Clinical management of autoimmune pancreatitis

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Abstract

Autoimmune pancreatitis (AIP) is a newly described entity with characteristic clinical, radiological, serological, and histological features, in which autoimmune mechanisms seem to be involved in pathogenesis. Many new clinical aspects of AIP have been clarified during 10 years, and AIP has become a distinct entity recognized worldwide. However, precise pathogenesis or pathophysiology remains unclear. As AIP responds dramatically to steroid therapy, accurate diagnosis of AIP is necessary to avoid unnecessary laparotomy or pancreatic resection. It is importance to misdiagnose pancreatic cancer as AIP as well as to misdiagnose AIP as pancreatic cancer. In the absence of a diagnostic serological marker for AIP, its diagnosis rests on identifying unique patterns of abnormalities. Japanese criteria are based on the minimum consensus features of AIP and aim to avoid misdiagnosis of malignancy. It contain 3 items: (1) enlargement of the pancreas and narrowing of the main pancreatic duct; (2) high serum gammaglobulin, IgG, or IgG4, or the presence of autoantibodies; (3) histological findings of lymphoplasmacytic infiltration and fibrosis in the pancreas. For diagnosing AIP, the presence of the imaging criterion is essential. Other clinical characteristics of AIP are elderly male preponderance, fluctuating obstructive jaundice without pain, occasional association with diabetes mellitus and extrapancreatic lesions, and favorite responsiveness to oral steroid therapy. Elevation of serum IgG4 levels and infiltration of abundant IgG4-positive plasma cells in various organs are rather specific in AIP patients. In an elderly male presenting obstructive jaundice and pancreatic mass, AIP should be considered as one of differential diagnoses.

Introduction

Sarles et al. [1] first reported a condition called "primary inflammatory sclerosis of the pancreas" and suggested an autoimmune cause for this condition. Some researchers also have proposed the possible role of autoimmunity in causing chronic pancreatitis. Since Yoshida et al. [2] proposed the concept of autoimmune pancreatitis (AIP) in 1995, many cases of AIP have been reported in the Western countries as well as in Japan, and AIP has become a distinct entity recognized worldwide. However, precise pathogenesis or pathophysiology remains unclear.
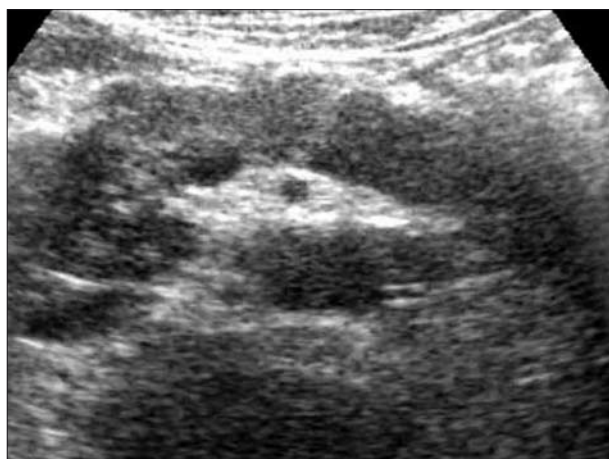
AIP has many clinical, radiological, serological and histopathological characteristics. However, in the absence of a diagnostic serological marker for AIP, AIP should be diagnosed currently on the basis of combination with these unique patterns of abnormalities. It is uppermost importance to misdiagnose AIP as pancreatic cancer. In North America, about 2.5% of pancreaticoduodenectomies are performed for AIP because of a mistaken diagnosis of pancreatic cancer [3], and AIP cases represent between 21% [4] and 23% [3] of pancreaticoduodenectomies performed for benign conditions. Although AIP dramatically responds to oral prednisolone therapy, there is no consensus on regimen of steroid therapy for AIP. This review focuses on clinical management of AIP, based on our experience of 35 cases of AIP.

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Diagnosis of AIP

Clinical features

AIP is diagnosed more commonly in elderly males [5]. The mean age of the patients is 68.5 years (range 29-83 years) and the male-to-female ratio is 4:1 in our series. In Korea, the mean age was 59.1 years (45-75 years), and the male-to-female ratio was 15:2 [6]. Typical presentation with severe abdominal pain and clinically acute pancreatitis is rarely seen. Obstructive jaundice due to associated sclerosing cholangitis occurs frequently (65% [6]-86% [7]). The jaundice sometimes fluctuates. Failure of pancreatic exocrine or endocrine function is frequently seen. Up to 50% of AIP patients present with glucose intolerance [8]. The diagnoses of diabetes mellitus and AIP are made simultaneously in many cases, but some cases show exacerbation of preexisting diabetes mellitus with the onset of AIP [8].

