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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

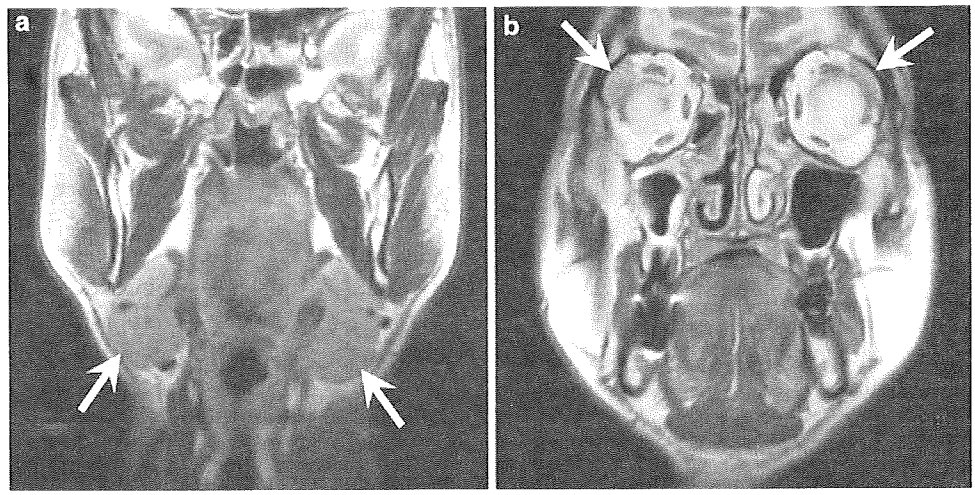

Fig. 1 T2-weighted MRI images of salivary gland [submandibular gland (**a**) and lachrymal gland (**b**)] swellings in an AIP patient. *Arrows* indicate swollen salivary and lachrymal glands. Homogeneous signal was shown by the submandibular gland, although vessels are recognized in it

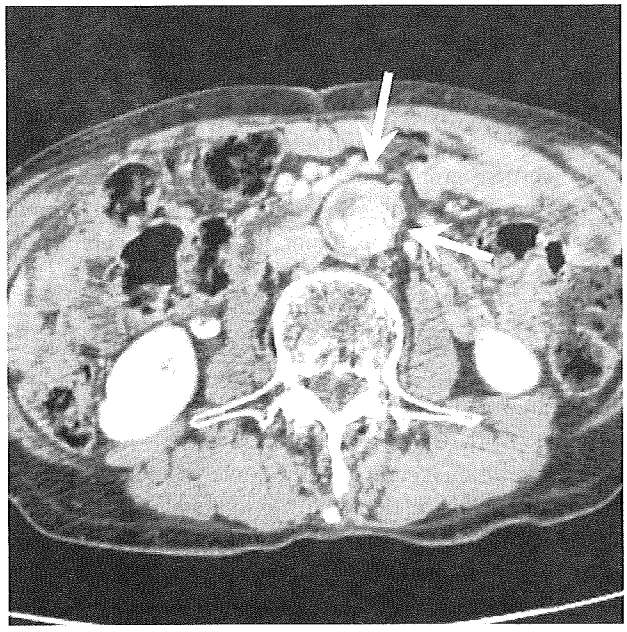

Fig. 2 CT shows retroperitoneal fibrosis around the aorta in an AIP patient. Calcification is seen in the aortic wall, and a soft tissue mass (*arrow*) surrounds the aorta

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

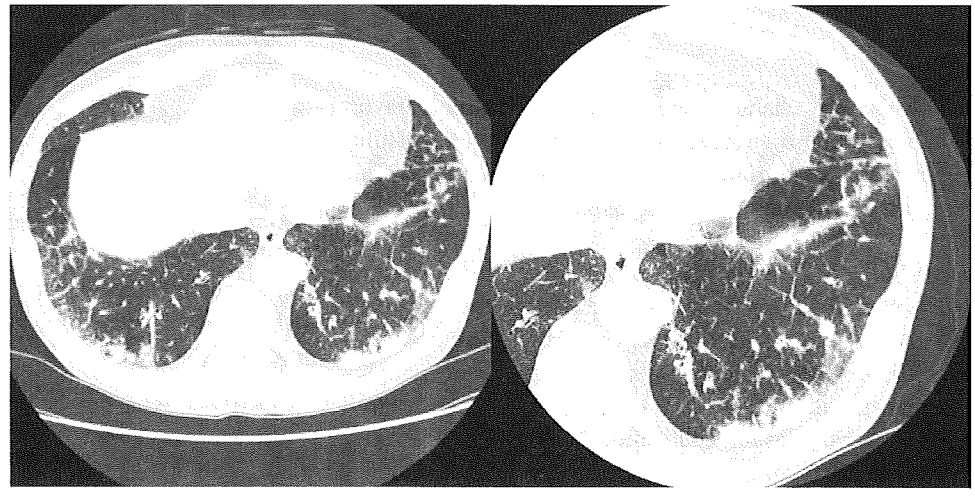

Fig. 3 CT of an AIP patient shows various lung lesions, bronchial wall thickening, nodules, interlobular thickening, and infiltration

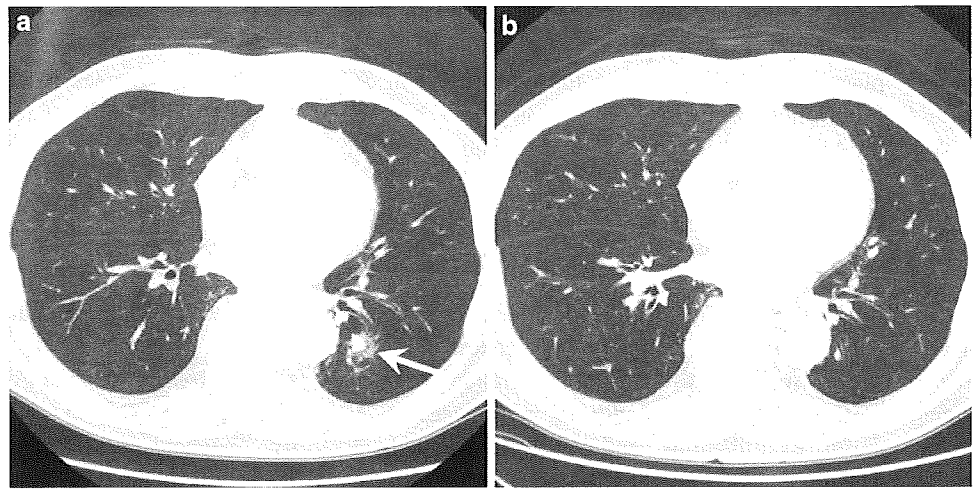

Fig. 4 CT shows nodular lesion of inflammatory pseudotumor (*arrow*) before corticosteroid therapy (**a**) in an AIP patient. After therapy, the nodular lesion disappeared (**b**)

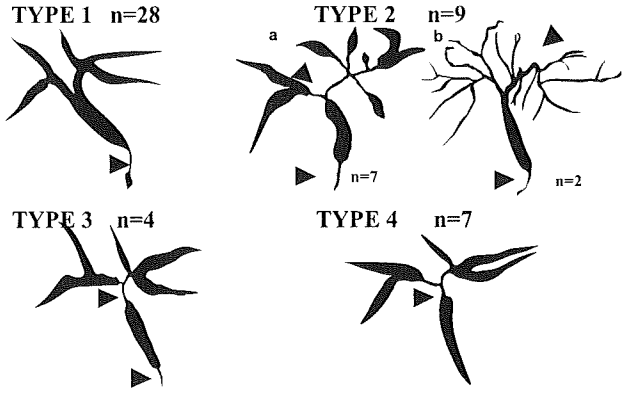

Fig. 5 Schematic classification of sclerosing cholangitis with AIP by cholangiography: stenosis only in the lower part of the common bile duct in type 1; stenosis in the intrahepatic and extrahepatic bile ducts in type 2; extended narrowing of intrahepatic bile ducts with prestenotic dilation in type 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

