Abstract

Although the pathogenesis of autoimmune pancreatitis is unclear, recent evidence of clinical aspects are presented: (i) mild abdominal symptoms, usually without acute attacks of pancreatitis; (ii) occasional existence of obstructive jaundice; (iii) increased levels of serum gammaglobulin, IgG or IgG4; (iv) presence of autoantibodies; (v) diffuse enlargement of the pancreas; (vi) irregularly narrowing of the pancreatic duct (sclerosing pancreatitis) with often intra-pancreatic biliary stenosis or coexistence of biliary lesions (sclerosing cholangitis similar to primary sclerosing cholangitis: PSC) on endoscopic retrograde cholangiopancreatographic (ERCP) images; (vii) fibrotic changes with lymphocyte and IgG4-positive plasmacyte infiltration, and obliterative thrombo-phlebitis; (viii) occasional association with other systemic lesions such as sialoadenitis, retroperitoneal fibrosis, interstitial renal tubular disorders, and (ix) effective steroid therapy. In addition to pancreatic and extra-pancreatic lesions, diabetes mellitus is occasionally responsive to steroid therapy. Further studies are needed to clarify the pathogenesis. (Internal Medicine 44: 1215–1223, 2005)

Key words: autoimmune pancreatitis, IgG4, lymphoplasmacytic, sclerosing pancreatitis

Introduction

Since Sarles et al observed a case of particular pancreatitis with hypergammaglobulinemia (1), occasional coexistence of pancreatitis with other autoimmune diseases such as Sjögren’s syndrome (SjS) (2), primary sclerosing cholangitis (PSC) (3) or primary biliary cirrhosis (PBC) (3), has been reported. These findings support the hypothesis that an autoimmune mechanism may be involved in the pathogenesis and pathophysiology in some patients with pancreatitis. Recently, similar cases without other autoimmune diseases have been reported, which leads us to the concept of an autoimmune-related pancreatitis, so called “autoimmune pancreatitis (AIP)” (4).

Here, we discuss the recent concept of AIP.

Definition and Concept of AIP

Although the pathogenesis and pathophysiology of AIP are still unclear, various clinical aspects have been reported (4–41). The characteristic findings in most cases of AIP can be summarized as follows (Table 1): (I) mild abdominal symptoms, usually without acute attacks of pancreatitis; (II) occasional existence of obstructive jaundice; (III) increased levels of serum gammaglobulin, IgG or IgG4; (IV) presence of autoantibodies; (V) diffuse enlargement of the pancreas; (VI) irregular narrowing of the pancreatic duct (sclerosing pancreatitis) often with intra-pancreatic biliary stenosis or coexistence of biliary lesions (sclerosing cholangitis) similar to primary sclerosing cholangitis (PSC) on endoscopic retrograde cholangiopancreatographic (ERCP) images; (VII) fibrotic changes with lymphocyte and IgG4-positive plasmacyte infiltration, and obliterative thrombo-phlebitis; (VIII) occasional association with other systemic lesions such as sialoadenitis, retroperitoneal fibrosis, interstitial renal tubular disorders, chronic thyroiditis, and (IX) effective steroid therapy. From these findings, recently, the diagnostic criteria of autoimmune pancreatitis have been proposed by the Japan Pancreatic Society in 2002 (Table 2) (15). Other nomenclature such as “chronic inflammatory sclerosis of the pancreas” (1), “lymphoplasmacytic sclerosing pancreatitis(LPSP)” (16), “pancreatitis showing the narrowing appearance of the pancreatic duct (PNPD)” (5), and “sclerosing pancreato-cholangitis” (14), “inflammatory pseudotumor of the pancreas” (17, 18), “tumefactive chronic pancreatitis” (13, 21, 22), “non-alcoholic duct destructive chronic pancreatitis” (24) or “IgG4-associated sclerosing disease” (25) have also been proposed. Although the prognosis of AIP is still unclear, a few long follow-up studies have suggested occasional formation of pancreatic stone (26). Cases of AIP reported in Japan is somewhat different from those in western countries, which often contain tumor forming pan-
Epidemiology of AIP

AIP is a rare disorder, although the exact prevalence is still unknown. We encountered 30 cases of AIP in 521 cases (6%) of chronic pancreatitis (28), which is a similar rate as a European multi-center study (13). Males are typically predominant and the ratio of males to females is reported to be 2–5 in Japan (19, 28, 34) and 2 in Europe (35). The mean age at diagnosis is over 55 years (19, 28, 34). Diabetes mellitus (DM) is observed in about half of the AIP patients (43–68%) and the majority of cases show type 2 diabetes mellitus (6, 9, 28).

