

Recent progress of IgG4-related hepatobiliary diseases with emphasis on pathologic aspects and differential diagnosis

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Abstract

IgG4-related disease usually presents with a mass-forming or regional lesion showing considerable lymphoplasmacytic infiltration with many IgG4-positive plasma cells, sclerosis, and obliterative phlebitis. Herein, recent progress of hepatobiliary IgG4-related diseases including IgG4-related sclerosing cholangitis (IgG4-SC), hepatic inflammatory pseudotumor (HIP), and autoimmune hepatitis (AIH), are reviewed. IgG4-SC mainly affects the extrahepatic and hilar bile ducts, and is almost always associated with autoimmune pancreatitis (AIP), a prototype of IgG4-related disease. IgG4-SC has a propensity to exaggerate focally, and such IgG4-SC could be categorized as an IgG4-related HIP, mainly belonging to the lymphoplasmacytic type of HIP. IgG4-related AIH is a chronic active hepatitis with many IgG4-positive plasma cells and increased serum IgG4 level. In conclusion, several hepatobiliary diseases which had been diagnosed as other diseases, can be reclassified as IgG4-related diseases, and several local factors peculiar to the hepatobiliary system may be responsible for the development of these diseases.

Keywords allergy; autoimmune hepatitis; autoimmune pancreatitis; fibrosis; IgG4; inflammatory pseudotumor; phlebitis; plasma cells; regulatory T cells; sclerosing cholangitis

Introduction

Since the 1990s, autoimmune pancreatitis (AIP) has been increasingly recognized as a special type of chronic pancreatitis.¹ Such patients show characteristically a swollen pancreas with

considerable lymphoplasmacytic infiltration with many IgG4+ plasma cells (IgG4-tissue positivity) and fibrosis, and respond well to steroid therapy. This type of lesion also involves extrapancreatic tissues, including the bile duct, salivary glands, retroperitoneum and cardiovascular system.^{2–4} Diseases of this type are now collectively called as IgG4-related disease,⁵ are clinically characterized by elevated serum IgG4 concentrations, a high prevalence in middle to old-aged adults with a preponderance among men, steroid sensitivity, and the frequent occurrence of non-organ-specific autoantibodies such as antinuclear antibodies. Not infrequently, IgG4-related disease affects more than one organ in the same individual.^{3,4} In addition, such cases are also frequently associated with lymphadenopathy showing follicular hyperplasia or Castleman-like lesions with IgG4-tissue positivity. It is becoming evident that several other diseases also show considerable infiltration of lymphoplasmacytes with IgG4-tissue positivity or elevated serum IgG4 level, making it important to distinguish IgG4-related disease as it responds well to steroid therapy.

Herein, the clinicopathological features of AIP with reference to IgG4-related disease are briefly reviewed. Then, the pathology and aetiopathogenesis of IgG4-related hepatobiliary disease are discussed in differentiation from other hepatobiliary diseases with IgG4-tissue positivity or elevated serum IgG4 level.

Autoimmune pancreatitis and IgG4-related sclerosing disease

The concept of AIP was first reported by Yoshida et al. as a specific type of chronic pancreatitis, mainly affecting elderly men, showing diffuse or regional swelling of the pancreatic parenchyma and irregular narrowing of the main pancreatic duct.¹ Histologically, AIP is characterized by considerable lymphoplasmacytic infiltration with variable acinar atrophy and loss and also periductal infiltrates of lymphocytes and plasma cells, and is also called lymphoplasmacytic sclerosing pancreatitis (LPSP).⁶ Additional characteristic features are also seen: (i) irregular or storiform fibrosis; (ii) extension of sclerosing inflammation to peripancreatic adipose tissue; and (iii) obliterative phlebitis. Eosinophilic infiltration is variably found. Hamano et al. reported that more than 90% of patients with AIP have high serum IgG levels, particularly IgG4, and many IgG4+ plasma cells are evident immunohistochemically in the affected pancreas.⁷ Most importantly, steroid therapy is effective, and the size of the pancreas returns to normal.

As for IgG4-related lesions in various organs, the following are representative: idiopathic retroperitoneal fibrosis, chronic sclerosing sialadenitis, Mikulicz's disease, periaortitis, and tubulointerstitial nephritis. Such diseases are now proposed to be collectively called IgG4-related diseases.^{3,5} In addition, a pseudotumorous variant of IgG4-related disease diagnosed as IgG4-related inflammatory pseudotumor has been reported in several organs.^{3,8} Interestingly, some of these diseases had already been reported as a disease family called multifocal fibrosclerosis proposed by Comings.⁹

At present, AIP is regarded as a pancreatic manifestation of IgG4-related disease.⁴ In general, one or several organs are affected synchronously or metachronously by this disease in various combinations. Interestingly, there are some characteristic features among the affected organs,³ suggesting the participation

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of common immunologic mechanisms, and also of a pathologic process peculiar to individual organs.^{3,5}

Regarding AIP, two types have been recently distinguished. Type 1 corresponds to a pancreatic manifestation of IgG4-related diseases as mentioned above, while type 2 AIP usually has no or very few IgG4-positive plasma cells and no elevation of serum IgG4 level. The two types share the same symptomatology and some histopathological features such as periductal lymphoplasmacytic infiltrates, though type 2 AIP shows so-called granulocytic epithelial lesion (GEL). Both types respond well to steroid treatment.

