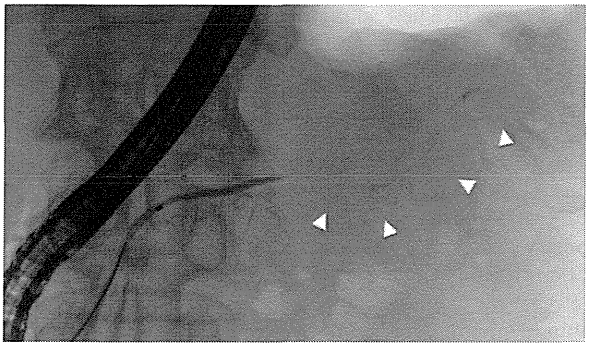

Figure 3 Endoscopic retrograde pancreatography shows focal stenosis in the pancreatic tail (arrowheads).

showed that MPD obstruction was less frequent in AIP than in pancreatic cancer (11% in AIP *vs* 60% in pancreatic cancer). A narrowed MPD portion of ≥3 cm in length (100% in AIP *vs* 22% in pancreatic cancer) and a maximal upstream MPD diameter of <4 mm (67% in AIP *vs* 4% in pancreatic cancer) were more common in AIP. They concluded that ERP findings showing longer stenosis of the MPD and a thinner MPD upstream from the stricture might be useful for the differential diagnosis of AIP from pancreatic cancer. Similarly, Takuma *et al.*[22] showed that skipped MPD lesions, a side branch derivation from a narrowed MPD, a narrowing of the MPD longer than 3 cm, and an upstream MPD dilatation of <5 mm were more frequent in AIP. In a multicenter, international study that addressed the role of ERP in AIP, Sugumar *et al.*[23] reported that the ability to diagnose AIP on the basis of ERP features alone was limited. The overall sensitivity, specificity, and interobserver agreement of ERP alone in the diagnosis of AIP were 44%, 92%, and 0.23, respectively. Importantly, they identified key features of AIP including long stricture (>1/3 the length of the MPD), lack of upstream dilatation from the stricture (<5 mm), multiple strictures, and side branches arising from strictured segments. Collectively, the ability to diagnose AIP could be improved with knowledge of the characteristic features on ERP.

Endoscopic cholangiogram

In addition to pancreatitis, AIP patients often develop extrapancreatic lesions such as biliary lesions, sialoadenitis, retroperitoneal fibrosis, enlarged hilar lymph nodes, and intestinal nephritis,[8] suggesting that AIP may be a systemic disorder or part of the so-called IgG4-related disease.[24] In the nationwide epidemiological survey of 2007, sclerosing cholangitis was the leading extrapancreatic lesion and was found in 53.4% of the patients.[25] Lesions of the biliary tract were specifically defined as IgG4-related sclerosing cholangitis (IgG4-SC).[26,27] IgG4-SC is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. Patients with IgG4-SC often present increased levels of

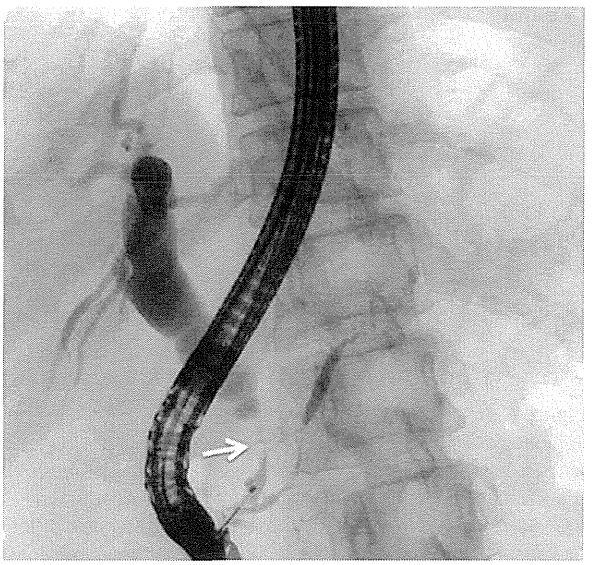

Figure 4 Endoscopic retrograde cholangiography reveals stenosis of the lower bile duct (arrow).

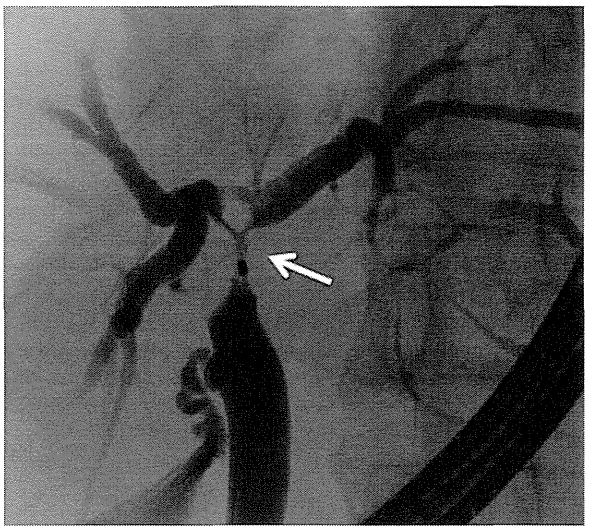

Figure 5 Endoscopic retrograde cholangiography shows stenosis of the hilar bile duct (arrow).

serum IgG4 and a dense infiltration of lymphocytes and plasma cells into the bile duct wall. Obstructive jaundice is frequently observed in IgG4-SC. The most common finding of IgG4-SC is intrapancreatic common bile duct involvement (Fig. 4), but biliary strictures can be observed anywhere in the biliary tree, including the hilar and intrahepatic bile ducts (Fig. 5). Differentiation of IgG4-SC from primary sclerosing cholangitis (PSC) and neoplastic lesions such as pancreatic and biliary cancers is very important.

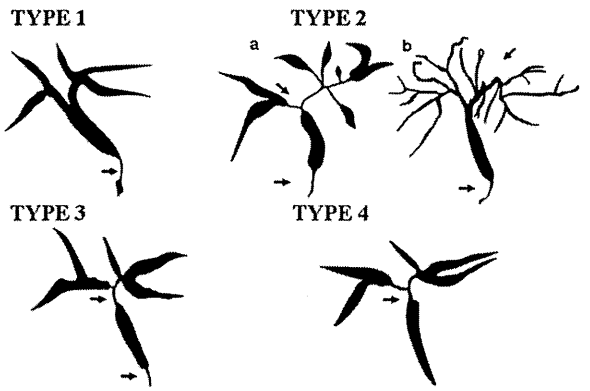

Figure 6 Schematic classification of cholangiographic findings in immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) (cited from Nakazawa *et al.* [28]). Type 1 IgG4-SC reveals stenosis in the intrapancreatic bile duct. Stenosis of the bile duct in type 2 IgG4-SC is located in the intrahepatic bile duct. Stenosis of the bile duct in type 3 IgG4-SC is shown in both hilar hepatic lesions and in the intrapancreatic bile duct. Type 4 IgG4-SC indicates stenosis in the hilar bile duct only.

Nakazawa *et al.*[28] reported the classification of IgG4-SC into four types based on the region of strictures revealed by cholangiography (Fig. 6). The endoscopic retrograde cholangiography (ERC) findings in type 1 might be similar to those in pancreatic head cancer, those of type 2 look like those in PSC, and those in types 3 and 4 are similar to those in cholangiocarcinoma. There are several cholangiographic findings that might be useful to differentiate IgG4-SC from PSC.[28,29] A beaded or 'pruned tree' appearance, band-like strictures, and diverticulum-like outpouchings are more frequent in PSC cases. Segmental strictures, long strictures with prestenotic dilatation, and strictures of the lower bile duct might suggest IgG4-SC. In addition to these differences on cholangiography, the clinical presentation might be different between IgG4-SC and PSC. PSC is often progressive and involves both the intra- and extrahepatic bile ducts, resulting in liver cirrhosis. IgG4-SC occasionally improves spontaneously and responds well to steroid therapy.[26] Serum IgG4 levels are increased in 74–90% of patients with IgG4-SC.[26,30] Importantly, an elevation of serum IgG4 levels is not specific to IgG4-SC. However, usually mild elevations of serum IgG4 were found in 12–22% of patients with PSC and in 8% of those with cholangiocarcinoma.[30,31] Therefore, increased IgG4 levels might be suggestive, but alone are not sufficient to differentiate IgG4-SC from other diseases. IgG4-SC should be carefully diagnosed on the basis of a combination of characteristic clinical, serological, and morphological features based on the cholangiographic classification, and after excluding similarly appearing diseases. Interestingly, Vosskuhl *et al.*[32] reported that IgG4 levels in bile juice were increased in patients with IgG4-SC, but not in those with PSC or cholangiocarcinoma. Measurement of bile IgG4 might be a new approach to distinguish IgG4-SC from other biliary diseases.

Biopsy from bile duct and duodenal papilla

The gold standard for the diagnosis of IgG4-SC is based on histology.[27] Endobiliary biopsy for bile duct strictures may be carried out on ERCP for the diagnosis and to relieve biliary stenosis in cases of suspected IgG4-SC. However, it is often difficult to obtain adequate tissue specimens of the bile duct for histological evaluation by a forceps biopsy. Biopsy specimens from the bile duct often contain clusters of epithelial cells alone without stroma.[33] Immunostaining for IgG4 may contribute to the diagnosis of IgG4-SC. Ghazale *et al.*[26] reported that histological diagnosis of IgG4-SC could not be made on any of 16 biopsy specimens obtained, although in all specimens there was adequate epithelial tissue. IgG4 immunostaining showed more than 10 IgG4-positive cells per high-power field in 14 out of 16 samples.[26] Obviously, diagnostic ability is affected by the amount of histological specimens acquired when using biopsy forceps. Improved biopsy forceps are needed to acquire adequate bile duct specimens for the diagnosis of IgG4-SC.

