IgG4-related sclerosing disease

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Abstract: Based on histological and immunohistochemical examination of various organs of autoimmune pancreatitis (AIP) patients, we have found dense infiltration of IgG4-positive plasma cells and T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show infiltration of abundant IgG4-positive plasma cells. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease. Some inflammatory pseudotumors may be involved in this disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected. The disease occurs predominantly in elderly males, is frequently associated with lymphadenopathy, and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. The precise pathogenesis and pathophysiology of IgG4-related sclerosing disease remain unclear. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery.

Key words: IgG4-related sclerosing disease, autoimmune pancreatitis, IgG4, sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis

1 Introduction

Yoshida et al. proposed the concept of autoimmune pancreatitis (AIP) in 1995 [1], and AIP has become a distinct entity recognized worldwide [2-4]. In AIP patients, serum IgG4 levels are frequently and significantly elevated, and various extrapancreatic lesions are present. Based on histological and immunohistochemical examination of various organs of AIP patients, we have found dense infiltration of IgG4-positive plasma cells and T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show infiltration of abundant IgG4-positive plasma cells. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease [5-8].

2 IgG4-related sclerosing disease

IgG4-related sclerosing disease is a systemic disease characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs such as the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, and etc. where tissue fibrosis with obliterative phlebitis is pathologically induced. AIP is not simply a pancreatitis but it is a pancreatic lesion reflecting an IgG4-related sclerosing disease. Some inflammatory pseudotumors may be involved in this disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (Fig.1). The disease occurs predominantly in elderly males, is frequently associated with

lymphadenopathy, and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. The precise pathogenesis and pathophysiology of IgG4-related sclerosing disease remain unclear. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery (Table 1) [5-8]. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [5,9].

Table 1. Clinicopathological Findings ofIgG4-related Sclerosing Disease

- Systemic disease characterized histopathologically by extensive IgG4-positive plasma cell infiltration of various organs together with T lymphocytes
- Major clinical manifestations are apparent in the organs in which tissues fibrosis with obstructive phlebitis is pathologically induced.
 Pancreas: autoimmune pancreatitis
 - Bile duct: sclerosing cholangitis Gallbladder: sclerosing cholecystitis Salivary gland: sclerosing sialadenitis Lacrimal gland: sclerosing dacryoadenitis Retroperitoneum: retroperitoneal fibrosis
- Some pseudotumors may be involved in this disease.
- · Possibility of close relationship to

multifocal fibrosclerosis

- Occasional association with lymphadenopathy
- Elderly male preponderance
- Frequent elevation of serum IgG4 levels
- Favorite response to steroid therapy
- Differentiation from malignant tumor is important.
- Precise pathogenesis and pathophysiology remain unclear





3 Autoimmune pancreatitis

AIP is a unique form of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. AIP occurs more commonly in elderly males. In our 57 AIP Patients, the mean age of the patients was 66.5 years (range, 25-83 years), and the male-to-female ratio was 4:1. The major clinical symptom is obstructive jaundice due to associated sclerosing cholangitis (70% in our series). Up to 50% of AIP patients present with glucose intolerance [10]. Levels of serum IgG4 are particularly high in AIP. Dense infiltration of IgG4-positive plasma cells is seen in various organs of AIP patients. These findings suggest that IgG4 plays a major role in the pathogenesis of AIP, although the trigger for the IgG4 elevation or its pathogenetic role in AIP has not been clearly disclosed [11,12].

It is of utmost importance that AIP be differentiated from pancreatic cancer, as some AIP patients in which pancreatic cancer is suspected undergo unnecessary laparotomy or pancreatic resection. Since there is currently no diagnostic serological marker for AIP, AIP should be diagnosed on the basis of the presence of a combination of abnormalities unique to AIP. The Japanese "Diagnostic Criteria for Autoimmune Pancreatitis" were revised in 2006 [13]. They consisted of three items: 1) radiological imaging showing diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas; 2) laboratory data demonstrating abnormally elevated levels of serum gammaglobulin or IgG, or IgG4, or the presence of autoantibodies; and 3) histological examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis. Diagnosis of AIP is made when either all 3 criteria are present or criterion 1 together with either criterion 2 or criterion 3 is present.

Radiologically, pancreatic enlargement is usually hypoechoic, sometimes with scattered hyperechoic spots on ultrasonography (Fig.2).



Fig.2 Ultrasonographic findings of AIP, showing hypoechoic pancreatic enlargement with scattered hyperechoic spots.

On dynamic CT, there is delayed enhancement of the enlarged pancreatic parenchyma. Typical AIP patients 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. Cases of focal enlargement of the pancreas are sometimes difficult to differentiate from pancreatic cancer.

Endoscopic retrograde

cholangiopancreatography (ERCP) discloses an irregular, narrow main pancreatic duct. In patients with segmental narrowing, absence of upstream dilatation of the main pancreatic duct is characteristic. (Fig.3).