Clinical Phenotypes and Extra-pancreatic Lesions

Etemad and Whitcomb proposed a new classification of chronic pancreatitis based on six risk factors (TIGAR-O classification) and classified AIP as isolated and syndromic types (43). However, along with accumulation of the cases, it has been clarified that the histopathologic findings of extra-pancreatic lesions are similar to those of pancreatic or bile ductal lesions, although other autoimmune diseases such as typical SjS, rheumatoid arthritis, or ulcerative colitis might be associated with AIP. The most common extra-pancreatic lesions are observed in the bile duct and salivary glands (Table 3) (10, 13, 14, 23, 25, 27), which had led us to the concept of “a complex syndrome” (2), “dry gland syndrome” (3), or “autoimmune exocrinopathy”. In addition to sialoadenitis and sclerosing cholangitis, other extra-pancreatic lesions such as retroperitoneal fibrosis, mediastinal lymphadenopathy or renal lesions often show similar histopathologic findings (13, 27–41). These findings suggest a similar mechanism in the development of extra-pancreatic lesions and pancreatic lesions.

Biliary duct

Patients with AIP most often show narrowing of the intra-pancreatic bile duct with dilatation of the upper biliary tract. Sclerosing changes of the bile duct similar to PSC as well as narrowing are often observed as “lymphoplasmacytic sclerosing pancreatitis with cholangitis” (16, 22), “sclerosing pancreato-cholangitis” (14, 30, 31). Different from PSC, IgG4-positive plasmacytes usually infiltrate around the bile duct (25, 27, 29) and administration of steroid generally shows therapeutic effects on biliary lesions associated with AIP (10, 12, 14, 27–34). Therefore, the mechanism of the development of biliary lesions in AIP may be different from typical PSC (14, 27–34). From the viewpoint of IgG4, it has been proposed that sclerosing pancreatitis and sclerosing cholangitis with infiltration of IgG4-positive plasmacytes could be a single disease entity (42). Future studies on the roles of IgG4 are necessary.

Salivary glands

Recently, sialoadenitis in AIP is thought to be sclerosing sialoadenitis similar to Mikulicz’s disease or Kuttner’s tumor rather than typical SjS (29, 44). In patients with sialoadenitis associated with AIP, anti-SSA or anti-SSB autoantibodies are rarely observed, but increased serum levels of IgG4 and infiltration of IgG4-positive plasmacytes are often observed, which suggests a mechanism similar to the pancreatic lesions (29, 38).

Diabetes mellitus

DM is often (43–68%) observed in patients with AIP (12, 28) and the majority of them show type 2 DM. Interestingly, some type 2 DM patients associated with AIP improve after steroid therapy (6, 9, 28). Although the mechanism is obscure, cytokines from T cells and macrophages suppressing the function of islet β-cells may be down-regulated by steroid (6, 9).

Retroperitoneal fibrosis

Retroperitoneal fibrosis with sclerosing cholangitis and pancreatitis, in which a dramatic response to corticosteroid therapy (17, 27–29), although the mechanism of pathophysiology is unclear. Fibrosis with infiltrating lymphocytes and IgG4-positive plasma cells, and similar findings in the pancreas, bile duct and salivary glands, is usually observed (29).
Other organs

Other organs such as the stomach (25, 29, 37, 38), intestine (24, 38), papilla of Vater (39), kidney (32, 33), lymph node (44), thyroid gland (45), and lung (46) may be involved in patients with AIP. Different from retroperitoneal fibrosis, pancreatic, biliary or salivary lesions, fibrosis is rarely observed in the gastro-intestinal tract, which suggests that IgG4-positive plasmacytes play no role in fibrosis.

Clinical Symptoms

Patients with AIP usually have no or only slight discomfort in the epigastrium or back, in addition to the symptoms related to other associated diseases (10, 12, 28). Thus, the clinical symptoms are different from those in acute or severe pancreatitis. More than a half of AIP patients show obstructive jaundice due to stenosis of the bile duct. The most common lesion inducing obstructive jaundice is stenosis of the intra-pancreatic common bile duct. Steroid is usually effective for the narrowing of the biliary and pancreatic ducts as well as for clinical and laboratory findings (12, 28).

