Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis of presumed autoimmune etiology. Many new clinical aspects of AIP have been clarified during the past 10 years, and AIP has become a distinct entity recognized worldwide. However, its precise pathogenesis or pathophysiology remains unclear. As AIP dramatically responds to steroid therapy, accurate diagnosis of AIP is necessary to avoid unnecessary surgery. Characteristic dense lymphoplasmacytic infiltration and fibrosis in the pancreas may prove to be the gold standard for diagnosis of AIP. However, since it is difficult to obtain sufficient pancreatic tissue, AIP should be diagnosed currently based on the characteristic radiological findings (irregular narrowing of the main pancreatic duct and enlargement of the pancreas) in combination with serological findings (elevation of serum γ-globulin, IgG, or IgG4, along with the presence of autoantibodies), clinical findings (elderly male preponderance, fluctuating obstructive jaundice without pain, occasional extrapancreatic lesions, and favorable response to steroid therapy), and histopathological findings (dense infiltration of IgG4-positive plasma cells and T lymphocytes with fibrosis and obliterative phlebitis in various organs). It is apparent that elevation of serum IgG4 levels and infiltration of abundant IgG4-positive plasma cells into various organs are rather specific to AIP patients. We propose a new clinicopathological entity, “IgG4-related sclerosing disease”, and suggest that AIP is a pancreatic lesion reflecting this systemic disease.

Key words: autoimmune pancreatitis, IgG4, chronic pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis

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Autoimmune pancreatitis

Concept of AIP
AIP is a unique form of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. AIP has many clinical, radiological, serological, and histopathological characteristics as follows: (1) elderly male preponderance; (2) frequent initial symptom of obstructive jaundice without pain; (3) occasional association with impaired pancreatic endocrine or exocrine function and various extrapancreatic lesions; (4) a favorable response to steroid therapy; (5) radiological findings of irregular narrowing of the main pancreatic duct and enlargement of the pancreas; (6) serological findings of elevation of serum γ-globulin, IgG, or IgG4 levels, along with the presence of some autoantibodies; and (7) histopathological findings of dense lymphoplasmacytic infiltration with fibrosis and obliterator phlebitis in the pancreas. Typical AIP shows diffuse changes of the pancreas, but several cases have shown segmental changes. Localized AIP may extend progressively to the whole pancreas. The current concept of AIP, including associated extrapancreatic lesions, suggests that AIP may be a systemic disease.

AIP has been described by various names reflecting different aspects of the entity and each emphasizing the clinical, radiological, or histological findings: for example, chronic inflammatory sclerosis of the pancreas, duct-narrowing chronic pancreatitis (DNCP), lymphoplasmacytic sclerosing pancreatitis, nonalcoholic duct destructive chronic pancreatitis, and idiopathic tumefactive chronic pancreatitis.

Prevalence
AIP is a rare disorder, but its exact incidence is unknown. In a nationwide survey conducted in Japan, 900 patients with AIP were identified, and the total number of patients treated for chronic pancreatitis in a year was estimated as 44,700. The prevalence rate of AIP among patients with chronic pancreatitis was 1.95% in this survey. We encountered 32 patients (8.4%) with AIP out of 380 patients with chronic pancreatitis clinically diagnosed in our institute. Other reported prevalence rates of AIP among chronic pancreatitis cases are 4.6% (21/451) in Japan, 5.4% (17/315) in Korea, and 6.0% (23/383) in Italy. In North America, about 2.5% of pancreaticoduodenectomies are performed for AIP because of a mistaken diagnosis of pancreatic cancer, and AIP cases represent between 21% and 23% of pancreaticoduodenectomies performed for benign conditions. Reported AIP cases are increasing with the growing awareness of this entity around the world.

Pathogenesis
Serum IgG4 is a subtype of IgG, and its levels are frequently elevated and particularly high in AIP. Dense infiltration of IgG4-positive plasma cells is seen in various organs of AIP patients. These results suggest that IgG4 plays a major role in the pathogenesis of AIP, although the trigger for the IgG4 elevation or its pathogenic role in AIP has not been clearly disclosed. Antilactoferrin and anti-carbonic anhydrase II (CA-II) antibodies are frequently detected in AIP patients. Therefore, lactoferrin and CA-II have been proposed as the target antigens, but this has not yet been fully confirmed. Although the actual effector cells of AIP have not been clearly delineated, the number of activated CD4- and CD8-positive T cells bearing HLA-DR is increased among the peripheral blood lymphocytes and in the pancreas of AIP patients. It has also been reported that this disease is closely associated with the HLA DRB1*0405-DQB1*0401 haplotype, suggesting that the specific peptide presented by these HLA molecules triggers the pathological process of the autoimmunity.

