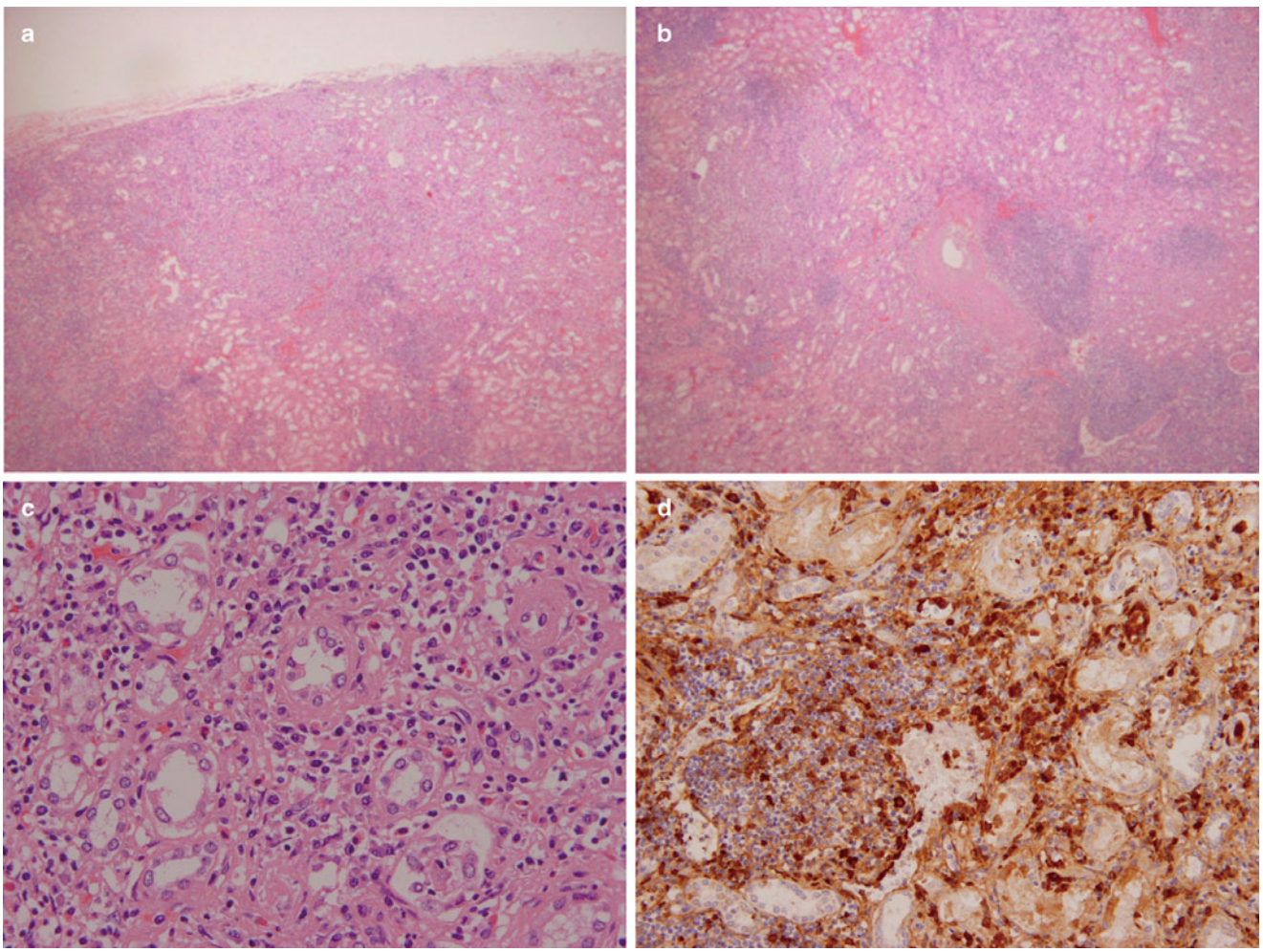

Fig. 31.8 Kidney lesions. The main lesions comprise marked lymphoplasmacytic cell infiltration in the tubular interstitium (**a**) and perivascular area (**b**), eosinophil infiltration (**c**), and abundant IgG4-positive plasmacytic cell infiltration (brown: IgG4 positive) (**d**)

Various observations have been made on the mechanisms possibly underlying any association between IgG4-RD and malignant tumors. In IgG4-RD, regulatory T cells (Treg) show a preferential increase [9], and it is known that Th2 cytokine becomes dominant [10]. Patients with cancer of the digestive organs also demonstrate a Th2 predominance among their peripheral blood T lymphocytes [11]. Serum concentrations of IL-10, a Th2 cytokine, have been reported to be elevated in patients with stomach cancer [12]. Furthermore, in patients with gastric and esophageal cancer Treg populations are significantly increased in both peripheral blood and tumor tissues [13], with Treg reported to exert not only a normal immunosuppressive action but also a tumor immunity suppressing one [14]. These immunological abnormalities, like those in IgG4-RD, are suggested to be possibly related to immune escape mechanisms of malignant tumors.

Kamisawa et al. found marked *K-ras* gene mutations in 8 of 11 cases of AIP [15]. *K-ras* gene mutations have also been found in the major papilla, gastric mucosa, and intestinal mucosa [16]. Treg and inflammation also play important roles in the development of *K-ras*-positive lung cancer in the mouse [17], while Treg infiltration and inflammatory fibrosis have been implicated in the occurrence of *K-ras* gene mutations [18].

