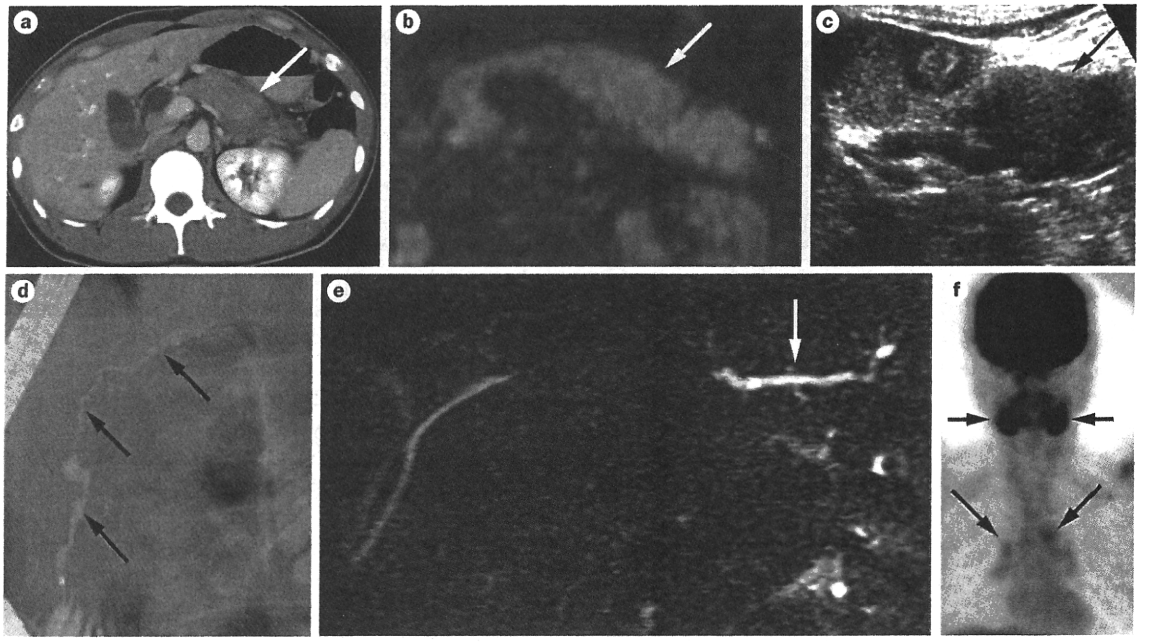

Figure 1 | Radiological findings of patients with autoimmune pancreatitis (AIP). **a** | Diffuse enlargement of the pancreas showing delayed enhancement with a capsule-like rim (arrow) on CT. **b** | Diffusion-weighted MRI showing diffuse high intensity area in the pancreas (arrow) (b = 800 mm^2/s). **c** | Segmental-type AIP of the pancreatic head obstructing the lower common bile duct on ultrasound (arrow). Such cases are difficult to differentiate from pancreatic cancer. **d** | Diffuse irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography. Degree of narrowing varies at different points along the duct (arrows). **e** | Magnetic resonance cholangiopancreatography does not show the narrowed portion of the main pancreatic duct, but the upstream dilatation is reduced compared with in pancreatic cancer (arrow). **f** | Whole-body ^{18}F-fluorodeoxyglucose (FDG)-PET coronal maximum intensity projection image showing pathologic FDG uptake in the salivary glands (short arrows) and hilar lymph nodes (long arrows) as well as in the pancreas.

enlargement of the pancreas is rather specific to AIP. However, segmental-type AIP involving one or two parts of the head, body or tail of the pancreas frequently forms a mass and is sometimes difficult to differentiate from pancreatic cancer (Figure 1c). Pancreatic calcification or a pseudocyst is uncommon. An irregular narrowing (<3 mm in diameter) of the main pancreatic duct is a characteristic pancreatographic finding of AIP. The degree of narrowing of the main pancreatic duct sometimes varies at different points along the duct in the same patient (Figure 1d). In patients with segmental-type AIP, the distal main pancreatic duct is less dilated than in patients with pancreatic cancer.[42] The rate of obstructive jaundice is low in patients with AIP who do not have involvement of the ventral pancreas.[47] Ultrasound scans or endoscopic ultrasonography (EUS) sometimes reveal thickening of the wall of the gallbladder or of the extrahepatic bile duct.[48] Magnetic resonance cholangiopancreatography (MRCP) cannot demonstrate narrowing of the main pancreatic duct in many cases (because of the poor spatial resolution), but less upstream dilatation of the main pancreatic duct is indicative of AIP (Figure 1e).[49] Stenosis of the portal vein or encasement of the peripancreatic arteries are frequent angiographic findings.[43,50] In our study of ^{18}F-fluorodeoxyglucose PET (FDG-PET), FDG uptake in the pancreas was observed in all 10 patients with AIP and 14 patients with pancreatic cancer, but the maximal standardized uptake value (SUVmax) was 5.2 in patients with AIP, while five patients with pancreatic cancer had SUVmax values greater than 5.2.[51] Abnormal extrapancreatic FDG uptake, such as in the lymph nodes or swollen salivary glands, is highly suggestive of AIP (Figure 1f).[51,52]

Histopathological findings

Extensive infiltration of $CD4^+$ or $CD8^+$ T lymphocytes and IgG4-positive plasma cells, and fibrosis in a periductal and interlobular distribution are common histological findings in surgical specimens of AIP (Figure 2a,b). Inflammatory cells frequently infiltrate the perineural space. The epithelium of the narrowed pancreatic duct is usually well preserved. Obliterative phlebitis is frequently detected in the pancreatic veins (Figure 2c).[1,7–10,53] Song *et al.*[54] reported histological recovery of the pancreas after steroid therapy for AIP.

