

## Review Article

# Autoimmune pancreatitis: an overview from pathologists' perspective with emphasis on recent advances

Sory J Ruiz<sup>1</sup>, Shetal N Shah<sup>2</sup>, Nirag Jhala<sup>3</sup>, Darshana Jhala<sup>4</sup>, Xiuli Liu<sup>1</sup>

<sup>1</sup>Department of Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio, USA; <sup>2</sup>Imaging Institute, Cleveland Clinic, Cleveland, Ohio, USA; <sup>3</sup>Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA; <sup>4</sup>Pathology and Laboratory Medicine Service, Philadelphia VAMC, University of Pennsylvania, Philadelphia, PA, USA

Received August 11, 2014; Accepted September 25, 2014; Epub December 15, 2014; Published December 30, 2014

**Abstract:** Autoimmune pancreatitis (AIP) is an inflammatory condition of the pancreas of unknown etiology. It is not a homogenous entity; two types have been recognized and they are currently named type 1 and type 2 AIP. Both types have overlapping radiological features and their clinical presentation can be similar, but their histologic appearance is different and the underlying pathophysiological processes appear to be different as well. Type 1 AIP, previously known as lymphoplasmacytic sclerosing pancreatitis, is part of the IgG4-related disease spectrum, a multisystemic fibroinflammatory condition that affects multiple organs in a synchronous or metachronous way. Type 2 AIP, previously known as duct-centric chronic pancreatitis or granulocyte epithelial lesion (GEL)-positive pancreatitis, is not part of the IgG4-related disease spectrum, and is not associated with other organ involvement. This review focuses on the most recent advances in their pathogenesis, diagnosis, and treatment with particular attentions to histologic diagnostic criteria. It also discusses the differential diagnoses.

**Keywords:** Autoimmune pancreatitis, IgG-4 related disease

## Introduction and history

In 1961 Sarles et al. reported 10 cases of recurrent pancreatitis with inflammatory fibrosis and without calcifications that differed in clinical presentation and histological features from other forms of pancreatitis. The term "primary inflammatory sclerosis of the pancreas" was used and later replaced by "primary non-calci-fying pancreatitis with hypergammoglobulinemia"; they noted that patients affected by this condition were older than patients with pancreatitis featuring calcifications and that they had hypergammoglobulinemia and jaundice [1, 2]. In 1991 Kawaguchi and colleagues, offered the first comprehensive histopathological descriptions of what he termed 'lymphoplasmacytic sclerosing pancreatitis with cholangitis'; what he described corresponds to the histological features of the cases described by Sarles et al. [3]. Multiple studies were later done by Japanese researchers. An autoimmune mechanism

was proposed for this type of pancreatitis by Yoshida et al. in 1995 given the presence of elevated serum levels of IgG autoantibodies, occasional association with other autoimmune diseases and effectiveness of steroid therapy [4]. It was not until 2001 that high serum levels of IgG4 were reported in patients with AIP in a study by Hamano et al. [5]. In 2002, the Japanese Pancreas Society (JPS) proposed the first set of consensus diagnostic criteria known as the JPS 2002 criteria for AIP [6] which were later revised in 2006 [7]. In 2003 Kamisawa et al. proposed that AIP was not an isolated condition but part of an IgG4-related systemic disease with extensive organ involvement [8].

In Europe in 1997 Ectors et al. presented the first description of the features of a histologically different type of pancreatitis, which they named "non-alcoholic duct destructive chronic pancreatitis" [9]. In 2003 Pearson et al. defined the diagnostic criteria for AIP cases that had

## Review of autoimmune pancreatitis

**Table 1.** Historic milestones of autoimmune pancreatitis diagnostic criteria

Year	Milestones
1961	Sarles et al. first reported chronic inflammatory sclerosis of the pancreas.
1995	Yoshida et al. proposed the concept of "autoimmune pancreatitis" and listed 12 features suggestive of autoimmune pancreatitis.
1997	Ectors et al. described 12 cases of non-alcoholic chronic pancreatitis with different histological features than those described by Sarles in 1961.
2001	Hamano et al. report that some cases of AIP are associated with high IgG4 serum levels.
2002	The JPS published the "Diagnostic Criteria for Autoimmune Pancreatitis, 2002" based on studies done mostly by Japanese researchers. A nationwide survey using its newly published criteria and estimated the prevalence of autoimmune pancreatitis in Japan.
2003	Kamisawa et al. proposed that autoimmune pancreatitis was part of an IgG4-related systemic disease with extensive organ involvement.
2003	Pearson et al. proposed the Italian criteria based on cases with the same histological features of the cases described by Ectors et al. in 1997.
2003	Notohara et al. proposed the existence of two different types of autoimmune pancreatitis with distinct histological and clinical features.
2006	Chari et al. proposed the HISORt criteria. Kim et al. proposed the Kim criteria.
2010	The Honolulu consensus characterized the clinical and histological differences between the two types of autoimmune pancreatitis. It proposed that the terms type 1 and type 2 AIP should be used.
2011	The International Association of Pancreatology published diagnostic criteria for type 1 and type 2 AIP.

the same histological features as reported by Ectors et al. and they proposed the term idiopathic duct-centric AIP [10].

The comparison and contrast of these two potentially distinct types of AIP were performed by Notohara K et al. In this report, two subtypes of AIP were proposed: lymphoplasmacytic sclerosing pancreatitis which is characterized by fibrosis, diffuse lymphoplasmacytic infiltrate and obliterative phlebitis and affects mostly elderly men, and duct-centric chronic pancreatitis which shows duct-centric inflammation with presence of neutrophils and damage of the epithelium and affects patients of all ages [11]. The spread of knowledge on AIP in the world promoted also its recognition in both other Asian countries and Western countries including the United States. In 2006, Chari and colleagues at the Mayo Clinic proposed a set of diagnostic criteria, which are somewhat different from those proposed by Pearson in 2003 and those proposed by JPS in 2006 [12].

The Honolulu consensus document published in 2010 offered a clear description and distinction of the histological and clinical features of AIP, it proposed that the terms type 1 and type 2 AIP should be used instead of lymphoplasmacytic sclerosing pancreatitis and duct-centric chronic pancreatitis respectively [13]. The milestones in characterization of AIP are listed in **Table 1**.

In 2011 the International Association of pancreatology published a set of diagnostic criteria for type 1 and type 2 AIP using clinical, serological, radiological and histological parameters as well as response to steroids [14].

### Type 1 AIP

#### *Etiology and pathogenesis*

Type 1 AIP is known to be part of the IgG4-related disease spectrum, a multisystemic fibro-inflammatory condition of unknown etiology that affects multiple organs such as, salivary and lacrimal glands, periorbital tissue, thyroid, lung, aorta, biliary tree, kidney, retroperitoneum, etc. [15].

Susceptibility to develop type 1 AIP as well as to other forms of IgG4-related disease has been mapped to some HLA serotypes such as HLA-DRB1\*0405 and HLA-DQB1\*0401 in the class

II and the ABCF1 proximal to C3-2-11 telomeric of HLA-E in the class I regions [16] as well as to single-nucleotide polymorphisms in genes involved in immune response such as Fc receptor-like 3, cytotoxic T-lymphocyte associated antigen 4 and tumor necrosis factor- $\alpha$  [17-19].

