Overview of Type 1 and Type 2 AIP

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Introduction

Autoimmune pancreatitis (AIP) is a peculiar form of pancreatitis that has been known for the last two decades. Sarles et al. [1] first reported pancreatitis associated with hypergammaglobulinemia in 1961. They suggested that autoimmunity was one of the etiologies of pancreatitis. The first case that led researchers to suggest a new concept of AIP was treated with steroids by gastroenterologists (led by Professor Tadashi Takeuchi) in Tokyo Medical Women's University, and the concept was proposed by Yoshida, a member of that group, in 1995 [2]. The characteristic histological feature of the AIP is lymphoplasmacytic sclerosing pancreatitis (LPSP) [3]. AIP has been increasingly seen over the last decade and is now considered a distinct entity [4, 5]. Based on histological and immunohistochemical examinations of various organs and extrapancreatic lesions of AIP patients, a new clinicopathological entity called "IgG4-related systemic disease" was proposed [4, 6]. AIP is now considered to be a pancreatic manifestation of IgG4-related disease [4, 5, 7].

Following retrospective, histological examinations of pancreases resected due to suspicion of pancreatic cancer from patients with mass-forming chronic pancreatitis, American and European pathologists described another unique histological pattern, which was described as idiopathic duct-centric pancreatitis (IDCP) [8] or AIP with granulocytic epithelial lesion (GEL) [9]. Presently, AIP related to IgG4 is called type 1 AIP, and the later AIP reported from Europe is called type 2 AIP [5, 10, 11]. However, different historical paths have been followed to that designation (Table 1.1) [1–3, 6, 8–20]. Many diagnostic criteria for AIP have been published [13–16]. Following several international symposia, international consensus diagnostic criteria, which can be used to diagnose type 1 and type 2 AIP separately, were published in 2011 [18].

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The First Report of AIP

A 68-year-old woman developed jaundice and was admitted to another hospital in 1993. Radiographic examinations showed pancreatic enlargement and common bile duct (CBD) obstruction. A tentative diagnosis of pancreatic cancer was made, and exploratory laparotomy was performed. The intraoperative diagnosis was advanced pancreatic cancer, and surgery was concluded without resecting the tumor or performing a biliary bypass procedure, and no biopsy specimens of the tumor were taken. After discharge, the patient presented at Tokyo Women's Medical University Hospital for further examination and treatment.

The patient had no history of alcohol abuse and no family history of pancreatic disease. She had no manifestations of sicca syndrome or any other collagen diseases. On physical examination, a hard, elastic mass with mild tenderness was palpated in the left upper quadrant of the abdomen in the area of the pancreas. The jaundice remitted spontaneously in the absence of any treatment. Though blood chemistry examinations showed evidence of cholestatic liver dysfunction, the total bilirubin level was normal. The pancreatic enzyme data showed an increased elastase-1 level with a low trypsin level, but she had normal lipase and pancreatic amylase levels. Levels of the tumor markers CA19.9, CEA, and Dupan-II were all within their normal ranges. Antinuclear antibody (ANA), anti-thyroglobulin antibody, and anti-microsomal antibody tests were positive. Her IgG level (2,960 mg/dL) was markedly elevated, with slight elevation of the IgE level (452 IU/mL). Though a 75-g oral glucose tolerance test showed a diabetic pattern, her HbA1c value was normal. An abnormally low value was obtained on the secretin test of exocrine pancreatic function.

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Table 1.1 Timeline of most important clinical observations in autoimmune pancreatitis

Year	Author	Reported findings
1961	Sarles et al. [1]	Idiopathic chronic pancreatitis associated with hypergammaglobulinemia; suggested an autoimmune mechanism
1991	Kawaguchi et al. [3]	Lymphoplasmacytic sclerosing pancreatitis (LPSP)
1995	Yoshida et al. [2]	Proposal of the concept of autoimmune pancreatitis (AIP)
2001	Hamano et al. [12]	Elevated serum IgG4 levels in AIP patients
2002	Japan Pancreas Society [13]	First diagnostic criteria for AIP
2003	Kamisawa et al. [6]	Proposal of IgG4-related systemic disease
2003	Notohara et al. [8]	Idiopathic duct-centric pancreatitis (IDCP)
2004	Zamboni et al. [9]	AIP with granulocyte epithelial lesion (GEL)
2006	Chari et al. [14]	HISORt criteria for AIP
2006	Kim et al. [15]	Korean diagnostic criteria for AIP
2008	Otsuki et al. [16]	Asian diagnostic criteria for AIP
2009	Kamisawa et al. [17]	Standard steroid treatment for AIP
2010	Chari et al. [10]	International consensus on classification of AIP into type 1 and type 2
2010	Sah et al.[11]	Clinical differences between type 1 and 2 AIP
2011	Shimosegawa et al. [18]	International Consensus Diagnostic Criteria
2011	Kamisawa et al. [19]	International survey of AIP
2013	Hart et al. [20]	International survey about long-term outcomes of AIP