Usefulness of IgG4 immunostaining of biopsy specimens obtained from the major papilla has been reported.[34–37] For the diagnosis of IgG4-SC, a biopsy of the duodenal papilla is safer, easier, and more reliable than obtaining a histological sample from the bile duct. Sensitivity and specificity for differentiation between IgG4-SC and PSC or biliary duct cancer were 52–80% and 89–100%, respectively.[34–37] Kubota *et al.*[35] reported that the characteristic duodenal endoscopic papillary features observed in patients with IgG4-SC, such as swollen papillae, may be helpful for discriminating IgG4-SC from PSC. Narrow-band imaging of the duodenal papilla might be useful for the differential diagnosis of these disorders.[38] In the ICDC,[17] endoscopic biopsy of the duodenal papilla is described as a useful adjunctive method.

Intraductal ultrasonography

Endoscopic transpapillary intraductal ultrasonography (IDUS) carried out after ERC is useful for the evaluation of bile duct wall thickening.[39,40] IDUS provides high-resolution images of the bile duct wall, which normally has inner hypoechoic and outer hyperechoic layers.[39,40] The characteristic IDUS findings in IgG4-SC are circular-symmetric wall thickness, a smooth outer margin, a smooth inner margin, and a homogeneous internal echo in the stricture of the bile duct (Fig. 7). IDUS findings regarding cholangiocarcinoma are a circular-asymmetric wall thickening, a notched outer margin, a rigid papillary inner margin, and a heterogeneous internal echo in the stricture. Naitoh *et al.*[41] reported that wall thickness in the non-stricture area of a cholangiogram was a useful parameter for differentiating IgG4-SC from cholangiocarcinoma, with an optimal cut-off value of

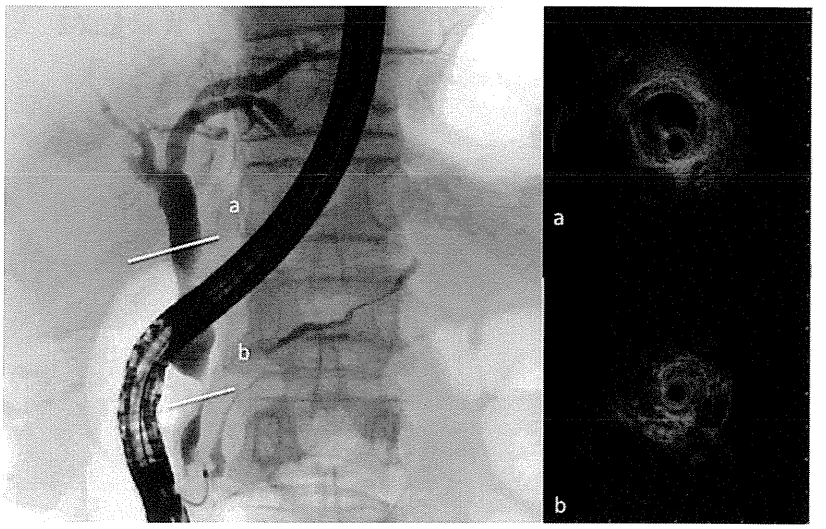

Figure 7 Intraductal ultrasonography (IDUS) findings. (a) In the non-stenotic portions where the cholangiogram result was normal, IDUS findings reveal wall thickening of the bile duct. (b) In the stenosis of the lower bile duct, IDUS findings also reveal wall thickening.

0.8 mm. IDUS combined with ERCP would give us valuable information for diagnosing IgG4-SC.

Peroral cholangioscopy

Peroral cholangioscopy has been developed over the past three decades to enable direct endoscopic diagnosis of bile duct lesions and targeted biopsies.[42,43] Itoi *et al.*[43] reported that dilated and tortuous vessels or partially enlarged vessels suggested IgG4-SC rather than PSC or cholangiocarcinoma. Further study is required to establish the role of peroral cholangioscopy in the diagnosis of IgG4-SC.

Endoscopic ultrasonography

Conventional imaging

Endoscopic ultrasonography (EUS) has become a routine modality for the evaluation of pancreatic masses because it provides fine imaging of the tumor and staging information. The compatible EUS finding for AIP is diffuse hypoechoic pancreatic mass lesion mimicking pancreatic cancer.[40,44,45] Some studies have tried to distinguish AIP from pancreatic cancer using conventional EUS images (Fig. 8). Hoki *et al.*[44] reported the conventional EUS features of AIP. With conventional EUS, diffuse hypoechoic areas, diffuse enlargement, bile duct wall thickening, and perihypoechoic margins are more frequent in AIP than in pancreatic cancer. However, it may be difficult to differentiate AIP from pancreatic cancer using conventional EUS imaging alone.

Contrast-enhanced harmonic EUS

An ultrasonographic contrast procedure was recently developed, and it made contrast-enhanced harmonic imaging of the pancreas using EUS possible.[46] Several studies have shown that contrast-enhanced harmonic EUS (CEH-EUS) could increase the accuracy of pancreatic cancer diagnosis by providing information about vascular patterns such as hypo-, hyper-, or isoenhancement (Fig. 9).[47–49] Imazu *et al.*[49] described the usefulness of CEH-EUS for differentiating AIP from pancreatic cancer by analyzing the perfusion quantitatively using a time-intensity curve.

Figure 8 Endoscopic ultrasonography (EUS). Conventional EUS findings show diffuse pancreatic enlargement with a heterogeneous hypoechoic pattern (arrowheads).

Elastography

EUS-elastography can now be used as a technique to distinguish between benign and malignant pancreatic masses.[50–52] The diagnostic ability of EUS-elastography to differentiate AIP from pancreatic cancer is still questionable.

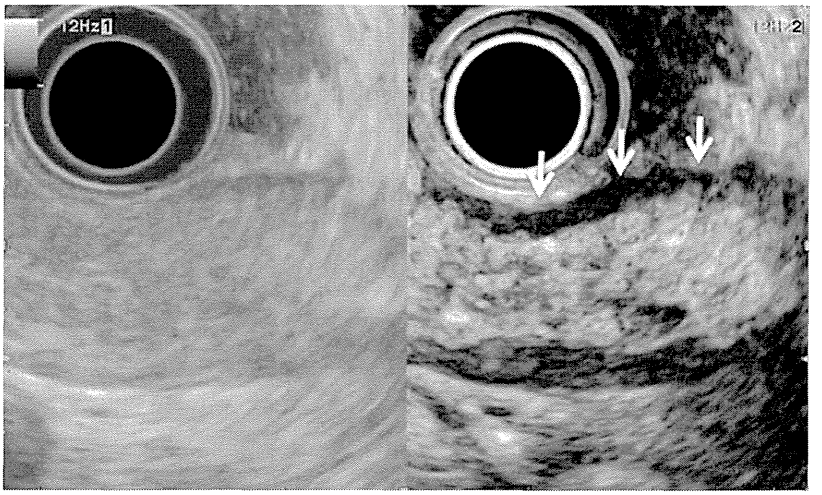

Figure 9 Contrast enhanced harmonic EUS (CEH-EUS). CEH-EUS findings reveal hypervascular pancreatic enlargement surrounded by hypovascular lesions (capsule-like rim) (arrows).

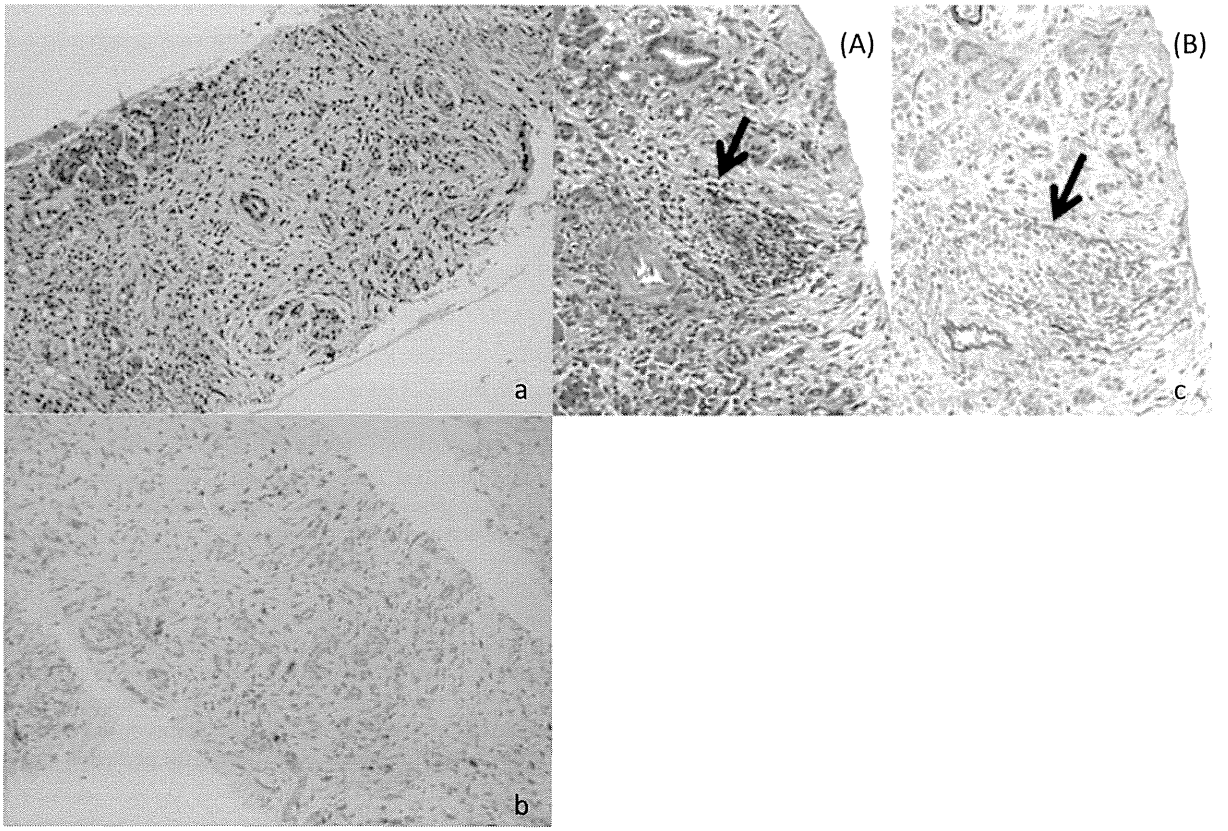

Figure 10 (a) High-power-field findings (400×) show lymphoplasmacytic infiltration and storiform fibrosis. (b) Immunohistochemical staining for immunoglobulin (Ig)G4. Abundant IgG4-positive plasma cells were found in the high-power field. (c) Obliterative phlebitis (arrow). (A) hematoxylin-eosin staining. (B) Elastica–Masson (EM) staining. The finding of obliterative phlebitis is clear in the EM staining.

