Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018

Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011

SUPPLEMENTAL DIGITAL CONTENT

SUPPLEMENTAL TABLE 1. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011 (The Japan Pancreas Society, the Research Program on Intractable Diseases from the Ministry of Labor, Health and Welfare of Japan)

Disease Concept

Autoimmune pancreatitis (AIP), widely reported in Japan, is suspected to involve an autoimmune mechanism in its pathogenesis, which is the pancreatic lesions of IgG4-related diseases. This disease is commonly seen in middle-aged to older males. Since it is often associated with pancreatic enlargement, mass formation and obstructive jaundice, differentiation from pancreatic or bile-duct cancers becomes necessary. Laboratory data frequently shows elevated levels of serum gammaglobulin, IgG, IgG4, or the presence of positive autoantibodies, and the disease is often associated with extra-pancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Histopathological study features lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by prominent infiltration of lymphocytes and IgG4-positive plasmacytes, storiform fibrosis, and obliterative phlebitis. Although treated effectively by steroid therapy, its long-term prognosis is not clear; relapse occurs often, and some cases are reported to be associated with pancreatic stones.

Meanwhile, besides IgG4 related pancreatitis, the United States and Europe have reported idiopathic duct-centric pancreatitis (IDCP) as an autoimmune pancreatitis; the clinical symptoms and pancreatic image findings are similar, but abnormal immunological findings are lacking compared to IgG4-related pancreatitis, and it is characterized by granulocytic epithelial lesions (GEL). It is seen in both genders with no significant differences, also in relatively young patients, and sometimes associated with inflammatory bowel disease. Steroid therapy is effective, and relapse is rare. Internationally, two subtypes of autoimmune pancreatitis have been proposed in the International Consensus of Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis: type 1 related with IgG4 (lymphoplasmacytic sclerosing pancreatitis: LPSP), and type 2 with neutrophil lesions (idiopathic duct-centric pancreatitis: IDCP). Since type 2 is extremely rare in Japan, the diagnostic criteria described here are intended to cover type 1, commonly seen in Japan, with type 2 noted only as reference.

Diagnostic Criteria

A. Diagnostic items

I. Enlargement of the pancreas
- a. Diffuse enlargement
- b. Segmental/focal enlargement

II. Image findings showing irregular narrowing of the main pancreatic duct
- a. ERP (endoscopic retrograde pancreatography)
- b. MRCP (magnetic resonance chorangiopancreatography)

III. Serological findings

Elevated levels of serum IgG4 (≥135 mg/dl)

IV. Pathological findings: among i)~v) listed below,
- a. three or more of i)~iv) are observed
- b. two of i)~iv) are observed
- c. v) is observed

i) Prominent infiltration of lymphocytes and plasma cells along with fibrosis
ii) More than ten IgG4-positive plasma cells per high-power microscopic field
iii) Storiform fibrosis
iv) Obliterative phlebitis
v) No neoplastic cells detected by EUS-FNA (endoscopic ultrasound-guided fine needle aspiration)

V. Other organ involvement (OOI): sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis, retroperitoneal fibrosis or kidney lesion

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SUPPLEMENTAL TABLE 1. *(Continued)*

a. Clinical lesions

Extra-pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis (Mikulicz disease), retroperitoneal fibrosis, or kidney lesion can be diagnosed with clinical and image findings.

b. Pathological lesions

Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis, retroperitoneal fibrosis or kidney lesion.

VI. Effectiveness of steroid therapy

A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytological examination using EUS-FNA (IVc). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis. Accordingly, VI includes IVc.

