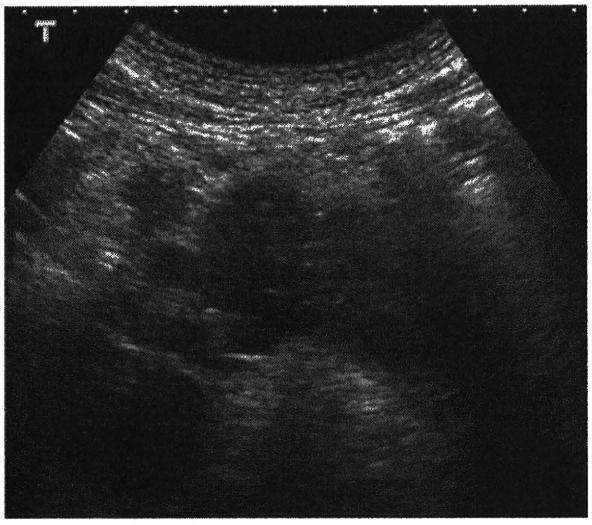

Fig. 1 Abdominal ultrasonography in AIP (diffuse type). A diffusely enlarged pancreas appears as a low echo area with high echoic spots and has a so-called "sausage-like" appearance

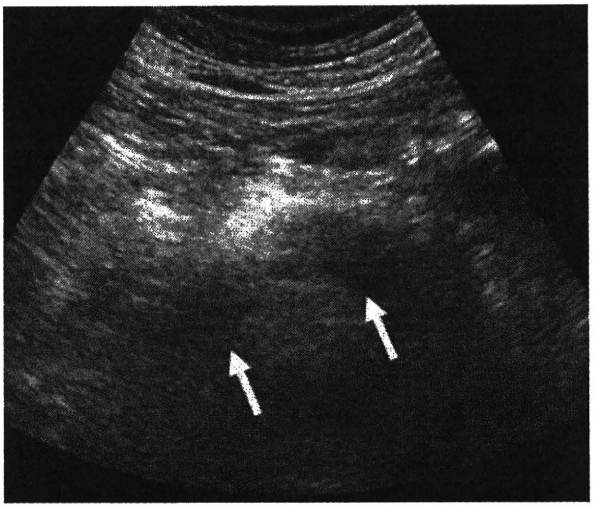

Fig. 3 Abdominal ultrasonography in AIP (multiple mass forming). Low echoic masses were observed in the pancreas head and body (*arrows*)

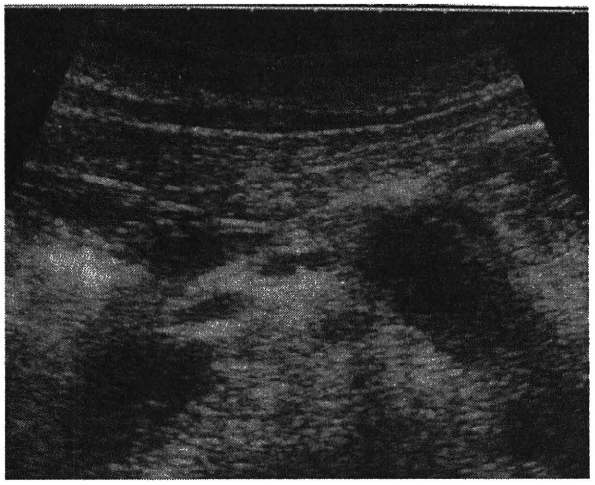

Fig. 2 Duct-penetrating sign by abdominal ultrasonography in AIP (tumor-forming type). The main duct is found to penetrate through the mass (duct-penetrating sign) in the case of a locally enlarged pancreas, which may be a useful sign for the differential diagnosis against pancreatic cancer

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

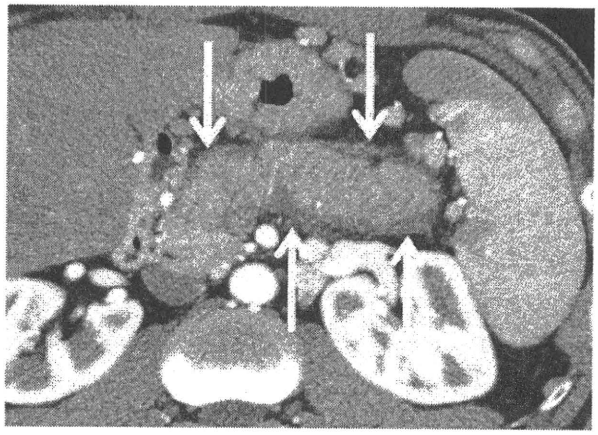

Fig. 4 Abdominal CT in AIP (parenchymal phase). The pancreatic parenchyma shows irregularly reduced enhancement. The marginal zone of the pancreas shows a capsule-like rim with more reduced enhancement

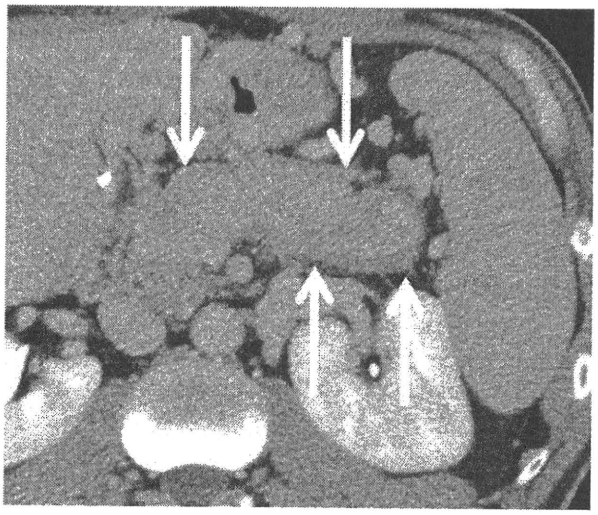

Fig. 5 Abdominal CT in AIP (delayed phase). The enhancement in the parenchyma and capsule-like rim become stronger in the delayed phase

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

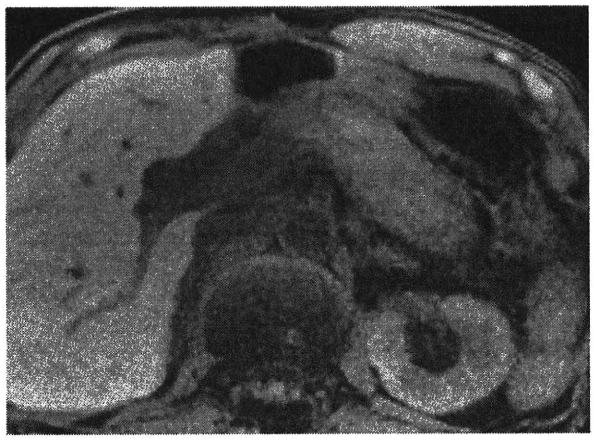

Fig. 6 T1-weighted MRI images of the pancreas. Swollen pancreas in the tail shows a lower signal than the liver

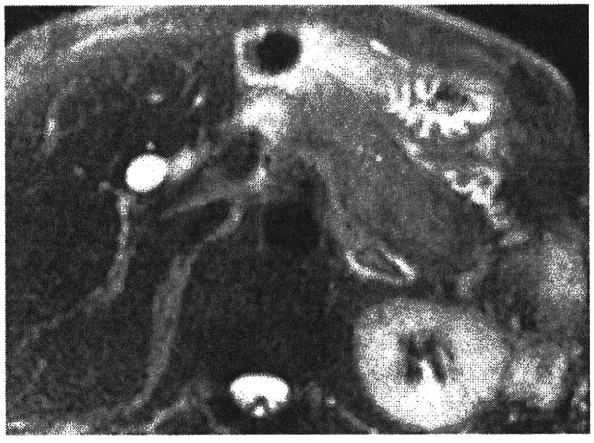

Fig. 7 T2-weighted MRI images of the pancreas. Swollen pancreas in the body and tail shows a higher signal than the liver

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).