Although these patients frequently have elevated serum levels of IgG4, some have non-specific autoantibodies in serum that are mostly IgG1-type and bind antigens that are expressed in exocrine organs including the pancreas such as anti-carbonic anhydrase-II, anti-carbonic anhydrase-IV, anti-lactoferrin, anti-plasminogen-binding protein, anti-heat-shock-protein-10 and anti-plasminogen-binding protein peptide autoantibodies [20-25]. The mechanism and role of these antibodies in the pathogenesis of type 1 AIP remains unknown.

The exact trigger of this immune-mediated process remains unknown. An etiologic role of *Helicobacter pylori* infection through molecular mimicry was proposed in two studies; there is homology between human carbonic anhydrase II and the  $\alpha$ -carbonic anhydrase of *Helicobacter pylori* as well as between human ubiquitin-protein ligase E3 component and n-recognition plasminogen-binding protein of *H. pylori*. The binding motif of the HLA molecule DRB1\*0405 corresponds to the homologous segment of the former cases. It has been proposed that antibodies against those two *H. pylori* antigens can behave as autoantibodies in genetically predisposed people [25, 26].

Regardless of the initial triggering, it is thought that there is a dysregulation of T lymphocytes in AIP; a transgenic animal study has indicated that dysregulation of myeloid dendritic cells contributes to the development of type 1 AIP by increasing activation of naïve CD4-positive T cells [27]. Overall, it is postulated that HLA-DR molecule presents antigen on the pancreatic ductal and acinar cells may activate interferon-gamma-producing CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes leading to subsequent tissue damage, inflammation and fibrosis in the absence of an effective negative regulation. It has been suggested that an immune reaction mediated by T-helper 2, regulatory T-cells and the cytokines produced by these cells produce the observed histomorphology of this disease. Increased expression of interleukin (IL) 4, IL5, IL10 and TGF- $\beta$ , probably produced by T-cells, has been



**Figure 1.** Radiographic findings of autoimmune pancreatitis in a patient with IgG4-related disease. A. Axial portal venous phase CT image demonstrates a “sausage-shaped” pancreas with loss of lobulation and low density capsule (arrow) and a dilated, irregular main pancreatic duct (arrow head). Incidental note made of biliary dilatation and biliary wall enhancement (\*) characteristic for IgG4-related disease. B. Transverse pancreatic ultrasound image illustrates a large hypoechoic area in pancreas (arrows). C. Axial fused FDG PET/CT image illustrates diffuse intense hypermetabolism of pancreas (arrow), suggesting active process, with a non-FDG avid capsule.

detected in the affected tissues and that correlates with some of the molecular and histological features: IL10 is thought to stimulate the production of IgG4 and TGF- $\beta$ 1 is thought to induce fibrosis [28, 29]. However, a recent study by Takeuchi et al. reported that in salivary glands involved by IgG4-related disease the increased IL4, IL10 and TGF- $\beta$  were produced not by T-cells but by mast cells, highlighting a potential role of mast cells [30].

## Patient demographics

Type 1 AIP typically affects elderly men. In the series from Japan, AIP is predominantly seen in men past middle age (95% patients are older than 45 years); males are nearly three times as likely as females to develop type 1 AIP. The prevalence of AIP in Japan is 0.82 per 100,000 [31]. Prevalence in western countries is not known but it is thought to be lower than in Japan. Co-existence of allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, etc has been reported in 36% to 44% of cases. Likewise mild peripheral blood eosinophilia and mildly elevated serum levels of IgE have also been frequently encountered [32, 33].

## Clinical presentation

Sixty eight to 75% of cases of type 1 AIP present with painless obstructive jaundice [31]. Other manifestations include abdominal pain (13% to 40%) and weight loss (45%). Less frequently patients manifest with steatorrhea. Very uncommonly, patients with type 1 AIP can present as acute pancreatitis (3% to 5%) [34, 35]. The obstructive jaundice is caused by either entrapment of the intrapancreatic bile duct in

the inflamed, enlarged and fibrotic pancreas or, often, due to a true involvement of the intra and/or extrahepatic bile duct when IgG4-related sclerosing cholangitis co-exists [36]. In addition, synchronous or metachronous involvement of other organs frequently occurs. Typically the pancreas is the first organ involved by disease and other organ involvement follows over months to years after the diagnosis of type 1 AIP.

## Imaging findings

Imaging findings of type 1 and type 2 AIP are very similar. The most common appearances on various imaging modalities are described below.

**Contrast-enhanced computed tomography (CT):** Pancreas imaging is most often performed with dual phase contrast-enhanced CT that includes a pancreas phase and a delayed portal venous phase. On cross-sectional CT images, AIP most commonly results in diffuse enlargement of the gland with loss of contour lobulation, acquiring the so-called “sausage-shaped pancreas” (Figure 1A). This is secondary to diffuse, extensive inflammation, edema, and fibrosis. Overall the gland demonstrates delayed pancreas phase enhancement compared to the normal gland. Frequently, a hypoenhancing capsule or halo is seen. The main pancreatic duct is frequently not visible during the pancreatic phase due to extensive edema; on occasion, the main pancreatic duct can appear dilated with strictured segments. Peripancreatic stranding is typically absent or minimal and other findings such as pancreatic calcifications and cysts are infrequently reported [37-39]. In

its focal, mass-like form, AIP results in focal enlargement of the gland and can mimic a pancreatic adenocarcinoma. In such a scenario, AIP shows hypo-enhancement during the pancreatic phase and becomes iso-to-hyperenhancing in the delayed portal venous phase, without significant upstream main duct dilatation or proximal gland atrophy [40]. After steroid treatment, typically there is normalization of gland with respect to enlargement and any ductal dilatation [41]. Extrapancreatic findings on CT, such as focal biliary dilatation, intra-abdominal adenopathy, retroperitoneal fibrosis and renal parenchymal abnormalities, can aid in the diagnosis of AIP (**Figure 1A**) [42].

*Magnetic resonance imaging (MRI):* The primary findings of AIP on MRI are similar to those on CT. On MRI, the gland is diffusely or focally enlarged. According to a study by Rehnitz et al. unenhanced MRI shows relatively decreased T1 signal intensity and minimally increased T2 signal intensity. Post contrast (Gadolinium), there is delayed parenchymal enhancement on pancreatic phase with iso-hyperenhancement on the late venous phase [38]. MRCP (magnetic resonance cholangiopancreatography) can demonstrate common bile duct or intrahepatic duct strictures as well as narrowing or strictures of the main pancreatic duct.

*Endoscopic retrograde cholangiopancreatography (ERCP):* On ERCP, AIP usually shows irregular, either diffuse or segmental, narrowing of main pancreatic duct. The segmental narrowing pancreatic duct is usually longer than 1/3 of the length of the main pancreatic duct. Even in those unusual cases where the narrowing is localized and extends to less than one-third of the length, the proximal duct rarely shows notable dilatation like in cancer [43]. Also, stenosis of the intrapancreatic portion of the common bile duct can be seen in AIP on ERCP.

*Abdominal ultrasound, endoscopic ultrasound (EUS):* Abdominal ultrasound is a widely utilized, accessible and noninvasive method for examining the abdomen and can aid in the initial diagnosis of AIP. On abdominal ultrasound, the pancreas is diffusely enlarged and demonstrates a diffusely hypoechoic pattern with hypoechoic foci and hyperechoic strands (**Figure 1B**). Sometimes a mass-like hypoechoic region is present (focal AIP), and when there is associated upstream main pancreatic duct dilatation

in a patient presenting with jaundice, findings overlap with that of pancreatic adenocarcinoma [44]. In addition, EUS is helpful in detecting bile duct wall thickening and more importantly, EUS can be used to guide tissue biopsy or fine needle aspiration for histologic and/or cytologic evaluation.

