

IgG4-related Sclerosing Disease

A Critical Appraisal of an Evolving Clinicopathologic Entity

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WHAT IS IgG4?

Immunoglobulin G4 (IgG4) is the least common of the 4 subclasses of IgG, namely IgG1, IgG2, IgG3, and IgG4, normally constituting only 3% to 6% of the entire IgG fraction.^{1,2} These subclasses of IgG show more than 95% homology in the amino acid sequences in the constant domains of the heavy chains. Their major differences lie in the composition and structure of the hinge region that has significant effects on the antigen binding and effector functions of the immunoglobulin molecules, resulting in different functional characteristics of each IgG subclass. For instance, IgG4, in contrast to the other IgG subclasses, does not activate complement and has a low affinity for target antigens.³ IgG4 is a T-helper cell 2-dependent isotype. Despite uncertainties about its normal function, IgG4 seems to play a significant role in allergic reactions, such as atopic eczema, bronchial asthma, and bullous skin lesions.⁴⁻⁷ In addition, IgG4 may act as a protective blocking antibody in allergen-induced IgE-mediated effector cell triggering in parasitic infestation.⁸

IgG4 has not attracted the attention of surgical pathologists until recognition of the syndrome of IgG4-related sclerosing disease in recent years, and the saga of this disease began with autoimmune pancreatitis.

THE CONCEPT OF AUTOIMMUNE PANCREATITIS

The concept that some cases of chronic pancreatitis had an autoimmune etiology was first raised by Sarles et al⁹ back in 1961. Yoshida et al¹⁰ subsequently refined the concept and introduced the term "autoimmune pancreatitis." Autoimmune pancreatitis was gradually recognized as a distinct entity, characterized by mass lesion in the pancreas, narrowing of pancreatic duct, painless obstructive jaundice, and favorable response to steroid therapy.

The purported autoimmune etiology was based on the association with various immune-mediated diseases, for example, Sjogren syndrome, sclerosing cholangitis, primary biliary cirrhosis, and inflammatory bowel disease^{11,12}; frequent presence of autoantibodies, for example, antinuclear antibodies (43% to 75%), rheumatoid factor (13% to 30%), anticarbonic anhydrase II (30% to 59%), and antilactoferrin (50% to 76%)¹³⁻¹⁶; and association with HLA DRB1*0405-DQB1*0401 haplotype as shown in 1 Japanese study.¹⁷ Pancreatitis with similar features can be reproduced in thymectomized mice immunized with lactoferrin or carbonic anhydrase II, or in rat administered amylase-sensitized CD4⁺ T lymphocytes.^{18,19}

Meanwhile, various histologic designations have been used by different investigators to emphasize selected aspects of the disease, such as lymphoplasmacytic

Abstract: An elevated serum titer of immunoglobulin G4 (IgG4), the least common (3% to 6%) of the 4 subclasses of IgG, is a surrogate marker for the recently characterized IgG4-related sclerosing disease. The syndrome affects predominantly middle-aged and elderly patients, with male predominance. The patients present with symptoms referable to the involvement of 1 or more sites, usually in the form of mass lesions. The prototype is IgG4-related sclerosing pancreatitis (also known as autoimmune pancreatitis), most commonly presenting as painless obstructive jaundice with or without a pancreatic mass. Other common sites of involvement are the hepatobiliary tract, salivary gland, orbit, and lymph node, but practically any organ-site can be affected, such as retroperitoneum, aorta, mediastinum, soft tissue, skin, central nervous system, breast, kidney, prostate, upper aerodigestive tract, and lung. The patients usually have a good general condition, with no fever or constitutional symptoms. Common laboratory findings include raised serum globulin, IgG, IgG4, and IgE, whereas lactate dehydrogenase is usually not raised. Some patients have low titers of autoantibodies (such as antinuclear antibodies and rheumatoid factor). The disease often shows excellent response to steroid therapy. The natural history is characterized by the development of multiple sites of involvement with time, sometimes after many years. However, the disease can remain localized to 1 site in occasional patients. The main pathologic findings in various extranodal sites include lymphoplasmacytic infiltration, lymphoid follicle formation, sclerosis and obliterative phlebitis, accompanied by atrophy and loss of the specialized structures of the involved tissue (such as secretory acini in pancreas, salivary gland, or lacrimal gland). The relative predominance of the lymphoplasmacytic and sclerotic components results in 3 histologic patterns: pseudolymphomatous, mixed, and sclerosing. Immunostaining shows increased IgG4⁺ cells in the involved tissues (>50 per high-power field, with IgG4/IgG ratio >40%). The lymph nodes show multicentric Castleman disease-like features, reactive follicular hyperplasia, interfollicular expansion, or progressive transformation of germinal centers, with the unifying feature being an increase in IgG4⁺ plasma cells on immunostaining. The nature and pathogenesis of IgG4-related sclerosing disease are still elusive. Occasionally, the disease can be complicated by the development of malignant lymphoma and possibly carcinoma.

Key Words: IgG4-related sclerosing disease, IgG4-related disease, autoimmune pancreatitis, sclerosing cholangitis, inflammatory fibrosclerosing lesion, inflammatory pseudotumor, lymphadenopathy, pseudolymphoma

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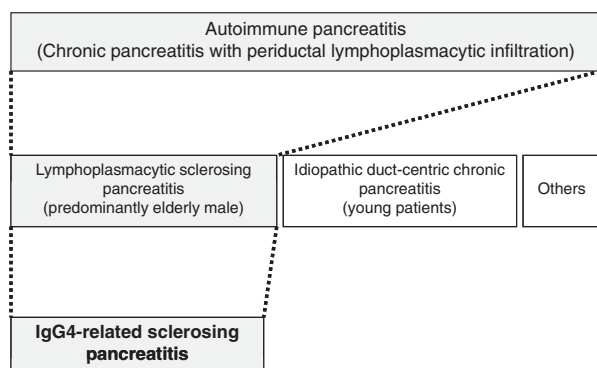


FIGURE 1. Evolution of the concept of IgG4-related sclerosing pancreatitis.

sclerosing pancreatitis,²⁰ nonalcoholic duct-destructive chronic pancreatitis,²¹ chronic sclerosing pancreatitis,²² pseudotumorous pancreatitis,²³ idiopathic-tumefactive chronic pancreatitis,²⁴ and duct-narrowing chronic pancreatitis.²⁵ It also became evident that the condition referred to as autoimmune pancreatitis is heterogeneous, encompassing at least 2 clinicopathologic entities: (1) lymphoplasmacytic sclerosing pancreatitis, and (2) idiopathic duct-centric chronic pancreatitis (Fig. 1).^{12,15,26,27} The former mainly affects elderly men with a mean age of 62 to 63.4 years, is commonly associated with proximal biliary tract, retroperitoneal, renal, and salivary disease, shows elevated serum IgG4 titer (next section), exhibits frequent relapse (47%), and histologically features diffuse dense lymphoplasmacytic infiltrates involving pancreatic lobules and ducts, sclerosis, and obliterative phlebitis. The latter, also known as autoimmune pancreatitis with granulocytic epithelial lesion, mainly affects younger patients with a mean age of 48 years without sex predilection, is associated with inflammatory bowel disease instead, does not usually show elevated serum IgG4 titer, infrequently relapses, and histologically features inflammatory infiltrates (including neutrophils) that are denser in the lobules than interlobular septa, transmural-mixed inflammatory infiltration of ducts, neutrophilic infiltration and destruction of ductal epithelium, and absence of phlebitis. The former type has recently been proposed to be designated type I autoimmune pancreatitis, and the latter type II autoimmune pancreatitis.²⁸

IgG4-RELATED SCLEROSING PANCREATITIS

In 2001, Hamano et al²⁹ reported elevated serum IgG4 (normal < 135 mg/dL) in a specific subtype of sclerosing pancreatitis (another term for autoimmune pancreatitis), but not in patients with pancreatic carcinoma, nonspecific chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Sjogren syndrome and normal individuals. IgG4⁺ plasma cells are also increased in the pancreas in these cases. Histologically, this subtype corresponds to lymphoplasmacytic sclerosing pancreatitis, but not idiopathic duct-centric chronic pancreatitis.^{30–34} All these findings have therefore helped define a distinct subtype of autoimmune pancreatitis, which is most appropriately designated “IgG4-related sclerosing pancreatitis.”

Clinical Features

IgG4-related sclerosing pancreatitis most commonly affects middle-aged and elderly men with a mean age of 59 to 68 years and a male-to-female ratio of 4 to 7.5: 1 (Table 1).^{35–37} The prevalence rate is 2% to 11% among patients with chronic pancreatitis,^{16,36,38} but accounts for 21% to 34% of benign conditions that had undergone pancreatoduodenectomies, reflecting its striking mimicry of pancreatic cancer on clinical and radiologic grounds.^{39,40}

Most patients present with painless obstructive jaundice and/or pancreatic mass. New-onset type II diabetes mellitus and steatorrhea are seen in some cases.^{16,41} However, systemic symptoms, such as fever, weight loss, and generalized malaise are rare. Imaging studies typically show enlargement of the pancreas, predominantly at the pancreatic head, and endoscopic retrograde cholangiopancreatography shows irregular narrowing of the pancreatic duct with or without stenosis of the common bile duct.⁴²

The disease responds well to steroid therapy, although relapses can occur on cessation of treatment. The usual treatment scheme is prednisone 40 mg/d for 4 weeks, tapering by 5 mg every week thereafter.⁴¹ Treatment response is accompanied by a decline in serum IgG4 titer and a reduction in IgG4⁺ cells in the involved tissues. A recent study also reports excellent response to Rituximab, which is postulated to act by depleting the pool of B lymphocytes that replenish short-lived IgG4-secreting plasma cells.⁴³

TABLE 1. Summary of Major Clinical Features of IgG4-related Sclerosing Disease

- A syndrome of unknown etiology
- Age: Mostly middle-aged and elderly
- Sex: Marked male predominance
- Presentation: Symptoms referable to involvement of 1 or more sites, usually in the form of mass lesion
- Commonest sites of involvement: pancreas (autoimmune/IgG4-related sclerosing pancreatitis), hepatobiliary tract, salivary gland, orbit, lymph node (most commonly mediastinal, intraabdominal and axillary)
- Other sites of involvement: practically any organ-site can be affected, such as retroperitoneum, aorta, mediastinum, soft tissue, skin, central nervous system, breast, kidney, prostate, upper aerodigestive tract, lung, thyroid
- Usually good general condition, with no fever or constitutional symptoms
- Common laboratory findings: ↑globulin, ↑IgG, ↑IgG4, ↑IgE, lactate dehydrogenase normal or only slightly raised; may have low titers of various autoantibodies (such as antinuclear antibodies, rheumatoid factor)
- Serum IgG4 titer tends to be higher in patients with multiple sites of involvement, i.e., high disease volume
- Excellent response to steroid therapy, although long-standing lesions with prominent sclerosis may not respond well
- Response to steroid is accompanied by a decline in serum IgG4 titer, and a reduction of lymphoid cells and IgG4⁺ plasma cells in involved tissues
- Clinical course: Additional sites of involvement will often appear with time, sometimes after many years. In rare cases, disease may remain localized to 1 site

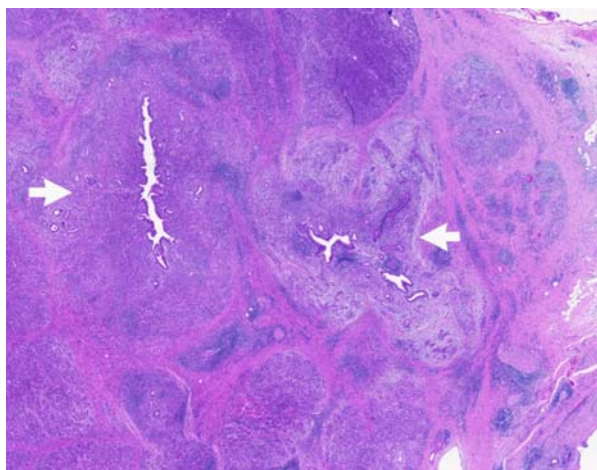


FIGURE 2. IgG4-related sclerosing pancreatitis. The lobular architecture is accentuated owing to sclerosis of the interlobular septa, and the lobules show variable lymphoplasmacytic infiltration. The ducts are conspicuous as a result of the prominent cuffs of inflammatory reaction (arrows).

Morphologic Features

The pancreas is firm with tan-whitish cut surfaces. The histologic triad is: (1) lymphoplasmacytic infiltrate, (2) sclerosis, and (3) obliterative phlebitis, always accompanied by atrophy and destruction of pancreatic acini. However, although the morphologic features are characteristic, they are not entirely specific, and thus a definitive diagnosis requires the demonstration of abundant IgG4⁺ plasma cells.

The lobular architecture of the pancreas is accentuated owing to sclerosis of the interlobular septa (Fig. 2). The extent of involvement varies greatly from lobule to lobule, ranging from no involvement, to moderate atrophy and inflammation, to total replacement by a fibroinflammatory process (Fig. 3). The pancreatic lobules show interstitial infiltration by plasma cells, small lymphocytes, and variable numbers of eosinophils, accompanied by atrophy or loss of acini. The lobular stroma shows variable degrees of sclerosis, which can exhibit a storiform character.^{41,42} There can be prominent edema or myxoid change (Fig. 3C). With time, extensive sclerosis results in loss of the lobular architecture.⁴⁴ The fibroinflammatory process can extend beyond the pancreas. In contrast to other types of chronic pancreatitis, hyperplasia of islets cells is uncommon.

The pancreatic ducts typically stand out owing to the presence of a periductal cuff of chronic inflammatory cells, accompanied by stromal reaction in the form of laminated sclerosis, with or without edema and myxoid change (Fig. 4). The ductal epithelium is not infiltrated by inflammatory cells. Irregular narrowing of the ductal lumen gives rise to the characteristic imaging findings.

Phlebitis, characterized by transmural inflammatory infiltration of the veins, with or without fibrous obliteration of the lumen, is almost always present (Fig. 5A). The arteries that lie adjacent to the veins are consistently spared in striking contrast, and can serve as landmark for identifying the neighboring obliterated veins. Elastic stain may be required to show obliterated veins, manifesting as arrays of interrupted corrugated fibers.

Lymphoid follicles can be present in the stroma. Sometimes fibroinflammatory mass lesions are formed,

which have been called “inflammatory pseudotumor” in the literature.⁴⁵ A feature that has received little attention in the literature is the tendency for the inflammatory cells to form cuffs around nerves (Fig. 5B). Plasma cells and lymphocytes can even infiltrate into the nerves.

Diagnostic Criteria of IgG4-related Sclerosing Pancreatitis

A correct preoperative diagnosis of IgG4-related sclerosing pancreatitis can spare the patient of a major operation for a steroid-responsive disease.⁴⁶ The cut-off number of IgG4⁺ plasma cells has not been standardized currently, but a number greater than 30 per high-power field has been reported to be reasonably specific.^{31–33} A recent study reports diffuse and dense infiltrate of IgG4⁺ cells, numbering more than 50 per high-power field, to be of high specificity (Fig. 3F).⁴⁷ In nonspecific chronic inflammation or pancreatic carcinoma, few scattered IgG4⁺ cells are seen. The number of IgG4⁺ plasma cells is more sensitive and specific than serum IgG4 titer as the latter is not elevated in approximately 30% of cases but in contrast is mildly elevated in 7% to 10% of patients with pancreatic carcinoma.^{41,48–51} Alternatively, the proportion of IgG4⁺/IgG⁺ cells can be used. Using a percentage from 10% to 47%, the sensitivity and specificity for the diagnosis reach 83% to 86% and 95% to 96%, respectively.^{34,52,53}

To aid in diagnosis, pancreatic biopsies are sometimes taken, but false-negative result can occur because the pancreas is often involved in a patchy fashion.⁵⁴ Endoscopic ampullary biopsy can be used as an alternative for diagnosis by display of increased IgG4⁺ cells.^{34,55,56} In most situations, the diagnosis of IgG4-related sclerosing pancreatitis requires a combination of clinical, laboratory, imaging, and histologic features. The diagnostic criteria have undergone several revisions and vary in different countries (Tables 2, 3).^{38,41,42,57–59} Nevertheless, the finding of the appropriate morphology together with a large number of IgG4⁺ plasma cells remains the gold standard of diagnosis. Imaging findings, extrapancreatic organ involvement, and response to steroid may help in establishing the diagnosis if tissue samples are not available.^{41,42,60–62}

IgG4-RELATED SCLEROSING PANCREATITIS IS BUT ONE MANIFESTATION OF THE SYSTEMIC IgG4-RELATED SCLEROSING DISEASE

IgG4-related sclerosing pancreatitis is frequently associated (49% to 80% of cases) with extrapancreatic lesions, and the list of involved organs has continued to grow.^{16,41,48,52,63–70} According to the study by Hamano et al.,⁴⁸ hilar lymphadenopathy occurs in 80.4%, extrapancreatic bile duct lesions in 73.9%, lacrimal and salivary gland lesions in 39.1%, hypothyroidism in 22.2%, and retroperitoneal fibrosis in 12.5%. The various sites of involvement exhibit similar morphologic features, the unifying feature being an abundance of IgG4⁺ plasma cells.^{71–73} Multiorgan involvement over time, with or without the pancreatic lesion, is therefore a characteristic feature of this systemic disease (Table 1).