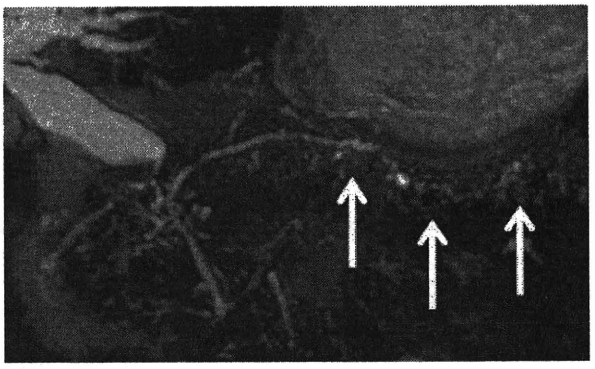

Fig. 8 3-D MRCP narrowing of the main pancreatic duct in the body and tail (*arrows*) is seen

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).

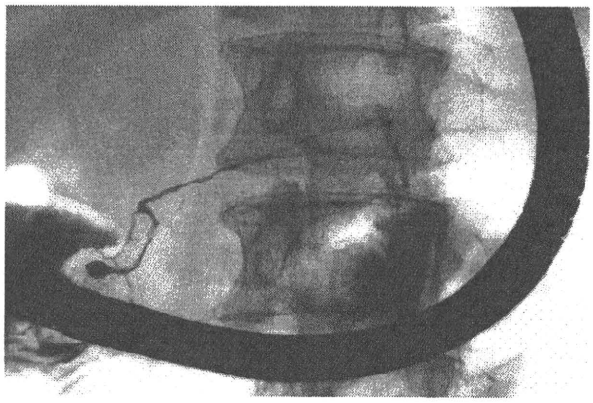

Fig. 9 Pancreatogram in AIP (diffuse). Diffusely irregular narrowing of the main pancreatic duct is seen from the pancreas head to tail

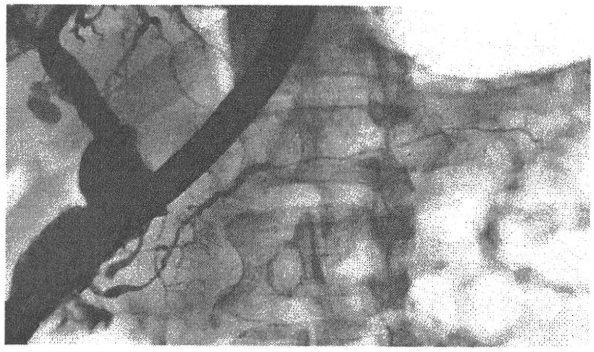

Fig. 10 Pancreatogram of AIP (segmental). Irregular narrowing of the main pancreatic duct is seen from the pancreas body to tail

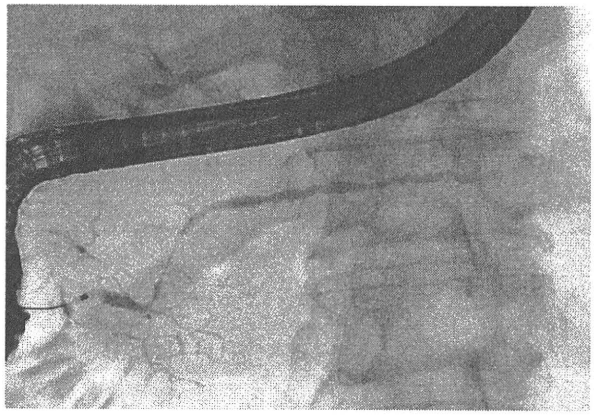

Fig. 11 Pancreatogram of AIP (focal). Irregular narrowing of the main pancreatic duct is seen in the pancreas head without dilation of the upper stream

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

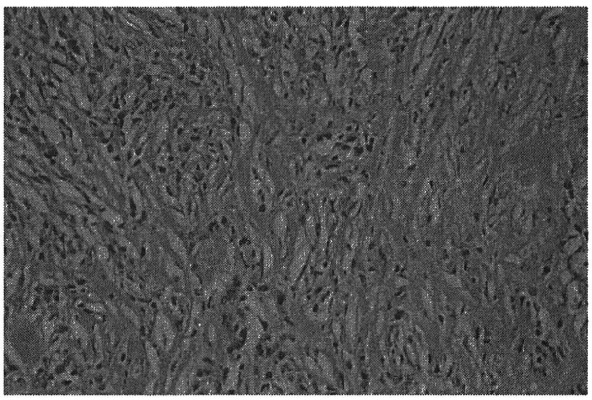

Fig. 12 Histopathological findings in AIP (LPSP). Fibrosis, prominent infiltration of lymphocytes and plasmacytes (lymphoplasmacytic sclerosing pancreatitis: LPSP) are seen

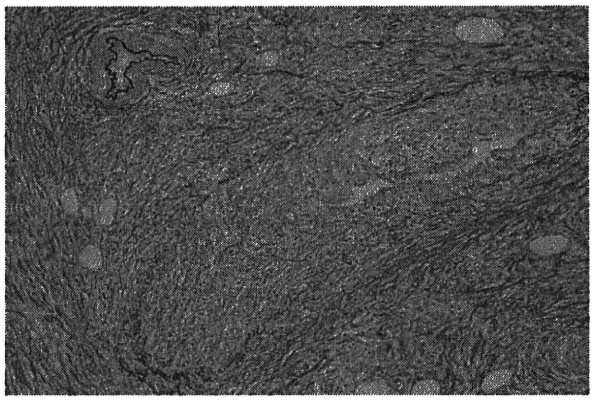

Fig. 14 Histopathological findings in AIP (elastica van Gieson staining). Stenosis or obstruction of vessels with infiltration of lymphocytes and plasmacytes, and fibrosis (obliterative phlebitis) is seen

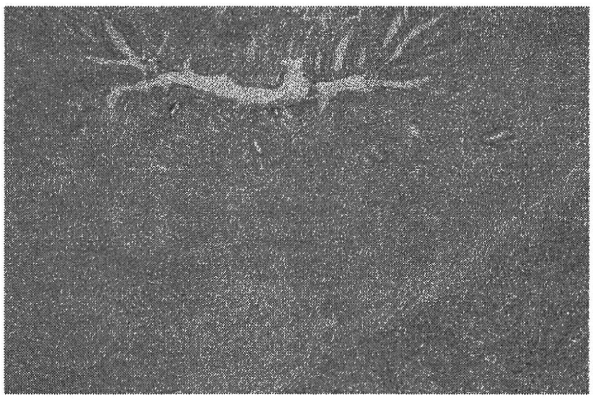

Fig. 13 Histopathological findings in AIP. Circumferential inflammation of LPSP around duct epithelium is seen

