CQ-IV-9) Do Pancreatic Exocrine and Endocrine Functions Improve After Steroid Therapy in AIP Patients?

- Pancreatic exocrine and endocrine functions improve after steroid therapy in some AIP patients. Many AIP patients with type 2 diabetes mellitus before AIP onset showed worsening of diabetes mellitus control after steroid therapy. (Level of recommendation: A)

Description

Many AIP patients have associated pancreatic exocrine and endocrine dysfunctions.[5,111,113] It has been reported that pancreatic exocrine and endocrine functions improved after steroid therapy in 38%[30] to 50%[31] and in 25%[30] to 45%[31] of AIP patients, respectively. Diabetes mellitus control worsens after steroid therapy in 75% of AIP patients with preexisting type 2 diabetes mellitus.[31]

CQ-IV-10) Is the Prognosis of AIP Good?

- The prognosis of AIP seems to be good during the short term with steroid therapy.
- It is unclear whether the long-term outcome is good because there are many unknown factors such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy. (Level of recommendation: B)

Description

Autoimmune pancreatitis responds well to steroid therapy, and remission can be induced in most AIP patients. However, with respect to the long-term outcome, there are many unknown factors such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy.

Nishino et al[30] reported that pancreatic atrophy developed in 33% of cases, and 1 patient developed early gastric cancer after 29 months of steroid therapy, and another patient developed advanced rectal cancer after 13 months of steroid therapy. According to Hirano et al,[116] unfavorable events occurred in 32% of AIP patients treated with steroid therapy during an average 41-month follow-up period, and they occurred in 70% of those without steroid therapy during an average follow-up of 61 months. Furthermore, 1 patient treated with steroid therapy died of acute myelocytic leukemia, 1 patient not treated with steroid therapy died of lung cancer, and 1 patient not treated with steroid therapy died of pancreatic cancer.[116] Kubota et al[112] also reported 5 patients whose conditions were diagnosed as a malignancy during follow-up (pancreatic cancer [n = 2], breast cancer [n = 2], and gastric cancer [n = 1]). Kamisawa et al[115] reported that marked atrophy of the pancreas was observed in 30% of AIP patients during follow-up.

CQ-IV-11) Is There any Relationship Between AIP and Pancreatic Cancer?

- There are a few articles reporting an AIP case developing pancreatic cancer, but it is unclear whether there is a relationship between AIP and pancreatic cancer. (Level of recommendation: B)

Description

It has been reported that chronic pancreatitis is one of the risk factors for pancreatic cancer. It has been reported that some AIP patients developed pancreatic atrophy or pancreatic stones. It is necessary to observe whether there is an association with pancreatic cancer and other malignancies in AIP patients treated with steroid for a long period because steroid therapy is immunosuppressive. Recently, there have been a few articles reporting an AIP case developing pancreatic cancer,[108,109,117,118] but it is unclear whether there is a relationship between AIP and pancreatic cancer.

CONCLUSIONS

In the present Japanese guideline for AIP, the 36 CQs and statements for (I) concept and diagnosis (13 CQS), (II) extrapancreatic lesions (6 CQs), (III) differential diagnosis (6 CQs), and (IV) treatment (11 CQs) have been established. Other than the Japanese diagnostic criteria for AIP, the Korean, Mayo's, and Asian diagnostic criteria have been proposed. Different from the Korean or Mayo's criteria, ERCP examination is mandatory, and effects of steroid or extrapancreatic lesions are not included in the Japanese diagnostic criteria. Further studies for the international guideline to improve the present guideline are needed after the international consensus for diagnostic criteria.

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REVIEW

Japanese consensus guidelines for management of autoimmune pancreatitis: I. Concept and diagnosis of autoimmune pancreatitis

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Abstract As the number of patients with autoimmune pancreatitis (AIP) is increasing in Japan, practical guidelines for managing AIP need to be established. Three committees [the professional committee for developing clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee of moderators] were organized. Fifteen AIP specialists extracted specific clinical statements from a total of 871 articles in the literature using a PubMed search (1963–2008) and a secondary database, and developed the CQs and statements. The expert panelists individually rated these clinical statements using a modified Delphi approach in which a clinical statement receiving a median score greater than 7 on a 9-point scale from the panel was regarded as valid. The professional committee developed 13, 6, 6, and 11 CQs and statements for the concept and diagnosis, extra-pancreatic lesions, differential diagnosis and treatment, respectively. The expert panelists regarded them as valid after two-round modified Delphi approaches. After evaluation by the moderators, the Japanese clinical guidelines for AIP were established. The digest versions of the present guidelines have been published in the official journal of the Japan Pancreas Society, "*Pancreas.*" Full versions divided into three series are scheduled to be published in the present and followings two issues in the *Journal of Gastroenterology* with approval of Professor Go VLW, the Editor-in-Chief of "*Pancreas.*"

Keywords Autoimmune pancreatitis · Guideline · Diagnosis · Treatment · Delphi method

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Introduction

Autoimmune pancreatitis (AIP) is accepted worldwide as a distinctive type of pancreatitis [1–4]. It is suspected that the pathogenesis of AIP involves autoimmune mechanisms. In addition to pancreatitis, patients with AIP often develop extra-pancreatic lesions such as biliary lesions, sialadenitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and interstitial nephritis, suggesting that AIP may be a systemic disorder [5–7]. Although the pathogenesis is still unclear, the most important issue in the management of AIP is to differentiate it from pancreatic and biliary malignancy. Recently, various diagnostic criteria for AIP have been proposed, including those of Japan [8], Korea [9, 10], the Mayo Clinic [11], and Asia [12]. As a

systemic corticosteroid is usually effective, the steroid effect is included in the diagnostic criteria proposed by Korea and the Mayo Clinic. Although Japanese criteria do not recommend facile therapeutic use of steroids [8], Asian criteria proposed by the Japan-Korea joint symposium permit it only when recommended by experts after a full negative workup of malignancy [12]. Although the numbers of patients with AIP are increasing in Japan, the clinical evidence is limited. Therefore, practical guidelines for managing AIP are needed. Most of the evidence levels of the specific clinical statements from 871 articles extracted from a Pub Med search (1963–2008) and from a secondary database were lower than the grade III proposed by the Agency for Health Care Policy and Research in 1993. Therefore, we have developed "the Japanese Consensus Guidelines for AIP" according to the modified Delphi approach [13–15]. This method, which provides panelists with the opportunity to discuss their judgments between the ratings' rounds, is suitable for the development of consensus guideline statements.

To establish consensus guidelines, three committees (the professional committee for developing clinical questions and statements by Japanese specialists concerning AIP, the expert panelist committee for rating statements using the modified Delphi method, and the evaluating committee of moderators) were organized (Table 1). In brief, during the first phase, 15 specialists (11 pancreatologists, two radiologists, one expert of respiratory system, and one pathologist), who were selected from the members of the Research Committee for Intractable Pancreatic Diseases, supported by the Ministry of Health, Labor, and Welfare of Japan, developed 36 clinical questions (CQs) and statements for (1) the concept and diagnosis (13 CQS), (2) extra-pancreatic lesions (6 CQs), (3) the differential diagnosis (6 CQs), and (4) treatment (11 CQs) based on the selected papers as described above. In the second phase, the expert panelists (ten pancreatologists) individually rated these clinical statements for appropriateness, and discussed areas of disagreement and uncertainty. Ratings of appropriate methods for management of AIP were developed using a modified Delphi approach [13–15]. Rating was on a 9-point scale, with 1 being highly inappropriate and 9 being highly appropriate. A clinical statement receiving a median score greater than 7 from the panel was regarded as valid. In the third phase, the specialists revised some of the clinical statements after discussion with expert panelists. During the third phase, 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 comprised one pancreatologist, one surgeon, one pathologist, and one internist who were also familiar with epidemiology and the modified Delphi approach. The moderators searched and reviewed the literature, collected clinical statements from the literature as well as from the professional group's survey, facilitated the panelist meetings, and analyzed the data obtained using the modified Delphi approach. Because available clinical evidence regarding diagnosis and management of AIP is limited, we could not set a suitable recommendation level for some clinical statements. In the present consensus-based guidelines, the statements for clinical practice receiving a score of 9 and less than 9 were evaluated as level A–D (Table 2).

