Int J Clin Exp Pathol 2010;3(5):491-504
www.ijcep.com /IJCEP1005001

Review Article

Autoimmune pancreatitis and IgG4-related systemic diseases

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Received May 5, 2010, accepted May 18, 2010, available online May 25, 2010

Abstract: Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis that is characterized by lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and increased IgG4$^+$ plasma cells. Serum IgG4 levels usually are elevated. Patients with AIP frequently have disease affecting other organs or sites; these tissues show similar histologic changes, including increased IgG4$^+$ plasma cell infiltrate and response to corticosteroid therapy. A new clinicopathologic concept of IgG4-related systemic disease (ISD) has been proposed. These diseases often are not limited to the pancreas, and the pancreas may not be involved at all. In this article, we review the literature and our own experience to detail the clinicopathologic features of AIP and extrapancreatic lesions in ISD.

Keywords: Autoimmune pancreatitis, IgG4, IgG4-related systemic disease

Introduction

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis, first described in 1961 as "primary inflammatory sclerosis of the pancreas" [1]. Subsequent reports have described the disease as lymphoplasmacytic sclerosing pancreatitis, chronic sclerosing pancreatitis, nonalcoholic duct-destructive chronic pancreatitis, and inflammatory pseudotumor [2-5]. The concept of AIP first was proposed by Yoshida et al [6] in 1995. In that report, a patient with chronic pancreatitis also had hyperglobulinemia, was autoantibody-positive, and responded to corticosteroid therapy. The authors suspected that the disease was caused by autoimmune factors. Since then, many studies of this unique type of chronic pancreatitis have shown that autoimmune mechanisms are involved in its pathogenesis.

AIP has become a widely accepted term because clinical, serologic, histologic, and immunohistochemical findings suggest an autoimmune mechanism. AIP is occasionally associated with other autoimmune disorders such as Sjogren syndrome, idiopathic retroperitoneal fibrosis, and inflammatory bowel disease (IBD) [6-9]. Most affected patients have hypergammaglobulinemia and increased serum levels of IgG, particularly IgG4 [10], [11]. Patients also may have autoantibodies directed against lactoferrin, carbonic anhydrase II and IV, rheumatoid factor, smooth muscle antigens, and nuclear antigens [8]. AIP is characterized histologically by a diffuse lymphoplasmacytic infiltration, accompanied by obliterative phlebitis and interstitial fibrosis [12, 13]. Immunohistochemical typing reveals a predominance of CD8$^+$ and CD4$^+$ T lymphocytes, with few B lymphocytes [14]. Importantly, increased IgG4$^+$ plasma cell infiltrate in the pancreas is a very useful marker for the histologic diagnosis of AIP[15-18]. Finally, AIP responds well to corticosteroid therapy [19-21].

Patients with AIP often have diseases affecting other organs or sites. The association of chronic pancreatitis with sclerosing cholangitis and Sjogren syndrome was recognized as early as 1984 [22]. Nearly 20 years later, the concept of a systemic IgG4 disease was introduced by Kamisawa et al [23], who showed that patients with AIP had extensive IgG4$^+$ plasma cell infiltrate in other organs, including peripancreatic tissue, bile duct, gallbladder, portal area of the liver, gastric mucosa, colonic mucosa, salivary

glands, lymph nodes, and bone marrow. They proposed the term "IgG4-related systemic disease" (ISD) to describe this condition. Their observations were confirmed by several subsequent studies [16, 18, 24-26]. ISD is defined as a syndrome characterized by elevated serum IgG4 levels, prominent lymphoplasmacytic infiltrates with increased $IgG4^+$ plasma cells, and dense sclerosis. The fibrosis associated with ISD may damage and even partially destroy an affected organ, but the inflammatory process typically responds to corticosteroid therapy [27]. Although the pancreas is the most commonly affected organ, the presence of AIP is not essential in this systemic disease. In the series by Kamisawa et al [28], 2 patients had AIP develop only during follow-up of sclerosing sialadenitis.

Extrapancreatic presentations can include sclerosing cholangitis, retroperitoneal fibrosis, sclerosing sialadenitis (Küttner tumor), lymphadenopathy, nephritis, and interstitial pneumonia. Increased $IgG4^+$ plasma cell infiltrate has been reported in sclerosing lesions from other organ sites, including inflammatory pseudotumors of liver, breast, mediastinum, orbit, and aorta, and it has been observed with hypophysitis and IgG4 -associated prostatitis [29-36]. Furthermore, we have observed abundant $IgG4^+$ plasma cells in Riedel thyroiditis, sclerosing mesenteritis, and inflammatory pseudotumor of the orbit and stomach. In this review, we describe the clinical and histologic presentations of AIP, its associated extrapancreatic manifestations, and other related entities.