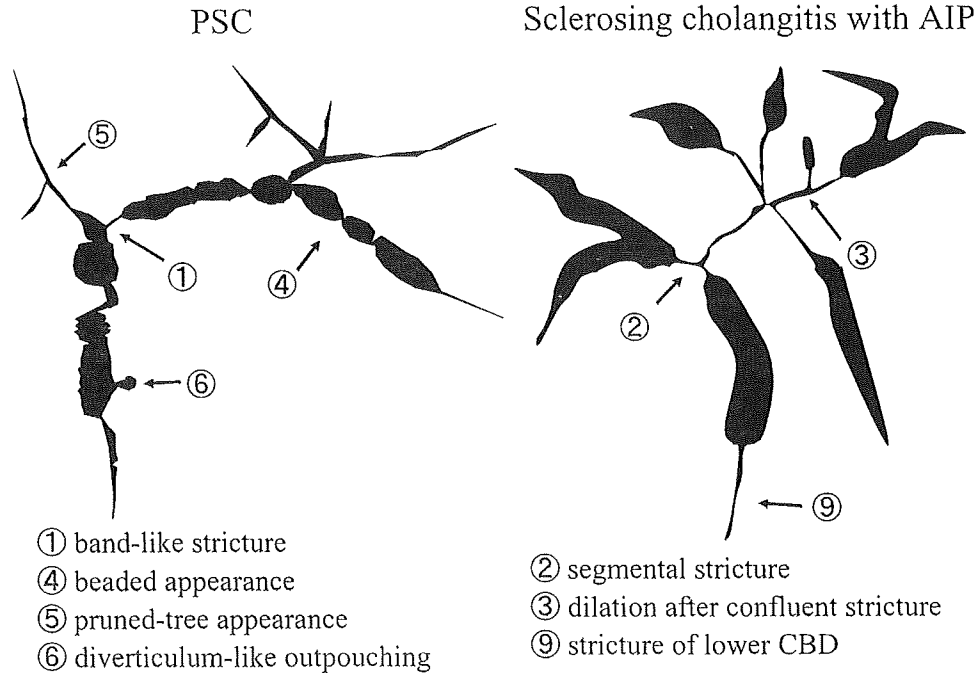

Fig. 6 Comparison of characteristic cholangiogram between AIP and primary sclerosing cholangitis (from Ref. [26])

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

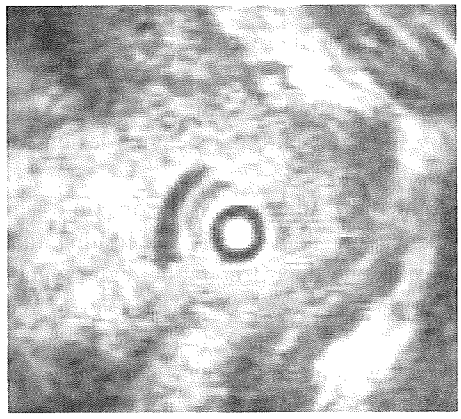

Fig. 7 IDUS shows lower bile duct stenosis caused by extrinsic compression due to a swollen pancreatic head in an AIP patient

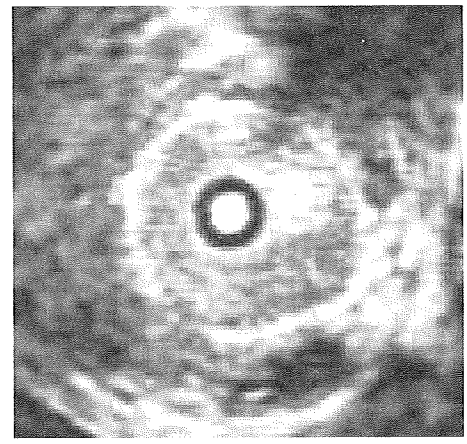

Fig. 8 IDUS shows lower bile duct stenosis caused by wall thickening of the bile duct in an AIP patient

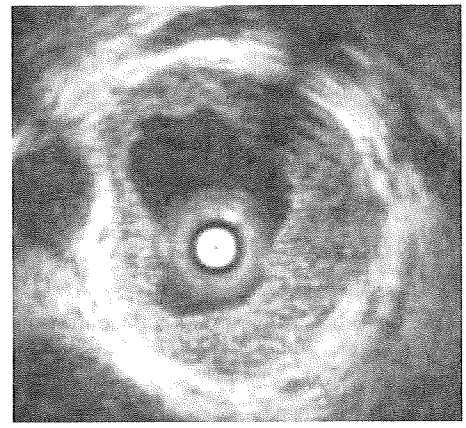

Fig. 9 IDUS shows upper bile duct stenosis caused by thickening of the inner hypoechoic zone in an AIP patient

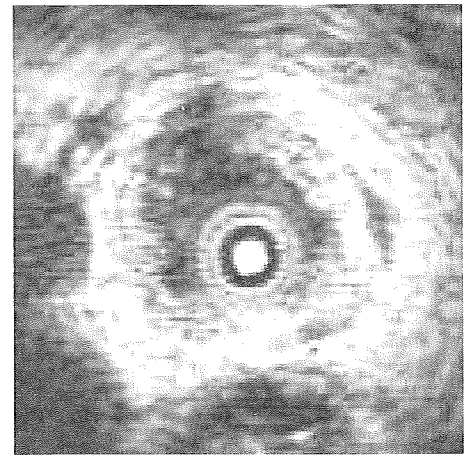

Fig. 10 IDUS shows upper bile duct stenosis with a slightly hyperechoic wall, scarce luminal dilatation and irregular surface in a PSC patient

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, scrclosing 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)

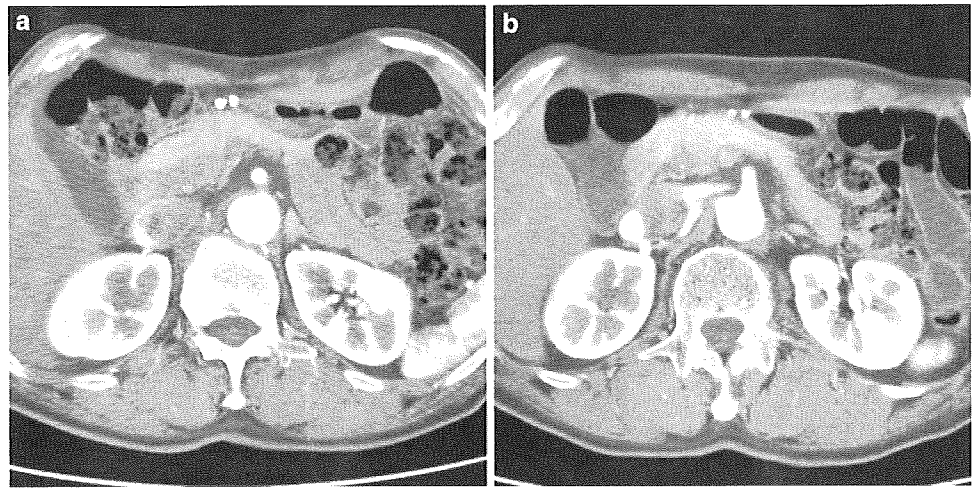

Fig. 11 **a** CT shows a localized mass lesion in the pancreatic head in an AIP patient. **b** After corticosteroid therapy, the localized mass lesion decreased in size