The digest versions of the present guidelines have been published in the official journal of the Japan Pancreas Society, "*Pancreas*" [16]. Full versions divided into three series are scheduled to be published in the represent and the following two issues of the *Journal of Gastroenterology* with approval of Prof. VLW Go, the Editor-in-Chief of the "*Pancreas*."

Table 1 Committee members for developing consensus-based guidelines for AIP

The professional committee for developing clinical questions and statements	Kazuichi Okazaki, Shigeyuki Kawa, Terumi Kamisawa, Tetsuhide Ito, Kazuo Inui, Hiroyuki Irie, Atsushi Irisawa, Keishi Kubo, Kenji Notohara, Osamu Hasebe, Yasunari Fujinaga, Hirotaka Ohara, Shigeki Tanaka, Takayoshi Nishino, Isao Nishimori
The expert panelist committee for rating statements by the modified Delphi method	Toru Shimosegawa, Tetsuhide Ito, Kazuo Inui, Hirotaka Ohara, Kazuichi Okazaki, Shigeyuki Kawa, Terumi Kamisawa, Shigeki Tanaka, Takayoshi Nishino, Isao Nishimori
The evaluating committee	Masao Tanaka, Keiko Shiratori, Koichi Suda, Toshimasa Nishiyama

Table 2 Consensus-based recommendation levels

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

Clinical questions and statements

I. Concept and diagnosis

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

- It is a unique form of pancreatitis that shows evidence of possible involvement of autoimmune mechanisms such as hypergammaglobulinemia, increased serum levels of IgG, increased serum levels of IgG4, or presence of autoantibodies, and effective response to steroid therapy.
- Autoimmune pancreatitis (AIP), as commonly observed in Japan, shows symptoms of lymphoplasmacytic sclerosing pancreatitis (LPSP) characterized by pronounced infiltration of lymphocytes and plasmacytes, infiltration of IgG4-positive plasmacytes, storiform fibrosis, and obliterative phlebitis.
- However, idiopathic duct-centric chronic pancreatitis (IDCP) or granulocyte epithelial lesions (GEL), commonly seen in Europe and the US, show neutrophilic lesions and therefore are different conditions than AIP.
- AIP may be a systemic disorder associated with pancreatic lesions, since the following disease concepts have also been proposed: IgG4-related sclerosing disorders, systemic IgG4-related plasmacytic syndrome (SIPS), or IgG4-positive multi-organ lymphoproliferative syndrome (IgG4-MOLPS).

Description Autoimmune pancreatitis is a disease concept originally proposed in Japan [1]. Because its characteristics are associated with evidence of possible involvement of autoimmune mechanisms such as hypergammaglobulinemia, increased serum levels of IgG, increased levels of IgG4 or presence of autoantibodies, and effective response to steroid therapy, the disease is defined as pancreatitis in which pathogenesis could possibly involve autoimmune mechanisms [1, 2, 8, 17, 18]. In Japan, it is commonly observed in elderly males and is comparable to lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by histopathological findings of abundant infiltration of lymphocytes and plasmacytes, infiltration of IgG4-positive plasmacytes, storiform fibrosis, and obstructive phlebitis [19]. Cases in young patients associated with ulcerative colitis, commonly reported in Europe and the US, show pathological neutrophilic lesions and are called idiopathic duct-centric chronic pancreatitis (IDCP) [20] or granulocyte epithelial lesions (GEL). Although their imaging findings show resemblance to those of AIP, there are not enough serological findings, so it is highly possible that their pathological conditions are different from AIP [21]. Since most cases in Japan show a diffusely enlarged pancreas and narrowing of the main pancreatic duct, it is believed that typical AIP lesions spread to over one-third of the pancreas; however, there are also cases of localized lesions or mass-forming types [8]. Upper abdominal discomfort, obstructive jaundice due to the stenosis of the biliary duct, and diabetes mellitus are the clinical features often observed [2]. Although the long-term prognosis of AIP is not clear, the formation of pancreatic stones has been reported. AIP is occasionally associated with lesions of organs other than the pancreas (sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, interstitial nephritis, etc.), suggesting that it may be a systemic disorder. Therefore, the following concepts have been proposed: IgG4-related systemic sclerosing disease [5], systemic IgG4-related plasmacytic syndrome (SIPS) [6], and IgG4-positive multi-organ lymphoproliferative syndrome (IgG4-MOLPS) [7]. Because in most cases sialadenitis is found to be negative for both the anti-SSA antibody and anti-SSB antibody, which are distinctive to Sjögren's syndrome [2], and the histopathological images show pronounced infiltration of IgG4-positive plasmacytes seen in Mikulicz's disease and Küttner's tumor, AIP is considered to be different from typical Sjögren's syndrome. Since sclerosing cholangitis-like lesions seen in patients with AIP show different responses to steroids and different prognosis from those with primary sclerosing cholangitis (PSC), and AIP is characterized by the infiltration of IgG4-producing plasmacytes, the two diseases are considered to be different pathological conditions.

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

- There are no specific symptoms seen in patients with AIP. However, in many cases, the patients show minor to no abdominal pain, obstructive jaundice, symptoms of diabetes mellitus, or accompanying extra-pancreatic lesions.

Description Patients with 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 almost none, if it even exists [2, 22–25]. There have been a few cases reported where the disease started as acute pancreatitis or severe pancreatitis [26, 27]. One-third to one-half of the patients show obstructive jaundice or mild abdominal pain, and 15% have back pain or weight loss [22, 27] (Table 3). More than half of the cases are associated with sclerosing cholangitis, diabetes mellitus, sclerosing sialoadenitis/dacryoadenitis, or retroperitoneal fibrosis, showing, in some cases, obstructive jaundice, polydipsia/polyuria or malaise, xerostomia/xerophthalmia, or hydronephrosis, respectively [7].

Table 3 Clinical symptoms of 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%

Modified from refs. [22, 24, 25, 28, 30]

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.
- In many cases, AIP is found when patients showing increased levels of biliary enzymes, obstructive jaundice, or diabetes mellitus are tested for pancreatic or biliary duct cancers in the differential diagnosis.
- In many cases, the enlarged pancreas demonstrated by abdominal ultrasonography leads to the detection of AIP.

Description In more than half of the cases, patients visit the hospital for symptoms such as minor abdominal pain, general malaise, jaundice, or dry mouth [1, 2, 6, 7, 22, 24, 26, 28]. A urine test or general blood biochemical test shows abnormal levels of pancreatic or biliary enzymes, or in some cases an increased level of CA19-9; pancreatic parenchymal imaging such as abdominal ultrasonography, CT, or MRI shows a diffusely or locally enlarged pancreas, or a pancreatic mass in some cases. In many cases the disease is found in the course of thedifferential diagnosis against pancreatic or biliary cancers [1, 2, 22–24, 28]. AIP is also found during the close examination of extra-pancreatic lesions; for example, during the differential diagnosis against primary sclerosing cholangitis (PSC); in examination in suspicion of Sjögren's syndrome by a head and neck otolaryngologist, ophthalmologist, or collagen disease-rheumatologist; or in examination for retroperitoneal fibrosis by a urologist. The rate of association with other autoimmune diseases is not clear; however, there have been reports, mainly in Europe and the US, of cases associated with juvenile ulcerative colitis showing evidence of idiopathic duct-centric chronic pancreatitis (IDCP) [20] or granulocyte epithelial lesion (GEL) [21]. Conversely, cases associated with ulcerative colitis or primary biliary cirrhosis are rarely seen in Japan [28].

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

- Although there are no disease-specific blood-biochemical findings, increased serum levels of pancreatic enzymes, biliary enzymes, and total bilirubin are commonly observed in AIP.
- 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.
- The combination of non-specific antibodies, such as serum IgG, antinuclear antibodies, or rheumatoid factor, shows sensitivity and specificity equivalent to IgG4.

Description Most AIP cases are discovered when patients show increased levels of biliary enzymes, obstructive jaundice, diabetes mellitus, etc., 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; 39–62% of cases exhibit an increase of total bilirubin, etc. [28–31]. 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% [28, 29], and the levels rarely become abnormally high. There have been reports of increased levels of peripheral eosinophil granulocytes [28] and activated T-lymphocytes (CD4-positive, CD8-positive) [29].