Although cytologic examination of EUS-guided fine-needle aspiration specimens is insufficient for diagnosing AIP, EUS-guided trucut biopsy can make a significant contribution to the diagnosis of AIP by histological examination.[55,56] Sensitivity of diagnosing AIP using EUS-guided trucut biopsy is reported to be 86–100%.[55,56]

Diagnostic criteria and differential diagnosis

AIP is diagnosed using a combination of clinical, laboratory and radiological findings. The Japanese 'Diagnostic Criteria for Autoimmune Pancreatitis' were proposed in 2002 and revised in 2006.[2] These criteria include radiological evidence of enlargement of the pancreas and

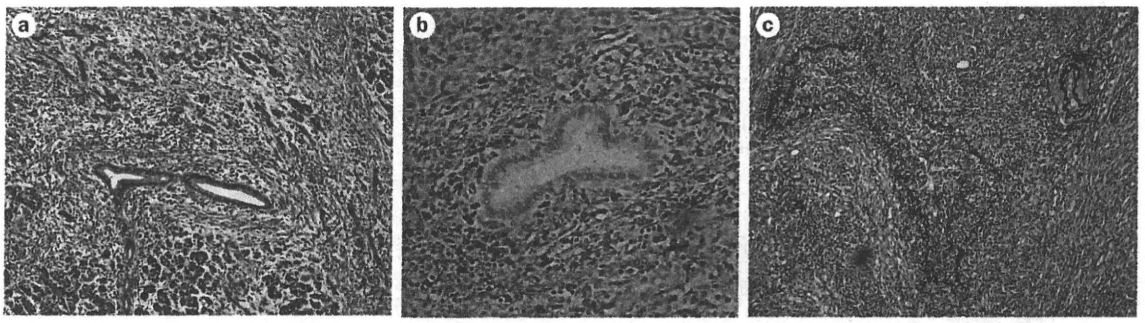

Figure 2 | Histological findings of the pancreas of patients with autoimmune pancreatitis. **a** | Prominent periductal and interlobular fibrosis with a dense lymphoplasmacytic infiltration and acinar destruction (H&E). **b** | Abundant infiltration of IgG4-positive plasma cells (IgG4 immunostaining). **c** | Obliterative phlebitis of the pancreatic veins with prominent lymphoplasmacytic infiltrate and fibrosis (Elastica Van Gienson).

irregular narrowing of the main pancreatic duct; laboratory findings of increased serum gammaglobulin, IgG and IgG4 levels, or the presence of autoantibodies; and histological evidence of lymphoplasmacytic infiltration and fibrosis in the pancreas. In 2006, new diagnostic criteria were proposed in Korea[57] and the USA[58] that included two more factors: response to steroid therapy and other organ involvement. Diagnostic criteria from the Mayo Clinic (known by the mnemonic HISORt) consist of characteristic features of AIP, including pancreatic histology and imaging, serology, other organ involvement and response to steroid therapy. In these criteria, histology is considered the gold standard for diagnosis of AIP.[58] In 2008, Japanese and Korean pancreatologists included response to steroid as an optional criterion in the Asian diagnostic criteria.[59] Revised HISORt criteria were proposed in 2009.[32]

The most important disease that should be differentiated from AIP is pancreatic cancer. In our comparative study between mass-forming AIP and pancreatic head cancer, fluctuating jaundice, salivary gland involvement and serum IgG4 elevation were more common in patients with AIP than in those with pancreatic cancer. Three CT findings (a capsule-like rim, delayed enhancement of the swollen pancreas and the presence of extrapancreatic lesions) and three endoscopic retrograde pancreatography findings (≥3 cm-long narrowed main pancreatic duct, maximal upstream main pancreatic duct <5 mm and skipped lesions) suggest AIP rather than pancreatic cancer.[60] On the basis of these factors, an algorithm can be used to determine how to manage patients. Patients with no imaging features that suggest AIP should be managed as having cancer; those with three or more imaging features, or two imaging features and increased serum IgG4 levels should be managed as having AIP and given steroid therapy. Those patients with only one imaging feature or patients with two imaging features without increased serum IgG4 levels should be given steroid therapy after a negative histological work-up using fine-needle aspiration.[60,61] IgG4 immunostaining of biopsy specimens taken from the major duodenal papilla of patients with AIP is useful to support the diagnosis of AIP.[62,63]

Although a steroid diagnostic trial is useful in some cases to differentiate AIP from pancreatic cancer,[64] it should only be performed with extreme caution by pancreatologists and in limited cases after a negative work-up for pancreatic cancer, including EUS-guided fine-needle aspiration.[59,65,66]

Treatment and prognosis

Although AIP improves spontaneously in some patients,[67] orally administered steroids are the standard therapy. It is important to distinguish AIP from pancreatic cancer before starting steroid therapy in order to avoid delaying surgery for pancreatic cancer, which could lead to cancer progression. The indications for steroid therapy in patients with AIP are symptoms such as obstructive jaundice, abdominal pain and hydronephrosis. Before steroid therapy, the blood glucose level should be controlled using insulin in patients with diabetes, and obstructive jaundice should be managed by endoscopic or transhepatic biliary drainage. An initial dose of oral prednisolone 0.6 mg/kg daily is recommended.[65,66] Morphological and serological evaluation of the effectiveness of steroid therapy should be performed 2 weeks after its initiation. A poor response to steroid therapy should raise the possibility of a diagnosis of pancreatic cancer and the need for re-evaluation of the diagnosis. If steroid therapy is effective, the dose should be tapered by 5 mg every 1–2 weeks until it reaches 15 mg per day. Careful monitoring of the patient's symptoms, as well as of the biochemical, serological and imaging findings, should be performed.[65,66] After this period, the steroid dose should be tapered more gradually to a maintenance dose over a period of 3–6 months.

To prevent relapse, steroid maintenance therapy (5 mg per day) for at least 6 months is recommended in almost all patients treated with steroids.[65] In patients who achieve complete remission 1 year after initial administration of steroids, maintenance therapy can be withdrawn. Withdrawal of maintenance therapy should be planned within at least 3 years of its initiation (Figure 3).[65,66]

Factors that predict disease relapse include the presence of proximal bile duct involvement[68] and persistent elevation of serum IgG4 levels.[65] In patients who relapse, re-administration or increasing the dose of steroid therapy[65,66,69] or the administration of immunosuppressive drugs, such as azathioprine,[33] is effective.

The long-term prognosis of AIP is still unclear because of many factors that may influence disease progression,