Although the many above-mentioned findings support an immunologic mechanism of AIP, target antigens for AIP have not been detected. Its preponderant occurrence in elderly men and markedly dramatic response to oral steroid therapy suggest that the pathogenesis of AIP might not be by an autoimmune mechanism but by some other mechanism such as an allergic reaction.

Clinical manifestations
AIP occurs predominantly in elderly men. In our series, the mean age of the patients was 68.3 years (range, 29–83 years) and the male-to-female ratio was 4:1. In a study in Korea, the mean age was 59.1 years (45–75 years), and the male-to-female ratio was 15:2. Patients rarely show typical features of pancreatitis, and the major presenting complaint is painless obstructive jaundice due to associated sclerosing cholangitis (65% or 86% of cases). The jaundice sometimes fluctuates. Diabetes mellitus, usually type 2, is often (41% or 76% of cases) observed. In many cases, the diagnoses of diabetes mellitus and AIP are made simultaneously; some patients show exacerbation of preexisting diabetes mellitus with the onset of AIP.

Tanaka et al. reported that diabetes mellitus with AIP was caused by T-cell-mediated mechanisms primarily involving islet β-cells as well as pancreatic duct cells. Pancreatic exocrine function is frequently impaired, but marked pancreatic insufficiency is uncommon. Some patients have other symptoms related to associated diseases, including salivary gland swelling due to sclerosing sialadenitis, hydronephrosis due to retroperitoneal fibrosis, and lymphadenopathy.
Laboratory findings

Few patients show marked elevation of serum pancreatic enzymes. The patients with biliary lesions show elevation of serum bilirubin and hepatobiliary enzymes. Some patients show peripheral eosinophilia or elevation of serum IgE levels. Hypergammaglobulinemia (>2.0 g/dl) and elevated serum IgG levels (>1800 mg/dl) are detected in 59%−76% and 53%−71% of AIP patients, respectively. A diagnostic autoantibody for AIP has not been detected. Autoantibodies including antinuclear antibody and rheumatoid factor are present in 43%−75% and 13%−30% of patients, respectively. Serological findings may change spontaneously during the course of AIP. In 2001, Hamano et al. reported that serum IgG4 levels are significantly and specifically high in AIP patients and are closely associated with disease activity. According to their report, the use of a cutoff value of 135 mg/dl for the serum IgG4 level resulted in a high rate of accuracy (97%), sensitivity (95%), and specificity (97%) for differentiating AIP from pancreatic cancer. Some AIP patients show elevated serum IgG4 levels in spite of normal IgG levels. However, the sensitivity of elevated serum IgG4 levels is 63%−68% in other reports. Elevation of serum IgG4 levels has been reported in a patient with pancreatic cancer.