Dietrich *et al.*[50] evaluated the usefulness of EUS-elastography in the diagnosis of AIP. EUS-elastography revealed a characteristic elastographic pattern of stiffness not only in the mass lesion but also in the surrounding pancreatic tissue. Mei *et al.*[52] reported a meta-analysis that evaluated EUS-elastography for the diagnosis of solid pancreatic masses. The sensitivity, specificity, and diagnostic odds ratio of EUS-elastography for the differentiation of benign from malignant solid pancreatic masses were 0.95 (95% confidence interval [CI], 0.94–0.97), 0.67 (95% CI, 0.61–0.73), and 42.28 (95% CI, 26.90–66.46). EUS-elastography is a promising diagnostic tool for the diagnosis of pancreatic masses; however, accuracy for the diagnosis of AIP or other pancreatic masses will need further improvement.

EUS-guided fine-needle aspiration and Trucut biopsy

The ICDC emphasize the importance of histological examinations in the diagnosis of AIP.[17] In the latest nationwide epidemiological survey of AIP patients who had visited hospitals in Japan in 2011, pancreatic tissues were obtained in 409 of 901 patients (45.4%) (Kanno A. *et al.*, unpubl. obs, 2014). Tissue samples were obtained by EUS-guided fine-needle aspiration (EUS-FNA) in 261 (63.8%) and by pancreatectomy in 65 patients (15.9%). In the ICDC, only tissue samples obtained by EUS-Trucut biopsy (TCB) or resection are considered suitable for histopathological diagnosis of AIP.[17,53] EUS-FNA using a 19-gauge (G) needle might be useful,[54] but these procedures have a potential risk of complications and require skill.[55] The reliability of EUS-FNA with a 22-G needle for the histological diagnosis of AIP has been recently reported.[56,57] Ishikawa *et al.*[56] reported that this procedure provides adequate histological samples for the diagnosis and differentiation of type 1 and 2 AIP, particularly seronegative cases. Kanno *et al.*[57] reported that the histological diagnosis of AIP could be made in 20 of 25 patients (80%) according to the ICDC (Fig. 10). To obtain sufficient histological samples, the authors emphasized the importance of careful sample processing after collection and rapid motion of the FNA needles. Because the speed with which the needle can be moved manually is limited, Kanno *et al.*[57] recommended the use of a spring-loaded biopsy needle. These new EUS-FNA needles improved the quality and quantity of the histological samples. Thus, EUS-FNA would provide new opportunities to diagnose AIP histologically.

FUTURE PERSPECTIVES OF ENDOSCOPY FOR THE DIAGNOSIS OF AIP AND IgG4-SC

THE ICDC WERE proposed to demonstrate a diagnostic algorithm and to provide flexibility in the diagnostic approach by considering the advantages and limitations of endoscopy.[17] When computed tomography (CT) or magnetic resonance imaging (MRI) findings are typical for AIP, diagnostic ERCP is not required. If pancreatic imaging yields indeterminate findings (segmental or focal enlargement) and localized narrowing of MPD, ERCP is basically required to make a diagnosis of definitive AIP. When a patient with a focal/segmental swelling of the pancreas does not fulfill two or more Level 1 criteria of the ICDC for type 1 AIP, pancreatic core biopsy is recommended for diagnosing AIP and differentiating it from pancreatic cancer. Moon and Kim[40] proposed an endoscopic strategy to distinguish AIP from pancreatobiliary malignancies; however, ERP has no role in the AIP diagnosis in this strategy. In cases of suspected AIP with obstructive jaundice associated with biliary strictures, we recommended an endobiliary biopsy to exclude malignancy at the time of carrying out ERCP for biliary decompression. Based on these guidelines, we propose an endoscopic strategy for diagnosing AIP (Fig. 11). Further studies will be required to assess the diagnostic abilities of several endoscopic tools, such as ERP and EUS-FNA.

CONCLUSIONS

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY and EUS play important roles in the differential diagnosis between AIP or IgG4-SC and pancreatobiliary malignancies. Various endoscopic devices have been developed for ERCP and EUS procedures and have improved the diagnostic capabilities of pancreatobiliary diseases. Because the gold standard for the diagnosis of AIP and IgG4-SC is based on histology, further improvements are required to obtain pancreatic tissues efficiently and safely.

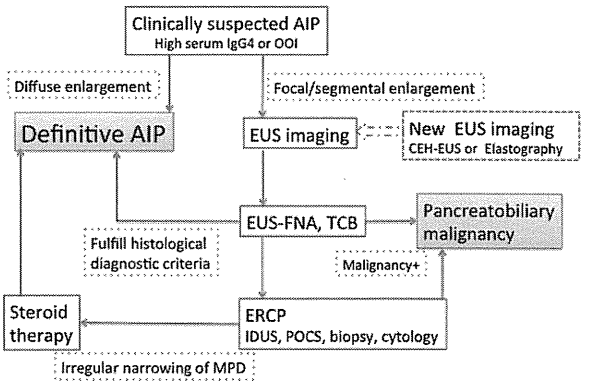

Figure 11 Endoscopic strategy for diagnosing autoimmune pancreatitis (AIP). CEH-EUS, contrast enhanced harmonic endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, EUS-guided fine-needle aspiration; IDUS, intraductal ultrasonography; IgG4, immunoglobulin G4; MPD, main pancreatic duct; OOI, other organ involvement; POCS, peroral cholangioscopy; TCB, Trucut biopsy.

ACKNOWLEDGMENTS

THIS WORK WAS supported in part by a Grant-in-Aid from Japan Society for the Promotion of Science (#25461020 to A. Kanno), the Research Committee of Intractable Pancreatic Disease (Principal investigators: Tooru Shimosegawa and Yoshifumi Takeyama) provided by the Ministry of Health, Labour and Welfare of Japan.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

REFERENCES

1 Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig. Dis. Sci.* 1995; **40**: 1561–8.
2 Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: A variant of primary sclerosing cholangitis extensively involving pancreas. *Hum. Pathol.* 1991; **22**: 387–95.
3 Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: Clinicopathologic features of 35 cases. *Am. J. Surg. Pathol.* 2003; **27**: 1119–27.
4 Klöppel G, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: Pathological, clinical, and immunological features. *Pancreas* 2003; **27**: 14–9.
5 Zamboni G, Lüttges J, Capelli P *et al.* Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: A study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch.* 2004; **445**: 552–63.
6 Sugumar A, Klöppel G, Chari ST. Autoimmune pancreatitis: Pathologic subtypes and their implications for its diagnosis. *Am. J. Gastroenterol.* 2009; **104**: 2308–10; quiz 2311.
7 Sah RP, Chari ST, Pannala R *et al.* Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010; **139**: 140–8; quiz e112-143.
8 Kamisawa T, Funata N, Hayashi Y *et al.* A new clinicopathological entity of IgG4-related autoimmune disease. *J. Gastroenterol.* 2003; **38**: 982–4.
9 Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas–an autonomous pancreatic disease? *Am. J. Dig. Dis.* 1961; **6**: 688–98.
10 Members of the Criteria Committee for Autoimmune Pancreatitis of the Japan Pancreas Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society (2002). *Suizo* 2002; **17**: 585–7. (in Japanese with English abstract.)
11 Okazaki K, Kawa S, Kamisawa T *et al.* Clinical diagnostic criteria of autoimmune pancreatitis: Revised proposal. *J. Gastroenterol.* 2006; **41**: 626–31.
12 Hamano H, Kawa S, Horiuchi A *et al.* High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N. Engl. J. Med.* 2001; **344**: 732–8.
13 Kim KP, Kim MH, Kim JC, Lee SS, Seo DW, Lee SK. Diagnostic criteria for autoimmune chronic pancreatitis revisited. *World J. Gastroenterol.* 2006; **12**: 2487–96.
14 Chari ST, Smyrk TC, Levy MJ *et al.* Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. *Clin. Gastroenterol. Hepatol.* 2006; **4**: 1010–6.
15 Pearson RK, Longnecker DS, Chari ST *et al.* Controversies in clinical pancreatology: Autoimmune pancreatitis: Does it exist? *Pancreas* 2003; **27**: 1–13.
16 Schneider A, Löhr JM. [Autoimmune pancreatitis]. *Internist (Berl.)* 2009; **50**: 318–30.
17 Shimosegawa T, Chari ST, Frulloni L *et al.* International consensus diagnostic criteria for autoimmune pancreatitis: Guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352–8.
18 The Japan Pancreas Society, the Ministry of Health and Welfare Investigation Research Team for Intractable Pancreatic Disease. Clinical diagnostic criteria for autoimmune pancreatitis 2011 (proposal). *Suizou* 2012; **27**: 17–25.
19 Shimosegawa T, Working Group Members of the Japan Pancreas Society, Research Committee for Intractable Pancreatic Disease by the Ministry of Labor, Health and Welfare of Japan. The amendment of the clinical diagnostic criteria in Japan (JPS2011) in response to the proposal of the International Consensus of Diagnostic Criteria (ICDC) for autoimmune pancreatitis. *Pancreas* 2012; **41**: 1341–2.
20 Okazaki K, Kawa S, Kamisawa T *et al.* Amendment of the Japanese consensus guidelines for autoimmune pancreatitis, 2013 I. Concept and diagnosis of autoimmune pancreatitis. *J. Gastroenterol.* 2014; **49**: 567–88.
21 Wakabayashi T, Kawaura Y, Satomura Y *et al.* Clinical and imaging features of autoimmune pancreatitis with focal pancreatic swelling or mass formation: Comparison with so-called tumor-forming pancreatitis and pancreatic carcinoma. *Am. J. Gastroenterol.* 2003; **98**: 2679–87.
22 Takuma K, Kamisawa T, Tabata T, Inaba Y, Egawa N, Igarashi Y. Utility of pancreatography for diagnosing autoimmune pancreatitis. *World J. Gastroenterol.* 2011; **17**: 2332–7.
23 Sugumar A, Levy MJ, Kamisawa T *et al.* Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: An international multicentre study. *Gut* 2011; **60**: 666–70.
24 Umehara H, Okazaki K, Masaki Y *et al.* Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod. Rheumatol.* 2012; **22**: 21–30.
25 Kanno A, Nishimori I, Masamune A *et al.* Nationwide epidemiological survey of autoimmune pancreatitis in Japan. *Pancreas* 2012; **41**: 835–9.
26 Ghazale A, Chari ST, Zhang L *et al.* Immunoglobulin G4-associated cholangitis: Clinical profile and response to therapy. *Gastroenterology* 2008; **134**: 706–15.