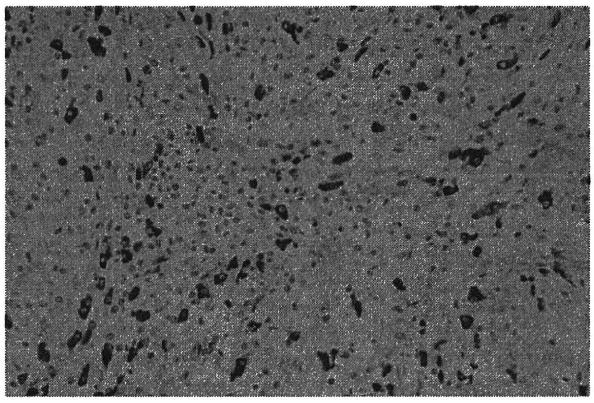

Fig. 15 Histopathological findings in AIP (immunostaining). Numerous IgG4-positive cells in LPSP are seen. Ratio of IgG4 to IgG1 is usually high in LPSP

[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]

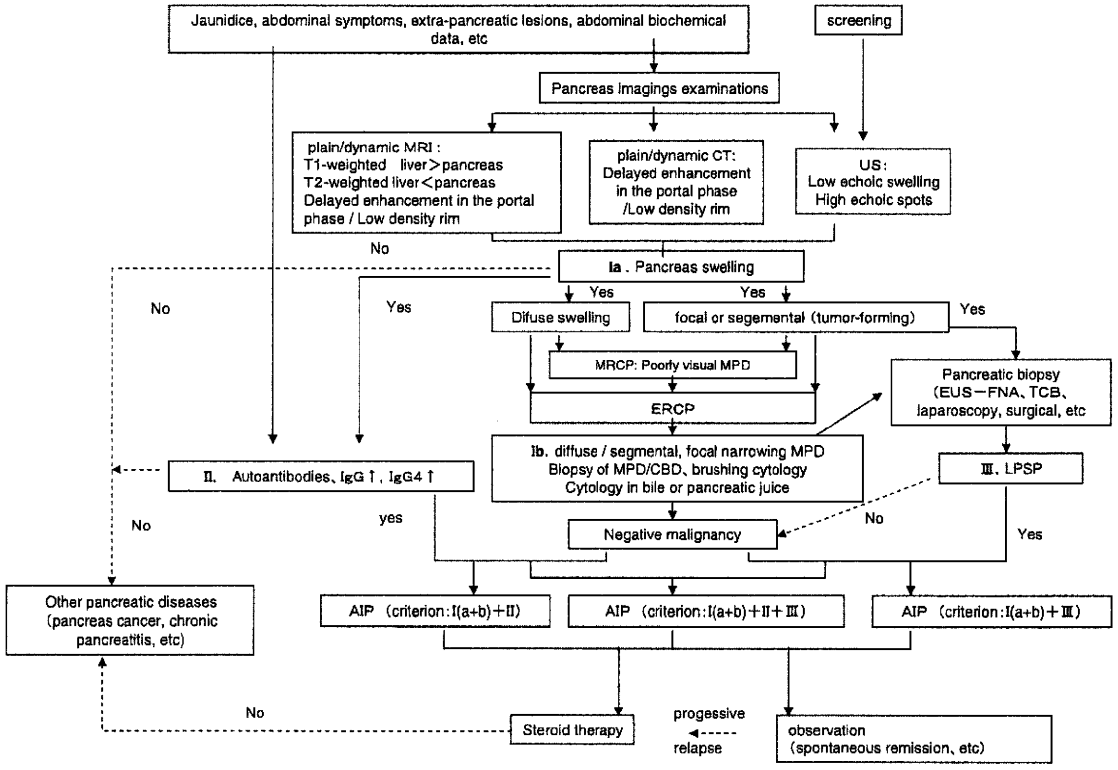

Fig. 16 Algorithm of diagnosis and management of AIP by the Japanese Diagnostic Criteria 2006

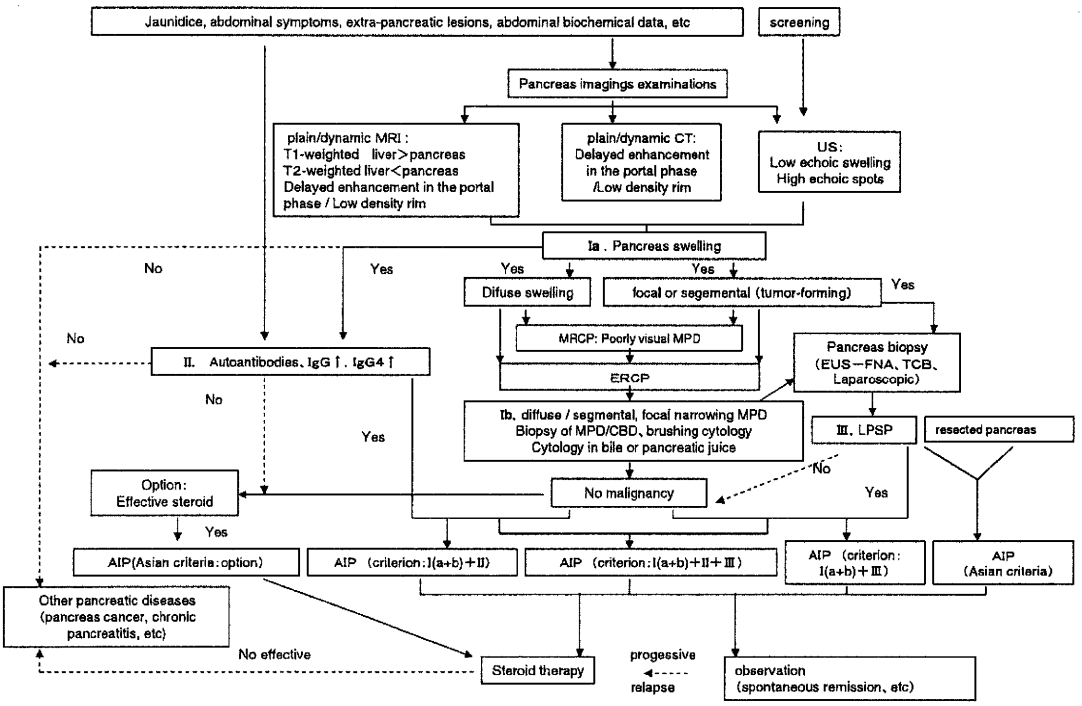

Fig. 17 Algorithm of diagnosis and management of AIP by Asian diagnostic criteria

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].

Acknowledgment This study was supported by the grant-in-aid for the Intractable Pancreatic Diseases, supported by the Ministry of Health, Labor, and Welfare of Japan.

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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REVIEW

Japanese consensus guidelines for management of autoimmune pancreatitis: II. Extrapancreatic lesions, differential diagnosis

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II. Extrapancreatic lesions, differential diagnosis

II-1. Extrapancreatic lesions

CQ-II-1-1. What kind of extrapancreatic lesions are complicated with AIP?

- A variety of extrapancreatic lesions are reported to be complicated with AIP. Among those cited are close association with lachrymal and salivary gland lesions, hilar lymphadenopathy, interstitial pneumonitis, sclerosing cholangitis, retroperitoneal fibrosis, and tubulointerstitial nephritis.

This article is the second of a three-article series on the Japanese consensus guidelines. Please see the first article in the series (doi:10.1007/s00535-009-0184-x) for the abstract, keywords, and names of committee members.