*Fluorine-18 fluorodeoxyglucose positron emission tomography/CT ( $^{18}\text{F}$ -FDG PET/CT):* There is little published literature in the use of FDG PET/CT in management of AIP. Diffuse pancreatic enlargement with “sausage-like” appearance with low attenuation of the outer edge or halo, in conjunction with significant diffuse FDG uptake in the pancreas is characteristic of AIP on FDG PET/CT (**Figure 1C**) [45].

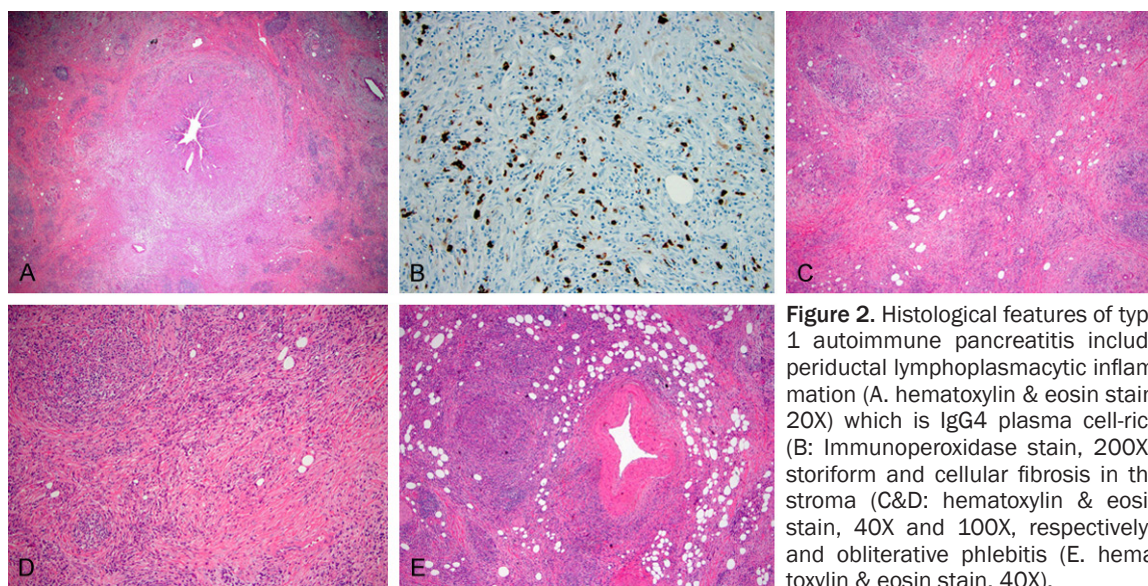
Limited experience suggests that  $^{18}\text{F}$ -FDG PET/CT can be a useful tool to differentiate AIP from pancreatic cancer. In AIP, the pancreas usually shows diffuse or multifocal, heterogeneous accumulation of  $^{18}\text{F}$ -FDG with a longitudinal shape and there is no significant gland atrophy or main upstream main duct dilatation. Often, FDG PET/CT can show extrapancreatic FDG-disease in the biliary tree, salivary glands, hilar and mediastinal lymph nodes, lung, pleura, and prostate, in setting of IgG4 systemic sclerosis. [46].

### *Laboratory findings and serum markers*

*Total immunoglobulin G (IgG):* Sarles et al. reported the presence of hypergammaglobulinemia in their series of cases of AIP [1]. Elevated levels of serum gamma globulin may be seen in a significant proportion of patients with AIP, the percentages vary among the studies, but most studies report this in approximately half of the patients [47].

*Immunoglobulin G subclass 4 (IgG4):* Elevation of serum IgG4 is considered one of the hallmarks of type 1 AIP and other manifestation of IgG4-related disease. It is seen in approximately 70% to 80% of cases. Normal values do not exclude the diagnosis [48]. On the other hand, elevated serum levels of IgG4 have been reported in multiple conditions. For example, elevation of IgG4 has been reported in 7% to 10% of patients with pancreatic cancer [49, 50]. A recent study reported that elevated IgG4 (> 135 mg/dL) level in serum had a sensitivity of 90% but a specificity of 60% for IgG4-related disease and that doubling the cut-off value only





**Figure 2.** Histological features of type 1 autoimmune pancreatitis include periductal lymphoplasmacytic inflammation (A. hematoxylin & eosin stain, 20X) which is IgG4 plasma cell-rich (B: Immunoperoxidase stain, 200X), storiform and cellular fibrosis in the stroma (C&D: hematoxylin & eosin stain, 40X and 100X, respectively), and obliterative phlebitis (E. hematoxylin & eosin stain, 40X).

improved the specificity to 91% while it decreased the sensitivity to 35% [51].

**IgG4+ plasmablasts:** Plasmablasts are an intermediate stage between activated B cells and plasma cells and they are CD19<sup>low</sup>CD20<sup>+</sup>CD38<sup>+</sup>CD27<sup>+</sup>. A recent study reported that all patients with IgG4-related disease had expanded number of IgG4+ plasmablasts, even those with normal serum levels of IgG4. This is not routinely used in clinical practice [52].

**Autoantibodies:** Up to 40% of patients with IgG4-related disease have non-specific autoantibodies that are mostly IgG1-type rather than IgG4-type. Though most of the antigens that the antibodies bind to are expressed in exocrine organs such as the pancreas, no disease-specific antibody has been identified. These autoantibodies include anti-carbonic anhydrase-II, anti-carbonic anhydrase-IV, anti-lactoferrin, anti-plasminogen-binding protein, anti-heat-shock-protein-10 and anti-plasminogen-binding protein peptide autoantibodies [20-25].

**Peripheral blood eosinophilia and elevation of IgE levels:** Mild peripheral blood eosinophilia (600-1500 cells/ $\mu$ L) is occasionally encountered in patients with type 1 AIP. Two studies have reported this finding in 11% and 16% of patients respectively. This correlates with co-existence of allergic diseases. Likewise mild elevation of serum levels of IgE has been reported in these patients. Two studies have reported this finding in 27% and 60% of patients respectively [32, 33].

## Histopathology

Type 1 AIP typically affects the head of the pancreas. On macroscopic examination, the pancreas is indurated. Generally there is focal or diffuse enlargement on the pancreas. Serial cross-sectioning shows gray-yellow discoloration without focal distinctive lesion; infrequently an ill-defined mass blending into the surrounding tissue can be present and grossly resembles a malignant lesion [1, 32]. The pancreatic duct wall is frequently thickened and longitudinally sectioning through the pancreatic duct usually reveals an irregularly narrowed duct without obvious post-stricture dilatation. Pseudocysts and intraductal calculi are usually absent; however rare cases may show focal calcification late in the course of the disease [53].

Type 1 AIP bears the histological features of IgG4-related disease [54]. Multiple organ-specific diagnostic algorithms of IgG4-related disease were proposed at the international symposium held in Boston in 2011. Generally a confident histological diagnosis requires the presence of 2 of 3 of the following characteristics, but sometimes, especially in limited samples, only one is present. In resection specimens of type 1 AIP generally the three of them are present.

**IgG4-rich dense lymphoplasmacytic infiltrate:** A dense mononuclear inflammatory infiltrate is present in the affected area (**Figure 2A**). The infiltrate is mainly composed of T-cells, B-cells,

and plasma cells. The lymphocytes are diffusely distributed but the plasma cells can be found in clusters or have a patchy distribution. Occasionally germinal centers are observed. Scattered histiocytes may be present. Generally few eosinophils are present, but sometimes a moderate number of them can be seen. The inflammatory cells are present around the ducts but it is not more prominent than in the area away from them. The epithelial lining of the duct is spared.