Diagnosis of IgG4-related disease

IgG4-related disease is diagnosed based on characteristic pathologic features, such as considerable lymphoplasmacytic infiltration, fibrosis, and obliterative phlebitis. While these findings are obvious and the diagnosis is not difficult in larger specimens, a pathologic diagnosis in smaller specimens is not easy.³ For example, obliterative phlebitis which is shown by Elastica van Gieson staining, is not usually identifiable in small specimens. Eosinophilic infiltration is not an absolute indication of this disease. As for IgG4-tissue positivity, more than 10 IgG4-bearing plasma cells/high power field (HPF), and an increased IgG4+ to IgG+ plasma cell ratio (IgG4/IgG ratio, more than 30%) are used to distinguish IgG4-related disease from other inflammatory conditions.⁵ The elevated IgG4 serum level, particularly higher than 135 mg/dl, is frequently but not always observed in these patients.⁷ Recently, it was shown that there are many Treg and FOXP3+ regulatory T cells (FOXP3(+) Treg) in the affected tissues,² and abundant infiltration by such Tregs may favour a diagnosis of IgG4-related disease.

Hepatobiliary diseases belonging to IgG4-related disease

Some hepatobiliary diseases have been found to be IgG4-related disease.^{2,8,10} They had been diagnosed as other diseases such as primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) before this entity had been recognized. Herein, the pathology of these newly reclassified diseases and their aetiopathogenesis is discussed here. In this review, the biliary tree is divided into the extrahepatic bile duct, right and left hepatic bile ducts, and intrahepatic large and small bile ducts.¹¹ The latter were composed of septal and interlobular bile ducts. Physiologically, peribiliary glands which are located within and outside the duct wall, are distributed along the intrahepatic large bile duct and extrahepatic bile duct.^{11,12} Similar glands are also located in the gallbladder neck.

IgG4-related sclerosing cholangitis

Sclerosing cholangitis is characterized by fibrosis and chronic inflammatory cell infiltration of the bile duct wall of the extrahepatic and intrahepatic bile ducts with luminal changes, and their distribution is segmental or diffuse. Its pathology and aetiology are heterogeneous.^{10,13,14} PSC is a prototype of sclerosing cholangitis and frequently associated with inflammatory bowel disease (IBD), particularly ulcerative colitis. Sclerosing cholangitis showing abundant IgG4+ plasma cell infiltration has recently emerged and is called IgG4-related sclerosing cholangitis (IgG4-SC).^{2,4,8}

IgG4-SC mainly affects elderly men, and is usually associated with AIP. Extrahepatic bile ducts, particularly intrapancreatic

portions, are affected in 95% of AIP cases and the hilar or intrahepatic large bile ducts are also affected in 40% of AIP patients, though a few cases of IgG4-SC without clinical evidence of AIP are reported. However, the common hepatic duct and extrapancreatic portion of the common bile duct are not usually affected. IgG4-SC is not associated with IBD. The affected bile ducts show prominent thickening of their wall, and look whitish, medullary and fleshy, and have a border that is rather clear, but merge slightly with the surroundings. The lumens of affected bile ducts are usually stenotic, and the proximal bile ducts are usually dilated. Serological findings reported in AIP are also found in IgG4-SC, and IgG4-SC responds well to steroid therapy.

Histologically, IgG4-SC shows considerable lymphoplasmacytic infiltration with fibrosis, and lymph follicle formation and obliterative phlebitis are occasionally found (Figure 1a–c). It is of interest that the peribiliary glands are more severely affected and inflammatory reactions are clearly oriented towards these glands, and these glands show epithelial damage and are destroyed. Biliary lining epithelial cells of the affected large bile ducts are relatively spared in IgG4-SC as seen in the pancreatic duct in AIP. This is in sharp contrast with PSC in which biliary lining epithelial cells show degeneration, loss and ulceration. Perineural lymphoplasmacytic infiltration and extension to the periductal connective tissue are also seen. The fibrosis in IgG4-SC is not dense or hyalinized.

Immunohistochemically, there are many IgG-positive plasma cells, a majority of which are positive for IgG4, in the affected bile duct and portal tracts (Figure 1d). IgM, IgA, IgG1, IgG2, and IgG3-positive cells are scarce.¹³ In IgG4-SC, proliferated lymphocytes are composed of T cells and also B cells, and CD4+ T cells are more common than CD8+ T cells.

Hepatobiliary lesions secondary to or associated with IgG4-SC:

smaller portal tracts remote from the affected hilar and perihilar large bile ducts also show IgG4-tissue positivity, a useful finding for the diagnosis of IgG4-SC. In our experience, a needle liver biopsy is useful for diagnosis in about one-fourth of IgG4-SC patients by showing IgG4-positive plasma cells in portal tracts.¹⁵ As for other hepatobiliary lesions, chronic cholestasis with frequent bile plugs, portal tract fibrosis and also biliary fibrosis due to biliary stenosis are found.¹⁵ Periductal concentric or onion-skinning fibrosis of interlobular or septal bile ducts was also seen, though significant biliary epithelial damage, lymphoplasmacytic cholangitis, bile duct scarring and ductopenia are not usually seen in IgG4-SC. Interface hepatitis of mild degree is found in one-fourth of IgG4-SC patients.

