

Clinical Aspects of Autoimmune Pancreatitis in Sjogren's Syndrome

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Over the past two decades, the quality of diagnostic imaging in the pancreas has been improved by technical and instrumental progress made in ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). The examination using ultrasound is inexpensive, non-invasive, and can be rapidly performed. It is often the test of choice in the evaluation of suspected pancreatic lesions. However, both the diagnosis of chronic pancreatitis at an early stage and the differential diagnosis between chronic pancreatitis and small pancreatic cancers are still difficult to make.

Ultrasonography of the abdomen has become a routine imaging test when patients have abdominal pain that may be of pancreatobiliary origin or when they have a periodical checkup. Therefore, an incidental finding of diffuse or focal swelling of the pancreas is one of the frequent diagnostic clues used to detect autoimmune pancreatitis and small pancreatic cancers. Such a focal pancreatic mass is often mistaken for a small localized pancreatic cancer even after extensive efforts are made to differentiate chronic pancreatitis from pancreatic cancer by using elaborate imaging modalities including fine needle aspiration biopsy (FNAB). Knowledge of autoimmune pancreatitis or chronic pancreatitis with irregular narrowing of the main pancreatic duct has become important for clinicians, because most patients respond to oral steroid therapy and it saves patients from unnecessary laparotomy and pancreas resection.

Over half the cases of autoimmune pancreatitis that have been reported are from Japan. We

would like to discuss the clinical features and the course of autoimmune pancreatitis associated with autoimmune diseases in Japan, especially Sjogren's syndrome (SjS), and also review the diagnostic and therapeutic aspects of the disease.

Historical Background of Autoimmune Pancreatitis

The concept of chronic pancreatitis associated with or caused by an autoimmune mechanism has been well described since the report of Sarles H *et al.* in 1961 [1]. A case of chronic pancreatitis associated with sclerosing pancreatitis and sicca complex was first reported by Waldram R *et al.* in 1975 [2]. In Japan, Nakamura M *et al.* first reported a successful case of steroid therapy involving pancreatitis associated with Sjogren's syndrome in 1976 [3] and then Nakano S *et al.* announced that, after oral steroid therapy, a pancreatic mass vanished in a patient with Sjogren's syndrome [4]. Toki F *et al.* reported on four cases of chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct in 1992 [5]. His group proposed that diseases with the following characteristics be referred to as "autoimmune pancreatitis" [6]: 1) increased serum gamma-globulin or IgG levels; 2) presence of autoantibodies; 3) diffuse enlargement of the pancreas; 4) diffuse irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (ERP); 5) fibrotic change with histopathologic lymphocytic infiltration; 6) absence of symptoms or only mild symptoms, usually with

an absence of acute attacks of pancreatitis; 7) constriction of the common bile duct in the pancreas with dilatation of the bile duct upstream; frequent observation of cholestatic liver dysfunction and hyperbilirubinemia; 8) no pancreatic calcification; 9) no pancreatic cysts; 10) occasional association with other autoimmune diseases; and 11) effectiveness of steroid therapy.

Four international meetings have been held in the past 30 years in an attempt to develop a clinically useful classification of inflammatory diseases of the pancreas. In the most recent meeting in Rome in 1988 [7], chronic pancreatitis was subclassified into three histologically distinct forms:

- 1) chronic calcifying pancreatitis, the commonest form of chronic pancreatitis by the occurrence of pancreatic calculi in an advanced stage of the disease;
- 2) chronic obstructive pancreatitis as defined by the second Marseilles meeting [8];
- 3) chronic inflammatory pancreatitis, compatible with autoimmune pancreatitis, characterized by the loss of pancreatic parenchyma which is replaced by fibrosis and infiltration with mononuclear cells.

In the third diagnostic criteria of chronic pancreatitis revised by the Japan Pancreas Society in 1995, autoimmune chronic pancreatitis was recognized as a subtype characterized by diffuse or focal irregular narrowing of the main pancreatic duct [9, 10].

Incidence and Prevalence of Autoimmune Pancreatitis

Nishimori I *et al.* reported 118 cases of autoimmune pancreatitis (AIP) from 40 institutions in Japan [11]. We, in Japan, have studied over 30 cases of chronic pancreatitis associated with Sjogren's syndrome; they were reported in English or Japanese language.

The incidence and prevalence of chronic pancreatitis in five prefectures in Japan (total population 10,456 thousand) in 1992 and 1993 were 5.48 and 5.93 patients per 100 thousand

inhabitants per year (incidence), and 9.13 and 4.78 patients per 100 thousand inhabitants (prevalence), respectively [12]. These figures were compatible with those reported by Worring H [13]. Although estimation of incidence and prevalence of autoimmune pancreatitis is difficult, the frequency of incidental detection of patients with autoimmune pancreatitis is increasing with the increase of examinations using imaging modalities such as CT, US, and MRI.

Clinical Pictures of Autoimmune Pancreatitis

Nishimori I *et al.* presented the clinical pictures of the 54 AIP cases successfully treated by means of steroid therapy as the clinical features of autoimmune pancreatitis. We also present the data of 33 cases of chronic pancreatitis with Sjogren's syndrome (CP-SjS) for comparison with the 54 AIP cases.