Autoimmune Pancreatitis

AIP is a rare disorder with characteristic clinical, histologic, and morphologic findings [21, 27]. Most of the literature about AIP comes from Japan, where the incidence appears to be increasing, perhaps because of increased recognition of the disease [37]. However, AIP has been described in several countries in Europe, as well as in the United States and Korea, which suggests that it is a worldwide entity [38]. Clinically, patients can present with abdominal pain, weight loss, and jaundice, and liver function tests will show an obstructive pattern. Imaging usually shows diffuse enlargement of the pancreas, but tumor-like local swelling can occur. The pancreatic duct is diffusely or segmentally narrowed. Such presentations of AIP mimic pancreatic cancer. Until recently, almost all AIP was diagnosed in patients undergoing pancreaticoduodenectomy for presumed pancreatic cancer[39, 40]. Despite growing awareness of the condition, differentiating between AIP and pancreatic cancer remains challenging, particularly for patients with radiologic evidence of a tumefactive lesion. Because the condition responds so well to corticosteroid treatment, the correct preoperative diagnosis is highly desirable. Recently, Mayo Clinic introduced criteria for diagnosing AIP; summarized by the mnemonic HISORt, these criteria include 5 cardinal features of AIP in histology, imaging, serology, other organ involvement, and response to corticosteroid therapy [41].

A possible marker for AIP is elevated serum levels of IgG4. A hallmark study by Hamano et al [10] reported that serum IgG4 levels were highly sensitive (95%) and highly specific (97%) for AIP. However, elevated IgG4 levels have been observed in patients with atopic dermatitis, asthma, some parasitic diseases, pemphigus vulgaris, and pemphigus foliaceus [42-45] , which suggests that it is not entirely AIP-specific. In a recent large cohort study, Ghazale et al [46] showed that elevated serum IgG4 levels were a characteristic but not diagnostic feature of AIP. Elevated IgG4 levels were observed in 3% to 10% of patients without AIP, including those with primary sclerosing cholangitis (PSC), pancreatic cancer, and acute and chronic pancreatitis, as well as patients without any pancreatic disease. Thus, elevated serum IgG4 levels alone are not sufficient to make the diagnosis of AIP.

Grossly, AIP may diffusely involve the entire pancreas, or it may focally affect the pancreatic head and mimic pancreatic cancer both clinically and radiologically [6, 47, 48]. Because of dense fibrosis, the pancreas is firm upon gross inspection. A distinct mass or nodule usually is not present, even though a tumescent mass may be suggested by imaging studies. The pancreatic parenchyma is fibrotic, and the lobulated architecture can be partially destroyed by fibrosis [2]. Calcification is an uncommon finding. The pancreatic duct may be diffusely or segmentally narrowed. The common bile duct often is involved and can have a thickened wall, narrowing, and dilation at the proximal part.

The typical histologic features of AIP are as follows: dense fibrosis with a focal storiform-like pattern that is intermixed with inflammatory

cells and diffuse, lymphoplasmacytic infiltration centered on pancreatic ducts, accompanied by obliterative phlebitis and acinar atrophy (**Figure 1A**) . The obliterative phlebitis (**Figure 1B**) is a very helpful feature when making a diagnosis of AIP, but it is not pathognomonic. Lymphoid aggregates can be identified in most cases in intrapancreatic and extrapancreatic tissue.

Two histologic subgroups of AIP have been recognized recently; they are designated as lymphoplasmacytic sclerosing pancreatitis (type 1) and idiopathic duct-destructive pancreatitis (type 2) [12, 49]. Type 1 AIP usually has the histologic features described above. Although the 2 groups have some histologic overlap, type 2 AIP is characterized by granulocytic epithelial lesions, which show neutrophils in the duct epithelium or duct epithelial damage in the lumen (or both) (**Figure 1C**) [13]. It is still unclear whether the 2 subgroups represent different diseases or different stages of the same disease. A recent, large, cohort study [50] showed that type 1 and type 2 AIP have distinct clinical profiles. Patients with type 1 AIP were older than those with type 2 AIP (mean [SD] age, 62 [14] vs 48 [19] years) and had a greater prevalence of increased serum levels of IgG4 (47/59 [80%] vs 1/6 [17%] patients). Patients with type 1 AIP were more likely to have proximal biliary, retroperitoneal, renal, or salivary disease (60% vs 0%) and also were more likely to have relapse (47% vs 0%). After a median follow-up of 58 months (for type 1 patients) and 89 months (for type 2 patients), the 5-year survival rates for both groups were similar to those of an age- and sex-matched US population.

