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How to diagnose autoimmune pancreatitis by the revised Japanese clinical criteria

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When diagnosing autoimmune pancreatitis (AIP), it is most important to differentiate it from neoplastic lesions such as pancreatic or biliary cancers. The revised diagnostic criteria are based on the minimum consensus of AIP in order to avoid misdiagnosing pancreas or biliary cancer as far as possible, but not for screening AIP. Therefore, it is recommended that facile therapeutic diagnosis by steroidal administration should be avoided. These criteria contain three approaches: pancreatic imaging, laboratory data, and histopathology. (i) Pancreatic image examinations show the narrowing of the main pancreatic duct and enlargement of the pancreas, which are characteristic of the disease. (ii) Laboratory data show the presence of autoantibodies or elevated levels of serum gammaglobulin, IgG, or IgG4. (iii) Histopathologial examinations of the pancreas show fibrosis and pronounced infiltration of cells, mainly lymphocytes and plasmacytes, which is called lymphoplasmacytic sclerosing cholangitis (LPSP). For a diagnosis of AIP, criterion (i) must be present, together with criterion (ii) and/or (iii). However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

Key words: autoimmune pancreatitis, IgG4, lymphoplasmacytic sclerosing cholangitis (LPSP), steroid therapy

Introduction

Currently in Japan, a diagnosis of autoimmune pancreatitis (AIP) is based on the "diagnostic criteria 2002 of AIP" proposed by the Japan Pancreas Society (Table 1).[1] However, the accumulation of more AIP cases has shown a slight change in the concept of AIP, which now includes extrapancreatic lesions and associated disorders. Therefore, a revised version of the diagnostic criteria has been proposed by the Research Committee of Intractable Diseases of the Pancreas, supported by the Japanese Ministry of Health, Labour, and Welfare (M. Otsuki, Chairman), and the Japan Pancreas Society.[2] Here, we describe how to diagnose AIP using the revised version of the clinical diagnostic criteria in Japan.

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Recent concept and definition of AIP

It is suspected that the pathogenesis of autoimmune pancreatitis (AIP) involves autoimmune mechanisms. Currently, the main observations in cases of AIP are the diffuse enlargement of the pancreas and the narrowing of the pancreatic duct, which are associated with findings that are suggestive of the involvement of autoimmune mechanisms such as increased levels of gammaglobulin and IgG, the presence of autoantibodies, and an effective response to steroid therapy. Patients with AIP often show discomfort in the epigastrium, obstructive jaundice due to bile-duct stricture, and diabetes mellitus. AIP is more common in middle-aged and elderly men. As shown in Table 2, recent attention to this disorder has clarified the clinical aspects of AIP. Patients with AIP often also have extrapancreatic lesions (Fig. 1) such as biliary lesions, sialadenitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and interstitial nephritis,[2–7] which suggests that AIP may be a systemic disorder. Sclerosing cholangitis is most commonly associated with AIP. This is different from primary sclerosing cholangitis (PSC) because it responds to steroid therapy, and because of the presence of IgG4-positive plasmacyte infiltration in the organs involved.[2–7] Sialadenitis that

Table 1. Diagnostic criteria 2002 of autoimmune pancreatitis (Japan Pancreatic Society)

1. Pancreatic imaging studies show diffuse narrowing of the main pancreatic duct with irregular walls (more than one-third of the length of the entire pancreas) and diffuse enlargement of the pancreas
2. Laboratory data demonstrate abnormally elevated levels of serum gammaglobulin, and/or IgG, or the presence of autoantibodies
3. Histopathological examination of the pancreas shows fibrotic changes with lymphocyte and plasma cell infiltration