Laboratory Data

Patients with AIP generally show increased levels of serum pancreatic enzymes, hypergammaglobulinemia, IgG, IgG4 and the presence of several autoantibodies such as ANA, ALF, ACA-II and rheumatoid factor (10, 12, 28) (Figs. 1, 2). Among them, increased serum IgG4 is observed in 68–90% of the Japanese patients with AIP (20, 23, 25, 28, 29), which suggests that increased IgG4 is one of the most characteristic findings of AIP in spite of a non-specific marker. Antibody against alpha-fodrin, which may be involved in SjS (47), is observed in some AIP cases (8). However, anti-mitochondrial (M2) antibody specific for PBS or anti-SSA/SSB antibody specific for SjS is rarely observed (Fig. 2) (10, 12, 28). The patients with biliary lesions show an abnormality in the serum level of bilirubin and hepatobiliary enzymes. In these cases, other liver diseases such as...
viral hepatitis, autoimmune hepatitis or PBC should be ruled out. After steroid therapy, many abnormal laboratory findings are reversible as well as the pancreatic and biliary images (10, 12, 28) (Fig. 3).

**Pancreatic and Biliary Imaging**

Computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (US) demonstrates the diffusely enlarged pancreas, so called ‘sausage-like’ appearance (Fig. 4), and a capsule-like rim that shows low density on CT and is hypo-intense on T2-weighted MR images, and delayed enhancement on dynamic MR imaging (46). Pancreatic calcification or pseudocyst is seldom observed. F-18 fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) shows accumulative signals in the pancreatic lesions similar to pancreatic cancer (12). ERCP images in the AIP patients show segmental or diffuse narrowing of the main pancreatic duct (4, 5) (Fig. 5). Although magnetic resonance cholangio-pancreatography (MRCP) poorly shows the stenosis of the pancreatic duct, it can well demonstrate stenosis of the bile ducts mainly in the intra-pancreatic area, resulting in dilatation of the upper biliary tract. Sclerosing changes of the extra-pancreatic bile ducts similar to PSC are sometimes observed (12, 23, 30, 31). Steroid therapy is usually effective for lesions in the biliary as well as pancreatic ducts.

![Figure 3](image-url). Effects of steroid therapy on the pancreatic exocrine (A) and endocrine function (B). (A): BT-PABA urine excretion test showed improvement of pancreatic exocrine function by steroid therapy. (B): HbA1c for the marker of diabetes was improved in two-thirds, but in one-third, it was poorly controlled.

![Figure 4](image-url). Computed tomography of the pancreas. The CT image shows the diffusely enlarged pancreas with its so-called “sausage-like” appearance before treatment. Swollen pancreas improved by steroid therapy.
Histopathology

Microscopic findings, if obtained, show fibrotic changes with infiltration of lymphocytes and plasmacytes mainly around the pancreatic duct and involved organs (5–8, 15, 17, 18, 22) (Figs. 6, 7). HLA-DR antigens are often expressed on the pancreatic duct or acinar cells (6, 10, 48–50). Although CD4+ and CD8+ HLA-DR+ T-cells predominantly infiltrate over B-cells in the periductal area, infiltration of plasma cells and lymph follicle formation are observed in many cases (7, 10, 28). Histological features of “sclerosing pancreatitis”, which are similar to the pancreatic findings, are termed lymphoplasmacytic sclerosing cholangitis (LPSP) (16, 22); (i) diffuse lymphoplasmacytic infiltration with pronounced acinar atrophy; (ii) marked fibrosis of the contiguous soft tissue as well as the total pancreas; (iii) obliterated phlebitis in and around the pancreas involving the portal vein; (iv) inflammatory wall thickness of the CBD and gallbladder; and (v) the minor salivary gland in the lip biopsy bearing inflammation similar to the pancreatic lesion or that in sicca syndrome. The major infiltrating cells are lymphoplasmacytes, suggesting dominant B-cell lineage. These findings suggest that the major phenotypes of infiltrating lymphocytes and the severity of fibrosis in the pancreas may differ in the various disease stages. Recently, different from LPSP, granulocyte-dominant histological findings of the pancreas are proposed as idiopathic duct-centric chronic pancreatitis (22) or granulocyte epithelial lesion (35). Therefore, it will be necessary to study whether the difference in histological features is attributed to the different pathogenetic mechanism or the difference of the stages of the disease.