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Description A variety of extrapancreatic lesions are reported to be complicated with AIP, and close associations have been pointed out with lachrymal and salivary gland lesions (Fig. 1) [1], hilar lymphadenopathy [2], sclerosing cholangitis [3, 4], retroperitoneal fibrosis (Fig. 2) [5], and tubulointerstitial nephritis [6]. Associations were also reported with hypophysitis [7], chronic thyroiditis [8], and prostatitis [9]. Other extrapancreatic involvements have been reported in a few cases [10–12]. Though it is not certain that all of them have a relation with AIP, extrapancreatic lesions are prevalent in the systemic organs (Table 1) [7–12], suggesting that AIP may be a member of IgG4-related diseases. The extrapancreatic lesions appear synchronously or metachronously with the pancreatic lesion(s), share the same pathological conditions, and show favorable response to corticosteroid therapy; these characteristics indicate a common pathophysiological background. The lesions are usually detected by image tests and blood tests (CT, MRI, gallium scintigraphy, FDG-PET, and hormone assay); however, these should be confirmed by histological findings. Extrapancreatic lesions sometimes mimic, or are misdiagnosed as, primary lesions of the corresponding organs: lachrymal and salivary gland lesions for Sjögren's syndrome, respiratory lesions for sarcoidosis, and sclerosing cholangitis for primary sclerosing cholangitis (PSC). Therefore, it is necessary to differentiate between IgG4-related diseases and inherent diseases of the corresponding organs. When the pancreatic lesion is obscured, it may be difficult to detect these presumably IgG4-related extrapancreatic lesions. However, recognition of these extrapancreatic lesions should also aid in the correct diagnosis of AIP.

CQ-II-1-2. How are extrapancreatic lesions diagnosed?

- The diagnosis of extrapancreatic lesions complicated with AIP is based on clinical findings that suggest close

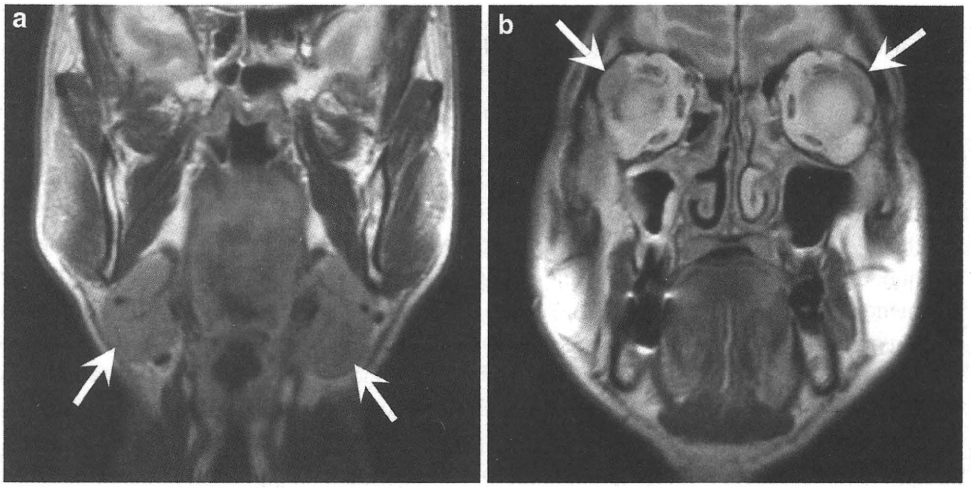

Fig. 1 T2-weighted MRI images of salivary gland [submandibular gland (**a**) and lachrymal gland (**b**)] swellings in an AIP patient. *Arrows* indicate swollen salivary and lachrymal glands. Homogeneous signal was shown by the submandibular gland, although vessels are recognized in it

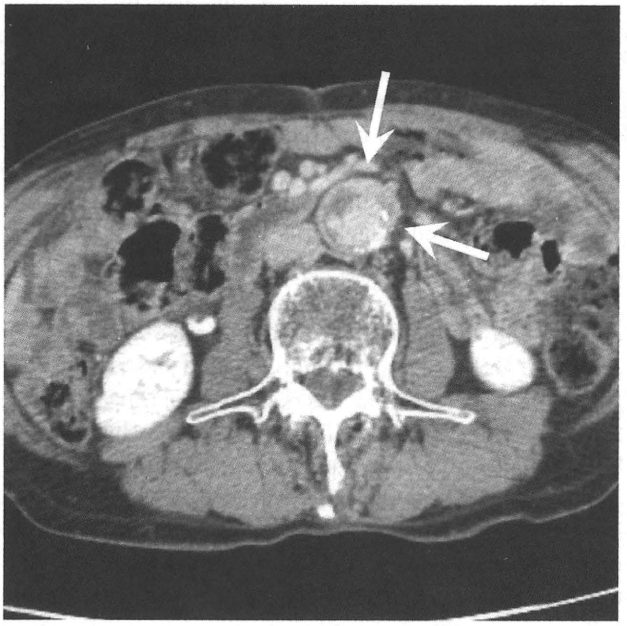

Fig. 2 CT shows retroperitoneal fibrosis around the aorta in an AIP patient. Calcification is seen in the aortic wall, and a soft tissue mass (*arrow*) surrounds the aorta

Table 1 Extrapancreatic lesions complicated with autoimmune pancreatitis

Close association
Lachrymal gland inflammation
Sialoadenitis
Hilar lymphadenopathy
Interstitial pneumonitis
Sclerosing cholangitis
Retroperitoneal fibrosis
Tubulointerstitial nephritis
Possible association
Hypophysitis
Autoimmune neurosensory hearing loss
Uveitis
Chronic thyroiditis
Pseudotumor (breast, lung, liver)
Gastric ulcer
Swelling of papilla of Vater
IgG4 hepatopathy
Aortitis
Prostatitis
Schonlein-Henoch purpura
Autoimmune thrombocytopenia

association, characteristic pathological findings, favorable response to corticosteroid therapy, and distinct differentiation from lesions of the corresponding organ. (Level of recommendation: B)

Description The evidence to support the association between extrapancreatic lesions and AIP are the following: (1) many reports indicating frequent or intimate co-occurrence, (2) pathological findings indicating severe lymphoplasmacytic infiltration and stiriform fibrosis, numerous IgG4-positive plasma cell infiltrations, and obliterative phlebitis, (3) favorable response to corticosteroid therapy or synchronous response to therapies, and (4) distinct differentiation from the lesions of the corresponding organ, such as salivary gland lesions from Sjögren's syndrome. Among many possible extrapancreatic lesions listed in Table 1, the following fulfill the above criteria: lachrymal and salivary gland lesions, respiratory lesions, sclerosing cholangitis, retroperitoneal fibrosis, and tubulointerstitial nephritis.

CQ-II-1-3. What are the differences between lachrymal and salivary gland lesions associated with AIP and those of Sjögren's syndrome?