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

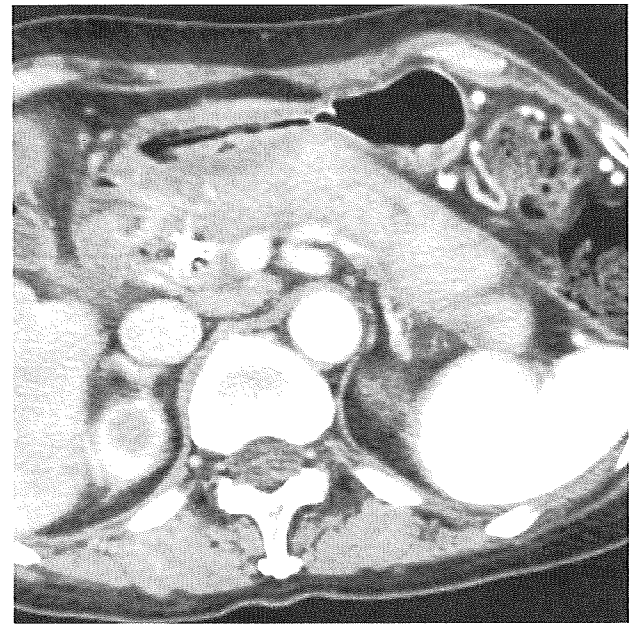

Fig. 12 CT shows capsule-like rim and smooth margin in an AIP patient

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

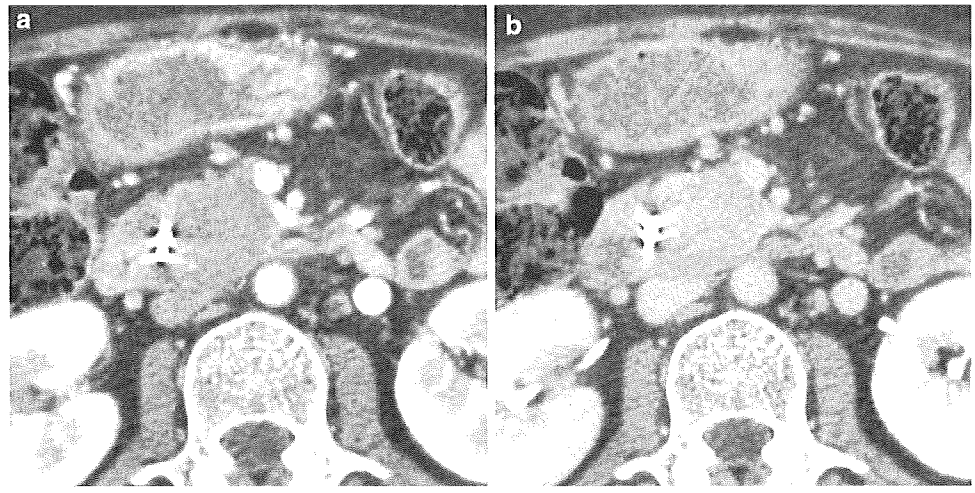

Fig. 13 **a** Contrast-enhanced CT of AIP shows a localized mass lesion in the pancreatic head in the early phase. **b** In the late phase, delayed homogeneous enhancement was seen in the mass lesion

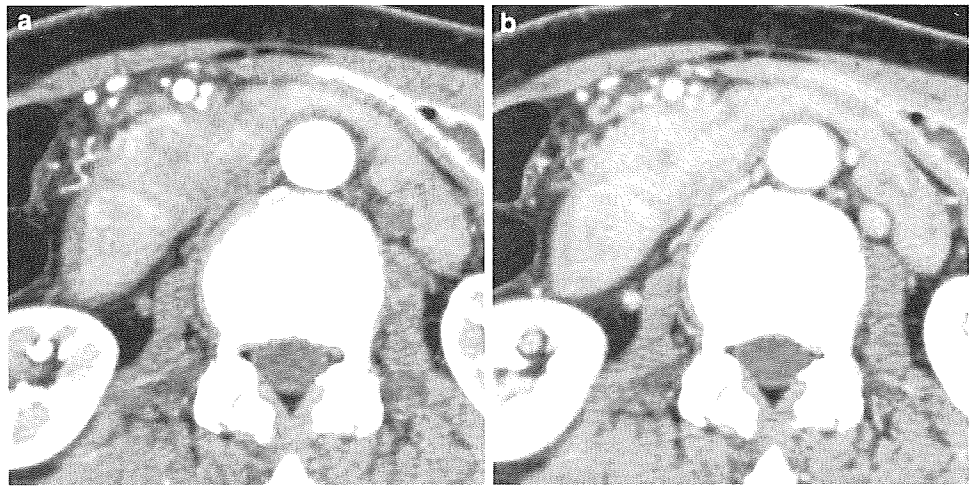

Fig. 14 **a** Contrast-enhanced CT of pancreatic cancer shows a localized mass lesion in the pancreatic head in the early phase. **b** In late phase, delayed heterogeneous enhancement was seen in the mass lesion

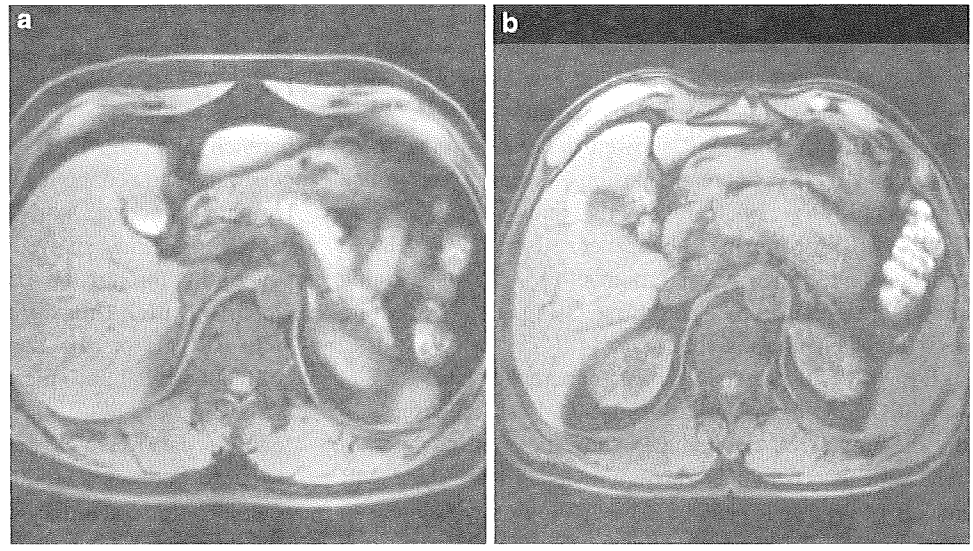

Fig. 15 **a** Fat-suppressed T1-weighted MR image of a normal pancreas showed high signal intensity compared to that of the liver. **b** Fat-suppressed T1-weighted MR image of AIP showed decreased signal in the pancreatic body and tail

