

LEADING ARTICLE

Autoimmune related pancreatitis

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Gut 2002;51:1-4

Since the first documented case of a particular form of pancreatitis with hypergammaglobulinaemia, similar cases have been reported, leading to the concept of an autoimmune related pancreatitis or so-called "autoimmune pancreatitis". Although it has not yet been widely accepted as a new clinical entity, the present article discusses the recent concept of autoimmune pancreatitis.

SUMMARY

Since Sarles *et al* reported a case of particular pancreatitis with hypergammaglobulinaemia, similar cases have been noted, which has led to the concept of an autoimmune related pancreatitis or so-called "autoimmune pancreatitis". The clinical characteristics are: (i) increased levels of serum gammaglobulin or IgG; (ii) presence of autoantibodies; (iii) diffuse enlargement of the pancreas; (iv) diffusely irregular narrowing images of the main pancreatic duct; (v) fibrotic changes with lymphocyte infiltration; (vi) no or only mild symptoms; (vii) rare pancreatic calcification or pancreatic cysts; (viii) occasional association with other autoimmune diseases; and (ix) effective steroid therapy. In addition to various systemic autoimmune diseases, diabetes mellitus or bile duct lesions responsive to steroid therapy are often observed. Further studies are needed to clarify the pathogenesis.

INTRODUCTION

Since Sarles *et al* observed a case of particular pancreatitis with hypergammaglobulinaemia,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.⁴⁻¹⁴ Recently, similar cases without systemic autoimmune diseases have been reported, which has led to the concept of an autoimmune related pancreatitis,¹³ so called "autoimmune pancreatitis (AIP)".⁵ Although it has not yet been widely accepted as a new clinical entity, the present article discusses the recent concept of AIP.

DEFINITION AND CONCEPT OF AIP

Although the pathogenesis and pathophysiology of AIP are still unclear, clinical aspects have been reported.⁴⁻¹⁴ The characteristic findings in most cases of AIP can be summarised as follows (table 1):

- (i) increased levels of serum gammaglobulin or IgG;
- (ii) presence of autoantibodies;
- (iii) diffuse enlargement of the pancreas;
- (iv) diffusely irregular narrowing of the main pancreatic duct and occasionally stenosis of the intrapancreatic bile duct on endoscopic retrograde cholangiopancreatographic (ERCP) images;
- (v) fibrotic changes with lymphocyte infiltration;
- (vi) no symptoms or only mild symptoms, usually without acute attacks of pancreatitis;
- (vii) rare pancreatic calcification or cysts;
- (viii) occasional association with other autoimmune diseases; and
- (ix) effective steroid therapy.

Other nomenclatures such as "chronic inflammatory sclerosis of the pancreas",¹ "sclerosing pancreatitis",¹⁵ "pancreatitis showing the narrowing appearance of the pancreatic duct (PNPD)",¹⁶ and "sclerosing pancreatocholangitis"¹⁴ have also been proposed. However, cases without evidence of autoimmunity should be classified as a different entity from AIP, even if steroid therapy is effective.

Primary and secondary AIP

Recently, cases of primary (or isolated) AIP without other autoimmune diseases have been reported. In contrast, occasional coexistence of pancreatitis with other systemic exocrinopathy has led to the concept of "a complex syndrome",² "dry gland syndrome",³ or "autoimmune exocrinopathy." The most commonly associated autoimmune disease is SjS.^{10-13 18} In addition, PSC, ulcerative colitis, or systemic lupus erythematosus was sometimes observed.^{17 18} However, it is still unclear whether or not the pathogenetic mechanism of secondary (or syndromic) AIP with other autoimmune diseases is different from primary AIP.^{13 17} It was noted that there is a possibility of developing systemic autoimmune diseases in patients previously diagnosed as having primary AIP.^{13 17}

Abbreviations: ACA-II, anticarbonic anhydrase II antibody; AIP, autoimmune related pancreatitis; ALF, antilactoferrin antibody; ANA, antinuclear antibody; CA-II, carbonic anhydrase-II; ERCP, endoscopic retrograde cholangiopancreatography; IL, interleukin; LF, lactoferrin; PBC, primary biliary cirrhosis; PNPD, pancreatitis showing the narrowing appearance of the pancreatic duct; PSC, primary sclerosing cholangitis; RF, rheumatoid factor; SjS, Sjögren's syndrome.

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Accepted for publication

Table 1 Characteristic findings of autoimmune pancreatitis

- Increased levels of serum gammaglobulin or IgG
- Presence of autoantibodies
- Diffuse enlargement of the pancreas
- Diffusely irregular narrowing of the main pancreatic duct on ERCP images
- Fibrotic changes with lymphocyte infiltration
- No symptoms or only mild symptoms, usually without acute attacks of pancreatitis
- Rare pancreatic calcification or pancreatic cysts
- Occasional association with other autoimmune diseases
- Effective steroid therapy
- Association with diabetes mellitus often improved by steroid therapy

ERCP, endoscopic retrograde cholangiopancreatography.