IgG4-rich dense lymphoplasmacytic infiltration is one criterion for type 1 AIP. IgG4 richness is defined as a ratio of Ig4+ to IgG+ plasma cell  $> 0.4$  and the number of IgG4+ plasma cell per high power field (hpf) must be  $> 10$  if the specimen is a biopsy or  $> 50$  if the specimen is a surgical resection (**Figure 2B**). Since the distribution of the IgG4+ plasma cells can be patchy the three hpf (40X) with the highest number of IgG4+ plasma cells should be used to obtain the Ig4+ to IgG+ plasma cell ratio and the average number of IgG4+ plasma cell per hpf used for quantification.

**Storiform fibrosis:** Dense fibrosis in a storiform pattern is present in the affected area (**Figure 2C, 2D**). But the fibroblasts or the myofibroblasts in the fibrotic area are frequently inconspicuous and obscured by dense lymphoplasmacytic infiltrate. Those fibroblasts and myofibroblasts lack of atypia or mitotic activity. The fibroinflammatory elements can extend to the peripancreatic tissue and can involve the intra-pancreatic portion of the common bile duct.

**Obliterative phlebitis:** This is the least common of three histopathological features of IgG4-related disease. A lymphoplasmacytic infiltrate involves the wall and the lumen of medium-sized veins (**Figure 2E**). The obliteration can be complete or partial. Sometimes obliterative phlebitis can be embedded in an area of dense inflammation and can be difficult to see; the presence of an apparently isolated artery should raise suspicion and prompt the pathologist to use stains that highlight the elastic layer of the vessels which can ease the detection of this feature.

Less frequently non-necrotizing arteritis can be present. In these cases a lymphoplasmacytic infiltrate is seen involving the wall of medium sized arteries and can also involve the lumen.

This histological feature is neither sensitive nor specific for the diagnosis of type 1 AIP [53].

### *Treatment and relapse*

While some cases of type 1 AIP can resolve spontaneously, most require treatment. Corticosteroids are the cornerstone of treatment for type 1 AIP. Multiple studies reported dramatic response rates with prolonged therapy including resolution or marked improvement of pancreatic and extra-pancreatic manifestations. An international study reported that 99% of type 1 AIP patients that were treated with steroids went into clinical remission but relapses occurred in 31% of patients and among those with co-existing IgG4-related sclerosing cholangitis 56% relapsed. Multiple relapses are not infrequent [55].

There is no definite consensus on a regimen to treat type 1 AIP. The Japanese consensus guidelines for treatment recommend an initial dose of prednisone of 0.6 mg/kg/day for 2 to 4 weeks that is tapered by 5 mg every 1 to 2 weeks depending on clinical symptoms, results of biochemical tests and images until a maintenance dose of 2.5 to 5 mg/day is reached over a period of 2 to 3 months. Then prednisone should be stopped within 3 years [56].

No definite consensus on how to treat relapses has been reached either, but rituximab and mycophenolate with or without steroids have shown efficacy, as well as other agents such as azathioprine, bortezomib, tamoxifen, infliximab and tacrolimus [57, 58].

## **Type 2 AIP**

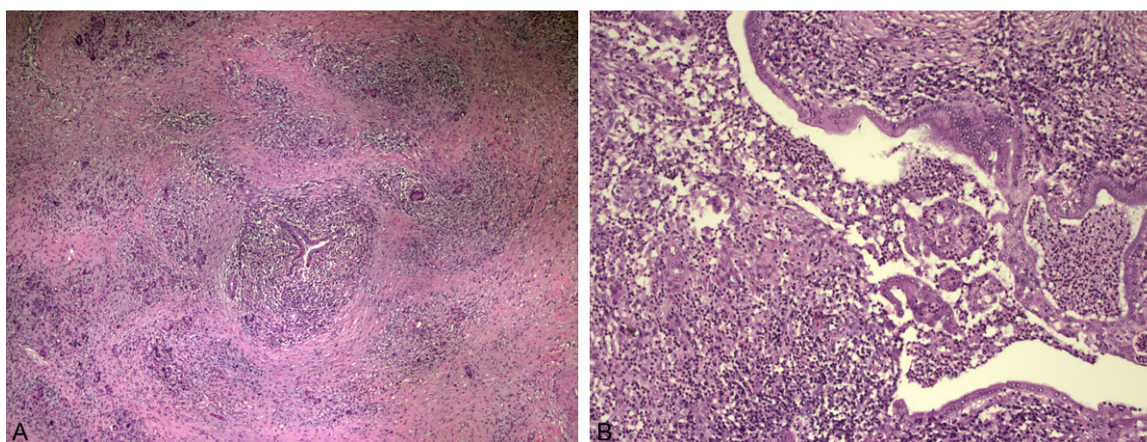
### *Etiology and pathogenesis*

Unlike type 1 AIP, type 2 AIP is not part of the IgG4-related disease spectrum and little is known about the underlying etiology of this immune-mediated form of pancreatitis. Finding such as elevated number of IgG4 plasma cells in the pancreas, elevated serum levels of IgG4, presence of autoantibodies are not features of type 2 AIP.

### *Patients demographics*

Type 2 AIP is more common in the fifth and sixth decades of life. There are not significant differences in gender distribution and the male: female ratio is approximately 1:1. Most reports are from western countries and it has





**Figure 3.** Histological features of type 2 autoimmune pancreatitis. A. Periductal lymphoplasmacytic infiltrate with granulocytic epithelial lesion (GEL) in the duct and hypocellular fibrosis in the interlobular areas (hematoxylin & eosin stain, 40X). B. Erosion and ulceration and neutrophilic infiltration of the epithelial lining of the pancreatic duct (hematoxylin & eosin stain, 200X).

**Table 2.** Clinicopathologic features differentiating type 1 and type 2 AIP

	Type 1	Type 2
Age	Elderly; 7 <sup>th</sup> decade	Middle age, 5 <sup>th</sup> and 6 <sup>th</sup> decades
Gender	M > F	M≈F
Presentation	Painless obstructive jaundice > abdominal pain	Abdominal pain > Painless obstructive jaundice
IgG4-related disease	Yes	No
Other organ involvement	Common	No
Ulcerative colitis	Rare	15%-30%
Response to steroids	Yes	Yes
Relapses	Common	Rare

rarely been reported in Asia [59]. 15% to 30% of cases of type 2 AIP are associated with ulcerative colitis [34, 59].

#### Clinical presentation

The most common symptom upon presentation is abdominal pain which is reported in 60% to 70% of cases. Obstructive jaundice occurs in 33% to 48% of cases. Acute pancreatitis is the initial presentation in 34% to 40% of cases [34, 59]. No useful biomarkers are available in the clinical practice and radiological findings largely overlap with those of type 1 AIP. Histology is the key to diagnose type 2 AIP.