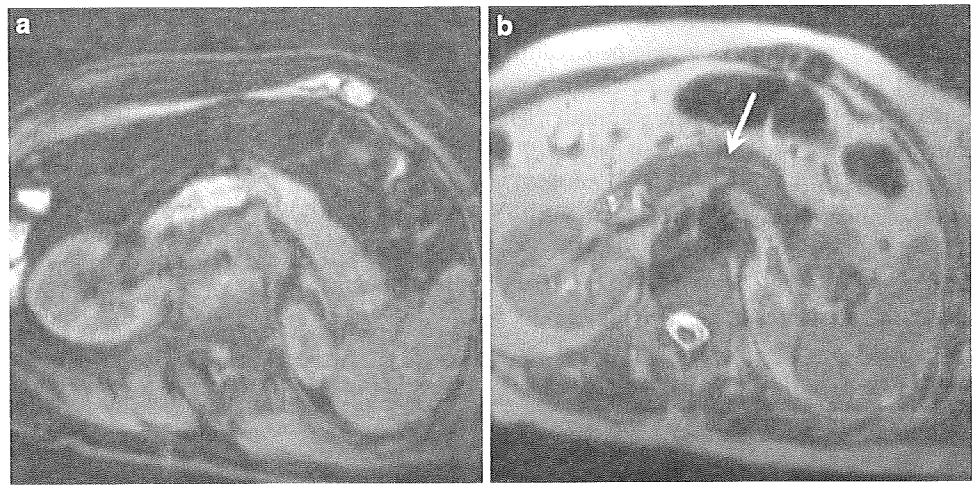

Fig. 16 **a** T2-weighted MR image of AIP shows high signal intensity. **b** T2-weighted MR images of AIP show the main pancreatic duct clearly penetrating through the mass lesion (*arrow*; duct penetrating sign)

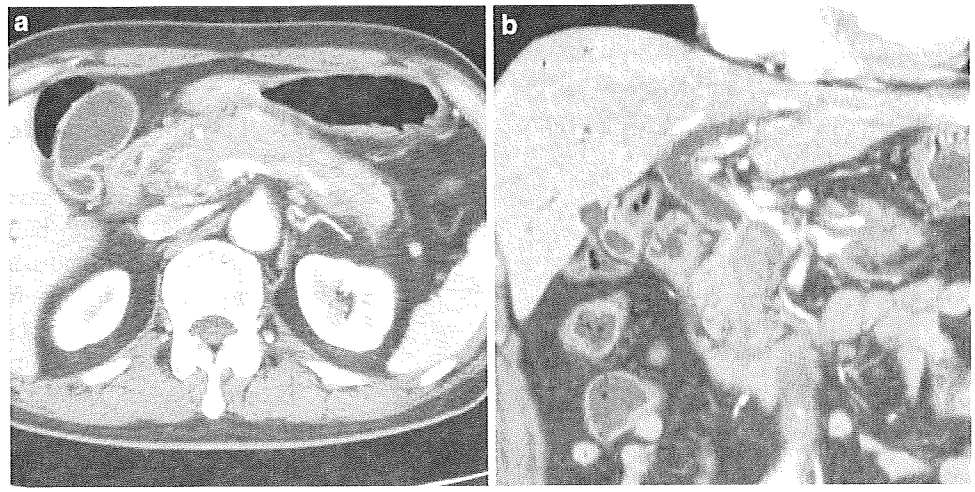

Fig. 17 CT shows thickening of **a** the gallbladder wall and **b** the bile duct wall in a patient with AIP

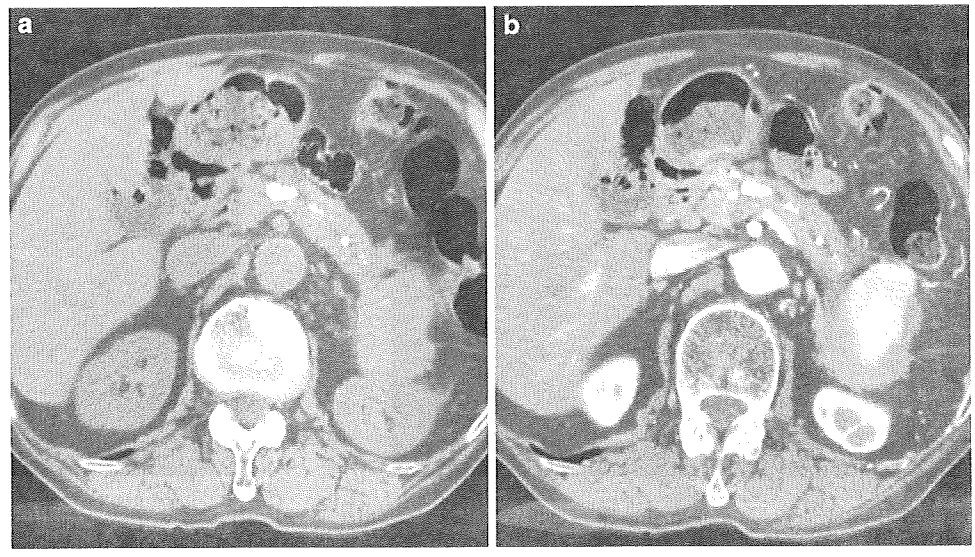

Fig. 18 CT shows intraductal pancreatic stone **a** before injection of contrast medium and **b** in the early phase (arterial phase) in a patient with AIP

severe calcification, in which case it becomes indistinguishable from ordinary chronic pancreatitis [51] (Fig. 18).

Like ERCP, MRCP also shows narrowing of the main pancreatic duct, but with low resolution. However, MRCP can image the distal duct even when ERCP shows only obstruction. In AIP, MRCP can show MPD dilatation, but shows comparatively poor images for MPD narrowing or side branch (versus ERCP). Like ERCP, MRCP shows mild or no distal dilatation in AIP (Fig. 19), but prominent dilatation in pancreatic cancer (Fig. 20).

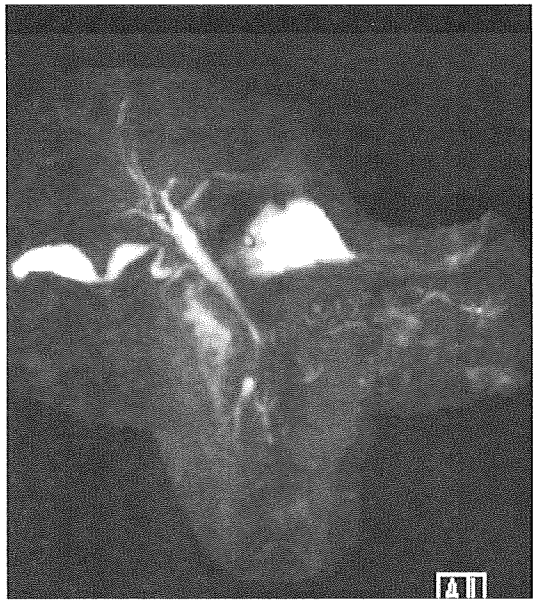

Fig. 19 MRCP shows minor or no distal dilatation in AIP after stenosis

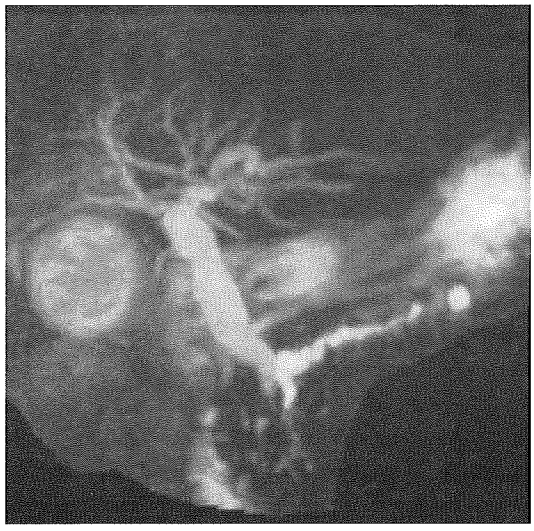

Fig. 20 MRCP shows prominent dilatation in pancreatic cancer after stenosis

CQ-II-2-4. What EUS findings are useful in differentiating between AIP and pancreatic cancer or ordinary chronic pancreatitis?