B. Diagnosis

I. Definite diagnosis

① Diffuse type

I a + <III/IVb/V(a/b)>

② Segmental/focal type

Ib + IIa+two or more of <III/IVb/V(a/b)>

Ib + IIa + <III/IVb/V(a/b)> +VI

Ib + IIb + <III/V(a/b)> + IVb + VI

③ Definite diagnosis by histopathological study

IVa

II. Probable diagnosis

Segmental/focal type

Ib + IIa + <III/IVb/V(a/b)>

Ib + IIb + <III/V(a/b)> + IVc

Ib + <III/IVb/V(a/b)> + VI

III. Possible diagnosis*

Diffuse type

Ia + II(a/b) + VI

Segmental type

Ib + II(a/b) + VI

*A case may be possibly type 2, although it is extremely rare in Japan.

"+" refers to "and", and "/" refers to "or".

Explanations

I. Enlarged pancreas

A diffusely enlarged pancreas with "sausage-like" appearance is highly specific to AIP. However, the problem is how to differentiate a segmentally/focally enlarged pancreas from pancreas cancer. For the definition of enlarged pancreas, many facilities use the criteria suggested by Haaga and consider the pancreas to be enlarged when "the width of the pancreatic head is more than one full transverse diameter of the vertebral body, and the width of the pancreatic tail is more than two-thirds of the transverse diameter of the vertebral body (which are approximately 3cm and 2cm for the pancreatic head and tail respectively)." Precise definition is difficult due to age-related influences; it may be considered as an enlarged pancreas if steroid therapy reduces the pancreas size.

1) Abdominal ultrasound: An enlarged pancreas often shows a hypo-echoic area with scattered hyper-echoic spots in it.
2) Abdominal CT·MRI: It is recommended to perform dynamic contrast-enhanced CT·MRI with bolus injection of contrast medium wherever possible. Useful findings for differentiation from pancreatic cancer are speckled/dotted enhancement and capsule-like rim at the parenchymal phase as well as delayed homogeneous enhancement. Capsule-like rim is seen as a band-like low intensity area on T2-weighed images. Duct-penetrating sign is another characteristic finding of focal AIP and is rarely seen.

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SUPPLEMENTAL TABLE 1. *(Continued)*

3) Even when characteristic findings for AIP can be found, careful diagnostic procedures should be conducted to exclude the possibility of pancreatic cancer if concurrent findings suggestive of cancer are present, such as upstream dilation of the main pancreatic duct, heterogeneous delayed enhancement, or severe stenosis of involved arteries.
4) FDG-PET: Abnormal intense uptake is often seen in active lesions; the uptake is reduced after steroid treatment.

II. Narrowing of the main pancreatic duct

Diffuse or segmental/focal irregular narrowing is seen in the main pancreatic duct (The pancreatic image findings described above may be observed retrospectively from the time of diagnosis).

ERP findings

Narrowing is referred to as being unlike the obstruction or stenosis, it extends to a certain degree and the duct diameter is smaller than normal, with some irregularities. In a typical case, the narrowing extends over one third (5cm) of the entire pancreatic duct; even when the lesion is segmental, no significant dilation is observed above the narrowed area upstream of the main duct. If the narrowing is short (less than about 3cm), it is difficult to differentiate from pancreatic cancer. The presence of side branches arising from narrowed portions of the main pancreatic duct or multiple skip lesions in the main pancreatic duct are effective in differentiating from pancreatic cancer.

MRCP findings

Narrowing or invisibleness of the main pancreatic duct is seen on MRCP and is extended to a certain degree, sometimes appearing as a multiple skip lesion. No significant dilation is observed above the narrowed area upstream of the main duct. It is usually difficult to evaluate side branches arising from narrowed portions of the main pancreatic duct. Although image quality of MRCP depends on the MR unit and scan parameters, it is necessary to acquire sufficient good quality images for the detailed evaluation of the pancreatic duct.

