Autoimmune Pancreatitis and IgG4-related Sclerosing Disease: An Emerging Disease Entity

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Alcohol consumption is the major cause of chronic pancreatitis. Autoimmunity is a rare but important cause of chronic pancreatitis. In 1995, Yoshida et al[1] first proposed the term *autoimmune pancreatitis* (AIP). They reviewed 11 patients with AIP in the literature and found that diffuse pancreas enlargement and diffuse irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatogram were major characteristic features. In addition, increased serum IgG is a serologic characteristic. The clinical, radiologic, histologic and serologic features and favorable response to steroids comprise the diagnostic criteria of AIP.[2] AIP is a clinically interesting entity and has become an important topic at worldwide digestive disease conferences in recent years.

Most cases of AIP have been reported from Japan. However, reports of AIP from Western countries have been increasing in recent years.[3–6] Most reports have shown that the disease predominantly affects middle-aged to elderly men.[6,7] The prevalence of AIP is not clear. According to a nationwide survey in Japan, the prevalence of patients with AIP was estimated to be 0.82 per 100,000.[7] The male to female ratio was 2.85:1, and the age of disease onset in 95% of the patients was over 45 years. The percentage of AIP in patients with chronic pancreatitis is reported to be 4.6–6%.[3] In this issue of the *Journal of the Chinese Medical Association*, Lin et al[8] report 5 cases of AIP in Taiwan. They retrospectively reviewed the patients' clinical presentations and treatment responses. There were 2 male and 3 female patients, with a mean age of 61 years.

Patients with chronic pancreatitis, especially AIP, and pancreatic cancer share many clinical features, such as obstructive jaundice, pancreatic mass, and stenosis of both pancreatic and bile ducts. Occasionally, AIP is diagnosed by histopathology after Whipple's operation has been undertaken as pancreatic malignancy is presumed with initial imaging studies. Patients with AIP rarely complain of severe abdominal pain typical of pancreatitis. The major presenting symptoms of AIP are obstructive jaundice, mild abdominal pain and weight loss. In Lin et al's report,[8] 4 of the 5 patients with AIP had these 3 major symptoms. In 2 patients, AIP was diagnosed after operation for presumed pancreatic tumor. Three of the 5 patients had diabetes mellitus. Diabetes mellitus is often noted in patients with AIP, with an incidence ranging from 42% to 76%.[3] Most of these cases are diagnosed as new-onset diabetes.

Although 4 diagnostic criteria from Japan, Korea, USA and Italy for AIP have been proposed, a consensus for establishing the diagnosis has not been achieved.[2] In the criteria from Japan and Korea, pancreatic imaging of diffuse pancreas enlargement together with main pancreatic duct narrowing is a mandatory criterion. At least 1 of the supportive criteria including serology (autoantibodies, IgG and IgG4), histopathology (fibrosis and lymphoplasmacytic infiltration) and response to steroid (not included in the criteria by the Japan Pancreas Society) is also required for the diagnosis of AIP. Comparison of imaging findings among AIP, alcoholic chronic pancreatitis and pancreatic cancer is shown in Table 1. Rare pancreatic calcification or cyst is a characteristic of AIP. If endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography is not done, the diagnosis of AIP would be somewhat difficult.

Hypergammaglobulinemia in patients with AIP ranges from 37% to 76%.[3] Increased serum IgG4 is a highly sensitive and specific marker for AIP.[4–6,9] The sensitivity of IgG4 for AIP is shown to be higher than

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Table 1. Comparison of imaging findings among autoimmune pancreatitis (AIP), alcoholic chronic pancreatitis (ACP) and pancreatic cancer

	AIP	ACP	Pancreatic cancer
Complete obstruction of MPD	Uncommon	Uncommon	Common
Ductal stricture	Multiple	Multiple	Single
Upstream MPD dilatation	Mild	Marked	Marked
Double duct sign	Common	Occasional	Common
Pancreatic parenchyma	Diffuse swelling	Atrophy	Focal mass
Calcification of pancreas	Uncommon	Common	Occasional
Pancreatic pseudocyst	Uncommon	Common	Uncommon