Involvement of gallbladder and papilla Vater in AIP or IgG4-SC

The gallbladder and duodenal papilla are also frequently affected in patients with AIP.¹⁶ However, the clinical features or symptoms due to these tissues can be unclear, nonspecific or non-significant.

IgG4-related chronic sclerosing cholecystitis (IgG4-CSC): in AIP/IgG4-SC, the gallbladder shows moderate or marked mucosal and transmural lymphoplasmacytic inflammatory infiltrates with IgG4-tissue positivity, extramural inflammatory nodules, tissue eosinophilia and obliterative phlebitis as seen in AIP or IgG4-SC. IgG4-tissue positivity could be helpful in differentiating it from

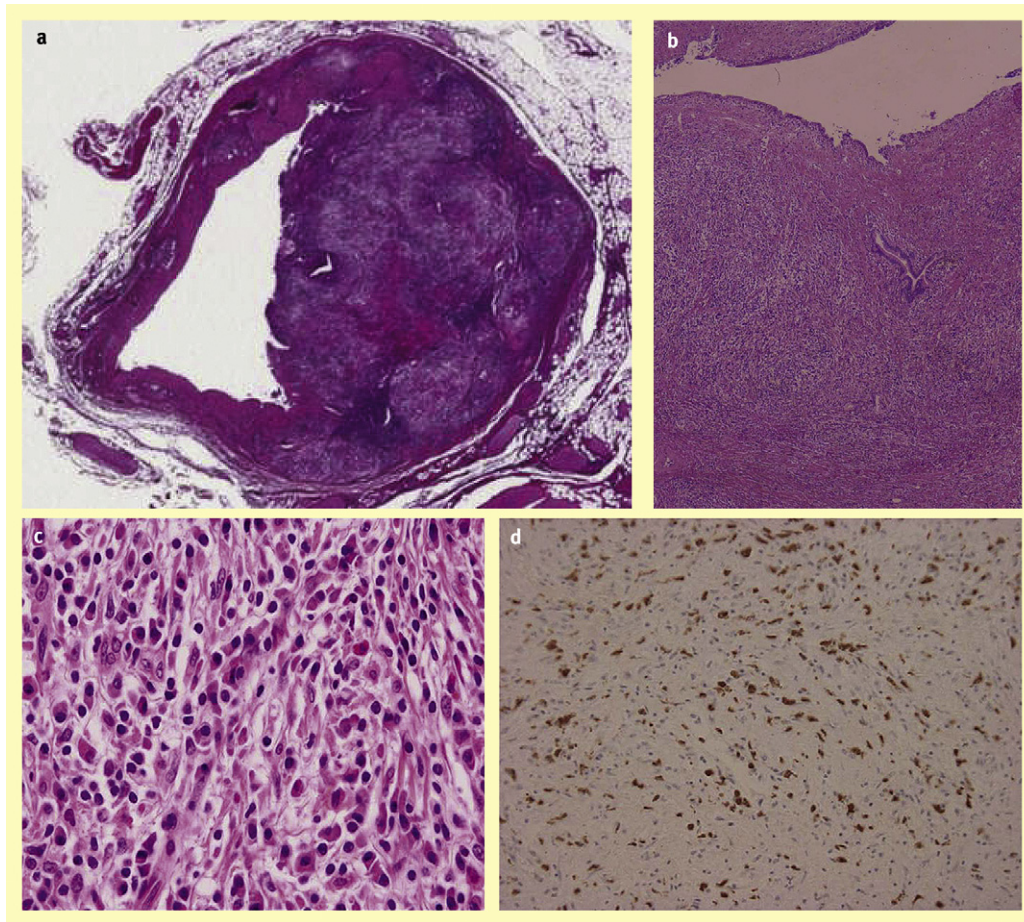


Figure 1 (a) About a half circumference of the extrahepatic bile duct is markedly inflamed, while the other part is apparently normal. IgG4-related sclerosing cholangitis. H&E. (b) The affected bile wall shows fibrosis and lymphoplasmacytic infiltration, rather diffusely. The lining biliary epithelia are relatively preserved. IgG4-related sclerosing cholangitis. H&E. (c) Lymphoplasmacytic infiltration and fibroblasts are seen. IgG4-related sclerosing cholangitis. H&E. (d) There are many IgG4-positive plasma cells in the affected bile ducts. Immunostaining for IgG4 and haematoxylin.

other cholecystopathies. The presence of a dense extramural inflammatory infiltrate, extramural inflammatory nodules, and >10 IgG4 plasma cells per HPF in the gallbladder favours the diagnosis of IgG4-CSC.

IgG4-tissue positivity in the duodenal papilla is found in AIP, and is helpful in the diagnosis of AIP. Kawakami et al. reported that the diagnostic sensitivity of IgG4 immunostaining of both ampullary and bile duct biopsy specimens was 52% (15/29) for symptomatic patients with AIP or IgG4-SC. Two-thirds of patients had more than 10 IgG4+ plasma cells in biopsy specimens. Furthermore, the bile duct biopsy specimens not only indicated the number of IgG4+ plasma cells but also showed other characteristic histological features, including storiform fibrosis.