#### Histopathology

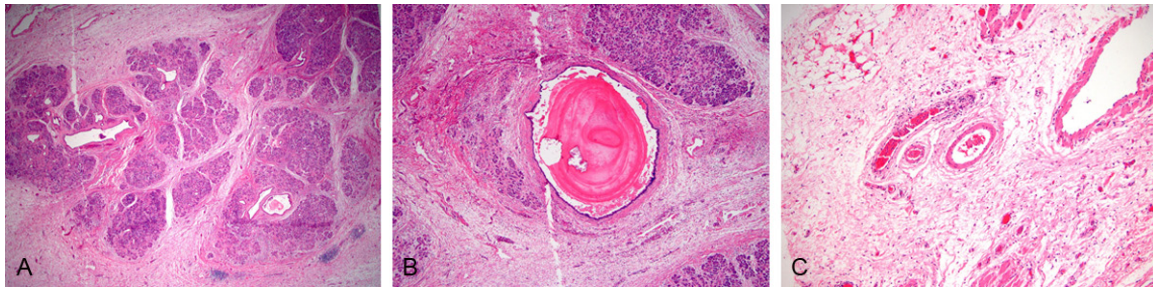
In type 2 AIP there is a dense periductal lymphoplasmacytic inflammation (**Figure 3A**). Pancreatic ducts of all sizes may be affected. Epithelioid granulomas can also be seen in the inflammatory infiltrate. There are neutrophils present in this lymphoplasmacytic infiltrate.

A characteristic form of neutrophilic injury called granulocytic epithelial lesion (GEL) is present in the pancreatic ducts; it consists of neutrophilic microabscesses in the lumen of the ducts. Erosion and ulceration of the epithelial lining can occur and lead to partial or total destruction of the pancreatic ducts (**Figure 3B**). The neutrophils also infiltrate the acinar component of the pancreas. There is hypocellular fibrosis in the interlobular areas that rarely arrange in a storiform pattern. Unlike type 1 AIP, obliterative phlebitis and increased number of IgG4+ plasma cell are seldom seen; although some veins might be involved by the lymphoplasmacytic infiltrate [60].

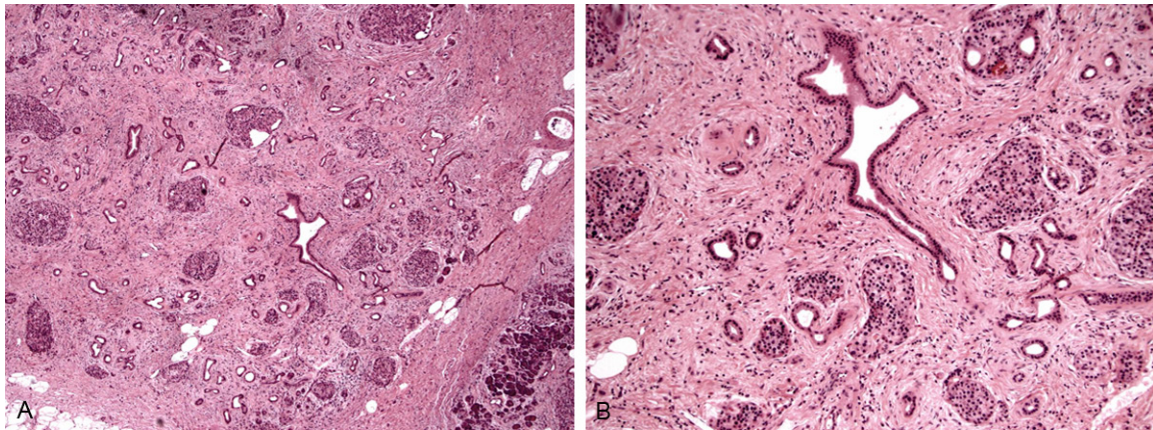
#### Treatment and relapse

The first line of treatment is steroids such as prednisone. Regimens are similar to those used in type 1 AIP, and final consensus on management has not been reached. According to a study 92% of patients with type 2 AIP go into remission with steroids. Relapses are not com-





**Figure 4.** A. Alcoholic chronic pancreatitis with interlobular fibrosis, paucity of inflammatory cells, and relative preservation of lobular architecture (hematoxylin & eosin stain, 20X). B. Proteinaceous concretion in one small duct (hematoxylin & eosin stain, 40X). C. Normal veins (hematoxylin & eosin stain, 100X).



**Figure 5.** Obstructive pancreatitis with profound lobular atrophy, paucity of inflammatory cells (A. hematoxylin & eosin stain, 40X), and endocrine hyperplasia (B. hematoxylin & eosin stain, 100X).

mon and they are reported to occur in 9% of cases. Multiple relapses are infrequent [55].

**Table 2** shows the main differences between type 1 AIP and type 2 AIP.

#### Differential diagnosis

##### *Conventional chronic pancreatitis (including alcoholic chronic pancreatitis)*

AIP must be differentiated from more common, “conventional” chronic pancreatitis which is characterized by extensive fibrosis, tissue necrosis or abscess, and stone formations. Some of these features, such as tissue necrosis and stone formation can be easily appreciated on macroscopic examination or radiographic studies. Microscopically, the pancreatic tissue shows interlobular or perilobular fibrosis. The fibrosis in chronic pancreatitis usually does not show a storiform pattern as is noted more commonly with AIP (**Figure 4A**). This fibrosis also is

generally not associated with significant mononuclear inflammation (**Figure 4A**). Proteinaceous concretion (**Figure 4B**) and calcification are common findings in conventional chronic pancreatitis. In addition, obliterative phlebitis, a more consistent finding of AIP is rarely noted with chronic pancreatitis (**Figure 4C**) [61].

##### *Obstructive pancreatitis*

Compared to AIP, obstructive pancreatitis shows more profound lobular atrophy but less inflammation (**Figure 5A**). Very often, endocrine hyperplasia may be seen in obstructive pancreatitis (**Figure 5B**). There is no evidence of increased number of IgG4+ plasma cells in the majority of obstructive pancreatitis cases.

##### *Inflammatory myofibroblastic tumor*

Inflammatory myofibroblastic tumor (IMT) is a challenging differential diagnosis for type 1 AIP (especially when there is mass-like lesion, wh-

ich is known as inflammatory pseudotumor). Both entities are characterized by, bland spindle cell proliferation and fibrosis, and inflammation rich in lymphocytes, plasma cells, and occasional histiocytes and eosinophils. In one study, Yamamoto H et al. has reported the use of immunohistochemical stain for ALK (anaplastic lymphoma kinase) and IgG4 in differentiating these two diseases; immunoreactivity of ALK is only seen IMT (in 68.2% cases) but not in AIP or other IgG4-related sclerosing diseases. IMT can have an increased number of IgG4+ plasma cell. Yamamoto H et al. reported that some cases had up to 40 IgG4+ cell per hpf but they found that the IgG4+ to-IgG+ plasma cell ratio was useful to differentiate this entity from IgG4-related inflammatory pseudotumor [62]. Saab ST et al. reported in a series of cases that some IMT can have up to 33 IgG4+ plasma cell per hpf but unlike the previous study, 6 of their 36 cases had an IgG4+ to-IgG+ ratio of more than 0.4 [63]. Other histological features must also be considered to make a final diagnosis. Obliterative phlebitis is infrequently seen in IMT (4.5%) and storiform fibrosis is not a feature of IMT.

### *Lymphoma*

Due to the dense lymphoplasmacytic infiltration in the pancreatic tissue, in rare cases, this degree of lymphocytic infiltration may raise a possibility of lymphoproliferative disorder, such as low-grade lymphoma. In such cases, immunohistochemical stains and flow cytometric analysis may help with the differentiation. Rarely, large B cell lymphoma may show a pattern of scattered large, atypical cells embedded in a markedly fibrotic stroma, mimicking AIP. In such cases, identification and confirmation of such lymphoma cells by immunohistochemical stain may help with the differentiation.