Radiological findings

Typical cases of AIP show diffuse enlargement of the pancreas, the so-called sausage-like appearance, on computed tomography (CT), ultrasonography (US), and magnetic resonance image (MRI). On dynamic CT and MRI, there is delayed enhancement of the swollen pancreatic parenchyma (Fig. 1a). The affected pancreatic lesion shows decreased intensity on the T1-weighted magnetic resonance image. Diffuse hypoechoic swollen pancreas with hyperechoic spots on US. Diffuse irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography. Degree of narrowing varies. Stenosis of the lower bile duct and segmental narrowing of the main pancreatic duct of the pancreatic head on endoscopic retrograde cholangiopancreatography. Upstream dilatation of the distal pancreatic duct is less noted than with pancreatic cancer. After steroid therapy, both stenosis of the bile duct and narrowing of the main pancreatic duct improved.
weighted image and increased intensity on the T2-weighted image compared with the signal intensity in the liver.\textsuperscript{51,53,54} Since inflammatory and fibrous changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low-density area on CT and as a hypointense area on a T2-weighted MRI (Fig. 1b), is detected in some cases.\textsuperscript{47,51–54} US shows an enlarged hypoechoic pancreas with hyperechoic spots (Fig. 1c).\textsuperscript{47,51,53} Pancreatic calcification or pseudocyst is uncommon. Some cases show a focal enlargement of the pancreas, similar to that seen with pancreatic cancer.\textsuperscript{47,55–57} On endoscopic retrograde cholangiopancreatography, an irregular, narrow main pancreatic duct is seen diffusely throughout the pancreas in typical cases. The degree of narrowing of the main pancreatic duct varies in the same patient (Fig. 1d). In some cases, there is segmental narrowing of the main pancreatic duct, but upstream dilatation of the distal pancreatic duct is less often noted than in pancreatic cancer (Fig. 1e).\textsuperscript{47,57} In a majority of AIP patients, both the ventral and dorsal pancreatic ducts are involved, while some patients show the involvement of only the dorsal pancreatic duct. Patients without involvement of the ventral pancreas tend rarely to present with obstructive jaundice.\textsuperscript{48,59} Stenosis of the extrahepatic or intrahepatic bile duct is frequently observed (Fig. 1e). Marked wall thickening of the extrahepatic bile duct or gallbladder is sometimes detected on US or endoscopic ultrasonography (EUS).\textsuperscript{53,60,61} Magnetic resonance cholangiopancreatography does not adequately show the narrow portion of the main pancreatic duct,\textsuperscript{54} but it can adequately demonstrate stenosis of the bile duct with dilatation of the upper biliary tract.\textsuperscript{53} Cervical, hilar, and abdominal lymphadenopathy is sometimes detected on CT.\textsuperscript{47,49} On angiography, encasement of the peripancreatic arteries and stenosis of the portal vein are sometimes observed.\textsuperscript{47,62} F-18 fluorodeoxyglucose (FDG) positron emission tomography occasionally demonstrates intense FDG uptake in the pancreas of AIP patients.\textsuperscript{63–65}

**Histopathological and immunohistochemical findings**

In gross appearance, the pancreas in AIP shows firm and mass-like enlargement with a thick capsule. The hallmark of the histological findings in the pancreas of AIP patients is dense inflammatory cell infiltration and fibrosis in a periductal and interlobular distribution (Fig. 2a). The inflammatory infiltrate consists mainly of lymphocytes and plasma cells with occasional formation of lymphoid follicles. Perineural infiltration is sometimes detected. Fibrosis is usually diffuse and dense, but loose with stromal edema in some cases. The acinar cells are then more or less replaced by inflammatory cells and fibrosis, and the lobular architecture of the pancreas is almost lost. The pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration (Fig. 2b). The infiltrate is primarily subepithelial, and the ductal epithelium is usually preserved except for sparse infiltration by lymphocytes. This is appropriately labeled as lymphoplasmacytic sclerosing pancreatitis. Another highly characteristic histological finding is obliterative phlebitis of the variably sized pancreatic veins and involvement of the portal vein with
lymphoplasmacytic infiltrate and proliferation of fibroblasts in and around the wall of the vein (Fig. 2c). Such an inflammatory process widely and intensely involves the contiguous soft tissue and peripancreatic retroperitoneal tissue. Saito et al. reported that histological recovery of the pancreas, including amelioration of the fibrosis and infiltration of inflammatory cells and a substantial increase in the number of acinar cells, was detected in a patient with AIP after steroid therapy. The wall of the bile duct and gallbladder thickness, histologically showing the same inflammatory process as that of the pancreas. Regional lymph nodes are swollen up to 2.0 cm in diameter, and show histologically marked follicular hyperplasia and dense plasmacytic infiltration in the paracortical and medullary regions.

These characteristic histological findings of AIP are detected during its active phase, and may be a gold standard for diagnosing AIP. However, diagnosing AIP on the basis of a biopsy or an EUS-guided fine-needle aspiration biopsy is sometimes difficult, because of the small sample size.

Immunohistochemically, infiltrating inflammatory cells in the pancreas consist of CD4- or CD8-positive T lymphocytes and IgG4-positive plasma cells (Fig. 3a). Dense infiltration (>30/high-power field [hpf]) of IgG4-positive plasma cells in the pancreas is not observed in chronic alcoholic pancreatitis or pancreatic cancer. Infiltration of abundant IgG4-positive plasma cells is also detected in various organs such as the peripancreatic retroperitoneal tissue, major duodenal papilla, biliary tract, intrahepatic periportal area (Fig. 3b), salivary glands (Fig. 3c), gastric mucosa, colonic mucosa, lymph nodes (Fig. 3d), or bone marrow of AIP patients.