Hepatic inflammatory pseudotumor

Hepatic inflammatory pseudotumor (HIP) is characterized by the irregular proliferation of fibroblasts intermixed with infiltrating inflammatory cells, mainly lymphocytes and plasma cells. It is regarded as a heterogeneous disease and subcategorized histologically into several types including a fibrohistiocytic type, lymphoplasmacytic type, and sclerosed or fibrosed type. The fibrohistiocytic type is characterized by xanthogranulomatous inflammation, multinucleated giant cells, and neutrophilic infiltration, and mostly occurs in the peripheral hepatic parenchyma

as a mass-forming lesion. In contrast, the lymphoplasmacytic type shows diffuse lymphoplasmacytic infiltration with variable eosinophilic infiltration, and is usually found around the hepatic hilar and perihilar region. Obliterative phlebitis and cholangitis with periductal fibrosis are common features of the lymphoplasmacytic type (Figure 2a,b).¹⁷ Interestingly, IgG4-positive plasma cells were significantly more numerous in the lymphoplasmacytic than fibrohistiocytic type. However, a few cases of fibrohistiocytic type had also relatively many IgG4-positive plasma cells. Taken together, a majority of lymphoplasmacytic HIPs may belong to the so-called IgG4-related diseases. In fact, such cases are known to respond well to steroid therapy. In contrast, fibrohistiocytic HIP might still be a heterogeneous group of disorders. Several cases of fibrohistiocytic type with relatively abundant IgG4-positive plasma cells could be IgG4-related disease with secondary histopathologic modifications.

HIP is not infrequently associated with AIP/IgG4-SC,^{2,17} and the pathogenesis may be similar or closely related to AIP and IgG4-SC. In HIP, the bile ducts and their surrounding tissues including peribiliary glands and connective tissue are severely inflamed and the inflammation expands into the surroundings, suggesting that such HIP is an exaggerated inflammatory condition in IgG4-SC.

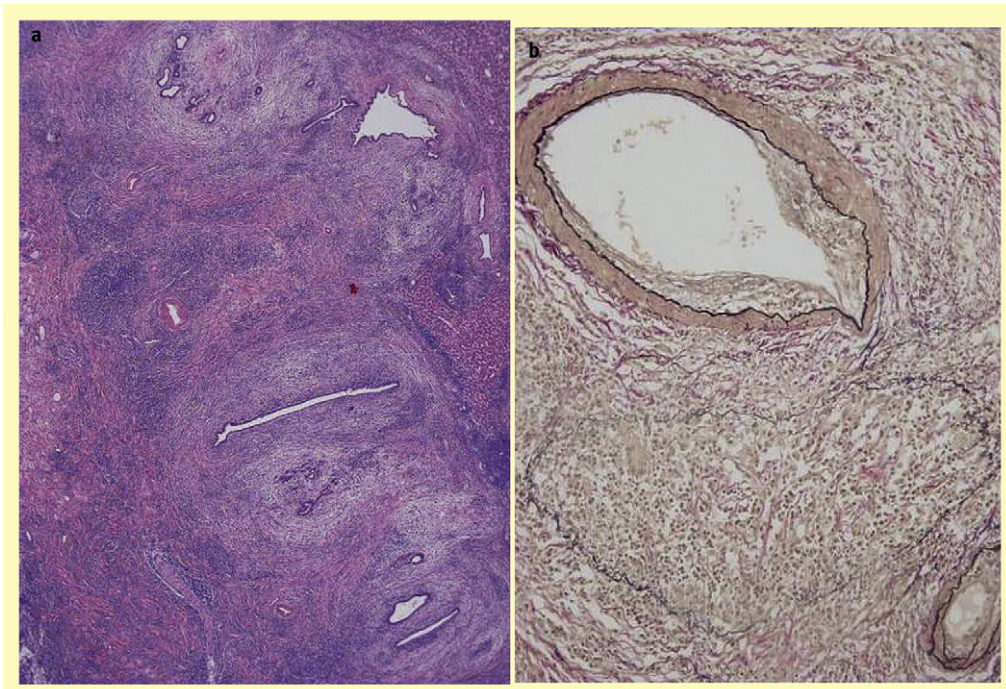


Figure 2 (a) There are massive inflammation involving bile ducts, peribiliary glands and surrounding connective tissue. Hepatic inflammatory tumour of lymphoplasmacytic type belonging to IgG4-related disease. H&E. (b) One vein shows obliterative phlebitis, and one artery also shows focal luminal changes. Hepatic inflammatory tumour of lymphoplasmacytic type belonging to IgG4-related disease. Elastica van Gieson stain.

IgG4-related autoimmune hepatitis

Autoimmune hepatitis (AIH) is an organ-specific autoimmune liver disease characterized by prominent interface hepatitis and a favourable response to steroid therapy.¹⁴ Recently, several AIH cases with abundant plasma cells with much IgG4-tissue positivity, prominent lobular hepatitis and interface hepatitis, and elevated level of IgG4 in serum, have been reported.¹⁸ These patients showed a good response to steroid therapy. High serum IgE concentrations were also pointed out. They are proposed to be called IgG4-related AIH. However, neither irregular fibrosis nor obliterative phlebitis was observed. The differences between IgG4-associated AIH and combined hepatic injury in AIP/IgG4-SC¹⁵ are considered to be: (a) patients with IgG4-associated AIH have a much higher degree of IgG4-bearing plasma cell infiltration in the liver compared to those with classical AIH; (b) rosette formation, interface hepatitis and other features characterizing AIH are obvious; and (c) no bile duct damage or loss is found. Such patients fulfilled the revised IAIHG disease score of AIH.¹⁴ Based on these findings, we have provisionally set the diagnostic criteria for IgG4-associated AIH as follows: (i) having definite AIH according to the IAIHG scoring system, (ii) serum IgG4 concentration ≥ 135 mg/dl, and (iii) immunostaining of IgG4 showing infiltration of ≥ 10 /HPF IgG4-bearing plasma cells in the portal tract.¹⁴ According to our survey, two patients (3.3%) met these criteria.