27 Ohara H, Okazaki K, Tsubouchi H *et al.* Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. *J. Hepato-biliary Pancreat. Sci.* 2012; **19**: 536–42.
28 Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. *Pancreas* 2006; **32**: 229.
29 Nakazawa T, Ohara H, Sano H *et al.* Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. *Gastrointest. Endosc.* 2004; **60**: 937–44.
30 Ohara H, Nakazawa T, Kawa S *et al.* Establishment of a serum IgG4 cut-off value for the differential diagnosis of IgG4-related sclerosing cholangitis: A Japanese cohort. *J. Gastroenterol. Hepatol.* 2013; **28**: 1247–51.
31 Zhang L, Lewis JT, Abraham SC *et al.* IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. *Am. J. Surg. Pathol.* 2010; **34**: 88–94.
32 Vosskuhl K, Negm AA, Framke T *et al.* Measurement of IgG4 in bile: A new approach for diagnosis of IgG4 associated cholangiopathy. *Endoscopy* 2012; **44**: 48–52.
33 Domagk D, Poremba C, Dietl KH *et al.* Endoscopic transpapillary biopsies and intraductal ultrasonography in the diagnostics of bile duct strictures: A prospective study. *Gut* 2002; **51**: 240–4.
34 Kamisawa T, Tu Y, Egawa N, Tsuruta K, Okamoto A. A new diagnostic endoscopic tool for autoimmune pancreatitis. *Gastrointest. Endosc.* 2008; **68**: 358–61.
35 Kubota K, Kato S, Akiyama T *et al.* Differentiating sclerosing cholangitis caused by autoimmune pancreatitis and primary sclerosing cholangitis according to endoscopic duodenal papillary features. *Gastrointest. Endosc.* 2008; **68**: 1204–8.
36 Moon SH, Kim MH, Park do H *et al.* IgG4 immunostaining of duodenal papillary biopsy specimens may be useful for supporting a diagnosis of autoimmune pancreatitis. *Gastrointest. Endosc.* 2010; **71**: 960–6.
37 Sepehr A, Mino-Kenudson M, Ogawa F, Brugge WR, Deshpande V, Lauwers GY. IgG4+ to IgG+ plasma cells ratio of ampulla can help differentiate autoimmune pancreatitis from other 'mass forming' pancreatic lesions. *Am. J. Surg. Pathol.* 2008; **32**: 1770–9.
38 Kubota K, Fujita Y, Sekino Y *et al.* Dynamic narrow-band imaging and detection of duodenal papillitis with increased IgG4+ plasma cells facilitated differential diagnosis in patients with hilar biliary stricture. *Gastrointest. Endosc.* 2014; **79** (Suppl): AB348.
39 Tamada K, Tomiyama T, Wada S *et al.* Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. *Gut* 2002; **50**: 326–31.
40 Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. *Gastrointest. Endosc.* 2012; **76**: 645–56.
41 Naitoh I, Nakazawa T, Ohara H *et al.* Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. *J. Gastroenterol.* 2009; **44**: 1147–55.
42 Awadallah NS, Chen YK, Piraka C, Antillon MR, Shah RJ. Is there a role for cholangioscopy in patients with primary sclerosing cholangitis? *Am. J. Gastroenterol.* 2006; **101**: 284–91.
43 Itoi T, Kamisawa T, Igarashi Y *et al.* The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. *J. Gastroenterol.* 2013; **48**: 504–14.
44 Hoki N, Mizuno N, Sawaki A *et al.* Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. *J. Gastroenterol.* 2009; **44**: 154–9.
45 Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. *Gastrointest. Endosc.* 2004; **60**: 927–36.
46 Fusaroli P, Saftoiu A, Mancino MG, Caletti G, Eloubeidi MA. Techniques of image enhancement in EUS (with videos). *Gastrointest. Endosc.* 2011; **74**: 645–55.
47 Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2011; **43**: 163–5.
48 Hocke M, Schulze E, Gottschalk P, Topalidis T, Dietrich CF. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J. Gastroenterol.* 2006; **12**: 246–50.
49 Imazu H, Kanazawa K, Mori N *et al.* Novel quantitative perfusion analysis with contrast-enhanced harmonic EUS for differentiation of autoimmune pancreatitis from pancreatic carcinoma. *Scand. J. Gastroenterol.* 2012; **47**: 853–60.
50 Dietrich CF, Hirche TO, Ott M, Ignee A. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2009; **41**: 718–20.
51 Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas: Feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. *Gastrointest. Endosc.* 2007; **65**: 971–8.
52 Mei M, Ni J, Liu D, Jin P, Sun L. EUS elastography for diagnosis of solid pancreatic masses: A meta-analysis. *Gastrointest. Endosc.* 2013; **77**: 578–89.
53 Levy MJ, Reddy RP, Wiersema MJ *et al.* EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest. Endosc.* 2005; **61**: 467–72.
54 Varadarajulu S, Fraig M, Schmulewitz N *et al.* Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy* 2004; **36**: 397–401.
55 Iwashita T, Yasuda I, Doi S *et al.* Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. *Clin. Gastroenterol. Hepatol.* 2012; **10**: 316–22.
56 Ishikawa T, Itoh A, Kawashima H *et al.* Endoscopic ultrasound-guided fine needle aspiration in the differentiation of type 1 and type 2 autoimmune pancreatitis. *World J. Gastroenterol.* 2012; **18**: 3883–8.
57 Kanno A, Ishida K, Hamada S *et al.* Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. *Gastrointest. Endosc.* 2012; **76**: 594–602.

〔特　　集〕自己免疫性膵炎の up-to-date

自己免疫性膵炎の全国調査

菅野　敦　正宗　淳　下瀬川　徹*

要　旨：Yoshida らにより疾患概念として自己免疫性膵炎（Autoimmune pancreatitis：AIP）が提唱されてから約 20 年が経過するが，その全体像については未だ不明な点が少なくない．我が国では厚生労働省の「難治性膵疾患に関する調査研究班」により，全国疫学調査がこれまでに 3 回行われている．最新の 2011 年の受療患者を対象として行われた第 3 回 AIP 全国調査では，年間推計受療者数は 5,745 人（95% 信頼区間：5,325～6,164 人），有病率は人口 10 万人あたり 4.6 人，罹患率は人口 10 万人あたり 1.4 人であった．2 次調査により，大部分の症例において血清 IgG4 が高値であることや，8 割以上にステロイド治療が行われているなど，我が国における AIP 診療の実態が明らかとなった．全国調査から得られた AIP の全体像をもとに，AIP の診断，治療，研究に関して今後さらなる展開が期待される．

索引用語：国際コンセンサス診断基準　年間受療者　罹患率　有病率

はじめに

自己免疫性膵炎（Autoimmune pancreatitis：AIP）は，1995 年に Yoshida らが提唱した疾患概念で，びまん性の膵腫大と膵管狭細像を特徴とする[1]．今までに数多くの知見が蓄積され，種々の診断基準が作成された．日本では，2002 年に最初の診断基準が制定され（日本膵臓学会自己免疫性膵炎診断基準 2002：AIP 診断基準 2002）[2]，2006 年の改訂（自己免疫性膵炎臨床診断基準 2006：AIP 診断基準 2006）[3]を経て，2010 年に制定された国際コンセンサス診断基準（International Consensus Diagnostic Criteria：ICDC）[4]をもとに日本の実状に合わせた日本膵臓学会自己免疫性膵炎臨床診断基準 2011（AIP 診断基準 2011）[5]が制定された．診断基準が異なること，時代の変遷により AIP の知見が蓄積したことなどから過去 3 回にわたり AIP の全国調査が行われた．本稿では，第 3 回 AIP 全国調査を中心に，日本における AIP の疫学について，診断基準の変遷とあわせて概説する[6,7]．

*東北大学大学院消化器病態学分野

AIP の実態調査

1995 年に AIP の疾患概念が提唱されたが[1] AIP の症例報告が増加するに伴い，本疾患の臨床像を把握するために，厚生労働省の「難治性膵疾患に関する調査研究班」（当時の研究代表者：小川道雄）が主体となり AIP の実態調査が行われた[8～11]．AIP の病理組織像[8]，ステロイド反応性を示した症例の臨床像[9]，AIP の臨床病理学的検討[10]，また AIP とアルコール性慢性膵炎の比較[11]などが行われた．これらの報告はいずれも AIP の特徴をよくとらえた報告だったが，当時は血清 IgG4 値の上昇も明らかにされていない時代であり，個々の症例の臨床像を把握するにとどまった．