III. Hematological examination

1) Patients with AIP often show elevated levels of serum gammaglobulin, IgG, or IgG4 and autoantibodies; an elevated level of serum IgG4 (135mg/dl or higher) is one criterion for the diagnosis. Although the diagnostic criteria defined in this paper reference only IgG4, since elevated levels of IgG4 are also observed in other diseases, including IgG4-related diseases of other organs (e.g. atopic dermatitis, pemphigus, asthma), it is not necessarily specific to AIP. Serum IgG4 is the best serum marker for differentiating from pancreatic cancer in terms of both sensitivity and specificity. However, caution is advised since elevated levels are also observed in some pancreatic or bile-duct cancers, and there are cases of pancreatic cancers associated with AIP. The significance of elevated serum IgG4 in the pathogenesis and pathophysiology of AIP is still not clear.
2) Autoantibodies such as antinuclear antibodies or rheumatoid factor become positive in some cases, from which AIP presence may be suspected.

IV. Pathological findings of the pancreas

AIP shows a specific pathological image, called LPSP, whose typical features are as follows:

1) Prominent infiltration of lymphocytes and plasmacytes, and fibrosis are observed. These are often accompanied by eosinophil infiltration, but without neutrophils infiltration in most cases. Lymphoid follicle formation may also be present. Inflammation is prominent in inter- and intra-lobular regions, peripancreatic fatty tissues, and around the epithelial cells of the pancreatic duct, however, infiltration of inflammatory cells into the epithelium of the pancreatic duct is rare.
2) Prominent infiltration of IgG4-positive plasmacytes is characteristic of this disease; resected pancreatic specimens show 50 or more positive plasmacytes per high-power microscope field (x400) in most cases. In order to make diagnosis possible for small needle biopsy specimens, the criterion of more than 10 per high-power microscope field has been adopted worldwide. Although this diagnostic criteria has also adopted that guideline, since there are inflammatory lesions or tumors other than AIP which also meet this criteria, IgG4-immunostaining alone is not sufficient for making a definite diagnosis.
3) Storiform fibrosis is a lesion comprised of inflammatory cell infiltration (lymphocytes, plasmacytes) and spindle-shaped cell hyperplasia, which presents complex cell arrangements characterized by the expression "storiform", and associated with differing degrees of fibrosis. The storiform fibrosis most often appears in the pancreatic rim and peripancreatic fat tissues.

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SUPPLEMENTAL TABLE 1. *(Continued)*

4) Obliterative phlebitis is a finding where lesions caused by the infiltration and fibrosis of lymphocytes and plasmacytes in inter-lobular regions and peripancreatic fat tissues extends into a vein to cause venous stenosis or occlusion.
5) Although EUS-FNA is a useful tool to exclude cancer, the absence of neoplastic cells alone is insufficient; it is also important to exclude cancer using the image findings shown in I-2). Moreover, the diagnostic process should be done carefully, with comprehensive evaluation of serological findings and other organ involvement.

Either a resected or biopsied pancreatic specimen may be used for the diagnosis. EUS-FNA cytological examination is extremely effective in differentiating AIP from malignant tumors, but is not effective in diagnosing AIP. EUS-FNA histological examination can provide a definite diagnosis of AIP if sufficient sample volume is obtained. Diagnosis of AIP using biopsied specimens requires caution, since pancreatic cancer also shows a large number of IgG4-positive plasmacytes in and around the pancreas in some cases, and pathological findings similar to LPSP in some isolated cases. Careful histological diagnosis is needed when atypical findings for AIP, such as necrosis, granuloma, and abundant neutrophil infiltration, are concurrently observed.

Notes Type 2 AIP (IDCP)

IDCP is a pancreatitis of unknown cause which is characterized by the infiltration of neutrophils into the lumen or epithelium of the interlobular pancreatic ducts. As in the case of LPSP, clinical differentiation from pancreatic cancer becomes an issue. Because of its similarity to LPSP in being associated with the infiltration and fibrosis of lymphocytes/plasmacytes around the pancreatic epithelium, IDCP was once thought to be in the same category as LPSP. Currently, IDCP cannot be diagnosed by images or clinical findings, and therefore requires histopathological examinations for the diagnosis. In addition, while resected or necropsied specimens of pancreas are large enough for a definite diagnosis, biopsied specimens are so small that a definite diagnosis is difficult in many cases. If typical pancreatic images of AIP are shown without abnormal hematological evidence, the disease could be either type 1 or type 2. Some of type 2 AIP present clinical symptoms or image findings similar to those of pancreatic cancer, which makes it extremely difficult to differentiate type 2 AIP from pancreatic cancer.