For a diagnosis, criterion 1 must be present, together with criterion 2 and/or 3

Table 2. Clinical characteristics of autoimmune pancreatitis

Age and sex
More common in elderly men
Clinical symptoms
Mild abdominal symptoms, usually without acute attacks of pancreatitis
Occasional existence of obstructive jaundice
Laboratory data
Increased levels of serum gammaglobulin, IgG, or IgG4
Presence of autoantibodies
Increased hepatobiliary or pancreatic enzymes
Impaired exocrine and endocrine function
Imaging of the pancreato-biliary system
Enlargement of the pancreas
Irregular narrowing of the pancreatic duct
Stenosis of the intrapancreatic bile duct
Sclerosing cholangitis similar to PSC
Histopathological findings of the pancreas
Interlobular fibrosis
Atrophic pancreatic lobule
Infiltration of lymphocytes and IgG4-positive plasmacytes
Obliterative thrombophlebitis
Occasional extrapancreatic lesions
Sclerosing cholangitis similar to PSC
Sclerosing sialadenitis
Retroperitoneal fibrosis
Interstitial nephritis
Chronic thyroiditis
Interstitial pneumonia
Lymphadenopathy (mediastinum/peritoneum)
Occasional association with other autoimmune diseases
Effective steroid therapy
Prognosis
Unclear long-term prognosis
Pancreatic stone formation in some cases

PSC, primary sclerosing cholangitis

coexists with AIP is negative in both anti-SSA and anti-SSB antibodies, and shows IgG4-positive plasmacyte infiltration, suggesting that it is different from typical Sjögren's syndrome, but is similar to sclerosing sialadenitis as observed in Mikulicz's disease and Kuttner's tumor.[2–4] Some patients with AIP show diabetes mellitus as well as a decline in exocrine pancreatic function. In some cases, steroid therapy improves endocrine and exocrine pancreatic dysfunction.

In Western countries, however, ulcerative colitis and the formation of tumors are more often associated with AIP than they are in Japanese patients,[8–10] which suggests that there are differences in the definition and concept of the disease in the West and in Japan. European and US reports of the destruction of the pancreatic duct epithelium in the presence of predominant neutrophils (idiopathic duct-centric chronic pancreatitis, IDCP, or granulocyte epithelial lesion, GEL) have not been confirmed in Japan owing to the limited number of studies, but this is expected to improve in the future.[6] Further studies are necessary to clarify the role of autoimmune mechanisms in AIP. Although the long-term prognosis for the disease is unclear, pancreatic stone formation has been found in some cases.

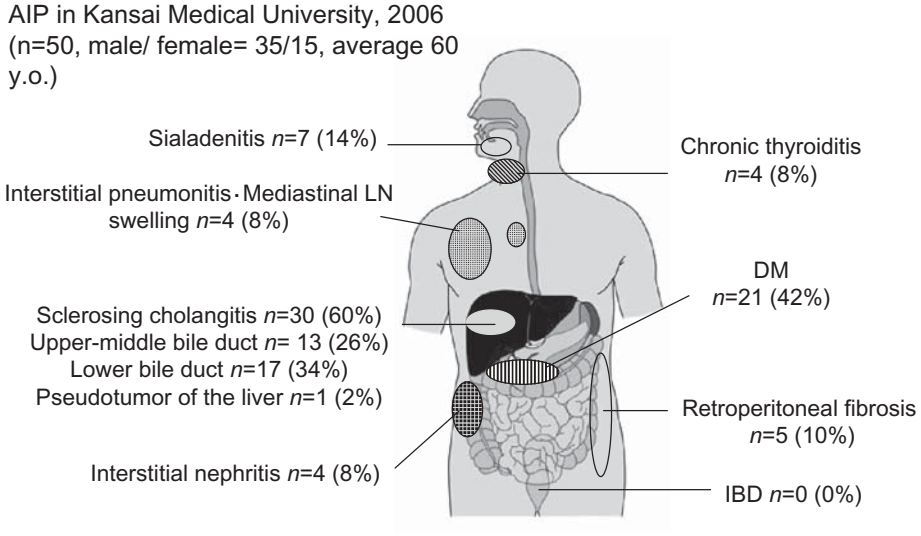

Fig. 1. Extrapancreatic lesions in 50 patients with autoimmune pancreatitis (*AIP*). The male/female ratio was 35/15, with an average age of 60 years. Sclerosing cholangitis, which contains upper-middle bile duct lesions similar to those of primary sclerosing cholangitis (PSC), which was found in 13 patients (26%), and stenosis of the lower bile duct, which was found in 17 patients (34%), were the most common conditions associated with AIP (60%). Diabetes mellitus (*DM*) was observed in 21 patients (42%), sialadenitis in 7 patients (14%), retroperitoneal fibrosis in 5 patients (10%), mediastinal LN swelling in 4 patients (8%), interstitial nephritis in 4 patients (8%), chronic thyroiditis in 4 patients (8%), interstitial pneumonitis in 1 patient (2%), and pseudotumor of the liver in 1 patient (2%), but there were no cases of ulcerative colitis. *IBD*, inflammatory bowel disease