Th2, Treg, cytokine, and genetic examinations were not performed in our patient. But during progression of the mucinous cystadenocarcinoma of the appendix IgG4-RD supervened, with the IgG4-related features showing transient improvement with corticosteroid therapy. After steroid cessation, however, the tumor recurred and worsened in parallel with worsening of the IgG4-related manifestations, raising the possibility that some kinds of tumor-related immunological abnormality may play roles in the development and/or progression of IgG4-RD.

IgG4-RD is characterized by good responsiveness to glucocorticoid treatment and is considered to be a benign disease, despite which attention must be paid to the possible supervention of malignant tumors. Because IgG4-RD occurs most frequently in elderly men in whom malignancies are also common, it is not yet possible to conclude whether the development of these two conditions in the same patient represents a mere coincidence or some more significant association. This issue will have to be decided in large-scale and long-term studies.

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32 Membranous Nephropathy with Glomerular IgG4 Deposition Without Tubulointerstitial Nephritis in a Patient with Typical IgG4-Related Pancreatic, Hepatic, and Lymph Node Lesions

Kazuhiro Hatta

32.1 Introductory Remarks

The most widely recognized renal complication of IgG4-RD is tubulointerstitial nephritis (TIN) [1], which is characterized by a distinctive form of fibrosis (storiform fibrosis) and IgG4-positive plasmacytic cell infiltration. Affected and unaffected portions of the kidney are usually demarcated clearly. Mass-like lesions, referred to as pseudotumors, may form. Glomerular lesions are also known to occur [2–10]. Membranous nephropathy (MN) and endocapillary proliferative glomerulonephritis, among others, have been reported [6–10]. The occurrence of MN in isolation, without concomitant TIN, has also been observed [10–12].

Here I present a case which was diagnosed in the 1980s as MN of unknown cause associated with pancreas and lymph node swelling. When the diagnosis was revisited 25 years later, reinterpretation of the histology, the performance of IgG4 staining, and recognition of the features of IgG4-RD in other organs led to reclassification of the patient's diagnosis as IgG4-related MN.

32.2 Case

In 1986, a 45-year-old man was admitted for an evaluation of eyelid swelling, proteinuria, and generalized edema. The pulmonary symptoms were accompanied by these symptoms. His medical history was remarkable for bronchial asthma and a sinobronchial syndrome that he had had for several years. He also had a history of swollen submandibular lymph nodes, detected at age 29. The nodes had been resected, but no details of the pathology were available. At the age of 31, a localized colon cancer had been detected on colonoscopy and was removed.

The patient's admission had been precipitated by the identification of proteinuria at a health screening examination. No improvement was seen with administration of a diuretic. He was admitted to the Department of General Internal Medicine in our hospital when diuretics failed to ameliorate his edema and the proteinuria was found to increase.

On admission, upper eyelid edema, bilateral submandibular gland swelling, and left axillary lymph node swelling were present. Lower extremity edema was also found.

Laboratory examination showed proteinuria (3+) without hematuria, and a 24-hour urine collection revealed that the patient had 4.5 g/day of protein in his urine. Both the serum creatinine and blood urea nitrogen concentrations were normal (1.1 mg/dL and 15 mg/dL, respectively). His hemoglobin was 16.4 g/dL. The white blood cell count was 7,600/mm^3 with 11 % eosinophils. The platelet count was 33.6×10^4/mm^3. The serum C-reactive protein concentration was not elevated (<0.2 mg/dL), but the total protein was 9.2 g/dL (normal: 6.7–8.1 g/dL). The serum albumin was low (2.7 g/dL; normal: 4.0–5.0 g/dL). Tests of liver and pancreatic function were within normal limits. Assays for antinuclear antibodies and rheumatoid factor were negative. The patient's serum concentrations of C3 and C4 were both normal (94 and 50 mg/dL, respectively). However, the serum IgG concentration was 5,295 mg/dL (normal: 870–1,700 mg/dL) and the IgE concentration was 756 IU/ml (normal: <250 IU/ml). Concentrations of IgM and IgA were within normal limits.

A computed tomographic (CT) study of the abdomen demonstrated intra-abdominal lymphadenopathy in the lesser curvature of stomach, mesentery, pancreatic anterior and posterior surfaces, hepatic hilus, and renal hilus (Fig. 32.1). No mass was seen in the pancreatic parenchyma. On endoscopic retrograde cholangiopancreatography, a ste-

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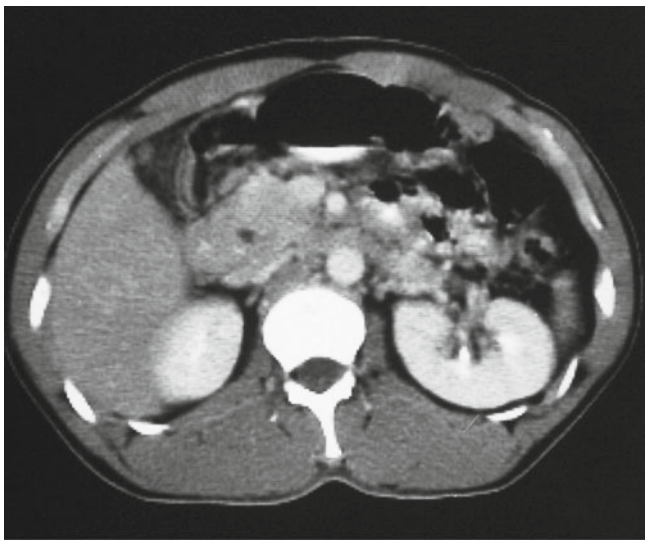