- Typical EUS findings of AIP include a relatively diffuse homogeneous hypoechoic pattern and linear or reticular (tortoiseshell pattern) hyperechoic inclusions. (Level of recommendation: B)
- Compared with chronic pancreatitis, pancreatic parenchyma of AIP showed a homogeneous hypoechoic pattern, but EUS findings characteristic of chronic pancreatitis (such as heterogeneous texture, lobular out gland margin, calcification, and hyperechoic ductal margin) were rarely found. (Level of recommendation: B)
- A localized mass of AIP also showed hypoechoic patterns, and linear or reticular (tortoiseshell pattern) hyperechoic inclusions, and the duct penetrating sign aids in the differentiation from pancreatic cancer. (Level of recommendation: B)
- EUS-FNA has diagnostic utility in discounting pancreatic cancer, but not in definitive diagnosis of AIP. (Level of recommendation: B)

Description There have been some reports regarding EUS findings of AIP, but few have described differentiation between AIP and pancreatic cancer or chronic pancreatitis. Useful findings for the differentiation are derived from EUS or US findings of each disease [51–56]. Typical EUS findings of AIP showed a diffuse hypoechoic pattern [52–56] (Fig. 21), which reflects severe inflammatory cell infiltration, whereas that of chronic pancreatitis showed a heterogeneous echo pattern even with severe inflammatory changes. Hyperechoic inclusions are found in both conditions, but those in AIP are seen less frequently and present characteristically as linear or reticular patterns

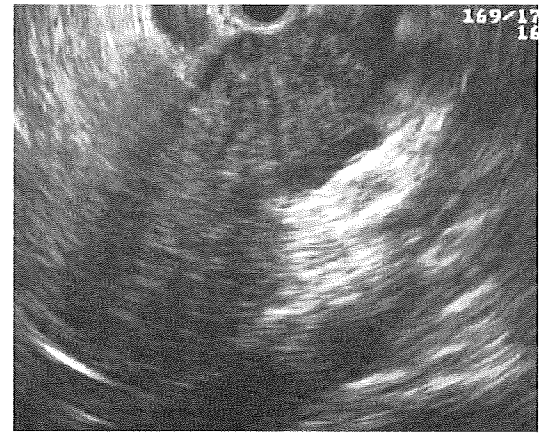

Fig. 21 EUS shows a diffuse hypoechoic pattern in the swollen pancreas of an AIP patient

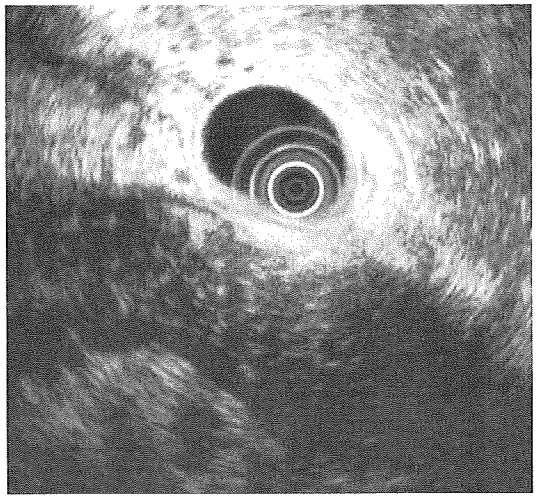

Fig. 22 EUS shows hyperechoic inclusions of linear or reticular patterns (tortoiseshell pattern) against the hypoechoic background in swollen pancreas of an AIP patient

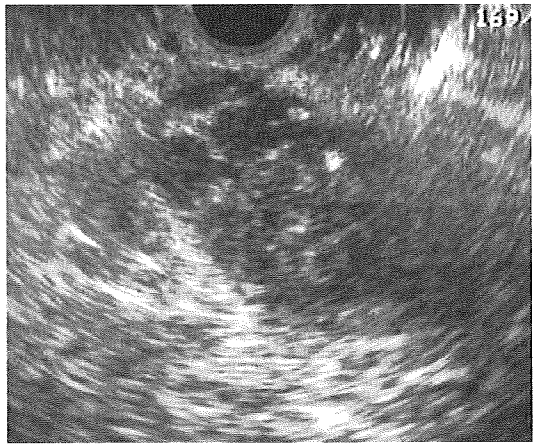

Fig. 23 EUS shows a localized mass of hypoechoic pattern with linear or reticular (tortoiseshell pattern) hyperechoic inclusions in an AIP patient

(tortoiseshell pattern) against the hypoechoic background in the post acute phase (Fig. 22). These findings seem to represent interlobular fibrosis. A lobular out gland margin, hyperechoic ductal margin, calcification, and cyst were generally found in cases of chronic pancreatitis, but were rarely found in the case of AIP. In addition, these hyperechoic inclusions found in AIP sometimes promptly disappear after corticosteroid treatment. A localized mass of hypoechoic pattern was found in both AIP and pancreatic cancer, but linear or reticular (tortoiseshell pattern) hyperechoic inclusions (Fig. 23) and the duct penetrating sign are generally found only in AIP (Fig. 24). Though lymph node swelling or vascular invasion was observed in the case of pancreatic cancer, differentiation between the

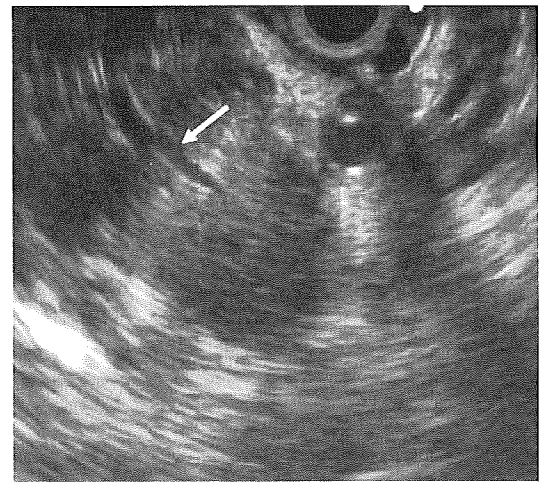

Fig. 24 EUS shows the pancreatic duct penetrating into the swollen pancreatic parenchyma (*arrow*; duct penetrating sign) in an AIP patient

two conditions is sometimes difficult and needs EUS-FNA [57]. EUS-FNA has diagnostic utility in discounting pancreatic cancer because of its high specificity (98–100%), but cannot give a definitive diagnosis of AIP because of a small sample volume [58, 59].

CQ-II-2-5. What pathological findings are useful for the differentiation between AIP and pancreatic cancer?