**Diagnostic criteria and differential diagnosis**

As it is usually difficult to take specimens from the pancreas, currently, AIP should be diagnosed on the basis of combination with clinical, laboratory, and imaging studies. The Japan Pancreas Society has proposed “Diagnostic Criteria for Autoimmune Pancreatitis, 2002,” containing three items: (1) radiological imaging showing diffuse enlargement of the pancreas and diffuse irregular narrowing of the main pancreatic duct (more than one-third the length of the entire pancreas); (2) laboratory data demonstrating abnormally elevated levels of serum γ-globulin or IgG, or the presence of autoantibodies; and (3) histological examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis. For the diagnosis of AIP, either all of the criteria should be present or criterion 1 together with either criterion 2 or criterion 3. The presence of the imaging criterion is essential for diagnosing AIP. These criteria are based on the minimum consensus features of AIP to avoid a misdiagnosis pancreatic cancer as far as possible. However, the accumulation of many AIP cases has revealed several diagnostic limitations to these criteria, and revised criteria has been proposed in 2006. According to these new criteria, cases showing localized ductal narrowing over less than one-third the length of the pancreas can be diagnosed, and serological findings showing elevation of the serum IgG4 level is included as one diagnostic factor. Recently, new diagnostic criteria have been proposed in Korea and the United States that include two more factors: response to steroid therapy and other-organ involvement.

The most important disease that should be differentiated from AIP is pancreatic cancer. Clinically, patients with pancreatic cancer and AIP share many features, such as being elderly, having painless jaundice, developing new-onset diabetes mellitus, and having elevated tumor markers. Radiologically, focal swelling of the pancreas, the “double-duct sign,” representing structures in both the biliary and pancreatic ducts, as well as angiographic abnormalities can sometimes be seen in both pancreatic cancer and AIP. As AIP responds dramatically to steroid therapy, accurate diagnosis of AIP can avoid unnecessary laparotomy or pancreatic resection. Imaging findings, such as a mass showing delayed enhancement and a capsule-like rim on dynamic CT or MRI, and segmental narrowing of the main pancreatic duct associated with a less-dilated upstream pancreatic duct, are all useful in differentiating pancreatic cancer from AIP. Measurement of serum IgG4 levels is a useful tool for differentiating between the two diseases. We preliminarily reported that IgG4-immunostaining of biopsy specimens taken from the major duodenal papilla of AIP patients may support the diagnosis of AIP.

Although improvement in clinical findings with steroid therapy may be useful in the differential diagnosis of AIP from pancreatic cancer, empiric administration of steroids should be avoided in order not to misdiagnose pancreatic cancer as AIP.

It is of uppermost importance to consider the possible presence of AIP in elderly patients presenting with obstructive jaundice and a pancreatic mass.

**Treatment and prognosis**

Some AIP patients improve spontaneously. Steroid therapy is clinically, morphologically, and serologically effective in AIP patients. In cases with obstructive jaundice, endoscopic or percutaneous transhepatic biliary drainage must be done, and in cases of diabetes mellitus, glucose levels must be controlled before steroid therapy is started. The preferred initial dose of prednisolone is 30–40mg/day, and it is tapered...
Fig. 3a–e. IgG4-immunostaining of various organs of patients with autoimmune pancreatitis. Dense infiltration of IgG4-positive plasma cells was detected in the pancreas (a), periportal area of the liver (b), salivary gland (c), lymph node (d), and associated retroperitoneal fibrous mass (e)
by 5 mg every 1–2 weeks. Serological and imaging tests are performed periodically after commencement of steroid therapy. Usually, pancreatic size is normalized within a few weeks, and biliary drainage becomes unnecessary within 1–2 months. Patients in whom complete radiological improvement is documented can stop their medication, but most other patients require continued maintenance therapy with prednisolone 5 mg/day. In half of steroid-treated patients, impaired exocrine or endocrine function improves. Some AIP patients relapse during maintenance therapy or after stopping steroid medication and should be retreated with high-dose steroid therapy. The indications for steroid therapy in AIP include obstructive jaundice due to stenosis of the bile duct or the presence of other associated systemic diseases, such as retroperitoneal fibrosis. Steroid therapy is also effective for sclerosing cholangitis that relapses after surgery.