Fig. 32.1 Abdominal CT 2-cm-diameter lymph nodes are seen on the lesser curvature of the stomach side and ventral side of the common hepatic artery. 1.5 × 3-cm lymph node swelling is also seen in the posterior pancreatic head. No masses were seen in the pancreas, and the pancreatic duct was not dilated

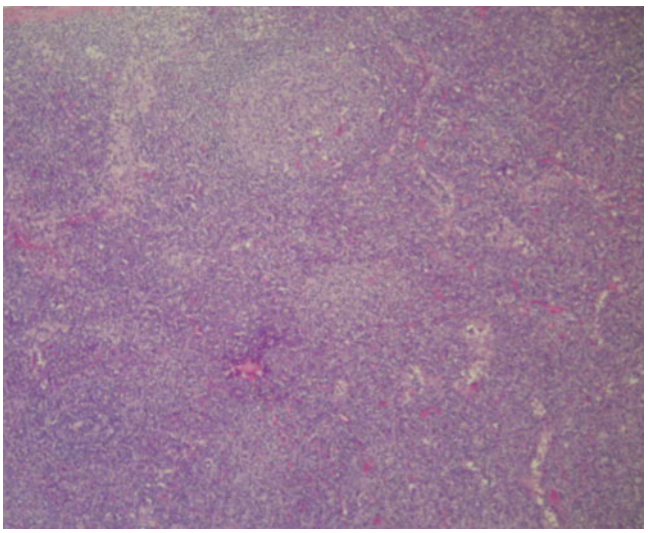

Fig. 32.3 Biopsy findings of lymph nodes. Germinal centers associated with lymph follicle hyperplasia were prominent. The follicular structure and mantle zone were both clear and well preserved. Plasma cell proliferation was marked interfollicularly and in the germinal centers, resembling the lymphoid hyperplasia seen in various autoimmune diseases such as rheumatoid arthritis

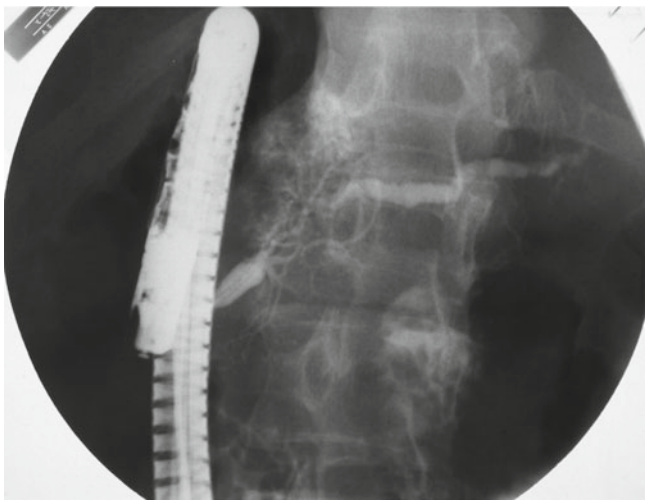

Fig. 32.2 ERCP: Stenosis of the main pancreatic duct extending over 1.5–2 cm from the orifice was found, making it necessary to rule out cancer. However, in the distal portion, the pancreatic duct was not markedly dilated. Such findings would be atypical for cancer, and chronic pancreatitis was considered a more likely diagnosis

nosis of the main pancreatic duct was found, extending 1.5–2 cm from the orifice (Fig. 32.2). The distal portion showed no clear dilatation. The common bile duct and secondary pancreatic ducts were normal. A diagnosis of chronic pancreatitis was rendered. The finding of multiple peritoneal lymph nodes in the setting of a history of colon cancer raised the possibility of a cancer recurrence.

An open procedure was performed to obtain sufficient tissue for diagnosis. The head of the pancreas was rock-hard on palpation, but there was no infiltration of the adjacent tissues. Severe pancreatic fibrosis, acinar disappearance, and lymphoplasmacytic cell infiltration were noted. Cancer was not detected on frozen section and this was later confirmed by permanent sections. Marked peritoneal lymphadenopathy was observed. Histopathological examination of the lymph nodes demonstrated marked lymph follicle hyperplasia associated with germinal centers, which required differentiation from follicular lymphoma. The follicular structure was preserved, however, and surface markers were polyclonal. Thus, the lesion was not considered to be neoplastic (Fig. 32.3). Plasma cells were prominent both in the interfollicular regions and in the germinal centers [cytoplasmic immunoglobulin (cIg) was polyclonal], with the findings resembling those of lymphoid hyperplasia as seen in autoimmune diseases such as rheumatoid arthritis. Differentiation from Castleman's disease with clinical correlation was also considered prudent.

In the liver, a substantial lymphoplasmacytic infiltrate was observed in Glisson's capsule (Fig. 32.4). The immunoglobulin stains on these lesions suggested polyclonality, and the immunostaining characteristics of the liver resembled those of the lymph nodes.

The renal tissue obtained by open biopsy showed spike formation on periodic acid methenamine silver staining. Immunofluorescence studies revealed marked granular staining of IgG, C3, and C1q along the capillary wall, consistent with idiopathic MN (Fig. 32.5).