- Compared with Sjögren's syndrome, lachrymal and salivary gland lesions associated with AIP show normal or slightly impaired exocrine function, presenting as slight or negligible dry eye and mouth. (Level of recommendation: B)
- Salivary gland lesions associated with AIP appear predominantly in the submandibular gland, whereas those associated with Sjögren's syndrome are frequently seen in the parotid gland. (Level of recommendation: B)
- Compared with those of Sjögren's syndrome, lachrymal and salivary gland lesions associated with AIP show negative results for SS-A/Ro and SS-B/La autoantibodies. (Level of recommendation: B)
- Compared with those of Sjögren's syndrome, lachrymal and salivary gland lesions associated with AIP show numerous IgG4-positive plasma cell infiltrations in the affected tissues. (Level of recommendation: B)
- Compared with those of Sjögren's syndrome, lachrymal and salivary gland lesions associated with AIP show favorable response to corticosteroid therapy. (Level of recommendation: B)

Description Symmetrical lachrymal and salivary gland lesions were found in 14–39% of patients with AIP (Fig. 1) [10–13] and were previously considered to be a complication with Sjögren's syndrome. Currently, these are thought to correspond to Mikulicz disease or Kuettner tumor (chronic sclerosing sialoadenitis) [14, 15]. Useful findings for the differentiation include the following: (1) Compared with those of Sjögren's syndrome, lachrymal and salivary gland lesions associated with AIP show normal or slightly impaired exocrine function, presenting as slight or negligible dry eye and mouth [13]; (2) salivary gland lesions associated with AIP show a preponderance of occurrence in the submandibular gland [16], whereas those with Sjögren's syndrome are frequently seen in the parotid gland; (3) lachrymal and salivary gland lesions associated with AIP show negative results for SS-A/Ro and SS-B/La autoantibodies; (4) lachrymal and salivary gland lesions associated with AIP show numerous IgG4-positive plasma cell infiltrations in the affected tissues; (5) lachrymal and salivary gland lesions associated with AIP show favorable response to corticosteroid therapy. Most lesions show bilateral symmetrical distribution, though there may be a few cases with unilateral distribution. For correct diagnosis, salivary gland biopsy is preferable, but the less invasive lip biopsy has been substituted for the examination of the small salivary gland.

CQ-II-1-4. What kind of respiratory lesions are associated with AIP?

- Respiratory lesions associated with AIP include interstitial pneumonia, inflammatory pseudotumor of the lung, and hilar or mediastinal lymphadenopathy. Pathology of these lesions shows numerous IgG4-bearing plasma cell infiltrations and favorable response to corticosteroid therapy. The lesions need to be differentiated from idiopathic interstitial pneumonia, sarcoidosis, and lung tumor. (Level of recommendation: B)

Description Interstitial pneumonia was complicated with AIP in 8–13% of patients [17, 18], showing a high serum KL-6 value and alveolar IgG4-bearing plasma cell infiltration [17, 18]. Thoracic CT showed various lung lesions, bronchial wall thickening, nodules, interlobular thickening, infiltration in the middle and lower lung fields (Fig. 3), and honeycombing in the lower lung field. Sometimes, respiratory lesions of interstitial pneumonia, asthma, and nodular lesions occur without pancreatic lesions [19, 20]. Inflammatory pseudotumor is another respiratory lesion

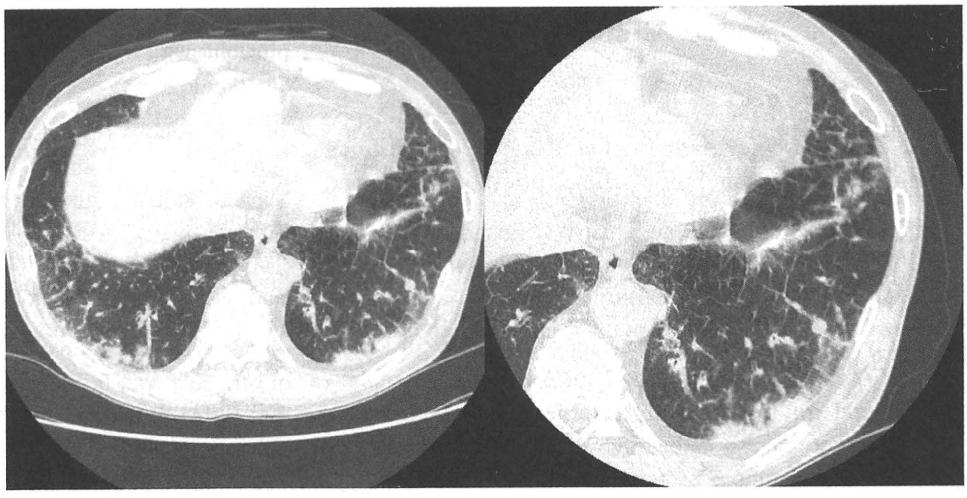

Fig. 3 CT of an AIP patient shows various lung lesions, bronchial wall thickening, nodules, interlobular thickening, and infiltration

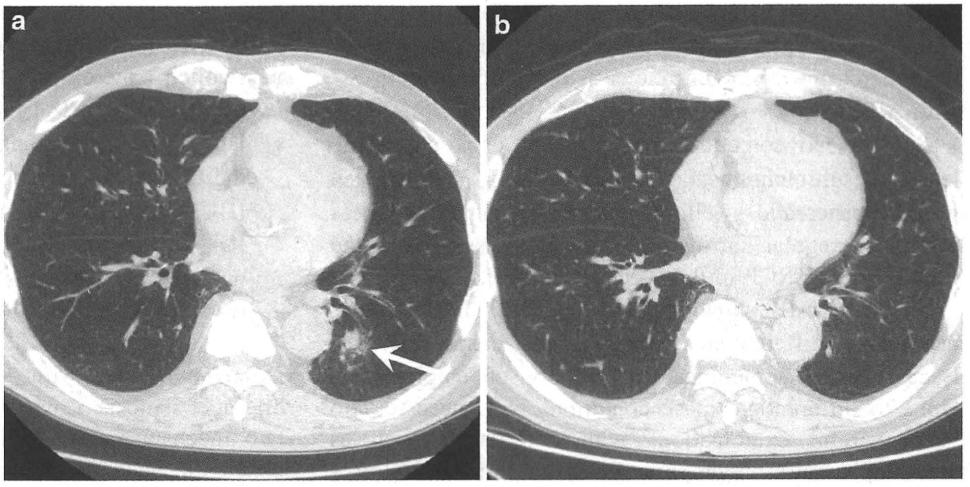

Fig. 4 CT shows nodular lesion of inflammatory pseudotumor (*arrow*) before corticosteroid therapy (**a**) in an AIP patient. After therapy, the nodular lesion disappeared (**b**)

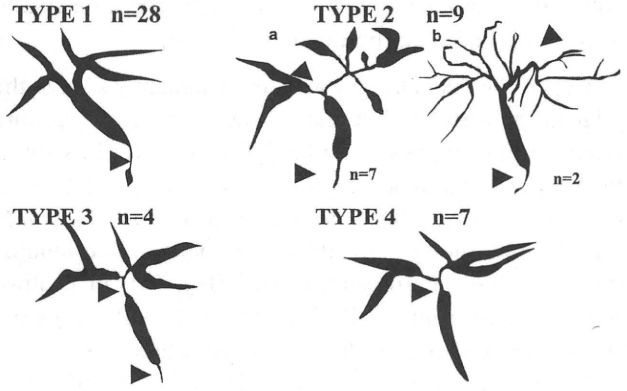

Fig. 5 Schematic classification of sclerosing cholangitis with AIP by cholangiography: stenosis only in the lower part of the common bile duct in type 1; stenosis in the intrahepatic and extrahepatic bile ducts in type 2; extended narrowing of intrahepatic bile ducts with prestenotic dilation in type 2a; extended narrowing of intrahepatic bile ducts without prestenotic dilation and reduced number of bile duct branches in type 2b; stenosis in both hilar hepatic lesions and the lower part of the common bile ducts in type 3; stenosis only in the hilar hepatic lesions in type 4 (from Ref. [22])

that corresponds to plasma cell granuloma showing lymphoplasmacytic infiltration, fibrosis, obstructive phlebitis, and IgG4-bearing plasma cell infiltration; these characteristics are also similar to that of pancreatic lesions [21]. Inflammatory pseudotumor is frequently misdiagnosed as lung tumor, but unlike lung tumor, shows favorable response to corticosteroid therapy (Fig. 4). Gallium scintigraphy showed hilar and mediastinal lymphadenopathy in 67% of patients, consistent with sarcoidosis; however, patients showed normal serum angiotensin-converting enzyme (ACE) levels and responded favorably to corticosteroid therapy [2].