The histologic diagnosis of AIP can be difficult, especially if the tissue sample is small (eg, from a core needle biopsy), and also because of patchy distribution of the disease [51]. After the report of elevated serum IgG4 levels in AIP by Hamano et al [10], numerous studies have evaluated the contribution of IgG4 immunohistochemical staining when diagnosing AIP [16-18, 23, 25]. Although all studies indicated that increased $IgG4^+$ plasma cell infiltrate in the pancreas was a helpful marker for AIP, like elevated serum IgG4 levels, it is not entirely specific for AIP. In our study [17], moderately increased $IgG4^+$ plasma cell infiltrate in the pancreas (>10 cells per high-powered field) could be seen in 72% of AIP (**Figure 1D**), but it also was present in 11% of patients with alcoholic chronic pancreatitis and 12% of patients with pancreatic adenocarcinoma. Findings of IgG4 immunostaining should be interpreted cautiously when the tissue sample is small and $IgG4^+$ plasma cell infiltrates are limited (ie, 5-10 cells per high-powered field). Because AIP is considered a systemic disease and high levels of IgG4 staining have been found in other organs of patients with AIP, some authors suggested that positive IgG4 staining in extrapancreatic tissue may confirm a definitive diagnosis of AIP for patients those with clinical evidence of pancreatic disease, thereby eliminating the need for pancreatic biopsy or surgical exploration [16, 18, 23, 52]. However, in our experience, IgG4 immunostaining on duodenal mucosa biopsy specimens from patients with known AIP did not show more $IgG4^+$ cells than control patients with normal mucosa or with giardiasis, celiac disease, peptic duodenitis, or adenoma. The diagnostic value of IgG4 immunostaining in extrapancreatic tissue for AIP is still undetermined.

Extrapancreatic Organ Involvement in ISD

Bile Duct

The biliary tract is the most commonly involved extrapancreatic site in ISD with AIP. Several case series have described the association between AIP and biliary strictures. The overall rate of extrahepatic bile duct involvement in AIP is 71% to 100% [23, 25, 28, 46, 53] [54]. In a recent review, we introduced the term "IgG4-associated cholangitis" (IAC) to describe biliary manifestations of ISD [55]. The involvement of the biliary tree in AIP usually is determined radiographically by bile duct wall thickening and biliary stricture. Although serum IgG4 elevation is characteristic of IAC, it is not a pathognomonic finding. The sensitivity of serum IgG4 for IAC in our study was 74%, similar to that seen in AIP [54]. The specificity and positive predictive value of elevated serum IgG4 levels for IAC is unknown.

Histologically, the bile duct wall is characterized by diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis with focal storiform-like pattern, and occasional obliterative phlebitis (**Figure 1E**). The biliary epithelium is usually spared of injury. The features are similar to changes in the pancreas. Immunohistochemically, moderate infiltration of $IgG4^+$ plasma cells

