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IgG4 cholangiopathy – Current concept, diagnosis, and pathogenesis

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Summary

IgG4 related cholangiopathy, a distinctive type of cholangitis of unknown origin, is characterized by increased serum levels of IgG4, massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the thickened bile duct wall, and good response to steroids. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis; IgG4-cholangiopathy is recognized as a biliary manifestation of IgG4-related disease. This condition can be diagnosed by a combination of imaging, serology, histopathology, and steroid responsiveness; however, cholangiographic features are often difficult to differentiate from primary sclerosing cholangitis, pancreatic cancer, or cholangiocarcinoma. The Japanese clinical diagnostic criteria for IgG4-related sclerosing cholangitis established in 2012 are useful in the diagnosis of IgG4-cholangiopathy. Although the precise pathogenic mechanism remains unclear, the development of IgG4-cholangiopathy may involve: susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and specific B cell responses.

Further studies on genetic backgrounds, disease specific antigens, and the role of IgG4 are necessary to clarify the pathogenesis.

Introduction

IgG4 related cholangiopathy is a distinctive type of cholangitis of unknown origin, which is characterized by increased serum levels of IgG4 [1], massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the bile duct wall and good response to steroids [1–3]. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis (AIP) [2,3], the concept of which was originally proposed by Yoshida *et al.* [4], and Hamano *et al.* reported increased serum levels of IgG4 in Japanese patients with AIP [1]. Now, it is recognized as a biliary manifestation of IgG4-related disease (IgG4-RD) [2–6]. Clinically, it is important to distinguish IgG4-cholangiopathy from malignancy such as cholangiocarcinoma, pancreas cancer, or a benign counterpart, PSC [2]. The organizing committee of the first international symposium on IgG4-RD in 2009 [6] proposed the nomenclature of "IgG4-related sclerosing cholangitis" (IgG4-SC) instead of "IgG4-associated cholangitis" which was recommended by the European Association for the Study of the Liver (EASL) [6]. Recently, the Japanese clinical diagnostic criteria 2012 for IgG4-SC have been proposed, although the pathogenic mechanisms remain unclear [2]. Here, we introduce the current concept, diagnosis, and recent advances in the pathogenesis of IgG4-SC.

Current concept and diagnosis of IgG4-SC

Classification of sclerosing cholangitis

Sclerosing cholangitis is classified into a primary type of unknown origin such as PSC or IgG4-SC, and secondary type with obvious pathogenesis (e.g., common bile duct (CBD) stone, cholangiocarcinoma, trauma, operation of biliary tract, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, or biliary injury of intra-arterial chemotherapy) (Table 1).

Prevalence of IgG4-SC

The prevalence of IgG4-SC still remains unclear. About 80% of AIP patients suffer complications with stenosis of the distal CBD with wall thickness [2,3,5]. This stricture might be due to both the thickening of bile duct and the effect of inflammation and/or edema of pancreas without CBD wall thickness. Based on these propositions, a recent Japanese national study analyzed 197 PSC and 43 IgG4-SC patients without AIP [7]. The male/female ratio was 106:91 (1.16:1) in PSC and 33:10 (3.3:1) in IgG4-SC and the mean age [min–max] was 48.1 [4.0–86.3] in PSC and 69.3

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Abbreviations: AIP, autoimmune pancreatitis; ANA, anti-nuclear antibody; CA-II, carbonic anhydrase-II; CBD, common bile duct; *CTLA-4*, cytotoxic T lymphocyte antigen-4; ERCP, endoscopic retrograde cholangio-pancreatography; FCRL, Fc-receptor-like; IFN-γ, interferon-γ; IgG4-RD, IgG4-related disease; IgG4-SC, IgG4-related sclerosing cholangitis; IL-4, interleukin-4; LF, lactoferrin; LPSP, lymphoplasmacytic sclerosing pancreatitis; PSC, primary sclerosing cholangitis.

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Table 1. Classification of sclerosing cholangitis.

Sclerosing cholangitis of unknown origin
Primary sclerosing cholangitis (PSC)
IgG4-related sclerosing cholangitis (IgG4-SC)
Secondary sclerosing cholangitis
Biliary lesion in AIDS patients
Cholangiocarcinoma
CBD stone
Postoperative/bile duct injury
Congenital biliary disorders
Chemical agents/drug-induced cholangitis
Ischemic biliary stenosis
Others

[47.6–87.4] in IgG4-SC [7]. Cholangiographic classification of IgG4-SC (Fig. 1) according to the clinical diagnostic criteria of IgG4-SC in 2012 [2] demonstrated that type IV, in which strictures of the bile duct are detected only in the hepatic hilar lesions similar to cholangiocarcinoma was the most common in cases of IgG4-SC without AIP [7].

Bile duct images of IgG4-SC

Cholangiogram

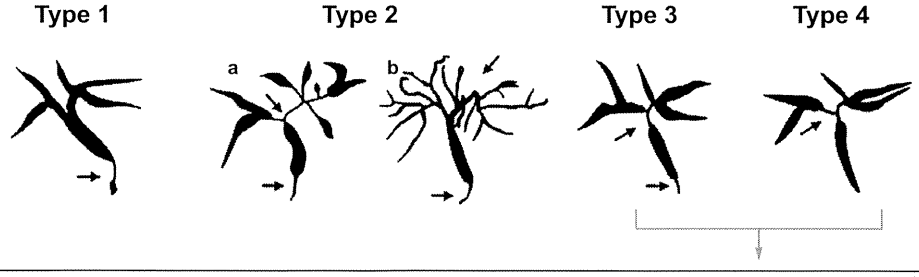
Four types of the characteristic cholangiographic features of IgG4-SC have been proposed based on the regions of stricture (Fig. 1) [2]. Type 1 IgG4-SC shows stenosis only in the distal CBD, which is often observed in pancreas cancer. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic/proximal bile ducts, should be differentiated from PSC. Type 3 and type 4 of IgG4-SC show stenosis in the hilar hepatic bile duct similar to hepatic hilar cholangiocarcinoma.

Circular/symmetric thickening of the bile duct

Circular and symmetric thickening of the bile duct wall, smooth outer and inner margin, and homogenous internal echo demonstrated by abdominal ultrasonography (US), abdominal computed tomography (CT), abdominal magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and intraductal ultrasonography (IDUS) are most characteristic images of the bile duct [2]. These characteristic features are recognized not only in the stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal in a cholangiogram [2].

Characteristic hematological findings

More than 80% of the patients with IgG4-SC show elevation of serum hepatobiliary enzymes, total bilirubin in cases of obstructive jaundice, and serum IgG4 levels (higher than the upper limit of normal value (ULN) of 135 mg/dl) [1,2]. However, elevation of serum IgG4 levels is not necessarily specific to IgG4-SC; it is also observed in atopic dermatitis, pemphigus, asthma, and some malignant cholangio-pancreatic diseases [2–6]. Cut-off values of serum IgG4 higher than x 2 ULN may be useful for more precisely differentiating IgG4-SC from PSC or cholangiocarcinoma [2,7].



Differential diagnosis			
	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer
Useful modalities			
	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O co-existence of IBD***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)

Fig. 1. Classification of cholangiography in IgG4-related sclerosing cholangitis. The characteristic features of IgG4-SC can be classified into 4 types based on the regions of stricture as revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, and it should be differentiated from chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Type 2 is further subdivided into 2 types. Type 2a, with narrowing of the intrahepatic bile ducts with prestenotic dilation and Type 2b, with narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, which is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of type 3 and type 4 need to be discriminated from those of cholangiocarcinoma. *IDUS, intraductal ultrasonography; **EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; ***IBD, inflammatory bowel disease. Modified from Hepatobiliary Pancreat Sci. 2012;19:536–542 [2], Copyright © 2013, with permission.

Other organ involvements (OOIs)

Most cases of IgG4-SC (80–90%) are associated with AIP. It is particularly difficult to accurately diagnose IgG4-SC without AIP [3,5]. Occasionally, IgG4-SC is associated with other systemic IgG4-RD such as IgG4-related symmetrical dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis [5,6]; these are helpful in the diagnosis of IgG4-SC. Unlike PSC, inflammatory bowel disease (IBD) is rarely observed in patients with IgG4-SC [2,6].

Histopathological findings of bile ducts

In IgG4-SC, massive infiltration of IgG4-positive plasma cells, storiform fibrosis, and/or obliterative phlebitis in the bile duct wall are characteristic and called lymphoplasmacytic sclerosing cholangitis (LPSC) [2,6]. Such fibroinflammatory involvement is mainly observed in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact [8]. Endoscopic transpapillary bile duct biopsy or cytological examinations are useful for differential diagnosis of cholangiocarcinoma, although it is difficult to take enough biopsy samples for characteristic histopathological findings of IgG4-SC [2]. Liver biopsy is sometimes useful in the diagnosis of IgG4-SC in cases of intrahepatic bile duct involvement [2].