第 1 回 AIP 全国調査

2001 年に Hamano らが，AIP において血清 IgG4 値が上昇することを報告した[12]．翌 2002 年に AIP 診断基準 2002 が発表され[2]，AIP の疾患概念が広く認知されるようになった．そこで，厚労省班会議（当時の研究代表者：大槻眞）により，初めて AIP の疫学調査が行われた[13,14]．対象症例は 2002 年の 1 年間に受療した AIP 患者とし，全

国の内科（消化器内科），外科（消化器外科）を標榜する病院を対象に層化無作為抽出法による調査が行われた[15]．その結果，AIP 診断基準 2002 を満たす AIP 患者 294 例が集積され，年間推計受療者数は 900 人（95% 信頼区間：670～1,100 人）と推計され，本疾患が希少疾患であることが明らかになった．一方，診断基準を満たさないが，AIP と考えられる患者が年間 800 人（95% 信頼区間：410～1,180 人）受療していることも推計された．診断基準を満たさない要因として，膵管狭細像が膵全体の 1/3 以下であった可能性が考えられた．

第 2 回 AIP 全国調査

2006 年に AIP 診断基準が改訂され（AIP 診断基準 2006）[3]，我が国において AIP の疾患概念はさらに浸透した．それと前後して，Mayo Clinic の HISORTs criteria[16,17]をはじめ，韓国[18]，イタリア[19]といった国々からも診断基準が提唱された．2008 年には，日本と韓国の専門家が集まり診断基準の統一が議論され Asian criteria[20]が提唱された．一方，組織学的検討から，AIP には IgG4 に関連した lymphoplasmacytic sclerosing pancreatitis（LPSP）[21]と，Idiopathic duct-centric chronic pancreatitis（IDCP）[22]の 2 つの組織型が存在することが明らかとなった．このような流れの中で，AIP 診断基準 2006 に基づく 2007 年 1 年間に受療した AIP 症例に関する第 2 回 AIP 全国調査が行われた[23]．

まず一次調査が行われ，日本における AIP の全体像が再調査された．前回と同様，全国の内科，外科を標榜する病院を対象に層化無作為抽出法による調査が行われた．1,069 例の AIP 症例が集積され，AIP の推計年間受療者数は，2,790 人（95% 信頼区間：2,540～3,040 人），年間罹患者数は，1,120 人（95% 信頼区間：1,000～1,240 人），有病率は人口 10 万人あたり 2.2 人，罹患率は人口 10 万人あたり 0.9 人と推計された．第 1 回 AIP 全国調査の年間推計受療者数が，疑い症例も含め 1,700 人だったのに比べて，1.64 倍に増加した．AIP 症例が増加した最大の要因として，疾患概念が一般臨床医にも浸透したことがあげられる．実際に，第 1 回全国調査では，厚労省研究班班員所属施設や大学病院などの特別階層病院にのみ症例が集中していたが，第 2 回調査では，より多くの病院からも症例が報告された．一次調査で AIP 症例ありと回答のあった 279 施設を対象として二次調査が行われた[24,25]．最終的に回答のあった施設は 125 施設で，男性 418 例，女性 114 例，不明 14 例の計 546 例が集計され，いくつかの重要な知見が得られた．画像診断では，多くの症例は典型的な，びまん性膵腫大と膵管狭細を呈していたが，膵癌との鑑別が必要な限局性の膵腫大や膵管狭細を呈している症例が約 30% 存在していた．血清学的項目では，AIP 診断基準 2006 に含まれていた IgG や抗核抗体などの陽性率は相対的に低かったのに対し，IgG4 高値を示した症例は 87.6% と高かった．一方，約 10% の症例で血清 IgG4 が正常範囲内であることも示され，これらの中に血清 IgG4 の上昇を伴わない疾患群が一部含まれている可能性が示唆された．さらに，多彩な膵外病変が合併することも明らかになり，膵臓以外の他臓器病変の検討の必要性が示された[26]．治療に関しては 80% 以上の症例でステロイドが投与されており，約 1/4 の症例が再燃を来していた．

第 3 回全国調査

2010 年に福岡で開催された International Association of Pancreatology と日本膵臓学会の joint meeting において，AIP の診断基準が討議され，国際コンセンサス診断基準（International Consensus Diagnositic Criteria：ICDC）が提唱された[4]．ICDC では，Honolulu consensus[27]を受けて，AIP を type 1 と type 2 に分類し，膵腫大，膵管狭細像，血清 IgG4，膵外病変，治療の項目を組み合わせて診断する．ICDC は，AIP 診断に関して詳細に記載されているために一般臨床医が日常診療に使用するには，やや繁雑であった．そこで ICDC を踏まえて，日本の実状に合わせた，より使いやすい診断基準として AIP 診断基準 2011 が作成された[5]．AIP 診断基準 2011 では，診断率の向上が期待されている[28]．この AIP 診断基準 2011 を用いて，2011 年の受療患者を対象に第 3 回 AIP 全国調査が厚労省班会議（当時の研究代表者：下瀬川徹）により実施された[29,30]．一次調査では，年間受療者数

が5,745人（95%信頼区間：5,325～6,164人），有病率は人口10万人あたり4.6人，罹患率は人口10万人あたり1.4人と推計された．推計年間受療者数は第2回調査の2,790人より2.1倍に増加していた．その要因として，前回同様，AIPの疾患概念が一般臨床医に浸透したことに加えて，AIP診断基準2011を用いたことが考えられる[28]．

第2回全国調査と同様に，一次調査でAIP症例ありと回答のあった356施設を対象として二次調査が行われた．以下に，その結果を記す．2011年に新たに罹患した患者を新規罹患患者，以前からAIPとして経過観察している症例を継続療養症例とした．

1．患者内訳

最終的に回答のあった施設は356施設中187施設（52.5%）で，男性703例，女性217例，不明16例の計936例が集計された．新規罹患患者は228例，継続療養患者は699例，不明9例，であった．平均年齢は66.3±11.5歳で，60～69歳と70～75歳の範囲に多くの患者が分布していた（Fig. 1）．

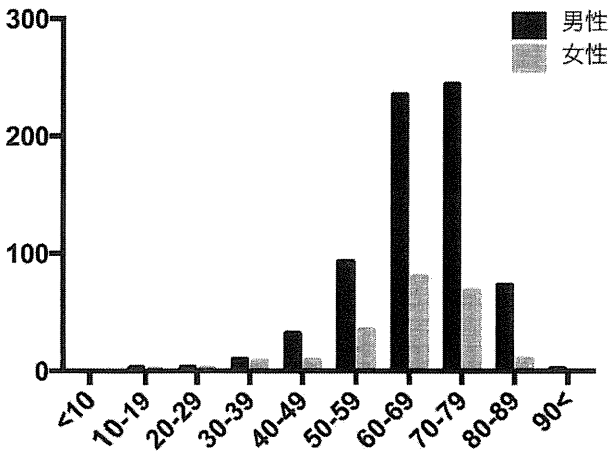

Fig. 1　第3回全国調査二次調査患者男女内訳

2．画像所見（Table 1）

画像上膵腫大を認めた症例は92.9%，認めなかった症例は7.1%であった．腫大を認めた830例中，膵全体の腫大（2/3以上）を呈した症例は52.6%と約半数であり，膵全体の1/3～2/3の腫大を呈するsegmental typeの症例は27.6%，1/3未満の腫大を呈するfocal typeの症例は17.7%，非典型例0.5%，無記入1.6%であった．膵管狭細を認めた症例は89.6%，認めなかった症例は10.4%であった．膵管狭細を呈した症例のうち，膵全体の膵管狭細を呈した症例は44.5%，1/3～2/3の膵管狭細を呈した症例は31.4%，1/3未満の膵管狭細を呈した症例は17.3%，多発例3.7%，無記入3.3%であった．

3．血清学的項目

高IgG4血症は83.4%（726/870例）と高い陽性率を示し，血清IgG4の平均値は533.0±540.9mg/dlであった．一方，抗核抗体の陽性率は33.5%（263/785例），高IgG血症は56.4%（486/862例），リウマチ因子（>20IU/ml）は21.7%（125/576例）であった．

4．病理組織学的所見（Fig. 2）

膵臓の組織が採取された症例は45.4%，採取されていない症例は54.6%であった．　組織検体は，

Table 1　画像所見

膵腫大	あり	830/893（92.9%）	なし	63/893（ 7.1%）
Diffuse（≥2/3）		437/830（52.6%）		
Segmental（1/3≤ <2/3）		229/830（27.6%）		
Focal（<1/3）		147/830（17.7%）		
非典型例		4/830（ 0.5%）		
無記入		13/830（ 1.6%）		
膵管狭細	あり	793/885（89.6%）	なし	92/885（10.4%）
Diffuse（≥2/3）		353/793（44.5%）		
Segmental（1/3≤ <2/3）		249/793（31.4%）		
Focal（<1/3）		137/793（17.3%）		
多発例		29/793（ 3.7%）		
無記入		25/793（ 3.3%）		