It remains, however, uncertain whether IgG4-associated AIH is one manifestation of AIH, belongs to IgG4-related disease, or is a manifestation of IgG4-SC. Interestingly, one patient with IgG4-associated AIH developed IgG4-SC after 5 years of follow-up. Because a bile duct biopsy was not done prior to treatment, the possibility that she had IgG4-SC at that time cannot be excluded.

Etiopathogenesis of IgG4-related hepatobiliary diseases

While the etiopathogenesis of hepatobiliary IgG4-related disease remains enigmatic, accumulating data suggest that both disordered immunological mechanism(s) and local anatomical and physiological factor(s) specific to the hepatobiliary system may contribute to the development of these diseases.

Altered humoral immunity

In IgG4-related disease, levels of γ -globulin and IgG, particularly IgG4, are elevated, and nonspecific autoantibodies such as ANA and rheumatoid factor are not infrequently detected in serum, suggesting an abnormality of humoral immunity. IgG4 is reported to be non-cytotoxic and has rather self-protective antibodies, while this IgG subclass is known as a pathogenic autoantibody in the development of autoimmune skin-diseases such as endemic pemphigus foliaceus.¹⁹ Patients with AIP reportedly exhibit high serum circulating immune complex values and decreased levels of various complements reflecting its active state. Reportedly, IgG4 subclass immune complexes lead to the formation of the membrane-attack complex in tissues by fixing the complement through the alternative pathway in membranous nephropathy. This hypothesis may be likely in IgG4-SC and also AIP because the deposition of IgG4 and complement was shown around the exocrine acini and small ducts of pancreas and also peribiliary glands of large bile ducts, suggesting the deposition of immune complexes to play a role in their pathogenesis.^{20,21} A similar deposition is reported in IgG4-related interstitial nephritis.

Predominance of Th2 reaction and disordered Treg

Recently, it was shown that IgG4-related disease is associated with over-production of helper type 2 (Th2) cytokines such as IL-4, IL-5

and IL-13 and also regulatory cytokines such as IL-10, and TGF- β , suggesting that IgG4-related disease is characterized by Th2 predominance. Regulatory cytokines such as IL-10 and TGF- β are also up-regulated and the expression of Foxp3 messenger RNA, a transcription factor specific for naturally arising CD4⁺, CD25⁺ Tregs, is also significantly increased, suggesting that CD4⁺/CD25⁺ Tregs are disordered in IgG4-related disease. The presence of these cytokines can explain the histopathological features shared by IgG4-related diseases: FOXP3 regulates both IgG4 production, as a result of inducing IL-10, and the fibrosis, as a result of inducing TGF- β .¹³

Allergy

In more than half of patients with IgG4-related disease, a history or synchronous affection of allergic disease is obtainable, and increased levels of serum IgE and eosinophilia are also pointed out,⁵ suggesting that it seems likely that IgG4-related disease may have the background of an allergic disease. For example, IgG4-related hepatobiliary disease may be an allergic reaction to intrinsic or extrinsic substrates present in bile or pancreatic juice, rendering the infiltration of eosinophils and IgG4-positive plasma cells, and further studies are mandatory to clarify the participation of allergy in this disease.

Local factors related to anatomy or physiology peculiar to individual organs involved

In AIP, the biliary tract including gallbladder is also frequently involved, and in almost all patients with hepatobiliary IgG4-related disease, AIP is present. However, the association of IgG4-sclerosing diseases of other organs is not so frequent in AIP or IgG4-related hepatobiliary diseases, suggesting that the hepatobiliary system and pancreas are closely correlated or simultaneously affected in this disease. Peribiliary glands, which are physiologically distributed around the extrahepatic and intrahepatic large bile ducts, are severely damaged in IgG4-SC² (Figure 3a–c). Interestingly, the pancreatic portion of the common bile duct and hilar and perihilar large bile ducts are preferentially affected in IgG4-SC. In these anatomical locations, peribiliary glands are densely and frequently distributed. Whereas the common hepatic duct and extrapancreatic portion of the common bile duct where peribiliary glands are scarce,¹² are not usually affected. Interestingly, small amounts of exocrine pancreatic acini are occasionally identifiable in these glands, and furthermore, the serous acini of the peribiliary glands contain enzymes of exocrine pancreas.¹² Taken together, it seems likely that exocrine acini of the pancreas in AIP and peribiliary glands in IgG4-SC are damaged, so these two diseases are so frequently associated in the same case, and that some antigen(s) or enzyme(s) located in pancreatic exocrine acini and peribiliary glands could be a target of immunological attack.