Table 3. Clinical diagnostic criteria of autoimmune pancreatitis 2006
(proposed by the intractable pancreatic diseases research team funded by the Ministry of Health, Labour and Welfare, and Japan Pancreatic Society)

1. Pancreatic imaging studies show narrowing of the main pancreatic duct and enlargement of the pancreas
2. Laboratory data show the presence of autoantibodies or elevated levels of serum gammaglobulin, IgG, or IgG4
3. Histopathological examinations of the pancreas show fibrosis and pronounced infiltration of cells, mainly lymphocytes and plasmacytes

For a diagnosis, criterion 1 must be present, together with criterion 2 and/or 3. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers

Revised version of the clinical diagnostic criteria for AIP in Japan[2]

When diagnosing AIP, it is most important to differentiate it from neoplastic lesions such as pancreatic or biliary cancers. The revised criteria[2] are therefore based on the minimum consensus of opinion in order to avoid misdiagnosing pancreatic or biliary cancer as far as possible, but it is not a comprehensive method of screening for AIP. Therefore, the criteria recommend that facile therapeutic diagnosis by steroidal administration should be avoided. These criteria contain three approaches: pancreatic imaging, laboratory data, and histopathology. (i) Pancreatic image examinations show the narrowing of the main pancreatic duct and enlargement of pancreas which are characteristic of the disease. (ii) Laboratory data show the presence of autoantibodies, or elevated levels of serum gammaglobulin, IgG, or IgG4. (iii) Histopathological examinations of the pancreas show fibrosis and pronounced infiltration of cells, mainly lymphocytes and plasmacytes. For a diagnosis, criterion (i) must be present, together with criterion (ii) and/or (iii). However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers (Table 3).

Image diagnosis

Image diagnosis is mandatory in the revised version, as it was in the original criteria, because abdominal ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI) are the first procedures for diagnosing pancreatic disorders, and endoscopic retrograde cholangiopancreatography (ERCP) is the most accurate diagnostic tool, especially when investigating pancreatic ducts.

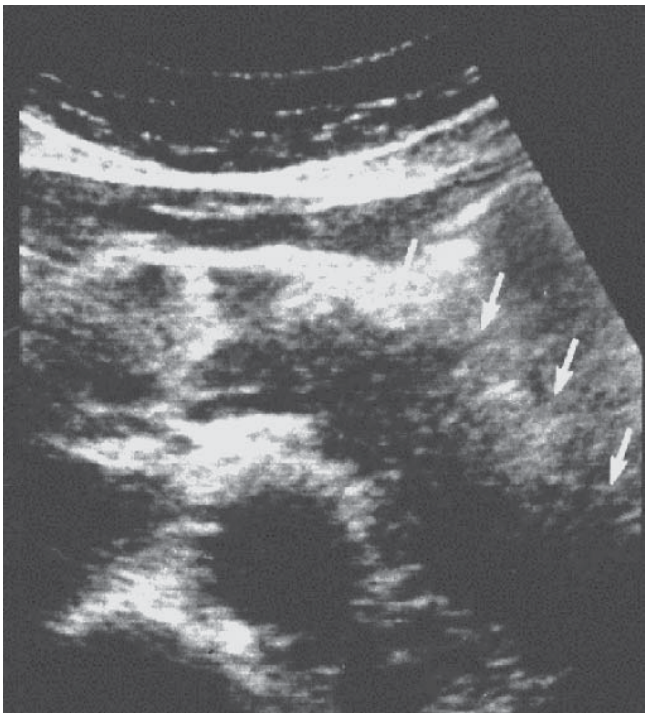

Fig. 2. Abdominal ultrasonographic image in AIP. Ustrasonography (US) showing a low-echo image with occasional scattered high-echo spots in the enlarged area