EPIDEMIOLOGY OF AIP

AIP is a rare disorder, although the exact prevalence is still unknown. More than 150 cases have been reported as AIP or PNPD in the Japanese literature.^{5–10 12 18} We identified 21 cases of AIP among our total of 451 patients with chronic pancreatitis.¹³ Although our study did not show different morbidities between the sexes, males were usually predominant in Japan.^{12 13 18} Mean age at diagnosis was more than 55 years.^{12 13 18}

“AIP is a rare disorder, although the exact prevalence is still unknown”

Diabetes mellitus was observed in about half of AIP patients (43–68%) and the majority showed type 2 diabetes mellitus.^{13 18 19} Although the exact morbidity of primary and secondary AIP is unclear, more than half of the cases were of the primary type.^{12 13 18}

PATHOPHYSIOLOGY OF AIP

Humoral immunity and target antigens

Occasional coexistence of pancreatitis with other autoimmune diseases suggests that there may be common target antigens in the pancreas and other exocrine organs, such as the salivary glands, biliary tract, and renal tubules. Several autoantibodies such as antinuclear antibody (ANA), antilactoferrin (LF) antibody (ALF), anticarbonic anhydrase II (CA-II) antibody (ACA-II), and rheumatoid factor (RF) were frequently detected in patients with AIP.^{12 13} CA-II and LF are distributed in the cells of several exocrine organs, including the pancreas, salivary glands, biliary duct, and distal renal tubules.¹² The high prevalence of these antibodies suggests that CA-II and LF may be candidates for the target antigens in AIP. However, it was found that these autoantibodies are not necessarily specific for AIP.¹² Although the majority of diabetic patients with associated AIP show type 2 diabetes mellitus, a few AIP patients with type 1A diabetes mellitus have autoantibodies against glutamic acid decarboxylase, β cell, or tyrosine phosphatase-like protein.^{9 19 20} Serum levels of IgG4, immune complexes, and the IgG4 subclass of immune complexes are often increased in AIP.²¹ As AIP patients rarely show clinical manifestations of immune complex diseases such as arthritis or glomerulonephritis, the clinical significance of increased IgG4 is still unclear.

Cellular immunity and effector cells

Although the effector cells of AIP have been poorly understood, activated CD4+ and CD8+ T cells bearing HLA-DR were increased in peripheral blood lymphocytes and the pancreas of AIP patients.¹² CD3+ T cells predominantly infiltrate the pancreas over B cells,^{6 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,^{6 10 22 23} 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.¹² Th1 cells, which produce interleukin (IL)-2, tumour necrosis factor α , and interferon γ , mediate cellular immunity, macrophage activation, cytotoxicity, and help in B cell production of opsonising and complement fixing antibodies.¹²

“Th1 cytokines may be essential in the induction and/or maintenance of AIP while Th2 cytokines may be involved in disease progression”

In contrast, Th2 cells, which produce IL-4, 5, 6, and 10, promote humoral and allergic responses.¹² In SJS²⁴ and PSC,²⁵ the major infiltrating cells in the tissue are CD4+HLA-DR+ Th1, although CD8+ and B cells are also present. In some cases of AIP, CD4+ Th1 cells are predominant over Th2 type cells.¹² Therefore, similar to SJS,²⁴ Th1 cytokines may be essential in the induction and/or maintenance of AIP while Th2 cytokines may be involved in disease progression, especially local B cell activation. An animal model of AIP, using neonatally thymectomised BALB/c mice immunised with CA-II or LF and transferred nude mice, showed that CD4+ Th1 cells are mainly involved in the early development of murine AIP.²⁶

ASSOCIATED DISEASES

Biliary ductal lesions

Patients with AIP often show narrowing of the common bile duct, mainly in the intrapancreatic area, which may result in dilatation of the upper biliary tract. The sclerosing changes of the extrapancreatic bile duct, similar to PSC, are reported as “lymphoplasmacytic sclerosing pancreatitis with cholangitis”,¹⁵ “sclerosing pancreatocholangitis”,¹⁴ or an “inflammatory pseudotumour from sclerosing cholangitis”.¹ In contrast with PSC, administration of steroid usually has therapeutic effects on biliary lesions in AIP.^{10 12 14} Therefore, the mechanism of the development of biliary lesions in AIP may be different from that of typical PSC.¹⁴

Diabetes mellitus

Diabetes mellitus is often (43–68%) observed in patients with AIP^{13 18 20} and the majority show type 2 or other specific type diabetes mellitus. Interestingly, some diabetes mellitus patients with associated AIP improve after steroid therapy.^{19 20} Although the mechanism is obscure, cytokines from T cells and macrophages suppressing the function of islet β cells may be downregulated by steroids.^{19 20}

Retroperitoneal fibrosis

In retroperitoneal fibrosis with sclerosing cholangitis and pancreatitis, a dramatic response to corticosteroid therapy has been observed,^{14 27} although the pathophysiology is unclear.