Extrapancreatic involvement by the disease can explain the earlier reported association of “autoimmune pancreatitis” with other “autoimmune diseases” such as primary sclerosing cholangitis, Sjogren syndrome, and retroperitoneal fibrosis, respectively.^{74,75} That is, the so-called associated conditions merely represent extrapancreatic manifestations of the same systemic disease rather than

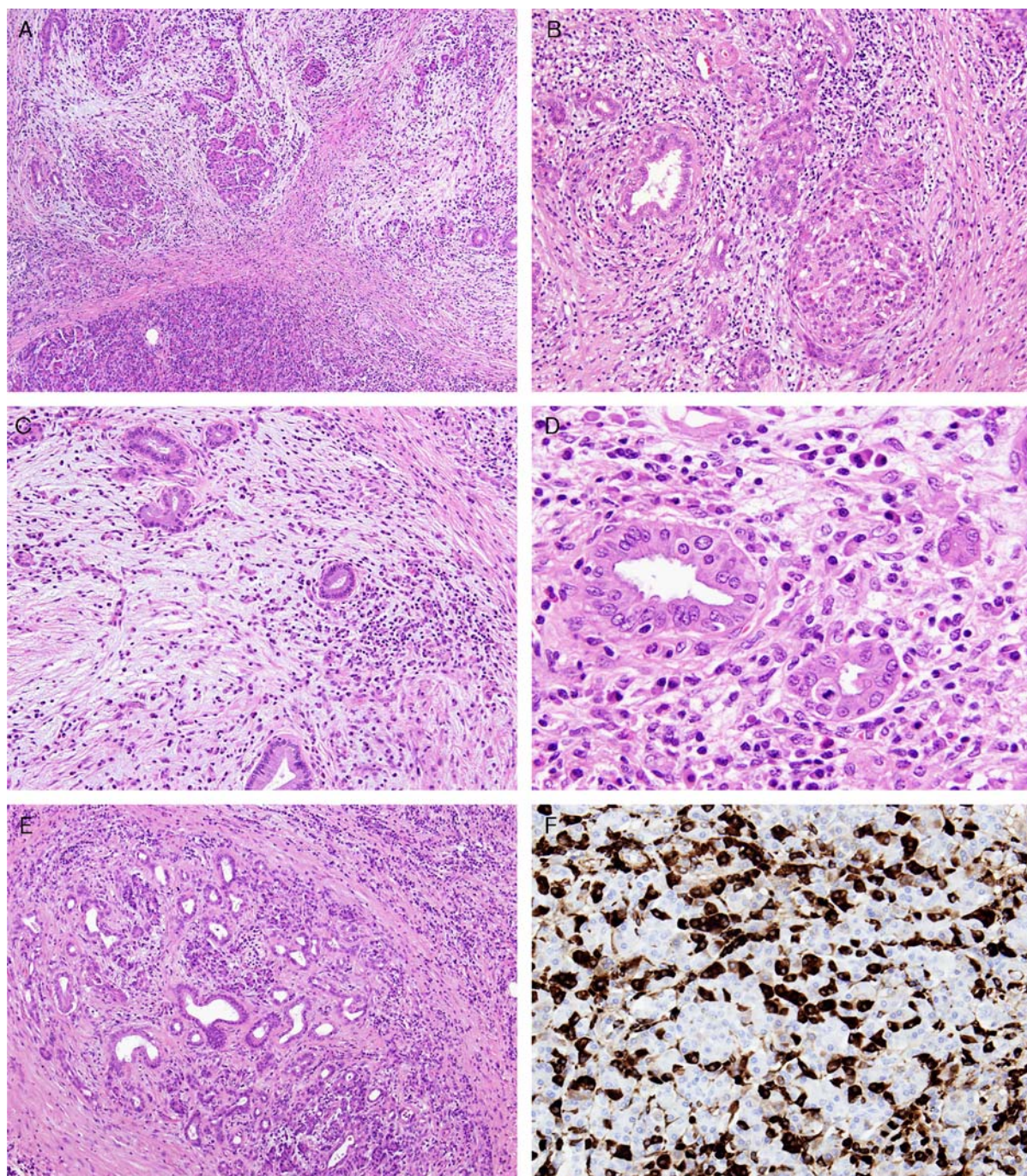


FIGURE 3. IgG4-related sclerosing pancreatitis. A, The different lobules often exhibit different degrees of involvement. The lobules in the upper field are markedly involved, while those in the lower field show only mild involvement. B, The involved lobule shows marked loss of acini, lymphoplasmacytic infiltration, and sclerosis. An islet is seen in this field. C, The inflamed stroma can show myxoid change. D, Acini have disappeared, and residual ductules lie in a fibroinflammatory background. E, A shrunken (atrophic) lobule with fibrosis and relatively mild inflammation, probably representing burned-out phase of the inflammatory process. F, Immunostaining for IgG4 reveals abundant positive plasma cells.

genuine autoimmune diseases.²⁸ These lesions may precede, coexist with, or develop subsequent to the pancreatic lesion, or even occur in the absence of pancreatitis.

Furthermore, increased IgG4⁺ plasma cells can be found in blind biopsies of apparently uninvolved organs,

such as the nasopharyngeal mucosa, gastric mucosa, intestinal mucosa, and bone marrow, lending further support to the systemic nature of the disease.^{67,71,76–78} This syndrome has been variously termed IgG4-related sclerosing disease,⁷⁹ IgG4-related disease,^{60–62,80} IgG4-related

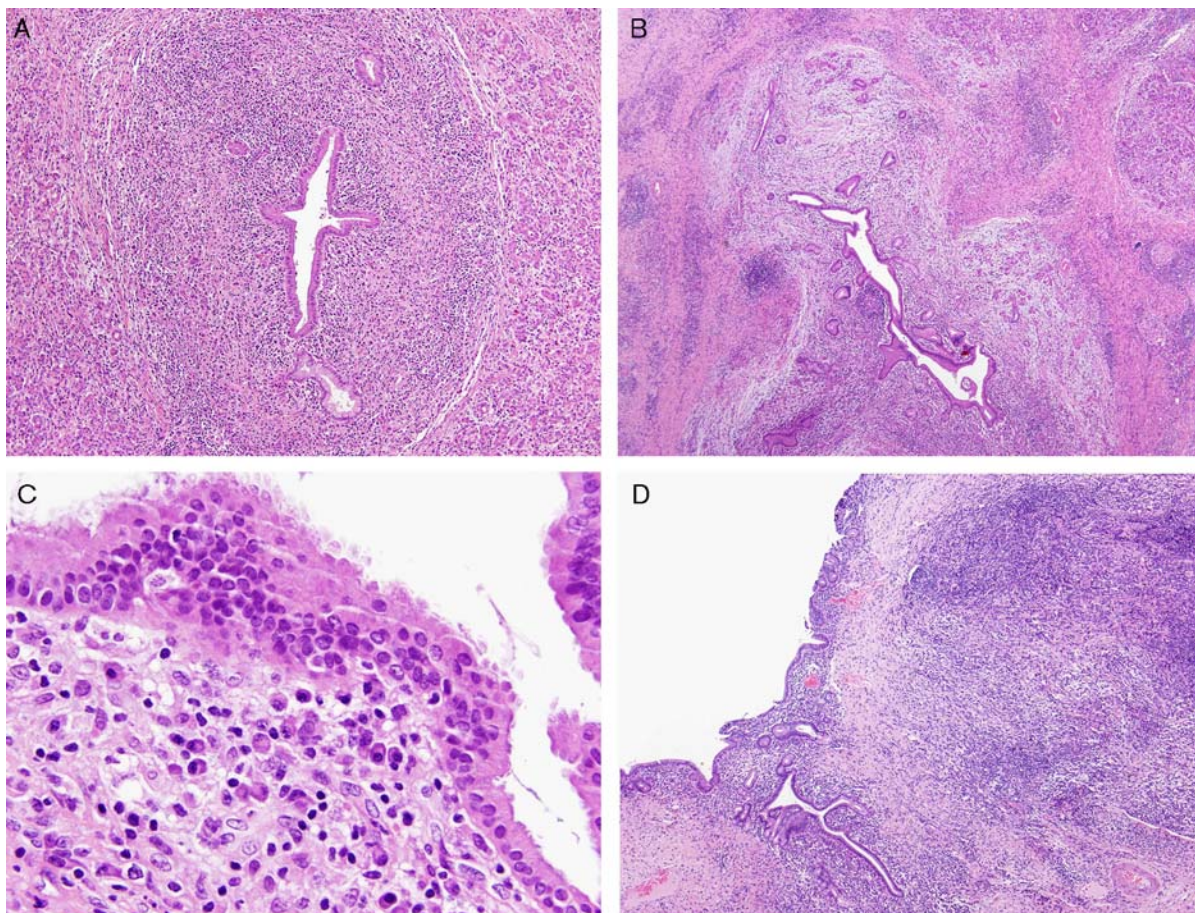


FIGURE 4. IgG4-related sclerosing pancreatitis. A, The small pancreatic duct is surrounded by a dense cuff of inflammatory cells. B, The pancreatic duct is conspicuous by virtue of the cuff of inflammatory reaction with myxoid change. Note narrowing of the ductal lumen. C, The pancreatic ductal epithelium is well preserved, while the stroma is infiltrated by plasma cells and lymphocytes. D, The main pancreatic duct shows transmurular inflammatory cell infiltration and sclerosis, with the inflammatory reaction being more dense away from the lumen.

autoimmune disease,⁷¹ hyper-IgG4 disease,⁸¹ IgG4-related systemic disease,⁴³ and IgG4-related systemic sclerosing disease.⁸² We prefer “IgG4-related sclerosing disease”

because this simple descriptive term reflects the current understanding of the disease without any speculation on the etiology and pathogenesis.

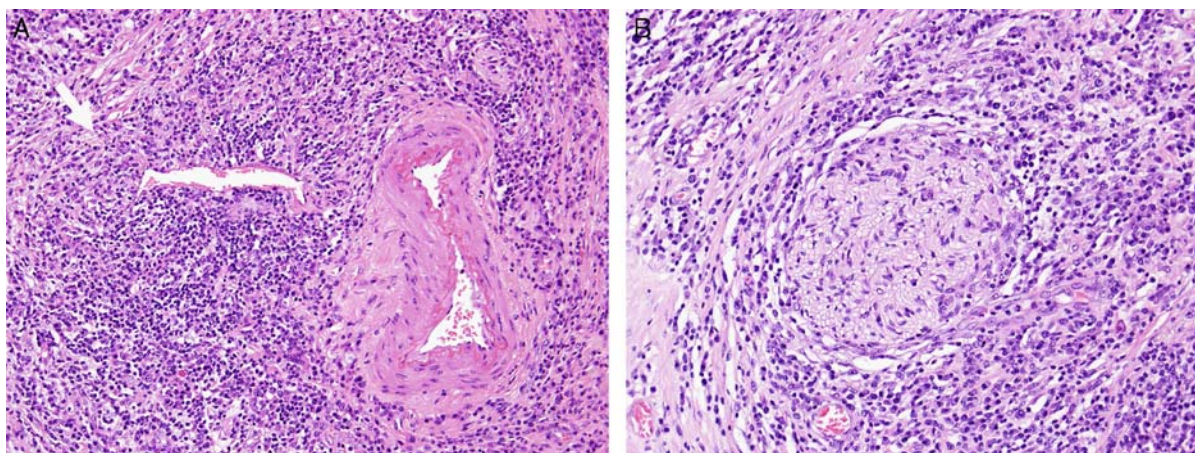


FIGURE 5. IgG4-related sclerosing pancreatitis. A, The vein, which shows heavy mural infiltration by lymphocytes and plasma cells (arrow), lies next to a spared artery. B, Perineural inflammatory cell infiltration is common.

TABLE 2. Asian Diagnostic Criteria (Japan-Korea Consensus) for Autoimmune Pancreatitis (IgG4-related Sclerosing Pancreatitis) (Adapted From Otsuki et al)⁴²

Criterion I—Imaging (both required)
1. Pancreatic parenchyma—diffuse/segmental/focal enlargement of the gland, occasionally with a mass and/or hypoattenuation rim
2. Pancreaticobiliary ducts—diffuse/segmental/focal pancreatic duct narrowing, often with stenosis of bile duct
Criterion II—Serology (1 required)
1. High levels of serum IgG or IgG4
2. Detection of autoantibodies
Criterion III—Histopathology of pancreatic biopsy
Lymphoplasmacytic infiltration with fibrosis and abundant IgG4 ⁺ cells
Criterion IV—Histopathology of resected pancreas
Lymphoplasmacytic sclerosing pancreatitis (storiform fibrosis, lymphoplasmacytic infiltration, periductal inflammation, obliterative phlebitis, numerous IgG4 ⁺ cells)
Optional criterion—Response to steroid therapy
Diagnostic trial of steroid therapy should be conducted only in patients fulfilling criterion I alone with negative work-up results for pancreatobiliary cancer
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled:
1. Criterion I + II
2. Criterion I + III
3. Criterion I + II + III
4. Criterion IV

EXTRAPANCREATIC LESIONS OF IgG4-RELATED SCLEROSING DISEASE: EXTRANODAL SITES

General Morphologic Features

The extranodal lesions of IgG4-related sclerosing disease are usually noncircumscribed, and can extend into the surrounding soft tissues. The histologic triad of lymphoplasmacytic infiltrate, sclerosis, and obliterative phlebitis as seen in IgG4-related sclerosing pancreatitis also applies. The relative proportion of the lymphoplasmacytic infiltrate and sclerosis in an individual case gives rise to a spectrum of histologic patterns: pseudolymphomatous, mixed, and sclerosing (Table 4). These patterns probably represent snap-shots in the temporal evolution of the disease, such that a case may evolve with time from pseudolymphomatous to mixed, and then to sclerosing pattern. In support of this postulation, the pseudolymphomatous pattern is more often observed in lacrimal gland, salivary gland, breast, and skin, sites in which mass lesions are easily palpable or noticed and hence present early.

The pseudolymphomatous pattern is characterized by a tumefactive dense infiltrate of small lymphocytes and plasma cells, which are interspersed with reactive lymphoid follicles and sometimes eosinophils (Fig. 6A). It can be mistaken for lymphoma, especially extranodal marginal zone lymphoma. Features against the latter diagnosis include absence of the following: lymphoepithelial lesions, lymphoid cells reminiscent of monocytoid B-cells, diffuse sheets of CD20⁺ B cells, light chain restriction, aberrant immunophenotype, and clonal immunoglobulin gene rearrangements.

The mixed pattern is the most common, characterized by patchy dense infiltrates of small lymphocytes and plasma cells, accompanied by significant sclerosis. Variable numbers of eosinophils and reactive lymphoid follicles are commonly present.

TABLE 3. Mayo Clinic Diagnostic Criteria for Autoimmune Pancreatitis (IgG4-related Sclerosing Pancreatitis): The HISORT Criteria⁴¹

Criterion H—Histology (at least one of the following)
1. Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis
2. Lymphoplasmacytic infiltrate, storiform fibrosis, abundant IgG4 ⁺ cells (≥ 10 HPF)
Criterion I—Imaging of pancreas
1. Typical—diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct
2. Others—Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; pancreatitis
Criterion S—Serology
Elevated serum IgG4 (normal: 8-140 mg/dL)
Criterion O—Other organ involvement (can be confirmed by biopsy or resolution/improvement with steroid therapy)
Hilar/intrahepatic biliary strictures; persistent distal biliary stricture; parotid/lacrimal gland involvement; mediastinal lymphadenopathy; retroperitoneal fibrosis
Criterion R—Response to steroid therapy
Resolution or marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled:
1. Criterion H
2. Criterion I + S
3. Strong clinical suspicion of autoimmune pancreatitis (idiopathic pancreatic disease + Criterion S and/or O) + Criterion R

The sclerosing pattern is characterized by a predominantly sclerotic process with poorly defined borders, sometimes with tentacle-like extensions into the surrounding tissues (Fig. 6B). Patchy aggregates of lymphocytes and plasma cells, with or without lymphoid follicles, are scattered in the lesion, and often occur with higher density in the peripheral than central zone. The sclerotic tissue shows inconspicuous fibroblasts, and can be lightly sprinkled with small lymphocytes and plasma cells. Obliterative phlebitis can often be identified except in small biopsies. The main differential diagnoses are nonspecific inflammation with fibrosis, and sclerosing malignancies (such as nodular sclerosis Hodgkin lymphoma showing obliterative sclerosis, sclerosing large B-cell lymphoma, sclerosing follicular lymphoma, primary or metastatic carcinoma with sclerotic stroma, and paucicellular variant of anaplastic thyroid carcinoma).

The frequency of phlebitis is variable. The veins show segmental or circumferential transmural infiltration by chronic inflammatory cells, and can show luminal occlusion by fibrous tissue (obliterative phlebitis) (Fig. 5A). Obliterated veins can be difficult to recognize without resort to elastic stains.

In the following sections, the morphologic features in common will not be repeated, while only the site-specific features will be emphasized.