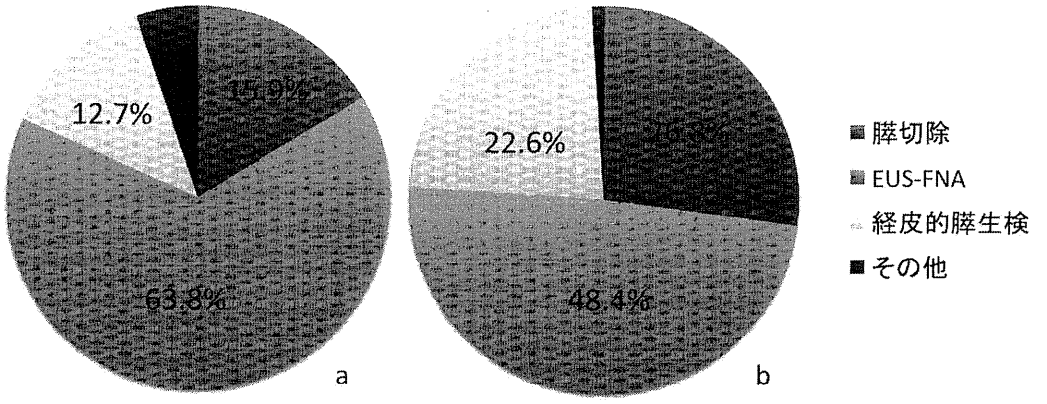

Fig. 2　組織学的診断のまとめ
a）第3回全国調査における組織診断法の内訳．b）第2回全国調査における組織診断法の内訳．

膵切除により得られた症例が15.9%，EUS-FNAで得られた症例は63.8%，経皮膵生検12.7%，その他5.1%，無記入2.4%であった．第2回全国調査における膵切除の割合が26.8%，EUS-FNAの割合が48.4%であったことから，膵切除が減少し，EUS-FNAを用いて膵臓の組織が採取された症例が増加した．

5．膵外病変

膵外病変を認めた症例は，57.9%（532/918例）であった．内訳は肝門部硬化性胆管炎95例，膵内硬化性胆管炎261例，涙腺・唾液腺炎153例，後腹膜線維症76例，腎病変36例，炎症性腸疾患22例（潰瘍性大腸炎20例，クローン病2例），肺病変38例，偽腫瘍7例（肺2例，肝臓7例），その他66例（重複あり）であった．

6．治　　療

ステロイドによる加療が行われた症例は82.3%（761/925例），ステロイドの投与が行われなかった症例は17.7%（164/925例）であった．ステロイドが投与された761例中，その有効性を確認できた症例は733例（96.3%）であった．初期投与量は40mgが19.2%（146/761例），30mgが62.8%（478/761例），20mgが4.7%（36/761例），その他13.4%（102/761例）であった．ステロイドによる維持療法が行われた症例は84.6%（644/761例）であった．

免疫調節薬が用いられた症例は10例のみであり，使用された薬剤はアザチオプリン（イムラン®）4例，シクロスポリン（ネオーラル®）1例，メソトレキセート1例，シクロフォスファミド（エンドキサン®）1例，インフリキシマブ（レミケード®）1例，タクロリムス（プログラフ®）1例，記載なし1例であった．リツキシマブ（リツキサン®）が用いられた症例はなかった．

7．臨床診断基準2011に基づいたAIP診断（Fig. 3）

今回の全国調査は，AIP臨床診断基準2011に基づいて行われた．確診と診断された症例は725例（77.5%）準確診と診断された症例は42例（4.5%），疑診は100例（10.7%），診断不可例は64例（6.8%），無記入・その他5例（重複あり）（0.5%）であった（Fig. 3a）．

血清IgG4が135mg/ml未満のIgG4陰性例115例に限って調べると，確診48例，準確診6例，疑診47例，診断不可13例と疑診例の割合が増加した（Fig. 3b）．

また，臨床診断基準2011を用いて炎症性腸疾患合併症例22例を診断すると，確診5例，準確診1例，疑診11例，診断不可5例と疑診例が50%を占めた（Fig. 3c）．

8．再燃（Table 2）

経過中，再燃を来した症例は22.2%（193/869例）であった．再燃臓器は膵臓107例（55.4%），肝門部硬化性胆管炎27例（14.0%），膵内硬化性胆管炎27例（14.0%），涙腺・唾液腺炎16例（8.3%），後腹膜線維症11例（5.7%），その他5例（2.6%）で

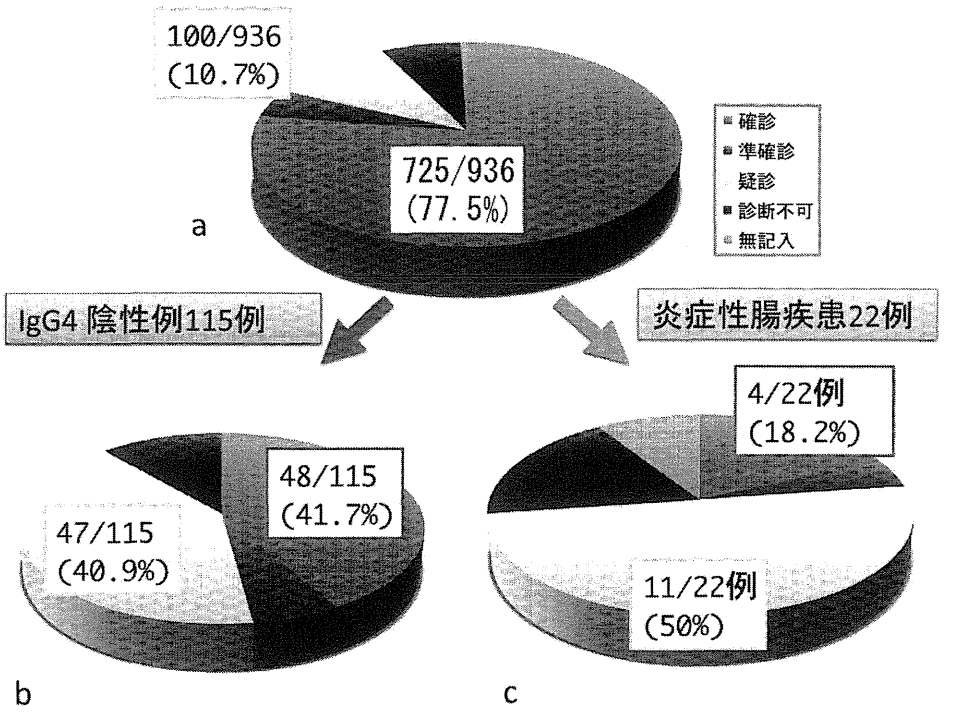

Fig. 3　臨床診断基準 2011 による診断
a）集積症例の臨床診断基準 2011 による診断の内訳．b）血清 IgG4 陰性例の臨床診断基準 2011 による診断の内訳．c）炎症性腸疾患の臨床診断基準 2011 による診断の内訳．

Table 2　再燃

再燃	193/869（22.2%）
膵臓	107 例（55.4%）
肝門部胆管炎	27 例（14.0%）
膵内胆管炎	27 例（14.0%）
涙腺・唾液腺炎	16 例（ 8.3%）
後腹膜線維症	11 例（ 5.7%）
その他	5 例（ 2.6%）

あった．膵腫大が再燃した 107 例中，同部位の再燃を来した症例は 72.0%（59/82 例），異なる部位の膵腫大を来した症例は 28.0%（23/82 例）（記載なし 25 例）であった．

9．予　　後

平均観察期間 1773.4±1089.9 日の間に死亡した症例は 17 例であった（生存 886 例，不明 22 例，無記入 11 例）．死因は癌死 4 例（膵癌 2 例，肺癌 1 例，胆管癌 1 例），肺炎 2 例，呼吸不全 1 例，事故 1 例，不明 2 例，記載なし 7 例であり，AIP と明らかに関連する死因は認めなかった．

悪性腫瘍を認めた症例は 11.8%（109/923 例）であった（無記入 10 例）．臓器別の症例数は，胃癌 21 例，大腸癌 16 例，肺癌 2 例，胆管癌 5 例，甲状腺癌 6 例，膀胱癌 9 例，腎細胞癌 7 例であり，膵癌は 7 例のみ（無記入 36 例）であった．

考　　察

第 3 回全国調査の二次調査では，AIP 臨床診断基準 2011 の診断項目を中心に調査が行われた．画像所見上，第 2 回調査と異なる点は，膵腫大と膵管狭細像を diffuse，segmental，focal の 3 つにわけて集計した点である．前回は膵全体の 1/3 以上と 1/3 未満の腫大に分けて回答を求め，約 30% の症例で 1/3 未満の腫大を呈していたが，今回の調査では，diffuse type が 52.6% と約半数であり，segmental type が 27.6%，focal type が 17.7% とより詳細に検討可能であった．膵管狭細に関してもほぼ同様の結果であった．びまん性の膵腫大を来す典型例が全体の約 1/2 に過ぎず，segmental type や focal type 症例が少なくないことも明らかになった．これら症例の診断においては，当然のことながら膵腫瘍との鑑別も重要となる．

AIP臨床診断基準改訂において，組織学的診断の重要性が増している．今回の組織学的所見の調査では，膵臓の組織採取率は前回調査と比較し，ほぼ同等であったが，切除症例が減少しEUS-FNAで膵組織が採取された症例が増加していた．適切な術前診断により不要な膵切除が減少していることが推察された．また，AIP診断におけるEUS-FNAの普及が明らかとなり，EUS-FNAによるAIPの組織採取率の改善とFNA検体を用いたAIPの組織診断法を確立することが重要と考えられた[31,32]．

全体として，77.5%の症例で確診所見が得られた一方，10.7%の症例が疑診に分類された．血清IgG4 135mg/dl未満の症例に限って検討すると，確診例は42%に減少し，疑診例が40.9%に増加した．また，炎症性腸疾患を合併した22例の診断は，確診4例，準確診1例，疑診11例，診断できない症例が4例と疑診例が50%を占めた．これらの症例のうち血清IgG4値が記載されていたのは，18例であり，そのうち3例のみで血清IgG4値が135mg/dlを超え，18例全体の平均値は68.4 mg/dlであった．このことはICDCにおけるtype 2 AIPやAIP-NOSが疑診例に多く含まれる可能性を示しており，臨床診断基準2011を用いた臨床研究を行う上で留意する必要が考えられた．