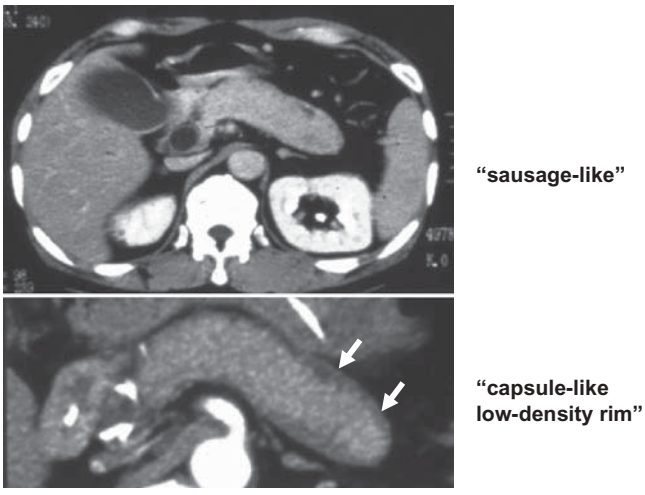

Fig. 3. Contrast-enhanced computed tomography (CT) image in AIP. Contrast CT generally shows a similar contrast effect as that seen in a normal pancreas, but with a sausage-like enlargement and/or a capsular-like low-density rim (*arrows*)

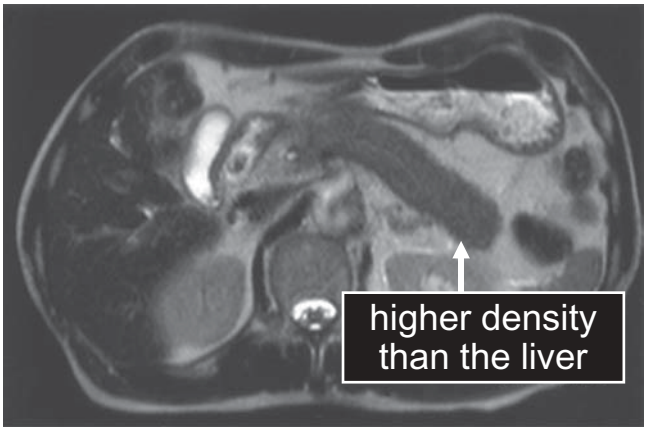

Fig. 4. Magnetic resonance image (MRI) in AIP. MRI shows diffuse or localized enlargement of the pancreas with a higher density in a T2-weighted image than in similar liver images

Enlargement of the pancreas

Abdominal ultrasonography (US), CT, and/or MRI show diffuse or localized enlargement of the pancreas. These pancreatic image findings may be observed retrospectively from the time of diagnosis. US shows low-echo images, occasionally with scattered high-echo spots in the enlarged area (Fig. 2). Contrast CT generally shows a similar contrast effect to that for a normal pancreas, but with a sausage-like enlargement, and/or a capsular-like low-density rim (Fig. 3). MRI shows diffuse or localized enlargement of the pancreas with a lower density in T1-weighted images and a higher density in T2-weighted images compared with those of the liver images (Fig. 4).

Narrowing of the pancreatic duct

The main pancreatic duct shows diffuse or localized narrowing. Unlike an obstruction or stricture, narrowing of the pancreatic duct extends over a larger range where the duct is narrowed with irregular walls. In typical cases, more than one-third of the entire length of the pancreatic duct is narrowed (Fig. 5A). Even in cases where the narrowing is localized and extends to less than one-third of the length, the upper stream of the main pancreatic duct rarely shows notable dilatation (Fig. 5B).

When the pancreatic images show typical findings but the laboratory data do not, there is a possibility of AIP. There are also some cases that meet only the imaging diagnostic criteria for AIP but do respond to steroid therapy.[2] However, without histopathological examinations, it is difficult to distinguish AIP from pancreatic cancer.