Figure 5. Effects of steroid therapy on endoscopic retrograde cholangiopancreatography. ERCP images of autoimmune pancreatitis. Both the intra-pancreatic common bile duct (a) and narrowing main pancreatic duct (b) and improved one month after steroid therapy (c).
Pathophysiology of AIP

Humoral immunity and target antigens
Occasional coexistence of pancreatitis with other extra-pancreatic lesions suggests that there may be common target antigens in the pancreas and other exocrine organs such as the salivary gland, biliary tract and renal tubules. Several autoantibodies such as antinuclear antibody (ANA), antilactoferrin (LF) antibody (ALF), anti-carbonic anhydrase-II (CA-II) antibody (ACA-II) and rheumatoid factor were frequently detected in patients with AIP (Fig. 2) (10, 12, 28). CA-II and LF are distributed in the ductal cells of several exocrine organs, including the pancreas, salivary gland, biliary duct and distal renal tubules (12). The high prevalence of these antibodies suggests that CA-II and LF may be the candidates for the target antigens in AIP (11, 36). However, it is noted that these autoantibodies are not necessarily specific for AIP (11). Although the majority of diabetic patients associated with AIP show type 2 DM, a few AIP patients with type 1A DM have autoantibodies against glutamic acid decarboxylase, beta-cell or tyrosine phosphatase-like protein (6, 9, 28). Serum levels of IgG4, immune complexes and the IgG4 subclass of immune complexes are often increased in AIP (20, 25). As complement does not combine with IgG4, it is unknown whether or not IgG4-immune complexes induce tissue damage as arthritis or glomerulo-nephritis.

Cellular immunity and effector cells
Although the effector cells of AIP have been poorly understood, the activated CD4+ and CD8+ T-cells bearing HLA-DR were increased in the peripheral blood lymphocytes and pancreas of AIP (11). CD3+ T-cells predominantly infiltrate in the pancreas over B cells (7, 10), although B cells, plasma cells and follicles are occasionally observed. HLA-DR antigens are expressed on the pancreatic duct cells as well as CD4+ T-cells (7, 10, 47, 48), which suggests that an autoimmune mechanism may be involved in inflammation. CD4+ T-cells are further subdivided into Th1 and Th2 cells based on profiles of cytokine production (11). Th1 cells, which produce IL-2, tumor necrosis factor (TNF)-α and IFN-γ, mediate cellular immunity, macrophage activation, cytotoxicity and help for B cell production of opsonizing and complement fixing antibodies (12). In contrast, Th2 cells,
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which produce IL-4, 5, 6 and 10, promote humoral and allergic responses (12). In sicca syndrome (49) and PSC (50), the major infiltrating cells in the tissue are CD4+ HLA-DR+ Th1 cells, although CD8+ and B-cells are also present. In some cases of AIP, CD4+ Th1-cells are predominant over Th2 type cells (11). Therefore, similar to sicca syndrome, Th1 cytokines may be essential in the induction of AIP, while Th2 cytokines may be involved in the progression of the disease process, especially maturation and proliferation of local B cells and plasmocytes. An animal model of AIP, using neonatally thymectomized BALB/c mice immunized with CA-II or LF and transferred nude mice, showed that the CD4+ Th1 cells are mainly involved in the early development of murine AIP (51).

Diagnosis and Differential Diagnosis of AIP

Although histological findings suggest immune-mediated inflammation, it is usually difficult to obtain a specimen from the pancreas. Therefore, it is important to make a diagnosis in combination with the clinical, laboratory findings, and imaging studies, that show a diffusely enlarged pancreas and narrowing pancreatogram. Increased serum levels of gammaglobulin, IgG, especially IgG4, IgG4 subclass of immune complexes, or autoantibodies such as ANF, ALF, ACA-II and RF may be useful for the diagnosis of AIP (10, 12, 28). The differential diagnosis of enlarged pancreas includes malignant lymphoma, plasmacytoma, metastatic cancer and diffuse infiltrative pancreatic carcinoma. Although the majority of AIP can be distinguished from other diseases with radiological imaging and immunological markers, some cases are difficult to distinguish from pancreas or bile duct cancer (12, 28).

Treatment and Prognosis

Intensive care for acute pancreatitis is usually unnecessary. In cases of jaundice, percutaneous transhepatic or endoscopic biliary drainage is often necessary, especially in cases complicated with bacterial infection. Steroid therapy is usually effective for extra-pancreatic lesions such as in the bile duct as well as in the pancreatic duct (12, 28). It is noted that some patients may spontaneously improve. Some AIP patients associated with type 2 DM may improve after
steroid therapy (6, 9). In the unresponsive cases of CBD stenosis to steroid therapy, surgical operation is often necessary not only for the relief of symptoms but also for differentiation from malignancy (28). The long-term prognosis of AIP is unknown. As the clinical and laboratory findings of most cases are reversible after steroid therapy, the prognosis of AIP may depend on the severity of complicated diseases such as other autoimmune diseases or diabetes mellitus.

Conclusion

In conclusion, recent studies support the concept of autoimmune pancreatitis, which appears to be a unique clinical entity. Further studies are necessary to clarify the pathogenesis as well as the long-term prognosis.

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