- Histological identification of carcinoma cells is a hallmark for the diagnosis of pancreatic cancer. (Level of recommendation: A)
- Inflammatory reactions can be commonly observed around pancreatic cancer. (Level of recommendation: A)
- Neutrophilic infiltrates, lobules with inflammatory infiltrates and edema, proliferation of plump fibroblasts, and lymphocyte-predominant infiltrates with scarce plasma cells are more common in pancreatic cancer than in AIP; these findings should not be regarded solely as diagnostic criteria for differentiation. (Level of recommendation: B)

Description Diagnosis of pancreatic cancer by pathological findings can be confirmed by histological identification of carcinoma cells. This is usually easy with resected specimens. However, it is common to observe inflammatory reactions around pancreatic cancer, and interpretation of biopsy specimens with inflammatory changes should be done carefully to correctly diagnose AIP. There has been insufficient evidence regarding the differentiation between AIP and pancreatic cancer based on pathological findings. Neutrophilic infiltrates, inflammatory infiltrates and edema in the lobules, proliferation of plump fibroblasts, and lymphocyte-predominant infiltrates

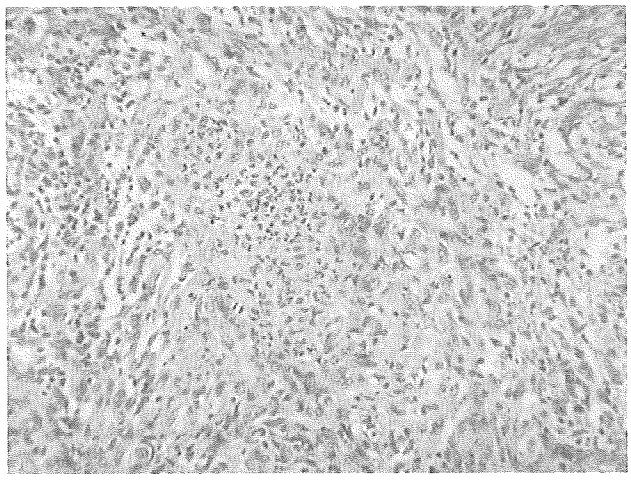

Fig. 25 Histopathological findings in pancreatic cancer showing a proliferation of plump fibroblasts (desmoplastic reaction; H&E staining). Neutrophilic infiltrates (microabscess) are seen in the central area

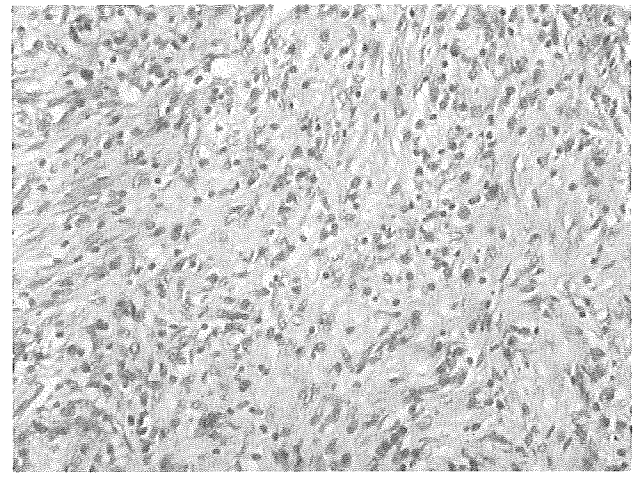

Fig. 27 Histopathological findings in pancreatic cancer showing lymphoplasmacytic infiltration and fibrosis around pancreatic cancer cells, which resemble LPSP (H&E staining)

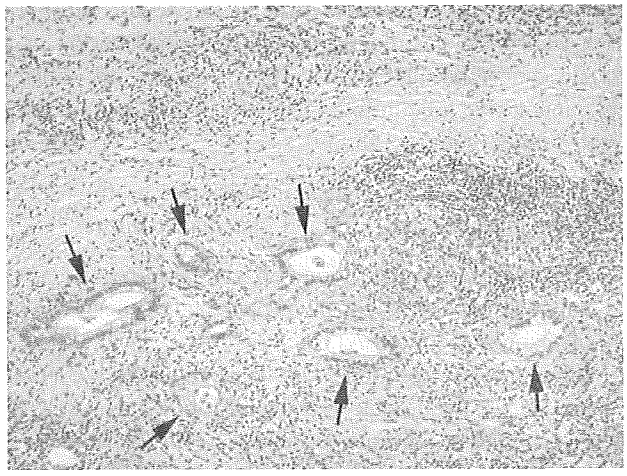

Fig. 26 Histopathological findings in pancreatic cancer showing predominant lymphocytic infiltration surrounding pancreatic cancer cells (*arrows*). Lymphoid follicle is seen on *right side*

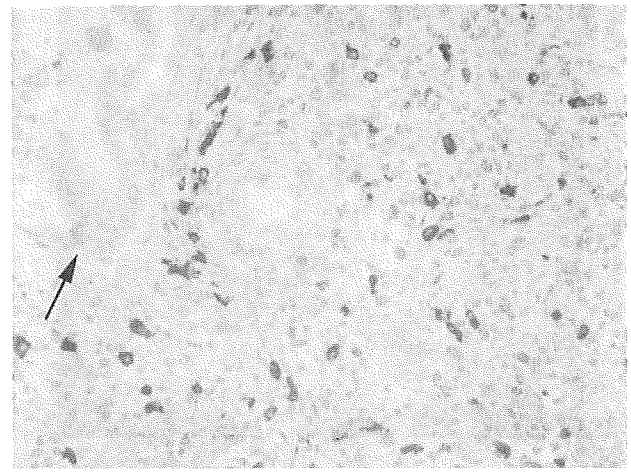

Fig. 28 Histopathological findings in pancreatic cancer showing numerous IgG4-positive plasma cells around pancreatic cancer cells (*arrows*) (IgG4 immunostaining staining)

with scarce plasma cells are more common in pancreatic cancer than in AIP (Fig. 25). Numerous plasma cell infiltrations are regarded as a characteristic finding of AIP, whereas predominant lymphocytic infiltration with scarce plasma cells is preferentially found at inflammatory sites of pancreatic cancer (Fig. 26). These findings in isolation should not be regarded as definitive diagnostic indications for AIP. In addition, lymphoid follicles are commonly seen in both pancreatic cancer and AIP, and should not be regarded as a diagnostic hallmark of AIP. Periductitis and obstructive phlebitis are characteristic findings for AIP; however, these are rarely found in biopsy specimens.

CQ-II-2-6. Can the histological features that characterize AIP be seen in pancreatic cancer?

- In rare cases, the reaction around pancreatic cancer histologically resembles autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis). (Level of recommendation: B)
- Numerous IgG4-positive plasma cells can be occasionally identified in pancreatic cancer. (Level of recommendation: B)

Description Rare pancreatic cancers reveal histological features that resemble AIP (Fig. 27) [60, 61]. Whether or

not these characteristic findings are found in pancreatic cancer, numerous IgG4-positive plasma cells are occasionally identified in pancreatic cancer (Fig. 28) [62–64].

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REVIEW

Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP

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Abstract Steroid therapy appeared to be a standard treatment for autoimmune pancreatitis (AIP), although some AIP patients improve spontaneously. The indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal pain, and back pain, and the presence of symptomatic extrapancreatic lesions. Before steroid therapy, jaundice should be managed by biliary drainage in patients with obstructive jaundice, and blood glucose levels should be controlled in patients with diabetes mellitus. For the initial oral prednisolone dose for induction of remission, 0.6 mg/kg/day is recommended. The initial dose is administered for 2–4 weeks, and the dose is tapered by 5 mg every 1–2 weeks, based on changes in the clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered to a maintenance dose (2.5–5 mg/day) over a period of 2–3 months. Steroid therapy should be stopped based on the disease activity in each case. Stopping of maintenance therapy should be planned within at least 3 years in cases with radiological and serological improvement. Re-administration or dose-up of steroid is effective for treating AIP relapses. The prognosis of AIP appears to be good over 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.