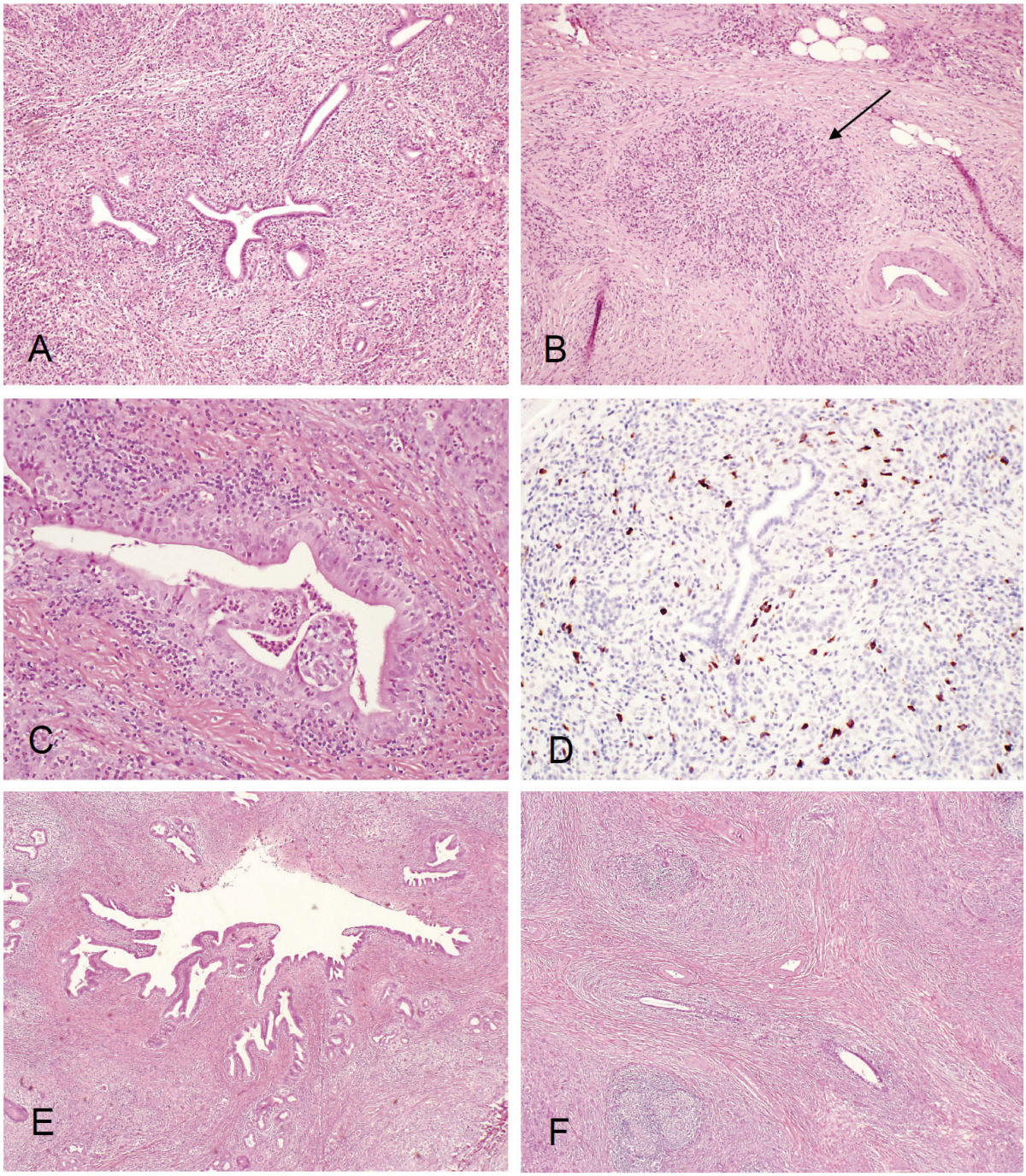

Figure 1. (A), Type 1 autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis): low power view showing periductal lymphoplasmacytic infiltrate and storiform fibrosis with inflammatory cellular stroma. (B), Obliterative phlebitis (arrow): dense peri- and intra-venular inflammatory infiltrate with fibrosis destroying the endothelium and obliterating the lumen. (C), Granulocyte epithelial lesion (GEL) in type 2 autoimmune pancreatitis (idiopathic duct centric pancreatitis): periductal lymphoplasmacytic and neutrophilic infiltrate with intra-epithelium and intra-lumen neutrophilic infiltrate; destruction of small ducts and ductal epithelium, lobular lymphoplasmacytic and neutrophilic infiltrate. (D), IgG4 immunostain: markedly increased (>30/high power filed) periductal IgG4+ plasma cell infiltrate. (E), IgG4 associated cholangitis: low power view showing periductal lymphoplasmacytic infiltrate and storiform fibrosis. (F), Chronic sclerosing sialadenitis (Küttner tumor) showing dense lymphoplasmacytic infiltrate and storiform fibrosis destroying glandular structures.

was observed in 88% of patients in our series [54].

Like AIP, other organ involvement is an important clue in the diagnosis of IAC. The presence of unexplained pancreatic disease in patients with biliary strictures should raise clinical suspicion for IAC. Although AIP is present in most patients with IAC, we recently identified 7 patients with IAC who had no obvious pancreatic disease (according to clinical and imaging criteria) and did not have elevated serum IgG4 levels. All underwent surgical exploration because of a high suspicion of extrahepatic cholangiocarcinoma. The resected specimen had typical histologic features of IAC, as described above, and all showed marked periductal $IgG4^+$ plasma cell infiltrate. Therefore the absence of AIP and normal serum IgG4 levels should not exclude IAC from the differential diagnosis. Like AIP, biliary strictures in IAC respond to corticosteroids. In our study [54], complete resolution of strictures or normalization of liver tests (or both) were observed in approximately two-thirds of patients, and improvement was noted for the remaining one-third.