Effectiveness of steroid therapy

In contrast to PSC or cholangiocarcinoma, the most characteristic feature of IgG4-SC is steroid responsiveness. It is important to make efforts of ruling out malignancy and to take enough biopsy samples. At many institutions, the therapeutic protocol for IgG4-SC follows that for AIP, such as oral prednisolone with the initial dose of 0.5–0.6/kg body weight/day [9]. If lesions do not respond to steroids, re-evaluation to rule out malignancy should be performed. In the refractory cases for oral steroids, it has been reported that steroid mini-pulse therapy [10], immunomodulators [11], and rituximab [12] are useful.

Diagnosis of IgG4-SC

In many cases of IgG4-SC, diagnosis can be made by a combination of characteristic biliary images (MRCP, ERCP, and EUS), increased serum levels of IgG4, coexistence of other organ involvements (OOIs), and characteristic histopathological features; however it is sometimes difficult to distinguish from PSC, cholangiocarcinoma, and pancreas cancer [2]. Based on these findings, the Japanese study group for IgG4-SC proposed the clinical diagnostic criteria for IgG4-SC [2] (Table 2). The effectiveness of steroid therapy is an optional diagnostic criterion to ensure accurate diagnosis of IgG4-SC like AIP only after negative workup of malignancy [2].

Recent advances in the pathogenesis of IgG4-SC

Although the precise pathogenic mechanism remains unclear, susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and specific B cell responses may be involved in the development of IgG4-cholangiopathy [5,3]. The class II antigen haplotype of the human major histocompatibility complex (HLA-DRB1*0405-DQB1*0401), polymorphisms of nuclear factor-κB and Fc-receptor-like (FCRL) 3 genes expressed on B cells have been reported in the Japanese patients with AIP [3].

Innate immunity

Recently, abnormal innate immunity has been demonstrated in patients with IgG4-RD. Activation of NOD-2 and TLR ligands on monocytes or basophils from patients with IgG4-related AIP enhance IgG4 responses via B cell activating factor (BAFF) and IL-13, although specific pathogens still remain unclear [13]. In animal models, activation of TLR3 (polyinosinic:polycytidylic acid) or TLR4 (LPS) can induce immune-mediated cholangitis, pancreatitis, and sialadenitis similar to human IgG4-RD [14].

Humoral immunity

Role of IgG4 in IgG4-SC

Although the association of IgE-mediated allergy and IgG4 antibodies is well known, IgG4 characteristics are still poorly understood. IgG4 has non-acting characteristics for immune responses, and is involved in a continuous process referred to as 'Fab-arm exchange', which is a swapping of a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule; this usually results in asymmetric antibodies with two different antigen-combining sites [3]. While these modified antibodies are hetero-bivalent, they behave as monovalent antibodies. Another aspect of IgG4 is that it mimics IgG rheumatoid factor (RF) activity by interacting with IgG [3]. IgG4 seems to be associated with a pathogenic effect in a few situations. In pemphigus, recognition of skin autoantigens (desmogleins) by IgG4 is at the origin of the disease process [3]. In contrast, increased inducible-memory Tregs in the periphery and liver tissues are positively correlated with serum levels of IgG4 [15]. In addition, prominent infiltration of Tregs upregulated IL-10 in livers of the patients with IgG4-SC [16]. These findings suggest that hypersecretory IgG4 from Tregs may be a secondary phenomenon of the development of IgG4-SC, whereas overproduction of IgG4 by BAFF from abnormal innate immunity-related cells such as monocytes or basophils, may be involved with development of IgG4-SC. Further studies are necessary to clarify the role of IgG4 in IgG4-RD.

The complement system

Patients in active stages of AIP occasionally show decreased complement (C3, C4) with elevated circulating immune complex as well as serum levels of IgG4 and the IgG4 subclass of immune complexes. However, a recent study showed that the classical pathway through IgG1 may be involved in activation of the complement system rather than mannose-binding lectin or alternative pathways through IgG4 [17].

Autoantibodies

Some patients with IgG4-related disease have non-specific antibodies such as an anti-nuclear antibody (ANA). From the view of IgG4 function, the big mystery is whether IgG4-related disease is an autoimmune or an allergic disease. However, the occasional coexistence of OOIs leads us to consider that there may be common target antigens in the involved organs, especially the pancreas, because of high incidence. Among candidate antigens

Table 2. The Japanese clinical diagnostic criteria 2012 for IgG4-related sclerosing cholangitis.

Diagnostic items
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the tickening of the bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Coexistence of autoimmune pancreatiti, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out
Diagnosis
Definite diagnosis
1. + 3.
1. + 2. + 4.a., b.
4.a., b., c.
4.a., b., d.
Probable diagnosis
1. + 2. + option
Possible diagnosis
1. + 2.
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility.

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previously reported [18], lactoferrin (LF), carbonic anhydrase (CA)-II, CA-IV, and pancreatic secretory trypsin inhibitor (PSTI) are distributed in the pancreas, salivary glands, biliary duct, lungs, and renal tubules. Immunization with CA-II or LF induced systemic lesions such as pancreatitis, sialadenitis, cholangitis, and interstitial nephritis in the mice models similar to human IgG4-RD [18].

Role of B cells

In addition to steroid and immune-modulators, B cell depletion by rituximab is a useful therapeutic strategy in IgG4-RD. Interestingly, rituximab reduces only the IgG4 subclass but no other subclasses of IgG1, IgG2, or IgG3 [19]. A recent study showed expansion of $IgG4^+$ B cell receptor (BCR) clones in blood and tissue of patients with active IgG4-cholangiopathy, and disappearance by corticosteroid treatment. These findings suggest that specific B cell responses may have a pivotal role in the pathogenesis of IgG4-SC [20].

Th1 and Th2 immune balance

The effector cells in IgG4-related diseases have been poorly understood. The $CD4^+$ T cells differentiate from naïve T cells (Th0) to Th1, Th2, Th17, and regulatory T (Treg) cells [3]. In the livers of IgG4-SC patients, a Th2 type immune reaction [16] is induced in addition to the Th1 responses [18]. Th2 cytokines may be involved in the progression of the disease process, especially the maturation and proliferation of local B cells and plasmacytes.

Regulatory T cells

Foxp3 is a member of the forkhead/winged-helix family of transcriptional regulators, and functions as the master regulator in the development and function of $CD4^+CD25^+$ regulatory T cells (Tregs) classified as naturally occurring $CD4^+CD25^+$ Tregs (nTregs) originating in the thymus and adaptive Tregs (aTregs) induced in the periphery by different antigens [15]. In IgG4-related diseases, circulatory naïve ($CD45RA^+$) Tregs are significantly decreased in the peripheral blood, whereas memory ($CD45RA^-$) Tregs are significantly increased [15]. In addition, prominent infiltration of Tregs with upregulation of IL-10 is observed in the liver of IgG4-SC patients [21]. These findings suggest that increased memory-Tregs in the periphery and local tissues may be an inhibitory immune response against inflammation, although decreased naïve Tregs may be pathogenic. The neonatally thymectomized (nTx)-BALB/c mice with CA-II or LF immunization and WBN/Kob rat models showed depletion of naïve Tregs and multi-organ inflammation similar to human IgG4-RD [5]. These animal models suggested that, in addition to depletion of naïve Tregs, macrophage activation and Th1 immune responses by $CD4^+/CD8^+$ T cells play major roles in the initial development of organ involvement.

Our hypothesis for the pathogenesis of IgG4-SC

Based on the above findings, we propose the pathogenic mechanisms in IgG4-SC/AIP outlined in Fig. 2. The basic concept is the biphasic mechanism of "induction" and "progression." Initially,