### *Pancreatic adenocarcinoma*

Pancreatic adenocarcinoma is the closest and most feared mimicry of AIP both clinically, radiographically, and sometimes macroscopically when there is a mass-forming lesion. However, finding of malignant epithelial cells in the tissue sections can confirm pancreatic adenocarcinoma, which may require extensive sampling of the lesion, either macroscopically obvious or subtle. Histological features present in pancreatic adenocarcinoma include anisonucleosis

greater than 4-to-1 in ductal epithelial cells, incomplete ductal lumens and ducts arranged haphazardly [64]. Storiform pattern of fibrosis and obliterative phlebitis are not features of pancreatic adenocarcinoma.

The presence of a peritumoral inflammatory rim with fibrosis has been described in pancreatic adenocarcinoma, sometimes the inflammatory component has an elevated number of IgG4+ plasma cell; thus, a needle biopsy sampling the periphery of this malignancy may be lack of malignant cell and present a significant number of IgG4+ plasma cells. Dhall et al. approached this issue in a study; 8/13 cases of peritumoral pancreatitis showed IgG4+ plasma cells ranging from 0 to 40 per hpf [65]. Exhaustive efforts must be made to rule-out malignancy when in doubt and patients with a provisional diagnosis of AIP should be followed clinically.

### **Histological diagnostic challenge**

#### *Resection specimen*

Diagnosis of AIP in resected specimen is usually straightforward. However, the ill-defined area in the resected specimen should be thoroughly sampled in order to confidently rule out minute pancreatic adenocarcinoma. When the case presents as chronic pancreatitis with equivocal histology in the absence of clinical history of excessive alcohol use, immunohistochemical stain for IgG4 and Movat stain will be helpful.

#### *Biopsy specimen*

Some authors have reported the usefulness of EUS-guided Trucut biopsy in diagnosing AIP in patients with obstructive jaundice. For example, Levy and colleagues reported the diagnostic usefulness of Trucut biopsy in three patients who had suspected pancreatic adenocarcinoma with planned surgical resection following indeterminate FNA cytology [66]. Overall, diagnosis of AIP on small core biopsy obtained either percutaneously or endoscopically under ultrasonography guidance is usually difficult because not all of the histologic features are present. For example, in one series, only 26% of EUS-guided core samples from patients with confirmed AIP had diagnostic histological features [67]. Detlefsen et al. conducted a study in

which 6 diagnostic criteria were applied to pancreatic core needle biopsies: GEL, more than 10 IgG4-positive plasma cells per hpf, more than 10 eosinophilic granulocytes per hpf, cellular fibrosis with inflammation, lymphoplasmacytic infiltration and venulitis. They found a cut-off level of 4 criteria identified 76% of cases of AIP. None of the non-AIP cases of this study had met more than 3 diagnostic criteria and GEL was the only finding that was not reported in these non-AIP cases [68]. Further studies are needed to confirm these findings and validate its clinical use.

The easy access of the ampulla of Vater makes biopsies from this site a potential alternative for the diagnosis of AIP. Sepehr et al. found that IgG4+ plasma cells were elevated both in ampullary and periampullary tissue in cases of type 1 AIP (> 10 per hpf), although cases of pancreatic adenocarcinoma and chronic pancreatitis less frequently had elevated number of IgG4+ plasma cells. They also reported that elevated IgG4+-to-IgG+ plasma cell ratio increased the specificity of this sample, using a cut-off of 0.15, the specificity was 96% [69]. Other studies have reported a high specificity of elevated number of IgG4+ plasma cell in ampullary biopsies for the diagnosis of type 1 AIP although they have not evaluated the IgG4+-to-IgG+ plasma cell ratio. A more recent study by Cebe et al. reported that elevated numbers of IgG4+ plasma cells in ampullary biopsies were not specific for type 1 AIP and that > 10 IgG4+ plasma cells could also be found in cases of pancreatic adenocarcinoma and celiac disease [70]. This highlights the importance of the IgG4+-to-IgG+ plasma cell ratio in the diagnosis of type 1 AIP and any other manifestation of the IgG4-related disease.

### *Fine needle aspiration specimen*

Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) is a powerful modality utilized to obtain preoperative diagnosis from solid and cystic pancreatic lesions. This modality is extremely helpful in obtaining diagnosis of pancreatic carcinoma and non-ductal neoplasms of the pancreas. Its value in providing preoperative diagnosis AIP is subjected to further investigations. In cases with indeterminate or negative cytology, the chance of having pancreatic adenocarcinoma is still higher than AIP. In addition, because the diagnosis of AIP relies on the preservation of architecture, FNA specimen

may not be suitable for the diagnosis. However, case reports of AIP correctly diagnosed on EUS-FNA cytology have been published [71]. The cytologic features of AIP reported in the literature include smears rich in inflammatory cells (mainly lymphoplasmacytic) and sparse epithelial cells lacking atypia [66]. In cases clinically suspicious for AIP, the absence of diagnostic features for AIP on FNA specimen does not rule out AIP.

### **AIP and malignancy**

Although a history of pancreatitis has been associated with a 7.2-fold increased risk estimate for pancreatic cancer, no definite association has been found between AIP and pancreatic cancer [72]. Nonetheless Gupta et al. reported a series of cases of patients with AIP, 7/11 patients with type 1 AIP had preinvasive ductal lesions (3/11 had pancreatic intraepithelial neoplasia (PanIN)2 and 1/11 had PanIN3), while 16/17 patients with type 2 AIP had preinvasive ductal lesions (4/17 had PanIN2 but none had PanIN3). A few reports of adenocarcinoma of the pancreas in patients with type 1 AIP have been reported [73]. Further studies are required but a possible increased risk for pancreatic carcinoma in patients with type 1 AIP and type 2 AIP cannot be ruled out.

### **Summary**

Type 1 AIP and type 2 AIP are unique forms of chronic pancreatitis which have been recently recognized as separated entities. Type 1 AIP is part of the IgG4-related disease spectrum. Both conditions are uncommon, but it is important to recognize them because they respond dramatically to corticosteroid treatment and more importantly, an accurate and timely diagnosis of them may decrease the number of unnecessary pancreatic resections. Because these are recently described entities, there is a great need for education. Efforts should be targeted to a variety of clinicians including internal medicine, general practitioners, gastroenterologist, hepatologists, general surgeons and surgeons specialized in hepatobiliary and pancreatic diseases, to increase the awareness of the condition. Educational efforts should also target both radiologists and pathologists as they play critical roles in the diagnosis of these rare conditions. As clinical experience with education on type 1 AIP and type 2 AIP increases,



refinement of diagnostic criteria through international and multidisciplinary collaboration, development of standardized therapeutic protocols will allow further optimization of care for our patients.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Xiuli Liu, Department of Anatomic Pathology, Cleveland Clinic 9500 Euclid Avenue/L25 Cleveland Clinic Cleveland, Ohio 44195 USA. Tel: 216-445-8745; Fax: 216-445-6967; E-mail: liux3@ccf.org