IAC can be confused with PSC, especially because of overlapping radiologic findings, but only the former responds well to corticosteroid therapy. Clinically, IAC usually occurs abruptly, with obstructive jaundice, compared with PSC; the PSC diagnosis often is made in asymptomatic patients after liver test abnormalities are identified [56]. Radiologic findings of IAC usually include segmental strictures, dilation after confluent stricture, and strictures of the lower common bile duct. IgG4 immunostaining shows that the degree of infiltration of $IgG4^+$ plasma cells around the bile duct in the portal areas and the extrahepatic bile duct is markedly lower with PSC than with AIP-associated cholangitis [57]. We recently found that nearly one quarter of explanted livers that carry a clinical diagnosis of PSC contain increased IgG4+ periductal plasma cell infiltrates and positive serum IgG4 levels. However, none of the explants show histologic features diagnostic of IAC. PSC with tissue IgG4 positivity has a more aggressive clinical course manifested by shorter time to transplant and a higher likelihood of recurrence than IgG4 negative PSC [58]. However, most PSC patients with elevated IgG4 had a good biochemical response to steroids [59].

Liver

Liver dysfunction frequently is observed in patients with AIP. It can be due either to extrahepatic obstructive lesions or to inflammatory liver injury. Hirano et al [60] reported lymphoplasmacytic infiltration in the portal area for 7 of 7 liver biopsy samples in their study. Another recent study [61] proposed the term "IgG4 -hepatopathy" and described 5 histologic liver patterns in AIP: 1) evident portal inflammation with or without interface hepatitis, 2) large bile-duct obstructive features, 3) portal sclerosis, 4) lobular hepatitis, and 5) canalicular cholestasis. Some of these histologic features coexisted in the same liver specimen. The number of $IgG4^+$ plasma cells was significantly higher in patients with AIP than in control patients with autoimmune hepatitis, primary biliary cirrhosis, PSC, or chronic viral hepatitis [62] and was significantly correlated with serum IgG4 concentration. Corticosteroid therapy reduces $IgG4^+$ plasma cell infiltration in the liver and ameliorates other histologic findings. Interestingly, a recent case report [63] described a patient with severe hepatitis, elevated serum IgG4 levels, and $IgG4^+$ plasma cell infiltrates in the liver, but the patient had no evidence of pancreatic disease.

Another aspect of liver involvement in ISD is hepatic inflammatory pseudotumor [32, 62]. The recent study by Zen et al [64] defined 2 types of hepatic inflammatory pseudotumors, fibrohistiocytic and lymphoplasmacytic. In their description, "histiocytic inflammatory pseudotumors were characterized by xanthogranulomatous inflammation, multinucleated giant cells, and neutrophilic infiltration, [which] mostly occurred in the peripheral hepatic parenchyma as mass-forming lesions. In contrast, lymphoplasmacytic inflammatory pseudotumors showed diffuse lymphoplasmacytic infiltration and prominent eosinophilic infiltration, and were all found around the hepatic hilum. In addition, venous occlusion with little inflammation and cholangitis without periductal fibrosis were frequently observed in the fibrohistiocytic type, whereas obliterative phlebitis and cholangitis with periductal fibrosis were common features of the lymphoplasmacytic type. IgG4-positive plasma cells were significantly more numerous in the lymphoplasmacytic than fibrohistiocytic type" [64]. The authors concluded that the lymphoplasmacytic type has histologic features similar to AIP and could belong to ISD.

Gallbladder

Gallbladders frequently are affected in AIP; they are characterized by a diffuse, acalculous, lymphoplasmacytic cholecystitis [65-67]. Although a pattern of diffuse, lymphoplasmacytic, chronic cholecystitis is highly specific for extrahepatic biliary tract disease, it does not distinguish between primary and secondary cholangiopathies such as PSC, malignancy-associated obstructive jaundice, or cholelithiasis [68]. Lymphoplasmacytic cholecystitis associated with AIP usually shows deep mural and extramural inflammation. Phlebitis and inflammatory nodules were more frequently noted in patients with AIP. AIP gallbladders show increased $IgG4^+$ plasma cell and higher $IgG4^+/IgG^+$ plasma cell ratios than gallbladders from patients with pancreatic carcinoma or PSC, and IgG4 immunostaining may be a useful marker for AIP-associated cholecystitis [65, 67].