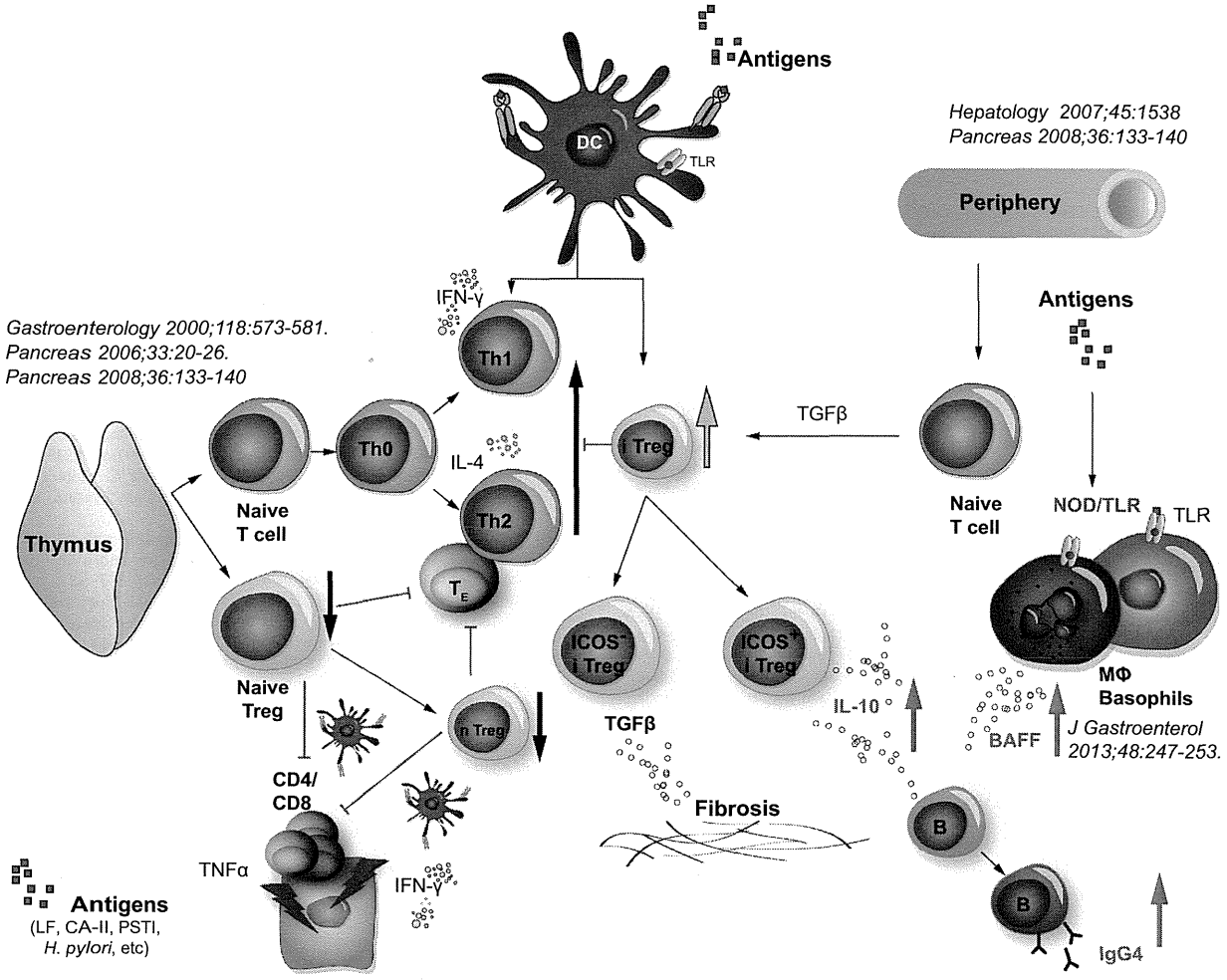

Fig. 2. Hypothesis for the pathogenesis of AIP and IgG4-related disease. In the central tolerance, naïve and natural regulatory T cells (Tregs) derived from the thymus suppress autoreactive CD4 or CD8 cells in the normal state. In the IgG4-related disease, the basic concept is the biphasic mechanism of "induction" and "progression". Initial response to antigens (LF, CA-II, CA-IV, PSTI, amylase-alpha, PBP peptide of *H. pylori*, etc.) might be induced by decreased naïve-Tregs. Th2 immune responses followed by Th1 type immune response with release of proinflammatory cytokines (IFN-γ, IL-1B, IL-2, TNF-α). In progression, Th2 type immune responses with producing IgG, IgG4 and autoantibodies may be involved in pathophysiology. IgG4 and fibrosis may be regulated by increased IL-10 and TGF-β secreted from inducible memory-Tregs, respectively. On the other hand, activation of NOD receptor or TLRs on monocytes or basophils increases IgG4 via upregulation BAFF and IL-13. iTreg, inducible Treg; TE, effector T cell; nTreg, natural Treg; BAFF, B cell activating factor. Modified from J Gastroenterol. 2011;46:277–288 [5], Copyright © 2012, with permission.

decreased naïve-Tregs may induce a Th1 immune response with the release of pro-inflammatory cytokines (IFN-γ, IL-1beta, IL-2, and TNF-α) to unknown antigens such as self-antigens (LF, CA-II, CA-IV, PSTI, and alpha-amylase) or microorganisms (*Helicobacter pylori*, commensal bacteria, and viruses). Subsequently, Th2 type immune responses may be involved in the disease progression. Production of IgG4 may be upregulated by BAFF from monocytes and basophils, and by IL-10 from inducible memory-Tregs. Tumor growth factor (TGF)-beta secreted from inducible memory-Tregs infiltrating into the involved organ may induce fibrosis.

Conclusion

In conclusion, recent advances support the concept of IgG4-SC, a unique clinical entity as a biliary manifestation of IgG4-RD. Although the pathogenic mechanism remains unclear, we proposed a hypothesis of the pathogenic mechanism of IgG4-SC. Further studies are necessary to clarify the pathogenesis including genetic backgrounds, disease specific antigens, and the role of IgG4.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Application of international consensus diagnostic criteria to an Italian series of autoimmune pancreatitis

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Abstract

Background: International consensus diagnostic criteria (ICDC) have been proposed to classify autoimmune pancreatitis (AIP) in type 1, type 2, or not otherwise specified.

Objective: Aim was to apply the ICDC to an Italian series of patients to evaluate the incidence and clinical profiles among different subtypes of AIP.

Methods: we re-evaluated and classified 92 patients diagnosed by Verona criteria, according to the ICDC.

Results: Out of 92 patients, 59 (64%) were diagnosed as type 1, 17 (18%) as type 2, and 15 (16%) as not otherwise specified according to the ICDC. A significant difference between type 1 and type 2 were found for age (54.5 ± 14.5 vs. 34.4 ± 13.9 respectively; $p < 0.0001$), male sex (76 vs. 47%; $p = 0.007$), jaundice (66 vs. 18%; $p = 0.002$) and acute pancreatitis (9 vs. 47%; $p < 0.0001$), elevated serum IgG4 levels (85 vs. 7%; $p < 0.0001$), inflammatory bowel disease (8 vs. 82%; < 0.0001), and relapse of the disease (34 vs. 6%; $p = 0.058$). Imaging and response to steroids in the not-otherwise-specified group were similar to type 1 and 2.

Conclusions: Type 1 has a different clinical profile from type 2 autoimmune pancreatitis. The not-otherwise-specified group has peculiar clinical features which are shared both with type 1 or type 2 groups.

Keywords

Autoimmunity, diagnosis, imaging, pancreatic diseases, pathology

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Introduction

Autoimmune pancreatitis (AIP) is a unique chronic inflammation of the pancreas.[1–4] Radiologically, the disease is characterized by focal or diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct (MPD).[5,6] The main clinical finding is a dramatic response to steroid.[2,7,8] Two histological subtypes in AIP have been recognized, type 1 and type 2.[4,9,10] The histological pattern of type 1 AIP is characterized by periductal infiltration of lymphocytes, abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Patients with type 1 AIP are often elderly men, with elevated levels of serum IgG4 and extrapancreatic lesions (e.g. sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis). In contrast, type 2 AIP is histologically characterized by the presence of granulocytic epithelial lesions[11,12] and absence of IgG4-positive plasma cells in pancreatic tissue. Patients with type 2 AIP are often younger with normal serum levels of IgG4 and frequently suffer from inflammatory bowel diseases, particularly ulcerative colitis.[13–16]

The diagnosis of AIP is challenging because several cases of AIP may closely mimic the pancreatic cancer.[17]

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Since AIP responds dramatically to steroid treatment, diagnostic criteria with a high accuracy are essential to avoid an unnecessary surgery. Up to now, several diagnostic criteria for AIP have been proposed.[3,9,18–20] In 2011, the International Association of Pancreatology proposed International Consensus Diagnostic Criteria (ICDC) to identify type 1 and type 2 AIP.[21] These criteria are composed of five cardinal features such as imaging of the pancreatic parenchyma and duct, serology, other organ involvement, histology, and response to steroid therapy, categorized as level 1 or 2 findings depending on the diagnostic reliability. Different from other criteria, the ICDC can diagnose type 1 and type 2 AIP independently. In addition, the ICDC defined the criteria for AIP not otherwise specified (AIP-NOS) for cases not diagnosed as type 1 and type 2 AIP.

In the present study, patients diagnosed as having AIP by Verona criteria[3] were reviewed and reclassified according to the ICDC. The aims were to examine the frequency of patients classified into type 1, type 2, and AIP-NOS by the ICDC and to compare clinical, radiological, and serological parameters among these groups.

Patients and methods

We included all patients enrolled in our prospectively collected database of AIP patients from January 2002 to March 2012 who met Verona criteria (Table 1).[3] Some patients had been included in previously published papers.[3,22,23] For the purpose of this study, these patients were reassessed radiologically and histologically and classified according to the ICDC.

Pathological findings were re-evaluated by two expert pathologists (GZ and PC). In operated patients, the diagnosis of subtype of AIP was based on histological findings on surgical specimens, according to the ICDC. In non-operated patients, the classification of AIP was based on the combination of the five cardinal features according to the ICDC.