Keywords Autoimmune pancreatitis · Steroid therapy · IgG4

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CQ-III-1. Do AIP patients improve spontaneously?

- Some AIP patients improve spontaneously. (Level of recommendation: B)

Description Swelling of the pancreas or irregular narrowing of the main pancreatic duct improves spontaneously without steroid therapy in some AIP patients. According to Wakabayashi et al. [1], pancreatic swelling was alleviated in 9 (24%) of 37 AIP patients with only conservative therapy, and of these, narrowing of the main pancreatic duct also improved after 3–60 months in 4 patients, remained unchanged in 3 patients, and worsened

in 2 patients. It has been reported that most AIP patients who improved spontaneously did not have bile duct stenosis [2, 3]. According to Kamisawa et al. [2], in 21 AIP patients, spontaneous improvement was detected in 2 non-jaundiced patients (10%). Kubota et al. [3] compared the clinicopathological parameters in 8 AIP patients with remission in the absence of steroid therapy and 12 patients with remission after steroid therapy, and they found an association between remission in the absence of steroid therapy and seronegativity for IgG4, absence of obstructive jaundice, absence of diabetes mellitus, and the presence of focal pancreatic swelling.

Ozden et al. [4] reported an AIP patient who showed spontaneous regression of biliary obstruction 2 months after biliary drainage, and the drainage catheter was removed. Araki et al. [5] reported the natural course of an AIP patient in whom a mass in the uncinate process of the pancreas spontaneously decreased in size and disappeared after 9 months; conversely, however, the mass in the tail increased in size.

CQ-III-2. What are the indications for steroid therapy in AIP patients?

- The indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal pain, and back pain, and the presence of symptomatic extrapancreatic lesions. (Level of recommendation: A)

Description According to the nationwide survey by the Research Committee of Intractable Pancreatic Diseases supported by the Ministry of Health, Labor, and Welfare of Japan [6], three quarters of all AIP patients received steroid therapy. The remission rate of steroid-treated AIP was 98%, which was significantly higher than that of patients without steroid therapy (88%), and the period necessary to achieve remission averaged 98 days in steroid-treated patients, which was significantly shorter than the average 142 days in patients without steroid therapy. Based on these findings, steroid therapy appeared to be a standard treatment for AIP.

Steroid therapy is effective for extrapancreatic lesions such as sclerosing cholangitis as well as the pancreatic lesion in AIP. AIP is frequently associated with stenosis of the bile duct due to sclerosing cholangitis, and obstructive jaundice is a frequent initial symptom. As 91% of AIP patients with obstructive jaundice underwent steroid therapy according to the nationwide survey [6], obstructive jaundice is the principal indication for steroid therapy [2, 6–10]. AIP patients rarely have the severe abdominal pain that occurs in acute pancreatitis, but persistent abdominal or back pain in AIP appears to be an indication for steroid therapy [2, 6–9]. Associated symptomatic extrapancreatic lesions, such as retroperitoneal fibrosis, interstitial pneumonia, tubulointerstitial nephritis, and hepatic or pulmonary pseudotumor, are indications for steroid therapy [2, 7, 9, 10].

As impaired pancreatic endocrine or exocrine function improved in some AIP patients, marked impairment of pancreatic endocrine or exocrine function may be one of the indications for steroid therapy [7, 10, 11]. Some AIP patients showing diffuse enlargement of the pancreas undergo steroid therapy even if they are asymptomatic [2, 9]. It may be better to follow up for 1–2 weeks before starting steroids in order to check for spontaneous regression. In principle, steroid therapy should be performed for patients diagnosed as having AIP, but a facile steroid trial to differentiate AIP from pancreatic cancer should be prohibited [12].

CQ-III-3. How do we perform initial steroid therapy?

- Before steroid therapy, jaundice should be managed by biliary drainage in patients with obstructive jaundice, and blood glucose levels should be controlled in patients with diabetes mellitus. For the initial oral prednisolone dose for induction of remission, 0.6 mg/kg/day is recommended. The initial dose is administered for 2–4 weeks and then gradually tapered. (Level of recommendation: B)

Description Before steroid therapy, it is important to distinguish AIP from pancreatic or biliary cancer with imaging studies and an endoscopic approach [9].

In cases with obstructive jaundice due to bile duct stenosis, endoscopic or transhepatic biliary drainage is performed. Cytologic examination of the bile is performed repeatedly. After cytologic examination, a plastic stent is sometimes inserted. Steroid therapy can be started without biliary drainage in cases with mild jaundice. Blood glucose levels should be controlled in patients with diabetes mellitus before steroid therapy [8, 9].

According to the nationwide survey by the Research Committee of Intractable Pancreatic Diseases [6], the initial oral prednisolone dose was 30 mg/day ($n = 54$) or 40 mg/day ($n = 32$) in 93 AIP patients treated with steroids. The period necessary to achieve remission from the start of initial administration averaged 70 days in patients treated with an initial prednisolone dose of 30 mg/day, which was not significantly different from the period (average 91 days) in those treated with an initial prednisolone dose of 40 mg/day. There were no significant differences in the initial prednisolone dose administered to AIP patients with obstructive jaundice between patients treated with steroids alone [0.60 ± 0.12 mg/kg/day (mean ± SD)] and those treated with biliary drainage and steroids (0.60 ± 0.17 mg/kg/day). A recent multicenter study showed similar results [9]. Given these findings, the

recommended initial oral prednisolone dose is 0.6 mg/kg/day, and it should be gradually tapered after 2–4 weeks of administration [9].

In western countries, it has been reported that AIP patients are treated with an initial prednisolone dose of 50–75 mg/day [13], 40 mg/day [14, 15], or 0.5 mg/kg/day [16]. Matsushita et al. [17] reported that steroid pulse therapy is useful and may prevent unnecessary surgery when oral steroid therapy is not indicated because of the required period for drug tapering.

CQ-III-4. How is the dose of steroid tapered?

- After 2–4 weeks at the initial dose, the dose is tapered by 5 mg every 1–2 weeks, based on changes in the clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered to a maintenance dose over a period of 2–3 months. (Level of recommendation: B)

Description In order to induce remission, after 2–4 weeks at the initial dose, the dose is tapered by 5 mg every 1–2 weeks, based on changes in clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered gradually to a maintenance dose, usually 5–10 mg/day [6, 8, 9, 18] (Fig. 1). After 15 mg/day, the dose is tapered more gradually, and the amount of steroid is reduced to a maintenance dose over a period of 3–6 months [9].

At the Mayo Clinic, an initial prednisolone dose of 40 mg/day was administered for 4 weeks, followed by tapering of 5 mg per week (total of 11 weeks of treatment) [14]. According to Park et al. [16] in Seoul, the induction dosage of prednisolone was initially administered at 0.5 mg/kg/day for 1–2 months and was gradually reduced by 5–10 mg per month to the maintenance dose, and maintenance therapy stopped completely after an average period of 6 months.

Because radiological improvement appears 1–2 weeks after the start of steroid therapy, morphological and serological evaluation for effectiveness of steroid therapy should be performed 1–2 weeks after starting steroid therapy. A poor response to steroid therapy should raise the possibility of pancreatic cancer and the need for re-evaluation of the diagnosis [9].

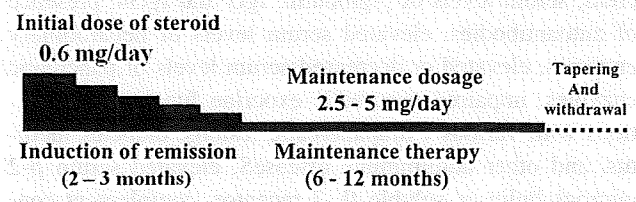

Fig. 1 Regimen of oral steroid therapy for AIP. Ref. [25] is partially modified

CQ-III-5. Is maintenance steroid therapy necessary?