Gastrointestinal Tract

Scattered $IgG4^+$ plasma cells usually are present in normal gastrointestinal mucosa. In the initial report describing ISD[23], increased $IgG4^+$ plasma cells were observed in the stomach and colon. Deheragoda et al [18] reported a marked increase in $IgG4^+$ plasma cells in gastrointestinal mucosa in AIP and suggested that immunostaining of involved tissue for IgG4 may be useful when AIP is suspected clinically. Another study suggested that IgG4-immunostaining of biopsy specimens from the major duodenal papilla may support the diagnosis of AIP [52]. However, the small number of patients in these studies limits the generalizability of these findings. In our experience, IgG4 immunostaining of duodenal mucosa biopsy specimens did not show more $IgG4^+$ cells in patients with AIP compared with controls.

IBD occasionally is associated with AIP [9, 13]. Zamboni et al [13] showed a high prevalence of IBD with AIP and convincingly showed that idiopathic duct-destructive pancreatitis and granulocytic epithelial lesions were more frequently associated with IBD. The clinical significance of this finding is unknown.

Salivary and Lacrimal Glands

Salivary and lacrimal glands are frequently involved in ISD [13] [23, 25, 69, 70]. Küttner tumor is a chronic, sclerosing sialadenitis that presents with asymmetric, firm swelling of the submandibular glands. Kitagawa et al [69] reported a series of 12 patients with Küttner tumors and reported that 5 had sclerosing lesions in extrasalivary glandular tissues. Geyer et al [71] reported 13 cases recently, of which 3 presented with ISD. Histologically, the salivary glands showed marked lymphoplasmacytic infiltration with fibrosis and the destruction of glandular lobules (Figure 1F). Obliterative phlebitis often was observed. Immunohistochemically, the proportion of $IgG4^+/IgG^+$ plasma cells was more than 45% in patients with Küttner tumor, whereas it was less than 5% for control patients with sialolithiasis or Sjögren syndrome. The similarity in clinicopathologic features between Küttner tumor and AIP suggests the same IgG4-related disease origin. Thus, IgG4immunostaining may be useful for distinguishing between chronic, sclerosing sialadenitis and other forms of sialadenitis.

Mikulicz disease is an idiopathic, bilateral, painless, and symmetric swelling of the lacrimal, parotid, and submandibular glands. Microscopically, tissues show marked lymphoplasmacytic infiltration, with lymphoid follicles surrounding solid epithelial nests (epimyoepithelial islands), stromal fibrosis, acinar atrophy and destruction, and lymphoepithelial lesions. Because Mikulicz disease and Sjögren syndrome are histologically similar, Mikulicz disease has been considered a subtype of Sjögren syndrome, even though the 2 diseases have some clinical differences. Patients with Mikulicz disease have elevated serum IgG4 concentrations and infiltration of $IgG4^+$ plasma cells into the lacrimal and salivary glands [70, 72-74]. Thus, Mikulicz disease is now considered as an ISD.

Sjögren syndrome occasionally is observed in patients with AIP [7, 22, 75, 76]. Although Sjögren syndrome has some histologic overlap with AIP, a few studies showed that the submandibular gland of patients with AIP differ from those with typical Sjögren syndrome. Serum IgG4 levels in Sjögren syndrome are significantly lower than those in patients with AIP [10, 74]. Rare $IgG4^+$ plasma cells are seen in Sjögren syndrome [69, 77], which suggests that IgG4 may not have an important role in the cause of Sjögren syndrome.

Kidney

Renal lesions in ISD usually present as tubu-

lointerstitial nephritis. Clinically, patients can present with renal insufficiency, vasculitis, or a "renal mass"; these symptoms often are associated with AIP [78-84]. Histologically, renal lesions are characterized by a densely patchy or diffuse tubulointerstitial lymphoplasmacytic infiltrate. Numerous eosinophils are often seen. Tubulitis and tubular injury are present, along with tubular atrophy and focally thickened tubular basement membranes. Glomeruli usually are uninvolved [82, 83]. Immunohistochemistry shows a marked increased IgG4$^+$ plasma cell infiltrate [80-83]. One study also showed IgG4 immune-complex deposits in the tubular basement membranes, as evidenced by immunofluorescence or immunohistochemistry and by electron microscopy [83]. Like AIP, tubulointerstitial nephritis associated with AIP usually responds favorably with corticosteroid therapy [84].