Immunological examinations show high incidences of hypergammaglobulinemia (43%), increased levels of serum IgG (62–80%), increased levels of serum IgG4 (68–92%) [2, 28, 31], antinuclear antibodies (40–64%), rheumatoid factor (25%), etc. [28, 29], although these 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 in high frequency, although they generally cannot be tested [28, 29]. Anti-SSA/B antibodies or anti-mitochondrial antibodies, on the other hand, are rarely seen [28, 29]. 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 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; however, the

sensitivity is equivalent to that for IgG [6, 31, 41] (refer to CQ-II-2-2).

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

- Autoimmune pancreatitis is often associated with pancreatic exocrine dysfunction and endocrine dysfunctions (diabetes mellitus); occurrence ratios are about 80 and 70%, respectively.

Description Autoimmune pancreatitis is in many cases associated with pancreatic exocrine dysfunction and endocrine dysfunction (diabetes mellitus). According to the fact-finding survey conducted in 2000 by the Ministry of Health and Welfare Investigation Research Committee for 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 in confirmed cases of chronic pancreatitis. On the other hand, 77.0% of the cases were reported to be associated with diabetes mellitus [32]. Studies by individual medical facilities reported that 83–88% of the cases were associated with secretion dysfunction and 42–78% with diabetes mellitus [32–35]. The diabetes mellitus accompanying AIP was analyzed in detail in the national fact-finding survey conducted in 2006 [30, 32]. Among those AIP patients who sought medical attention during the 1-year period of 2002, 66.5% of cases were found to be associated with diabetes mellitus; of these patients, 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 [30, 32], 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 cannot 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 ancinar 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 the pancreatic ducts [34–37]. In contrast, the mechanism of pathogenesis of diabetes mellitus is assumed to be affected by both of the following disorders [35, 37]: 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 [2, 38]. Future discussions, however, are necessary [37].

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

- Abdominal ultrasonography is effective for the diagnosis of AIP (level of recommendation: A).
- Ultrasonographic 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 Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2006 [17, 39] defines that a "diffusely or locally enlarged pancreas is detected by abdominal US, X-ray, or MRI." Ultrasonography is the initial clinical examination serving as the tool to diagnose AIP. In some cases, patients are found to have AIP during their physical examinations [40].

A diffusely enlarged pancreas appears as a low-echo area in general (Fig. 1) and has a so-called "sausage-like" appearance [41]. No dilatation of the main pancreatic duct is seen in most cases. The enlarged area shows a low echo image, in some cases with scattered high echo spots [42]. In the case of a locally enlarged pancreas, it becomes an issue to distinguish it from pancreatic cancer or mass-forming pancreatitis with the differential diagnosis. Although dilatation of the main pancreatic duct is not seen in most cases, some patients may show minor dilation, which makes the differential diagnosis difficult. Conversely, if the main duct is found to penetrate through the mass (Fig. 2), it (the duct-penetrating sign) may be a useful sign that can be used for the differential diagnosis against pancreatic cancer [43, 44]. In some cases, there may be many low echo mass images in the pancreatic parenchyma (Fig. 3), which makes it difficult to differentiate AIP from malignant lymphoma or metastatic pancreatic tumors.

Some patients with AIP show thickened bile duct walls; the occurrence rate has been reported to be about 60% [45]. A thickened bile duct wall is characterized by layered or parenchymal low-echo wall thickening [46]. There have been some cases where the thick wall centering around the extrahepatic bile duct extends over to the intrahepatic bile duct or gallbladder [45–47]. The wall thickening has been studied in detail with intraductal ultrasonography (IDUS) [48]. Although wall thickening of narrowed areas is not clear, since areas other than the narrowed area show thickening of the internal low echo layer while maintaining the high echo image for the outer, it is assumed that the thickening is happening on the bile duct wall itself [49].

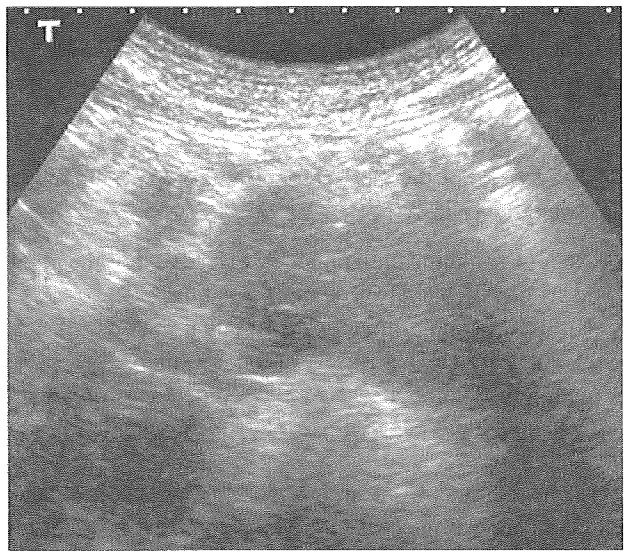

Fig. 1 Abdominal ultrasonography in AIP (diffuse type). A diffusely enlarged pancreas appears as a low echo area with high echoic spots and has a so-called "sausage-like" appearance

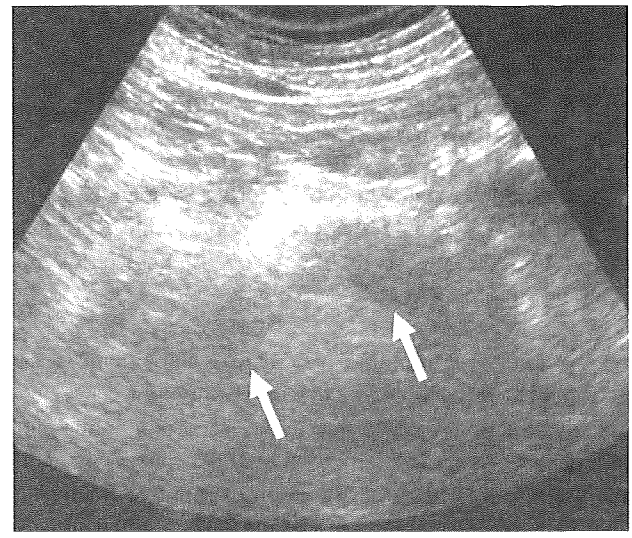

Fig. 3 Abdominal ultrasonography in AIP (multiple mass forming). Low echoic masses were observed in the pancreas head and body (*arrows*)

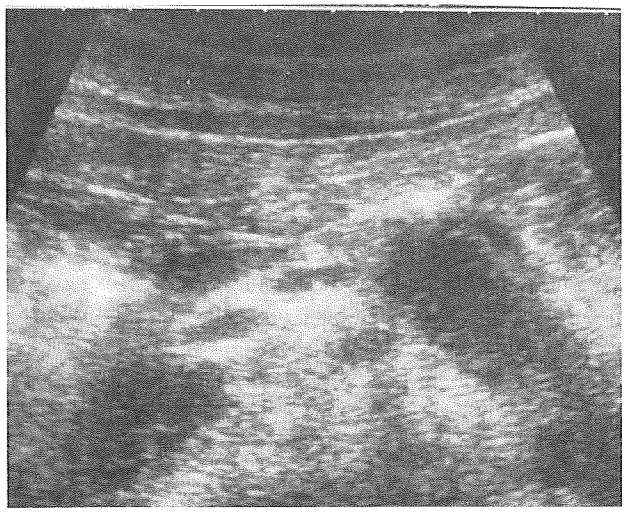

Fig. 2 Duct-penetrating sign by abdominal ultrasonography in AIP (tumor-forming type). The main duct is found to penetrate through the mass (duct-penetrating sign) in the case of a locally enlarged pancreas, which may be a useful sign for the differential diagnosis against pancreatic cancer

Some recent reports have discussed the usefulness of contrast-enhanced ultrasonography in the diagnosis to differentiate AIP from pancreatic cancer [50–52]. Reports have shown that while in the case of pancreatic cancer only the rim of the mass was stained with the presence of tumor vessels, in the case of AIP, the entire mass was stained with no presence of tumor vessels. However, reports have also shown that for AIP, findings varied depending on the stage of the disease; the areas of stronger inflammation and immature fibrosis were stained strongly, whereas the areas of weaker inflammation and older fibrosis were stained weakly [51].

CQ-I-7. What are the characteristic findings of abdominal computed tomography (CT) in AIP?