MPD = main pancreatic duct.

that of IgG.[3] Can IgG4 distinguish AIP from pancreatic cancer? Ghazale et al[5] measured serum IgG4 levels (normal, 8–140 mg/dL) in 45 patients with AIP and 135 patients with pancreatic cancer. They found that the sensitivity and specificity of elevated serum IgG4 (> 140 mg/dL) for the diagnosis of AIP were 76% and 93%, respectively. Serum IgG4 levels were elevated in 10% of pancreatic cancer patients. Conversely, CA19-9 levels > 100 U/mL were found in 9% of AIP patients, compared with 71% of pancreatic cancer patients.[5] In Lin et al's report,[8] serum IgG levels were measured in 4 patients and found to be increased in all of them. Antinuclear antibody was positive in 3 patients. Unfortunately, IgG4 was not measured in their study.

Extrapancreatic involvement is a particular feature of AIP. Intrahepatic and exprahepatic duct (including hilar area) stricturing is increasingly recognized as a part of the spectrum of AIP.[6] What is the difference in the imaging of bile duct abnormalities between AIP with sclerosing cholangitis and primary sclerosing cholangitis? Nakazawa et al[10] reported that the abnormal intrahepatic ducts in AIP are characterized by segmental stricture or long stricture with prestenotic dilatation, while band-like stricture, beaded or pruned-tree appearance, and diverticulum-like formation are more commonly seen in primary sclerosing cholangitis. Other autoimmune manifestations accompanying AIP include Sjögren's syndrome, psoriasis, inflammatory bowel disease, rheumatoid arthritis, renal mass, tubulointerstitial nephritis, sclerosing cholecystitis, sclerosing cholangitis, stenosis of intrahepatic bile ducts, sclerosing sialoadenitis, swelling of cervical lymph nodes, and retroperitoneal fibrosis. Histopathologic findings of these extrapancreatic lesions are lymphoplasmacytic infiltration with fibrosis and obliterated phlebitis, similar to those of the pancreas. Association of AIP with other autoimmune diseases was reported in 12–50% of patients.[3] In the report of Lin et al,[8] only 1 of the 5 patients with AIP had associated autoimmune disease (Sjögren's syndrome). Because of the demonstration of extrapancreatic involvement in many patients with AIP, *autoimmune pancreatitis* was supposed to be too restrictive a term. *IgG4-related systemic/sclerosing disease* has been proposed.[11]

A good response to steroids is a characteristic of AIP. Church et al[6] followed-up 11 patients and showed rapid symptomatic response to steroids within the first 4 weeks, and liver biochemistry improvement within 2 months and imaging resolution in all patients. Biliary stents were placed in 7 patients, and all stents were removed without recurrence of jaundice over a median follow-up of 8 months.[6] AIP was reported to progress in the absence of steroids. Optimum treatment regimens have not been determined for patients with AIP. The recommended dosage of oral prednisolone is 30–40 mg daily, then gradually reduced over 2–3 months to a maintenance dose of 2.5–10 mg daily according to response.[6] Recurrence of AIP after steroid therapy is not well known. Disease relapse occurred in 55% of patients with AIP on low-dose steroids or following cessation.[6] Most of these patients responded to increased steroids and the addition of azathioprine. In the report of Lin et al,[8] steroid therapy was given to 3 patients who were responsive, but 2 patients experienced recurrence.

Is a persistently elevated or increasing serum IgG4 level on steroids a predictor of disease relapse? Does AIP predispose to pancreatic or biliary malignancy as in the case of chronic pancreatitis or primary sclerosing cholangitis? Could steroid therapy alter the course of the disease? Long-term follow-up studies are required to answer these questions.

In conclusion, knowledge of AIP and IgG4-related sclerosing disease has been emerging and attracting more attention in recent years. Although it is a relatively rare disease, early and accurate diagnosis may avoid unnecessary operation and lead to good treatment response. What constitutes optimal long-term management needs further investigation.

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