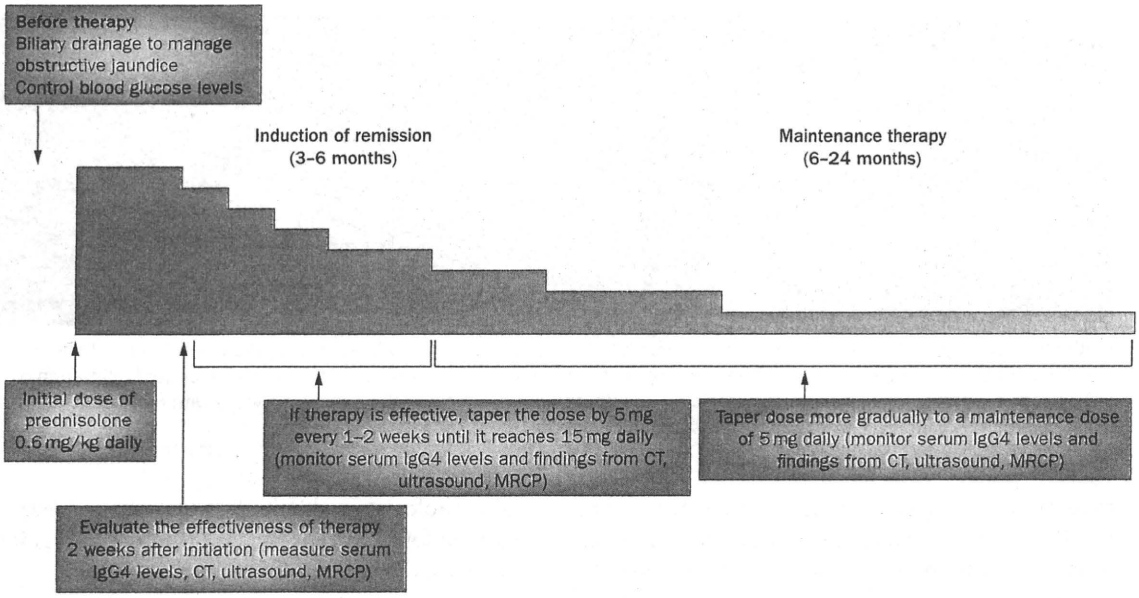

Figure 3 | Standard treatment strategy for autoimmune pancreatitis. An initial dose of prednisolone 0.6 mg/kg daily is recommended, which should be tapered gradually if therapy is effective. The effectiveness of steroid therapy should be monitored throughout by morphological and serological evaluation. To prevent relapse, steroid maintenance therapy is recommended for at least 6 months. Abbreviation: MRCP, magnetic resonance cholangiopancreatography.

such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy.[66,70] A study has shown that the pancreas becomes atrophic in 12 of 41 (29%) patients 1 or 2 years after starting steroid therapy.[69] Kawa *et al.*[71] reported that pancreatic stone formation was detected in 7 of 21 (33%) patients who experienced a relapse of AIP. 11 cases of pancreatic cancer associated with AIP have been reported.[12] Although it is unclear whether there is a relationship between AIP and pancreatic cancer, frequent *KRAS* mutations have been detected in gastrointestinal regions, as well as in pancreatobiliary regions, in patients with AIP.[72,73]

Idiopathic duct-centric pancreatitis

From retrospective, histological examination of the resected pancreases of patients with mass-forming chronic pancreatitis, American and European pathologists have described another unique histological pattern in AIP and termed it idiopathic duct-centric pancreatitis (IDCP),[74] or AIP with granulocytic epithelial lesion (GEL).[75]

IDCP is a form of pancreatitis characterized by neutrophilic infiltration in the pancreas, which is not seen in LPSP. Obliterative phlebitis and infiltration of IgG4-positive cells are uncommon in IDCP. The need for histological examination to diagnose IDCP at present makes clinical diagnosis difficult. IDCP is sometimes detected in Western countries, but is uncommon in Japan and Korea.[74–77] On the basis of early reports, it seems that IDCP affects younger patients than LPSP, may not have a male preponderance and does not generally involve other organs, except for some association with IBD.[74,75] Frulloni *et al.*[78] found that a high proportion of Italian patients with AIP were women, they had a low average age (43.4 years), a low prevalence of serum IgG4 elevation, frequent associations with acute pancreatitis (32%) and ulcerative colitis (30%), and rare involvement of other organs. This clinical profile of Italian patients with AIP suggests that a fair proportion of them had IDCP. At our institution, abdominal pain and increased serum amylase levels are more frequent in young patients with AIP than middle-aged or elderly patients, which could be indicative of IDCP.[79] LPSP and IDCP are clinicopathologically different entities (Table 1), and have been designated as AIP type 1 and AIP type 2, respectively.[76,77,80,81] Further study is necessary to clarify this subtype of AIP.

IgG4-related sclerosing disease

Fibrosis and extensive infiltration of IgG4-positive plasma cells and T lymphocytes is detected in the peripancreatic retroperitoneal tissue, bile duct wall, periportal area of the liver, gallbladder wall, salivary glands and the pancreas of many patients with AIP.[7–10,53] Various extrapancreatic lesions associated with AIP also show these peculiar histological findings.[7–10,53] Serum IgG4 levels are significantly and frequently elevated in patients with AIP.[39] Pancreatic and extrapancreatic lesions of AIP improve after steroid

Table 1 | Clinicopathological features of LPSP and IDCP

Clinicopathological feature	LPSP	IDCP
Age	Elderly	Young or middle-aged
Gender affected	Male > female	Male ≥ female
Sclerosing extrapancreatic lesions	Frequent	Rare
Acute pancreatitis	Rare	Occasional
IBD	Rare	Occasional
Elevation of serum IgG4 levels	Frequent	Rare
Infiltration of IgG4-positive cells	Frequent	Rare
Neutrophilic infiltration	Rare	Frequent

Abbreviations: IDCP, idiopathic duct-centric pancreatitis; LPSP, lymphoplasmacytic sclerosing pancreatitis.

Box 1 | Clinicopathological findings of IgG4-related sclerosing disease

- Systemic disease characterized by extensive IgG4-positive plasma cell and T-cell infiltration of various organs
- Major clinical manifestations are apparent in the organs in which tissues fibrosis with obstructive phlebitis is pathologically induced: autoimmune pancreatitis; cholangitis; cholecystitis; sialadenitis; dacryoadenitis; retroperitoneal fibrosis; pseudotumor
- Elderly male preponderance
- Frequent elevation of serum IgG4 levels
- Responsive to steroid therapy
- Occasional association with lymphadenopathy
- Precise pathogenesis and pathophysiology remain unclear

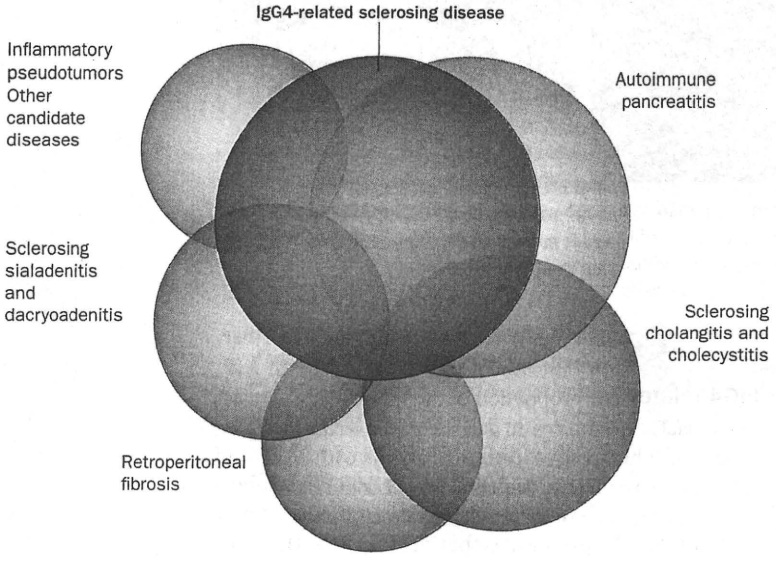

Figure 4 | Schematic illustration of the concept of IgG4-related sclerosing disease, which is a systemic disease in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs. Autoimmune pancreatitis may be one manifestation of this disease; other organs with tissue fibrosis and obliterative phlebitis also show clinical manifestations.