- Abdominal CT images of patients with AIP show a diffusely or locally enlarged pancreas. The dynamic CT shows a distinctive delayed enhancement pattern with various images depending on the activity or stages of the disease (level of recommendation: A).
- If a capsule-like rim is observed, the patient is highly suspected of having AIP (level of recommendation: A).

Description Typical AIP exhibits a diffusely enlarged pancreas [17]. The pancreatic parenchyma is replaced by fibrosis, which causes a reduced enhancement effect during the "pancreatic parenchymal phase" and shows less absorption compared to the normal pancreas (Fig. 4). Due to the delayed enhancement in fibrosis areas, a certain level of enhancement is seen in the "portal phase," and the enhancement continues into the "delayed phase" where the enhancement becomes stronger compared to the normal pancreas (Fig. 5). Consequently, the dynamic CT enhancement pattern of AIP shows a slow and delayed enhancement pattern. However, because a weak fibrosis shows a similar enhancement pattern as in normal pancreatitis, even in the absence of delayed enhancement, the possibility of AIP cannot be denied [41].

A "capsule-like rim" is a relatively distinctive CT feature of AIP [52] (Figs. 4, 5). It is a band-like structure that appears to surround all or part of the lesions; it shows lower

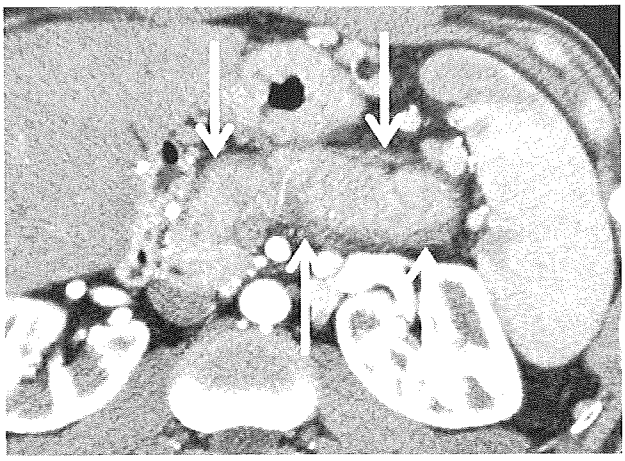

Fig. 4 Abdominal CT in AIP (parenchymal phase). The pancreatic parenchyma shows irregularly reduced enhancement. The marginal zone of the pancreas shows a capsule-like rim with more reduced enhancement

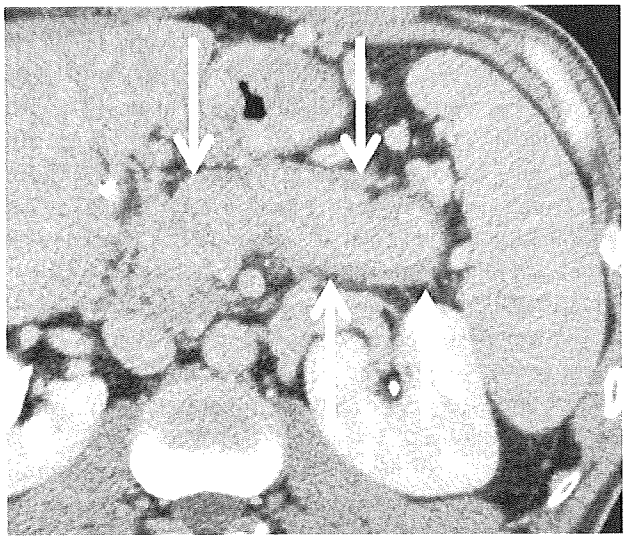

Fig. 5 Abdominal CT in AIP (delayed phase). The enhancement in the parenchyma and capsule-like rim become stronger in the delayed phase

absorption than pancreatic parenchyma of the lesion during the pancreatic parenchymal phase and shows a delayed enhancement pattern with dynamic CT [52]. While these findings may indicate the fibrosis of the rim of the lesion, the frequency of such findings varies depending on the report [52, 53]. This finding, however, is specific to AIP and is not seen in any other diseases. If a capsule-like rim is observed, the chance of the patient having AIP is high; a locally enlarged pancreas is an especially useful sign to distinguish AIP from pancreatic cancer [41] (refer to CQ-III-3).

Autoimmune pancreatitis exhibits many different CT images. Many AIP patients are elderly people; because their pancreases are atrophied to begin with, an enlarged pancreas from the disease is not seen clearly. In some cases, the pancreatic enlargement is verified only after steroid treatment by comparing the size before and after the treatment. There are cases where no abnormality other than a minor diffusely enlarged pancreas is found, partial dilatation of the main duct is pronounced, cystic lesions that appear to be pseudocysts are involved, or the pancreatic parenchyma shows obvious calcification. It must be realized that the absence of typical CT images can not be the reason to exclude AIP from consideration [41].

CQ-I-8. What are the characteristic findings of magnetic resonance imaging (MRI) in AIP?

- MR images of AIP show a diffusely enlarged pancreas with distinctive characteristics, such as a low signal on T1-weighted images and a delayed enhancement pattern on dynamic MR images (level of recommendation: A).
- A "capsule-like rim" reflects strong fibrosis of the peripancreatic lesion, which is highly specific for AIP (level of recommendation: A).
- At this moment, magnetic resonance cholangiopancreatography (MRCP) is not recommended for the accurate evaluation of the narrowing of the main pancreatic duct (level of recommendation: B).

Description MR images of AIP show a diffusely or locally enlarged pancreas, like other image examinations do [17]. The basic MR images used to examine AIP are T1-weighted images, T2-weighted images, and dynamic MRI; AIP lesions show a low signal on T1-weighted images (Fig. 6). The normal pancreas shows a higher signal than the liver on T1-weighted images; therefore, the pancreas showing a lower signal than the liver is judged to be abnormal. However, since a low signal is also seen in pancreatic cancer or normal chronic pancreatitis, it is not a characteristic finding of AIP [51]. The T2-weighted images may show a slightly low signal in strong fibrosis and a slightly strong signal in weak fibrosis [41] (Fig. 7). Meanwhile, the dynamic MR image shows a delayed enhancement pattern, as is seen in the dynamic CT [52] (refer to CQ-II-7).

Because a capsule-like rim is sometimes seen on MR images in patients with AIP, it can be used as a supplementary diagnostic tool for the disease; the capsule-like rim is extracted as a low signal on T2-weighted images reflecting strong fibrosis. Dynamic MR images show a delayed enhancement pattern [52, 53].

It is currently difficult to use MRCP pancreatic images for the diagnosis of AIP [2]. However, recent significant progress in MRI technologies has made it possible to

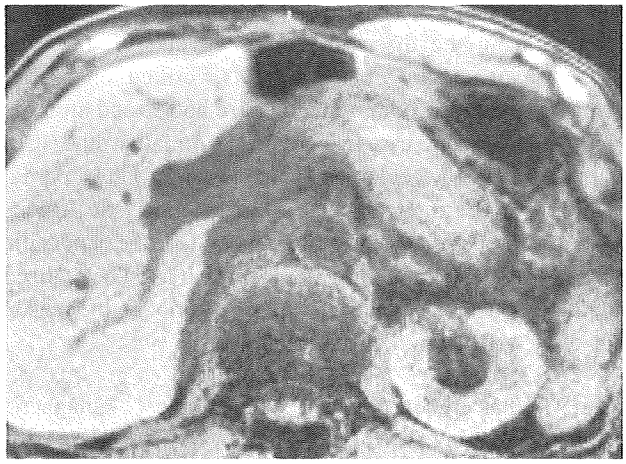

Fig. 6 T1-weighted MRI images of the pancreas. Swollen pancreas in the tail shows a lower signal than the liver

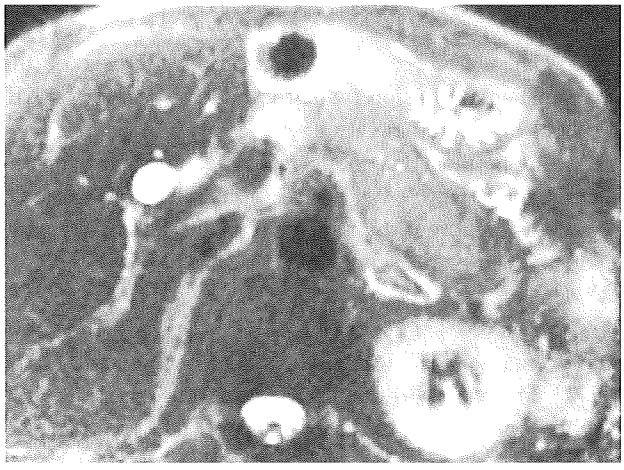

Fig. 7 T2-weighted MRI images of the pancreas. Swollen pancreas in the body and tail shows a higher signal than the liver

extract images of the normal main pancreatic duct by 3-D MRCP without fail (Fig. 8). Therefore, if the main pancreatic duct is not extracted by 3-D MRCP, it may be an indication of prominent stenosis. Since further image quality improvement can be expected for MRCP with the introduction of 3-Stela MRI technology, it is possible that MRCP will be used to evaluate the therapeutic effect or monitor the progress of AIP in the future [41].