V. Other organ involvement: OOI

1) Other organ involvement (OOI) observed in AIP refers to the IgG4 related lesions associated with type 1.
2) Other organs reported to be affected include the central nervous system, lacrimal/salivary glands, thyroid glands, lungs, biliary duct, liver, gastrointestinal tracts, gallbladder, kidneys, prostate glands, retroperitoneum, and lymph nodes. In the lymph nodes and lacrimal glands, however, fibrosis is scarce; not all of these organs have established concepts of their lesions. If the following conditions are met, there may be a close relation with AIP, although no clear basis is available.
    1. Investigations/reports of many cases show association with AIP.
    2. The histopathological findings feature lympoplasmacytic infiltration with fibrosis (often storiform in morphology), obliterative phlebitis, and numerous IgG4-positive plasmacytes.
    3. Steroid therapy is effective; or, the onset and offset of the effect synchronizes between pancreatic lesions and the lesions in question.
    4. There are clear points that differentiate from diseases of each organ.

Diseases that satisfy the above conditions include sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis (Mikulicz disease), retroperitoneal fibrosis, respiratory lesions, and kidney lesion (tubulo-interstitial nephritis). Currently consensus is limited to sclerosing cholangitis, sclerosing dacryoadeniti/sialadenitis retroperitoneal fibrosis and kidney lesion. These lesions could present simultaneously or in a metachronous manner with that of AIP.

3) Sclerosing cholangitis

1. The sclerosing cholangitis associated with AIP shows lesions over a wide area of the bile duct system; the stenosis of the lower bile duct caused by AIP must be differentiated from that caused by pancreatic cancer or cancer of the lower bile duct, and the stenosis of the intrahepatic and hilar bile ducts caused by AIP must be differentiated from that caused by primary sclerosing cholangitis (PSC) or bile duct cancer. It is necessary to make careful and comprehensive differentiation using not only the bile duct images but also endoscopic ultrasoundscopy (EUS), intraductal ultrasonography (IDUS), cytological and/or histological diagnosis, etc.

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2. PSC is a different entity from the sclerosing cholangitis seen in AIP, because their responses to steroid therapy and prognoses are different. Findings characteristic to PSC are band-like strictures (e.g. short band-like strictures of 1-2mm), a beaded appearance (e.g. alternating short strictures and dilatations), a pruned tree appearance (e.g. a reduced number of intrahepatic duct branches), and diverticulum-like outpouching.
3. It is controversial among specialists whether to include cases showing only lower bile duct stenosis within IgG4-related sclerosing cholangitis, or to view them as part of the pancreatic lesions. The findings in bile duct lesions effective in diagnosing AIP are stenosis of the intrahepatic and hilar bile ducts and the sclerosing images or wall thickening of the upper and middle bile ducts.
4. Most of the pathological studies show a thickened bile duct and prominent transmural infiltration and fibrosis of lymphocytes and plasmacytes. Many IgG4-positive plasmacytes are observed in the lesions. The epithelium of the bile duct remains normal in most cases. Storiform fibrosis and obstructive phlebitis are also observed.
5. The IgG4 immunostaining of enlarged duodenal papillary biopsy specimens may be useful as a supporting diagnosis, although this enlargement is infrequent. An enlarged duodenal papillary is considered to be spread from lesions of the pancreatic head, and therefore is not in the scope of extra-pancreatic lesions (other organ involvement).