Fig.3 ERCP findings of AIP, showing irregular narrowing of the main pancreatic duct

In our AIP patients,

hypergammaglobulinemia and elevated serum IgG levels are detected in 33% and 56%, respectively, while autoantibodies, including antinuclear antibody and rheumatoid factor, were present in 44% and 16%. Serum IgG4 levels are frequently and significantly elevated in AIP patients [14]. According to the report by Okazaki et al., anti-lactoferrin antibody, anti-carbonic anhydrase-II (CA II) antibody, anti-pancreatic secretory trypsin inhibitor (PSTI) antibody, and anti-smooth muscle antibody were detected in 75%, 55%, 25%, and 15% of their 54 AIP patients [15]. The sensitivity of elevated serum IgG4 levels was 80% in our series.

Histologically, dense lymphoplasmacytic infiltration, and interlobular and periductal fibrosis were detected in the pancreas of AIP patients (Fig. 4). These lesions are called as lymphoplasmacytic sclerosing pancreatitis (LPSP) [16]. Immunohistochemically, infiltrated lymphocytes were mainly T lymphocytes, and many plasma cells were positive for anti-IgG4 antibody (Fig.5). The pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration. Another characteristic histological finding is obliterative phlebitis involving minor and major veins, including the portal vein.



Fig. 4 Dense infiltration of lymphocytes and plasma cells and interlobular fibrosis in the pancreas of an AIP patient.



Fig.5 Immunohistochemical finding of AIP, showing abundant infiltration of IgG4-positive plasma cells in the pancreas (IgG4-immunostaining).

AIP responds dramatically well to corticosteroid. Oral steroid is a standard therapy for AIP. The indications for steroid therapy in AIP are symptoms such as obstructive jaundice due to sclerosing cholangitis, abdominal pain, and the presence of other associated systemic diseases, such as retroperitoneal fibrosis.

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 predonisolone is usually started at 0.6mg/kg/day, and then it is tapered by 5 mg every 1-2 weeks. To prevent relapses, continued maintenance therapy with prednisolone 5 mg/day is sometimes required. In half of steroid-treated patients, impaired exocrine or endocrine function improved. About 20-30% of AIP patients relapse during maintenance therapy or after steroid medication is stopped and they should be retreated with high-dose steroid therapy [17,18].

The long-term prognosis of AIP is not well known. Recurrent attacks of AIP resulting in pancreatic stone formation have been reported in some cases [19,20].

4 IgG4-related sclerosing cholangitis

Primary sclerosing cholangitis (PSC) occurs during the 30s-40s and is frequently associated with inflammatory bowel disease [21]. Stenosis occurred in the lower part of the common bile duct in 70% of our AIP patients. Stenosis of the bile duct improved dramatically after steroid therapy, and biliary drainage tube can be withdrawn within a month. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of PSC. Elevation of serum IgG4 is frequently observed in patients with IgG4-related sclerosing cholangitis, and it responds dramatically to steroid therapy, unlike PSC. Clinically, patients with IgG4-related sclerosing cholangitis are older at diagnosis than patients with PSC. The histological appearance is transmural fibrosis. dense fibrosis with infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis in the bile duct wall

and the periportal area of the liver, in contrast to PSC. Given the age at onset, associated diseases, pancreatographic findings, response to steroid therapy, prognosis, and IgG4-related serological and immunohistochemical data, IgG4-related sclerosing cholangitis is a different disease from PSC [22,23].

5 IgG4-related sclerosing cholecystitis

Thickening of the gallbladder was detected on US and/or CT in 32% of our AIP patients. Dense infiltration of IgG4-positive plasma cells and lymphocytes, as well as transmural fibrosis, was detected in the gallbladder wall [24].

6 IgG4-related sclerosing sialadenitis and dacryoadenitis

Swelling of the bilateral salivary glands was present in 25% of our AIP patients, and it was associated with cervical or mediastinal lymphadenopathy. Swelling of the bilateral lacrymal glands was associated in one AIP patient. Swelling of the salivary and lacrymal glands and the lymph nodes improved after steroid therapy. In the salivary glands of these patients, dense infiltration of IgG4-positive plasma cells and fibrosis were detected. Mikulicz's disease is a unique condition that refers to bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands. Patients with Mikulicz's disease lack anti-SS-A and anti-SS-B antibodies, but frequently have

elevated serum IgG4 levels. Infiltration of many IgG4-positive plasma cells into the lacrimal and salivary glands has been detected in Mikulicz's disease. Thus, Mikulicz's disease appears to be salivary gland lesions of IgG4-related systemic disease [25,26].

7 IgG4-related retroperitoneal fibrosis

Retroperitoneal fibrosis was present simultaneously or metachronously in 7% of our AIP patients. Dense infiltration of IgG4-positive plasma cells and obliterative phlebitis were found in both the pancreas and the retroperitoneal fibrous mass. Both the retroperitoneal fibrosis and AIP resolved after steroid therapy [27,28].

8 Other IgG4-related sclerosing diseases

Some cases of inflammatory pseudotumors of the liver [29], lung [30,31], and hypophysis [31,32]; interstitial pneumonia [33,34]; tubulointerstitial nephritis [35,36]; prostatitis [37]; and aortitis [38,39] may be included in IgG4-related sclerosing disease.

9 Conclusions

IgG4-related sclerosing disease is a new clinicopathological systemic entity. It is characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs, and major clinical manifestations are apparent in the organs, in which tissues fibrosis with obliterative phlebitis is pathologically induced. As steroid therapy is effective, accurate diagnosis is necessary.

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