Hepatobiliary System

Bile Ducts

Biliary tract involvement (IgG4-related sclerosing cholangitis) is found in 50% to 90% of patients with IgG4-related sclerosing pancreatitis, manifesting as obstructive jaundice or fever.^{20,45,83-89} Rarely, it occurs in

TABLE 4. Morphologic Spectrum of IgG4-related Sclerosing Disease in Extranodal Sites

	Pseudolymphomatous Pattern	Mixed Pattern	Sclerosing Pattern
Lymphoid component	Prominent and dense infiltrate of lymphocytes and plasma cells, often accompanied by interspersed reactive lymphoid follicles	Moderately prominent lymphoplasmacytic infiltrates, often accompanied by scattered reactive lymphoid follicles	Patchy aggregates of lymphocytes and plasma cells, with or without lymphoid follicle formation
Sclerosis	Relatively minor	Obvious, taking the form of broad bands and delicate strands	Sclerotic tissue constitutes the major bulk of the lesion
Phlebitis	Phlebitis uncommonly seen	Variable	Obliterative phlebitis commonly found
Borders of lesion	Circumscribed or ill-defined	Circumscribed or ill-defined	Ill-defined
Sites of disease commonly exhibiting the morphologic pattern	Lacrimal gland, salivary gland, breast, skin	Miscellaneous sites	Retroperitoneum (retroperitoneal fibrosis); mediastinum (mediastinal fibrosis); orbit (orbital inflammatory fibrosclerosing lesion)

the absence of pancreatic lesion. It mainly affects the extrahepatic segment, particularly the intrapancreatic portion, of the bile duct, but the intrahepatic segment can sometimes be involved.⁸⁵ The lesion is often misdiagnosed on clinical and radiologic grounds as hilar cholangiocarcinoma.⁸⁵ The involved bile ducts exhibit transmural lymphoplasmacytic infiltrate with variable numbers of eosinophils, fibrosis, and obliterative phlebitis (Fig. 7). The lumens of the ducts become narrowed as a result of the periductal fibrosis and inflammation. The fibroinflammatory process typically extends to the peribiliary glands and/or the surrounding tissues (Fig. 7B).⁸⁵ Large numbers of IgG4⁺ plasma cells are seen on immunohistochemical staining.

The main differential diagnosis is primary sclerosing cholangitis, a chronic inflammatory process of the biliary tree of unknown etiology showing ductal and periductal dense fibrosis, luminal stenosis, obliteration, and dilatation.⁹⁰ It seems that at least a proportion of cases reported as such represent IgG4-related sclerosing cholangitis.^{85,87,89,91–94} In a recent series of 127 archival cases of primary sclerosing cholangitis, elevated serum IgG4 is found in 9% of the patients,⁹⁵ and this group of patients also have a lower frequency of inflammatory bowel disease.

Primary sclerosing cholangitis is a progressive disease that requires liver transplantation, whereas IgG4-related sclerosing cholangitis responds favorably to steroid in most cases.^{84,86} These 2 conditions are compared and contrasted in Table 5.^{88,89,96} Stated simply, the inflammatory reaction of primary sclerosing cholangitis tends to be “centripetal” with respect to the ductal lumen, frequently accompanied by degeneration and destruction of biliary epithelium, whereas that of IgG4-related cholangitis tends to be “centrifugal,” not uncommonly accompanied by mini-fibroinflammatory nodules.

Gall Bladder

Involvement of the gall bladder, manifesting as diffuse acalculous cholecystitis, is found in up to 25% of patients with IgG4-related sclerosing pancreatitis.⁹⁷ Concurrent IgG4-related sclerosing cholangitis is common. In contrast with the nonspecific acalculous diffuse cholecystitis, which is seen occasionally in patients with primary sclerosing cholangitis, pancreatic carcinoma, and bile duct stones,⁹⁸ IgG4-related cholecystitis shows predominant extramural involvement and subserosal inflammatory nodules (Fig. 8).⁵³ That is, the inflammatory reaction tends to be bottom-heavy.

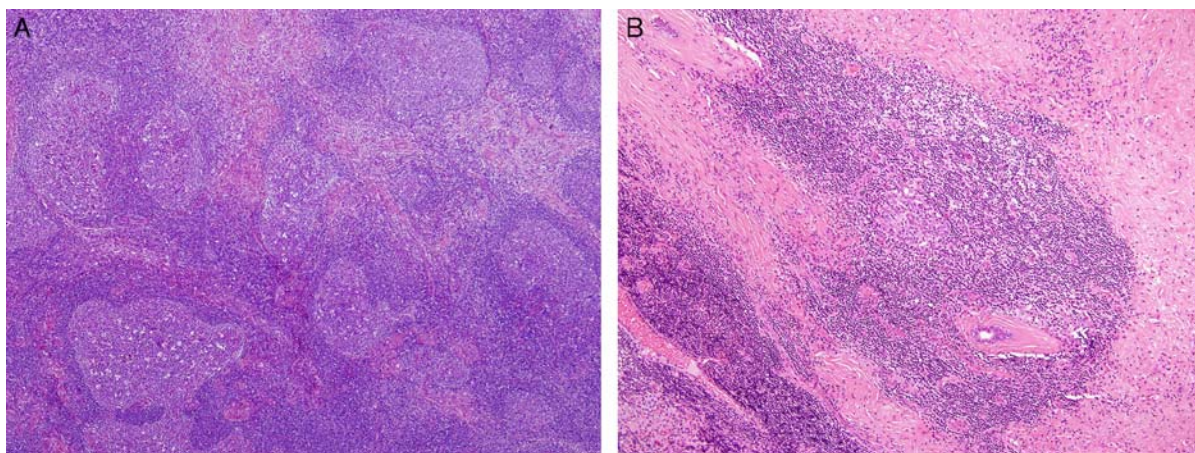


FIGURE 6. IgG4-related sclerosing dacryoadenitis. A, A pseudolymphomatous example characterized by a dense lymphoid infiltrate with lymphoid follicle formation. B, A sclerosing example with effaced normal architecture. The residual duct in the right lower field provides the only evidence of a preexisting lacrimal gland.

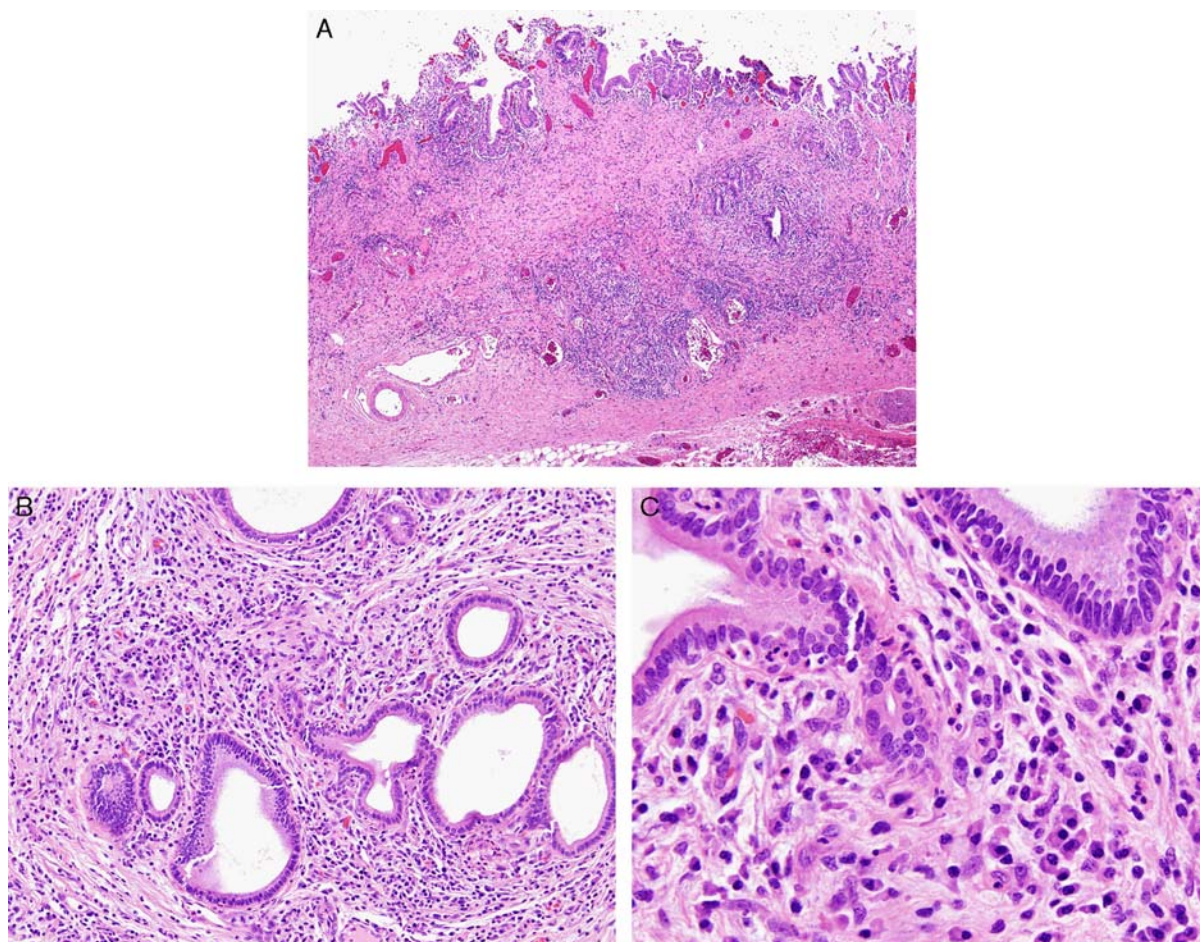


FIGURE 7. IgG4-related sclerosing cholangitis involving common bile duct. A, The common bile duct shows sclerosis and transmural inflammatory infiltration with a bottom-heavy pattern. B, The peribiliary glands are surrounded by inflammatory cells. C, The surface epithelium is spared, and the stroma is infiltrated by lymphocytes and plasma cells.

Liver

The hepatic manifestation is most frequently in the form of mass lesion designated as “inflammatory pseudotumor” in the literature.^{45,99,100} The lesion usually involves the hepatic hilum and is centered on the bile ducts, featuring lymphoplasmacytic infiltrate, sclerosis, and obliterative phlebitis. Sclerosing cholangitis is almost invariably present. IgG4-related hepatic “inflammatory pseudotumor” likely represents IgG4-related sclerosing cholangitis with exaggerated fibroinflammatory nodule formation (Fig. 9). The lesion differs morphologically from bona fide inflammatory pseudotumor (including inflammatory myofibroblastic tumor) of the liver in the absence of significant spindle cell (myofibroblastic) proliferation, the absence of ALK expression (as found in a proportion of cases of inflammatory myofibroblastic tumors), and the presence of abundant IgG4⁺ plasma cells and phlebitis.^{101,102} It differs from inflammatory pseudotumor-like follicular dendritic cell sarcoma in the lack of atypical spindle cells, follicular dendritic cell markers, and Epstein-Barr virus.¹⁰³

Apart from the mass-forming lesion, hepatic involvement may present with abnormal liver function tests. Five patterns can be seen in the liver biopsies (IgG4-hepatopathy), including portal inflammation with or without interface hepatitis, large bile-duct obstructive features,

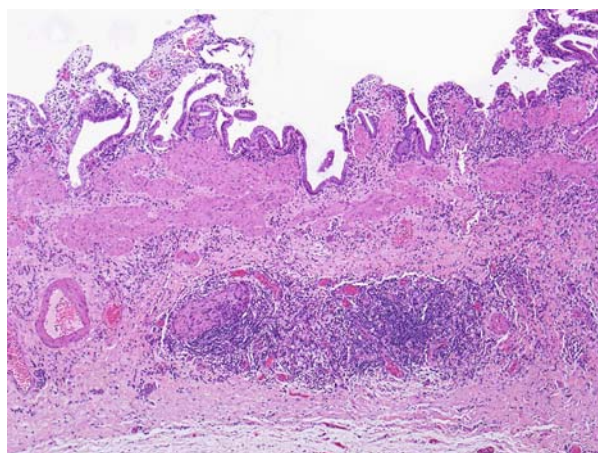
portal sclerosis, lobular hepatitis, and canalicular cholestasis (Fig. 10).¹⁰⁴ The number of IgG4⁺ plasma cells is increased, which is in contrast with autoimmune hepatitis, primary biliary sclerosis, primary sclerosing cholangitis, and chronic viral hepatitis in which only rare IgG4⁺ plasma cells are found.¹⁰⁴ Recently, a case of IgG4-associated autoimmune hepatitis has been described. The female patient presented with chronic hepatitis and cholecystitis with raised serum IgG4 level. The morphologic features of the liver overlapped with those of conventional autoimmune hepatitis except for the presence of many IgG4⁺ plasma cells and the absence of autoantibodies against smooth muscle, double-stranded DNA, and mitochondria.¹⁰⁵

Orbit, Including Lacrimal Glands

The lacrimal glands and the orbital soft tissues are commonly involved by IgG4-related sclerosing disease, and may represent the first manifestation of the syndrome. Interestingly, the conjunctiva is not affected. The patients typically present with unilateral or bilateral, painless orbital swellings of long duration with no significant impairment of visual acuity or keratoconjunctivitis sicca symptoms.^{60,67,106} The clinical findings can be indistinguishable from lymphoma. Although there is usually good response

TABLE 5. Comparison Between IgG4-related Sclerosing Cholangitis and Primary Sclerosing Cholangitis

	IgG4-related Sclerosing Cholangitis	Primary Sclerosing Cholangitis
Nature of disease	A fibroinflammatory condition of unknown etiology, constituting a component of IgG4-related sclerosing disease	Progressive inflammatory destructive lesion of the biliary tree, leading to irregular stenosis of bile ducts. It has been suggested to represent an autoimmune disease
Sex	More marked male predominance (M: F = 4-5: 1)	Male predominance (M: F = 2-3: 1)
Age	Older: middle-aged to elderly (mean age 62-65 y)	Young adult (most commonly 20-50 y)
Clinical presentation	Most present with obstructive jaundice; some may also have weight loss, abdominal pain, or steatorrhea	Commonly asymptomatic, being incidentally found to have raised serum liver enzymes, especially alkaline phosphatase. Occasional patients present with right upper abdominal pain, fever, fatigue, pruritus, and/or obstructive jaundice
Associated diseases	IgG4-related sclerosing pancreatitis (92-100% of cases) and/or other components of IgG4-related sclerosing disease	Ulcerative colitis (70% of cases)
Serum IgG4 titer	Elevated in most cases	Not elevated in most cases
Pattern of bile duct involvement	Extrahepatic bile duct involvement alone in ~50%; extrahepatic and intrahepatic bile duct involvement in ~40%; sole involvement of intrahepatic bile ducts in 8%	Usually involves both intrahepatic and extrahepatic bile ducts (~90%), although sole involvement of intrahepatic ducts or extrahepatic ducts can occur
Cholangiographic findings	Longer segments of stricture (> 3 mm), often accompanied by prestenotic dilatation of the bile ducts. Segmental stenosis of pancreatic duct and distal common bile duct is almost always present	Alternating band-like strictures (1-2 mm) and dilated segments of bile ducts result in a beaded appearance. There can be outpouchings resembling diverticula, often protruding between adjacent strictures. In late phase, decreased intrahepatic branching results in a "pruned tree" appearance
Natural history	Good response to steroid therapy, but relapse may occur after steroid withdrawal	Progressive, resulting in biliary cirrhosis and eventually liver failure, requiring liver transplantation
Salient histologic findings	• Extrahepatic bile duct and major intrahepatic ducts: transmural lymphoplasmacytic infiltration and sclerosis, resulting in thickening of wall; bile duct epithelium spared; peribiliary glands always involved; inflammation tends to be more severe toward the adventitial aspect • Portal tract bile ducts: bile duct epithelium spared; portal tract shows variable lymphoplasmacytic infiltration and variable sclerosis (less striking compared with primary sclerosing cholangitis); may be accompanied by miniature fibroinflammatory nodules • Onion-skin type concentric periductal fibrosis is not a feature	• Extrahepatic bile duct: mural fibrosis, often with extension into adventitial fat; nonspecific chronic inflammatory cell infiltrate • Major intrahepatic ducts: dilatation, fibrosis, or fibrous obliteration • Portal tract bile ducts: intact, epithelial degeneration (with or without lymphocyte infiltration), or fibrous scar. "Onion-skin" type periductal fibrosis, found in about half of cases, is characteristic • Variable infiltration of lymphocytes, plasma cells and eosinophils in portal tracts; inflammatory cells may spill over into periportal parenchyma
IgG4 immunohistochemistry	Large numbers of IgG4 ⁺ cells, with high percentage of IgG4 ⁺ /IgG ⁺ cells	Few IgG4 ⁺ cells

**FIGURE 8.** Gall bladder involved by IgG4-related sclerosing disease. Note the characteristic bottom-heavy inflammatory infiltrate.

to steroid therapy, advanced disease may not respond, probably because of nonreversibility of sclerosis. Intraorbital extension may occasionally lead to optic nerve atrophy and blindness.⁶⁷

The morphologic features of lacrimal gland involvement (IgG4-related chronic sclerosing dacryoadenitis) are similar to those of IgG4-related sclerosing disease in other organs, except that obliterative phlebitis is infrequent (see Table 6) (Figs. 6, 11, 12).^{60,67} With time, there is extensive sclerosis and loss of acini, accompanied by a decrease in the inflammatory component. Many a time, no lacrimal acini or ductal structures can be identified in the specimen, rendering it impossible to ascertain whether the lesion represents a burnt-out lacrimal gland or has originated from the orbital soft tissue (Fig. 6B). Lesions centered in the orbital soft tissue tend to show prominent sclerosis (orbital inflammatory fibrosclerosing lesion or so-called inflammatory pseudotumor) (Fig. 13), although occasional cases may show dense lymphoid infiltrate with features of localized lymphoid hyperplasia (pseudolymphomatous pattern).