Following this open biopsy of several involved organs, the diagnostic conclusions in 1986 were as follows: (1)

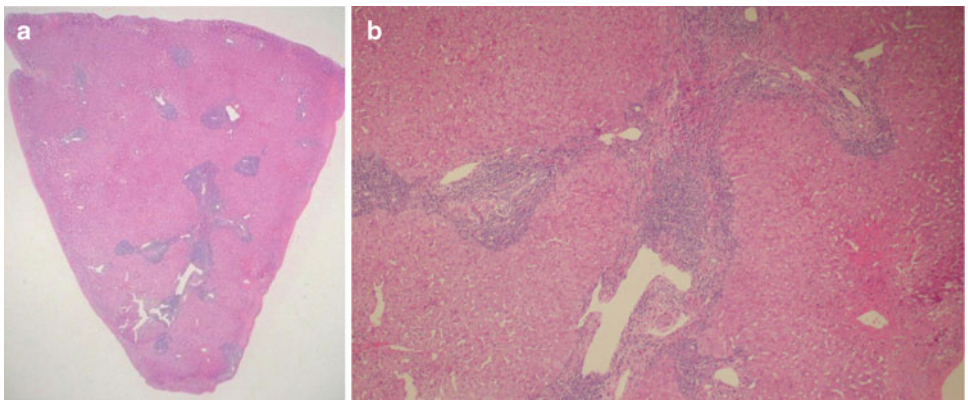

Fig. 32.4 Biopsy findings of the liver. Copious lymphoplasmacytic cell infiltration was seen especially in Glisson's capsule. (**a**) Weakly magnified HE staining; (**b**) HE staining ×100

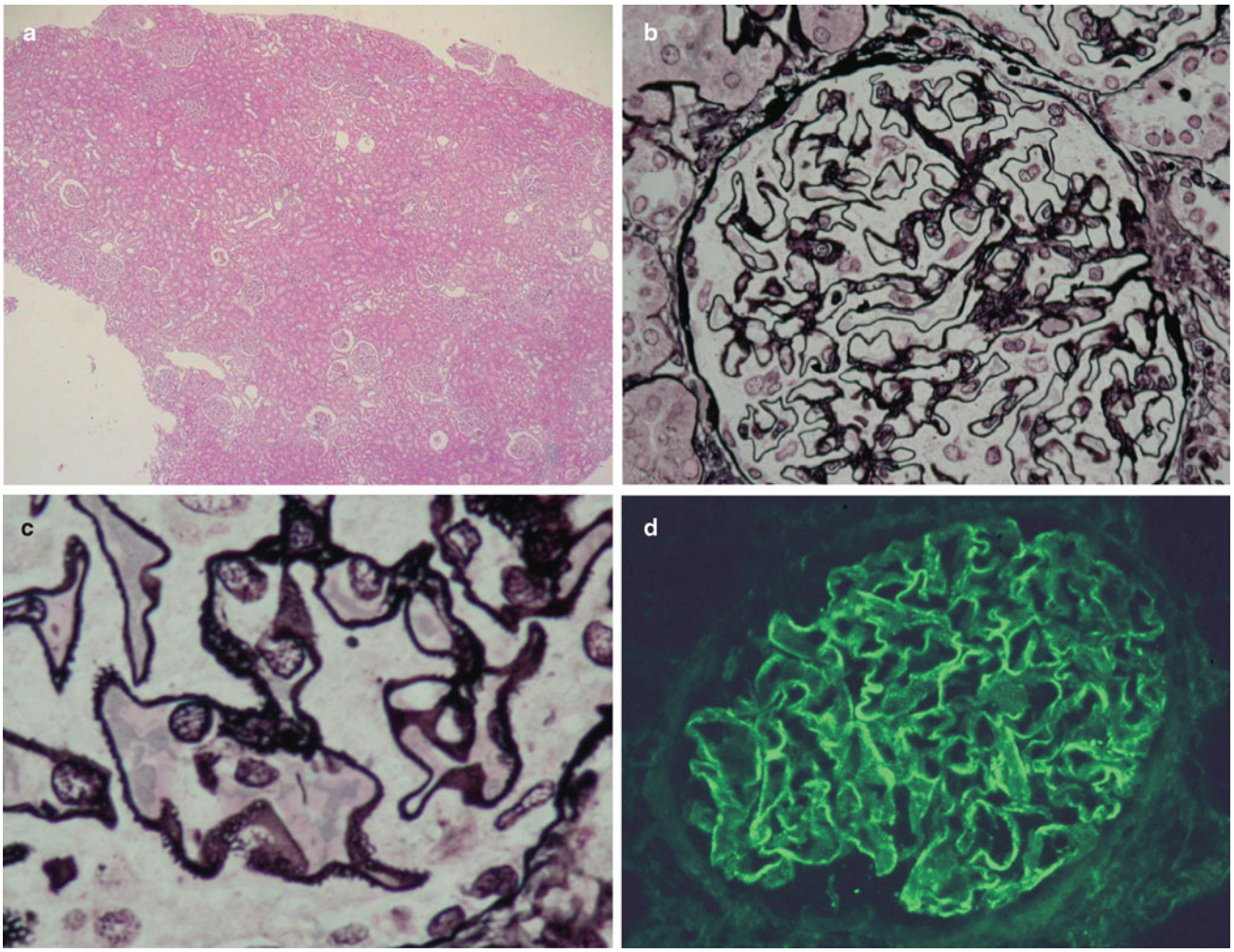

Fig. 32.5 Biopsy findings of the kidney. (**a**) On HE staining, cell infiltration of the interstitium is not found. (**b, c**) On PAM staining a spiked and stippled pattern is seen. (**d**) Immunofluorescence method shows granular deposition of IgG along the capillary wall

reactive follicular hyperplasia (lymph node); (2) reactive hepatitis; (3) chronic pancreatitis; and (4) idiopathic MN. Findings within the lymph nodes, liver, and pancreas were considered to represent a state of hyperimmune reactivity, but no precipitating factor such as drug allergy, autoimmune disease, or malignant neoplasm could be identified. The ultimate cause of the patient's presentation remained unclear at that time.

