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EDITORIAL

Diagnostic criteria for autoimmune pancreatitis in Japan

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Abstract

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis of presumed autoimmune etiology. Currently, AIP should be diagnosed based on combination of clinical, serological, morphological, and histopathological features. When diagnosing AIP, it is most important to differentiate it from pancreatic cancer. Diagnostic criteria for AIP, proposed by the Japan Pancreas Society in 2002 first in the world, were revised in 2006. The criteria are based on the minimum consensus of AIP and aim to avoid misdiagnosing pancreatic cancer as far as possible, but not for screening AIP. The criteria consist of the following radiological, serological, and histopathological items: (1) radiological imaging showing narrowing of the main pancreatic duct and enlargement of the pancreas, which are characteristic of the disease; (2) laboratory data showing abnormally elevated levels of serum γ-globulin, IgG or IgG4, or the presence of autoantibodies; (3) histopathological examination of the pancreas demonstrating marked fibrosis and prominent infiltration of lymphocytes and plasma cells, which is called lymphoplasmacytic sclerosing pancreatitis (LPSP). For a diagnosis of AIP, criterion 1 must be present, together with criterion 2 and/or criterion 3. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancer.

Key words: Autoimmune pancreatitis; Diagnostic criteria; IgG4; Lymphoplasmacytic sclerosing pancreatitis

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology[1]. Since Yoshida *et al*[2] proposed AIP as a diagnostic entity in 1995, many cases of AIP have been reported in Japan. As there is currently no diagnostic serological marker for AIP, AIP should be diagnosed on the basis of presence of a combination of abnormalities unique to AIP. In 2002, the Japan Pancreas Society established the "Diagnostic Criteria for Autoimmune Pancreatitis"[3] consisting of the following 3 items: (1) radiological imaging showing diffuse enlargement of the pancreas and diffuse irregular narrowing of the main pancreatic duct (more than one-third of the entire pancreas); (2) laboratory data demonstrating abnormally elevated levels of serum gamma globulin or IgG, or the presence of autoantibodies; and (3) histological examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis. With accumulation of AIP cases, the concept of AIP has changed slightly, and the AIP criteria 2002 are becoming inadequate. Therefore, they were revised in 2006 by the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor and Welfare and the Japan Pancreas Society[4]. In 2006, two new sets of diagnostic criteria for AIP were proposed, in Korea[5] and USA, respectively[6]. Currently, there are several diagnostic criteria for AIP in the world. We describe the clinical diagnostic criteria for AIP in Japan.

CLINICAL DIAGNOSTIC CRITERIA FOR AUTOIMMUNE PANCREATITIS 2006

The diagnostic criteria for AIP in Japan are based on the minimum consensus of AIP and aim to avoid

misdiagnosing pancreatic cancer as far as possible, but not for screening AIP. Therefore, the criteria emphasize the importance of imaging studies. In the 2002 criteria[3], extent limitation on main pancreatic duct involvement (more than one-third the length of the entire pancreas) was required to diagnose only typical AIP cases and to avoid the possible inclusion of pancreatic cancer. However, with the accumulation of more AIP cases, it has become clear that, in several cases that are strongly suspected of having AIP, the degree of narrowing of the main pancreatic duct is less than one-third of the entire pancreas[5-7]. Furthermore, serum IgG4 levels are rather significantly and specifically elevated in AIP patients[8]. Thus, the 2006 criteria[4] delete the requirement that "more than one-third of the entire pancreas" is involved, allowing segmental AIP cases to be diagnosed. Furthermore, the 2006 criteria[4] include elevation of the serum IgG4 level as a diagnostic factor. Finally, the 2006 criteria[4] stress the need to exclude malignant diseases such as pancreatic or biliary cancer, before making the diagnosis of AIP (Table 1).

Table 1 Clinical diagnostic criteria for autoimmune pancreatitis 2006[4]

Clinical diagnostic criteria
1 Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI)
2 High serum γ-globulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3 Marked inter-lobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the peri-ductal area, occasionally with lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criterion 2 and/or criterion 3. Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or criterion 3, are fulfilled. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

The preface of the criteria is described below[4]. It is suspected that the pathogenesis of autoimmune pancreatitis (AIP) involves autoimmune mechanisms. Currently, the main cases observed for characteristic findings of AIP are the diffuse enlargement of the pancreas and the narrowing of the pancreatic duct, which are associated with the findings that are suggestive of the involvement of autoimmune mechanisms such as increased levels of γ-globulin and IgG, the presence of autoantibodies, and the effective response to steroid therapy. In some cases, AIP shows extra-pancreatic manifestations such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, suggesting that AIP is a systemic disease. In Western countries, AIP is occasionally observed in association with ulcerative colitis and formation of tumors, suggesting that it is somewhat contrary to the definition and concept of the disease adopted in Japan.

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 males. Although long-term prognosis of the disease is not clear, pancreatic stone formation has been found in some cases. When diagnosing AIP, it is important to differentiate it from neoplastic lesions such as pancreatic or biliary cancer, and to avoid facile therapeutic diagnosis by steroidal administration. The present criteria, therefore, are based on the minimum consensus of AIP to avoid mis-diagnosing pancreas or biliary cancer as far as possible, but not for screening AIP.