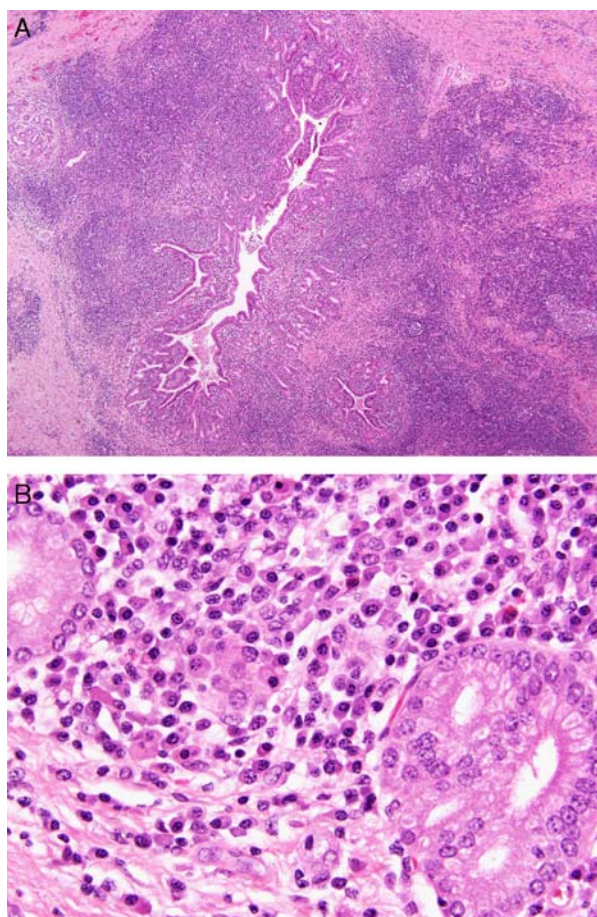


FIGURE 9. Liver involvement by IgG4-related sclerosing disease with fibroinflammatory nodule (so-called inflammatory pseudotumor) formation. A, The nodule is centered on an intrahepatic bile duct, which shows dense inflammatory cell infiltration and sclerosis. The fibroinflammatory process extends centrifugally into the hepatic parenchyma. B, The peribiliary glands are involved by the inflammatory process. Some eosinophils are also seen.

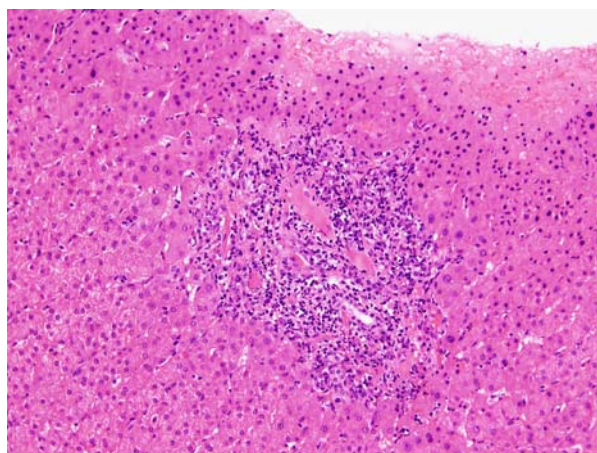


FIGURE 10. Liver involved by IgG4-related sclerosing disease. The portal tract shows heavy infiltration by lymphocytes and plasma cells. The bile duct in the portal tract is intact.

TABLE 6. Morphologic Features of IgG4-related Sclerosing Disease in the Pancreas, Salivary Gland, and Lacrimal Gland

Morphologic features in common

- Sclerosis of interlobular septa, accentuating the lobular architecture
- Interstitial infiltration of lymphocytes and plasma cells, accompanied by variable degrees of sclerosis
- Nonuniform involvement of different lobules
- Atrophy and loss of acini

Morphologic features often prominent in pancreas but not salivary or lacrimal gland

- Thick cuffs of chronic inflammatory cell infiltrate and stromal reaction around ducts
- Stromal edema or myxoid change in some affected lobules
- Phlebitis, often with obliterative features

Morphologic features often prominent in salivary or lacrimal gland but not pancreas

- Reactive lymphoid follicles
- Collagenous sheaths around small ducts

Salivary Gland

The submandibular glands are frequently involved by IgG4-related sclerosing disease, also known as chronic sclerosing sialadenitis or Kuttner tumor, in which patients present with unilateral or bilateral hard masses clinically indistinguishable from a neoplasm.^{52,107–109} Of note, in the submandibular gland, 92% to 100% of chronic sclerosing sialadenitis have been shown to be IgG4-related, while 33% of all cases of nonspecific chronic sialadenitis are found to be IgG4-related.^{52,62,110} It is important to recognize the IgG4-related group because some patients subsequently develop IgG4-related lesions in other sites. The parotid glands are sometimes involved either alone or together with the submandibular glands. The morphologic features of salivary gland involvement are identical to those observed in the lacrimal gland (Table 6) (Fig. 14).

Bilateral lacrimal and salivary glands can be involved simultaneously, in keeping with Mikulicz disease, which is defined clinically as bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands of unknown etiology for more than 3 months.¹¹¹ Unfortunately, Mikulicz disease is often confused in the literature with Sjogren syndrome, a distinct autoimmune disease featuring keratoconjunctivitis sicca, xerostomia, intermittent swelling of the salivary or lacrimal glands, presence of anti-Ro/SSA and anti-La/SSB autoantibodies, and morphologically represented by lymphoepithelial sialadenitis. Mikulicz disease merely denotes a constellation of clinical findings that can be caused by many different conditions, whereas Sjogren syndrome is a distinct disease entity. That is, while Sjogren syndrome may account for a proportion of cases of Mikulicz disease, IgG4-related sclerosing dacryoadenitis/sialadenitis is a major cause of Mikulicz disease.^{112,113}

Retroperitoneum, Mesentery, Mediastinum, and Aorta

Multifocal fibrosclerosis (inflammatory fibrosclerosing lesion) is an intriguing idiopathic syndrome characterized by fibrosis that often involves multiple organ systems, and this entity is often confused in the literature with inflammatory pseudotumor and inflammatory myofibroblastic tumor (Table 7).¹¹⁴ Comings et al¹¹⁵ initially reported retroperitoneal fibrosis, mediastinal fibrosis, Riedel thyroiditis, orbital pseudotumor, and sclerosing

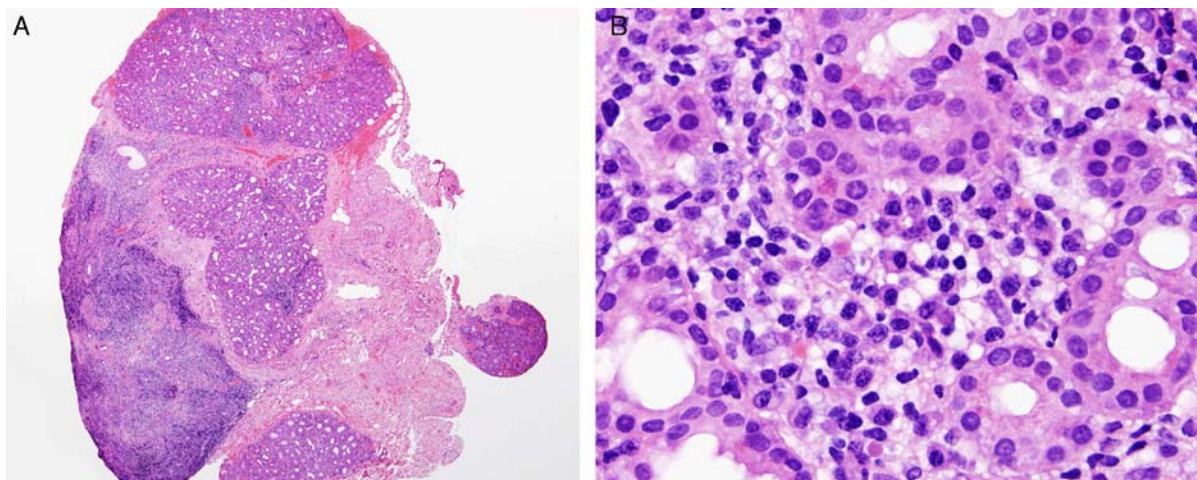


FIGURE 11. IgG4-related sclerosing dacryoadenitis. A, There is variation in the degree of involvement in the different lobules, with the one in the left field being most severely affected. Note also the interlobular sclerosis. B, The lobules show interstitial lymphoplasmacytic infiltration and loss of acini.

cholangitis in 2 members of a family. Subsequently, many cases were reported showing 2 or more of these entities and involvement of the kidney, lacrimal gland, pancreas, small bowel mesentery, meninges, and pelvic mesocolon.^{116–123} All these lesions share the same morphologic features of patchy lymphoplasmacytic infiltrate, sclerosis, and phlebitis (Fig. 15),¹²⁴ essentially identical to those of IgG4-related sclerosing disease. In fact, it has long been known that some cases of inflammatory fibrosclerosing lesion are associated with pancreatitis.^{122,125–127} Thus, it comes as no surprise when a significant proportion of cases of retroperitoneal fibrosis,^{128–130} sclerosing mesenteritis,¹³¹ mediastinal fibrosis,⁶³ and periaortitis and/or inflammatory aortic aneurysm (usually abdominal aorta, rarely aortic arch)^{70,132–137} are recently shown to harbor large numbers of IgG4⁺ plasma cells, and hence represent members of IgG4-related sclerosing disease (Figs. 15, 16). Currently, it is unclear whether the group with no significant increase in IgG4⁺ cells has different etiologies or represents burnt out IgG4-related sclerosing disease.

The response of inflammatory fibrosclerosing lesions to steroid therapy may not be satisfactory,¹³¹ perhaps because steroid is ineffective in reversing advanced fibrosis.

Lung and Pleura

Lung involvement by IgG4-related sclerosing disease may present as asymptomatic incidental finding of lung shadows, cough, blood-stained sputum, hemoptysis, dyspnea, pleural effusion, or chest discomfort.^{65,101,138,139} On imaging, there are solitary or multiple lung nodules, or consolidation with a peribronchial distribution and hilar lymphadenopathy.¹⁴⁰ The clinical course is benign with good response to steroid and/or immunosuppressant.¹⁰¹

Several histologic patterns of pulmonary involvement are recognized: solid nodular, bronchovascular, and alveolar interstitial.¹³⁹ The solid nodular type comprises a peripheral or hilar tumefactive lesion showing sclerosis and lymphoplasmacytic infiltration, and encompasses “inflammatory pseudotumor with IgG4⁺ plasma cells.”⁶⁵

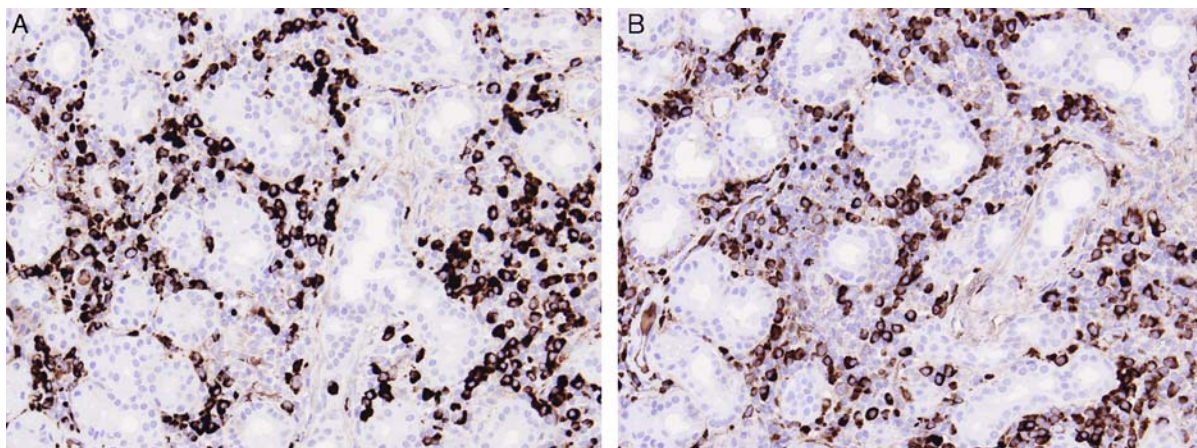


FIGURE 12. IgG4-related sclerosing dacryoadenitis, immunostaining. A, Numerous IgG4⁺ plasma cells are present, with some forming aggregates. B, There is a comparable number of IgG⁺ cells. Thus the IgG4/IgG ratio in this case is 100%.

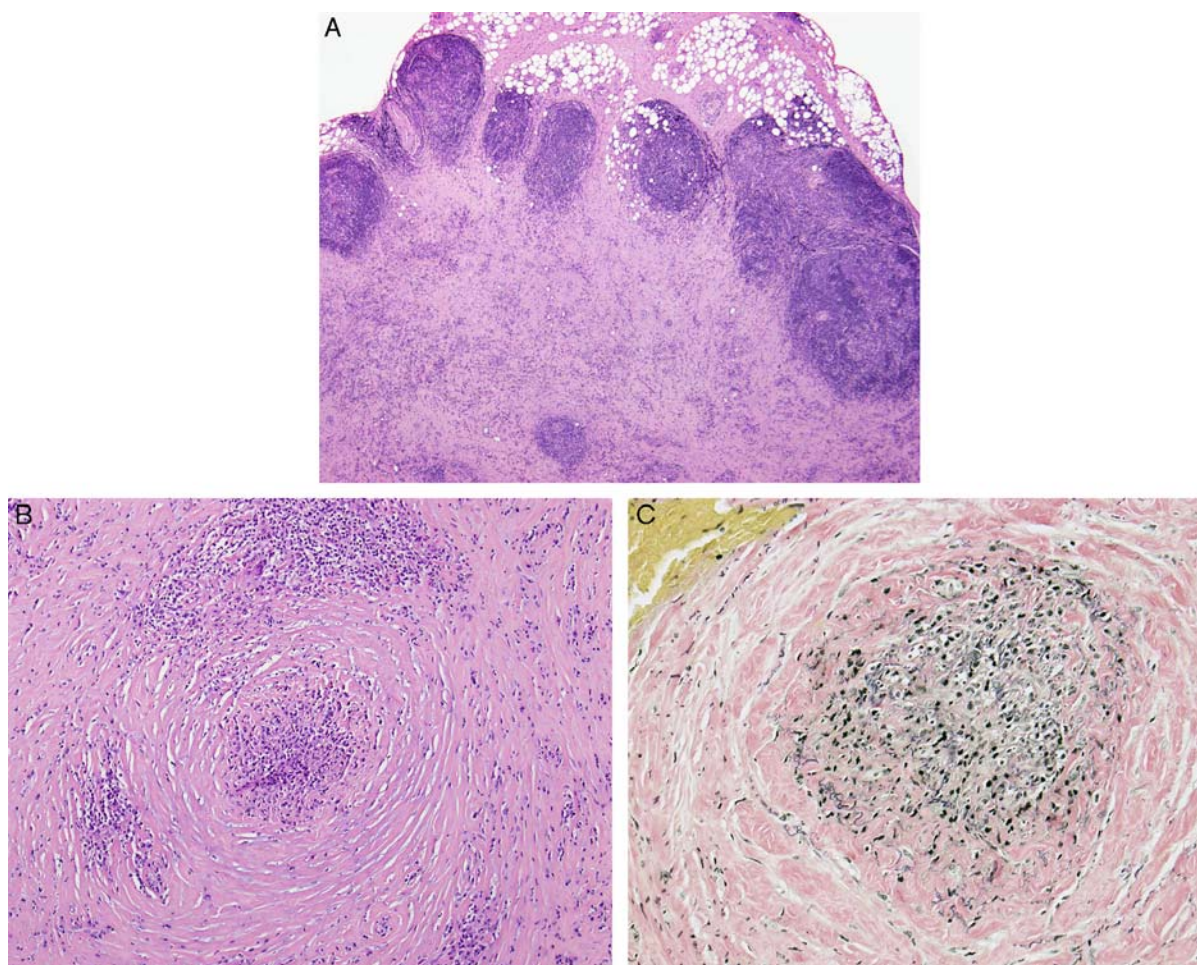


FIGURE 13. IgG4-related sclerosing disease presenting as orbital soft tissue mass. A, The infiltrative lesion is predominantly sclerosing, with lymphoid aggregates concentrated in the peripheral portion (upper field). B, An obliterated vein (obliterative phlebitis) is evident. C, Elastic van Gieson stain highlights the broken residual corrugated elastic fibers of the vein.

The adjacent alveoli show interstitial infiltration of lymphocytes and plasma cells. When the lesion occurs at the pulmonary hilum, there is sclerosing inflammation of the bronchial wall, always accompanied by involvement of the bronchial glands.

The bronchovascular type is characterized by lymphoplasmacytic infiltrate with a lymphangitic distribution, with expansion of the alveolar interstitium, and extension along the bronchovascular bundles, interlobular septa, and pleura (Fig. 17). Lymphatic dilatation with histiocytes showing emperipolesis of lymphocytes can be seen in some cases.¹³⁸

In the alveolar interstitial type, the lymphoplasmacytic infiltrate is confined to the alveolar interstitium, histologically indistinguishable from nonspecific interstitial pneumonia.

Eosinophils are commonly present among the inflammatory infiltrates, and lymphoid follicles are present in about half of the cases. In contrast with other sites of disease where veins are selectively involved, the arteries are also frequently involved and obliterated.^{138,139} The vascular involvement is characterized by endothelialitis, in which lymphoplasmacytic infiltrate in the subendothelium results in narrowing and obliteration of the vascular lumen.

Either the visceral or parietal pleura can be involved, usually in the form of fibrous thickening accompanied by chronic inflammatory cell infiltrate.¹³⁹ Fibrinous exudates can be present.¹³⁸

Breast

IgG4-related sclerosing mastitis can present as single or multiple painless masses in 1 or both breasts, with or without evidence of systemic IgG4-related sclerosing disease.^{66,141} Morphologically it features dense lymphoplasmacytic infiltrates with lymphoid follicle formation, patchy fibrosis, and atrophy of mammary lobules (Fig. 18). Some lymphoid follicles show regressive changes mimicking the follicles seen in hyaline-vascular Castleman disease. Phlebitis is found in some cases. Because of the dense lymphoplasmacytic infiltration, the lesion can be mistaken for lymphoma.