To obtain the images of the pancreatic duct, it is necessary to use endoscopic retrograde cholangiopancreatography (ERCP) as well as direct images taken during the operation or on specimens. For a firm diagnosis, it is currently difficult to depend entirely on magnetic resonance cholangiopancreatography (MRCP).

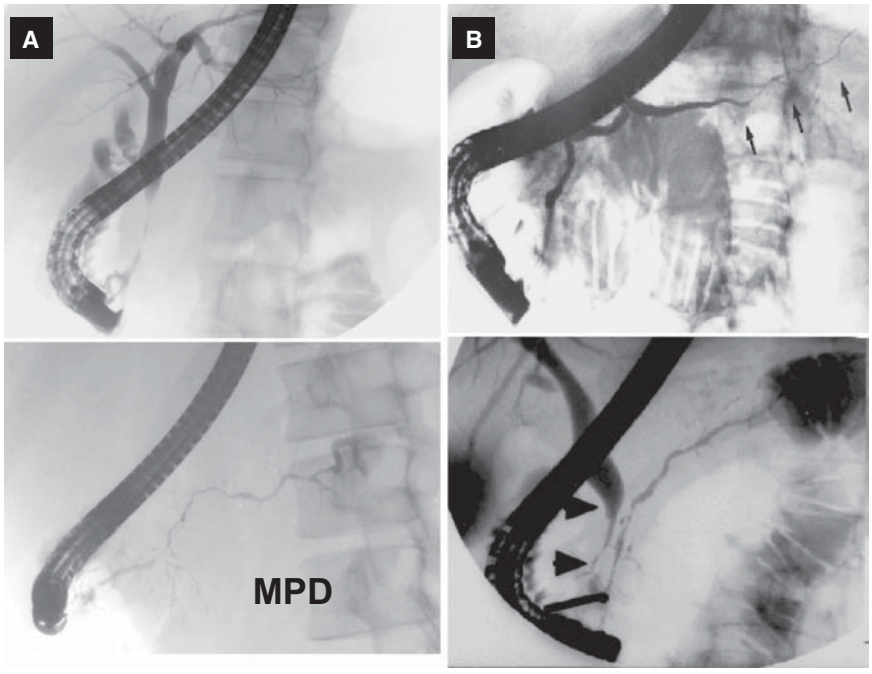

Fig. 5. Endoscopic retrograde cholangiopancreatography (ERCP) images in AIP. Unlike an obstruction or a stricture, the narrowing of the pancreatic duct extends over a larger range where the duct is narrowed with irregular walls. In the diffuse type of AIP (**A**), more than one-third of the entire length of the pancreatic duct is narrowed. In the focal type of AIP (**B**), the upper stream of the main pancreatic duct rarely shows notable dilatation. *MPD*, main pancreatic duct