AIP patients frequently have various extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis [9]. Sclerosing cholangitis is most frequently associated with AIP. Stenosis of the lower bile duct is usually detected. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of primary sclerosing cholangitis [10,11]. Swelling of the bilateral salivary glands was detected in 8 (23%) of 35 patients with AIP in our series. Hydronephrosis due to retroperitoneal fibrosis was detected in 4 AIP patients. All these extrapancreatic lesions show similar histopathological findings to those in the pancreas and also respond well to steroid therapy [10-14].

Laboratory findings

Marked elevation of serum pancreatic enzymes is rarely seen. Hypergammaglobulinemia (>2.0 g/dl) and elevated serum IgG levels (>1 800 mg/dl) are detected in 59%-76% [12-14] and 53% [6]-71% [12] 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 them, respectively [13-15]. Serum IgG4 levels are rather significantly and specifically high (>135 mg/dl) in AIP patients. The sensitivity of elevated serum IgG4 levels is reported to be 63%-95% [6,16-18]. Elevation of serum IgG4 levels was reported in a patient with pancreatic cancer [19].

Radiological findings

On ultrasonography (US), an enlarged hypoechoic pancreas is characteristically detected in AIP (*Fig. 1*) [14,20]. On dynamic computed tomography (CT), there is delayed enhancement of the enlarged pancreatic parenchyma (*Fig. 2*) [14,20]. Typical AIP cases show diffuse enlargement of the pancreas, the so-called sausage-like appearance. Since inflammatory and fibrous changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low density on CT, is detected in some cases [14,20]. Pancreatic calcification or pseudocyst is rarely seen. Some cases show a focal enlargement of the pancreas, similar to that seen with pancreatic cancer (*Fig. 3*). Endoscopic retrograde cholangiopancreatography (ERCP) discloses an irregular, narrow (<3 mm in diameter) main pancreatic duct (*Fig. 4*). In patients with segmental narrowing, absence of upstream dilatation of the main pancreatic duct is characteristic [14]. Stenosis of the extrahepatic or intrahepatic bile duct is frequently observed. Marked wall thickening of the extrahepatic bile duct or gallbladder is sometimes detected on US or endoscopic ultrasonography (EUS) [20,21]. Magnetic resonance cholangiopancreatography does not adequately show the narrow portion of the main pancreatic duct, but it can adequately demonstrate stenosis of the bile duct with dilatation of the upper biliary tract [22].

Histopathological findings

The histological finding of AIP is characteristic, that is, dense lymphoplasmacytic infiltration with fibrosis of the pancreas (*Fig. 5*). Lymphoid follicles are occasionally formed. The acinar cells are replaced by inflammatory cells and fibrosis, and the lobular architecture of the pancreas is almost lost. Pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration. Another characteristic histological finding is obliterative phlebitis involving minor and major veins, includ-

**Figure 3.** Ultrasonography showing a focal enlargement of the pancreas similar to pancreatic cancer

Figure 4. Endoscopic retrograde pancreatography showing diffuse irregular narrowing of the main pancreatic duct

Figure 5. Histological findings of the pancreas of a patient with autoimmune pancreatitis showing dense lymphoplasmacytic infiltration and fibrosis with acinar destruction (Hematoxylin-eosin)
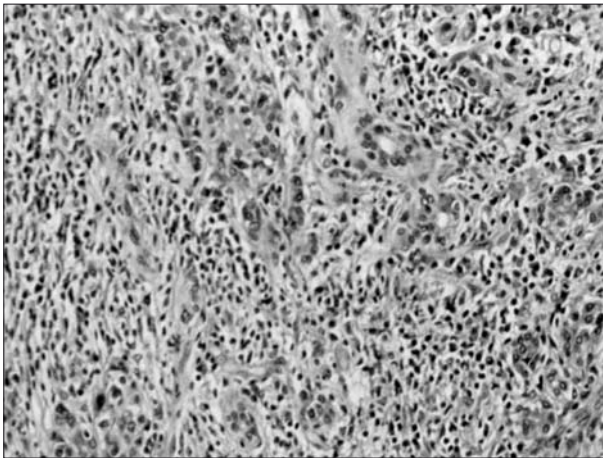
Figure 6. IgG4-immunostaining of the pancreas of a patient with autoimmune pancreatitis showing dense infiltration of IgG4-positive plasma cells
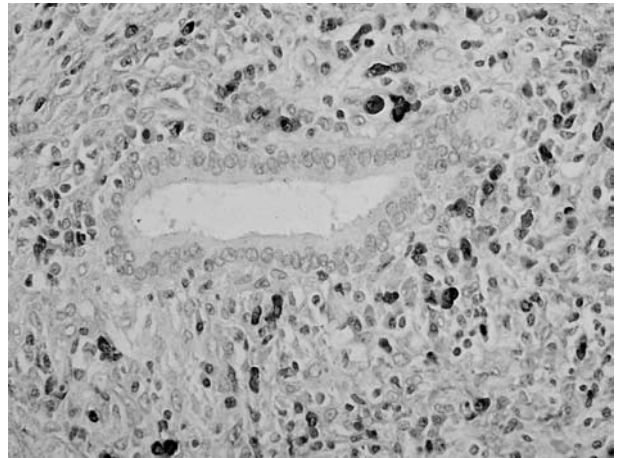
ing the portal vein. Such an inflammatory process widely and intensely involves the contiguous soft tissue, peripancreatic retroperitoneal tissue, and the thickened wall of the bile duct and gallbladder [14,23,24].