Kidney and Urinary Tract

Renal involvement may present with impaired renal function with or without proteinuria.^{142–145} Imaging studies show ill-defined nodular masses in the kidneys, sometimes leading to nephrectomy for the exclusion of renal malignancy (Fig. 19).¹⁴⁴ The most common morphologic findings

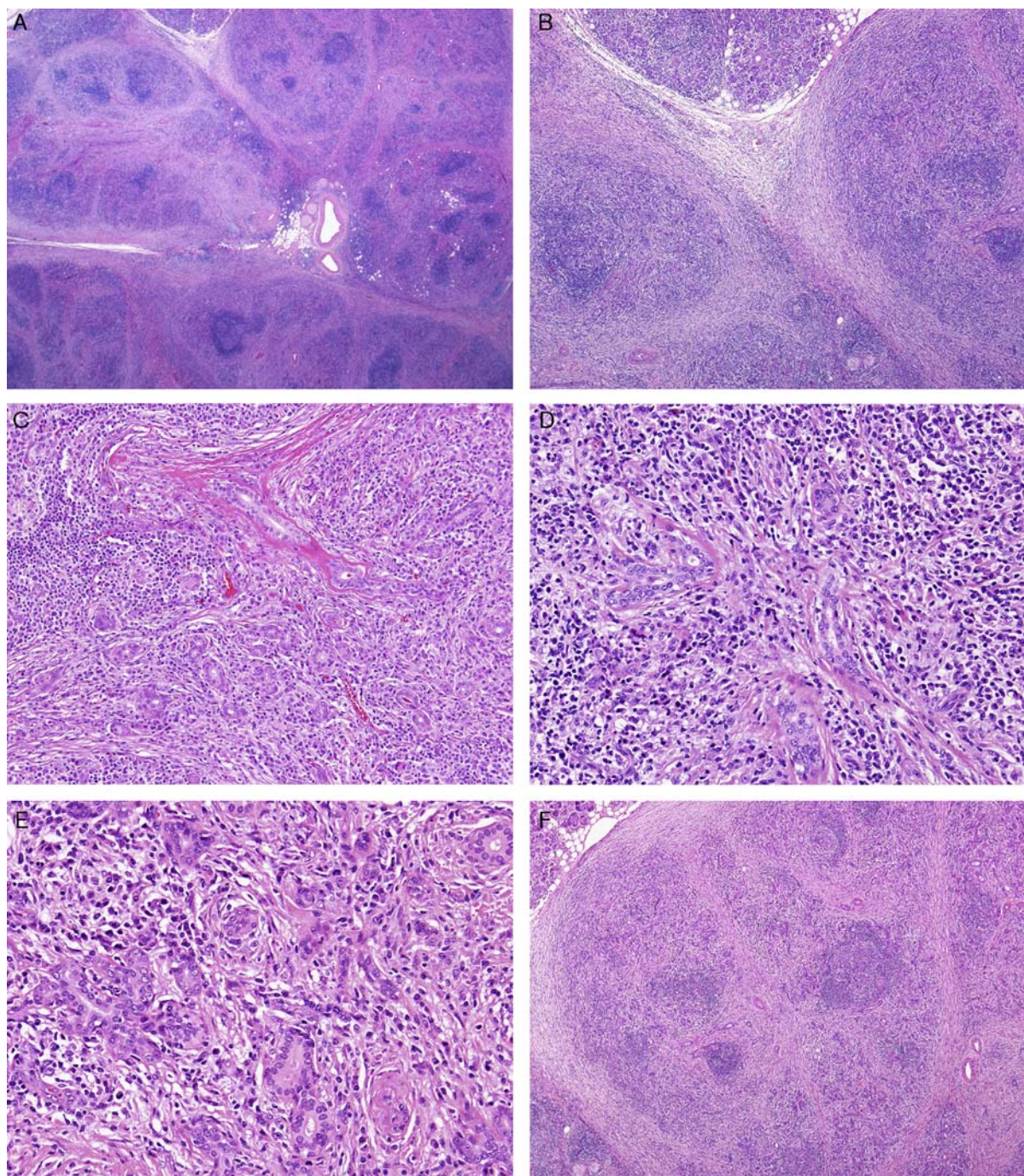


FIGURE 14. IgG4-related chronic sclerosing sialadenitis of submandibular gland. A, Interlobular septa sclerosis results in the accentuation of the lobular architecture. B, The upper lobule shows relatively minor involvement compared with other lobules. C, The lobules show lymphoplasmacytic infiltration, delicate sclerosis, and loss of acini. Periductal sclerosis is a common finding. D, This lobule shows total loss of acini. Only the small ducts remain in the fibroinflammatory background. E, The lobule shows storiform sclerosis and infiltration by plasma cells and lymphocytes. F, Marked sclerosis and destruction of lobules results in a cirrhosis-like picture.

are zonal tubulointerstitial nephritis with IgG4⁺ plasma cell-rich inflammatory infiltrate, fibrosis, and tubular atrophy (Fig. 20). IgG4 electron-dense deposits can be shown in the peritubular basement membrane by electron microscopy. Although the glomeruli are usually spared,

occasional cases can show concurrent membranous nephropathy with subepithelial IgG4 immune complex deposition.^{143,146,147} It is currently uncertain whether the glomerulonephritis component represents part of the IgG4-related nephropathy or merely a coincidental finding. The

TABLE 7. Distinction Between Multifocal Fibrosclerosis (Inflammatory Fibrosclerosing Lesion) and Inflammatory Pseudotumor

	Multifocal Fibrosclerosis	Inflammatory Pseudotumor
Nature of lesion	An inflammatory fibrosclerosing process, with a significant proportion of cases representing IgG4-related sclerosing disease. Typically includes: • Retroperitoneal fibrosis • Mediastinal fibrosis (sclerosing mediastinitis) • Sclerosing (retractile) mesenteritis • Idiopathic cervical fibrosis • Orbital inflammatory fibrosclerotic lesions • Inflammatory periaortitis • Riedel thyroiditis	Many cases are neoplastic (inflammatory myofibroblastic tumor and inflammatory pseudotumor-like follicular dendritic cell sarcoma), some are postinflammatory, reparative or of uncertain nature (inflammatory pseudotumor not otherwise specified), and rare cases are due to infection (such as mycobacterial spindle cell pseudotumor)
Clinical findings	Presenting with mass lesion, and symptoms vary according to site of the disease, for example, ureteric obstruction may occur in retroperitoneal fibrosis	Presenting with mass lesion, occasionally accompanied by systemic inflammatory symptoms
Gross features	Usually a poorly defined mass lesion	A discrete well-defined mass
Salient histologic findings	• The sclerotic lesion merges gradually with the surrounding fibrous tissue, and thus it is often difficult to define the borders (margins) • Patchy lymphoplasmacytic infiltration • Sclerotic stroma, with few spindly fibroblasts and myofibroblasts • Phlebitis	• The lesion is often well delineated from the surrounding; can be circumscribed or infiltrative • Moderate-to-marked lymphoplasmacytic infiltration, often evenly distributed throughout the lesion • Presence of a significant population of spindly cells (myofibroblasts, spindly histiocytes, or neoplastic cells) • Phlebitis usually absent
Immuno-histochemistry	No significant population of actin+ myofibroblasts. IgG4+ plasma cells are increased in a proportion of cases	Variable depending on the nature of the spindly cells • Inflammatory pseudotumor: actin+, cytokeratin⁻/+, ALK⁺/- • Inflammatory pseudotumor-like follicular dendritic cell sarcoma: CD21+, EBER+ • Inflammatory pseudotumor NOS: actin+, cytokeratin⁻/+, ALK⁻, EBER⁻ • Infective type: CD68+, actin⁻/+ • No increase in IgG4+ plasma cells

tubulointerstitial nephritis usually responds to steroid, whereas the response of membranous glomerulonephritis is variable.

IgG4-related chronic sclerosing pyelitis and “inflammatory pseudotumor” of the ureter presenting as hydronephrosis have recently been described.^{148,149}

Skin

Skin involvement can occur as part of systemic manifestation or an isolated lesion in IgG4-related sclerosing disease.^{64,150} The lesions manifest as plaques or nodules most commonly in the head and neck region. Histologically, there is dermal and subcutaneous nodular lymphoid infiltration with follicles formation and stromal fibrosis. The infiltrate is rich in IgG4+ plasma cells, small lymphocytes, and sometimes plasmablasts and eosinophils (Fig. 21). These lesions are traditionally diagnosed as cutaneous pseudolymphomas.

Central Nervous System

Central nervous system involvement is very rare, and the most commonly reported site is the pituitary gland (IgG4-related infundibulo-hypophysitis), usually manifesting with hypopituitarism, diabetes insipidus, and/or local mass effect (such as headache and blurring of vision).^{151–157} There is marked male predominance. Imaging studies show thickening of pituitary stalk and/or pituitary mass. With

steroid therapy, the lesion shrinks remarkably, and hormonal insufficiency may also abate.¹⁵⁶ Some patients have concomitant meningeal involvement in the form of hypertrophic pachymeningitis and parasinusitis, with extension to the sellar and parasellar structures.¹⁵⁶ Histologically, the pituitary shows patchy or extensive interstitial infiltration of lymphocytes and plasma cells, accompanied by loss of pituitary cells (2Fig. 22A). The surrounding meninges, particularly the dura, shows fibrosis and patchy chronic inflammation (Fig. 22B).

A case of dural involvement at the thoracic spinal cord has recently been reported (IgG4-related sclerosing pachymeningitis) (Fig. 23).¹⁵⁸ It is likely that at least a proportion of cases described in the literature as idiopathic hypertrophic pachymeningitis represent this entity, especially those cases associated with multifocal fibrosclerosis (retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, or orbital pseudotumor), an entity now known to belong to the spectrum of IgG4-related sclerosing disease.^{159,160}

In a study of 4 cases of intracranial inflammatory pseudotumor, Lui et al¹⁶¹ reported that 3 cases (1 each occurring in lateral ventricle, frontal lobe, frontotemporal lobe) had increased IgG4+ plasma cells, and therefore suggested that some inflammatory cell-rich inflammatory pseudotumors of the central nervous system represent IgG4-related sclerosing disease. Although the IgG4/IgG

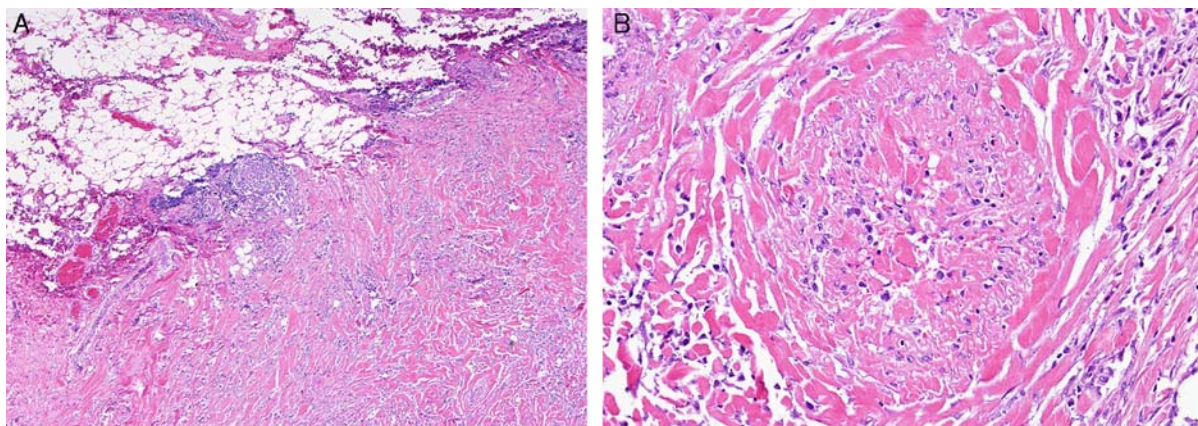


FIGURE 15. IgG4-related mediastinal fibrosis. A, The borders of the sclerotic lesion are infiltrative. B, An obliterated vein is evident in the sclerotic stroma.

ratio is elevated (70% to 80%), the absolute IgG4⁺ cell count (36 to 46 per high-power field) is below 50 per high-power field threshold that we adopt, and the patients have no other manifestations of systemic IgG4-related sclerosing disease. Thus, it is unclear whether these cases represent bona fide examples of this disease.

Thyroid

In patients with autoimmune pancreatitis, 26.8% show biochemical evidence of hypothyroidism, often accompanied by circulating antithyroglobulin antibody.¹⁶² The pathologic basis for this phenomenon has not yet been clarified.

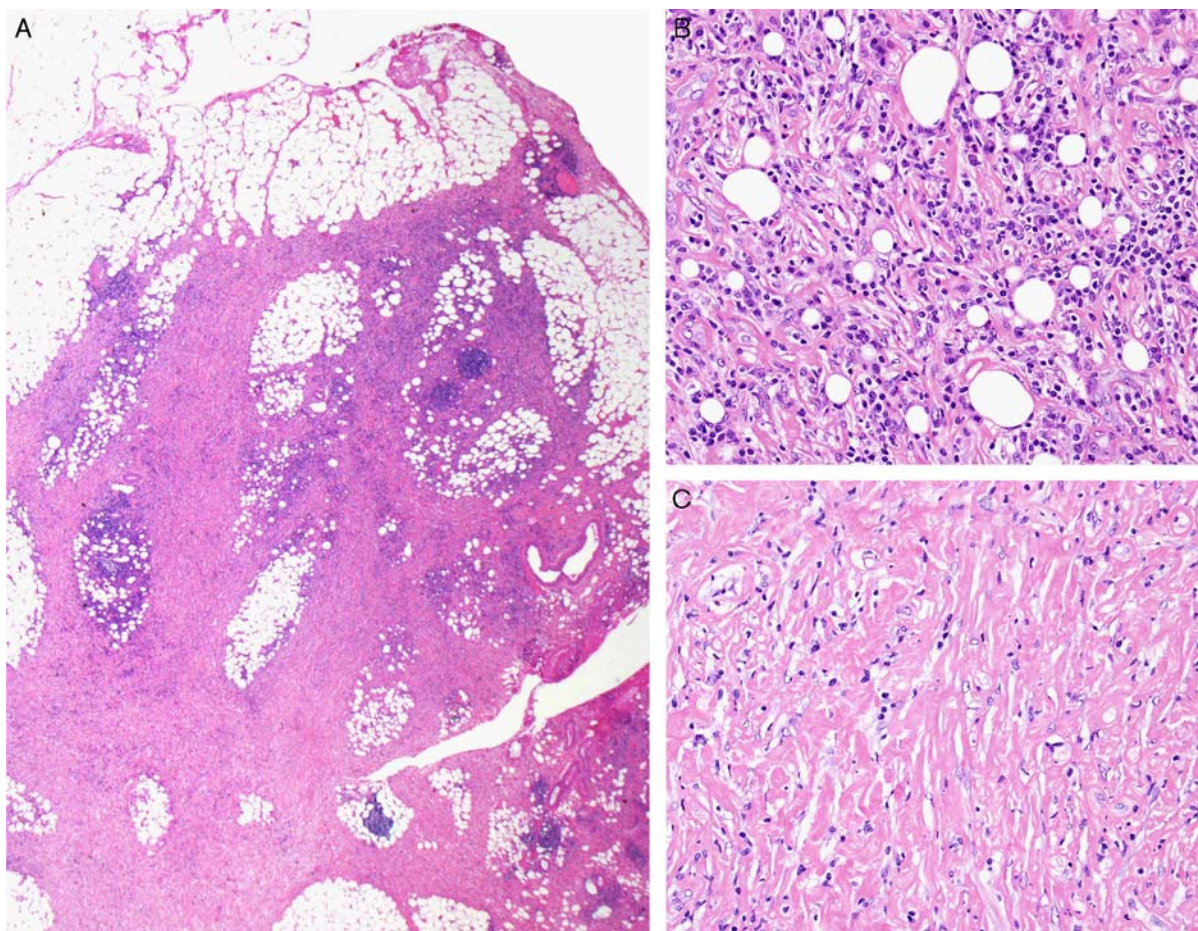


FIGURE 16. IgG4-related retroperitoneal fibrosis. A, The fibroinflammatory process shows infiltrative borders. B, Some foci are richly infiltrated by plasma cells and lymphocytes. C, Most areas are densely sclerotic with only a light sprinkling of chronic inflammatory cells.