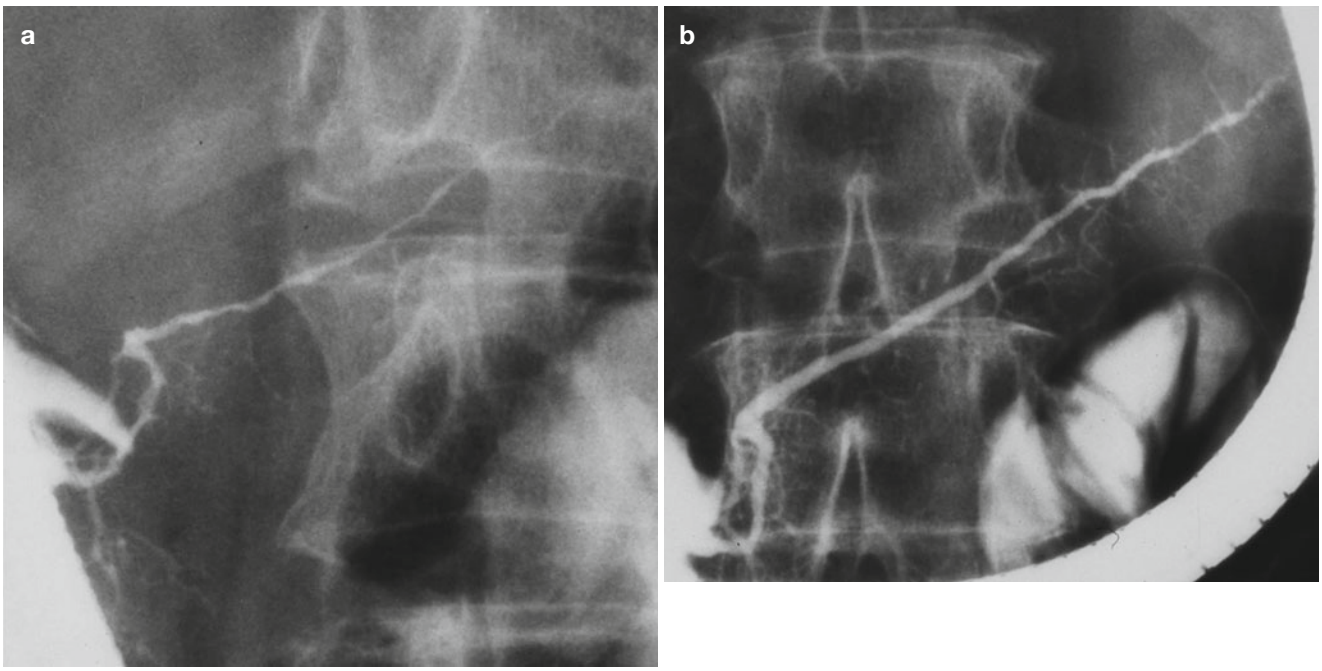

Fig. 1.1 Endoscopic retrograde pancreatography of the first reported case [2]. Diffuse irregular narrowing of the main pancreatic duct (**a**) improved after steroid therapy (**b**)

Ultrasonography showed diffuse enlargement of the pancreas with a slight hypoechoic pattern and CBD dilatation. On CT scans, diffuse pancreatic enlargement was seen, with homogeneous staining of the pancreas on contrast CT. On endoscopic retrograde pancreatography (ERP), the main pancreatic duct showed diffuse narrowing, and the main pancreatic duct wall was irregular (Fig. 1.1a). Histological examination of a needle biopsy specimen of the pancreas showed severe fibrotic change and lymphocyte and plasma cell infiltration.

Based on the above findings, chronic pancreatitis was diagnosed, an autoimmune mechanism was suspected to be involved in its pathogenesis, and it was suggested that steroid therapy would be effective. The patient was given oral prednisolone 40 mg/day for 1 week, followed by gradual tapering. The pancreas showed a dramatic decrease in size 8 weeks after the start of steroid therapy, and the CBD dilatation decreased from 11 to 8 mm. ERP done 4 weeks after the start of steroid therapy showed resolution of the narrowing of the main pancreatic duct, though mild irregularity of its wall

remained (Fig. 1.1b). The IgG levels became normal, and the ANA, anti-thyroglobulin antibody, and anti-microsomal antibody titers decreased. The cholestatic liver dysfunction and exocrine pancreatic dysfunction showed complete resolution, and the patient was discharged after an uneventful course.