CQ-II-1-5. How can the differentiation be made between sclerosing cholangitis associated with AIP and primary sclerosing cholangitis (PSC) or biliary malignancies?

- The differentiation between sclerosing cholangitis associated with AIP and PSC or biliary malignancies should be done carefully and based collectively on the clinical features, image tests (such as cholangiography, ultrasonography, EUS, IDUS, CT, and MRI), and pathological findings. (Level of recommendation: A)

Description Sclerosing cholangitis associated with autoimmune pancreatitis (SC with AIP) is characteristically seen as lower (intrapancreatic) bile duct stenosis, but is sometimes distributed widely in the biliary system showing restricted stenosis from hilar to extra-hepatic bile ducts and multiple stenosis of intra-hepatic bile ducts (Fig. 5) [22]. Lower bile duct lesions need to be differentiated from pancreatic cancer or common bile duct cancer, whereas intrahepatic and hilar bile duct lesions need to be differentiated from primary sclerosing cholangitis (PSC) and cholangiocarcinoma, respectively.

SC with AIP showed a preponderance among elderly males and was frequently complicated with obstructive jaundice, whereas PSC was found more commonly in young and middle-aged patients and was sometimes complicated with inflammatory bowel diseases [11, 23–25]. Cholangiography of SC with AIP showed lower bile duct stenosis and relatively long stricture from the hilar to intrahepatic biliary systems with simple distal dilatation [23, 24], whereas those of PSC showed characteristic findings of band-like stricture (short stricture within 1–2 mm), beaded appearance, pruned tree appearance, and diverticulum-like outpouching (Fig. 6) [23, 24, 26]. Ultrasonography of SC with AIP showed wall thickening of intra- or extra-hepatic bile ducts. Pathological findings of bile duct wall in SC with AIP showed similar findings to the pancreatic tissue [27–29]. Inflammation associated with SC with AIP was found in the whole layer of the bile duct wall, but inflammation associated with PSC was found

predominantly at the inner portion with only slight changes at the outer portion. Liver biopsy showed numerous IgG4-bearing plasma cell infiltrations at the portal area in SC with AIP, but only few in PSC [24, 27–30].

SC with AIP sometimes showed slight or no pancreatic lesions, resulting in misdiagnosis as PSC [25, 31, 32]. Even without pancreatic swelling, pancreatography sometimes discloses irregular narrowing of the MPD, suggesting the usefulness of ERCP in these occasions [32].

SC with AIP showing localized bile duct stenosis needs to be differentiated from bile duct cancer [33, 34]. Because it is sometimes difficult for cholangiography alone to differentiate these conditions, it is necessary to make careful examinations with other tests such as endoscopic ultrasonography (EUS), intraductal ultrasonography (IDUS), cytology, and tissue biopsy [33, 34]. IgG4-positive plasma cell infiltration found in the bile duct wall supports the diagnosis of SC with AIP [25, 31]. Characteristic IDUS findings are thickening of the inner hypoechoic zone and preservation of the luminal and outer hyperechoic zone. IDUS sometimes showed thickening of the bile duct wall, whereas cholangiography showed normal findings. These characteristic findings will aid the differentiation between the two conditions (refer to CQ-II-1-6). SC with AIP also shows an inflammatory pseudotumor like an outgrowing tumor of the bile duct, which can be misdiagnosed as bile duct cancer.

CQ-II-1-6. What are the characteristic IDUS findings of sclerosing cholangitis associated with AIP?

- Lower bile duct stenosis associated with AIP is caused by two mechanisms: (1) extrinsic compression by a swollen pancreas head and (2) thickening of the bile duct wall. (Level of recommendation: B)
- Upper bile duct changes were predominantly seen in the hilar to intra-hepatic bile duct system, for which IDUS showed thickening of the inner hypoechoic zone. IDUS sometimes showed wall thickening of the bile duct where cholangiography showed normal findings. (Level of recommendation: B)

Description SC with AIP consists of lower and upper bile duct stenosis. Lower bile duct stenosis was caused by two mechanisms, extrinsic compression by the swollen pancreatic head (Fig. 7) and wall thickening of the bile duct (Fig. 8). In contrast with bile duct cancer, IDUS of SC with AIP showed concentric wall thickening demonstrating delayed enhancement by Levovist [35, 36].

Upper bile duct changes were predominantly seen in the hilar to intra-hepatic bile duct system—these changes are reminiscent of those seen in PSC, for which IDUS showed thickening of the inner hypoechoic zone (Fig. 9). Though differentiation by IDUS alone is difficult, IDUS changes seen in PSC showed slightly hyperechoic, scarce luminal dilatation and an irregular surface (Fig. 10). In contrast with bile duct cancer, IDUS of SC with AIP commonly showed preservation of the outer hyperechoic zone.

IDUS sometimes showed thickening of the bile duct wall, whereas cholangiography showed normal findings. Though the thickening of the bile duct wall is

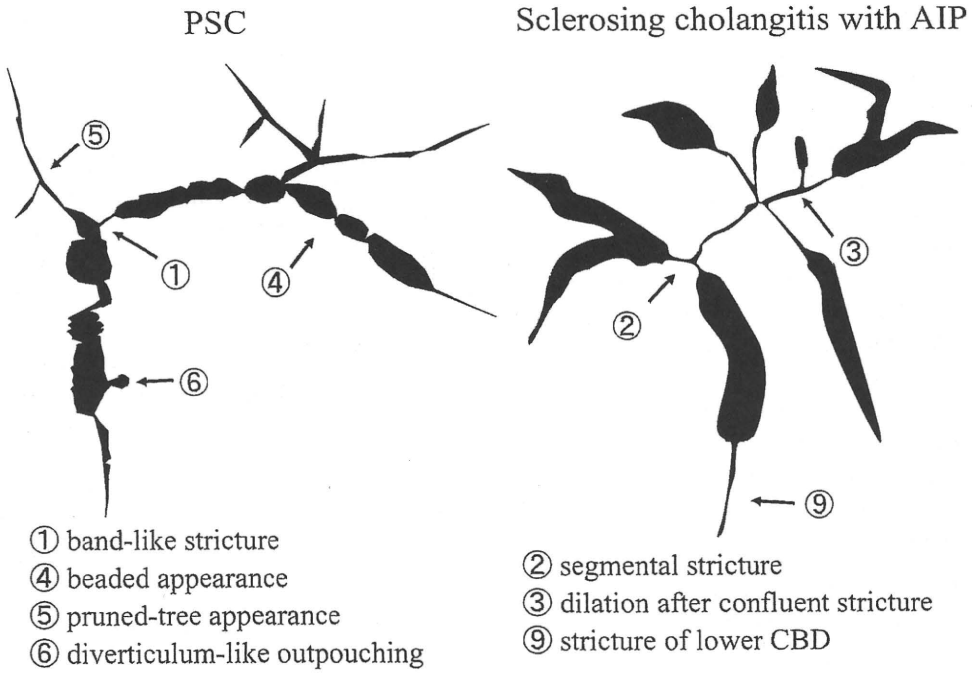

Fig. 6 Comparison of characteristic cholangiogram between AIP and primary sclerosing cholangitis (from Ref. [26])

predominantly seen in cancer invasion or PSC [37], biliary drainage also induces thickening of the bile duct wall; therefore, an IDUS survey should be done before biliary drainage [37].