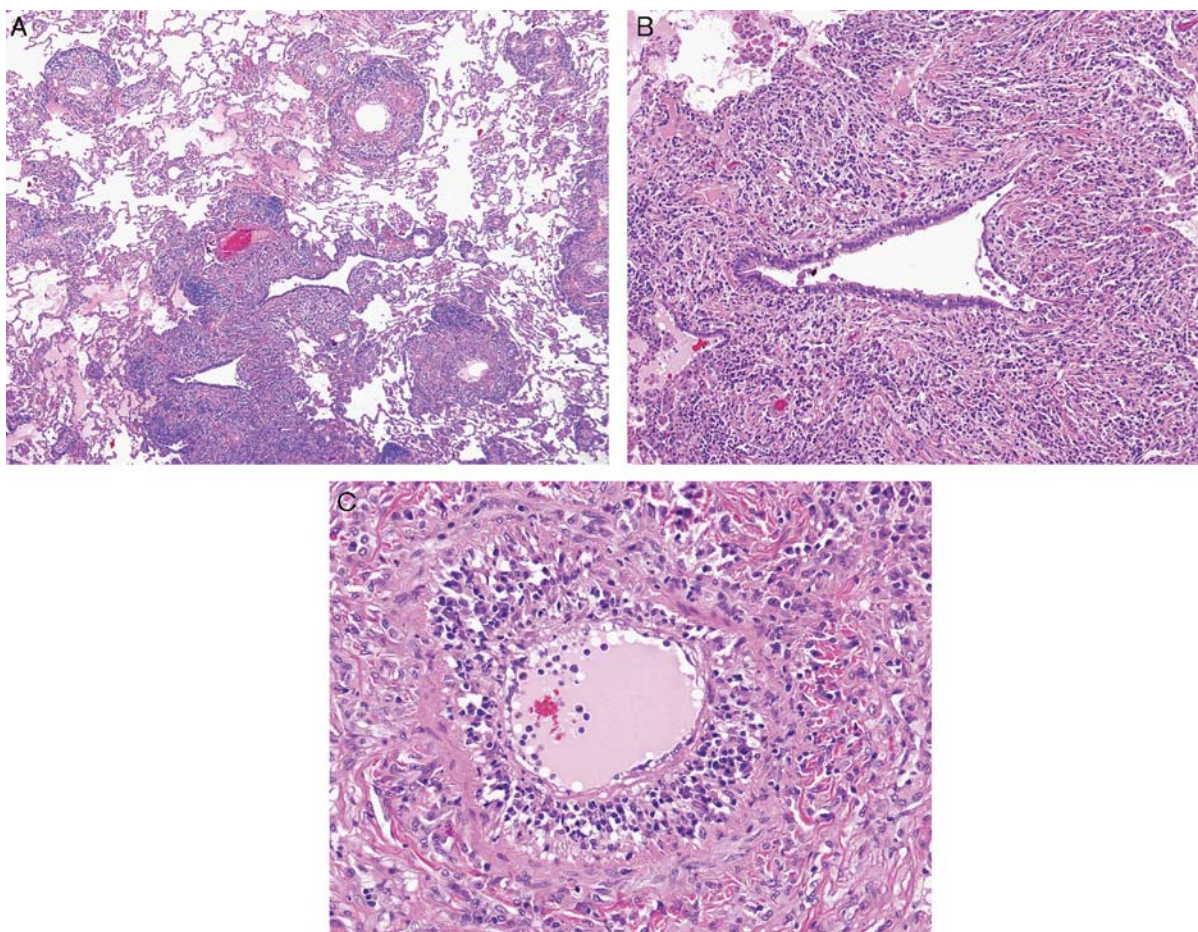


FIGURE 17. Lung involvement by IgG4-related sclerosing disease, bronchovascular type. A, The lymphoplasmacytic infiltrate surrounds the bronchovascular bundles. B, Small bronchus surrounded by a dense cuff of inflammatory cells. C, A pulmonary artery showing lymphoplasmacytic infiltration.

On the basis of immunohistochemistry, Li et al divide 70 cases of Hashimoto thyroiditis into 2 groups: IgG4-related ($n = 19$) and non-IgG4-related ($n = 51$).^{163,164} The former group shows more severe stromal fibrosis, lympho-

plasmacytic infiltration, and thyroid follicular cell degeneration than the latter group. Furthermore, the IgG4-related group is associated with a lower female-to-male ratio, more rapid progress, subclinical hypothyroidism, and higher level

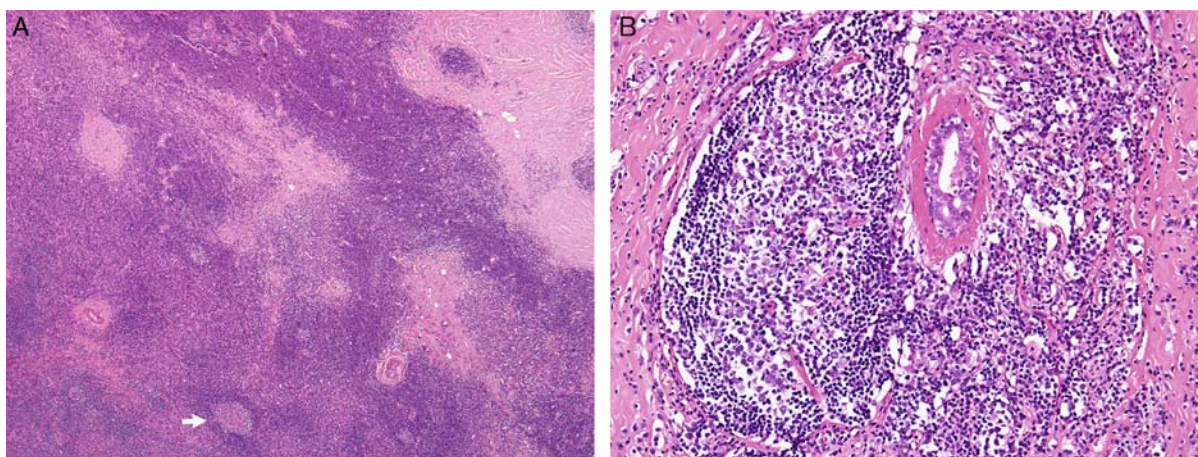


FIGURE 18. IgG4-related sclerosing mastitis. A, The dense lymphoplasmacytic infiltration results in the mimicry of lymphoma. Sclerotic bands are present. Some interspersed lymphoid follicles (arrow) are present. B, A residual terminal duct with periductal sclerosis is identified within the fibroinflammatory process.



FIGURE 19. Computed tomogram of the abdomen, showing kidney involvement by IgG4-related sclerosing disease. Note bilateral hilar lesions extending into the renal parenchyma.

of circulating thyroid autoantibodies. Thus, it seems that hypothyroidism in patients with autoimmune pancreatitis may result from an IgG4-related thyroiditis masquerading as Hashimoto thyroiditis.

Riedel thyroiditis, a vanishingly rare disease, is a known component of multifocal fibrosclerosis.¹⁶⁵ While the latter is shown to represent IgG4-related sclerosing disease in a significant proportion of cases, it has been assumed that Riedel thyroiditis also belongs to this spectrum of disease. However, only lately are immunohistochemical studies available to verify this assumption.^{166,167}

Other Organs

IgG4-related sclerosing disease has been reported to involve the prostate (Fig. 24),^{168–170} seminal vesicles,¹⁷¹ maxillary sinus and nasal septum,¹⁷² paranasal sinus,¹⁷³ and pericardium.¹⁷⁴ We have also encountered examples of cervical soft tissue involvement, consistent with the so-called idiopathic cervical fibrosis (Fig. 25).^{175,176}

It remains to be determined whether the entity described as “autoimmune esophagitis” with increased tissue IgG4⁺ cells, presenting as a mass lesion of the lower esophagus, represents part of the spectrum of IgG4-related sclerosing disease.¹⁷⁷

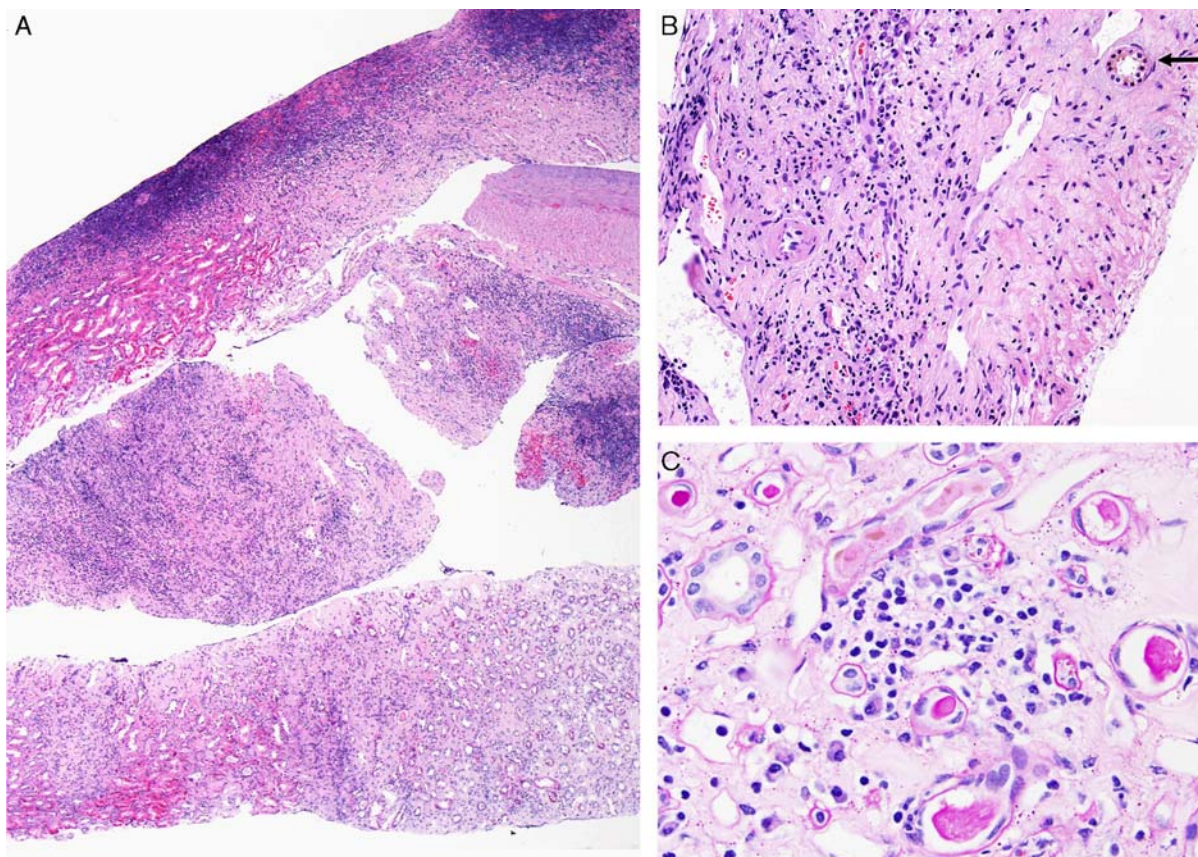


FIGURE 20. Kidney involvement by IgG4-related sclerosing disease (same case as Fig. 19). A, The renal biopsy shows several strips of tissue exhibiting variable degrees of involvement by the fibroinflammatory process. B, In this focus, the renal parenchyma is almost totally replaced by fibroinflammatory process. Only a single residual tubule is seen (arrow). C, The PAS stain shows that the lymphoplasmacytic infiltrate is located in the interstitium. Tubulitis is not evident in this case.

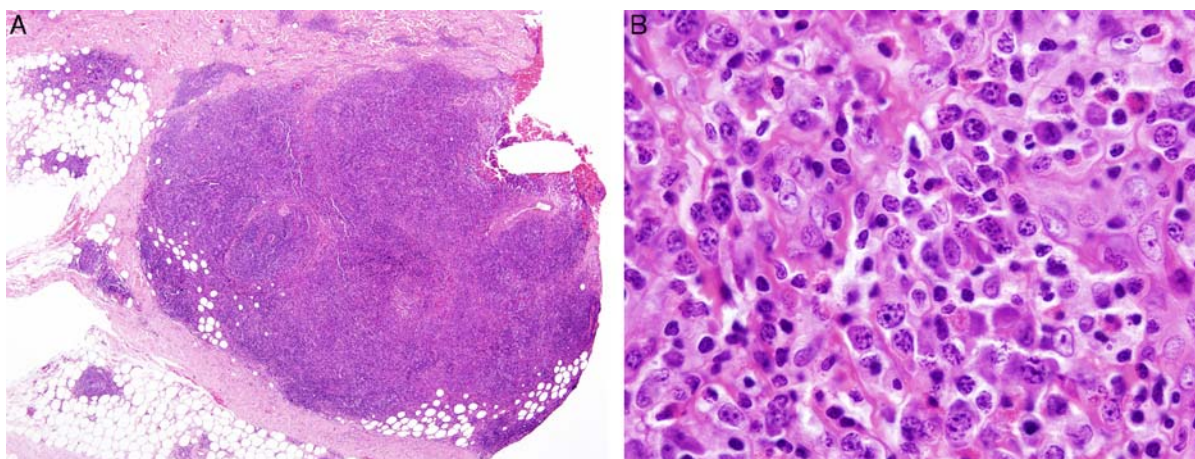


FIGURE 21. Cutaneous involvement by IgG4-related sclerosing disease. A, The pseudolymphomatous pattern results from a dense lymphoplasmacytic infiltrate located in the dermis and subcutis. B, The infiltrate comprises immunoblasts, immature plasma cells, plasma cells, and eosinophils.

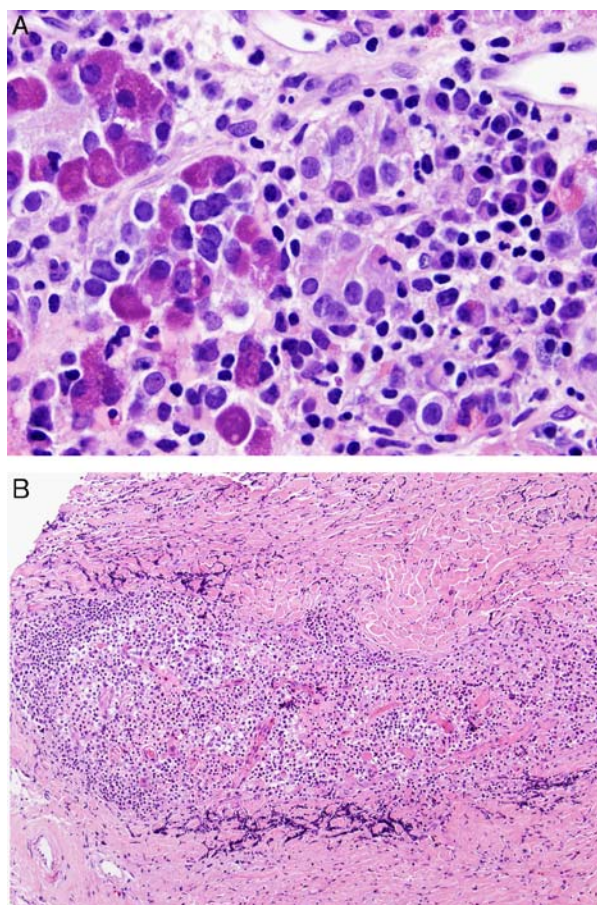


FIGURE 22. Pituitary involvement by IgG4-related sclerosing disease. A, The pituitary gland shows patchy dense infiltration of plasma cells and lymphocytes, accompanied by the loss of anterior pituitary cells. B, The surrounding dura shows sclerosis and patchy lymphoid infiltration with lymphoid follicle formation.

Splenic sclerosing angiomatoid nodular transformation (SANT) shows some features reminiscent of IgG4-related sclerosing disease, such as increased plasma cells and sclerosis.¹⁷⁸ Increased IgG4⁺ plasma cells are found in this lesion,^{179,180} but a relationship with IgG4-related sclerosing disease remains tenuous as other manifestations of the syndrome have so far not been documented in these patients.

EXTRAPANCREATIC LESIONS OF IgG4-RELATED SCLEROSING DISEASE: LYMPH NODE

Clinical Features of IgG4-related Lymphadenopathy

On imaging studies, lymphadenopathy is detected in up to 80% of patients with autoimmune (IgG4-related sclerosing) pancreatitis.⁴⁸ Multiple lymph nodes are usually involved, the commonest being mediastinal, intraabdominal, and axillary.

IgG4-related lymphadenopathy can take several clinical scenarios.^{68,150,181} Asymptomatic enlarged regional lymph nodes can be found in resection specimens (such as pancreas or submandibular gland), or discovered incidentally on imaging of patients with known IgG4-related sclerosing disease. Lymphadenopathy can develop subsequent to a diagnosis of extranodal IgG4-related sclerosing disease. Sometimes lymphadenopathy is the initial presentation of IgG4-related sclerosing disease, and extranodal involvement can be discovered during work-up or on follow-up in some of the patients.