Two expert radiologists (RM and RN) separately reviewed the findings on the computed tomography (CT) and/or magnetic resonance imaging (MRI) at the clinical onset and after steroids, when used. They categorized parenchymal and ductal changes into level 1 or 2 findings according to the ICDC. Furthermore, possible other organ involvement in abdomen was also carefully evaluated. According to the classification of other organ involvement in the ICDC, segmental/multiple proximal (hilar/intrahepatic) bile duct stricture, and retroperitoneal fibrosis were categorized as level 1 and renal involvement as level 2. In case of disagreement, the final decision was made by consensus.

Presence or history of symmetrically enlarged salivary/lachrymal glands (level 2 in other organ involvement of type 1) and inflammatory bowel disease (level 2 in other organ involvement of type 2) and the histological findings of biopsies were retrieved from the clinical records of patients.

Serum levels of IgG4 were evaluated at the clinical onset of the disease. The upper limit of normal value was 135 mg/dl, in accordance with the previous papers.[3,24,25]

If patients were treated with steroid as the initial therapy, the response was also retrieved. Response to steroid was defined as clinical and morphological resolution of the pancreatic changes or other organ involvement.

Finally, two clinicians (LF and TI) separately evaluated the five cardinal features and classified AIP

Table 1. Verona criteria for autoimmune pancreatitis

Category	Verona criterion
Suggestive radiological features (CT or MRI)	Diffuse or focal involvement of the pancreas
	Delayed enhancement in the involved parenchyma
	No dilation of the main pancreatic duct in diffuse form
	No extra-pancreatic or vascular involvement
Association with autoimmune diseases	Ulcerative colitis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, retroperitoneal fibrosis, autoimmune thyroiditis, tubulointerstitial nephritis, uveitis, and Mikulicz's disease
Consistent cytological or histological features	Periductal lymphoplasmacytic infiltration
	Presence of granulocytic epithelial lesions
	Negative for epithelial atypia
Response to steroid therapy	Clinical: resolution of symptoms/signs of AIP
	Radiological (CT or MR): disappearance/significant reduction in the size of the involved pancreas, normalization of the main pancreatic duct

CT, computed tomography; MR, magnetic resonance.

patients according to the ICDC. In case of disagreement, the final decision was made by consensus.

The patients were therefore classified in the following four groups: type 1 AIP (definitive or probable); type 2 AIP (definitive or probable); AIP-NOS; probable AIP (that fulfilled the Verona criteria but not the ICDC).

To compare the clinical profiles and outcomes of the different groups of patients, we evaluated the following variables: age at the clinical onset of the disease and sex; alcohol and smoking habits; medical history; symptoms at the clinical onset of the disease (acute pancreatitis, abdominal pain, weight loss, jaundice, steatorrhoea, none); diabetes; pancreatic exocrine insufficiency; association with other autoimmune diseases; initial therapy for the disease (steroid, resection, no treatment); relapse of the disease; use of immunosuppressant drugs. Patients were divided on the basis of alcohol consumption in two groups: teetotalers (no drinkers) and drinkers. Patients were also divided on the basis of smoking habits: non-smokers and smokers.

The diagnosis of diabetes was defined as fasting glucose level higher than 127 mg/dl. Pancreatic exocrine insufficiency was diagnosed on the basis of clinical steatorrhoea or faecal elastase $1 < 100$ μg/g of stool. Acute pancreatitis was diagnosed in the presence of epigastric pain and serum pancreatic amylase or lipase higher than 3× the upper normal limit. Autoimmune diseases other than other organ involvement reported in the ICDC were recorded as other autoimmune diseases.

Steroid therapy was performed with the oral administration of prednisone. The initial dose of prednisone was 1 mg/kg of body weight per day for 2–3 weeks. It was then tapered by 5 mg every week up to suspension.

Relapse of AIP was defined as the reappearance of pancreatic or extrapancreatic involvement after steroid withdrawal.

Statistical analysis

Differences among each group were analysed using the chi-squared test or Fisher's Exact test for qualitative variables and Kruskal–Wallis test for quantitative variables. A p-value >0.05 was considered statistically significant. Mean and standard deviation are reported.

Results

Patient characteristics

A total of 123 patients were in our prospective database of AIP. Thirty-one patients were excluded from this study (22 did not meet Verona criteria, three underwent surgery in other institutions, and six were referred to our centre after steroid therapy). A total of 92 patients (60 males and 32 females, mean age at the clinical onset 49.3 ± 16.2 years) were studied. The characteristics of analysed patients are summarized in Table 2.

Diabetes was observed in 11 patients (12%; seven at clinical onset, four during steroid treatment) and pancreatic exocrine insufficiency was observed in 29 (32%).

CT or MRI revealed diffuse enlargement of the pancreas in 42 patients (46%) and focal enlargement in 50 (54%). On magnetic resonance cholangiopancreatography with secretin stimulation (available in 61 patients), long or multiple strictures of MPD was observed in 50 patients (82%) and short (focal) narrowing of MPD in 11 patients (18%).

Table 2. Patient characteristics

Parameter	Patient population ($n = 92$)
Male sex	60 (65)
Age at onset (years)	49.3 ± 16.2
Drinkers	21 (23)
Alcohol/day (g)	23.1 ± 24.8
Smokers	22 (24)
Cigarettes/day	15.9 ± 6
Symptom at clinical onset	
Body weight loss	66 (72)
Jaundice	49 (53)
Acute pancreatitis	19 (21)
Abdominal pain	8 (9)
Diabetes	7 (8)
Steatorrhoea	10 (11)
None	7 (8)
PEI	29 (32)
Enlargement of pancreas	
Diffuse	42 (46)
Focal	50 (54)
Narrowing of MPD	
Long or multiple stricture	50 (82)
Focal narrowing	11 (18)
Elevated serum IgG4	
>2 × upper normal limit	28 (37)
1–2 × upper normal limit	14 (18)
None	34 (45)
Other organ involvement	34 (37)
Inflammatory bowel disease	20 (22)
Initial therapy	
Steroid	74 (80)
Resection	16 (17)
No treatment	2 (3)
Relapse	24 (26)

Values are n (%) or mean ± SD.
MPD, main pancreatic duct; PEI, pancreatic exocrine insufficiency.

Serum levels of IgG4 at the clinical onset of the disease were available in 76 out of 92 patients (83%). Serum levels of IgG4 were higher than 2× upper normal limit in 28 (37%) patients, 1–2× upper normal limit in 14 (18%), and normal in 34 (45%).

Other organ involvement was observed in 34 (37%). Twenty patients (22%) had inflammatory bowel disease. The association with other autoimmune diseases was observed in 11 patients (12%). The spectrum of autoimmune diseases included autoimmune gastritis ($n=2$), autoimmune thyroiditis ($n=4$), erythema nodosum ($n=1$), systemic lupus erythaematosus ($n=1$), autoimmune thrombocytopenia ($n=1$), retro-ocular fibrosis ($n=1$), pulmonary fibrosis ($n=1$), celiac disease ($n=1$), autoimmune prostatitis ($n=1$), autoimmune neuritis ($n=1$), and autoimmune encephalitis ($n=1$).

Sixteen out of 92 patients (17%) underwent surgery. Out of the remaining 76 patients, 74 patients (97%) were treated with steroid. Immunosuppressant drugs were used in 28 patients (31%), mainly azathioprine ($n=22$), cyclosporine ($n=2$), tamoxifen ($n=2$) methotrexate ($n=1$), and 6-mercaptopurin ($n=1$). The indications for the use of immunosuppressant drugs were relapse of AIP in 19 patients, associated autoimmune diseases in six, and high levels of serum IgG4 after steroid treatment in three.

Recurrence of the disease was observed in 24 out of 92 patients (26%), in 19 out of 76 (25%) non-operated, and in five out of 16 operated patients (31%). All operated patients with recurrence were treated with steroids.

Diagnosis according to the ICDC for AIP

According to the ICDC, 59 patients (64%) were diagnosed as type 1 AIP, 17 (18%) as type 2, 15 (16%) as AIP-NOS, and one (1%) as probable AIP. The algorithms following the ICDC for the diagnosis of AIP type 1, type 2, and NOS are reported in Figures 1 and 2.