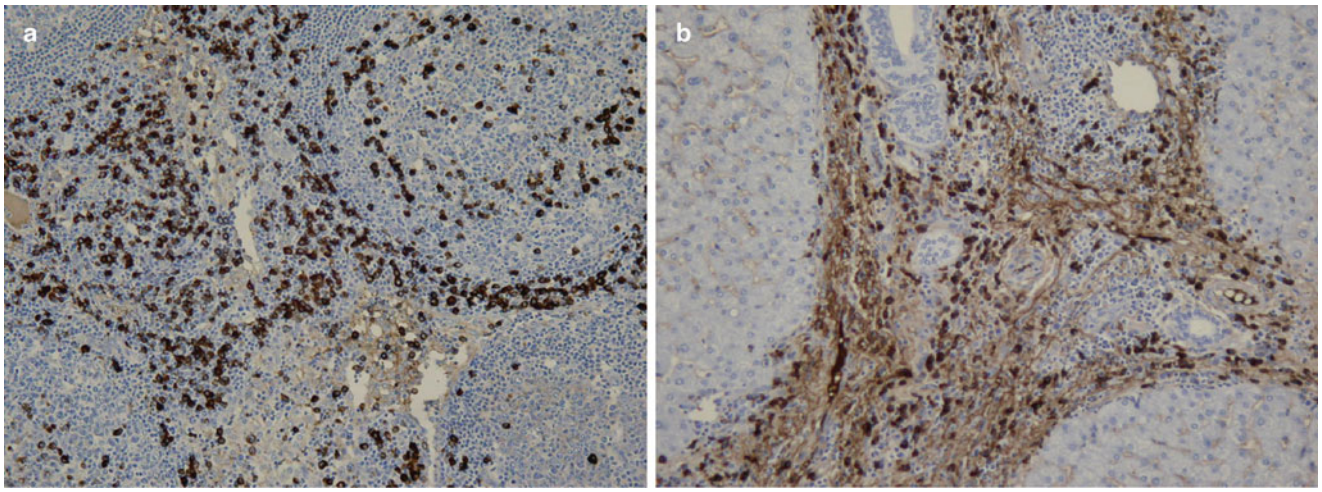

Fig. 32.6 IgG4-positive plasmacytic cell infiltration. (**a**) IgG4-positive plasmacytic cell infiltration of lymph nodes. (**b**) IgG4-positive plasmacytic cell infiltration of Glisson's capsule. Marked IgG4-positive plasmacytic cell infiltration is found in all tissues

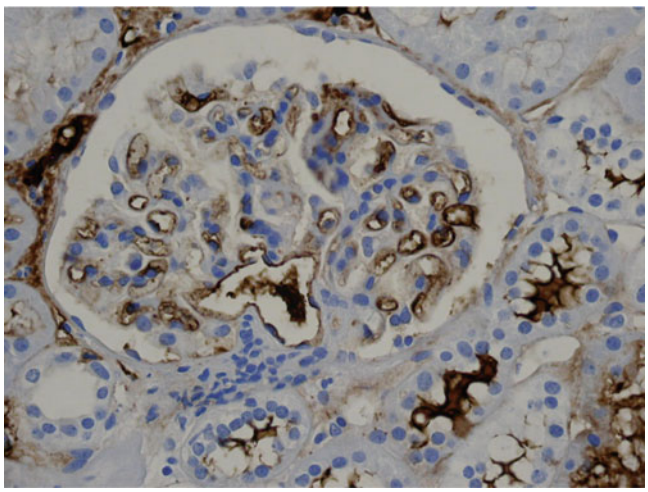

Fig. 32.7 IgG4 staining of glomerular basement membrane. IgG4 deposition is found in the glomerular capillary wall

The patient was treated with prednisolone 40 mg/day, which led to the reduction of edema within a few days. Within one month, the proteinuria also decreased, and the submandibular gland swelling subsided.

In 2008, an assay for IgG4 on the patient's stored serum showed an elevated value of 1,180 mg/dL. Biopsy tissue obtained in 1986 was again immunostained and revealed copious infiltration of IgG4-positive plasmacytic cells in the lymph nodes, liver, and pancreas, suggesting IgG4-RD (Fig. 32.6). Since IgG4-positive plasma cell infiltration was seen in various organs other than the kidney, and the serum IgG4 value was elevated, IgG4-RD was diagnosed. In the kidney, the capillary wall was positively stained for IgG4 (Fig. 32.7).

32.3 Discussion

We report a patient with nephrotic syndrome with typical IgG4-related lesions in the pancreas, liver, and lymph nodes. His renal lesion was revealed to be MN with glomerular IgG4 deposition without TIN. TIN and mass-forming lesions are well-recognized manifestations of IgG4-related kidney disease [1], while glomerular lesions are also sometimes seen [2–10]. MN has been the most frequently described [6–10], but membranoproliferative glomerulonephritis and other glomerulopathies have been reported as well. Almost all of these glomerular lesions have been noted to complicate TIN associated with IgG4-positive plasma cell infiltration. To date, we are aware of reports of seven patients in whom IgG4-related MN has occurred in the absence of concomitant TIN [10–12]. In some of these latter cases, proteinuria first appeared during the course of IgG4-RD [10, 11], whereas in the present case, in contrast, the onset of systemic edema with proteinuria led to the detection of systemic IgG4-RD involvement in multiple organs.