治療としては，80%以上の症例に対してステロイド投与が行われ，有効性も96.3%と極めて良好であった．近年，免疫調節薬によるAIP治療の報告が散見される[33~35]が，本調査での使用例は10例のみであった．免疫調節薬使用にあたっては保険診療の適応や副作用などの課題も多く，今後の検討が必要と考えられた．

今回の調査では経過観察期間中に死亡した症例が17例あった．AIPに直接関連した死因は認めず，AIPが予後の良い疾患であることが確認された．さらに，悪性腫瘍は，11.8%（109/923例）で認められ，うち膵癌は7例であった．今回の全国調査では，AIPにおける悪性腫瘍や膵癌の発症に関する適切な比較対照がないため，その評価が難しく，さらなる調査が必要と考えられた．

ま と め

日本におけるAIPの疫学について概説した．日本では診断基準の作成，改訂に合わせて，過去に3回の全国調査が行われ，様々な知見が得られた．全国調査から得られたAIPの全体像をもとに，AIPの診断，治療，研究に関して新たな展開が期待される．

文　献

1) Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 1995; 40: 1561-8.
2) 日本膵臓学会．日本膵臓学会自己免疫性膵炎診断基準2002．膵臓 2002；17：585-7.
3) 厚生労働省難治性膵疾患調査研究班・日本膵臓学会．自己免疫性膵炎臨床診断基準2006．膵臓 2006；21：395-7.
4) Shimosegawa T, Chari ST, Frulloni L, et al. International Consensus Diagnostic Criteria for Autoimmune Pancreatitis: Guidelines of the International Association of Pancreatology. Pancreas 2011; 40: 352-8.
5) 日本膵臓学会・厚生労働省難治性膵疾患調査研究班．報告　自己免疫性膵炎臨床診断基準2011．膵臓 2012；27：17-25.
6) 菅野　敦，正宗　淳，下瀬川徹．自己免疫性膵炎の疫学調査．消化器内科 2014；59：456-61.
7) 正宗　淳，菅野　敦，下瀬川徹．わが国における実態—2011年全国疫学調査の結果を中心に—．肝胆膵 2015（印刷中）.
8) 西森　功，須田耕一，大井　至，他．いわゆる自己免疫性膵炎の実体調査—膵組織の得られた症例における病理学的所見の検討—．厚生省特定疾患対策研究事業難治性膵疾患に関する調査研究班．平成11年度研究報告書，2000：56-65.
9) 西森　功，須田耕一，大井　至，他．いわゆる自己免疫性膵炎の実体調査—ステロイド剤が奏功した症例における臨床像の検討—．厚生労働省特定疾患対策研究事業難治性膵疾患に関する調査研究班．平成12年度研究報告書，2001：72-83.
10) 須田耕一，西森　功，大井　至，他．いわゆる自己免疫性膵炎の臨床病理学的検討．厚生労働省特定疾患対策研究事業難治性膵疾患に関する調査研究班．平成13年度研究報告書，2001：84-91.
11) 西森　功，須田耕一，大井　至，他．いわゆる自己免疫性膵炎の実態調査—膵癌およびアルコール性慢性膵炎との対比—．厚生労働省特定疾患対策研究事業難治性膵疾患に関する調査研究班．平成13年度研究報告書，2002：100-10.
12) Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pan-

creatitis. N Engl J Med 2001; 344: 732–8.
13) 西森　功．自己免疫性膵炎の疫学調査，厚生労働省特定疾患対策研究事業 難治性膵疾患に関する調査研究班 平成14年度総括・分担研究報告書，2003：169–72.
14) 西森　功，大槻　眞．自己免疫性膵炎の疫学調査，厚生労働省特定疾患対策研究事業 難治性膵疾患に関する調査研究班 平成15年度総括・分担研究報告書，2003：183–7.
15) 厚生労働省特定疾患難病の疫学調査班（班長：大野良之）．難病の患者数と臨床疫学像把握のための全国疫学調査マニュアル．名古屋大学医学部予防医学研究室，1994：1–32.
16) Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 2006; 4: 1010–6.
17) Chari ST, Takahashi N, Levy MJ, et al. A diagnosistic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol 2009; 7: 1097–103.
18) Kim KP, Kim MH, Kim JC, et al. Diagnostic criteria for autoimmune chronic pancreatitis revisited. World J Gastroenterol 2006; 12: 2487–96.
19) Pearson RK, Longnecker DS, Chari ST, et al. Autoimmune pancreatitis: does it exist? Pancreas 2003; 27: 1–13.
20) Otsuki M, Chung JB, Okazaki K, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan–Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol 2008; 43: 403–8.
21) Kawaguchi K, Tsuruta K, Okamoto A, et al. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol 1991; 22: 387–95.
22) Notohara K, Burgart LJ, Yadav D, et al. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. Am J Surg Pathol 2003; 27: 1119–27.
23) 西森　功．自己免疫性膵炎の実態調査（第2回全国調査）．厚生労働省難治性膵疾患に関する調査研究班．平成22年度総括・分担研究報告書．厚生労働省難治性膵疾患に関する調査研究班．仙台：東北大学生活協同組合，2010：222–5.
24) 下瀬川徹．自己免疫性膵炎の実態調査（第2回全国調査）．二次調査，厚生労働省難治性膵疾患に関する調査研究班．平成22年度総括・分担研究報告書．厚生労働省難治性膵疾患に関する調査研究班．仙台：東北大学生活協同組合，2011：227–31.
25) Kanno A, Nishimori I, Masamune A, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan. Pancreas 2011; 41: 835–9.
26) Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4–related disease (IgG4–RD), 2011. Mod Rheumatol 2012; 22: 21–30.
27) Chari ST, Kloeppel G, Zhang L, et al. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreas 2010; 39: 549–54.
28) Sumitomo K, Uchida K, Mitsuyama T, et al. A proposal of a diagnostic algorithm with validation of International Consensus Diagnostic Criteria for autoimmune pancreatitis in a Japanese cohort. Pancreatology 2013; 13: 230–7.
29) 下瀬川徹．自己免疫性膵炎の実態調査（第3回全国調査）．厚生労働省難治性膵疾患に関する調査研究班．平成24年度総括・分担研究報告書．厚生労働省難治性膵疾患に関する調査研究班．仙台：東北大学生活協同組合，2013：273–6.
30) Kanno A, Masamune A, Okazaki K, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan in 2011. Pancreas 2015 (in press).
31) Kanno A, Ishida K, Hamada S, et al. Diagnosis of autoimmune pancreatitis by EUS–FNA by using a 22–gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc 2012; 76: 594–602.
32) Ishikawa T, Itoh A, Kawashima H, et al. Endoscopic ultrasound–guided fine needle aspiration in the differentiation of type 1 and type 2 autoimmune pancreatitis. World J Gastroenterol 2012; 18: 3883–8.
33) Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4–associated cholangitis: clinical profile and response to therapy. Gastroenterlogy 2008; 134: 706–15.
34) Topazian M, Witzig TE, Smyrk TC, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4–associated cholangitis. Clin Gastroenterol Hepatol 2008; 6: 364–6.
35) Hart PA, Topazian MD, Witzig TE, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut 2013; 62: 1607–15.

Nationwide epidemiological survey of autoimmune pancreatitis in Japan

Atsushi KANNO, Atsushi MASAMUNE, and Tooru SHIMOSEGAWA*

Key words: International Consensus Diagnostic Criteria, Estimated number of patients, Annual incidence rate, Prevalence rate

Although almost 20 years have passed since autoimmune pancreatitis (AIP) was proposed as a diagnostic entity by Yoshida et al., the epidemiology, pathology, and optimal treatment of this disease remain largely unknown. To clarify the clinico-epidemiological features of AIP in Japan, the Research Committee of Intractable Pancreatic Diseases, supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD) conducted nationwide epidemiological surveys of AIP in 2003, 2007 and 2011. In this third survey, AIP patients who had visited selected hospitals in 2011 were surveyed. AIP was diagnosed according to the revised clinical diagnostic criteria for AIP (JPS2011). The estimated total number of AIP patients in 2011 was 5,745 (95% confidence interval: 5,325–6,164), with an overall prevalence rate of 4.6 per 100,000 population. The number of patients, who were newly diagnosed as AIP, was estimated to be 1,808 (95% confidence interval, 1,597–2,018), with an annual incidence rate of 1.4 per 100,000 population. The sex ratio (male to female) was 3.2 and the mean age was 66.3 ± 11.5. Among the 936 patients whose detailed clinical information was available, 86.4% of the patients presented high serum IgG4 levels (≥135 mg/dl) and 82.3% received steroid therapy. The data obtained by the nationwide survey will contribute to clarify the current clinicopathological features of AIP in Japan.

* Division of Gastroenterology, Tohoku University Graduate School of Medicine (Miyagi)

Advances in Medical Sciences 60 (2015) 211–215

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

Assessment in steroid trial for IgG4-related sclerosing cholangitis

Susumu Iwasaki [a], Terumi Kamisawa [a,*], Satomi Koizumi [a], Kazuro Chiba [a], Taku Tabata [a], Sawako Kuruma [a], Yui Kishimoto [b], Yoshinori Igarashi [b]

[a] Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan
[b] Division of Gastroenterology and Hepatology, Omori Medical Center, Toho University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 26 November 2014
Accepted 23 February 2015
Available online 7 March 2015

Keywords:
IgG4
Sclerosing cholangitis
Cholangiocarcinoma
Primary sclerosing cholangitis

ABSTRACT

Purpose: Response to steroids is included in the diagnostic criteria for IgG4-related sclerosing cholangitis (IgG4-SC). To assess how to appropriately conduct steroid trials for IgG4-related SC, we examined the clinical pictures of steroid responsiveness in IgG4-SC patients.
Material and methods: A total of 29 patients with IgG4-SC (lower bile duct involvement, $n = 29$; hilar/intrahepatic bile duct involvement, $n = 6$) initially treated with steroids were enrolled in this study. Blood biochemistry was examined at about 5, 10 and 15 days after commencing steroid therapy. Endoscopic retrograde cholangiography (ERC) and magnetic resonance cholangiopancreatography (MRCP) were performed after steroid administration in 18 and 25 patients, respectively.
Results: In 19 patients without biliary drainage, elevated serum levels of total bilirubin, alanine aminotransferase, and alkaline phosphatase were halved in 50%, 25%, and 44% of patients at about 5 days after starting steroids, and in 17%, 38%, and 44% at about 10 days. Responsiveness to steroids could be evaluated at 1–2 weeks on ERC or MRCP, but response was lower in the hilar/intrahepatic bile duct than in the lower bile duct.
Conclusions: Steroid responsiveness of IgG4-SC is recommended to be assessed by blood biochemistry at 5 and 10 days and on MRCP and/or ERC at 1–2 weeks after starting steroid.