CQ-I-9. What are the characteristic findings of positron emission tomography (PET) and gallium-scintigram in AIP?

- Patients with AIP show accumulation of Ga-67 and FDG in the pancreatic and extra-pancreatic lesions, which disappear shortly after steroid treatment. The characteristic accumulation pattern and kinetics in the pancreatic and extra-pancreatic lesions after the steroid treatment can be used for the diagnosis of the disease (level of recommendation: B).

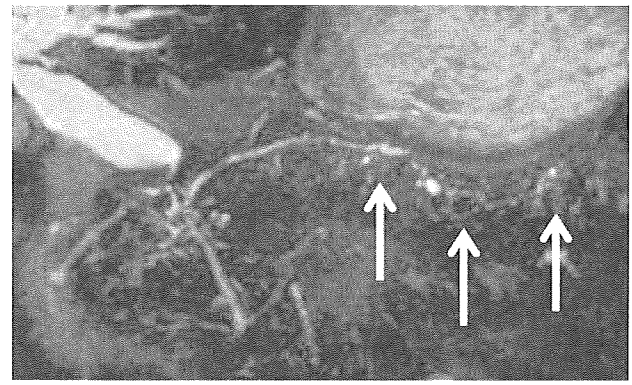

Fig. 8 3-D MRCP narrowing of the main pancreatic duct in the body and tail (*arrows*) is seen

Description Gallium scintigraphy shows accumulation of gallium citrate (Ga-67) in localized pancreatic lesions in patients with AIP; in the past, some such cases were diagnosed as pancreatic malignant lymphoma [54]. The accumulation of Ga-67 is found not only in pancreatic lesions, but also in extra-pancreatic lesions such as in the hilar lymph nodes, lacrimal gland, or salivary gland. The accumulation is positive at about 70% for pancreatic lesions and hilar lymph nodes, and about 20% for lacrimal/salivary glands. The accumulation reflects high disease activity and disappears quickly after steroid treatment [55]. Therefore, the distribution of Ga-67 accumulation and the kinetics after steroid treatment can be used for the diagnosis of the disease.

FDG-PET (fluorine-18 fluorodeoxyglucose positron emission tomography) is useful for the diagnosis of pancreatic cancer. However, high accumulation of FDG (90% or higher) is also observed in patients with AIP; the accumulation corresponds to the prominent inflammatory cell infiltration areas [56–59]. FDG also accumulates in extra-pancreatic lesions such as in the salivary gland, a wide range of lymph node lesions, retroperitoneal fibrosis, or the prostate gland [60–62]. Accumulated FDG in pancreatic or extra-pancreatic areas disappears quickly after steroid treatment [59]. The following criteria are useful in distinguishing AIP from pancreatic cancer: extensive or multiple accumulations of FDG in the pancreas, or distinctive accumulation in extra-pancreatic lesions in the salivary gland, retroperitoneal fibrosis, or prostate gland [59, 60]. It is not clear at this point whether the disappearance of FDG following steroid treatment can be used as a differential diagnostic criterion since there have been no reports on pancreatic cancer in this regard.

CQ-I-10. What are the characteristic findings of endoscopic retrograde cholangiopancreatography (ERCP) in AIP?

- Endoscopic retrograde cholangiopancreatography shows narrowing of the main pancreatic duct characteristic to AIP (level of recommendation: A).
- Autoimmune pancreatitis may be associated with stenosis of the bile duct (level of recommendation: A).

Description Endoscopic retrograde cholangiopancreatography shows narrowing of the main pancreatic duct, which is characteristic of AIP; this finding is used as the basis for diagnosis [60–79]. Narrowing of the pancreatic duct is usually diagnosed from ERCP images. The narrowing of the pancreatic duct is defined as being: "unlike the obstruction or stenosis, the narrowing extends to a certain degree and the duct diameter is smaller (narrower) than normal, with some irregularities" [17, 71, 75] (Fig. 9).

The Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006 states that diagnosis of the disease requires pancreatic images showing "the distinctive narrowing of the main pancreatic duct," where the narrowing may be diffuse or local. The typical case shows the narrowing extending over one-third of the entire pancreatic duct (Fig. 10). Even when the narrowing is localized to less than one-third of the entire duct, in most cases no significant dilatation is observed above the narrowed area upstream of the main duct [71, 74] (Fig. 11).

The range of narrowing varies: in a typical case the narrowing extends over one-third of the entire main pancreatic duct; there are, however, other cases where the narrowing is localized to less than one-third, or the lesions are located at the head and tail of the duct [74, 75]. If the narrowing is localized, it is necessary to consider differentiating the disease from pancreatic cancer [72, 73, 75].

About 80% of patients with AIP show stenosis of the bile duct [64–68]. Although most of the stenosis is found in the lower bile duct, it can also be detected in the extra- or intra-hepatic bile ducts [64–68].

CQ-I-11. What are the characteristic histopathological findings in AIP?

- Histopathological findings of AIP are characterized by the fibrosis with strong lymphoplasmacytic infiltration that gives rise to distinctive inflammatory findings, such as circumferential inflammation around duct epithelium and obstructive phlebitis (level of recommendation: A).
- A number of infiltrations of IgG4-positive plasma cells are observed in the lesions (level of recommendation: A).

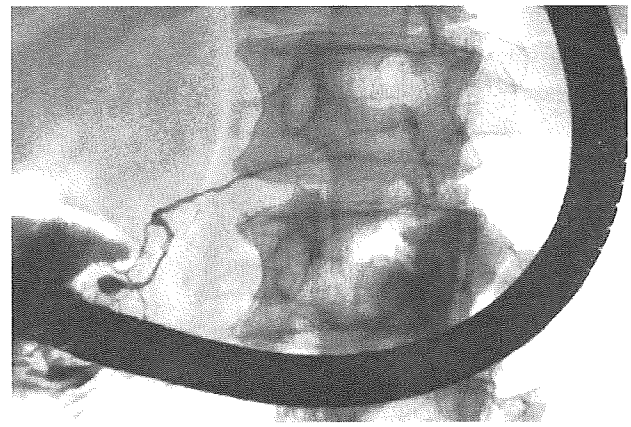

Fig. 9 Pancreatogram in AIP (diffuse). Diffusely irregular narrowing of the main pancreatic duct is seen from the pancreas head to tail

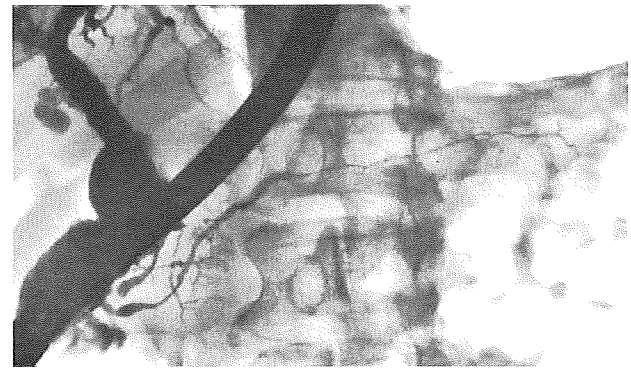

Fig. 10 Pancreatogram of AIP (segmental). Irregular narrowing of the main pancreatic duct is seen from the pancreas body to tail