Table 2 | Incidence of extrapancreatic lesions of autoimmune pancreatitis

Extrapancreatic lesion	Our series (%)	Japan[84] (%)	Korea[34] (%)	USA[85] (%)	Italy[78] (%)
Sclerosing cholangitis*	8	26	7	35	NA
Sclerosing sialadenitis	24	14	4	15	NA
Retroperitoneal fibrosis	6	10	3	8	2
Hilar lymphadenopathy	12	8	1	NA	NA
Renal lesions	14	8	NA	NA	2
Ulcerative colitis	3	0	3	NA	30

*Proximal bile duct. Abbreviation: NA, not available.

therapy. Therefore, we proposed a novel clinicopathological entity: 'IgG4-related sclerosing disease' (Box 1, Figure 4).[7-10] Organs with tissue fibrosis and obliterative phlebitis, such as the pancreas, salivary gland and retroperitoneum, show clinical manifestations of this disease. Given that a mass is formed in most cases of IgG4-related sclerosing disease, a malignant tumor is frequently suspected on initial presentation. Clinicians should consider IgG4-related sclerosing disease in the differential diagnosis to avoid unnecessary surgery.

We found that in patients with AIP who had high serum IgG4 levels, extrapancreatic lesions were more frequently detected,[82] and more IgG4-positive plasma cells infiltrated the various organs.[83] The reported incidence of extrapancreatic lesions in patients with AIP is summarized in Table 2.[34,78,84,85]

Although the etiology of multifocal fibrosclerosis, which is a fibroproliferative systemic disorder with multiple manifestations (including sclerosing cholangitis, retroperitoneal fibrosis, fibrosis of the salivary glands, Riedel's thyroiditis and fibrotic pseudotumor of the orbit), is unknown,[86,87] it may correspond to IgG4-related sclerosing disease.[53] Two similar concepts, IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS)[88] and systemic IgG4-related plasmacytic syndrome (SIPS),[89] have also been proposed.

IgG4-related sclerosing cholangitis

IgG4-related sclerosing cholangitis is frequently associated with AIP. In many patients with AIP, the stenosis is located in the lower part of the common bile duct (79% in our series[90]). Sclerosing cholangitis in the intrahepatic or the hilar hepatic bile duct of patients with AIP (9% in our series[90]) demonstrates a cholangiographic appearance similar to primary sclerosing cholangitis (PSC). Bile duct stricture limited to the distal intrapancreatic portion is not usually regarded as an extrapancreatic lesion of AIP because stenosis of the lower bile duct is sometimes induced by compression by the swollen pancreas. Histologically, IgG4-related sclerosing cholangitis consists of transmural fibrosis (Figure 5a) and dense infiltration of IgG4-positive plasma cells and T lymphocytes, along with their infiltration and fibrosis in the periportal area of the liver (Figure 5b). Compared with patients with PSC, a preponderance of males, older age, obstructive jaundice, segmental stenosis of the lower bile duct, elevation of serum IgG4 levels, association with other sclerosing diseases, response to steroid treatment and abundant infiltration of IgG4-positive plasma cells are significantly more frequent in IgG4-related sclerosing cholangitis.[90,91] A diffusely distributed, beaded and pruned-tree appearance, and association with ulcerative colitis were more common in patients with PSC. Given these findings, it seems that IgG4-related sclerosing cholangitis is distinct from PSC.[90,91]

IgG4-related sclerosing cholecystitis

Ultrasound and/or CT revealed that the gallbladder wall was thickened in 32% of patients with AIP in our series.[10] IgG4-related sclerosing cholecystitis consists of transmural fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes.[92,93]

IgG4-related sialadenitis and dacryoadenitis

Swelling of the salivary glands and lacrimal glands was reported in 24% and 3% of patients with AIP, respectively, and has been associated with cervical or mediastinal lymphadenopathy.[9,10] Swelling of these glands improved after steroid therapy. Histopathologic analysis of these lesions revealed sclerosing sialadenitis[94] and

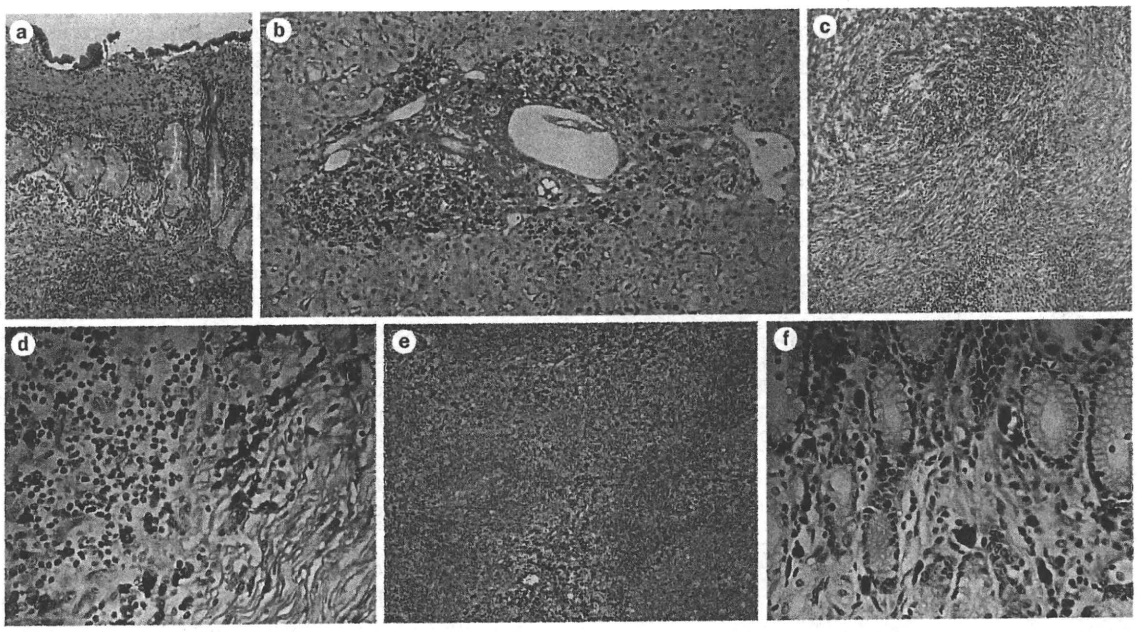

Figure 5 | Histological findings of IgG4-related sclerosing diseases. **a** | IgG4-related sclerosing cholangitis, consisting of transmural fibrosis and lymphoplasmacytic infiltration (H&E). **b** | Abundant infiltration of IgG4-positive cells in the periportal area of the liver (IgG4 immunostaining). **c** | IgG4-related sclerosing sialadenitis showing interstitial fibrosis and lymphoplasmacytic infiltration (H&E). Abundant infiltration of IgG4-positive cells in the **d** | salivary gland, **e** | lymph node, and **f** | gastric mucosa (IgG4 immunostaining).