The long-term prognosis of AIP is not well known. In our 1- to 22-year follow-up study of AIP patients, the prognosis was almost always good, except in two patients who progressed to pancreatic insufficiency after resection. It has been reported that recurrent attacks of AIP result in pancreatic stone formation in some cases.

**Clinical subtype**

Some young patients suffer from AIP. These young AIP patients are more likely to have abdominal pain and serum amylase elevation than middle-aged or elderly patients. According to American and Italian reports, AIP patients with neutrophilic infiltration in the epithelium of the pancreatic duct are younger, more commonly have inflammatory bowel disease, and have a weaker association with sialadenitis than patients without neutrophilic infiltration. AIP might be a heterogeneous disease with different clinical aspects, and these patients with young onset might be another subtype from the usual AIP as defined in Japan. Further international study of a larger series of clinically relevant subtypes of AIP is necessary.

**Extrapancreatic lesions of AIP**

AIP patients frequently have various extrapancreatic lesions. Since these extrapancreatic lesions show similar histopathological findings to those in the pancreas, they are possibly induced by the same IgG4-related fibroinflammatory mechanisms as AIP.

Multifocal fibrosclerosis is an uncommon fibroproliferative systemic disorder with multiple manifestations, including sclerosing cholangitis, fibrosis of the salivary glands, retroperitoneal fibrosis, Riedel’s thyroiditis, and fibrotic pseudotumor of the orbit. As histopathological findings of these disorders are similar, fibrotic changes with lymphoplasmacytic infiltration and occasional phlebitis, it has been suggested that they are all interrelated and probably represent different manifestations of a common disorder of fibroblastic proliferation. Several cases of pancreatic pseudotumor or chronic pancreatitis associated with multifocal fibrosclerosis have been reported. The development of specific inflammation in extensive organs as well as in the pancreas in AIP patients strongly suggests a close relationship between AIP and multifocal fibrosclerosis.

**Sclerosing cholangitis**

Sclerosing cholangitis is a heterogeneous disease that may be associated with choledocholithiasis, biliary tumor, or infection. Sclerosing cholangitis of unknown origin is called primary sclerosing cholangitis (PSC). PSC is progressive, despite conservative therapy, and involves the intra- and extrahepatic bile ducts, resulting in liver cirrhosis. The effect of steroid therapy is questionable, and liver transplantation currently provides the greatest hope for a possible cure. It occurs in patients in their 30s and 40s and is frequently associated with inflammatory bowel disease. The pancreatogram is not abnormal in most cases.

Sclerosing cholangitis associated with AIP responds dramatically well to steroid therapy. The histological findings of sclerosing cholangitis associated with AIP include transmural fibrosis and dense lymphoplasmacytic infiltration of the bile duct wall along with lymphoplasmacytic infiltration and fibrosis in the periportal area of the liver. Compared with PSC, lymphoplasmacytic infiltration is more dense, the degree of fibrosis is less severe, and onion skin appearance is rarely observed. Dense infiltration of IgG4-positive plasma cells has been detected in the bile duct wall and the periportal area of patients with AIP, but it has not been detected in those of patients with PSC. Furthermore, elevation of serum IgG4 levels was not detected in our three patients with PSC. Given the age at onset, associated diseases, pancreaticographic findings, response to steroid therapy, prognosis, and IgG4-related serological and immunohistochemical data, sclerosing cholangitis associated with AIP should be differentiated from PSC. In particular, discrimina-
tion between the two diseases is necessary before making therapeutic decisions.

Recently, three cases (in a 50-year-old woman, a 56-year-old man, and a 77-year-old man) of sclerosing cholangitis with elevated serum IgG4 levels and dense infiltration of IgG4-positive plasma cells in the bile duct wall but with no apparent pancreatic lesions compatible with AIP were reported.9 It is likely that these patients had an IgG4-related systemic disease with no clinical manifestations other than sclerosing cholangitis.