Accordingly, when MN associated with elevated serum IgG values and hypocomplementemia is encountered, systemic screening for IgG4-RD should be performed. Systemic lupus erythematosus (SLE) is an important entity in the differential diagnosis.

The IgG subclasses comprising the deposits in the various glomerulonephritides differ in individual cases. Imai et al. reported the involvement of IgG4 and IgG3 in the deposits as immune complexes in idiopathic MN and membranoproliferative glomerulonephritis, respectively [13]. Subsequently, in idiopathic MN, the main IgG deposited in the capillary wall has been shown to be IgG4, and the principal autoantibody associated with idiopathic MN—directed against anti-M-type phospholipase A2 receptor (PLA2R)—is known to be an IgG4

autoantibody [14]. On the other hand, in secondary MN like that seen in SLE, both IgG2 and IgG3 are deposited. Although primary MN and MN associated with IgG4-RD share IgG4-dominant deposits on the glomerular capillary wall, Alexander et al. clearly demonstrated that MN associated with IgG4-RD may be not occasional co-occurrence of primary MN but secondary because immunostaining for anti-phospholipase A2 receptor (PLA2R) antibodies disclosed negative staining for anti-PLA2R in eight patients with MN and IgG4-RD while primary MN controls were anti-PLA2R positive [12].

The high frequency of malignancy noted in the past history of IgG4-RD or during its clinical course has attracted attention recently [15]. The present case experienced colon cancer at the age of 31 years, which is an atypically early age of occurrence for this malignancy. This and the high frequency of similar cases suggest that some etiological relationship may exist between the occurrence of malignancy and that of IgG4-RD, but more such cases will need to be collected and analyzed before the etiological significance of malignancy in IgG4-RD can be clarified.

In the present case, pancreatic biopsy and liver biopsy tissues as well as peritoneal lymph node tissue obtained by laparotomy all showed pathological findings consistent with IgG4-RD, but since at the time of the initial diagnosis the disease concept of IgG4-RD had not yet been established, a hyperimmune reactivity state with idiopathic chronic inflammation associated with systemic lymphoproliferation was diagnosed and treated with corticosteroids. In such cases, it is important to meticulously record the past history prior to the establishment of the disease concept of IgG4-RD in diagnosing IgG4-RD.

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IgG4-Related Kidney Disease with Retroperitoneal Fibrosis in a Patient with Diabetes Mellitus

33

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33.1 Case

A 74-year-old Japanese man had a 20-year history of treatment for type 2 diabetes mellitus and hypertension and had suffered from Alzheimer's disease for 12 years. Although detailed data were not available regarding his blood glucose control, he had been treated with insulin for several years at a psychiatric hospital. He had been referred to a medical clinic 3 years earlier, at which time proteinuria (3+ by qualitative analysis) and decreased renal function (serum creatinine 1.34 mg/dL) had been noted. A diagnosis of diabetic nephropathy was rendered and the patient was treated with ACE inhibitors, angiotensin II receptor blockers, and insulin. Over the ensuing three-year period, the serum creatinine level rose gradually from 1.34 to 1.75 mg/dL. Although the patient was asymptomatic and his general condition was unchanged, the pace of his renal dysfunction then quickened, with a rise in the serum creatinine from 1.75 to 3.44 mg/dL (over a 3-month period). The patient was referred to our hospital under a suspicion of exacerbation of diabetic nephropathy.

On physical examination, the patient was obese, afebrile, and had a blood pressure of 140/60 mmHg. Both submandibular glands were palpable and leg edema was evident. Diabetic retinopathy was not seen in the ophthalmic examination. Laboratory findings (Table 33.1) showed mild anemia, mild eosinophilia, hypergammaglobulinemia, hypocomplementemia, and renal dysfunction (serum creatinine 4.22 mg/dL) with massive proteinuria and mild hematuria. The levels of serum IgG and IgG4 were markedly elevated at 4,305 and 1,370 mg/dL, respectively. Although antinuclear antibody (ANA) was positive, anti-DNA antibody was not elevated. Cryoglobulin, antineutrophil cytoplasmic antibody (ANCA), and M-protein were not detected.

A computed tomography (CT) examination showed right hydronephrosis, soft tissue-density lesions around the abdominal aorta as well as both iliac arteries and the right ureter (Fig. 33.1a), a smooth pancreatic tail contour, and bilateral pulmonary consolidation. Gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys, lungs, and the lower abdominal regions. Because of bilateral submandibular gland enlargement, a minor salivary gland (lip) biopsy was performed. This biopsy revealed abundant IgG4+plasma cell infiltration (IgG4+/IgG+plasma cells >40 %) and the patient was diagnosed as having IgG4-related disease (IgG4-RD). Following the placement of ureteral stents, the CT findings of right hydronephrosis improved (Fig. 33.1b).

Despite resolution of the hydronephrosis, the serum creatinine concentration increased to 4.65 mg/dL, prompting a right renal biopsy. The light microscopy specimen contained 8 glomeruli, all of which were globally sclerotic. Diffuse interstitial inflammation of lymphocytes and plasma cells was evident, accompanied by marked fibrosis (Fig. 33.2). Immunohistochemistry demonstrated an IgG4+/IgG+ratio >40 %. The patient was diagnosed as having IgG4-related kidney disease (IgG4-RKD) as well as retroperitoneal fibrosis and treated with prednisolone 30 mg daily (0.6 mg/kg/day). The creatinine level rapidly improved to 2.67 mg/dL one week after the start of treatment, although more intensive insulin therapy became necessary for worsening of blood glucose control. A CT scan repeated 1 month after the initiation of treatment demonstrated diminution in the size of the kidneys, salivary glands, and retroperitoneal soft tissue-density lesions (Fig. 33.1c). Five months after the start of treatment, the serum creatinine level had decreased to 1.50 mg/dL. Proteinuria persisted at the same level (3.5 g/ day).