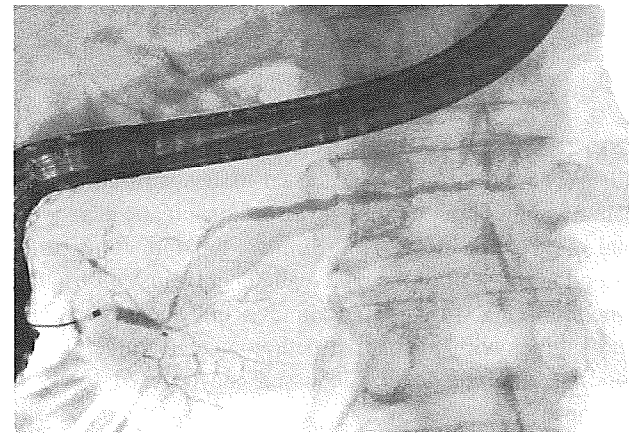

Fig. 11 Pancreatogram of AIP (focal). Irregular narrowing of the main pancreatic duct is seen in the pancreas head without dilation of the upper stream

Description The histological image of AIP is called "lymphoplasmacytic sclerosing pancreatitis (LPSP)," which is characterized by the fibrosis associated with prominent infiltration of lymphocytes and plasmacytes

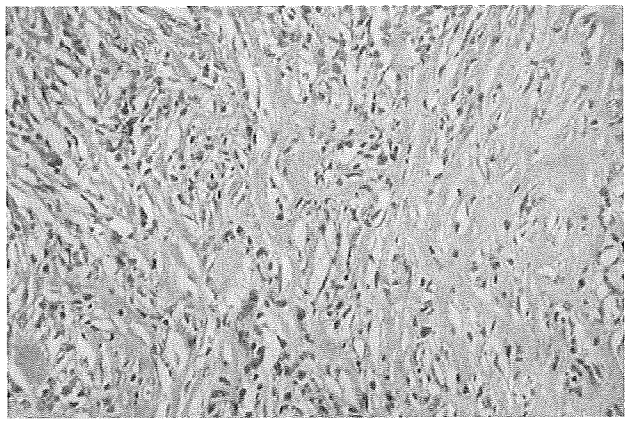

Fig. 12 Histopathological findings in AIP (LPSP). Fibrosis, prominent infiltration of lymphocytes and plasmacytes (lymphoplasmacytic sclerosing pancreatitis: LPSP) are seen

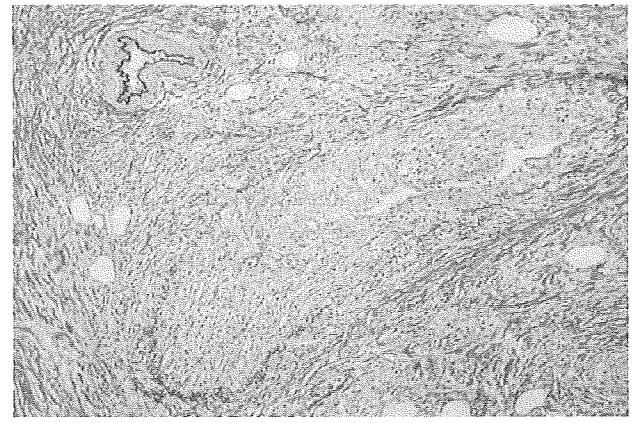

Fig. 14 Histopathological findings in AIP (elastica van Gieson staining). Stenosis or obstruction of vessels with infiltration of lymphocytes and plasmacytes, and fibrosis (obliterative phlebitis) is seen

Fig. 13 Histopathological findings in AIP. Circumferential inflammation of LPSP around duct epithelium is seen

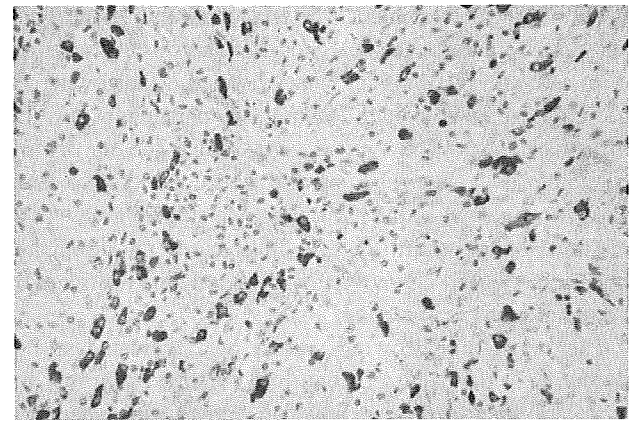

Fig. 15 Histopathological findings in AIP (immunostaining). Numerous IgG4-positive cells in LPSP are seen. Ratio of IgG4 to IgG1 is usually high in LPSP

[20, 21, 80–85] (Fig. 12). Such inflammation, observed diffusely in the pancreas or the fat tissues surrounding the pancreas, involves various levels of pancreatic parenchymal destruction (Fig. 13). Similar inflammations often extend to the wall of the pancreatic duct, veins (obstructive phlebitis) (Fig. 14), or the common bile duct (sclerosing cholangitis) with distinctive pathological features. Therefore, the excised pancreatic tissue can be used solely to diagnose AIP.

Immunostaining of the lesions shows a number of IgG4-positive plasmacytes [83, 84, 86, 87] (Fig. 15). There has been an indication that the ratio of IgG4-positive plasmacytes to IgG subclass antibodies is increased. However, no consensus has been established yet as to how many or what percentage of IgG4-positive plasmacytes must be observed for the diagnosis of AIP. Because there have been a few cases reported where IgG4-positive plasmacytes appear in patients with pancreatic cancer or alcoholic pancreatitis, IgG4-positive plasmacytes cannot be used as the sole basis for the diagnosis of AIP [81, 84].

In Europe and the US, there have been reports of chronic pancreatitis characterized by the infiltration of neutrophils into the epithelium of the main pancreatic duct, which is referred to as either "idiopathic duct-centric chronic pancreatitis" or "autoimmune pancreatitis with granulocyte epithelial lesions" [19–21, 78, 81, 84, 85]. A number of pathologists in Europe and the US believe that this form of pancreatitis should be included in AIP. However, because such pancreatitis is seen more in younger people with no gender difference, is associated with inflammatory bowel disease, and does not show abnormal IgG4, IgG or autoantibodies, it is proposed to be different from lymphoplasmacytic sclerosing pancreatitis (LPSP). The original version of diagnostic criteria proposed by the Mayo Clinic clearly define that LPSP is the only AIP [85, 87]; we take the same stand here in Japan [26]. A consensus has

Table 4 Comparison of diagnostic criteria for AIP

	Revised JPS criteria 2006	Mayo criteria (HISORt)	Revised Korean criteria	Asian criteria
ERCP with CT/MRI	Mandatory ERCP	ERCP/MRCP	ERCP/MRCP	Mandatory ERCP
Blood	g-glb/IgG/IgG4/autoAb	IgG4	IgG/IgG4/autoAb	IgG/IgG4/autoAb
Histology	LPSP	LPSP/IgG4 + cell (>10/HPF)	LPSP/IgG4 + cell (>10/HPF)	LPSP IgG4 + cell in the resected pancreas
Steroid response	No	Yes	Yes	Yes
Extrapancreas	Exclude (suggestive AIP)	Include	Include	Exclude (suggestive AIP)

been reached to classify LPSP as AIP; however, further discussion is necessary to clarify the significance of IDCP that involves the infiltration of neutrophils. It is desirable not to include IDCP in AIP at this moment.

CQ-I-12. How to diagnose AIP?

- A comprehensive diagnosis must be performed based on pancreatic imaging, serological, and histopathological findings. In Japan, as defined by the Clinical Diagnostic Criteria 2006, the diagnosis of AIP requires specific image findings, along with serological and/or histopathological evidence (level of recommendation: A).
- The presence of extra-pancreatic lesions may suggest the possibility of AIP (level of recommendation: A).