## References

- [1] Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis* 1961; 6: 688-698.
- [2] Sarles H, Muratore R, Sarles JC, Gaini M, Camatte R, Pastor J, Guien C. Aetiology and pathology of chronic pancreatitis. *Br J Gastroenterol* 1965; 7: 75-120.
- [3] Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol* 1991; 22: 387-395.
- [4] Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995; 40: 1561-1568.
- [5] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344: 732-738.
- [6] Members of the Criteria Committee for Autoimmune Pancreatitis of the Japan Pancreas Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society (in Japanese). *J Jpn Pan Soc* 2002; 17: 585-587.
- [7] Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, Ohara H, Ito T, Kiriya S, Inui K, Shimosegawa T, Koizumi M, Suda K, Shiratori K, Yamaguchi K, Yamaguchi T, Sugiyama M, Otsuki M; Research Committee of Intractable Diseases of the Pancreas. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. *J Gastroenterol* 2006; 41: 626-631.
- [8] Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982-984.
- [9] Ectors N, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, Lankisch P, Stolte M, Lüttges J, Kremer B, Klöppel G. Non-alcoholic duct destructive chronic pancreatitis. *Gut* 1997; 41: 263-268.
- [10] Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, Cavallini G. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? *Pancreas* 2003; 27: 1-13.
- [11] Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003; 27: 1119-1127.
- [12] Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORT criteria. *J Gastroenterol* 2007; 42: 39-41.
- [13] Chari ST, Kloepfel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T; Autoimmune Pancreatitis International Cooperative Study Group (APICS). Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. *Pancreas* 2010; 39: 549-554.
- [14] Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L; International Association of Pancreatologists. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatologists. *Pancreas* 2011; 40: 352-358.
- [15] Stone JH, Zen Y, Deshpande V. IgG4-Related Disease. *N Engl J Med* 2012; 366: 539-551.
- [16] Ota M, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S. Two critical genes (HLA-DRB1 and ABCF1) in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics* 2007; 59: 45-52.
- [17] Umemura T, Ota M, Hamano H, Katsuyama Y, Kiyosawa K, Kawa S. Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients. *Gut* 2006; 55: 1367-1368.
- [18] Chang MC, Chang YT, Tien YW, Liang PC, Jan IS, Wei SC, Wong JM. T-cell regulatory gene CTLA-4 polymorphism/ haplotype association with autoimmune pancreatitis. *Clin Chem* 2007; 53: 1700-1705.
- [19] Umemura T, Ota M, Hamano H, Katsuyama Y, Muraki T, Arakura N, Kawa S, Kiyosawa K. Association of autoimmune pancreatitis with cyto-



- toxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008; 103: 588-594.
- [20] Uchida K, Okazaki K, Konishi Y, Ohana M, Takakuwa H, Hajiro K, Chiba T. Clinical analysis of autoimmune-related pancreatitis. *Am J Gastroenterol* 2000; 95: 2788-2794.
- [21] Nishimori I, Bratanova T, Toshkov I, Caffrey T, Mogaki M, Shibata Y, Hollingsworth MA. Induction of experimental autoimmune sialoadenitis by immunization of PL/J mice with carbonic anhydrase II. *J Immunol* 1995; 154: 4865-4873.
- [22] Asada M, Nishio A, Uchida K, Kido M, Ueno S, Uza N, Kiriya K, Inoue S, Kitamura H, Ohashi S, Tamaki H, Fukui T, Matsuura M, Kawasaki K, Nishi T, Watanabe N, Nakase H, Chiba T, Okazaki K. Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis. *Pancreas* 2006; 33: 20-26.
- [23] Endo T, Takizawa S, Tanaka S, Takahashi M, Fujii H, Kamisawa T, Kobayashi T. Amylase alpha-2A autoantibodies: novel marker of autoimmune pancreatitis and fulminant type 1 diabetes. *Diabetes* 2009; 58: 732-737.
- [24] Takizawa S, Endo T, Wanja X, Tanaka S, Takahashi M, Kobayashi T. HSP 10 is a new autoantigen in both autoimmune pancreatitis and fulminant type 1 diabetes. *Biochem Biophys Res Commun* 2009; 386: 192-196.
- [25] Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009; 361: 2135-2142.
- [26] Guarneri F, Guarneri C, Benvenga S. *Helicobacter pylori* and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? *J Cell Mol Med* 2005; 9: 741-744.
- [27] Boomersshine CS, Chamberlain A, Kendall P, Afshar-Sharif AR, Huang H, Washington MK, Lawson WE, Thomas JW, Blackwell TS, Bhowmick NA. Autoimmune pancreatitis results from loss of TGF signaling in S100A4-positive dendritic cells. *Gut* 2009; 58: 1267-1274.
- [28] Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, Nakanuma Y. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007; 45: 1538-1546.
- [29] Miyoshi H, Uchida K, Taniguchi T, Yazumi S, Matsushita M, Takaoka M, Okazaki K. Circulation naïve and CD4+CD25<sup>high</sup> regulatory T cells in patients with autoimmune pancreatitis. *Pancreas* 2008; 36: 133-140.
- [30] Takeuchi M, Sato Y, Ohno K, Tanaka S, Takata K, Gion Y, Orita Y, Ito T, Tachibana T, Yoshino T. T helper 2 and regulatory T-cell cytokine production by mast cells: a key factor in the pathogenesis of IgG4-related disease. *Mod Pathol* 2014; 27: 1126-36.
- [31] Nishimori I, Tamakoshi A, Otsuki M; Research Committee on Intractable Diseases of the Pancreas, Ministry of Health, Labour, and Welfare of Japan. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol* 2007; 42: 6-8.
- [32] Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2009; 21: 1136-1139.
- [33] Kuruma S, Kamisawa T, Tabata T, Chiba K, Iwasaki S, Fujiwara T, Kuwata G, Egarashira H, Koizumi K, Koizumi S, Endo Y, Fujiwara J, Arakawa T, Momma K. Allergen-specific IgE antibody serologic assays in patients with autoimmune pancreatitis. *Intern Med* 2014; 53: 541-543.
- [34] Song TJ, Kim JH, Kim MH, Jang JW, Park do H, Lee SS, Seo DW, Lee SK, Yu E. Comparison of clinical findings between histologically confirmed type 1 and type 2 autoimmune pancreatitis. *J Gastroenterol Hepatol* 2012; 27: 700-708.
- [35] Law R, Bronner M, Vogt D, Stevens T. Autoimmune pancreatitis: a mimic of pancreatic cancer. *Cleve Clin J Med* 2009; 76: 607-615.
- [36] Zen Y, Nakanuma Y, Portmann B. Immunoglobulin G4-related sclerosing cholangitis: pathologic features and histologic mimics. *Semin Diagn Pathol* 2012; 29: 205-211.
- [37] Suzuki K, Itoh S, Nagasaka T, Ogawa H, Ota T, Naganawa S. CT findings in autoimmune pancreatitis: assessment using multiphase contrast-enhanced multisection CT. *Clin Radiol* 2010; 65: 735-743.
- [38] Rehnitz C, Klauss M, Singer R, Ehehalt R, Werner J, Büchler MW, Kauczor HU, Grenacher L. Morphologic patterns of autoimmune pancreatitis in CT and MRI. *Pancreatol* 2011; 11: 240-251.
- [39] Sahani DV, Kalva SP, Farrell J, Maher MM, Saini S, Mueller PR, Lauwers GY, Fernandez CD, Warshaw AL, Simeone JF. Autoimmune pancreatitis: imaging features. *Radiology* 2004; 233: 345-52.
- [40] Chang WI, Kim BJ, Lee JK, Kang P, Lee KH, Lee KT, Rhee JC, Jang KT, Choi SH, Choi DW, Choi DI, Lim JH. The clinical and radiological characteristics of focal mass-forming autoimmune pancreatitis: comparison with chronic pancreatitis and pancreatic cancer. *Pancreas* 2009; 38: 401-408.
- [41] Manfredi R, Graziani R, Cicero C, Frulloni L, Carbognin G, Mantovani W, Mucelli RP. Autoimmune pancreatitis: CT patterns and their changes after steroid treatment. *Radiology* 2008; 247: 435-43.