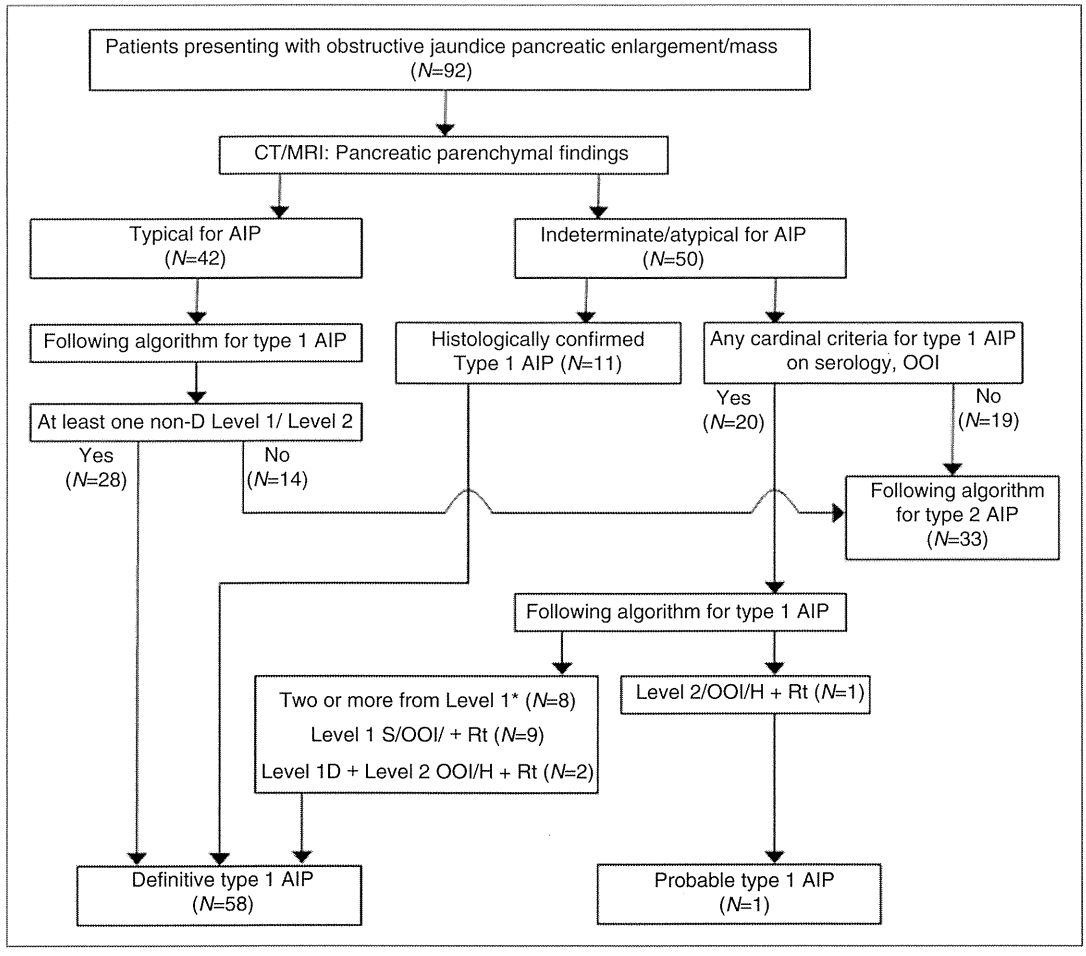

Figure 1. Flow chart of diagnosis according to the ICDC algorithm for type 1 AIP.
*Level 2D is counted as level 1 in this setting.

Definitive diagnosis of type 1 or type 2 AIP was made in 63 out of 76 not operated patients (83%). All but one of the 59 patients (98%) with type 1 were classified as 'definitive', in 11 based on histology in surgical specimens and in 48 based on the other the ICDC. Five out of 17 patients (29%) with type 2 were classified as 'definitive' on the basis of histology in surgical specimens and the remaining 12 non-operated patients (71%) as 'probable'.

Five type 1 AIP patients with ulcerative colitis fulfilled the diagnostic criteria of probable type 2 as well. However, these patients were included in type 1 AIP according to algorithm of the ICDC.[18]

Pancreatic biopsies or aspiration cytology were performed in 57 out of 76 non-operated patients (75%). The histological findings excluded pancreatic cancer and showed only suggestive findings for AIP (lymphoplasmacytic infiltration and fibrosis).

Comparison of cardinal features in the ICDC among type 1 AIP, type 2 AIP, and AIP-NOS

The results of classification in five ICDC cardinal features are shown in Table 3. The frequency of levels 1 and 2 in parenchymal and ductal imaging criteria is not different among groups. The frequency of levels 1 and 2 in serology criterion was significantly higher in type 1 compared to type 2 AIP (56 and 7% in level 1, 29 and 0% in level 2, respectively, $p < 0.0001$).

Other organ involvement was observed in 34 patients (58%) with type 1 AIP, whereas inflammatory bowel disease was diagnosed more frequently in type 2 (84%) compared to type 1 AIP (8%; $p < 0.0001$).

Response to steroid was observed in all non-surgical patients.

Comparison of clinical profiles and outcomes among type 1 AIP, type 2 AIP, and AIP-NOS

The demographic characteristics, clinical profile, laboratory data, and pancreatic imaging of type 1, type 2, and AIP-NOS are summarized in Table 4. The single patient with probable AIP by the ICDC was excluded.

Males were more frequently observed in type 1 compared to type 2 and AIP-NOS (76, 47, and 40%, respectively; $p = 0.007$). Type 2 patients were significantly younger (34.4 ± 13.9 years) than type 1 (54.5 ± 14.5 years; $p < 0.0001$) and AIP-NOS (45.7 ± 14.9; $p < 0.0001$). The frequency of drinkers and smokers was comparable among groups, as well as the mean consumption of alcohol and cigarette smoking in drinkers and smokers (Table 4). The frequency of jaundice at the onset in type 1 was significantly higher than that in type 2 (66 vs. 18%, respectively; $p = 0.002$).

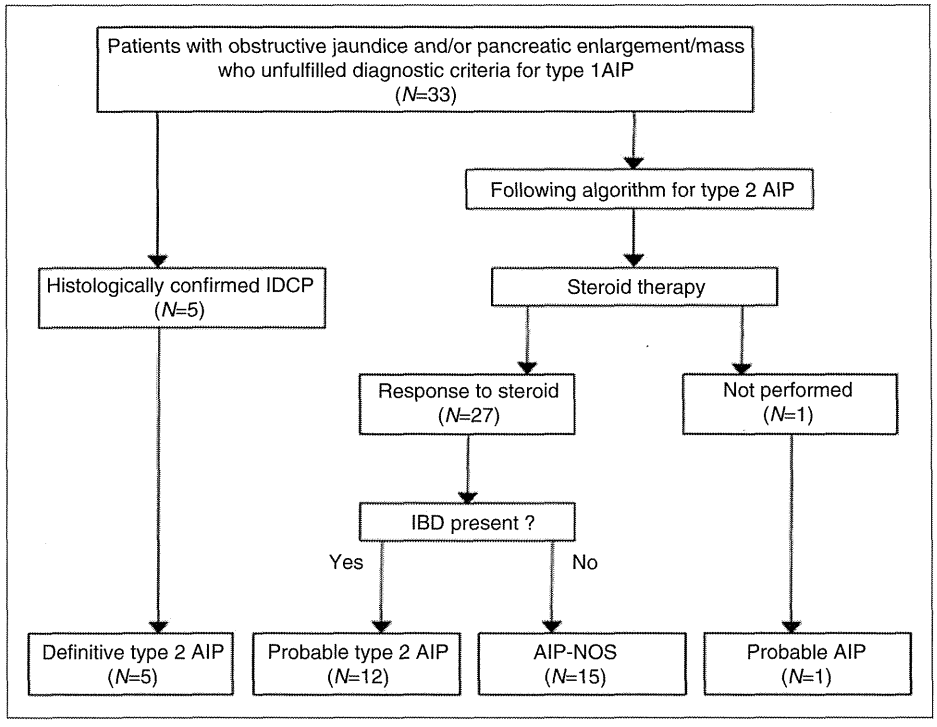

Figure 2. Flow chart of diagnosis according to the ICDC algorithm for type 2 AIP and AIP-NOS.

Table 3. Cardinal features of the international consensus diagnostic criteria in the study population according to final classification of autoimmune pancreatitis

Cardinal features	AIP type 1 ($n=59$)	AIP type 2 ($n=17$)	AIP-NOS ($n=15$)	p-value
Parenchymal imaging				
Level 1	28 (47)	8 (47)	5 (33)	NS
Level 2	31 (53)	9 (53)	10 (67)	
Ductal imaging				
Level 1	30 (86)	8 (80)	11 (73)	NS
Level 2	5 (14)	2 (20)	4 (27)	
Serology IgG4				
Level 1	27 (56)	1 (7)	0	<0.0001
Level 2	14 (29)	0	0	
Normal	7 (15)	14 (93)	12 (100)	
Other organ involvement				
Level 1	26 (44)	0	0	<0.0001
Level 2	8 (14)	0	0	
No	25 (42)	17 (100)	15 (100)	
Inflammatory bowel disease				
Level 2	5 (8)	14 (82)	0	<0.0001
No	54 (92)	3 (18)	15 (100)	
Histology of surgical specimens				
Level 1	11 (19)	5 (29)	0	<0.0001
No	46 (81)	12 (71)	15 (100)	
Response to steroid in non-operated patients				
Yes	47 (98)	12 (100)	15 (100)	NS
No	1 (2)	0	0	

Values are *n* (%).
AIP, autoimmune pancreatitis; NOS, not otherwise specified.