In patients with IgG4-related hepatobiliary disease, autoantibodies against carbonic anhydrase II, lactoferrin, amylase, and pancreatic secretory trypsin inhibitor which are located in the lining epithelial cells of the bile ducts and pancreatic ducts, are frequently detected.⁵ Aoki et al. recently found that the normal epithelia of the pancreatic ducts and bile ducts reacted with IgG4 from patients' sera.²⁰ Such IgG4 antibodies showed decreased reactivity with these tissues after steroid therapy, suggesting that the reaction of IgG4 with the suspected antigen in these duct cells

could be responsible for pancreato-biliary lesions in IgG4-related disease. Recently, Detlefsen et al.²¹ reported the deposition of IgG4 in peribiliary glands and pancreatic acini in IgG4-related cholangitis and AIP, supporting the above-mentioned suggestions.

IgG4-tissue positivity in other hepatobiliary diseases

Lymphoplasmacytic infiltration by IgG4-positive plasma cells, a feature of IgG4-related disease, can be also seen in other diseases. For example, suppurative granulation tissue may contain numerous IgG4-positive plasma cells. Considerable IgG4-positive plasma cells can be also seen in pancreatic carcinomas, and some patients with pancreatic carcinoma have elevated serum IgG4 level.²² The following hepatobiliary diseases show clinical features resembling hepatobiliary IgG4-related diseases and are also variably associated with lymphoplasmacytic infiltration and IgG4-tissue positivity, resembling IgG4-related hepatobiliary diseases. A cautious approach is thus necessary for pathologists to determine whether a condition is a IgG4-related disease, particularly in the case of small specimen.

Primary sclerosing cholangitis (PSC)

PSC and IgG4-SC share many clinical and laboratory features, and cholangiographic studies of IgG4-SC show multiple strictures, and narrowing and obliteration of the biliary tree as seen in PSC. However, IgG4-SC responds well to steroid therapy, but PSC does not respond.

Histological differences between PSC and IgG4-SC: in PSC, inflammation is more pronounced on the luminal side, with erosion or ulceration of the duct lining, and cholangitis is also distributed diffusely, but unevenly, along the biliary tract. In IgG4-SC, the bile duct walls and peribiliary glands are severely affected, and erosion or ulceration of the duct epithelia or xanthogranulomatous lesions are rare.¹ PSC is a progressive and fatal disease leading to biliary cirrhosis and cholangiocarcinoma (CC) with biliary intraepithelial neoplastic lesions (BillNs) in advanced cases,²³ though such complications are rare in IgG4-SC.²⁴ While liver cirrhosis related to IgG4-SC is rare, this may be due to the fact that IgG4-SC is commonly resected or treated with steroids at an early stage on clinical suspicion of malignancy or IgG4-SC, thus precluding the progression of IgG4-SC.²⁴

While increased serum IgG4 level and also IgG4-tissue positivity in IgG4-SC are very helpful for a differential diagnosis from PSC, they are not absolute indicators.

PSC with IgG4-tissue positivity and/or increased serum IgG4 level: about 5–23 % of PSC show tissue IgG4-positivity and/or increased serum IgG4 level.²⁴ That is, according to a Mayo Clinic report, 9 % of PSC patients have high serum IgG4 concentrations. In that report, the patients with elevated IgG4 level had higher total bilirubin concentration and PSC Mayo risk scores. Histologically, nearly one-quarter of explanted livers in cases of PSC also reportedly contained increased IgG4⁺ periductal plasma cell infiltrates. IgG4-tissue positivity in the liver strongly correlated with moderate-to-marked periductal lymphoplasmacytic inflammation, while none had storiform fibrosis or obliterative phlebitis. PSC with tissue IgG4-positivity has a more aggressive clinical course such as shorter time to transplant and higher risk of recurrence after transplant.