The lymphadenopathy can be asymptomatic or produce mass effects, such as hydronephrosis from compression on the ureter, or lower limb swelling because of venous compression in the pelvic region.⁶⁸

When the lymphadenopathy is generalized, the clinical impression is often that of lymphoma, multicentric Castleman disease, or disseminated malignancy. In contrast with these entities, the lymph nodes are generally not very large (less than 2 cm), constitutional symptoms, such as fever

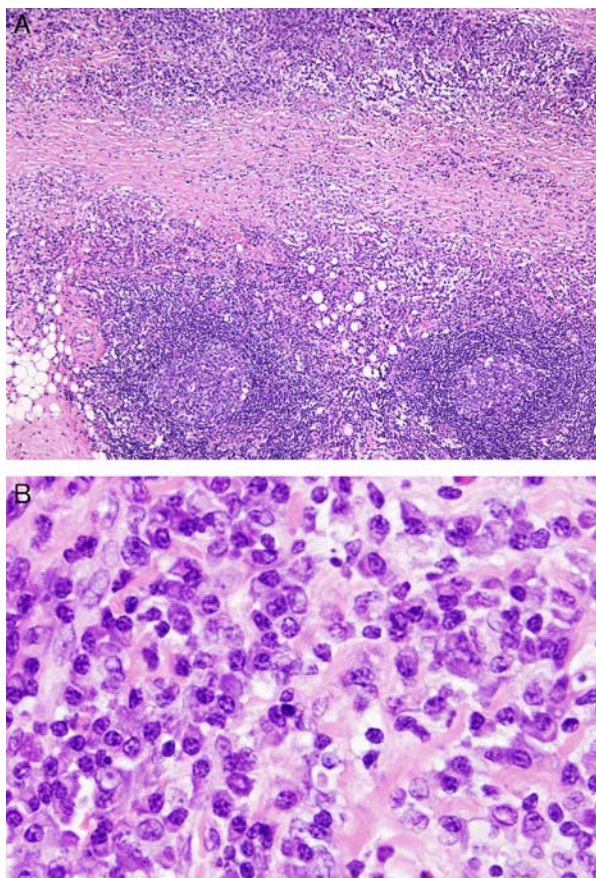


FIGURE 23. IgG4-related sclerosing pachymeningitis. A, The spinal dura shows sclerosis and lymphoplasmacytic infiltration with lymphoid follicle formation. B, Plasma cells and lymphocytes are present in a sclerotic stroma.

and weight loss are usually absent, and serum lactate dehydrogenase level is normal or only minimally raised. Laboratory investigations show raised serum IgG4 and IgG, polyclonal hypergammaglobulinemia, raised ESR, and sometimes low-titer autoantibodies.^{68,150}

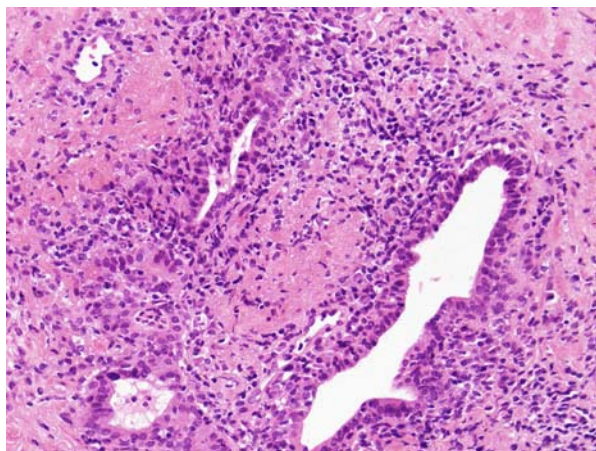


FIGURE 24. Prostatic involvement by IgG4-related sclerosing disease. The stroma of the prostate shows infiltration by lymphocytes and plasma cells, accompanied by fibrosis.

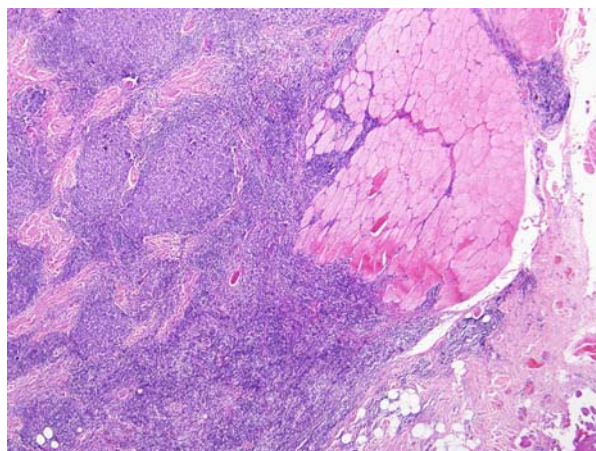


FIGURE 25. Cervical soft tissue involved by IgG4-related sclerosing disease (so-called idiopathic cervical fibrosis). The infiltrative process extends into skeletal muscle. Note the dense lymphoplasmacytic infiltrate traversed by thin sclerotic bands.

Morphologic Features of IgG4-related Lymphadenopathy

The morphologic features of IgG4-related lymphadenopathy differ from those of extranodal sites in that there is usually no sclerosis or phlebitis. We postulate that the nodal changes do not represent the fibroinflammatory lesions characteristic of IgG4-related sclerosing disease, but rather reflect the immune disturbance that underlies the syndrome.

We originally described 3 histologic patterns, but we and others have since observed 2 additional patterns.^{61,68,80,150} These include: multicentric Castleman disease-like (type I), follicular hyperplasia (type II), interfollicular expansion (type III), progressive transformation of germinal center-like (type IV), and nodal inflammatory pseudotumor-like (type V). The unifying feature is the presence of abundant IgG4⁺ cells. Although Sato et al⁸⁰ emphasize differential localization of IgG4⁺ plasma cells to the interfollicular areas in types I, II, III, and V, and follicle centers in type IV,¹⁵⁰ most cases show IgG4⁺ cells in both compartments

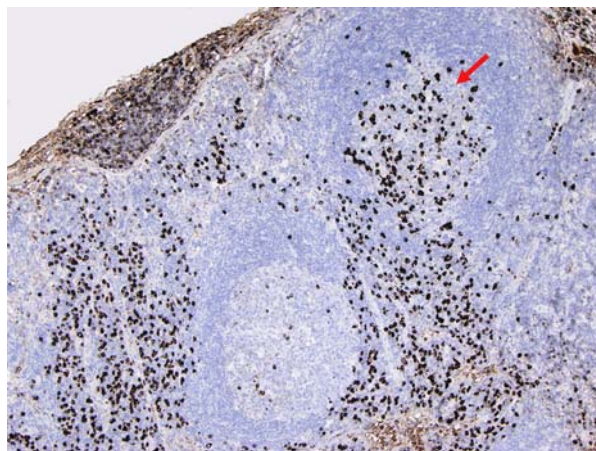


FIGURE 26. IgG4-related lymphadenopathy, immunostained for IgG4. As commonly the case, positive cells are distributed both in germinal centers (arrow) and interfollicular regions.

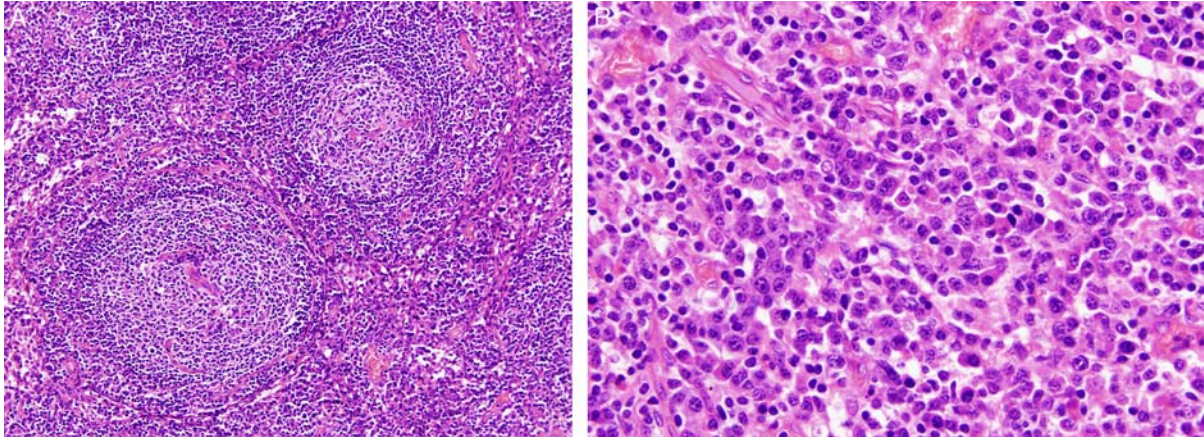


FIGURE 27. IgG4-related lymphadenopathy, type I. A, The lymphoid follicles are penetrated by hyalinized venules and the interfollicular zone is richly vascular, reminiscent of Castleman disease. B, The interfollicular zone is rich in plasma cells.

(Fig. 26). Staining for kappa and lambda light chains shows a polytypic pattern.

In type I (multicentric Castleman disease-like), the architecture is preserved. Admixed with usual hyperplastic follicles are follicles showing variable degrees of regressive changes and penetration by hyalinized blood vessels (Fig. 27). The interfollicular region shows increased high endothelial venules and many plasma cells. Some eosinophils can be present. The features are reminiscent of

multicentric Castleman disease, especially in the presence of multifocal lesions, hypergammaglobulinemia, and raised ESR (Table 8).^{68,150,182,183} The morphologic features also overlap with those of autoimmune disease-associated lymphadenopathy as seen in rheumatoid arthritis,^{184,185} and the so-called idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia (some cases of which probably represent IgG4-related lymphadenopathy).¹⁸⁶

TABLE 8. Distinction Between IgG4-related Lymphadenopathy and Multicentric Castleman Disease^{68,150,179,183}

	IgG4-related Lymphadenopathy	Multicentric Castleman Disease
Clinical presentation	Asymptomatic lymph node enlargement, with or without known features of IgG4-related sclerosing disease. Rarely, mass effect from the lymphadenopathy, such as obstructive uropathy. No constitutional symptoms.	Abrupt or gradual onset of symptoms, with multiple lymphadenopathy and constitutional symptoms, such as malaise, fever, weight loss, night sweat, anorexia. Some also show hepatosplenomegaly.
Age	Middle-aged or elderly, with median age of 69 y	Middle-aged or elderly, with median age of 64 years (range 19 to 85 y)
Sex	More marked male predilection, with M:F = 8:1	M:F = 2:1
Body cavity effusions	Very rare	Ascites, pleural effusion, and pericardial effusion are common
Anemia	Sometimes present, but often mild	Common, often moderate-to-severe (< 10g/dL)
Serum albumin level	Normal	Decreased
Serum immunoglobulin level	↑IgG (including ↑IgG4), ↑IgE	↑IgG, ↑IgM, ↑IgA
Serum interleukin-6	Not increased or only mildly increased	Typically increased
Serum C-reactive protein	Not increased or only mildly increased	Typically increased
Natural history	Benign clinical course; good response to steroid therapy; may develop other sites of disease on follow-up	Unpredictable clinical course, but often with high mortality. Many patients die within the first year, and median survival is only 29 months. Outcome may improve with anti-interleukin-6 receptor antibody therapy.
Pathologic features	Preserved architecture. Variable histology, with follicles ranging from usual-looking, hyaline-vascular type, regressed to progressively transformed. Interfollicular zone often rich in plasma cells	Preserved architecture. Prominent lymphoid follicles, many showing expansion and hypervascularity or regressive changes. Interfollicular zone shows florid plasmacytosis. Sinuses often distended with hyperchromatic lymph.
Immunohistochemistry	Increased IgG4 ⁺ cells in lymph node; no immunoglobulin light chain restriction	No significant increase in IgG4 ⁺ cells. Plasma cells in occasional cases can show light chain restriction. HHV8 ⁺ cells often present in multicentric Castleman disease occurring in patients with human immunodeficiency virus infection

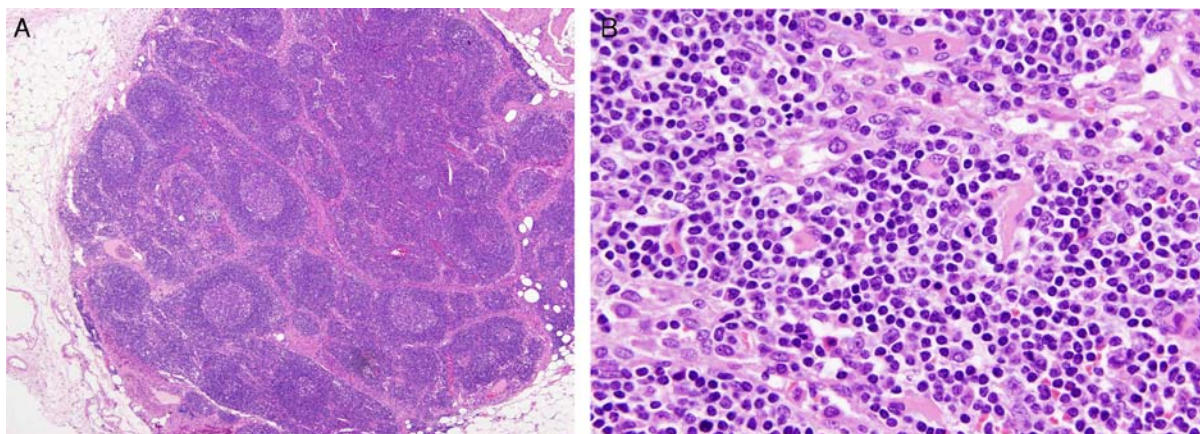


FIGURE 28. IgG4-related lymphadenopathy, type II. A, The lymph node features usual reactive follicular hyperplasia. B, The interfollicular zone population includes lymphocytes and plasma cells.

In type II (follicular hyperplasia), the lymph nodes exhibit usual reactive follicular hyperplasia (Fig. 28). There may or may not be obvious plasmacytosis in the interfollicular zone. Some eosinophils may be present.

Type III (interfollicular expansion) features marked distortion of the architecture by interfollicular expansion. Lymphoid follicles are sparse and often atrophic. The

expanded interfollicular zone shows prominent high endothelial venules, small lymphocytes, immunoblasts, plasmablasts, mature plasma cells, immature plasma cells, and eosinophils (Fig. 29). This pattern often raises the possibility of an angioimmunoblastic T-cell lymphoma. However, there is no definite cytologic atypia, clusters of clear cells, aberrant immunophenotype in the T cells, or

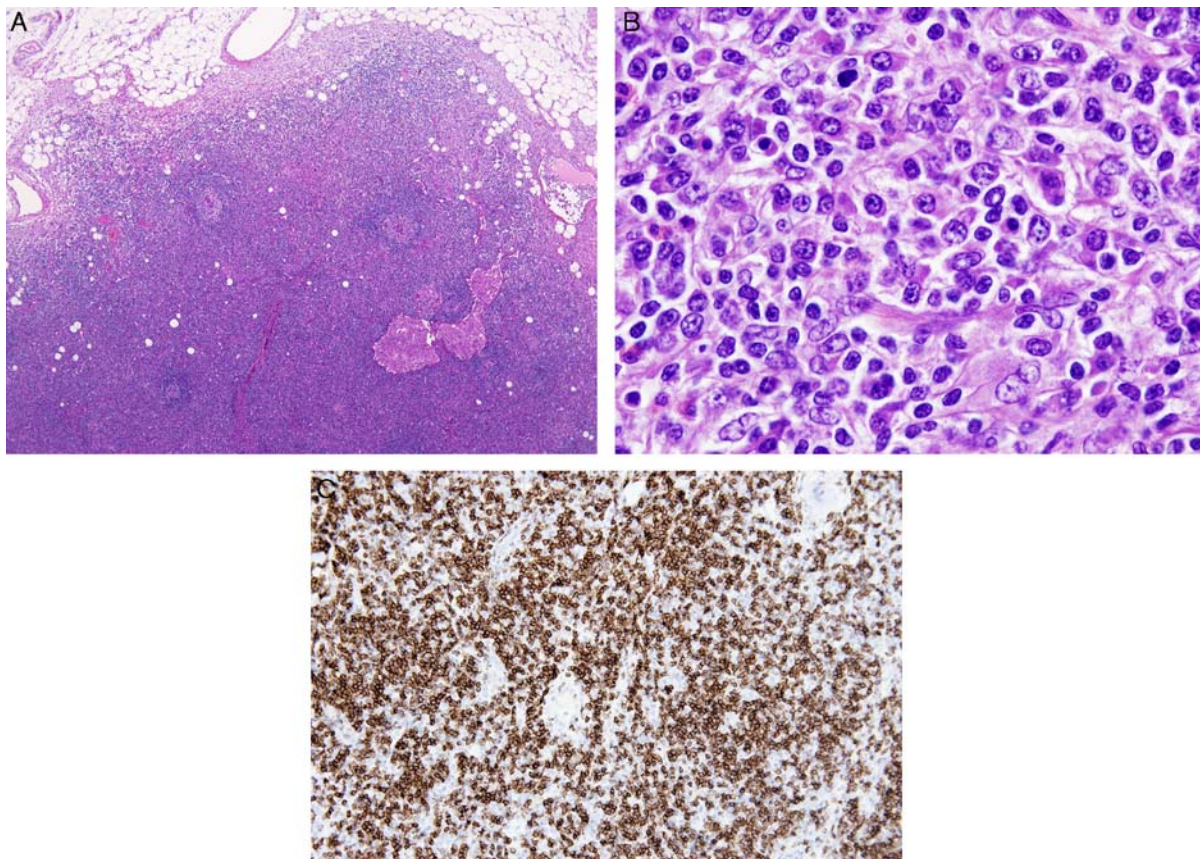


FIGURE 29. IgG4-related lymphadenopathy, type III. A, The lymph node has patent sinuses. The interfollicular zone is markedly expanded, and the scattered follicles are atrophic. B, The interfollicular zone is rich in high endothelial venules, lymphoid cells, and plasma cells. Occasional large lymphoid cells are admixed. C, Immunostaining for CD3 shows many positive cells.

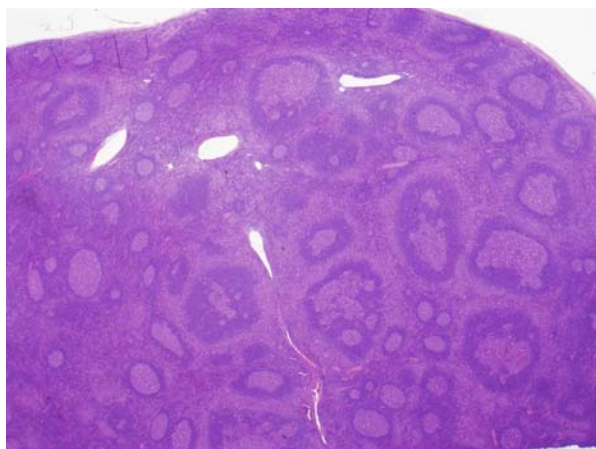


FIGURE 30. IgG4-related lymphadenopathy, type IV. Progressive transformation of germinal center pattern, with scattered lymphoid follicles being enlarged to several times the diameter of the background usual reactive follicles. The germinal centers of the transformed follicles become irregular-shaped and segmented.

extrafollicular follicular dendritic cell proliferation. Notwithstanding, the distortion of architecture is so unnerving that a diagnostic label of “atypical lymphoid hyperplasia” is frequently rendered if the possibility of IgG4-related lymphadenopathy has not been entertained.