Acute pancreatitis developed more frequently in type 2 AIP and AIP-NOS compared with type 1 AIP (47 and 40 vs. 9%; $p<0.0001$). Asymptomatic patients were observed only in type 1 AIP (11%). A higher proportion of patients suffered from diabetes and pancreatic exocrine insufficiency in type 1 than in the two other groups, but there was no significant difference among each group. Relapse of the disease after steroid therapy was observed in 20 of 59 patients (34%) with type 1, in three of 15 patients (20%) with AIP-NOS, and in one operated patient (6%) with type 2 ($p=0.058$).

Discussion

The results of this study described the application of the ICDC in AIP patients diagnosed by Verona criteria.

Firstly, all but one of the patients diagnosed as suffering from AIP by Verona criteria fulfilled the ICDC. Therefore, a positive AIP diagnosis by Verona criteria correctly identifies AIP, without discriminating between the subtypes. A patient who fulfilled Verona criteria (suggestive radiology, consistent pathological findings on pancreatic biopsies and association with ulcerative colitis) did not meet the ICDC because she did not undergo steroid treatment (intolerance previously documented) and a spontaneous remission was later observed. Some cases of AIP have been reported in the literature showing spontaneous clinical and radiological remission without steroid therapy.[23] Since response to steroid treatment is included as cardinal feature, some AIP cases with spontaneous resolution may be misclassified by the ICDC. In such patients, histology obtained by core needle biopsy may be needed for the diagnosis of AIP.

Secondly, type 1 AIP was the most frequent subtype in this Italian series. It is known that type 1 and type 2 AIP substantially differ in terms of demography, symptoms at clinical onset, and relapse. The distinctions of these clinical profiles and outcome between two subtypes were largely in agreement with those reported in previous studies.[9,13–16] However, some aspects (sex distribution in type 2 and mean age at the onset in type 1) are different.[10–13] A possible explanation for this discrepancy may be that only 17% of patients had a histologically proven type 1 and type 2 AIP diagnosed in surgical specimens.

Table 4. Epidemiological and clinical findings of the groups of patients classified by the international consensus diagnostic criteria

Parameters	AIP type 1 ($n=59$)	AIP type 2 ($n=17$)	AIP-NOS ($n=15$)	p-value
Male sex	45 (76)	8 (47)	6 (40)	0.007
Age at onset (years)	54.5 ± 14.5	34.4 ± 13.9	45.7 ± 14.9	<0.0001
Drinkers	14 (24)	3 (18)	3 (20)	NS
Alcohol/day (g)	25.4 ± 29.1	18.3 ± 12.6	18.3 ± 18.9	NS
Smokers	10 (17)	6 (35)	5 (33)	NS
Cigarettes/day (n)	16.7 ± 4.5	15 ± 7.7	13.4 ± 6.1	NS
Symptom at clinical onset				
Body weight loss	45 (76)	11 (65)	9 (60)	NS
Jaundice	39 (66)	3 (18)	7 (47)	0.002
Acute pancreatitis	5 (9)	8 (47)	6 (40)	<0.0001
Abdominal pain	4 (7)	3 (18)	1 (7)	NS
Diabetes	5 (8)	1 (6)	1 (7)	NS
Steatorrhoea	8 (14)	2 (12)	0	NS
None	6 (11)	0	0	0.048
Other autoimmune diseases	8 (14)	1 (6)	2 (13)	NS
PEI	21 (36)	5 (29)	3 (20)	NS
Relapse	20 (34)	1 (6)	3 (20)	0.058
Immunosuppressant drugs	25 (42)	0	3 (20)	0.002

Values are n (%) or mean ± SD.
AIP, autoimmune pancreatitis; MPD, main pancreatic duct; NOS, not otherwise specified; PEI, pancreatic exocrine insufficiency.

Parenchymal and ductal the ICDC are similar and not statistically different between type 1 and type 2 AIP, as well as the response to steroids. Therefore, in clinical practice, imaging and response to steroids cannot distinguish type 1 from type 2 AIP. On the contrary, serum IgG4, other organ involvement, and histology are significantly different in the two groups. Recent papers reported a low sensitivity of serum IgG4 levels for the diagnosis of AIP (53–90%),[14,24,26,27] ranging from 63 to 76% in type 1 and 0 to 23% in type 2 AIP.[13–16,28] Applying the ICDC, elevation of serum IgG4 levels was more frequently observed in type 1 AIP (85%) than in type 2 AIP patients (7%). A single patient with a histological definitive diagnosis of type 2 AIP had marked elevation of serum IgG4 levels (290 mg/dl). We do not have any explanation for that, but we may only postulate an overlap syndrome between the two subtypes.

Inflammatory bowel disease in the ICDC addressed to a diagnosis of type 2 AIP. The prevalence of inflammatory bowel diseases, particularly ulcerative colitis, in patients with type 2 AIP ranges between 16 and 33%,[3,9,14,28–30] only occasionally in type 1 AIP (up to 6%).[15,28,30,31] In the current study, all five of 59 patients (8%) classified as type 1 AIP with ulcerative colitis meet the ICDC for type 2 AIP. Since the ICDC suggest that such patients are firstly classified into type 1 disease, the ICDC may misclassify the type 2 disease.

This is the first study, to our knowledge reporting the clinical, radiological, and serological features of AIP-NOS, and this study classified 16% of the patients as AIP-NOS.[21] Other organ involvement, serology, and histology were lacking in this group, as expected. Imaging features and response to steroids in AIP-NOS group were similar to those in type 1 and 2 AIP groups. The clinical and epidemiological parameters in AIP-NOS group were different from those in type 1 and type 2 AIP. While the frequency of AIP-NOS patients presenting with jaundice as initial symptom was intermediate between those of type 1 and type 2 AIP, type 2 and AIP-NOS were similar in prevalence of acute pancreatitis. Moreover, AIP-NOS patients suffer from clinical relapse similarly to type 1, as confirmed by the use of immunosuppressant drugs. The clinical characteristics of AIP-NOS are unknown, and the only data available are clinical profiles of seronegative AIP patients for serum IgG4 levels.[32–34]. The most recent study reported that, among the seronegative AIP group, patients were more likely to have type 1 rather than type 2 AIP if they are older than 50 years or have other organ involvement or disease relapse.[34] We can postulate that some AIP-NOS patients are IgG4-seronegative type 1 AIP. However, we cannot exclude an undiagnosed type 2 AIP or an overlap syndrome.

Pancreatic core needle biopsy is reported to be a good method to diagnose both type 1 and type

2 AIP.[35–37] In our study, core biopsy or aspiration cytology was performed in 75% of non-operated patients. Histology excluded pancreatic adenocarcinoma but did not meet the ICDC. Suggestive pathology is a Verona criterion for the diagnosis of AIP but do not reach level 1 or 2 for the ICDC. This reflects the aim of Verona criteria, used for the diagnosis of AIP, but not the ICDC, used to define the subtypes of the disease. Despite the lack of histological cardinal feature, we were able to classify the subtype of AIP in most part of patients (84%).

The limitation of the study is the lack of serum levels of IgG4 at the clinical onset in 17%, leading probably to misclassification of AIP. However, since 11 out of these patients lacking serum IgG4 levels were classified as type 1 AIP, the diagnosis of subtype of AIP may be mistaken in only five patients: two with type 2 AIP and three with AIP-NOS.

In conclusion, patients diagnosed as type 1 AIP by the ICDC have different clinical profiles and outcomes from those as type 2 AIP. Clinical features of AIP-NOS are sometimes similar to those observed in type 1 AIP and other times with type 2 AIP. We cannot exclude an overlap syndrome as a separate entity. The ICDC may misclassify AIP cases with a spontaneous remission and patients with inflammatory bowel disease.

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Conflict of interest

The authors declare that there is no conflict of interest.

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The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013
I. Concept and diagnosis of autoimmune pancreatitis

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Abstract
Background In response to the proposal of the international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP) and the Japanese diagnostic criteria in 2011, the 2009 Japanese consensus guidelines for managing AIP required revision.
Methods Three committees [the professional committee for making clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators] were organized. Fifteen specialists for AIP extracted the specific clinical statements from 1,843 articles published between 1963 and 2012 (obtained from Pub Med and a secondary database, and developed the CQs and statements. The expert panel individually rated the clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than seven on a nine-point scale from the panel was regarded as valid.
Results The professional committee created 13 CQs and statements for the current concept and diagnosis of AIP, 6 for extra-pancreatic lesions, 6 for differential diagnosis, and 11 for treatment.
Conclusion After evaluation by the moderators, amendments to the Japanese consensus guidelines for AIP have been proposed for 2013.

This article is the first of a three-article series on the Japanese consensus guidelines. The members of the Working Committee are listed in the "Appendix 2" in the text.