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Table 33.1 Laboratory data of the present case on admission to our hospital

RBC		327×10^4	/mm^3	AST	16	IU/L	CRP	1.08	mg/dL	(*N*<0.05)
Hb		9.2	g/dL	ALT	11	IU/L	RF	8	IUm/L	(*N*<20)
Ht		29.0	%	ALP	279	IU/L	IgG	4,305	mg/dL	(N: 870–1,700)
WBC		8,500	/mm^3	LDH	189	IU/L	IgG4	1,370	mg/dL	(*N*<105)
	Ba	0	%	TB	0.3	mg/dL	IgA	222	mg/dL	(N: 110–410)
	Eo	7.5		Amy	80	IU/L	IgM	49	mg/dL	(N: 35–220)
	St	4.7		CK	61	IU/L	IgE	416	IU/mL	(*N*<500)
	Seg	54.7		BUN	48.0	mg/dL	C3	44	mg/dL	(N: 65–135)
	Mo	5.7		Cr	4.22	mg/dL	C4	3	mg/dL	(N: 13–35)
	Ly	27.4		UA	6.6	mg/dL	CH50	15	U/mL	(N: 30–45)
Plt		7.9×10^4	/mm^3	TP	8.6	g/dL	ANA	×160	(homo)	
				Alb	40.2	%	aDNA-Ab	8	IU/mL	(*N*<6)
				γ	45.5	%	aSSA-Ab	(−)		
Proteinuria (3±)		3.26	g/day	HbA1c	5.6	%	aSSB-Ab	(−)		
Hematuria (±)							aSm-Ab	(−)		
	RBC	1–4	/HPF				aRNP-Ab	(−)		
24 h	Ccr	11.5	mL/min				MPO-ANCA	(−)		
Urinary β2-microglobulin 295,000 μg/day (*N*: 30–370)							PR3-ANCA	(−)		
							Cryoglobulin	(−)		
							M-protein	(−)		

h hour, *Ccr* creatinine clearance, *N* normal range

33.2 Discussion

Radiological and serological examinations are necessary in cases of chronic kidney disease when acute-on-chronic renal failure ensues. In this patient, CT examination demonstrated right hydronephrosis with retroperitoneal fibrosis. Renal failure associated with retroperitoneal fibrosis is usually caused by urinary tract obstruction [1]. The failure of the patient's renal function to improve after resolution of the hydronephrosis suggested the possibility of parenchymal kidney disease. Although diabetes mellitus was one potential etiology of the renal disease in this patient [2], he had no evidence of diabetic retinopathy and his glycosylated hemoglobin (HbA1c) level was normal, urging a more detailed search for other medical renal disease.

Retroperitoneal fibrosis has now been identified as part of the IgG4-RD spectrum [3, 4]. The patient showed swelling of the bilateral salivary glands, high serum IgG and IgG4 concentrations, hypocomplementemia, and numerous IgG4-positive plasma cells in the minor salivary glands, all features compatible with IgG4-RD [3, 4]. In IgG4-RD, various organ involvement can occur simultaneously, and some IgG4-RKD are associated with IgG4-related retroperitoneal fibrosis [5].

In the present case, the right kidney was slightly atrophic but the left kidney had hypertrophied. Gallium-67 accumulation was observed in both kidneys. Because the specimen was obtained from an atrophic right kidney, all of the glomeruli were globally sclerotic and fibrosis was marked. However, tubulointerstitial nephritis consisting of lymphocytes and plasma cells was also evident and we therefore treated the patient with prednisolone. His renal function rapidly improved with steroid therapy, and the patient avoided progression to end-stage renal disease.

Definitive statements about the etiology of the patient's proteinuria and slowly progressive renal dysfunction before his abrupt decline in kidney function are not possible, unfortunately, because data from the period before the abrupt renal decline are not available. The rapid deterioration of renal function, however, was clearly caused by IgG4-RKD. The patient's renal involvement responded quickly to glucocorticoid therapy, with swift improvement in renal function and a reduction in kidney size.

Because steroid therapy is usually quite effective in IgG4-RD [3, 4], an accurate diagnosis is important. If IgG4-RD had not been suspected, a rapid progression of renal failure in the patient would have been ascribed to exacerbation of diabetic nephropathy. It is necessary to be aware of IgG4-RD in patients with renal failure of unknown etiology, especially when retroperitoneal fibrosis or hypergammaglobulinemia is also present. Furthermore, complications of IgG4-RKD should be borne in mind in patients with retroperitoneal fibrosis, even when they are suspected of having other chronic kidney diseases.