4) Sclerosing dacryoadenitis/sialadenitis

1. Sclerosing dacryoadenitis/sialadenitis associated with AIP shows no or slight (if any) symptoms of dry eye or dry mouth caused by decreased function of the lacrimal glands. Unlike Sjögren's Syndrome which is often associated with swollen parotid glands, sialadenitis seen in AIP often demonstrates swollen submandibular glands and responds very well to steroid therapy. While most enlargement of the lacrimal and salivary glands is symmetrical, enlargement of the salivary glands is part of the enlarged submandibular, sublingual, or minor salivary glands. Dacryoadenitis/sialadenitis in most cases test negative for anti SS-A antibody and anti SS-B antibody, which is different from Sjögren's Syndrome. The disease can be diagnosed based on the diagnostic criteria of the organs (diagnostic criteria for IgG4-related Mikulicz disease, Japan Sjögren's Syndrome Study Group, 2008), however, if prominent infiltration of IgG4-positive plasmacytes are observed, it may be diagnosed by labial lip biopsy analysis.
2. Pathological findings show the disappearance of acinar cells in the lobule, prominent infiltration of lymphocytes and plasmacytes, formation of lymphoid follicles, and interlobular fibrosis. In some cases, the lobular structure may be destroyed, and prominent infiltration and fibrosis of lymphocytes and plasmacytes may form diffuse lesions. Many of the plasmacytes are IgG4 positive. Storiform fibrosis and obliterative phlebitis may be observed, although the incidence rate is lower compared with that of AIP.

5) Retroperitoneal fibrosis

1. Due to diffuse hyperplasmia and the inflammation of fibrous connective tissues on and around the retroperitoneum, abdominal CT/MRI images show soft tissue masses in the retroperitoneum, sometimes around the abdominal aorta. This can cause ureteral obstruction, and subsequent hydrophrosis occasionally provide a clue for diagnosis. In some cases, the disease is associated with dilated lesions of the abdominal aorta and the condition known as inflammatory abdominal aortic aneurysm may be present; however, it is difficult to differentiate said aortic aneurysm from those caused by other etiologies.
2. Pathological study shows mass lesions formed by prominent infiltration of lymphocytes and plasmacytes with fibrosis. Many IgG4-positive plasmacytes are seen in the lesions. Storiform fibrosis and obliterative phlebitis are also seen very frequently.

6) Kidney lesion

1. In the patients who are suspected AIP and undergo abdominal contrast-enhanced CT, decreased enhancement of renal parenchyma, suggesting IgG4-related kidney disease (IgG4-RKD), is occasionally seen.
2. IgG4-RKD usually displays histological tubulointerstitial nephritis along with mild urinary findings and hypocomplementemia, but sometimes shows proteinuria when glomerular involvement is present. Although IgG4-RKD typically exhibits normal or only slightly reduced renal function, it can also progress to an advanced stage of severe renal deficiency.

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SUPPLEMENTAL TABLE 1. *(Continued)*

3. Characteristic image findings of contrast-enhanced CT include renal parenchymal lesions seen as multiple decreased enhancement areas (small peripheral cortical nodules, round or wedge-shaped lesions), solitary mass (hypo-vasucular), or renal pelvic wall thickening without irregular lumen. Non-contrast CT may also disclose diffuse renal enlargement.

VI. Effectiveness of steroid therapy

Targets are the lesions for which image evaluation is possible; clinical conditions or hematological findings are not subject to effect evaluations. If no sufficient effect is seen within 2 weeks, reexamination is necessary. Effort should be made to take biopsies for pathological examination as much as possible, and facile diagnostic treatment with steroids should be strictly avoided. The administration of steroids may be effective in improving malignant lymphoma.

VII. Endocrine and exocrine pancreatic functions

Typical AIP shows impaired exocrine pancreatic functions and diabetes. There are quite a few cases where steroid administration is effective in improving impaired endocrine and exocrine pancreatic functions.

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