Retroperitoneum and Mesentery

Retroperitoneal fibrosis is a disease characterized by the proliferation of fibrous tissue in the retroperitoneum (specifically, marked lymphoplasmacytic infiltrations encompassed by a dense fibrosis). The lesions show active and chronic inflammatory infiltration and sclerosis, and lymphoid follicles with germinal centers are also present. Most infiltrating IgG$^+$ plasma cells are IgG4$^+$ [85].No causative factor is identified for most patients, although autoimmune mechanisms have been suggested. Some cases of retroperitoneal fibrosis associated with AIP have been reported [9, 85-88] and were resolved by corticosteroid therapy. Serum IgG4 levels were elevated for most patients.

Sclerosing mesenteritis is a rare fibroinflammatory disorder of unknown cause; it primarily affects the small bowel mesentery. Histologically, the most frequent finding is prominent fibrosis with scant inflammation and some fat necrosis. Involvement of the pancreas in patients with sclerosing mesenteritis has been reported previously [89, 90]. One study showed that 33% of patients with sclerosing mesenteritis have abundant IgG4$^+$ plasma cell infiltrates in the tissue [91]. The authors speculated that IgG4-related immunopathologic processes also might be involved in the pathogenesis of some cases of sclerosing mesenteritis.

Thyroid

About a quarter of patients with AIP have clinically significant hypothyroidism [25, 92]. Patients with hypothyroidism more commonly have antithyroglobulin antibodies than those without hypothyroidism, but other laboratory test findings are similar, including serum IgG4 concentration. No histologic findings or tissue samples showing IgG4$^+$ plasma cell infiltrate were available. The authors suggested evaluating thyroid function in patients with AIP. [92]

Riedel thyroiditis is an uncommon form of chronic thyroiditis, in which the thyroid gland is replaced by fibrous tissue. Although the cause of Riedel thyroiditis is unclear, it is considered part of a systemic fibroinflammatory process also involving other organs; it may be associated with retroperitoneal fibrosis, sclerosing mediastinitis, sclerosing cholangitis, or orbital pseudotumors [93, 94]. We have observed numerous IgG4$^+$ plasma cells in Riedel thyroiditis. Like inflammatory pseudotumors in other organs, Riedel thyroiditis likely also is an IgG4-related systemic fibroinflammatory process.

Breast

Inflammatory pseudotumor of the breast is an extremely rare condition. A case of IgG4-related inflammatory pseudotumor of the breast has been reported [36]. This patient presented with an induration in the left breast, and the lesion had histologic features similar to those of AIP. Furthermore, the patient also had elevated serum IgG4 levels and many IgG4$^+$ plasma cells within the lesion. This case may be a manifestation of ISD in breast.

Lung

Pulmonary involvement in ISD can present as interstitial pneumonia or as an inflammatory pseudotumor. Hamed et al [95] described a patient with a lung nodule that mimicked lung cancer clinically. The patient also had elevated serum IgG4 levels and inflammatory lesions in his prostate, submandibular glands, and bile ducts. The biopsy of the lung nodule showed many IgG4$^+$ plasma cells. A final diagnosis of ISD was made and the patient was treated with corticosteroids.

Two patients with AIP-associated interstitial pneumonia have been reported. Taniguchi et al [96] described a patient with bilateral, interstitial pneumonia of the lower lung fields during follow-up for AIP. A transbronchial lung biopsy

Table 1. Organs affected by IgG4-related systemic disease

Organ or Site	Clinicopathologic Features	References
Pancreas	Lymphoplasmacytic sclerosing pancreatitis (type 1 autoimmune pancreatitis) Idiopathic, duct-centric, chronic pancreatitis or granular epithelial lesion (type 2 autoimmune pancreatitis)	10, 12, 13, 16, 17, 21, 27, 38, 41, 49, 50
Bile duct	Sclerosing cholangitis or IgG4-associated cholangitis Inflammatory pseudotumor	46, 53, 54, 55, 56
Liver	Sclerosing cholangitis involving intrahepatic ducts Portal inflammation, with or without interface hepatitis Large bile-duct obstruction Portal sclerosis Lobular hepatitis Canalicular cholestasis Inflammatory pseudotumor	35, 60-64
Gallbladder	Diffuse, acalculous, lymphoplasmacytic cholecystitis	65-68
Gastrointestinal tract	Increased IgG4-positive cells in mucosa Inflammatory bowel disease	13, 18, 23, 52
Salivary and lacrimal glands	Küttner tumor (chronic sclerosing sialadenitis) Mikulicz disease Chronic, sclerosing dacryoadenitis	69-74
Kidney	Tubulointerstitial nephritis Membranous glomerulopathy, with IgG4 immune complex deposits in tubular basement membrane	78-84
Retroperitoneum and mesentery	Retroperitoneal fibrosis Sclerosing mesenteritis	85-91
Thyroid	HypothyroidismRiedel thyroiditis	92-94
Breast	Inflammatory pseudotumor	36
Lung	Interstitial pneumonia Inflammatory pseudotumor	97-101
Aorta	Inflammatory abdominal aortic aneurysm	31, 32
Orbit	Inflammatory pseudotumor	30
Mediastinum	Sclerosing mediastinitis	29
Pituitary gland	Hypophysitis Inflammatory pseudotumor	33
Prostate	IgG4-associated prostatitis	34
Lymph nodes	Castleman disease–like lymphadenopathy Lymphadenopathy with follicular hyperplasia Lymphadenopathy with interfollicular expansion by immunoblasts and plasma cells	100-103