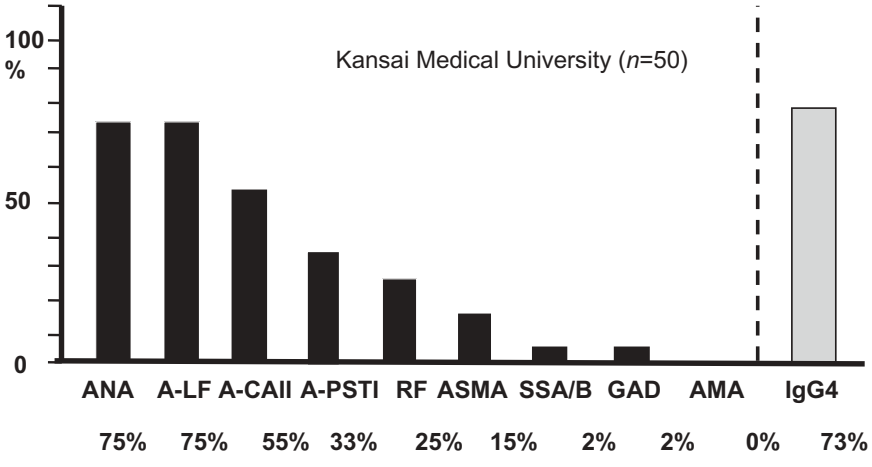

Fig. 6. Prevalence of autoantibodies in AIP. Antinuclear antibody (*ANA*) was observed in 75% of patients, antilactoferrin (*A-LF*) in 75%, anti-CAII antibodies (*A-CAII*) in 55%, anti-PSTI (*A-PSTI*) in 33%, rheumatoid factor (*RF*) in 25%, and antismooth muscle antibody (*ASMA*) in 15%. However, anti-SSA -SSB antibody (2%), antiglutamate dehydrogenase (*GAD*) antibody (2%), and antimitochondrial antibody (*AMA*) were very rarely identified in AIP

Laboratory data

In many cases, patients with AIP show increased levels of serum gammaglobulin, IgG, or IgG4. High serum IgG4, however, is not specific to AIP, since it is also observed in other disorders such as atopic dermatitis, pemphigus, and asthma. Currently, the significance of high serum IgG4 in the pathogenesis and pathophysiology of AIP is unclear. Although increased levels of serum gammaglobulin (≥2.0 g/dl), IgG (≥1800 mg/dl), and IgG4 (≥135 mg/dl) may be used as criteria for the diagnosis of AIP, further studies are necessary. Public medical insurance in Japan does not cover measuring serum IgG4 levels in AIP.

Autoantibodies such as antinuclear, antilactoferrin, anticarbonic anhydrase (CA) II antibodies, and anti-PSTI, rheumatoid factor are often present. However, anti-SSA, -SSB, or antimitochondrial antibodies are very rarely identified in AIP (Fig. 6).

Pathological findings

Fibrotic changes associated with pronounced infiltration of lymphocytes and plasmacytes are seen (Fig. 7A), and the formation of lymphoid follicles may also be observed. In many cases, the infiltration of IgG4-positive plasmacytes is found (Fig. 8). The infiltration

of cells is observed more around the pancreatic duct than in the lobules, and is also found in the interlobular fibrous area.

Narrowing of the pancreatic duct is due to cellular infiltration around the pancreatic duct, and atrophic features are observed with pancreatic acini. Obliterative phlebitis is also often observed (Fig. 7B).

Although fine-needle biopsy under ultrasonic endoscopy (EUS–FNA) is useful in differentiating AIP from malignant tumors, a diagnosis may be difficult if the specimen is too small.

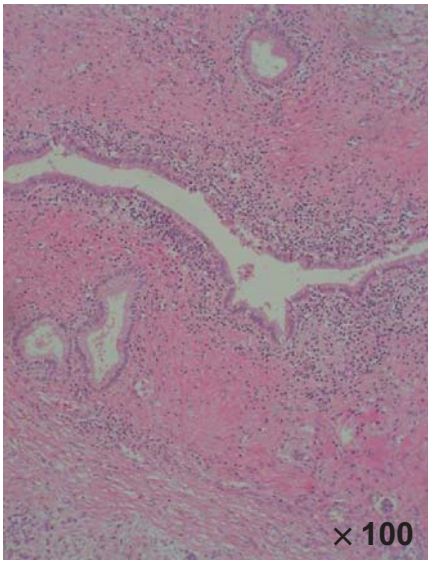

Fig. 7. Histopathology of AIP. Fibrotic changes associated with pronounced infiltration of lymphocytes and plasmacytes are observed around the pancreatic duct

Can AIP can be diagnosed by imaging data and an effective response to steroid therapy alone?

The biggest problem in diagnosing AIP is how to distinguish it from pancreatic or biliary cancers. Under the original diagnostic criteria, which took a stance to rule out pancreatic cancers, 20% to 30% of actual AIP cases were being overlooked.[2,8] Even using the revised criteria, there are some cases (around 10%) that meet only the imaging diagnostic criterion but still respond to steroid therapy. When the pancreatic images show typical findings but laboratory data do not, there is a possibility of AIP. However, without histopathological examinations, it is difficult to distinguish AIP from pancreatic cancer. Moreover, it is unclear whether patients with AIP also have pancreatic cancer. Therefore, the Japanese criteria recommend that facile therapeutic diagnosis by steroidal administration should be avoided.