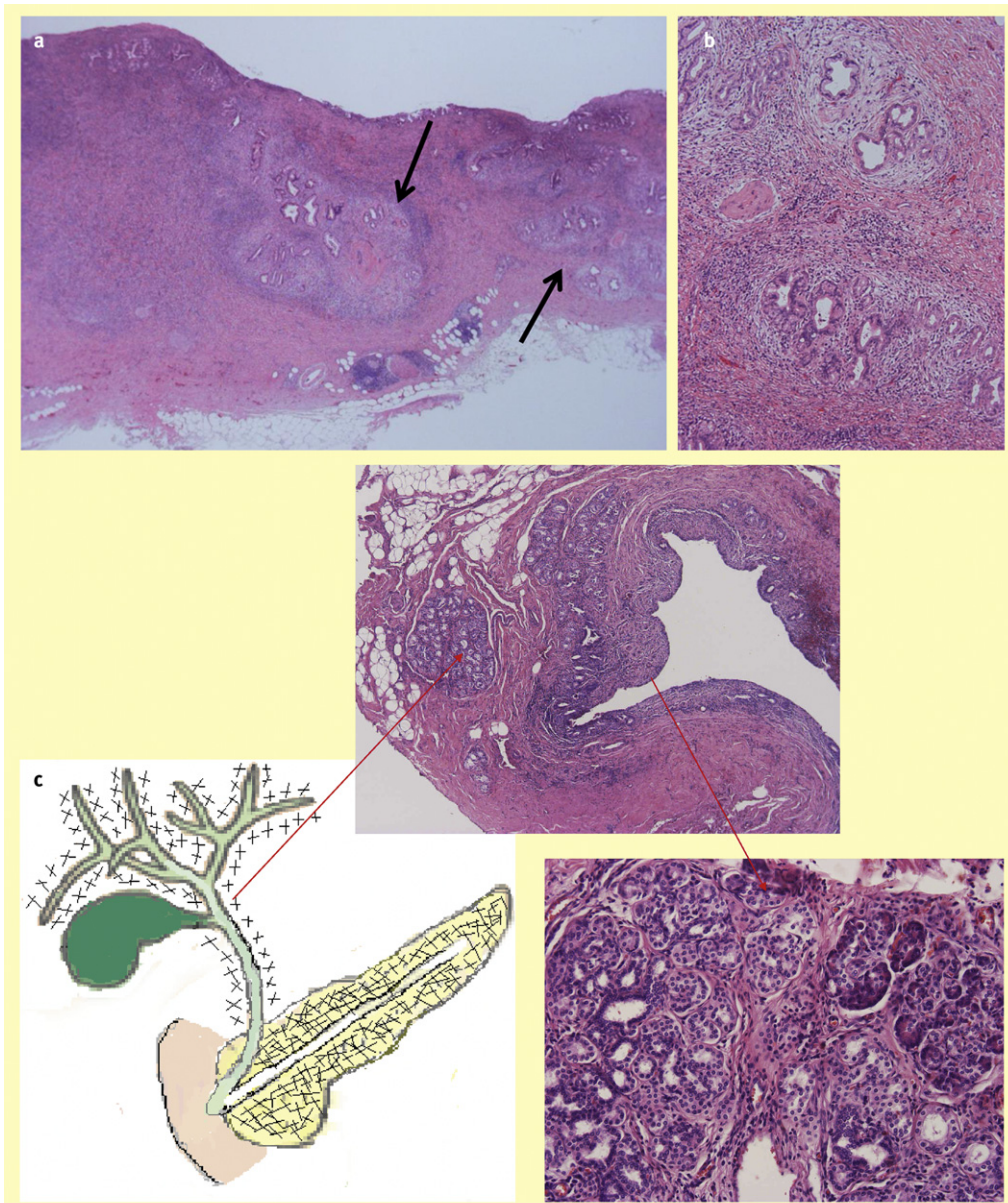


Figure 3 (a) The extrahepatic bile duct shows chronic inflammatory cell infiltration and fibrosis. Inflammation is more accentuated and active around the peribiliary glands (arrows). IgG4-related sclerosing cholangitis. H&E. (b) Peribiliary glands show active inflammation with oedematous changes, lymphoplasmacytic infiltration and fibrosis. IgG4-related sclerosing cholangitis. H&E. (c) Around the extrahepatic bile duct of an apparently normal liver, there are peribiliary glands (upper part). Serous acini with a few amount of exocrine acini are found within these glands (right part). The schema shows distribution of peribiliary glands along the biliary tree (x).

Furthermore, some PSC cases show extensive infiltration of IgG4-positive plasma cells as seen in IgG4-SC. For example, Zen et al. reported that 2 (5%) of 41 cases transplanted for advanced PSC had a high number of IgG4-positive plasma cells within the large bile duct lesion, whereas those cells were scarce in the remaining cases.²⁴

IgG4-positive plasma cells accumulated mainly in (xantho) granulomatous tissue within large bile ducts. Except for the presence of IgG4-positive plasma cells, there was no significant histological or clinical difference between IgG4-positive and negative PSC cases.

While a similar lymphoplasmacytic cholecystitis as seen in IgG4-SC has been reported in other cases of cholecystitis such as

choledocholithiasis and PSC, the demonstration of increased IgG4-positive plasma cells by use of an immunohistochemical stain is a helpful approach for differential diagnosis.

Cholangiocarcinoma and other biliary malignancies

As IgG4-SC or IgG4-related HIP usually presents as a mass or regional lesion with fibrosis and cholangiographic features similar to cholangiocarcinoma (CC) and IgG4-SC may mimic hilar CC more often than PSC, they should be carefully differentiated from hepatobiliary malignancies. In addition, elevated serum level of IgG4 is found in about 20% of CC patients, which makes the differentiation more complicated and difficult, clinically. In fact, until recently, many cases of IgG4-SC or IgG4-