- [42] Sugumar A, Chari S. Autoimmune pancreatitis: an update. *Expert Rev Gastroenterol Hepatol* 2009; 3: 197-204.
- [43] Sumimoto K, Uchida K, Mitsuyama T, Fukui Y, Kusuda T, Miyoshi H, Tomiyama T, Fukata N, Koyabu M, Sakaguchi Y, Ikeura T, Shimatani M, Fukui T, Matsushita M, Takaoka M, Nishio A, Okazaki K. A proposal of a diagnostic algorithm with validation of International Consensus Diagnostic Criteria for autoimmune pancreatitis in a Japanese cohort. *Pancreatology* 2013; 13: 230-237.
- [44] Buscarini E, De Lisi S, Arcidiacono PG, Petrone MC, Fuini A, Conigliaro R, Manfredi G, Manta R, Reggio D, De Angelis C. Endoscopic ultrasonography findings in autoimmune pancreatitis. *World J Gastroenterol* 2011; 17: 2080-2085.
- [45] Zhang J, Shao C, Wang J, Cheng C, Zuo C, Sun G, Cui B, Dong A, Liu Q, Kong L. Autoimmune pancreatitis: whole-body 18F-FDG PET/CT findings. *Abdom Imaging* 2013; 38: 543.
- [46] Ozaki Y, Oguchi K, Hamano H, Arakura N, Muraki T, Kiyosawa K, Momose M, Kadoya M, Miyata K, Aizawa T, Kawa S. Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. *J Gastroenterol* 2008; 43: 144-151.
- [47] Ryu JK, Chung JB, Park SW, Lee JK, Lee KT, Lee WJ, Moon JH, Cho KB, Kang DW, Hwang JH, Yoo KS, Yoo BM, Lee DH, Kim HK, Moon YS, Lee J, Lee HS, Choi HS, Lee SK, Kim YT, Kim CD, Kim SJ, Hahm JS, Yoon YB. Review of 67 patients with autoimmune pancreatitis in Korea: a multicenter nationwide study. *Pancreas* 2008; 37: 377-385.
- [48] Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol* 2011; 23: 108-113.
- [49] Raina A, Krasinskas AM, Greer JB, Lamb J, Fink E, Moser AJ, Zeh HJ 3rd, Slivka A, Whittcomb DC. Serum immunoglobulin G fraction 4 levels in pancreatic cancer: elevations not associated with autoimmune pancreatitis. *Arch Pathol Lab Med* 2008; 132: 48-53.
- [50] Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS, Farnell MB. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007; 102: 1646-1653.
- [51] Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis* 2014; [Epub ahead of print].
- [52] Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, Kulikova M, Deshpande V, Pillai S, Stone JH. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2014; [Epub ahead of print].
- [53] Kojima M, Sipos B, Klapper W, Frahm O, Knuth HC, Yanagisawa A, Zamboni G, Morohoshi T, Klöppel G. Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. *Am J Surg Pathol* 2007; 31: 521-528.
- [54] Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181-1192.
- [55] Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, Frulloni L, Go VL, Gress TM, Kim MH, Kawa S, Lee KT, Lerch MM, Liao WC, Löhr M, Okazaki K, Ryu JK, Schleinitz N, Shimizu K, Shimosegawa T, Soetikno R, Webster G, Yadav D, Zen Y, Chari ST. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut* 2013; 62: 1771-1776.
- [56] Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M; Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol* 2010; 45: 471-477.
- [57] Hart PA, Topazian MD, Witzig TE, Clain JE, Gleeson FC, Klebig RR, Levy MJ, Pearson RK, Petersen BT, Smyrk TC, Sugumar A, Takahashi N, Vege SS, Chari ST. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* 2013; 62: 1607-1615.
- [58] Sodikoff JB, Keilin SA, Cai Q, Bharmal SJ, Lewis MM, Raju GS, Willingham FF. Mycophenolate mofetil for maintenance of remission in steroid dependent autoimmune pancreatitis. *World J Gastroenterol* 2012; 18: 2287-2290.
- [59] Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJ, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas* 2011; 40: 809-814.
- [60] Zhang L, Chari S, Smyrk TC, Deshpande V, Klöppel G, Kojima M, Liu X, Longnecker DS, Mino-

- Kenudson M, Notohara K, Rodriguez-Justo M, Srivastava A, Zamboni G, Zen Y. Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. *Pancreas* 2011; 40: 1172-1179.
- [61] Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. *Lancet* 2011; 377: 1184-1197.
- [62] Yamamoto H, Yamaguchi H, Aishima S, Oda Y, Kohashi K, Oshiro Y, Tsuneyoshi M. Inflammatory myofibroblastic tumor versus IgG4-related sclerosing disease and inflammatory pseudotumor: a comparative clinicopathologic study. *Am J Surg Pathol* 2009; 33: 1330-1340.
- [63] Saab ST, Hornick JL, Fletcher CD, Olson SJ, Coffin CM. IgG4 plasma cells in inflammatory myofibroblastic tumor: inflammatory marker or pathogenic link? *Mod Pathol* 2011; 24: 606-612.
- [64] Cioc AM, Ellison EC, Proca DM, Lucas JG, Frankel WL. Frozen section diagnosis of pancreatic lesions. *Arch Pathol Lab Med* 2002; 126: 1169-1173.
- [65] Dhall D, Suriawinata AA, Tang LH, Shia J, Klimstra DS. Use of immunohistochemistry for IgG4 in the distinction of autoimmune pancreatitis from peritumoral pancreatitis. *Hum Pathol* 2010; 41: 643-652.
- [66] Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, Pearson RK, Rajan E, Topazian MD, Yusuf TE, Chari ST, Petersen BT. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest Endosc* 2005; 61: 467-472.
- [67] Bang SJ, Kim MH, Kim do H, Lee TY, Kwon S, Oh HC, Kim JY, Hwang CY, Lee SS, Seo DW, Lee SK, Song DE, Jang SJ. Is pancreatic core biopsy sufficient to diagnose autoimmune chronic pancreatitis? *Pancreas* 2008; 36: 84-89.
- [68] Detlefsen S, Mohr Drewes A, Vyberg M, Klöppel G. Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria. *Virchows Arch* 2009; 454: 531-539.
- [69] Sepehr A, Mino-Kenudson M, Ogawa F, Brugge WR, Deshpande V, Lauwers GY. IgG4+ to IgG+ plasma cells ratio of ampulla can help differentiate autoimmune pancreatitis from other "mass forming" pancreatic lesions. *Am J Surg Pathol* 2008; 32: 1770-1779.
- [70] Cebe KM, Swanson PE, Upton MP, Westerhoff M. Increased IgG4+ cells in duodenal biopsies are not specific for autoimmune pancreatitis. *Am J Clin Pathol* 2013; 139: 323-329.
- [71] Salla C, Chatzipantelis P, Konstantinou P, Karoumpalis I, Pantazopoulou A, Tsiotos G. EUS-FNA contribution in the identification of autoimmune pancreatitis: a case report. *JOP* 2007; 8: 598-604.
- [72] Bracci PM, Wang F, Hassan MM, Gupta S, Li D, Holly EA. Pancreatitis and pancreatic cancer in two large pooled case-control studies. *Cancer Causes Control* 2009; 20: 1723-1731.
- [73] Gupta R, Khosroshahi A, Shinagare S, Fernandez C, Ferrone C, Lauwers GY, Stone JH, Deshpande V. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma? a retrospective analysis of pancreatic resections. *Pancreas* 2013; 42: 506-510.