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Introduction

Since Yoshida et al. [1], first proposed the concept of autoimmune pancreatitis (AIP) in 1995, AIP has been accepted worldwide as a distinctive type of pancreatitis [1–6]. Due to the increasing numbers of cases, several issues in the management of AIP were raised in Japan. These issues are (1) diagnosis and management of atypical or indeterminate AIP, (2) differentiation from pancreas cancer, (3) evaluation of OOIs, (4) diagnosis and treatment of recurrent cases, and (5) different diagnostic criteria in Japan and other countries [4, 5]. To resolve these issues, the Japan Pancreas Society (JPS) and the Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD-MHLWJ), proposed the Japanese consensus guidelines for the management of AIP in 2009 [6]. In 2011, the International Consensus Diagnostic Criteria for AIP (ICDC) [9] were proposed. The ICDC proposed two subtypes, type 1 AIP, which is associated with IgG4, and type 2 AIP, which is associated with granulocytic epithelial lesion (GEL). Lymphoplasmacytic sclerosing pancreatitis (LPSP) is a pancreatic manifestation of IgG4-related disease (IgG4-RD) characterized by increased serum IgG4 and abundant infiltration of IgG4-positive plasmacytes, obliterative phlebitis and storiform fibrosis. In Japan, LPSP is more often observed, whereas idiopathic duct-centric chronic pancreatitis (IDCP) characterized by GEL is rare [4–8]. One of the major differences between the 2002 and 2006 Japanese criteria and the ICDC is in the therapeutic use of steroids. The previous Japanese criteria [3–5] did not recommend facile therapeutic use of steroids. The revised version of the JPS criteria (JPS-2011) for type 1 AIP [10, 11] was proposed in response to the ICDC's inclusion of response to steroid treatment. The number of publications on AIP increased from 871 to 1,843 between 2008 and 2012 (in the PubMed database). In light of this additional research, the Japanese consensus guidelines need to be revised. Most of the evidence levels of the specific clinical statements and a secondary database were still lower than grade III as proposed by the Agency for Health Care Policy and Research in 1993. Therefore, we have developed the revised version of the consensus guidelines using the modified Delphi approach [5–8, 12]. Briefly, to establish consensus, three committees (the professional committee for making clinical questions and statements by Japanese specialists for AIP, the expert panel committee for rating statements using the modified Delphi method, and the evaluating committee comprised of moderators) were organized. During the first phase, 15 specialists (11 pancreatologists, 2 radiologists, 1 respiratory system expert and 1 pathologist) were selected from the members of the RCIPD-MHLWJ. These specialists revised the 36 clinical questions (CQs) and statements for (1) concept and diagnosis (13 CQs), (2) extra-pancreatic lesions (6 CQs), (3) differential diagnosis (6 CQs) and (4) treatment (11 CQs) based on the selected papers [6–8], which focus on the concept and diagnosis CQs.

The expert panelists (ten pancreatologists) individually rated the clinical statements for appropriateness, and discussed areas of disagreement and uncertainty [5–8, 12]. Ratings of appropriate methods for the management of AIP were developed using a modified Delphi approach. Rating was on a nine-point scale, with one being highly inappropriate and nine being highly appropriate. A clinical statement receiving a median score greater than seven was regarded as valid. The specialists revised some of the clinical statements after discussion with expert panelists, and then the revised clinical statements were rated again. Based on the two-round modified Delphi approach, guideline statements for diagnosis and management of AIP were developed. In addition to the specialist and expert panels, the moderators included one pancreatologist, one surgeon, one pathologist and one internist, each of whom were also familiar with epidemiology and the modified Delphi approach [5–8]. The moderators reviewed the literature, collected clinical statements from the literature as well as from a survey of the professionals, facilitated the panelist meetings, and analyzed the data. Because available clinical evidence regarding the diagnosis and management of AIP is limited, we could not set a suitable recommendation level for some clinical statements. In the revised consensus-based guidelines, the statements for clinical practice were evaluated as "strongly recommendable" (level A) or "strongly unrecommendable (level D)" for receiving a score of nine, and "ordinarily recommendable" (level B), "unrecommendable" (level C), or

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"conflicting benefits and harms" (level I) for that less than nine according to the grading proposed by United States Preventive Services Task Force [13].

Clinical questions and statements

I. Concept and Diagnosis

CQ-I-1. What is "autoimmune pancreatitis (AIP)"?

- AIP is a distinct form of pancreatitis clinically characterized by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis and therapeutically by a dramatic response to steroids.
- AIP is classified as two subtypes, type 1 and type 2. Type 1 AIP is more prevalent in Japan; references to AIP in Japanese literature usually mean type 1 AIP.
- Type 1 AIP is lymphoplasmacytic sclerosing pancreatitis (LPSP) characterized by massive infiltration of lymphocytes and plasmacytes, especially IgG4-positive plasmacyte; storiform fibrosis; and obliterative phlebitis. It is a pancreatic manifestation of a systemic disorder, IgG4-related disease (IgG4-RD).
- Type 2 AIP (also called IDCP) or AIP with GEL, is more commonly observed in Europe and the United States. Type 2 AIP exhibits neutrophilic lesions and, therefore, is a different condition from type 1 AIP.

Description AIP is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis and therapeutically by a dramatic response to steroids.

The original concept of AIP was proposed in Japan [1] and was defined as a pancreatitis whose pathogenesis could possibly involve autoimmune mechanisms [1–8]. Autoimmune mechanisms were suspected due to characteristic findings, such as hypergammaglobulinemia, increased serum levels of IgG or IgG4, presence of autoantibodies, and effective response to steroid therapy. Patients with AIP occasionally exhibit other organ involvement (OOI) such as sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, enlarged coeliac and hilar lymph nodes, chronic thyroiditis, or interstitial nephritis. All of them show similar pathological findings with abundant infiltration of IgG4-positive cells as well as high serum IgG4, which support the possibility that AIP is a systemic disorder associated with pancreatic lesions. After several proposals of nomenclatures such as the IgG4-related systemic sclerosing disease [14], systemic IgG4-related plasmacytic syndrome (SIPS) [15] and IgG4-positive multi-organ lymphoproliferative syndrome (IgG4 MOLPS), [16] the consensus nomenclature of IgG4-related disease (IgG4-RD) [17–20] was proposed. Therefore, AIP related to IgG4 is now regarded as a pancreatic manifestation of IgG4-RD. Histopathological findings show lymphoplasmacytic sclerosing pancreatitis (LPSP) [21] characterized by (1) massive infiltration of lymphocytes and plasmacytes, (2) especially IgG4-positive plasmacytes more than 10 cells/high power field (400×), (3) storiform fibrosis, and (4) obliterative phlebitis. It is commonly seen in elderly males, and is comparable to lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by histopathological findings of pronounced infiltration of lymphocytes and plasmacytes, infiltration of IgG4-positive plasmacytes, storiform fibrosis, and obstructive phlebitis.

Cases associated with ulcerative colitis in young patients, mainly reported in Europe and the US, show typical pathological neutrophilic lesions called IDCP [22] or AIP with GEL [23, 24]. In addition to histopathological findings, no hematological markers suggest that their pathological conditions are different from LPSP [11]. Although typical pancreatic images in both LPSP and IDCP show diffuse swelling of more than one-third of the pancreas, some atypical and indeterminate cases of segmental/focal swelling or mass-forming type [9–11] are necessary to be differentiated from pancreatic cancer. Based on these findings, the recent international consensus diagnostic criteria (ICDC) for AIP [9] proposed the current concept of AIP and classification as two subtypes, type 1 (LPSP) and type 2 AIP (IDCP). As most of AIP are type 1 AIP in Japan [10, 11], use of the simple term of AIP usually means type 1 AIP in the present guidelines (Table 1).

CQ-I-2. Are there characteristic clinical symptoms in AIP?

- There are no specific symptoms seen in patients with AIP. However, in many cases, patients with type 1 AIP

Table 1 Recommendation levels based on consensus

Level A	Recommendation that procedure or treatment is useful or effective
Level B	Recommendation in favor of procedure or treatment being useful or effective
Level C	Recommendation's usefulness or efficacy less well established
Level D	Recommendation that procedure or treatment is not useful or effective but may be harmful
Level I	The balance of benefits and harms cannot be determined, because evidence is lacking, of poor quality, or conflicting

http://www.ahrq.gov/clinic/3rduspstf/ratings.htm

show; obstructive jaundice; symptoms of diabetes mellitus; accompanying extra-pancreatic lesions, and minor to no abdominal pain. Those with type 2 AIP commonly have abdominal pain and acute pancreatitis.

Description Patients with type 1 AIP do not show the type of severe abdominal pain seen in those with acute pancreatitis or with acute exacerbation of chronic pancreatitis. Abdominal pain is mild to nonexistent, [5, 19, 25–28] although there have been a few cases reported where the disease started as acute pancreatitis or severe pancreatitis [29, 30]. One-third to one-half of patients show obstructive jaundice or mild abdominal pain, and 15 percent have shown back pain or weight loss [31, 32]. More than half of cases are associated with sclerosing cholangitis, diabetes mellitus, sclerosing sialoadenitis/dacryoadenitis, or retroperitoneal fibrosis, showing obstructive jaundice, polydipsia,/polyuria or malaise, xerostomia/xerophthalmia, or hydronephrosis, respectively [31]. Those with type 2 AIP commonly have abdominal pain and acute pancreatitis [9] (Table 2).