dacryoadenitis[95] with fibrosis and dense infiltration of IgG4-positive plasma cells (Figure 5c,d). Swelling of the salivary glands preceded AIP in eight patients in our series.[96] Recently, Mikulicz's disease has been recognized as the same lesion as IgG4-related sclerosing sialadenitis and dacryoadenitis.[89] Salivary gland and lacrimal gland functions were impaired in patients with AIP and improved after steroid therapy.[35,97,98]

IgG4-related retroperitoneal fibrosis

Retroperitoneal fibrosis was reported preceeding AIP ($n = 1$), simultaneous with AIP ($n = 2$), and subsequent to AIP ($n = 1$) in 56 patients with AIP.[96] Retroperitoneal mass consisted of dense fibrosis with infiltration of IgG4-positive plasma cells and obliterative phlebitis, and improved with steroid therapy.[99]

IgG4-related tubulointerstitial nephritis

Tubulointerstitial nephritis is sometimes associated with AIP.[100] Takahashi *et al.*[101] reported that 14 (35%) patients with AIP had renal involvement and the renal lesions improved with steroid therapy. CT revealed nodular cortical renal lesions in 14% of patients in our series.[102] Many IgG4-positive plasma cells infiltrated the renal interstitium.[100]

IgG4-related interstitial pneumonia

Interstitial pneumonia with infiltration of IgG4-positive plasma cells in the thickened interstitium and alveoli seems to be a pulmonary manifestation of IgG4-related systemic disease and is also responsive to steroid therapy.[103,104] Pulmonary nodular lesions were also reported in some patients with AIP on CT.[104]

IgG4-related inflammatory pseudotumors

IgG4-related inflammatory pseudotumors (of the liver,[105] lung[106] and breast[107]) with fibrosis, dense infiltration of IgG4-positive plasma cells and lymphocytes and obliterative phlebitis have been reported in patients with or without AIP. Hypophysitis that presented with hypopituitarism and swelling of the pituitary lesion with abundant infiltration of IgG4-positive plasma cells has also been reported in association with AIP.[108]

IgG4-related lymphadenopathy

According to Hamano *et al.*,[109] pulmonary hilar lymphadenopathy was the most frequent extrapancreatic lesion (80%) of AIP and it disappeared after steroid therapy. Cheuk *et al.*[110] reported that the histological features of the lymph nodes of IgG4-related sclerosing disease could be categorized into three patterns: Castleman disease-like; follicular hyperplasia; and interfollicular expansion by IgG4-positive cells (Figure 5e).

Other candidate IgG4-related diseases

Other reported lesions that may be associated with IgG4-related disease are prostatitis,[111] inflammatory abdominal aortic aneurysm[112] and gastrointestinal lesions (Figure 5f).[113–115]

Conclusions

AIP is a unique form of pancreatitis in which the pathogenesis is suspected to involve autoimmune mechanisms. This disease seems to represent one manifestation of IgG4-related sclerosing disease. AIP should be diagnosed on the basis of a combination of characteristic clinical, serological, morphological and histopathological features.

IgG4-related sclerosing disease is a systemic disease, in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs. Organs with tissue fibrosis and obliterative phlebitis show clinical manifestations. Although a malignant tumor is frequently suspected on initial presentation, clinicians should consider IgG4-related sclerosing disease in the differential diagnosis to avoid unnecessary surgery.

Review criteria

We searched MEDLINE from 1992 to March 2010 for relevant English-language articles, using a combination of the search terms "autoimmune pancreatitis", "IgG4", "sclerosing cholangitis", and "sclerosing sialadenitis". Additional sources were identified by scanning the bibliographies of original and review articles.

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Acknowledgments

This work was partially supported by a grant-in-aid for refractory pancreatic disease from the Ministry of Health, Labor and Welfare of Japan.

J Gastroenterol (2010) 45:471–477
DOI 10.1007/s00535-010-0221-9

REVIEW

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

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Received: 4 February 2010 / Accepted: 4 February 2010 / Published online: 9 March 2010

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

This article is the third of a three-article series on the Japanese consensus guidelines. The first and second articles are available at doi:10.1007/s00535-009-0184-x and doi:10.1007/s00535-009-0197-5, respectively. Names of committee members are provided in the first article.

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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 $\pm$ 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].

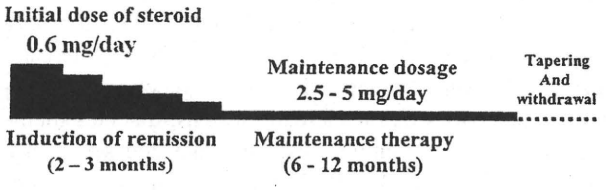

Fig. 1 Regimen of oral steroid therapy for AIP. Ref. [25] is partially modified

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).

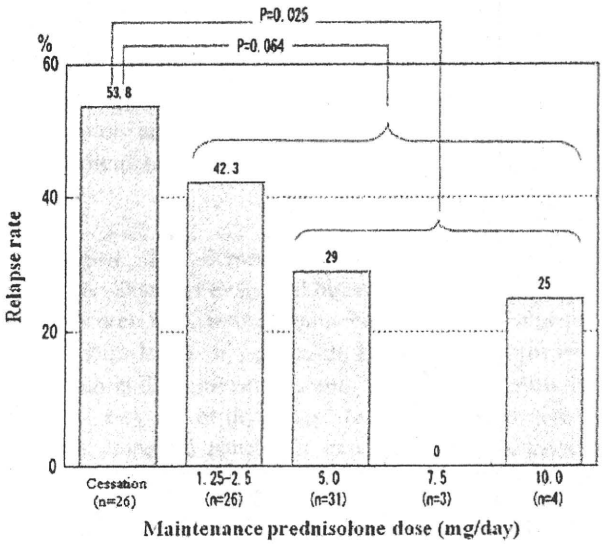

Fig. 2 Relationship between relapse rate of AIP and prednisolone dose during maintenance steroid therapy

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.