Description The Japan Pancreas Society took the initiative and proposed the world's first clinical diagnostic criteria for autoimmune pancreatitis in 2002 [86, 89], which was then revised in 2006 by the joint efforts of the Ministry of Health and Welfare Research Committee for Intractable Pancreas Disease and the Japan Pancreas Society [17, 69, 72] (see Appendix). The basic concepts were established based on the following minimal consensus: (1) the criteria apply to the diagnosis performed by not only the pancreatologists or gastroenterologists but also the general clinicians; (2) the criteria are used to distinguish and exclude malignant disorders such as pancreatic cancer or bile duct cancer as much as possible; (3) the criteria are applied, pathologically, to the clinical cases showing evidence of lymphoplasmacytic sclerosing pancreatitis (LPSP); (4) the criteria are used to diagnose pancreatic lesions, although the disease may be systemic; and (5) diagnostic trials of steroid therapy must be avoided. The basic idea is to perform the diagnosis based on (1) specific image findings (a mandatory requirement), along with (2) serological and/or (3) histopathological evidence [17, 87, 90].

According to the Clinical Diagnostic Criteria 2006, the pancreatic images specific to AIP can be confirmed retrospectively from the time of diagnosis. Although some patients with pancreatic cancer show high levels of IgG4, patients with AIP show significantly higher levels of serum IgG4 with much higher rates; the diagnostic sensitivity of IgG4 levels for AIP is high [30, 38]. Besides in Japan, diagnostic criteria for AIP have also been proposed by the Mayo Clinic in the US [88] and in South Korea [76, 91] (Table 4). The Asian Diagnostic Criteria were proposed jointly by researchers in Japan and South Korea [92] (Table 5). Use of the response to steroid treatment as a diagnostic option can only be implemented by specialists; in Japan, it is recommended that the diagnosis should be made based on the Diagnostic Criteria 2006. The differences between Japan and Western countries in the diagnosis of AIP are the observation of ERCP images, response to steroid treatment, and extra-pancreatic lesions [93] (Fig. 16). Although the presence of extra-pancreatic lesions is not listed as a diagnostic tool in the Diagnostic Criteria 2006

Table 5 Asian criteria

Criterion I. Imaging (both required)
Imaging of pancreatic parenchyma
Diffusely/segmentally/focally enlarged gland, occasionally with mass and/or hypoattenuated rim
Imaging of pancreaticobiliary ducts
Diffuse/segmental/focal pancreatic ductal narrowing, often with the stenosis of bile duct
Criterion II. Serology (one required)
Elevated level of serum IgG or IgG4
Detected autoantibodies
Criterion III. Histopathology of pancreatic biopsy lesion
Lymphoplasmacytic infiltration in fibrosis, common with abundant IgG4-positive cell infiltration
Option: response to steroids
Diagnostic trial of steroid therapy could be done carefully in patients fulfilling criterion 1 alone with negative workup for pancreatobiliary cancer by experts
Diagnosis of AIP is made when any two criteria including criterion I are satisfied or histology of lymphoplasmacytic sclerosing pancreatitis is present in the resected pancreas

Ref [92]

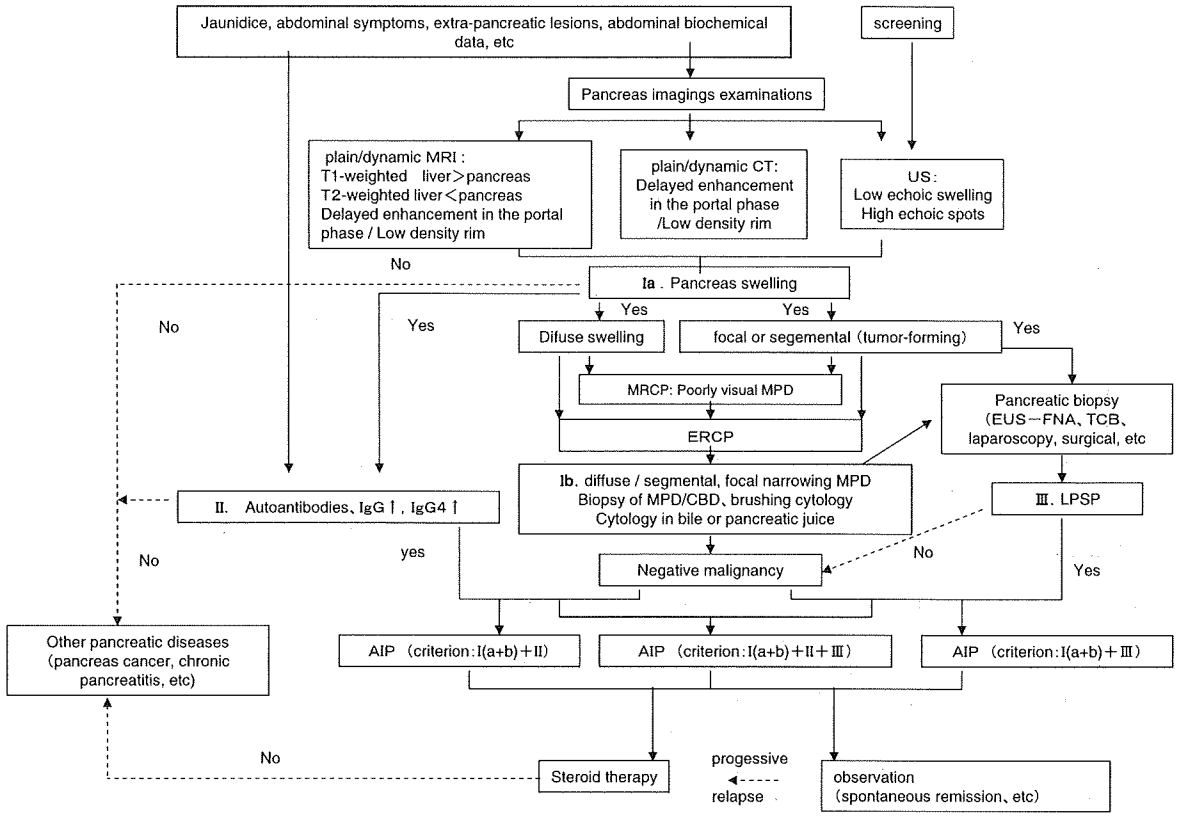

Fig. 16 Algorithm of diagnosis and management of AIP by the Japanese Diagnostic Criteria 2006

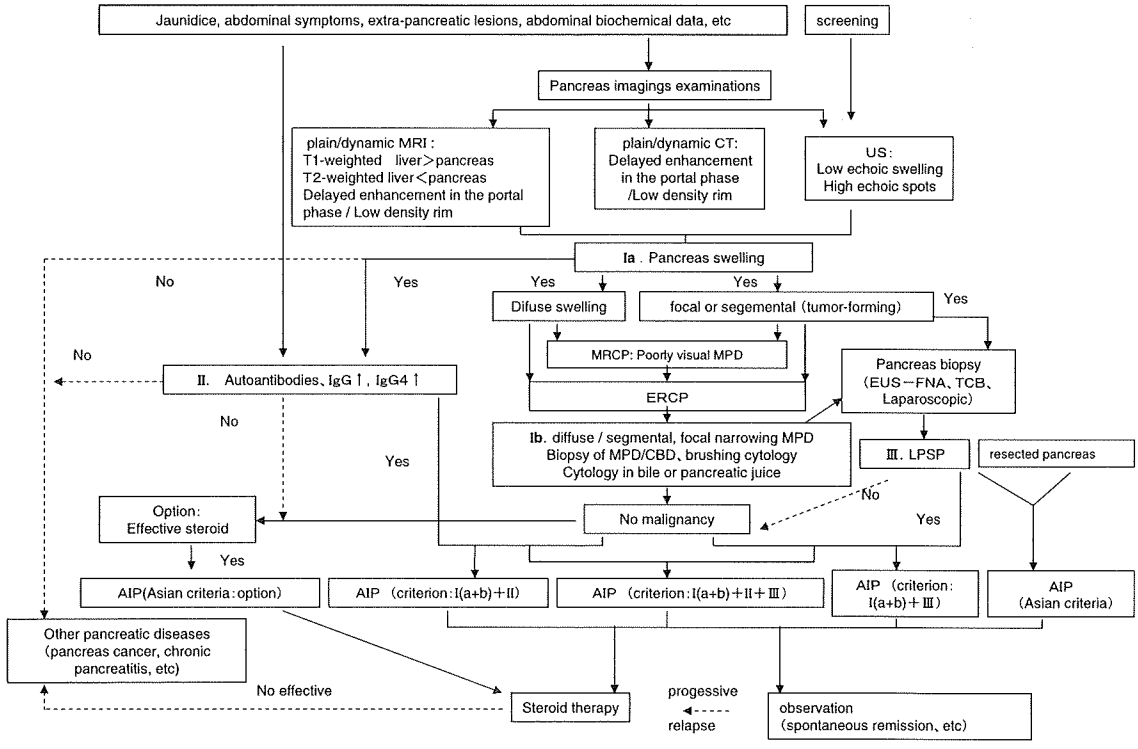

Fig. 17 Algorithm of diagnosis and management of AIP by Asian diagnostic criteria

or the Asian Diagnostic Criteria, a complete examination is important because the presence of extra-pancreatic lesions may be indicative of AIP (Fig. 17). A report has shown that if infiltration of IgG4-positive plasmacytes is observed in the biopsy of the duodenal papillary mucosa, the chance of the patient having AIP is high [94].