Based on the findings described above, AIP would have been considered today, but AIP did not exist as a concept at that time. Although the patient had an abdominal mass, pancreatic cancer was unlikely, because her general condition was good, she had no abdominal pain, and spontaneous resolution of her jaundice occurred over a 1-month period in the absence of any treatment. The presence of "diffuse irregular narrowing of the main pancreatic duct" on ERP had been noticed in several previous chronic pancreatitis patients, but its cause was unknown. However, the case reported above suggested that an autoimmune mechanism may have also been involved in the pathogenesis of previous cases.

This is the first case of AIP ever reported, and it was the first case treated with a steroid, and because of the steroid therapy's remarkable efficacy, surgery based on suspicion of pancreatic cancer has become unnecessary in cases with similar findings. Although this was only a report of a single case, the concept of AIP as a new clinical entity was proposed [2].

Type 1 AIP

Clinical Features

AIP is frequent in elderly males. According to a nationwide survey [21] in Japan, the male-to-female ratio of AIP patients was 3.7, with a mean age of 63.0 years. In the USA, the mean age was 61 years, and 85 % was male [22]. Obstructive jaundice induced by sclerosing cholangitis is the predominant initial symptom (74 % in the Komagome Hospital series [23]), and the jaundice sometimes fluctuates. Other symptoms include abdominal or back pain, weight loss, and anorexia. Diabetes mellitus (DM), usually type 2, is found in about half of AIP patients. The diagnoses of DM and AIP are made simultaneously in most patients, but some patients show exacerbation of preexisting DM with the onset of AIP [24, 25]. Mild or moderate pancreatic exocrine dysfunction is frequently detected [24]. Signs of associated extrapancreatic lesions, such as swelling of the salivary glands, hydronephrosis, and lymphadenopathy, are sometimes seen.

Laboratory Features

Liver and biliary enzymes and total bilirubin are frequently increased. Elevation of serum pancreatic enzymes was sometimes detected, but their levels were rarely abnormally high. Peripheral eosinophilia ($\geq$600 cells/mm^3) and elevation of serum IgE levels were present in 11 and 34 %, respectively [26]. Elevation of serum IgG levels, positive antinuclear antibody (ANA), and positive rheumatoid factor (RF) were seen in 56.9, 33.6, and 27.3 %, respectively [21]. Serum IgG4 levels are frequently increased (77 % in the Komagome Hospital series [27], 81 % in the USA [22], and 68 % in Korea [28]). However, serum IgG4 levels are also elevated in some patients with pancreatic cancer (4 % (5/116) in the Komagome Hospital series [27] and 7 % (5/71) in the University of Pittsburgh Medical Center series [29]).

Imaging Features

The typical pancreatic imaging of AIP is diffuse enlargement and effacement of the lobular contour of the pancreas, with enhancement of the enlarged pancreas in the delayed phase of dynamic CT and MRI. A capsule-like rim that surrounds the pancreas is rather specific to AIP patients [30, 31]. On diffusion-weighted magnetic resonance imaging, AIP and pancreatic cancer are seen as high signal intensity areas, which are frequently diffuse or multiple in AIP patients, while they are solitary in pancreatic cancer patients [32].

Ultrasound examination shows an enlarged hypoechoic pancreas with hyperechoic spots [4]. Irregular narrowing (<3 mm in diameter) of the main pancreatic duct is a characteristic pancreatographic finding of AIP. The degree of narrowing of the main pancreatic duct can sometimes differ in the same patient [33–35]. MRCP cannot demonstrate the narrowing of the main pancreatic duct in many cases, but AIP is suggested by the presence of less upstream dilatation of the main pancreatic duct [36]. On fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET), both AIP and pancreatic cancer patients showed FDG uptake in the pancreas, but abnormal extrapancreatic FDG uptake, such as extensive lymphadenopathy or swollen salivary gland, is highly suggestive of AIP [37].

Histopathological Features

The histological findings in the pancreas of AIP (LPSP) are abundant infiltration of T lymphocytes and IgG4-positive plasma cells and fibrosis in a periductal and interlobular distribution. The epithelium of the narrowed pancreatic duct is usually well preserved. Obliterative phlebitis is frequently seen in the variably sized pancreatic veins [2, 38, 39].

Diagnostic Criteria and Differential Diagnosis

Recently, the ICDC [18] for AIP were developed to diagnose AIP safely, avoid misdiagnosing pancreatic cancer as AIP, and diagnose AIP when it presents acutely. The criteria for type 1 and type 2 AIP were developed independently, and the

diagnosis of AIP is made based on one or more of the following cardinal features: imaging characteristics of the pancreatic parenchyma and pancreatic duct, serology, other organ involvement, pancreatic histology, and the optional criterion of response to steroid therapy. Each feature has been categorized as either level 1 or 2 depending on its diagnostic reliability.