These characteristic histological findings of AIP are detected during its active phase, and can be gold standard for diagnosing AIP [25]. However, diagnosing AIP on biopsy or endoscopic ultrasound-guided fine needle aspiration biopsy (FNAB) is sometimes difficult, because of small sample size.

Immunohistochemically, infiltrating inflammatory cells in the pancreas consist of CD4- or CD8-positive T lymphocytes and IgG4-positive plasma cells (*Fig. 6*). Dense infiltration 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 peripancreatic retroperitoneal tissue, major duodenal papilla, biliary tract, intrahepatic periportal area, salivary glands, gastric mucosa, colonic mucosa, lymph nodes and bone marrow of AIP patients [14,23,24]. We suggested that AIP might be a pancreatic lesion of IgG4-related systemic disease [23,26].

Diagnostic criteria and differential diagnosis

The Japan Pancreas Society has proposed "Diagnostic Criteria for Autoimmune Pancreatitis" in 2002 [27,28], and it was revised in 2006 [29]. It contains three items: (1) radiological imaging showing diffuse or localized enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct; (2) laboratory data demonstrating high serum gammaglobulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor; and (3) histological examination of the pancreas showing marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells. Diagnosis of AIP is established when criterion 1, together with either criterion 2 and/or criterion 3, are fulfilled. 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.

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,

Figure 7. **Computed tomography of the patient of *Fig. 2*, which was taken 3 weeks after commencement of steroid therapy. Enlarged pancreas was normalized**

having painless jaundice, developing new-onset diabetes mellitus, and having elevated tumor markers [14]. Radiologically, focal swelling of the pancreas, the "double-duct sign" representing strictures in both the biliary and pancreatic ducts, as well as angiographic abnormalities, can sometimes be seen in both pancreatic cancer and AIP [14]. 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, and segmental narrowing of the main pancreatic duct associated with less dilated upstream pancreatic duct, are all useful in differentiating pancreatic cancer from AIP. Measurement of serum IgG4 levels is a useful tool to differentiate between the two diseases. IgG4-immunostaining of biopsy specimens taken from the major duodenal papilla of AIP patients may be useful to support the diagnosis of AIP [30]. Although improvement in clinical findings with steroid therapy may be useful in the differential diagnosis of AIP from pancreatic cancer, diagnostic steroid trial should be avoided not to misdiagnose pancreatic cancer as AIP. It is of uppermost important to consider the presence of AIP in elderly patients presenting obstructive jaundice and pancreatic mass.

Treatment and prognosis

The dramatic response to corticosteroid is a well-known phenomenon in AIP, but a regimen of steroid therapy has not been established [6,31,32]. Before steroid therapy is started, endoscopic or percutaneous transhepatic biliary drainage must be done in cases with obstructive jaundice, and glucose levels must be controlled in cases with diabetes mellitus. Oral prednisolone is usually initiated at 30-40 mg/day and it is tapered by 5 mg every 1-2 weeks. Serological and imaging tests are followed periodically after commencement of steroid therapy. Usually, pancreatic size is normalized within a few weeks (*Fig. 7*), and biliary drainage becomes unnecessary during 1-2 months. Patients in whom complete radiological improvement is documented can stop their

medication. To prevent relapses without complete discontinuation of steroid, continued maintenance therapy with prednisolone 5 mg/day is sometimes required. In half of steroid-treated patients, impaired exocrine or endocrine function improved [8]. Some AIP patients relapse during maintenance therapy or after stop of 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 which relapses after surgery [33].

The long-term prognosis of AIP is not well known. It is reported that recurrent attacks of AIP resulted in pancreatic stone formation in some cases [7].

Conclusion

AIP is a distinctive type of pancreatitis that shows reversible improvement with oral steroid therapy. AIP has many clinical, serological, morphological, and histopathological characteristic features. AIP should be diagnosed carefully based on combination of these findings. In an elderly male presenting obstructive jaundice and pancreatic mass, AIP should be considered as one of differential diagnoses to avoid unnecessary surgery.

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