CQ-I-13. Can the response to steroid therapy be used for diagnosis?

- If a patient responds to steroid treatment, it indicates that he/she may have AIP. However, because response to steroid treatment does not exclude the possibility of the patient having pancreatic cancer, facile diagnostic treatment is not recommended (level of recommendation: B).

In Japan, the effect of steroid treatment on pancreatic and extra-pancreatic lesions are excluded from the AIP diagnostic criteria based on the following reasons: (1) autoimmune hepatitis is the only autoimmune disease that uses the effect of steroid treatment as a diagnostic criteria; (2) the clinical significance is different between the case of autoimmune hepatitis requiring differentiation from chronic hepatitis of other pathogenesis and the case of AIP requiring differentiation from pancreatic cancer or bile duct cancer; (3) no evidence exists to show that the use of steroids does not affect the success of an operation or the long-term prognosis; (4) there is a danger that therapeutic diagnosis by steroid administration may be used as an easy solution to differentiate AIP from malignant tumors such as pancreatic cancer; (5) the standards were established for not only pancreatologists, but also gastroenterologists or general physicians; (6) in Japan, the objective of the diagnostic criteria is not so much to find AIP, but rather to eliminate the misdiagnosis of diseases with malignant tumors as often as possible; (7) there have been reports of AIP associated with pancreatic cancer [17]. In contrast, the diagnostic criteria proposed by South Korea [88, 91] and the Mayo Clinic [85, 88] include response to steroid treatment. The Asian Diagnostic Criteria proposed jointly by Japan and South Korea in 2008 [89, 92] state that if the possibility of pancreatic cancer is excluded by a reliable exclusive diagnosis using endoscopic ultrasound guided-fine needle aspiration (EUS-FNA) or the like, the effect of steroid treatment may be used as a diagnostic criterion. Meanwhile, there have been reports of pancreatic cancers associated with AIP (refer to treatment, prognosis CQ-IV-10, 11). Therefore, if a patient responds to steroid treatment, it may suggest that he/she has AIP; however, since it does not exclude malignant tumors such as pancreatic cancer or deny the association of pancreatic cancer, facile diagnostic treatment must be avoided [17, 90, 93].

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Appendix: Clinical Diagnostic Criteria of Autoimmune Pancreatitis (revised proposal) (proposed by the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor, and Welfare, and Japan Pancreas Society)

It is suspected that the pathogenesis of autoimmune pancreatitis (AIP) involves autoimmune mechanisms. Currently, the main cases observed for characteristic findings of AIP are the diffuse enlargement of the pancreas and the narrowing of the pancreatic duct, which are associated with the findings that are suggestive of the involvement of autoimmune mechanisms such as increased levels of γ-globulin and IgG, the presence of autoantibodies, and the effective response to steroid therapy. In some cases, AIP shows extra-pancreatic manifestations such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, suggesting that AIP is a systemic disease. In Western countries, AIP is occasionally observed in association with ulcerative colitis and the formation of tumors, which suggests that it is somewhat contrary to the definition and concept of the disease adopted in Japan.

Patients with AIP often show discomfort in the epigastrium, obstructive jaundice due to bile duct stricture, and diabetes mellitus. AIP is more common in middle-aged and elderly males. Although the long-term prognosis of the disease is not clear, pancreatic stone formation has been found in some cases.

When diagnosing AIP, it is important to differentiate it from neoplastic lesions, such as pancreatic or biliary cancers, and to avoid facile therapeutic diagnosis by steroid administration. The present criteria, therefore, are based on the minimum consensus about AIP to avoid misdiagnosing pancreatic or biliary cancer as far as possible, but not for screening AIP.

Clinical diagnostic criteria

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).
2. High serum γ-globulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.

3. Marked inter-lobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the peri-ductal area, occasionally with lymphoid follicles in the pancreas.

For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3.

Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or 3, are fulfilled.

However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

Imaging studies

1. Diffuse or localized swelling of the pancreas

Abdominal ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI) show diffuse or localized swelling of the pancreas.

(a) The US feature of pancreatic swelling is usually hypoechoic, sometimes with scattered echogenic spots.
(b) Contrast-enhanced CT generally shows delayed enhancement similar to a normal pancreas with sausage-like enlargement and/or a capsular-like low density rim.
(c) MRI shows diffuse or localized enlargement of the pancreas with lower density in T1-weighed images and higher density in T2-weighed images compared with each of the liver images.

2. Narrowing of the pancreatic duct

The main pancreatic duct shows diffuse or localized narrowing.

(a) Unlike obstruction or stricture, narrowing of the pancreatic duct extends over a larger range where the duct is narrowed with irregular walls. In typical cases, more than one-third of the entire length of the pancreatic duct is narrowed. Even in cases where the narrowing is segmental and extends to less than one-third, the upper stream of the main pancreatic duct rarely shows notable dilatation.
(b) When the pancreatic images do show typical findings but laboratory data do not, there is a possibility of AIP. However, without histopathological examinations, it is difficult to distinguish AIP from pancreatic cancer.
(c) To obtain images of the pancreatic duct, it is necessary to use endoscopic retrograde cholangiopancreatography (ERCP) and additionally the direct images taken during the operation or on specimens. Currently, it is difficult to depend on magnetic resonance cholangiopancreatography (MRCP) for the diagnosis.

3. The pancreatic image findings described above may be observed retrospectively from the time of diagnosis.

Laboratory data

1. In many cases, patients with AIP show increased levels of serum γ-globulin, IgG, or IgG4. High serum IgG4, however, is not specific to AIP, since it is also observed in other disorders such as atopic dermatitis, pemphigus, or asthma. Currently, the significance of high serum IgG4 in the pathogenesis and the pathophysiology of AIP is unclear.
2. Although increased levels of serum γ-globulin (≥2.0 g/dl), IgG (≥1,800 mg/dl), and IgG4 (≥135 mg/dl) may be used as criteria for the diagnosis of AIP, further studies are necessary. Health insurance in Japan does not cover the cost of measuring serum IgG4 levels in AIP.
3. Autoantibodies such as antinuclear antibody and rheumatoid factor are often detected in patients with AIP.

Pathohistological findings of the pancreas

1. Fibrotic changes associated with prominent infiltration of lymphocytes and plasma cells, occasionally with lymphoid follicles, are observed. In many cases, infiltration of IgG4-positive plasma cells is observed.
2. Lymphocytic infiltration is prominent in the peri-ductal area, together with and inter-lobular fibrosis, occasionally including intra-lobular fibrosis.
3. Inflammatory cell infiltration involves the ducts and results in diffuse narrowing of the pancreatic duct with atrophy of acini.
4. Obliterative phlebitis is often observed.
5. Although fine-needle biopsy under ultrasonic endoscopy (EUS-FNA) is useful in differentiating AIP from malignant tumors, the diagnosis may be difficult if the specimen is too small.

Endocrine and exocrine function of the pancreas

Some patients with AIP show a decline of exocrine pancreatic function and diabetes mellitus. In some cases, steroid therapy improves endocrine and exocrine pancreatic dysfunction.

Relationship to extra-pancreatic lesions and other associated disorders

AIP may be associated with sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Most AIP

patients with sclerosing sialadenitis are negative for both anti-SSA and anti-SSB antibodies, which may suggest that AIP is different from Sjogren's syndrome. Scleroing cholangitis-like lesions accompanying AIP and primary sclerosing cholangitis (PSC) respond differently to steroid therapy and follow different prognoses, which suggests that they are not the same disorder. Further studies are necessary to clarify the role of autoimmune mechanisms in AIP.

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