**Sclerosing sialadenitis (Kuttner’s tumor and Mikulicz’s disease)**

Sclerosing sialadenitis has been referred to as Kuttner’s tumor, on account of its presentation as a firm swelling of the salivary gland that is difficult to differentiate from a neoplasm.94 Mikulicz’s disease is a unique condition that involves enlargement of the lacrimal and salivary glands associated with prominent mononuclear infiltration.95 The pathogenesis of Kuttner’s tumor and Mikulicz’s disease is unknown.

Some cases of AIP associated with Sjögren’s syndrome have been reported.87,96 In our series, swelling of the salivary glands was detected in 7 of 30 (23%) patients with AIP, and it was associated with cervical or mediastinal lymphadenopathy. In these patients, the salivary glands showed dense infiltration of IgG4-positive plasma cells and fibrosis. However, only a few (<3/hpf) IgG4-positive plasma cells were seen to infiltrate the salivary glands of 50 patients with Sjögren’s syndrome, and serum IgG4 levels were not elevated in ten patients with Sjögren’s syndrome.8 Salivary gland function examined by sialochemistry and salivary gland scintigraphy was markedly impaired in many patients with AIP.40 In three cases, retroperitoneal fibrosis occurred 10 to 18 months before the onset of AIP. Dense infiltration of IgG4-positive plasma cells and obliterative phlebitis were found in both the pancreas and retroperitoneal fibrous mass (Fig. 3e). These retroperitoneal fibrotic lesions associated with AIP seem to be retroperitoneal lesions of IgG4-related systemic disease. In all nine of the patients who were treated with steroids, both the retroperitoneal fibrosis and AIP were resolved. Recently, a case of a 52-year-old man with retroperitoneal and mediastinal fibrosis who exhibited elevation of serum IgG4 levels in the absence of AIP was reported.14

**Retroperitoneal fibrosis**

In 1948, Ormond99 described two patients who presented with anuria caused by bilateral ureteral obstruction due to envelopment and compression of the ureters by an inflammatory retroperitoneal process identified as idiopathic retroperitoneal fibrosis. Idiopathic retroperitoneal fibrosis is an uncommon entity of obscure origin usually confined to the retroperitoneal space and the pelvic brim.

A total of ten patients (ten men; average age, 63.5 years), including our four patients, have been reported to have retroperitoneal fibrosis associated with AIP.46,100–103 In three cases, retroperitoneal fibrosis occurred 10 to 18 months before the onset of AIP. Dense infiltration of IgG4-positive plasma cells and obliterative phlebitis were found in both the pancreas and retroperitoneal fibrous mass (Fig. 3e). These retroperitoneal fibrotic lesions associated with AIP seem to be retroperitoneal lesions of IgG4-related systemic disease. In all nine of the patients who were treated with steroids, both the retroperitoneal fibrosis and AIP were resolved.

**Lymphadenopathy**

Little attention has been given to lymph node swelling in AIP patients. In a study using gallium-67 scintigraphy, pulmonary hilar gallium-67 uptake was found in 16 of 24 patients with AIP.104 In our series, abdominal lymphadenopathy of up to 2 cm in diameter was observed in five of eight patients at laparotomy, and cervical or mediastinal lymphadenopathy of up to 1.5 cm in diameter was observed in 7 of 28 patients on CT.8 In all these cases, the lymphadenopathy disappeared after steroid therapy. Furthermore, cervical lymphadenopathy was obvious in five of six patients with IgG4-related sclerosing sialadenitis. Dense infiltration of IgG4-positive plasma cells was detected in all abdominal lymph nodes (AIP, n = 6; and sclerosing sialadenitis, n = 1) and cervical lymph nodes (AIP, n = 2; and sclerosing sialadenitis,
n = 3) (Fig. 3c). However, only a few IgG4-positive plasma cells were seen to infiltrate abdominal lymph nodes of patients with chronic alcoholic pancreatitis or pancreatic cancer, or cervical lymph nodes of patients with Sjögren’s syndrome.8

Sclerosing cholecystitis

In our series, thickening of the gallbladder was detected on US or CT in 11 of 32 (34%) patients with AIP. Dense infiltration of IgG4-positive plasma cells and lymphocytes, as well as transmural fibrosis, was detected in the gallbladder wall of six of eight examined patients.105

Interstitial pneumonia

A 63-year-old man had concurrent interstitial pneumonia and AIP, both of which improved after steroid therapy. Transbronchial lung biopsy showed dense infiltration of IgG4-positive plasma cells in the alveolar septum.106 Recently, Hirano et al.107 reported that 4 (four men; average age, 69.5 years) of 30 patients with AIP had pulmonary involvement, and they showed good response to steroid therapy.