In type IV (progressive transformation of germinal center-like), among usual hyperplastic follicles, occasional follicles show several-fold enlargement, thick mantles, and blurred germinal centers (Fig. 30). Some follicles, usual or transformed, may contain plasma cells in the germinal centers.

Type V (nodal inflammatory pseudotumor-like) is the least common, characterized by focal replacement of the nodal parenchyma by sclerotic tissue, which is sprinkled with lymphocytes, plasma cells, and eosinophils.

TABLE 9. Histologic Criteria of IgG4-related Sclerosing Disease

All of the following criteria have to be satisfied:

(1) Compatible morphology:

Extranodal sites*

- (a) Lymphoplasmacytic infiltration ± lymphoid follicles
- (b) Sclerosis
- (c) ± Phlebitis; arteries always spared except in the lung
- (d) No significant population of proliferated myofibroblasts

Lymph node

- (a) Increased plasma cells
- (b) Usual reactive lymphoid follicles ± hyaline-vascular follicles, or interfollicular expansion with increased activated lymphoid cells

(2) Absolute number of IgG4⁺ cells > 50/HPF†

(3) Percentage of IgG4⁺/IgG⁺ cells > 40%†

*Not all features may be present in small biopsies.

†For enumeration of IgG4⁺ or IgG⁺ cells, select areas with the highest density of positive cells. Three high-power fields (HPF) are counted, and an average number of positive cells per HPF is calculated. One HPF covers an area of 0.196 mm² (× 40 objective, × 10 eyepiece, 20 mm field of view).

DIAGNOSTIC CRITERIA FOR IgG4-RELATED SCLEROSING DISEASE

Our proposed histologic diagnostic criteria are listed in Table 9. We require elevation in both the absolute number of IgG4⁺ cells and IgG4⁺/IgG⁺ ratio as a prerequisite for the diagnosis (Fig. 31).⁶¹ Why not just use an absolute IgG4⁺ plasma cell count alone? IgG4⁺ cells normally account for approximately 5% of all IgG⁺ cells, and therefore they can be present in significant numbers in any inflammatory lesions containing numerous plasma cells (most of which express IgG) even though the percentage still falls in the normal range. Then why not just accept a high IgG4⁺/IgG⁺ percentage as being diagnostic? In lesions with a very low number of plasma cells, a misleadingly high IgG4⁺/IgG⁺ percentage may sometimes result, for example, 3 IgG4⁺ cells/HPF, and 6 IgG⁺ cells/HPF, giving a high percentage of 50%.

Our proposed criteria are more stringent than those used by many other investigators. Whereas this may lead to some bona fide cases being missed, liberal criteria may result in the disease category becoming a meaningless waste-basket. On encountering cases with compatible morphology but borderline cell counts (such as 45 IgG4⁺ cells per HPF, with IgG4/IgG ratio of 35%), we usually give a descriptive diagnosis (such as “fibroinflammatory lesion”) followed by the qualifier “with increased IgG4⁺ cells,” and advise further work-up and follow-up to determine if this could represent IgG4-related sclerosing disease.

A raised serum IgG4 level (> 135 mg/dL) is helpful but not essential for diagnosis.⁵⁸ Serum IgG4 titer seems to correlate with disease activity and the number of involved organs, and normal serum IgG4 can occur.^{29,49} In contrast, elevated serum IgG4 is well known in other diseases, such as atopic dermatitis,¹⁸⁷ parasitic diseases,⁸ pemphigus vulgaris, and pemphigus foliaceus,¹⁸⁸ and even pancreatic carcinoma.⁵⁰

OTHER ENTITIES WITH INCREASED IgG4⁺ CELLS

As stated above, even in the presence of large numbers of IgG4⁺ plasma cells and a high IgG4/IgG ratio, compatible morphology and appropriate clinical findings are still required for diagnosis. For instance, in rheumatoid arthritis, large numbers and a high proportion of IgG4⁺ plasma cells are found in occasional cases.^{68,138} The morphologic features and clinical findings are, however, obviously not compatible with IgG4-related sclerosing disease.

Cutaneous Rosai-Dorfman disease has recently been reported to harbor many IgG4⁺ plasma cells, and thus proposed to belong to the IgG4-related sclerosing disease family.¹⁸⁹ As this disease predominantly affects young patients instead of middle-aged or elderly patients and the distinctive S100⁺ large histiocytes are never a feature of IgG4-related sclerosing disease, we believe Rosai-Dorfman disease is not a member of IgG4-related sclerosing disease, and there is no overlap between these conditions as suggested by some investigators.¹⁹⁰

Increased IgG4⁺ plasma cells are reported in cutaneous plasmacytosis, perforating collagenosis, autoimmune atrophic gastritis (pernicious anemia), and sclerosing variant of mucoepidermoid carcinoma of salivary gland, but these entities are not related to IgG4-related sclerosing disease.^{191–194}

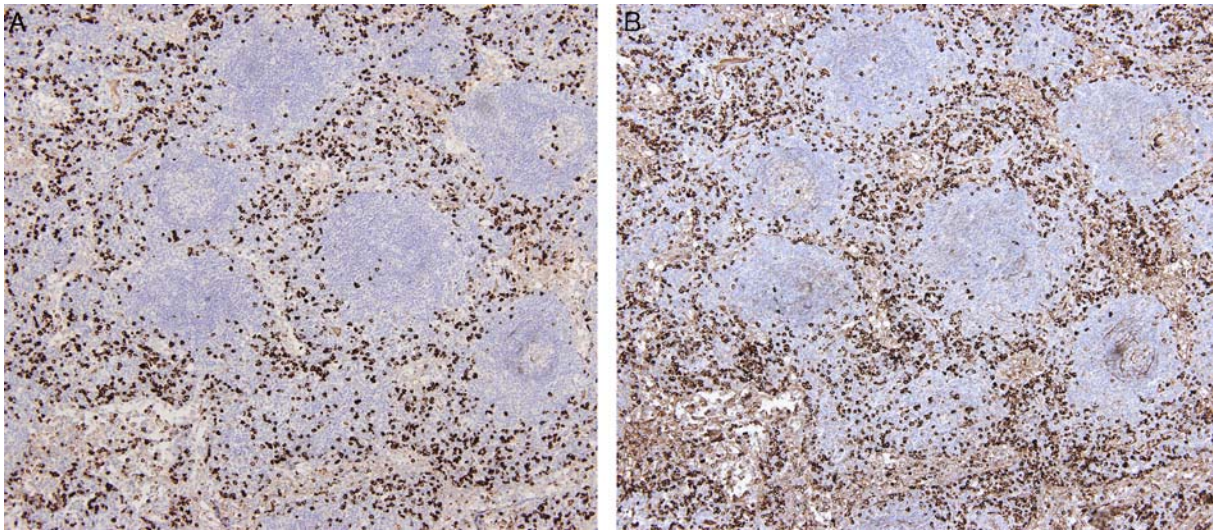


FIGURE 31. IgG4-related lymphadenopathy, immunostaining. A, Immunostaining shows numerous IgG4⁺ cells in the interfollicular zone. B, More IgG⁺ cells are present in a corresponding field. The IgG4/IgG ratio in this case is 70%.

PATHOGENESIS

The pathogenesis of IgG4-related sclerosing disease is poorly understood. IgG4 probably only represents a surrogate marker rather than playing a pathogenetic role. The disease is probably not autoimmune in nature, but is rather a hypersensitive/allergic reaction (Table 10).¹⁹⁵

Some studies have shown the association of autoimmune (IgG4-related) pancreatitis with gastric ulcer and/or *Helicobacter pylori* infection.^{77,196,197} Of note, there is a significant homology between human carbonic anhydrase II and α -carbonic anhydrase of *H. pylori*.¹⁹⁹ Okazaki et al¹⁹⁸ postulate that the pathogenesis of autoimmune pancreatitis involves a biphasic “induction” and “progression” mechanism. The initial response to self-antigens (such as lactoferrin, carbonic anhydrase, pancreatic secretory trypsin inhibitor, and α -fodrin) and molecular mimicry (*H. pylori*) are induced by decreased naive regulatory T cells, and T-helper 1 cells release proinflammatory cytokines. In the chronic stage, progression is mediated by increased memory regulatory T cell and T-helper 2 cell immune responses. In fact, the infiltrate often shows a mixed population of T and B cells, with increased CD4⁺, CD25⁺, FOXP3⁺ regulatory T cells.^{85,195,200} T-helper cell 2 cytokines (interleukin-4, interleukin-5, and interleukin-13) and regulatory cytokines (interleukin-10 and transforming growth factor) are all upregulated in the involved tissues.^{80,195,201} Enhanced T-helper type 2 responses to

intestinal microflora has also been postulated to underlie the immunopathogenesis.⁷⁸

On the basis of the ultrastructural finding of electron-dense deposits of immune complexes in the basement membranes of pancreatic acini and renal tubules, an immune-mediated pathogenesis has been postulated.³² However, as IgG4 does not activate the classic complement pathway, it remains to be proven whether immune complexes mediate tissue injury in this disease.

In a recent study, screening of pooled IgG from patients with autoimmune pancreatitis shows reactivity with peptide AIP (1 to 7), which is found in the serum samples from 90% of patients with autoimmune pancreatitis, only 10% of patients with pancreatic cancer, and 0% from healthy controls.²⁰² The peptide shows homology with plasminogen-binding protein of *H. pylori* and with ubiquitin-protein ligase E3 component n-recogin 2, an enzyme highly expressed in pancreatic acinar cells. These findings suggest a possible role of *H. pylori* and molecular mimicry in the development of autoimmune pancreatitis.

MALIGNANCIES ASSOCIATED WITH IgG4-RELATED SCLEROSING DISEASE

Malignant Lymphoma

Recently, we reported 3 cases of localized lymphoma (2 marginal zone lymphomas and 1 follicular lymphoma)

TABLE 10. Evidence in Support of or Against an Autoimmune Etiopathogenesis of IgG4-related Sclerosing Disease

Arguments Suggesting an Autoimmune Nature	Arguments Against an Autoimmune Nature
Circulating autoantibodies present in many patients	Predilection for elderly men, which contrasts with the striking female predominance found in autoimmune diseases
Association with other autoimmune diseases, for example, Sjogren syndrome	Autoantibodies are nonspecific and may merely be consequence of tissue injury
Excellent response to steroid	The reported associated “autoimmune diseases” represent tissue involvement by IgG4-related sclerosing disease instead, i.e., not genuine Sjogren syndrome
	The dramatic and durable response to steroid is more suggestive of a hypersensitivity reaction

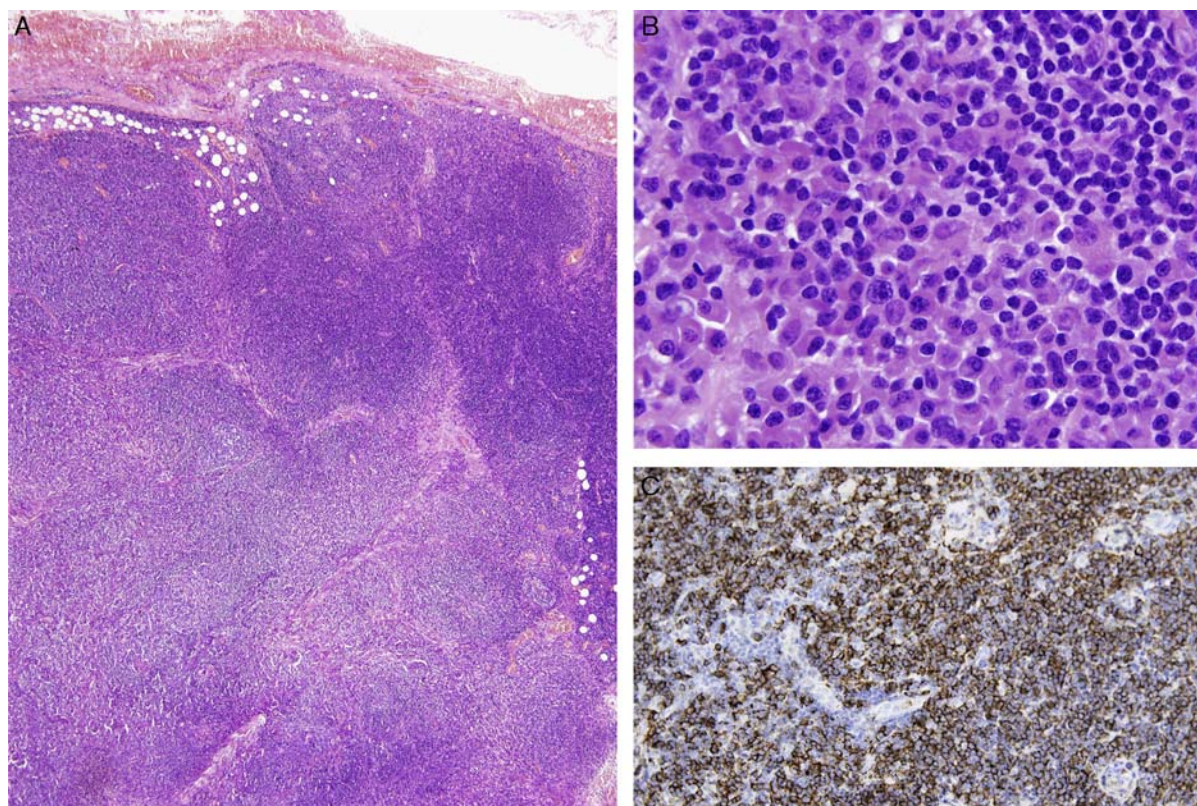


FIGURE 32. Extranodal marginal zone lymphoma complicating IgG4-related sclerosing dacryoadenitis. A, The tissue shows diffuse dense infiltrate. B, The infiltrate comprises small lymphoid cells and plasma cells. C, On immunostaining, sheets of CD20⁺ cells are seen.

that arose in the setting of IgG4-related chronic sclerosing dacryoadenitis (Fig. 32).^{61,203} We have since encountered an example of composite marginal zone lymphoma and classical Hodgkin lymphoma associated with IgG4-related sclerosing disease of the cervical soft tissue.¹⁷⁶ In a report on 21 cases of ocular adnexal IgG4-related sclerosing disease, Sato et al briefly alluded to 2 cases of supervening ocular marginal zone lymphoma,⁶⁰ and updated to a total

of 7 cases in a recent review article.⁸⁰ Thus, it seems that the lymphoid proliferation associated with IgG4-related sclerosing disease may provide the substrate for the emergence of lymphoma, akin to the development of extranodal marginal zone lymphoma in the acquired or autoimmune chronic inflammatory background of the stomach (*H. pylori* infection), salivary gland (Sjogren syndrome), and thyroid (Hashimoto thyroiditis).²⁰⁴ Of interest, in a recent epidemiologic study from the Mayo Clinic, 3 cases of lymphoma (2 large B-cell lymphomas and 1 B-cell lymphoma unspecified) were found on follow-up of 111 patients with IgG4-related sclerosing disease, suggesting that the syndrome increases the risk of developing lymphoma in various sites.²⁰⁵ Further work is required to confirm IgG4-related sclerosing disease as a risk factor for lymphoma.

TABLE 11. Clues to Diagnosis of IgG4-related Sclerosing Disease

The possibility of IgG4-related sclerosing disease should be seriously considered in the following scenarios, especially if there is evidence of concomitant or history of pancreatic, lacrimal gland, or salivary gland lesions.

Extranodal sites:

- Unexplained abundance of mature plasma cells
- Morphologic features of pseudolymphoma
- Morphologic features of inflammatory fibrosclerosing lesion
- Morphologic features of “inflammatory pseudotumor” with many plasma cells and no significant population of myofibroblasts

Lymph node:

- Morphologic features suggestive of multicentric Castleman disease in a patient with otherwise good general condition
- Atypical lymphoid hyperplasia rich in plasma cells
- Morphologic features reminiscent but falling short of angioimmunoblastic T-cell lymphoma in a patient with good general condition and normal or marginally raised serum lactate dehydrogenase level

Carcinoma

Several cases of ductal adenocarcinoma of the pancreas, with 1 case showing high-grade intraepithelial neoplasia, have been described in association with IgG4-related sclerosing pancreatitis.^{206–209} A retrospective and comparative study has shown autoimmune pancreatitis to be associated with an increased risk for pancreatic carcinoma, at least comparable with that of chronic pancreatitis, not otherwise specified.²¹⁰ One case each of salivary duct carcinoma, pulmonary adenocarcinoma, and gastrointestinal clear cell sarcoma has also been reported in the parotid gland, lung, and small intestine, respectively

with features of IgG4-related sclerosing disease in the background.^{139,211,212} Further studies are required to ascertain if there is any causal relationship between the carcinoma and IgG4-related sclerosing disease.

CONCLUSIONS

The clinicopathologic features of IgG4-related sclerosing disease are still evolving as more sites of involvement and a broader histologic spectrum are recognized in this new entity. The clues to diagnosis are summarized in Table 11. We believe strict criteria are necessary in its diagnosis (Table 9) lest the entity may become a meaningless wastebasket.²¹³ There is still a lot to be learned about the pathogenesis, in particular, the role of IgG4, in the development of the disease.

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