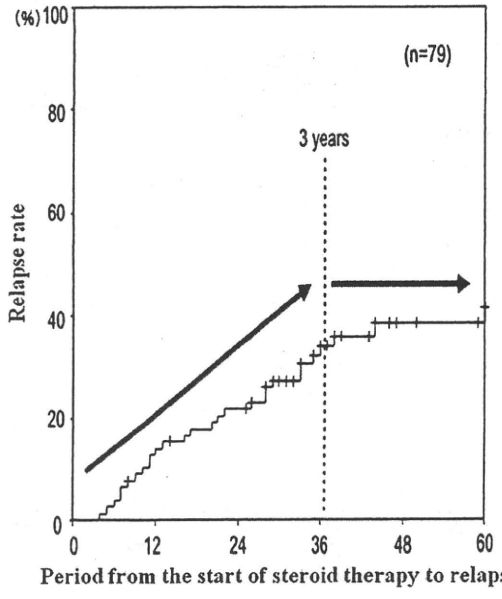

Fig. 3 Relapse rate of AIP and period from the start of steroid therapy to relapse

- 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 ± 8.9 months, 1–30 months, $n = 14$) and non-relapsed cases after stopping steroid therapy (13.5 ± 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

to 1.83 after steroids. These findings suggest that the scoring system reflects disease activity of AIP. However, it is unclear whether the system can predict early AIP relapse. Cutoff values suggesting relapse are also unknown [23].

CQ-III-8. How are AIP relapses treated?

- Re-administration or dose-up of steroid is effective for treating AIP relapses.
- Remission can be obtained with the same prednisolone dose as the initial dose in most relapsed AIP cases, but it may be necessary to taper more gradually. (Level of recommendation: I)

Description Remission can be obtained with re-administration or dose-up of steroid in most relapsed AIP cases. According to Kamisawa et al. [10], 4 AIP patients who relapsed at pancreatic or extrapancreatic lesions during maintenance therapy obtained remission with dose-up (30 mg/day) of steroid. Nishino et al. reported that bile duct stenosis and swelling of the salivary glands relapsed during steroid tapering in 1 and 3 patients respectively, but they improved with dose-up steroid. They also tapered the steroid more gradually (1 mg/2 weeks) as compared with the speed of initial therapy in relapsed cases [22]. At the Mayo Clinic, second relapse occurred in 4 of 11 patients with first relapse, despite slow steroid tapering after the second induction therapy. They also reported that immunomodulatory drugs such as azathioprine (initial dose of 50 mg/day, increasing to 2–2.5 mg/kg) and mycophenolate mofetil (initial dose of 500 mg twice daily, increasing to 750 mg twice daily) were effective in 7 relapsed AIP patients, and none of these patients relapsed (median follow-up period on immunomodulatory drugs alone, 6 months; range, 2–19 months) [20]. Although immunomodulatory drugs appear to prevent relapse and to maintain remission, indications for these drugs should be judged carefully based on their adverse effects.

CQ-III-9. Do pancreatic exocrine and endocrine functions improve after steroid therapy in AIP patients?

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

Description Many AIP patients have associated pancreatic exocrine and endocrine dysfunction [2, 7, 11, 24–26]. It has been reported that improvement of pancreatic exocrine and endocrine function was detected after steroid therapy in 38% [22] to 50% [25] and 25% [22] to 45% [25] of AIP patients, respectively. It has also been suggested as a mechanism of improvement in pancreatic exocrine and endocrine functions after steroid therapy that steroid suppresses lymphoplasmacytic cell infiltration and fibrosis, permitting the attenuation of blood flow [26] and further regenerating islet cells by suppression of cytokine production [27]; however, the precise mechanisms remain unclear.

Diabetes mellitus control worsens in 75% of AIP patients with type 2 diabetes mellitus before AIP onset after steroid therapy [25]. DM also develops after steroid therapy in some AIP patients [24, 25]. We should therefore take occurrence of DM into consideration in patients who continuously undergo steroid therapy.

CQ-III-10. Is the prognosis of AIP good?

- 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. (Level of recommendation: B)

Description The relapse rate of AIP is reported to be 10% [10] to 53% [20] in patients treated with steroids, and 28% [28] to 35% [20] in those without steroid therapy.

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

Nishino et al. [22] reported that pancreatic atrophy developed in 33% of 12 patients, and 1 patient developed early gastric cancer after 29 months of steroid therapy, while another patient developed advanced rectal cancer after 13 months of steroid therapy. According to Hirano et al., unfavorable events occurred in 32% of AIP patients treated with steroid therapy during an average 41-month follow-up period, and they occurred in 70% of those without steroid therapy during an average follow-up of 61 months. Furthermore, 1 patient treated with steroid therapy died of acute myelocytic leukemia, 1 patient not treated with steroid therapy died of lung cancer, and 1 patient not treated with steroid therapy died of pancreatic cancer [19]. Kubota et al. [3] also reported 4 patients who were diagnosed as having a malignancy during follow-up (pancreatic cancer, $n = 2$; breast cancer, $n = 2$; gastric cancer, $n = 1$). Kamisawa et al. [10] reported that marked atrophy of the pancreas was observed in 30% of AIP patients during follow-up. Park et al. [16] reported that 13 (33%) of 40 patients treated with steroids relapsed during a median follow-up period of 40 months, with 7 relapsing on the maintenance dose of prednisolone (2.5–7.5 mg/day), and the remaining 6 patients relapsing while off steroids. According to Ghazale et al. [20],

16 (53%) of 30 patients treated with steroids relapsed during a median follow-up period of 30 months. They also reported that 7 of 53 AIP patients died and that pancreatic cancer and metastatic pancreatic cancer developed.

In 37 AIP patients who underwent pancreatoduodenectomy, no patients relapsed during a median follow-up period of 33 months, and 68% subjectively rated their quality of life as better [29]. On the other hand, among 29 surgically resected AIP patients, 8 (28%) relapsed at a median time to recurrence of 11 months during a median follow-up period of 38 months [28]. Schneldorfer et al. [30] reported that in 8 surgically resected AIP patients, improved quality of life (QOL) was seen in almost half of patients, but 2 (25%) patients relapsed.

CQ-III-11. Is there any relationship between AIP and pancreatic cancer?

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

Description It has been reported that chronic pancreatitis is one of the risk factors for pancreatic cancer [31]. It has been reported that some AIP patients developed pancreatic atrophy or pancreatic stones [32, 33]. AIP occurred predominantly in the elderly males. It is necessary to observe whether there is an association with pancreatic cancer and other malignancies in AIP patients treated with steroid for a long period, since steroid therapy is immunosuppressive. Periodic checks of serum tumor markers are necessary during follow-up.

There have been 6 recent papers reporting AIP cases developing pancreatic cancer [34–39]. The locations of these cancers were the pancreatic head ($n = 1$), body ($n = 3$), and tail ($n = 2$). All patients were males, and average age was 72 years (62–80 years). Three pancreatic cancers were diagnosed simultaneously with AIP, and the other 3 cancers were diagnosed 3–5 years after the onset of AIP. Kamisawa et al. [40] reported frequent and significant K-ras mutations in the pancreas of AIP patients. However, it is unclear whether there is a relationship between AIP and pancreatic cancer.