- To prevent relapse, maintenance therapy (2.5–5 mg/day) is recommended. (Level of recommendation: B)

Description There have been no prospective studies on the necessity of maintenance therapy in steroid therapy for AIP. In Japan, steroid therapy is usually stopped after some period of maintenance therapy. The relapse rate of AIP during or after steroid therapy is reported to be 10% (4/41) [10] to 53% (16/30) [20].

At the Mayo Clinic, initial steroid therapy finished after 11 weeks, and maintenance therapy was not performed. Under this regimen, 16 (53%) of 30 AIP patients associated with sclerosing cholangitis relapsed within median 3 months (0–14 months) after therapy, and this rate did not differ from the relapse rate in surgically treated patients (44%; 8/18) [20].

According to the survey by the Research Committee of Intractable Pancreatic Diseases [21], 38 (40%) of 96 AIP patients who underwent maintenance therapy relapsed, and of these, relapse occurred only in the pancreas in 19 (50%), only in extrapancreatic lesions in 11 (29%), and in both lesions in 8 (21%). The relapse rate of patients during maintenance therapy with prednisolone of more than 5 mg/day was 26% (10/38), which was significantly lower than the rate (54%, 14/26) in patients who stopped maintenance therapy ($p < 0.05$) (Fig. 2).

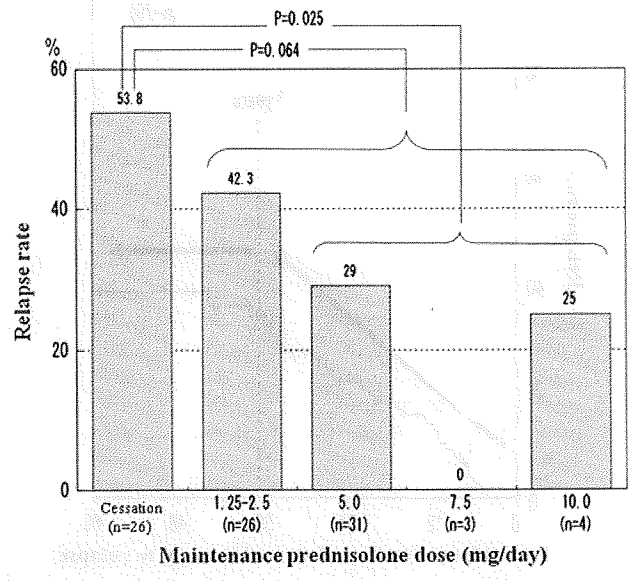

Fig. 2 Relationship between relapse rate of AIP and prednisolone dose during maintenance steroid therapy

Based on these findings, maintenance steroid therapy appears to be effective in preventing AIP relapse. As the anti-inflammatory and immunosuppressive effects of steroids appear to suppress the activity of AIP, maintenance therapy by prednisolone by at least 5 mg/day is recommended. However, as some patients do not relapse without maintenance therapy, and some patients relapse during steroid tapering [20, 22] or during maintenance therapy with relatively high doses of prednisolone, in order to judge the indications of maintenance therapy, it is important to evaluate disease activity in the patient. The Research Committee of Intractable Pancreatic Diseases compared the clinical features of patients with and without relapse, and reported that the clinical features of patients who tended to relapse included pancreatic enlargement of more than one-third of the entire pancreas, association with extrapancreatic lesions diagnosed by Gallium scintigraphy, and association with extrapancreatic sclerosing cholangitis [21]. In a Mayo Clinic report [20], the presence of proximal extrahepatic/intrahepatic strictures was predictive of relapse in AIP patients with sclerosing pancreatitis. Hirano et al. [19] also reported that obstructive jaundice at onset was a significant predictive factor for relapse of AIP.

CQ-III-6. When should steroid therapy be stopped?

- Steroid therapy should be stopped based on the disease activity in each case.

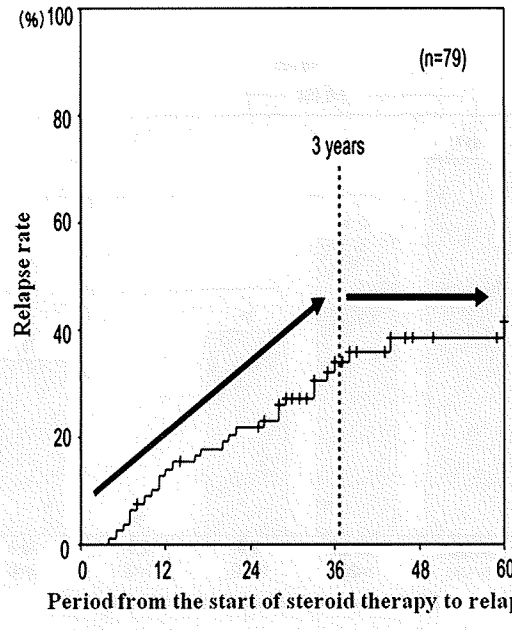

Fig. 3 Relapse rate of AIP and period from the start of steroid therapy to relapse

- Stopping of maintenance therapy should be planned within at least 3 years, in cases with radiological and serological improvement. (Level of recommendation: I)

Description There is no consensus about the duration of steroid therapy in AIP patients. According to Kamisawa et al. [10], steroid medication was stopped an average of 19.5 months after the start of steroid therapy in 9 patients with complete morphological and serological resolution, and none of these patients relapsed.

According to the survey by the Research Committee of Intractable Pancreatic Diseases [21], most patients relapsed within 3 years from the start of steroid therapy (Fig. 3). In those patients relapsing after 3 years, the incidence of patients stopping steroid therapy was higher than that of cases during maintenance therapy. There were no differences in the period of steroid therapy between relapsed cases after stopping steroid therapy (12.8 $\pm$ 8.9 months, 1–30 months, $n = 14$) and non-relapsed cases after stopping steroid therapy (13.5 $\pm$ 10.5 months, 1–31 months, $n = 11$).

Maintenance therapy is effective to prevent relapse. However, since AIP patients are typically elderly and are at high risk of developing steroid-related complications, such as osteoporosis and diabetes mellitus, cessation of the medication should be attempted. Cessation of maintenance therapy should be planned within at least 3 years, in cases with radiological and serological improvement. When stopping medication, it is necessary to evaluate disease activity. After stopping medication, patients should be followed up for relapse of AIP [9, 21].

CQ-III-7. Is early prediction of AIP relapse possible?

- In patients with a relapse of AIP, pancreatic enlargement on imaging, elevated serum IgG4 levels, elevated serum hepatobiliary and pancreatic enzymes, re-appearance of extrapancreatic lesions, elevated soluble IL-2 receptor or immune complex, and consumption of complement are detected. (Level of recommendation: B)

Description The Research Committee of Intractable Pancreatic Diseases evaluated disease activity of AIP using score. Scores took into account enlargement of the pancreas, serum levels of γ-globulin, IgG and IgG4, presence of autoantibodies, elevated serum levels of hepatobiliary enzymes, elevated or decreased serum levels of pancreatic enzymes, impaired pancreatic exocrine function, associations with various extrapancreatic lesions, diabetes mellitus, and other autoimmune diseaseS, elevated serum β-2 microglobulin or soluble IL-2 receptor, complement consumption, and elevation of immune complexes. Score of AIP activity was 12.2 before steroid therapy and decreased