Changes shown by cholangiography in SC with AIP are promptly ameliorated after corticosteroid therapy. The thickening of the bile duct wall as shown by IDUS is also ameliorated in parallel with a decrease of cell infiltration and edema, resulting in the elevation of the echo level in the thickened wall. However, unlike the amelioration evident by cholangiography, changes indicated by IDUS tend to persist.

II-2. Differential diagnosis [38]

CQ-II-2-1. What are the clinical symptoms or findings useful in differentiating between AIP and pancreatic cancer?

- Clinical findings useful in differentiating between AIP and pancreatic cancer include abdominal pain, weight loss, obstructive jaundice, and extrapancreatic lesions. (Level of recommendation: B)

Description Abdominal pain in pancreatic cancer is severe, persistent, and progressive, sometimes requiring narcotics, whereas that in AIP is mild, such as discomfort in the upper abdomen [39–45]. Weight loss is frequently seen in pancreatic cancer, whereas it is rarely seen in AIP. However, weight loss in AIP patients can be seen in cases where diabetes mellitus is not under control. Jaundice in pancreatic cancer is progressive, but that in AIP fluctuates, occasionally subsiding spontaneously, and responds well to corticosteroid therapy [39–45]. In AIP, symptoms associated with various extrapancreatic lesions include swelling of the lachrymal and salivary glands, jaundice due to sclerosing cholangitis, hydronephrosis due to retroperitoneal fibrosis, hypothyroidism, hypophysitis, and prostatitis [39–45]. In pancreatic cancer, the symptoms associated

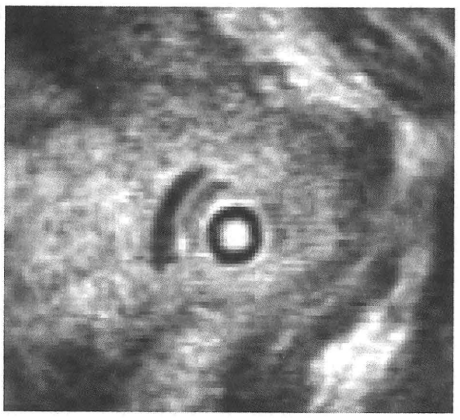

Fig. 7 IDUS shows lower bile duct stenosis caused by extrinsic compression due to a swollen pancreatic head in an AIP patient

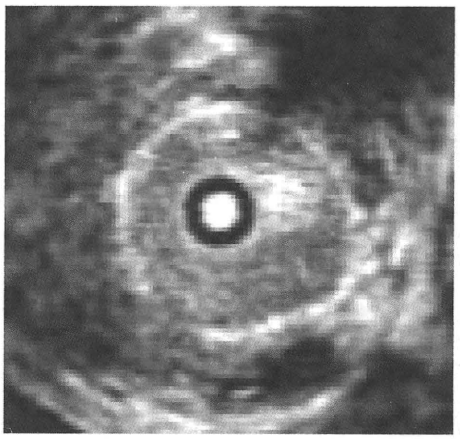

Fig. 8 IDUS shows lower bile duct stenosis caused by wall thickening of the bile duct in an AIP patient

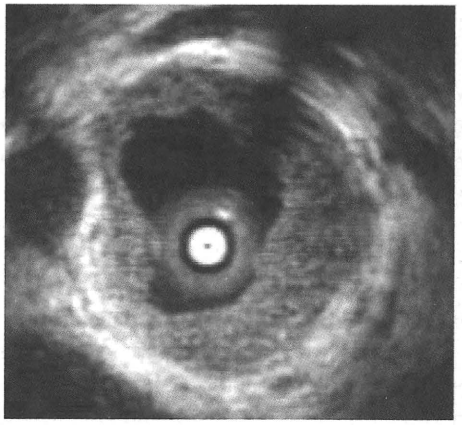

Fig. 9 IDUS shows upper bile duct stenosis caused by thickening of the inner hypoechoic zone in an AIP patient

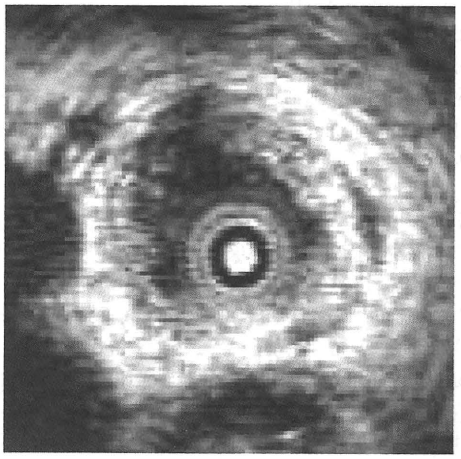

Fig. 10 IDUS shows upper bile duct stenosis with a slightly hyperechoic wall, scarce luminal dilatation and irregular surface in a PSC patient

Table 2 Clinical features useful for the differentiation between autoimmune pancreatitis and pancreatic cancer

	Autoimmune pancreatitis	Pancreatic cancer
Abdominal pain	(−)–(±) Rare	(+)–(+++) Frequent, progressive
BW loss, icterus	(−) Frequent, fluctuate	(+)–(+++) Progressive
Extrapanc lesions	PSL-responsive lacrymal gland, salivary gland, screlosing cholangitis, retroperitoneal fibrosis, etc.	PSL-non-responsive metastatic lesions surrounding tissues

with apparent extrapancreatic lesions were restricted to lower bile duct stenosis, metastatic lesions, or direct invasions (Table 2).

CQ-II-2-2. Does a high serum IgG4 concentration rule out the possibility of pancreatic cancer?

- In terms of sensitivity, specificity, and accuracy, elevated IgG4 is the best marker for differentiating between AIP and pancreatic cancer; however, a few patients with pancreatic cancer have been reported to show high serum IgG4 concentrations, suggesting that high serum IgG4 concentration cannot rule out the presence of pancreatic cancer. (Level of recommendation: B)

Description High serum IgG4 concentration is frequently found in AIP [25, 42, 45, 46]. In normal subjects, IgG4 consists of 4–6% of total IgG, and its serum elevation has been known to be seen in restricted conditions, such as allergic disease, parasite infestation, and pemphigus vulgaris. Similarly to normal subjects, serum elevation of IgG4 is scarcely found in other pancreatic diseases and related autoimmune diseases, such as pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren's syndrome; this indicates that high serum IgG4 concentration is specifically found in AIP. Furthermore, numerous IgG4-bearing plasma cell infiltrations in the pancreatic tissue are a diagnostic hallmark [5].

Comparison of various markers in differentiating between AIP and pancreatic cancer using identical sera showed that the best results are obtained using IgG4, which shows 86% sensitivity, 96% specificity, and 91% accuracy (Table 3). IgG4 was therefore adopted as the best marker in the Japanese diagnostic criteria of 2006 [41]. However, serum IgG4 elevation or numerous IgG4-bearing plasma cell infiltrations have been reported to be also found in a few patients with pancreatic cancer [45]. Evidently, high serum IgG4 concentration and numerous IgG4-positive plasma cell infiltrations in pancreatic tissue are not completely specific for AIP and cannot exclude the presence of pancreatic cancer.