showed marked thickening of the alveolar septum, with considerable lymphoplasmacytic infiltrate and increased $IgG4^+$ cells. Nieminen et al [97] also reported a patient with idiopathic pancreatitis, sclerosing cholangitis, sialadenitis, and nodular interstitial pneumonia. In both cases, patients responded to corticosteroid therapy.

IgG4-related immunopathologic processes might be involved in the pathogenesis of the

pulmonary lesions. Zen et al [98] reported 9 patients with pulmonary inflammatory pseudotumors; the pseudotumors had histologic features similar to those of AIP, with dense lymphoplasmacytic infiltrates intermixed with fibrosis and, in some cases, prominent eosinophilic infiltration, irregular narrowing of bronchioles entrapped in nodules, and an interstitial pneumonia pattern at the boundaries of nodules. Obliterative phlebitis was present in all cases, and 5 lesions also had obliterative arteritis. Shrestha et al [99] described lung biopsies of 6 patients with AIP; specimens showed endothelialitis of pulmonary vessels, active fibrosis, lymphangitic inflammatory infiltrates rich in plasma cells and histiocytes (with or without nodule formation), and fibrinous pleuritis. Immunostaining showed many $IgG4^+$ plasma cells diffusely distributed within nodules.

Lymph Node

Concomitant lymphadenopathy is common in ISD [100-102]. A recent study [103] detailed morphologic features of the lymph nodes in ISD. The authors categorized these features into 3 patterns: 1) Castleman disease–like features, 2) follicular hyperplasia, and 3) interfollicular expansion by immunoblasts and plasma cells. However, lymph nodes often lacked typical storiform fibrosis or phlebitis. When compared with 54 control lymph nodes from patients with various reactive conditions, the percentage of $IgG4^+/IgG^+$ plasma cells in patients with AIP and lymphadenopathy was markedly elevated (mean, 62% vs. 9.9%). Most patients responded to corticosteroid therapy. The clinical significance of lymph node involvement in ISD remains uncertain.

Summary

Since the term “autoimmune pancreatitis” was first introduced by Yoshida et al [6] in 1995, tremendous clinical, serologic, radiologic, and pathologic studies to characterize this relatively new entity. To facilitate clinical management of AIP, diagnostic criteria have been established, and serologic markers and pathologic features have been identified. Cumulatively, the evidence suggests that AIP is a part of a new clinicopathologic entity of IgG4-related autoimmune diseases. The extrapancreatic lesions typically have pathologic features similar to those of AIP; they are characterized by lymphoplasmacytic infiltrate with dense fibrosis, obliterative phlebitis, and increased $IgG4^+$ plasma cells. Serum IgG4 levels are often elevated, but this is not a disease-specific finding. Not all ISD patients have AIP, although the pancreas is the most commonly involved organ.

Importantly, AIP is frequently associated with various extrapancreatic lesions. The involvement of other organs has been widely reported (**Table 1**), and the prevalence and distribution of extrapancreatic lesions has been proposed in a recent study [25]. ISD can affect only 1 organ (usually presenting as an inflammatory pseudotumor), or it can affect 2 to 4 organs. It is particularly important for surgical pathologists to be aware of this disease and to make the correct diagnosis; treatment with corticosteroids will result in rapid and sustained resolution without unnecessary surgical procedures.

Abbreviations: AIP, autoimmune pancreatitis; IAC, IgG4-associated cholangitis; IBD, inflammatory bowel disease; ISD, IgG4-related systemic disease; PSC, primary sclerosing cholangitis

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