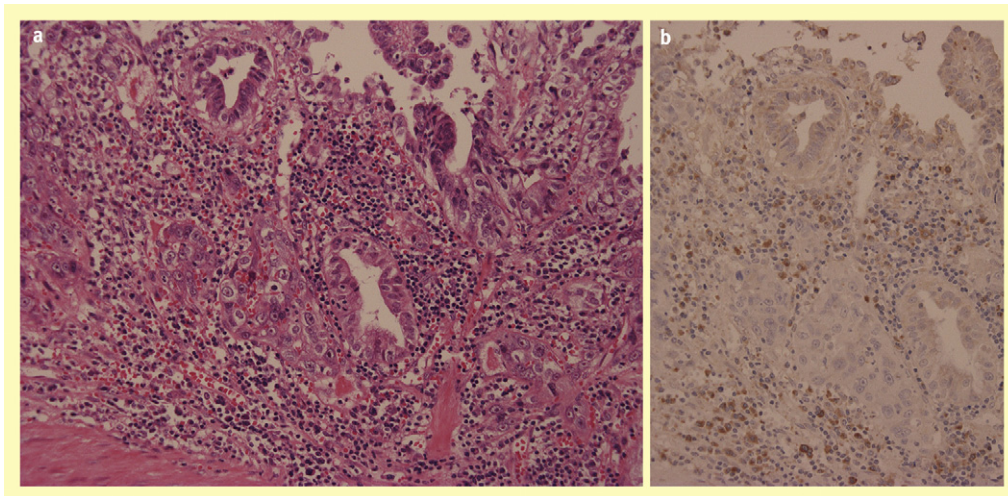


Figure 4 (a) Cholangiocarcinoma of the extrahepatic bile duct. There are many lymphoplasmacytic infiltration in the stroma. H&E. (b) There are many IgG4-positive plasma cells in chronic inflammatory cell infiltration of the cholangiocarcinoma of the extrahepatic bile duct. Immunostaining for IgG4 and haematoxylin.

related HIP were misdiagnosed as CC, and these patients underwent unnecessary surgical resection.

To pathologists, the differentiation of CC from IgG4-related HIP or SC is not an easy task in smaller specimens, because CC itself and its surrounding biliary mucosa is not infrequently associated with lymphoplasmacytic infiltration, and there are also foci of IgG4-positive plasma cell infiltration in CC and surrounding tissue including the biliary mucosa (Figure 4a,b). According to our study, about 30% of CC showed variable infiltration of IgG4-positive plasma cells in the cancerous mucosa including BillN lesions and more frequently in the invasive areas, when examined in surgically resected specimens (Kimura et al., in submission). However, storiform fibrosis or occlusive phlebitis was not evident, suggesting that the mechanism of IgG4-positive plasma cell infiltration in CC is different from that in IgG4-related diseases. Tregs are known to be increased in number in carcinomas and precancerous lesions and also in peripheral blood, and are involved in immune escape from the host. It seems conceivable that IgG4-positive cells may infiltrate and proliferate in response to chemokines released from Tregs. A similar phenomenon was also already pointed out in pancreatic carcinoma.²⁵

The identification of evident carcinomas in specimens excludes a diagnosis of IgG4-SC. However, it is difficult to differentiate IgG4-positive plasma cells in the surrounding mucosa of a carcinoma from IgG4-SC, and recently, biliary carcinomas and BillN lesions arising in IgG4-SC have been occasionally reported. These cases may be a burden for pathologists. Of course, an exact diagnosis may help prevent unnecessary surgery for IgG4-related disease.

IgG4-tissue positivity in autoimmune hepatitis

AIH and AIP share several clinical and pathological features such as high serum levels of immunoglobulin G and non-organ-specific autoantibodies and lymphoplasmacytic infiltration. So far, little is known about the possible involvement of IgG4, a hallmark of AIP, in ordinary AIH. Recently, Chung et al. recently reported that 9 of 26 patients with AIH showed more than five IgG4-positive plasma cells (/HPF) in the liver.

Interestingly, the patients with PBC and with HCV hepatitis showed no or less than four IgG4-positive plasma cells in the liver. These patients with IgG4-positive AIH also showed increased serum levels of IgG, while serum IgG4 level was not elevated in these patients. This type of AIH showed very good response to steroid therapy in comparison with IgG4-negative AIH. While more studies are mandatory for this type of AIH, this AIH seems to be different from IgG4-related AIH reported by Umehara et al.¹⁸

Localized fibro-inflammatory lesions including hepatic inflammatory pseudotumors

There have been no systematic studies on the prevalence of IgG4-positive plasma cells and their significance in miscellaneous localized fibro-inflammatory lesions. In our experience, there is occasional clustering of IgG4-positive plasma cells in miscellaneous hepatobiliary diseases such as *hepatolithiasis*, bacterial cholangitis and biliary diseases with granulomatous changes, though their significance remains unclear. HIP, particularly fibrohistiocytic HIP, is characterized by xanthogranulomatous inflammation, multinucleated giant cells, and neutrophilic infiltration. This type seems to be heterogeneous in its pathogenesis, and some cases showed variable amounts of IgG4-positive plasma cells.

In pathologic consideration whether these condition(s) with variable IgG4-positive plasma cells belong to IgG4-related disease with histopathological modification or novel type of IgG4-related disease, demonstration of increased serum level of IgG4 (more than 135 mg/dl) and association of well-known IgG4-related diseases in addition to considerable IgG4-positive plasma cells and obliterative phlebitis in the affected tissue(s) are necessary.

In conclusion, IgG4-related hepatobiliary diseases, which are now regarded as a part of a family of IgG4-related disease, were discussed with reference to their pathology, etiopathogenesis and differential diagnosis. This field is expanding rapidly and new information and new comers will be discovered regarding the hepatobiliary system. ◆

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Research directions

- New member of IgG4-related disease is still being discovered every year.
- Coexistence of other member of IgG4-related disease may be mandatory for identification of new member of this disease.
- Considerable infiltration of IgG4-positive plasma cells and elevation of IgG4 serum level should be shown.

Practice points

These three findings are necessary to make a diagnosis of IgG4-related sclerosing cholangitis:

- Considerable lymphoplasmacytic infiltration with many IgG4-positive plasma cells.
- Storiform fibrosis or wavy fibrosis and obliterative phlebitis.
- Association of autoimmune pancreatitis.