Furthermore, description note of the criteria is reported as below[4]: (Ⅰ) Imaging studies: (1) Diffuse or localized swelling of the pancreas. Abdominal ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI) show diffused or localized swelling of the pancreas. (A) The US feature of pancreatic swelling is usually hypoechoic, sometimes with scattered echogenic spots. (B) Contrast-enhanced CT generally shows delayed enhancement similar to normal pancreas with a sausage-like enlargement, and/or a capsular-like low density rim. (C) MRI shows diffuse or localized enlargement of the pancreas with a lower density in T1-weighed image and a higher density in T2-weighed image compared with each of the liver images. (2) Narrowing of the pancreatic duct. The main pancreatic duct shows diffuse or localized narrowing. (A) Unlike 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 pancreatic duct is narrowed. Even in cases where the narrowing is segmental and extends to less than one-third, the upper stream of the main pancreatic duct rarely shows notable dilatation. (B) When the pancreatic images do 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. (C) To obtain the images of pancreatic duct, it is necessary to use endoscopic retrograde the cholangiopancreatography (ERCP), and additionally the direct images taken during the operation or on specimens. Currently, the diagnosis is difficult to depend on magnetic resonance cholangiopancreatography (MRCP). (3) The pancreatic image findings described above may be observed retrospectively at the time of diagnosis. (Ⅱ) Laboratory data: (1) In many cases, patients with AIP show increased levels of serum γ-globulin, 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, or asthma. Currently, the significance of high serum IgG4 in the pathogenesis and the pathophysiology of AIP are unclear. (2) Although increased levels of serum γ-globulin (≥ 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. Health insurance in Japan does not cover the cost of measuring serum IgG4 levels in AIP patients. (3) Autoantibodies, such as antinuclear antibody and rheumatoid factor, are often detected in patients with AIP. (Ⅲ) Pathohistological findings of the pancreas: (1) Fibrotic changes associated with prominent infiltration of lymphocytes and plasma cells, occasionally with lymphoid follicles, are observed. In many cases, infiltration of IgG4-positive plasma cells is observed. (2) Lymphocytic infiltration is prominent

in the peri-ductal area, together with inter-lobular fibrosis, occasionally including intra-lobular fibrosis. (3) Inflammatory cell infiltration involving the ducts results in diffuse narrowing of the pancreatic duct with atrophy of acini. (4) Obliterative phlebitis is often observed. (5) Although fine needle biopsy under ultrasonic endoscope (EUS-FNA) is useful in differentiating AIP from malignant tumors, diagnosis may be difficult if the specimen is too small. (IV) Endocrine and exocrine function of the pancreas: Some patients with AIP show decline of exocrine pancreatic function and diabetes mellitus. In some cases, steroid therapy improves endocrine and exocrine pancreatic dysfunction.

AIP may be associated with sclerosing cholangitis and sialadenitis, or retroperitoneal fibrosis. Most of AIP patients with sclerosing sialadenitis are negative for both anti-SSA and anti-SSB antibodies, suggesting that AIP is different from Sjogren's syndrome. Sclerosing cholangitis-like lesions accompanying AIP and primary sclerosing cholangitis (PSC) respond differently to steroid therapy and follow different prognoses, suggesting that they are not the same disorder. Further studies are necessary to clarify the role of autoimmune mechanisms in AIP.

In the diagnostic criteria in Korea[5] and the United States (Mayo Clinic)[6], "response to steroid" is included as one of the diagnostic items. When response to steroid therapy is added to the criteria, the diagnostic sensitivity is increased. Since relief of narrowing of the pancreatic duct can be seen as early as 2 wk after steroid therapy in AIP cases, it dose not occur in pancreatic cancer cases. The Korean investigators advocate a short trial of steroid therapy to differentiate AIP from pancreatic cancer in cases that do not fulfill the Japanese criteria[5]. We also agree that a trial of steroid therapy can be used to assist in making the diagnosis when it is used appropriately. However, since general physicians who are not pancreatologists use the criteria, it is possible that the facile use of steroid trials will delay pancreatic cancer surgery, which could lead to cancer progression in some cases. Therefore, "response to steroid" is excluded in the diagnostic criteria in Japan[4,9,10].

AIP with neutrophilic infiltration in the epithelium of the pancreatic duct (idiopathic duct-centric chronic pancreatitis: IDCP, or granulocyte epithelial lesion: GEL) has been reported by American[11] and Italian[12] pathologists. These patients showing different clinicopathological features from AIP are defined in Japan as follows: no prediction for elderly males, frequent association with inflammatory bowel disease, and weaker association with other sclerosing diseases. Histopathological finding of AIP in Japan is lymphoplasmacytic sclerosing pancreatitis (LPSP), and the above Western AIP cases have not been confirmed in Japan owing to the limited number of studies.

AIP patients usually have various extrapancreatic lesions such as sclerosing cholangitis and sialadenitis, and retroperitoneal fibrosis[13]. The histopathological findings of these extrapancreatic lesions are uniformly fibrosis with marked infiltration of IgG4-positive plasma cells and lymphocytes, which are similar to those in the pancreas[14,15]. Therefore, the recent concept of AIP suggests that AIP is a pancreatic lesion of IgG4-related systemic disease[1,15,16]. In the future, criteria for AIP might develop into criteria for IgG4-related systemic disease.

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