Table 3 Comparison of various markers in the differentiation between autoimmune pancreatitis and pancreatic cancer using identical sera

	Sensitivity (AIP $n = 100$) (%)	Specificity (vs. PC $n = 80$) (%)	Accuracy (vs. PC)
IgG4	86	96	91
IgG	69	75	72
ANA (anti-nuclear antibody)	58	79	67
RF (rheumatoid factor)	23	94	54
IgG4+ANA	95	76	87
IgG+ANA	85	63	75
IgG4+IgG+ANA	95	63	81
IgG4+RF	90	90	90
IgG+RF	78	73	76
IgG4+IgG+RF	91	71	82
ANA+RF	69	60	78
IgG4+ANA+RF	97	73	86
IgG+ANA+RF	91	61	78
IgG4+IgG+ANA+RF	97	61	81

AIP autoimmune pancreatitis, *PC* pancreatic cancer

CQ-II-2-3. What CT and MRI findings are useful in differentiating between AIP and pancreatic cancer?

- Characteristic CT and MRI findings of AIP are smooth margins and capsule-like rims. (Level of recommendation: A)
- Contrast-enhanced CT often shows delayed enhancement in pancreatic lesions of both AIP and pancreatic cancer. However, contrast-enhanced images are generally homogeneous in AIP, but heterogeneous in pancreatic cancer; this distinction should aid in the differentiation of these conditions. (Level of recommendation: B)
- T1-weighted MR images of AIP showed low signal intensity for pancreatic parenchyma lesions. (Level of recommendation: B)
- T2-weighted MR images of AIP sometimes showed the main pancreatic duct clearly penetrating through the mass lesion, the duct-penetrating sign, which was not found in the pancreatic cancer. (Level of recommendation: A)
- Localized swelling in AIP was sometimes difficult to differentiate from that in pancreatic cancer, but it showed marked amelioration after corticosteroid therapy in the case of AIP. (Level of recommendation: A)

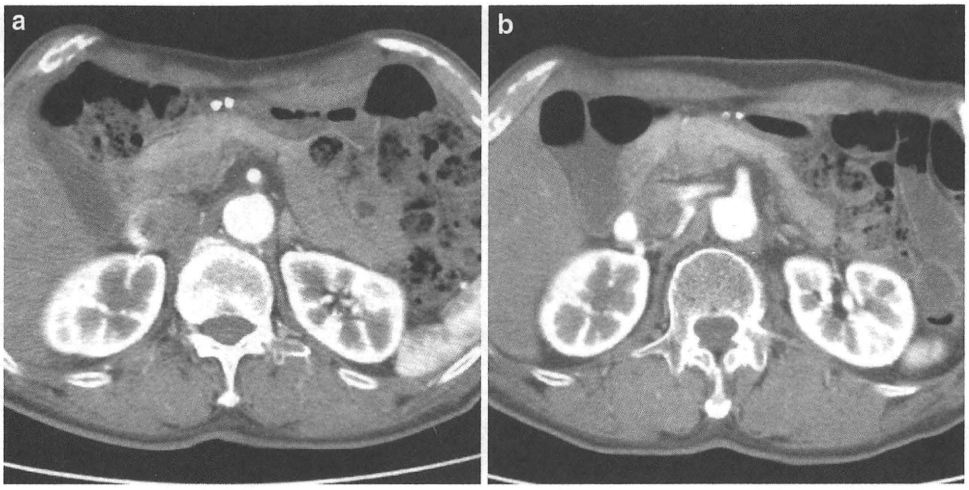

Fig. 11 **a** CT shows a localized mass lesion in the pancreatic head in an AIP patient. **b** After corticosteroid therapy, the localized mass lesion decreased in size

Description Autoimmune pancreatitis sometimes shows a focal mass in CT and MRI, which should be differentiated from those of pancreatic cancer (Fig. 11a). Pancreatic swelling found in AIP was drastically ameliorated after corticosteroid therapy (Fig. 11b). However, because pancreatic mass lesions are more common in pancreatic cancer than in AIP, much attention should be paid in diagnosing mass-forming AIP.

One characteristic CT and MRI finding of the pancreas margin in AIP is a capsule-like rim [47–49], which is prominent at the body and tail region and represents severe fibrotic changes (Fig. 12). CT and MRI images of an aged pancreas showed a lobulated margin and cobblestone-like texture, whereas those of AIP showed a smooth margin, probably since it is in its early stage (Fig. 12).

For CT image analysis of pancreatic lesions, dynamic CT with rapid infusion of contrast material is essential. We should check the early phase (pancreatic parenchymal phase) when parenchyma of normal pancreas stains, and late phase that corresponds to the equilibrium stage of contrast medium between intra- and extra-vascular fluids. In the late phase, intense staining indicates fibrosis. Contrast-enhanced CT of AIP showed delayed homogeneous enhancement in pancreatic lesions, which represented widespread loss of parenchyma and severe fibrosis (Fig. 13). That of pancreatic cancer also shows delayed enhancement; however, in contrast to AIP, its staining shows heterogeneous patterning (Fig. 14), reflecting necrosis or bleeding in the tumor [48].

For MR image analysis of pancreatic lesions, T1-weighted MR images are essential, and combination with the fat-suppressed method can show detailed changes of pancreatic parenchyma. Fat-suppressed T1-weighted MR images of a normal pancreas showed high signal intensity compared to those of the liver, whereas those of AIP showed decreased signal, reflecting loss of normal

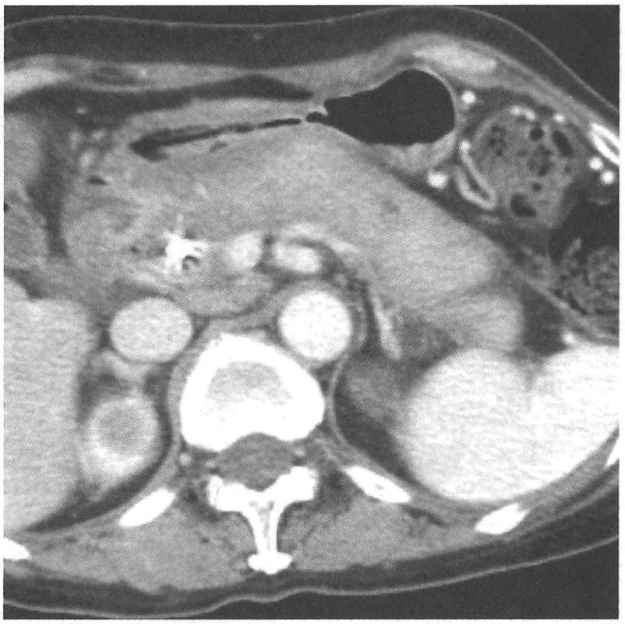

Fig. 12 CT shows capsule-like rim and smooth margin in an AIP patient

parenchyma (Fig. 15). T2-weighted MR images of AIP generally showed high signal intensity, reflecting severe lymphoplasmacytic infiltration. T2-weighted MR images of AIP sometimes showed the main pancreatic duct clearly penetrating through the mass lesion (duct penetrating sign), which was useful for differentiation [50] (Fig. 16).

In AIP, CT or MRI sometimes shows thickening of the gallbladder wall and bile duct wall even without duct stenosis (Fig. 17) [48, 49], whereas such findings are rarely found in pancreatic cancer.

These findings including pancreatic swelling are characteristically seen in the active stage of AIP. However, AIP may progress to intraductal stone formation after several attacks of relapse, resulting in pancreatic juice stasis and