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 13} Thus clinical symptoms are different from acute or severe pancreatitis. Obstructive jaundice due to stenosis of the intrapancreatic common bile duct is characteristic of AIP, which is rare in other types of pancreatitis. Steroids are usually effective on narrowing of the biliary and pancreatic ducts as well as on clinical and laboratory findings.^{5-10 13}

LABORATORY DATA

Patients with AIP usually show increased levels of serum pancreatic enzymes, hypergammaglobulinaemia, and the presence of several autoantibodies such as ANA, ALF, ACA-II, and RF.^{10 13} Antibodies against α -fodrin, which may be involved in SjS,²⁸ are observed in some AIP cases.¹³ However, antimitochondrial (M2) antibody specific for PBS is rarely observed.^{10 13} Patients with stenosis of the common bile duct show abnormalities of serum 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 reversed.^{5-10 13}

PANCREATIC AND BILIARY IMAGING

Computed tomography, magnetic resonance imaging, or ultrasonography demonstrates the diffusely enlarged pancreas, so-called "sausage-like" appearance, and a capsule-like rim that appears as low density on computed tomography, as hypointense on T2 weighted magnetic resonance images, and as delayed enhancement on dynamic magnetic resonance imaging.^{13 29} Pancreatic calcification or pseudocyst is seldom observed. F-18 fluoro-2-deoxy-D-glucose-positron emission tomography shows cumulative signals in the pancreatic lesions similar to pancreatic cancer.¹³ ERCP images in AIP patients show segmental or diffuse narrowing of the main pancreatic duct.^{5 16} Although magnetic resonance cholangiopancreatography is poor in showing stenosis of the pancreatic duct, it can adequately demonstrate stenosis of the bile ducts, mainly in the intrapancreatic area, resulting in dilatation of the upper biliary tract. Sclerosing changes of the extrapancreatic bile ducts similar to PSC are sometimes observed.¹⁰⁻¹⁴ Steroid therapy is usually effective for changes in the biliary as well as the pancreatic ducts.^{9 13 14}

HISTOPATHOLOGY

Microscopic findings, if obtained, show fibrotic changes with infiltration of lymphocytes and plasmacytes mainly around the pancreatic duct.^{5-8 18} HLA-DR antigens are often expressed on pancreatic duct or acinar cells.^{6 10 22 23} In some cases, CD4+HLA-DR+ T cells predominantly infiltrate over CD8+ T and B cells in the pancreas^{6 10} while plasma cells and lymph follicles are observed in other cases. Histological features of "sclerosing pancreatitis" from the autopsy specimen are somewhat similar to AIP but are extremely unique, for example¹⁵:

- (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 common bile duct and gall bladder; and
- (v) the minor salivary gland in the lip biopsy bearing inflammation similar to the pancreatic lesion or that in SjS.

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 be different in the different disease stages. Therefore, it will be necessary to study whether the difference in histological features is attributed to the different pathogenetic mechanism or differences in the stages of the disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF AIP

Although histological findings suggest immune mediated inflammation, it is usually difficult to take specimens from the pancreas. Therefore, it is important to make a diagnosis in combination with 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 a diagnosis of AIP.^{12 13} The differential diagnosis of a diffusely enlarged pancreas includes malignant lymphoma, plasmacytoma, metastatic cancer, and diffuse infiltrative pancreatic carcinoma. Most cases of AIP can be distinguished from other such diseases by radiological imaging.^{10 13 16 29} However, it is often difficult to distinguish AIP from cancer of the pancreas head or diffuse cancer.^{10 13} Although improvement in clinical findings with steroid therapy may be useful in the differential diagnosis of AIP from pancreas cancer,^{10 13} easy administration of steroids should be avoided as much as possible.

TREATMENT AND PROGNOSIS

In most AIP patients, intensive treatment for acute pancreatitis is not required. In cases of jaundice, percutaneous transhepatic or endoscopic biliary drainage is often required, especially in cases complicated by bacterial infection. Steroid therapy is usually effective for narrowing of the bile ducts as well as pancreatic duct.^{5-10 13 30} It has been noted that some patients may spontaneously improve without any treatment.^{10 13 30} Some AIP patients with associated type 2 or other specific type diabetes mellitus may improve after steroid therapy.^{19 20 30} In unresponsive cases of common bile duct stenosis to steroid therapy, surgery is often necessary not only for the relief of symptoms but also for differentiation from malignancy.^{9 30}

"In most AIP patients, intensive treatment for acute pancreatitis is not required"

The long term prognosis of AIP is unknown. As the clinical and laboratory findings of most cases are reversible after steroid therapy,^{9 10 13 30} the prognosis of AIP may depend on the severity of the complicating diseases, such as other autoimmune diseases or diabetes mellitus.

CONCLUSIONS

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

ACKNOWLEDGEMENTS

This study was supported by: (1) Grant-in-Aid for Scientific Research (C) from the Ministry of Culture and Science of Japan (11670495), (2) Grant-in-Aid for "Research for the Future" Program from the Japan Society for Promotion of Science (JSPS-RFTF97I00201), and (3) supporting research funds from the Japanese Foundation for Research and Promotion of Endoscopy (JFE-2001).

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