The male female ratio was 1.84 in the 54 AIP cases and 0.74 in the 33 CP-SjS cases, and the age of onset was over 50 years in more than three quarters of the cases both in the 54 AIP cases and 33 CP-SjS cases. The age of onset occurs 10 to 20 years later than that of chronic pancreatitis of other etiologies.

Abdominal pain and jaundice of the cholestatic type were the two most common complaints and both were observed in one third of the two groups. Abdominal pain was less frequent and severe in autoimmune pancreatitis than in other types of chronic pancreatitis.

Complications of Other Autoimmune Diseases

Sjogren's syndrome was associated with a quarter of the 54 AIP cases. The second most common complicating factor was primary sclerosing cholangitis (PSC, 13%) followed by systemic lupus erythematoses (SLE) [11]. In the 33 CP-SjS cases, association of PSC was found in 5 cases and SLE in 2 cases.

Laboratory Findings

Serum liver enzyme abnormality of a mild cholestatic type was observed in about 40-60% of the 54 AIP cases.

Elevated levels of serum gamma-globulin was present in 43% of the 54 AIP cases, IgG in 62% and non-specific autoantibodies in 36%.

Serum pancreatic amylase increased in 37% of the 54 AIP cases and pancreatic isoamylase decreased in 13%. Serum lipase also increased in 36% of the cases and decreased in 13%; immunoreactive trypsin increased in 45% and decreased in 14% [11]. These abnormal findings were almost similar in the 33 CP-SjS cases.

Pancreatic Function

Exocrine pancreatic insufficiency compatible with definite or probable chronic pancreatitis [9, 10], was found in all 10 patients studied by secretin test in the 54 AIP cases and in eight of the nine patients studied by secretin test in the 33 CP-SjS cases. Recovery of exocrine pancreatic function was reported after oral steroid therapy [3, 4]. Two thirds of the patients of both groups showed a diabetic pattern on a 75 g glucose tolerance test. Exocrine and endocrine pancreatic insufficiencies are similar to those observed in other types of chronic pancreatitis.

Pancreatic Imaging Studies

US or CT revealed diffuse (69%) or focal (24% in the head and 7% in the tail) enlargement of the pancreas in the 54 AIP cases [11]. Over 90% of the 33 CP-SjS cases also presented pancreatic enlargement on initial examination with US or CT. Fluctuation in the extent of the enlargement was observed on follow-up studies by CT or US.

Diffuse or focal narrowing of the main pancreatic duct was demonstrated in 61% of the 54 AIP cases and in 89% of the 33 CP-SjS cases on ERP. Focal enlargement of the pancreas colocalized with stenosis of the main

pancreatic duct is a very difficult problem in the differential diagnosis of chronic pancreatitis from small pancreatic cancers. For these cases, FNAB [14, 15] and intraductal US (IDUS) [14, 16] can help in the differential diagnosis. Another probable solution can be obtained from follow-up imaging studies performed within four weeks after oral steroid therapy.

Pathological Findings

Biopsy of the pancreatic tissue was obtained in 25 of the 54 AIP cases and the characteristic findings of pancreatic pathology were loss of the parenchyma, interstitial fibrosis and mononuclear lymphocytic infiltration with occasional formation of lymph follicles [11]. These fibrotic and infiltrative changes were more prominent around the pancreatic duct and its branches, which can be ascribed to the narrowing of the main pancreatic duct and enlargement of the pancreas. The pathogenesis of the disease is not clear at this point. The autoimmune mechanism has been postulated but there has been no definite evidence.

Diagnosis

In a patient presenting with chronic pancreatitis with elevated IgG, positive antinuclear antibodies, enlargement of the pancreas on US or CT, and/or irregular narrowing of the main pancreatic duct on ERP or MRI, autoimmune pancreatitis is suspected when pancreatic cancer and other neoplastic pancreatic disease can be ruled out.

Histological confirmation of interstitial fibrosis and mononuclear lymphocytic infiltration of the pancreas is needed for a definite diagnosis of autoimmune pancreatitis. FNAB can be a useful diagnostic tool in autoimmune pancreatitis.

Treatment

Oral steroid therapy (oral prednisolone 30-40 mg/day for 3-4 weeks) is effective in the relief of pain and jaundice, as well as in the reduction of the pancreatic enlargement and irregular

narrowing of the pancreatic duct. However, contribution of steroid therapy to long-term prognosis requires further confirmation.

Observation of focal enlargement of the pancreas and narrowing of the pancreatic duct during steroid therapy can be used as a therapeutic diagnosis for differentiation of pancreatic cancer and pancreatitis.

Conclusions

Recognition of the disease [17, 18] is clinically important because it is reversible when diagnosed and treated correctly and saves patients from unnecessary surgery due to misdiagnosis of pancreatic cancer.

Key words Autoimmune Diseases, Diagnosis, Pancreatic Neoplasms, Pancreatitis, Therapeutics

Abbreviations AIP: autoimmune pancreatitis; CP-SjS: chronic pancreatitis with Sjogren's syndrome; CT: computed tomography; ERP: endoscopic retrograde pancreatography; FNAB: fine needle aspiration biopsy; IDUS: intraductal ultrasonography; MRI: magnetic resonance imaging; PSC: primary sclerosing cholangitis; SjS: Sjogren's syndrome; SLE: systemic lupus erythematoses; US: ultrasonography

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