The most important disease to rule out when considering a diagnosis of AIP is pancreatic cancer. CT findings (a capsule-like rim, delayed enhancement of the swollen pancreas, and presence of extrapancreatic lesions) and ERP findings (≥3-cm-long narrowed main pancreatic duct, maximal upstream main pancreatic duct <5 mm, side branch derivation from the narrowed portion, and skipped lesions) suggest AIP rather than pancreatic cancer [33, 35, 40]. However, especially in segmental-type AIP, a histological approach with endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) plays an important role in confirming the diagnosis and excluding malignancy [41]. IgG4-immunostaining of biopsy specimens taken from the major duodenal papilla of AIP patients is useful to support the diagnosis of AIP [41–43].

Although a diagnostic trial of steroid therapy is useful in some cases to differentiate AIP from pancreatic cancer, it requires extreme caution and should be only be undertaken by pancreatologists in limited cases after a negative workup for pancreatic cancer, including EUS-FNA [18, 38].

Treatment

Although spontaneous improvement of AIP is seen in some patients, the standard therapy for AIP is oral steroid [17, 44, 45]. It is vitally important to distinguish AIP from pancreatic cancer before steroid therapy is started. In the Japanese standard regimen [44, 45] of steroid therapy for AIP, the indications for steroid therapy are principally symptoms such as obstructive jaundice and hydronephrosis. Before steroid therapy, the blood glucose level should be controlled using insulin in patients with DM, and in patients with obstructive jaundice, the jaundice is usually managed by endoscopic or transhepatic biliary drainage. The recommended initial dose of oral prednisolone is 0.6 mg/kg/day. Morphological and serological evaluations of the effectiveness of steroid treatment are performed 2 weeks after its start. A poor response to steroid therapy should raise the possibility of pancreatic cancer and the need to reevaluate the diagnosis. When steroid therapy is effective, the steroid dose is tapered by 5 mg every 1–2 weeks to a maintenance dose over a period of 3–6 months, while the patient's symptoms, as well as the biochemical, serological, and imaging findings, are carefully monitored. Relapses of AIP are frequent (around 30 %) [19, 20]. To prevent relapse, steroid maintenance therapy (5 mg/day) is recommended for at least about 6 months. Predictors of disease relapse include the presence of proximal bile duct involvement [20, 46] and persistent elevation of serum IgG4 levels [17]. In relapsed cases, re-administration or dose-up of steroid [17, 44, 45] and administration of immunosuppressive drugs such as azathioprine [47, 48] or rituximab [48, 49] are effective.

Prognosis

The short-term prognosis of AIP appears good with steroid therapy. However, the long-term outcome is unclear, because there are many unknown factors, such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy. In 27 % of cases, the pancreas became atrophic 1 or 2 years after the initiation of steroid therapy [50]. Pancreatic duct stones are more likely to occur in patients with at least one relapse (14.4 %), compared with those who have never had a relapse (4.0 %) [20]. Nine cases of pancreatic cancer associated with AIP have been recently reported, but whether there is a relationship between AIP and pancreatic cancer is unclear [45].

Type 2 AIP

Type 2 AIP is defined by the histological features of IDCP or GEL [8, 9]. The characteristic histological finding is ductal epithelial granulocytic infiltration leading to ductal damage, which is not seen in LPSP. Obliterative phlebitis and IgG4-positive cell infiltration are uncommon in IDCP [51]. Type 2 AIP is sometimes found in Western countries, but it appears uncommon in Japan and Korea [20]. Unlike type 1 AIP, type 2 AIP appears not to be a systemic disease, but rather a pancreas-specific disease. Type 2 AIP affects younger patients, and there is no male preponderance. It is not associated with increased serum IgG4 levels or with OOI typically seen in type 1 AIP. Acute pancreatitis and inflammatory bowel disease are sometimes associated with type 2 AIP [11, 20]. Currently, there is no serological biomarker for type 2 AIP, and the need for histological examination to diagnosis makes its clinical diagnosis difficult. Type 2 AIP also responds well to steroids. The relapse rate following steroid therapy was lower in type 2 AIP (15.3 %) than in type 1 AIP (35.8 %). Relapses in type 2 AIP were limited to the pancreas, while relapses occurred in various areas including the pancreas and biliary tree in type 1 AIP [20]. The clinical spectrum and long-term outcomes of medically treated type 2 AIP are still unclear.

Conclusions

Type 1 AIP is a pancreatic lesion of IgG4-related systemic disease, while type 2 AIP is a pancreas-specific disorder that is not associated with IgG4. Both AIPs are

clinicopathologically, regionally, and ethnically different entities, sharing a need for accurate differentiation from pancreatic cancer. Further investigation is necessary to clarify the pathogenetic mechanisms including more definite serological markers and identification of the best diagnostic and therapeutic strategies.

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