CQ-I-3. How is AIP found?

- In many cases, patients go to see doctors with complaints such as minor abdominal pain, general malaise, jaundice, or dry mouth (Level of recommendation: B).
- In many cases, AIP is found when patients who have increased levels of biliary enzymes, obstructive jaundice, or diabetes mellitus are tested for pancreatic or biliary duct cancers in a differential diagnosis (Level of recommendation: B).
- In many cases, an enlarged pancreas demonstrated by abdominal ultrasonography leads to the detection of AIP (Level of recommendation: B).

Description In more than half of AIP cases, patients visit the hospital for symptoms such as minor abdominal pain, general malaise, jaundice, or dry mouth [1, 25–32]. A urine test or general blood biochemical test shows abnormal levels of pancreatic or biliary enzymes. In other cases, an increased level of CA19-9 is observed; pancreatic imaging tests such as abdominal ultrasound, CT or MRI show a diffusely or locally enlarged pancreas, or a pancreatic mass may also be found. In many cases the disease is found in the course of a differential diagnosis against pancreatic or biliary cancers [1, 6–11, 25–32]. AIP is also found during the close examination of extra-pancreatic lesions; e.g., during the differential diagnosis against primary sclerosing cholangitis (PSC); in examination of suspected Sjögren's syndrome by a head/neck-otolaryngologist, ophthalmologist, or collagen disease-rheumatologist; or in examination for retroperitoneal fibrosis by an urologist. The rate of association with other autoimmune diseases is not clear. There have been reports, mainly in Europe and the United States, of cases associated with juvenile ulcerative colitis showing evidence of IDCP [9, 22] or GEL [23, 24]. Conversely, cases associated with ulcerative colitis or primary biliary cirrhosis are rarely seen in Japan [6–8].

Table 2 Clinical symptoms in AIP

Obstructive jaundice	33–59 %
Abdominal pain	32 %
Back pain	15 %
Body weight loss	15 %
Anorexia	9 %
General fatigue	9 %
Abnormal stool	7 %
Fever	6 %
No symptoms	15 %

CQ-I-4. What are the characteristic blood-biochemical and immunological findings in AIP?

- Although there are no disease-specific serum biochemical findings, increased serum levels of pancreatic enzymes, biliary enzymes and total bilirubin are commonly observed in AIP (Level of recommendation: A).
- Serum levels of IgG4 have the highest diagnostic value as a single serological diagnostic method among all the available ones; however, it is not disease specific (Level of recommendation: A).
- High serum IgG or the presence of non-specific antibodies such as antinuclear antibodies or rheumatoid factor suggest the possibility of AIP (Level of recommendation: B).

Description Most cases of AIP are discovered when patients show increased levels of biliary enzymes, obstructive jaundice, or diabetes mellitus, which are usually reflected in biochemical tests. Abnormal biliary findings are seen in many cases; 60–82 % of cases exhibit an increase of biliary enzymes: and 39–62 % of cases exhibit an increase of total bilirubin [32–35]. Compared to cases of acute pancreatitis or acute exacerbation of chronic pancreatitis, the occurrence rate of abnormal levels of serum pancreatic enzymes is lower, 36–64 % [32, 33], and the levels rarely become abnormally high. There have been reports of increased levels of peripheral eosinophil granulocytes [32] and activated T-lymphocytes (CD4-positive, CD8-positive) [33].

Immunological examinations show high incidences of hypergammaglobulinemia (43 %), increased levels of serum IgG (62–80 %), increased levels of serum IgG4 (68–92 %) [32–35]), antinuclear antibodies (40–64 %), rheumatoid factor (25 %) [32, 33] and Th2 predominance

over Th1 in the local lesions [36, 37]. However, these results are not disease-specific. Some reports have shown the presence of autoantibodies, such as anti-carbonic anhydrase II antibodies (55 %) or anti-lactoferrin antibodies (75 %) in patients with AIP, although they generally cannot be tested [32, 33]. Anti-SSA/B antibodies or anti-mitochondrial antibodies, on the other hand, are rarely seen [32, 33]. Among all serological diagnostic methods, an increased level of serum IgG4 has the highest diagnostic value as a single method because of its sensitivity (80 %) and its specificity (98 %) in differentiating AIP from pancreatic cancer; however, it is not disease specific. The sensitivity and specificity of serum IgG are 70 and 75 %, respectively, and the positive ratios of antinuclear antibodies and rheumatoid factor are 60 and 20–30 %, respectively. Even when IgG is combined with antinuclear antibodies or rheumatoid factor, the sensitivity is 91 % but the specificity is 61 %; the specificity is lower than that for IgG4, although the sensitivity is equivalent to that for IgG4 [34]. (Refer to CQ-III-2).

CQ-I-5. Are there pancreatic exocrine and endocrine dysfunctions?

- AIP is often associated with pancreatic exocrine and endocrine dysfunctions (e.g., diabetes mellitus). Occurrence ratios are about 80 and 70 % for exocrine and endocrine dysfunctions, respectively, (Level of recommendation: A).

Description AIP is in many cases associated with pancreatic exocrine and endocrine dysfunction (e.g., diabetes mellitus.) According to the fact-finding survey conducted in 2000 by the Ministry of Health and Welfare Investigation Research Team for Special Intractable Pancreas Disease, 80.6 % of the cases studied showed abnormal pancreatic exocrine function [in which the abnormality is defined as 70 % or lower secretion in the BT-PABA (PFD test)], and 70.0 % of the cases showed exocrine dysfunction (as determined by the secretin test), comparable to that of confirmed cases of chronic pancreatitis. Additionally, 77.0 % of the cases were reported to be associated with diabetes mellitus [31]. Studies by individual medical facilities have reported that 83–88 % of the cases were associated with secretion dysfunction, and 42–78 % with diabetes mellitus [38–40]. The diabetes mellitus accompanying AIP was analyzed in detail in a national fact-finding survey conducted in 2006 [35]. Among those AIP patients who sought medical treatment in 2002, 66.5 % of cases were found to have associated diabetes mellitus; Of those, 33.3 % had diabetes mellitus prior to the onset of AIP, and 51.6 % started developing diabetes mellitus around the same time as the onset of pancreatitis. Among those patients having diabetes mellitus, 14 % developed diabetes after steroid treatment [35], suggesting that such diabetes may be caused by long-term steroid treatment. There are some cases where pancreatic endocrine dysfunction was improved by steroid treatment; however, since not all cases improved, it can be stated that medical conditions that have progressed far enough to cause some degree of organic change can not be reversed. (Refer to CQ-IV-9.)

In AIP, the mechanism of pathogenesis of pancreatic exocrine dysfunction is assumed to involve the following: decreased secretion of pancreatic enzymes associated with collapsed acinar cells caused by pronounced cellular infiltration mainly of plasmacytes and fibrosis; and obstructed flow of pancreatic juice due to inflammatory cell infiltration around the pancreatic ducts and subsequent narrowing of pancreatic ducts [35, 39–41]. A recent study suggested that mislocalization of the cystic fibrosis transmembrane conductance regulator (CFTR), which plays a central role in pancreatic duct HCO_3^- secretion, and up-regulation of aquaporin-1 (AQP1) on the plasma membrane and in the cytoplasm of pancreatic duct cells may be involved in the development of AIP [42]. Corticosteroids reduce inflammation and restore both digestive enzyme and HCO_3^- secretion in patients with AIP by regenerating acinar cells and correcting CFTR localization in pancreatic duct cells [42]. In contrast, the mechanism of pathogenesis of diabetes mellitus is assumed to be affected by both obstructed blood flow of endocrine glands (islets of Langerhans) associated with the fibrosis of exocrine glands, and damaged islets of Langerhans due to the spreading of inflammation [40, 41].

CQ-I-6. What are the characteristic findings of abdominal ultrasonography in AIP ?

- Abdominal ultrasonography is effective for the diagnosis of AIP. Ultrasonic findings in patients with AIP are characterized by a diffusely or locally enlarged pancreas with low echo; A diffusely enlarged pancreas is called a "sausage-like" pancreas. (Level of recommendation: A).

Description The Japanese Clinical Diagnostic Criteria of Autoimmune Pancreatitis [3–5, 10, 11] states that a "diffusely or locally enlarged pancreas is detected by an abdominal ultrasound test, an abdominal X-ray test, or an abdominal MRI test." Ultrasonography is the initial clinical test performed, and serves as a tool to diagnose AIP. However, in some cases, patients are found to have AIP during physical examinations [43].

A diffusely enlarged pancreas appears as a low-echo area in general (Fig. 1a) and has a so-called "sausage-like" appearance [44]. No dilatation of the main pancreatic duct