Acknowledgments This study was supported by the grant-in-aid for the Refractory Pancreatic Disease from the Ministry of Labor, Health, and Welfare of Japan.

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IgG4-related sclerosing disease

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Abstract: Based on histological and immunohistochemical examination of various organs of autoimmune pancreatitis (AIP) patients, we have found dense infiltration of IgG4-positive plasma cells and T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show infiltration of abundant IgG4-positive plasma cells. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease. Some inflammatory pseudotumors may be involved in this disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected. The disease occurs predominantly in elderly males, is frequently associated with lymphadenopathy, and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. The precise pathogenesis and pathophysiology of IgG4-related sclerosing disease remain unclear. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery.

Key words: IgG4-related sclerosing disease, autoimmune pancreatitis, IgG4, sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis

1 Introduction

Yoshida et al. proposed the concept of autoimmune pancreatitis (AIP) in 1995 [1], and AIP has become a distinct entity recognized worldwide [2-4]. In AIP patients, serum IgG4 levels are frequently and significantly elevated, and various extrapancreatic lesions are present. Based on histological and immunohistochemical examination of various organs of AIP patients, we have found dense infiltration of IgG4-positive plasma cells and T

lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show infiltration of abundant IgG4-positive plasma cells. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease [5-8].

2 IgG4-related sclerosing disease

IgG4-related sclerosing disease is a systemic disease characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs such as the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, and etc. where tissue fibrosis with obliterative phlebitis is pathologically induced. AIP is not simply a pancreatitis but it is a pancreatic lesion reflecting an IgG4-related sclerosing disease. Some inflammatory pseudotumors may be involved in this disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (Fig.1). The disease occurs predominantly in elderly males, is frequently associated with lymphadenopathy, and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. The precise pathogenesis and pathophysiology of IgG4-related sclerosing disease remain unclear. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery (Table 1) [5-8]. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [5,9].

Table 1. Clinicopathological Findings of IgG4-related Sclerosing Disease

- Systemic disease characterized histopathologically by extensive IgG4-positive plasma cell infiltration of various organs together with T lymphocytes
- Major clinical manifestations are apparent in the organs in which tissues fibrosis with obstructive phlebitis is pathologically induced.
  Pancreas: autoimmune pancreatitis
  Bile duct: sclerosing cholangitis
  Gallbladder: sclerosing cholecystitis
  Salivary gland: sclerosing sialadenitis
  Lacrimal gland: sclerosing dacryoadenitis
  Retroperitoneum: retroperitoneal fibrosis
- Some pseudotumors may be involved in this disease.
- Possibility of close relationship to

multifocal fibrosclerosis
- Occasional association with lymphadenopathy
- Elderly male preponderance
- Frequent elevation of serum IgG4 levels
- Favorite response to steroid therapy
- Differentiation from malignant tumor is important.
- Precise pathogenesis and pathophysiology remain unclear

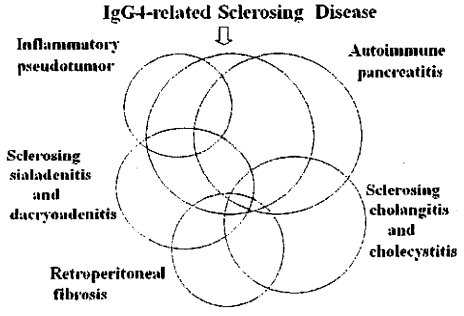

Fig.1 Schematic illustration of IgG4-related sclerosing disease

3 Autoimmune pancreatitis

AIP is a unique form of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. AIP occurs more commonly in elderly males. In our 57 AIP Patients, the mean age of the patients was 66.5 years (range, 25-83 years), and the male-to-female ratio was 4:1. The major clinical symptom is obstructive jaundice due to associated sclerosing cholangitis (70% in our series). Up to 50% of AIP patients present with glucose intolerance [10].

Levels of serum IgG4 are particularly high in AIP. Dense infiltration of IgG4-positive plasma cells is seen in various organs of AIP patients. These findings suggest that IgG4 plays a major role in the pathogenesis of AIP, although the trigger for the IgG4 elevation or its pathogenetic role in AIP has not been clearly disclosed [11,12].

It is of utmost importance that AIP be differentiated from pancreatic cancer, as some AIP patients in which pancreatic cancer is suspected undergo unnecessary laparotomy or pancreatic resection. Since there is currently no diagnostic serological marker for AIP, AIP should be diagnosed on the basis of the presence of a combination of abnormalities unique to AIP. The Japanese "Diagnostic Criteria for Autoimmune Pancreatitis" were revised in 2006 [13]. They consisted of three items: 1) radiological imaging showing diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas; 2) laboratory data demonstrating abnormally elevated levels of serum gammaglobulin or IgG, or IgG4, or the presence of autoantibodies; and 3) histological examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis. Diagnosis of AIP is made when either all 3 criteria are present or criterion 1 together with either criterion 2 or criterion 3 is present.

Radiologically, pancreatic enlargement is usually hypoechoic, sometimes with scattered hyperechoic spots on

ultrasonography (Fig.2).

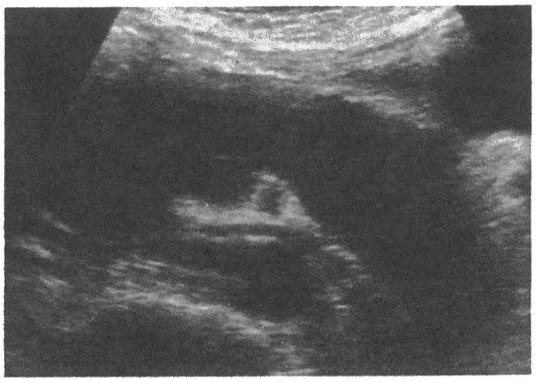

Fig.2 Ultrasonographic findings of AIP, showing hypoechoic pancreatic enlargement with scattered hyperechoic spots.

On dynamic CT, there is delayed enhancement of the enlarged pancreatic parenchyma. Typical AIP patients show diffuse enlargement of the pancreas, the so-called sausage-like appearance. Since inflammatory and fibrous changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low density on CT, is detected in some cases. Cases of focal enlargement of the pancreas are sometimes difficult to differentiate from pancreatic cancer.

Endoscopic retrograde cholangiopancreatography (ERCP) discloses an irregular, narrow main pancreatic duct. In patients with segmental narrowing, absence of upstream dilatation of the main pancreatic duct is characteristic. (Fig.3).