Tubulointerstitial nephritis

Two cases (in a 64-year-old man108 and a 66-year-old man109) of tubulointerstitial nephritis associated with AIP have been reported. Both diseases improved after steroid therapy. The renal biopsy done in one case showed IgG4-positive staining along the tubular basement membrane and infiltration of IgG4-positive plasma cells into the tubulointerstitium.

Hepatic inflammatory pseudotumor

Hepatic inflammatory pseudotumor is a rare benign lesion characterized by polyclonal lymphoplasmacytic infiltration with fibrosis and is sometimes misdiagnosed as primary hepatic malignant tumor. In two reported cases (a 48-year-old man65 and a 79-year-old man110) of hepatic inflammatory pseudotumor associated with AIP, the tumor showed dense infiltration of IgG4-positive plasma cells, fibrosis, and obliterative phlebitis. Both the hepatic inflammatory pseudotumor and AIP improved after steroid therapy. Zen et al.112 found extensive and dense fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes, and obliterative phlebitis was seen in the bile duct lesions of five patients (five men; average age, 65.0 years) with a hepatic inflammatory pseudotumor associated with sclerosing cholangitis. This suggests that these conditions could be included in a common disease entity.

Inflammatory pseudotumor of the lung

We treated a 63-year-old man who had a concurrent inflammatory pseudotumor of the lung and AIP, both of which improved after steroid therapy. The resected lung tumor showed dense infiltration of IgG4-positive plasma cells and lymphocytes intermixed with fibrosis and obliterative phlebitis. Zen et al.112 reported nine cases (five men, four women; average age, 56.8 years) with an inflammatory pseudotumor of the lung that had the same pathological findings as those mentioned above; no cases were associated with AIP, and two cases were associated with sclerosing sialadenitis or lymphadenopathy.

Other reported lesions associated with AIP are pseudotumor of the hypophysis,111 immune thrombocytopenic purpura,112,113 autoimmune sensorineural hearing loss,113 hypothyroidism,114 anosmia,115 and loss of taste.115

IgG4-related sclerosing disease

By histologically and immunohistochemically examining various organs of AIP patients, dense infiltration of IgG4-positive plasma cells as well as CD4- or CD8-positive T lymphocytes and fibrosis have been observed in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas of AIP patients.7,8,32 All extrapancreatic lesions associated with AIP such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis show infiltration of abundant IgG4-positive plasma cells, but the infiltration is not detected in those of PSC, Sjögren’s syndrome, sialolithiasis, chronic alcoholic pancreatitis, or pancreatic cancer. Both pancreatic and extrapancreatic lesions of AIP respond well to steroid therapy, being different from PSC.

We therefore propose the existence of a novel clinicopathological entity, an IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis, and retroperitoneal fibrosis with lymphadenopathy. It is histopathologically characterized by extensive IgG4-positive plasma cell and T-lymphocyte infiltration of various organs. Major clinical manifestations are apparent in the pancreas, bile duct, salivary glands, and retroperitoneum, in which tissues fibrosis with obliterative phlebitis is pathologically induced. AIP is not simply a pancreatitis, but it is, in fact, a pancreatic lesion reflecting an IgG4-related systemic disease. Sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis associated with AIP are different from PSC, Sjögren’s syndrome, and so-called idiopathic retroperitoneal fibrosis. Most IgG4-related sclerosing diseases have been found to be associated
Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery.

Conclusion

AIP has many clinical, serological, morphological, and histopathological characteristic features. AIP should be diagnosed based on combination of these findings. In an elderly man presenting with obstructive jaundice and a pancreatic mass, AIP should be considered as one of the differential diagnoses to avoid unnecessary surgery.

We proposed a new clinicopathological entity of IgG4-related sclerosing disease. It is characterized by extensive IgG4-positive plasma cell and T-lymphocyte infiltration of various organs, and major clinical manifestations are apparent in the pancreas, bile duct, retroperitoneum, and salivary glands, in which tissues fibrosis with obliterative phlebitis is pathologically induced. Much work needs to be done internationally to understand the full spectrum of this disease.

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