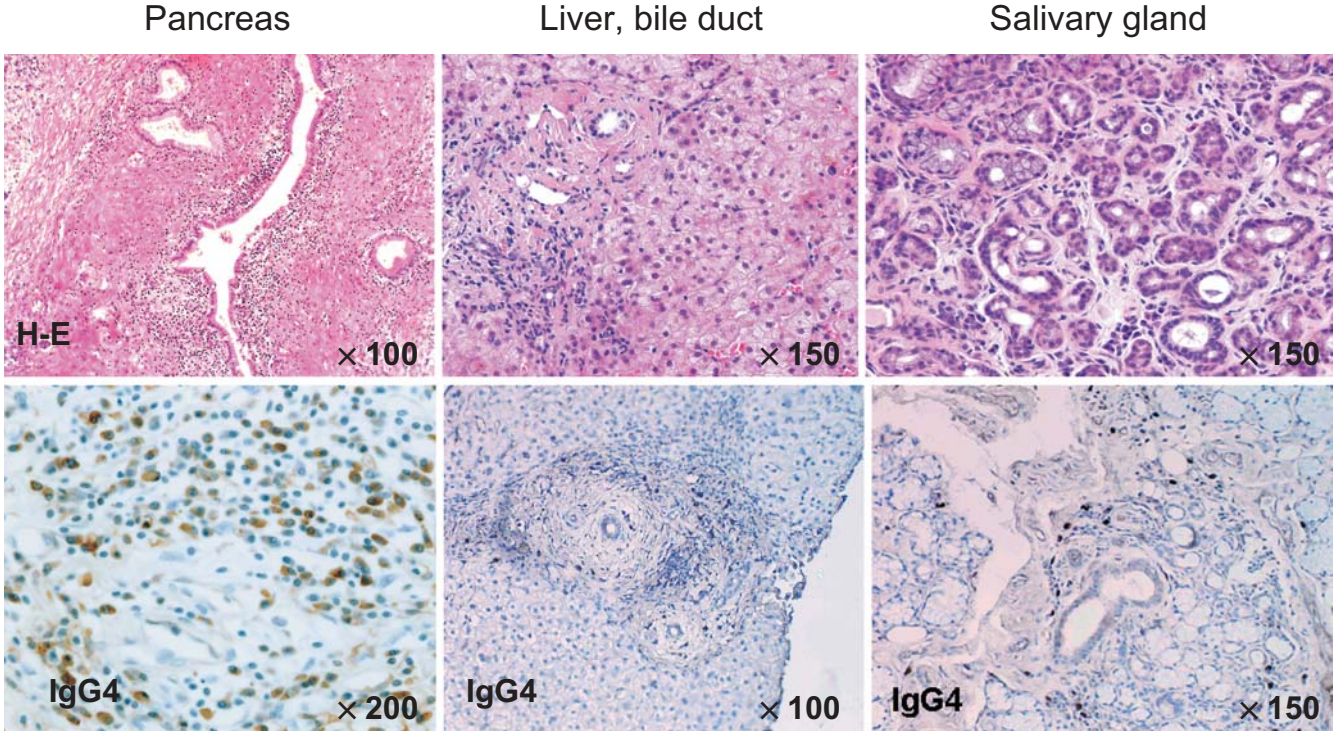

Fig. 8. Histopathology of the pancreas, bile duct, and salivary gland. Extrapancreatic lesions are similar to the fibrosis, lymphocytes, and IgG4-positive plasmacytic infiltration seen in the pancreas

Conclusion

Recently, there have been an increasing number of reports about autoimmune pancreatitis. The recent concept that AIP includes extrapancreatic lesions and associated disorders suggests that AIP may be a systemic disorder. Although there is a limit to the possibility of establishing diagnostic criteria that satisfy everyone, the Japanese clinical criteria[2] are based on a minimum consensus of opinion in order to avoid misdiagnosing malignancy as far as possible, but it is not a comprehensive method for screening for AIP.

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