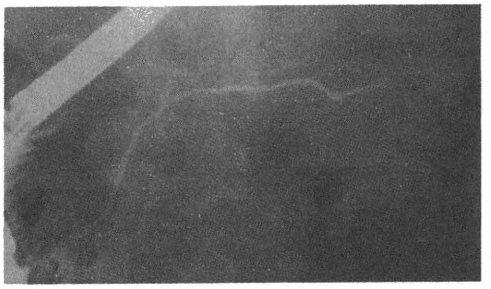

Fig.3 ERCP findings of AIP, showing irregular narrowing of the main pancreatic duct

In our AIP patients, hypergammaglobulinemia and elevated serum IgG levels are detected in 33% and 56%, respectively, while autoantibodies, including antinuclear antibody and rheumatoid factor, were present in 44% and 16%. Serum IgG4 levels are frequently and significantly elevated in AIP patients [14]. According to the report by Okazaki et al., anti-lactoferrin antibody, anti-carbonic anhydrase-II (CA II) antibody, anti-pancreatic secretory trypsin inhibitor (PSTI) antibody, and anti-smooth muscle antibody were detected in 75%, 55%, 25%, and 15% of their 54 AIP patients [15]. The sensitivity of elevated serum IgG4 levels was 80% in our series.

Histologically, dense lymphoplasmacytic infiltration, and interlobular and periductal fibrosis were detected in the pancreas of AIP patients (Fig. 4). These lesions are called as lymphoplasmacytic sclerosing pancreatitis (LPSP) [16]. Immunohistochemically, infiltrated lymphocytes were mainly T lymphocytes, and many plasma cells were

positive for anti-IgG4 antibody (Fig.5). The pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration. Another characteristic histological finding is obliterative phlebitis involving minor and major veins, including the portal vein.

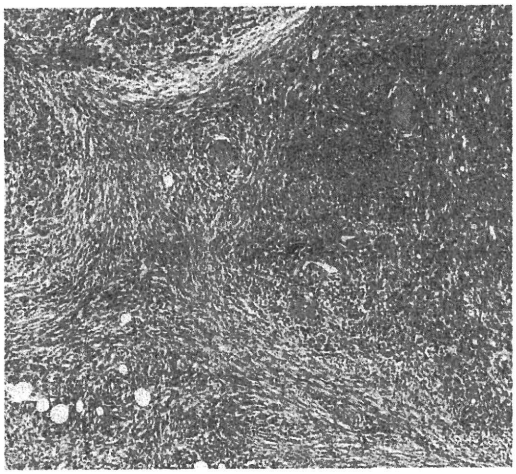

Fig. 4 Dense infiltration of lymphocytes and plasma cells and interlobular fibrosis in the pancreas of an AIP patient.

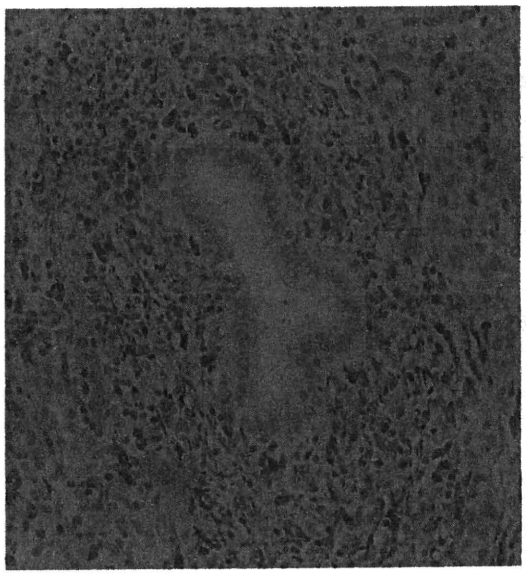

Fig.5 Immunohistochemical finding of AIP, showing abundant infiltration of IgG4-positive plasma cells in the pancreas (IgG4-immunostaining).

AIP responds dramatically well to corticosteroid. Oral steroid is a standard therapy for AIP. The indications for steroid therapy in AIP are symptoms such as obstructive jaundice due to sclerosing cholangitis, abdominal pain, and the presence of other associated systemic diseases, such as retroperitoneal fibrosis.

Before steroid therapy is started, endoscopic or percutaneous transhepatic biliary drainage must be done in cases with obstructive jaundice, and glucose levels must be controlled in cases with diabetes mellitus. Oral predonisolone is usually started at 0.6mg/kg/day, and then it is tapered by 5 mg every 1-2 weeks. To prevent relapses, continued maintenance therapy with prednisolone 5 mg/day is sometimes required.

In half of steroid-treated patients, impaired exocrine or endocrine function improved. About 20-30% of AIP patients relapse during maintenance therapy or after steroid medication is stopped and they should be retreated with high-dose steroid therapy [17,18].

The long-term prognosis of AIP is not well known. Recurrent attacks of AIP resulting in pancreatic stone formation have been reported in some cases [19,20].

4 IgG4-related sclerosing cholangitis

Primary sclerosing cholangitis (PSC) occurs during the 30s-40s and is frequently associated with inflammatory bowel disease [21]. Stenosis occurred in the lower part of the common bile duct in 70% of our AIP patients. Stenosis of the bile duct improved dramatically after steroid therapy, and biliary drainage tube can be withdrawn within a month. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of PSC. Elevation of serum IgG4 is frequently observed in patients with IgG4-related sclerosing cholangitis, and it responds dramatically to steroid therapy, unlike PSC. Clinically, patients with IgG4-related sclerosing cholangitis are older at diagnosis than patients with PSC. The histological appearance is transmural fibrosis, dense fibrosis with infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis in the bile duct wall and the periportal area of the liver, in contrast to PSC. Given the age at onset, associated diseases, pancreatographic findings, response to steroid therapy, prognosis, and IgG4-related serological and immunohistochemical data, IgG4-related sclerosing cholangitis is a different disease from PSC [22,23].

5 IgG4-related sclerosing cholecystitis

Thickening of the gallbladder was detected on US and/or CT in 32% of our AIP patients. Dense infiltration of IgG4-positive plasma cells and lymphocytes, as well as transmural fibrosis, was detected in the gallbladder wall [24].

6 IgG4-related sclerosing sialadenitis and dacryoadenitis

Swelling of the bilateral salivary glands was present in 25% of our AIP patients, and it was associated with cervical or mediastinal lymphadenopathy. Swelling of the bilateral lacrymal glands was associated in one AIP patient. Swelling of the salivary and lacrymal glands and the lymph nodes improved after steroid therapy. In the salivary glands of these patients, dense infiltration of IgG4-positive plasma cells and fibrosis were detected. Mikulicz's disease is a unique condition that refers to bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands. Patients with Mikulicz's disease lack anti-SS-A and anti-SS-B antibodies, but frequently have