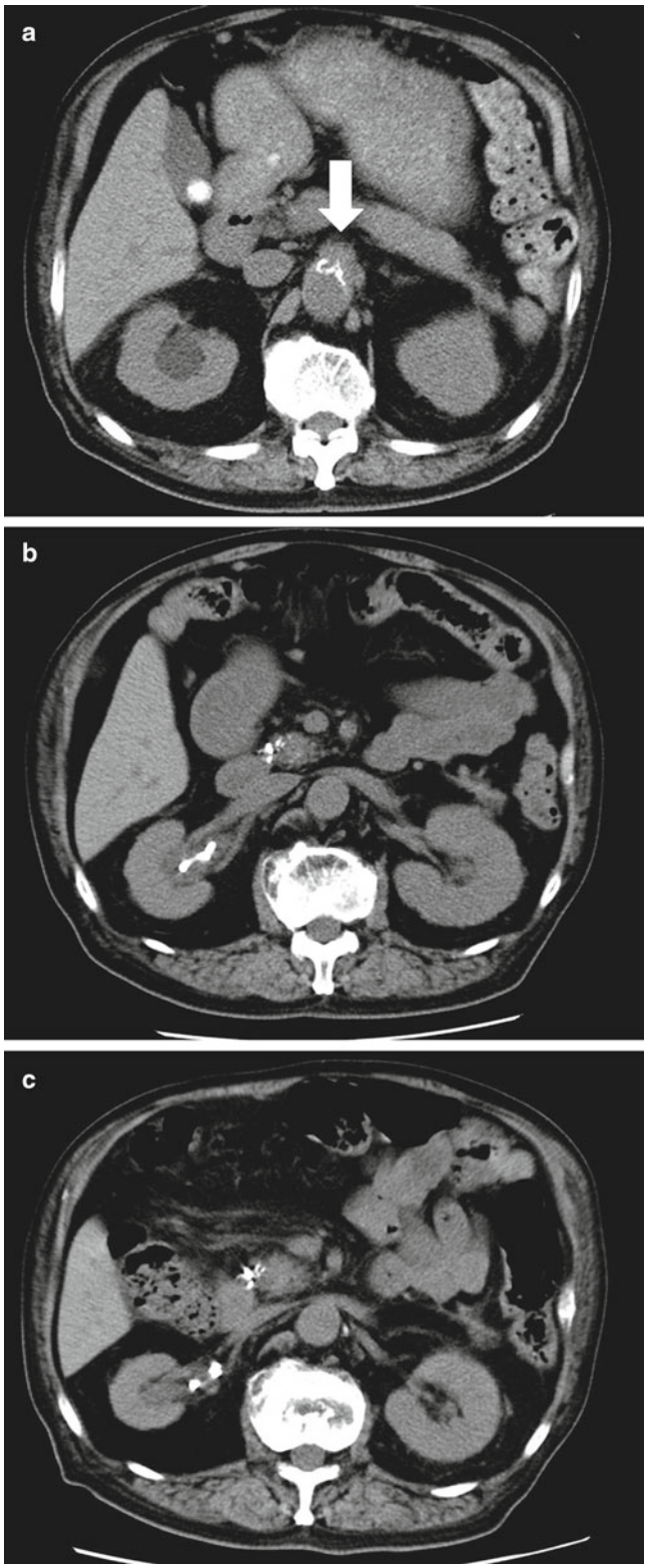

Fig. 33.1 Computed tomography (CT) findings in the patient. (**a**) Right hydronephrosis and soft tissue-density lesions around the abdominal aorta (*arrow*) were observed on admission. (**b**) After ureteral stents were placed, the right hydronephrosis subsided. The left kidney was hypertrophic, whereas the right kidney was slightly atrophic. (**c**) At 1 month after the start of steroid treatment, both kidneys had diminished in size

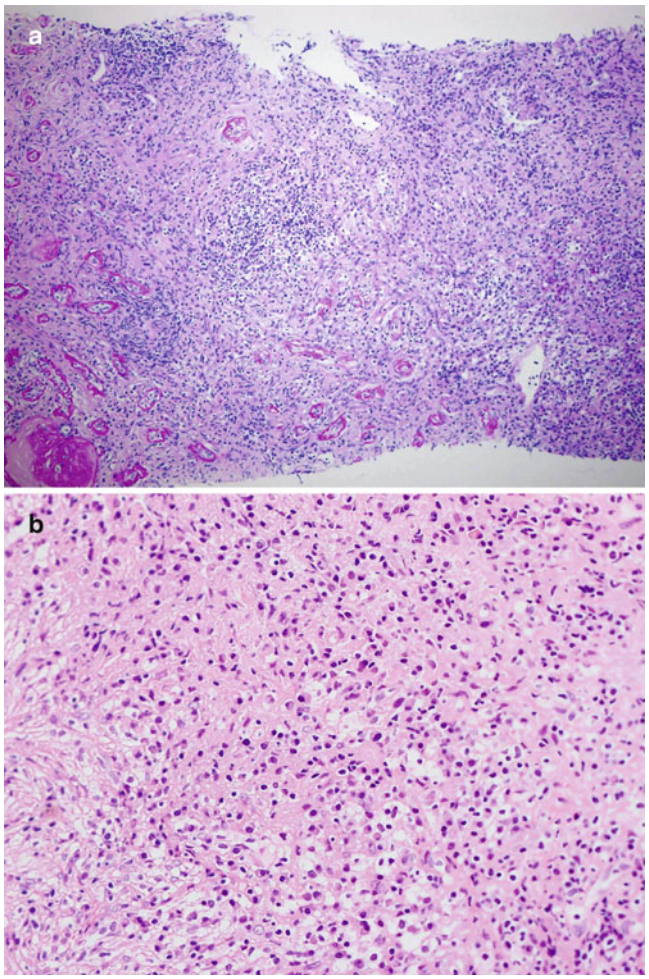

Fig. 33.2 Biopsy of the right kidney showed diffuse renal interstitial inflammation composed of lymphocytes and plasma cells, with fibrosis and tubular atrophy. ((**a**) PAS stain ×100, (**b**) H&E stain ×200)

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