1. Introduction

IgG4-related disease is a newly developed systemic disease entity characterized by tumorous swelling of affected organs and elevated serum IgG4 levels [1]. Autoimmune pancreatitis (AIP) is the prototypical IgG4-related disease, and IgG4-related sclerosing cholangitis (IgG4-SC) is a biliary manifestation of IgG4-related disease [2,3].

IgG4-SC is frequently associated with AIP, and the lower bile duct is most frequently involved. These cases need to be differentiated from pancreatic carcinoma and lower bile duct carcinoma. If stenosis develops in the hilar and/or intrahepatic bile duct, the cholangiographic appearance is similar to that of primary sclerosing cholangitis (PSC) [4,5]. PSC progresses despite medical treatment, and liver transplantation provides the greatest potential for cure. As IgG4-SC responds well to steroid, differentiating IgG4-SC from PSC is important to provide an appropriate treatment regimen. Another important disease that should be differentiated from IgG4-SC is cholangiocarcinoma. The radiological features of IgG4-SC involving the hilar bile duct are quite similar to those of hilar cholangiocarcinoma [4–7].

According to the clinical diagnostic criteria of IgG4-SC 2012 [7], IgG4-SC is diagnosed based on a combination of biliary tract imaging, elevation of serum IgG4 levels, other organ involvements such as AIP, histological features, and an optional criterion of the effectiveness of steroid therapy. As taking adequate specimens by transpapillary bile duct biopsy is difficult, differentiation between IgG4-SC and bile duct carcinoma or PSC is sometimes clinically difficult. Steroid responsiveness may assure the diagnosis of IgG4-SC. However, to avoid cancer progression in resectable patients during a steroid trial, assessing steroid responsiveness within a short duration is necessary. To determine when and how we judge steroid responsiveness in a steroid trial, we examined clinical pictures of responsiveness to steroid in IgG4-SC patients.

2. Patients and methods

This retrospective study was approved by the institutional review board at Tokyo Metropolitan Komagome Hospital, and informed consent for all invasive procedures was obtained from all patients prior to participation.

* Corresponding author at: Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. Tel.: +81 3 3823 2101; fax: +81 3 3824 1552.
E-mail address: kamisawa@cick.jp (T. Kamisawa).

http://dx.doi.org/10.1016/j.advms.2015.02.006
1896-1126/

2.1. Patients

Participants comprised 29 patients (19 men, 10 women; median age, 71 years; range, 52–76 years) with IgG4-SC who were diagnosed according to the clinical diagnostic criteria of IgG4-SC 2012 [7] and were initially treated with steroids. All cases were associated with type 1 AIP. Stenosis of the lower bile duct was detected in all patients, and stenosis of the hilar bile duct either with ($n = 2$) or without ($n = 4$) intrahepatic bile duct involvement was also detected in 6 patients. According to cholangiographic classification of IgG4-SC [7], cholangiograms were classified into type 1 ($n = 23$), type 2 ($n = 2$), and type 3 ($n = 4$). Apparent jaundice (serum total bilirubin (T. Bil) level ≥3 mg/dl) was detected in 10 patients.

Before steroid therapy, endoscopic retrograde cholangiography (ERC) was successfully performed in 26 patients with bile cytology with or without bile duct brushing, or bile duct biopsy. Cannulation to the bile duct was unsuccessful in 3 patients. Magnetic resonance cholangiopancreatography (MRCP) was performed in 28 patients, excluding one patient who had metallic clips. MRCP was done using a 1.5-T magnetic resonance imaging machine by two-or three-dimensional coronal heavily T2-weighyted single-shot rapid acquisition with relaxation enhancement.

2.2. Regimen of steroid therapy

Endoscopic and percutaneous transhepatic biliary drainage was performed before steroid therapy in 9 patients and 1 patient, respectively. The initial dose of oral prednisolone was 30 mg/day in 26 patients and 40 mg/day in 3 patients according to the standard regimen of the initial dose (0.6/mg/kg/day). The initial dose was administered in 3–4 weeks, and was gradually tapered by 5 mg/day every 2 weeks. Biochemical and serological blood tests, such as liver enzymes and IgG4 levels, and imaging modalities such as MRCP, computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP) were performed periodically after commencing steroid therapy [8].

2.3. Assessment of responsiveness to steroids

Biochemical blood tests including T. Bil (normal, 0.8–1.1 mg/dl), alanine aminotransferase (ALT) (normal, 30–46 IU/l), and alkaline phosphatase (ALP) (normal, 150–233 IU/l) were examined at about 5 days (4–6 days), about 10 days (9–11 days), and about 15 days (14–16 days) after commencement of steroid therapy. When the abnormally elevated level before steroids showed a drop more than 10%, it was regarded as decrease.

ERC was performed in 18 patients, at about 1 week (5 and 9 days, $n = 2$), about 2 weeks (12–16 days, $n = 7$), about 3 weeks (19–24 days, $n = 4$), and ≥4 weeks (30–78 days, $n = 5$) after starting steroid. MRCP was performed in 25 patients, at about 1 week (8–10 days, $n = 4$), about 2 weeks (13–17 days, $n = 10$), about 3 weeks (19–23 days, $n = 7$), and ≥4 weeks (29–55 days, $n = 4$) after starting steroid. Stenosis from sclerosing cholangitis was classified into 4 degrees: complete obstruction, 0; marked stenosis (≥2/3), 1; moderate stenosis (<2/3), 2; and almost normal, 3.

3. Results

All patients responded well to steroid therapy and achieved remission, including of other associated IgG4-related diseases. All biliary drainage tubes were withdrawn at a mean of 16 days (range, 9–30 days) after starting steroid administration.

3.1. Biochemical blood tests

In the 19 patients without biliary drainage, serum levels of T. Bil, ALT, and ALP were elevated to more than double the upper limit of normal in 6, 8, and 9 patients before steroid therapy, respectively. At about 5 days after starting steroids, serum levels of T. Bil, ALT, and ALP decreased in 5 (83%), 6 (75%), and 8 (89%) patients. Serum ALP levels decreased in 1 patient at about 10 days. Time to halving of serum T. Bil level was about 5 days in 3 patients (50%), about 10 days in 1 (17%), and about 15 days in 1 (17%) (Fig. 1a). Time to halving of serum ALT level was about 5 days

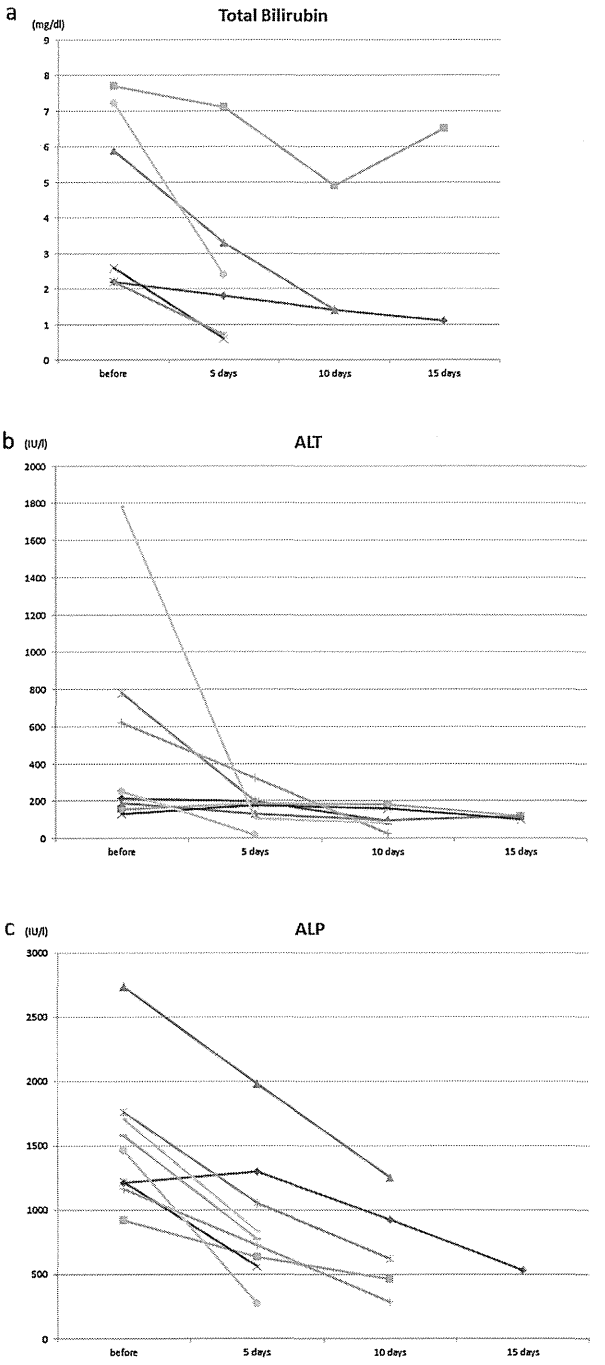

Fig. 1. (a) Changes in serum levels of total bilirubin after steroid therapy. (b) Changes in serum levels of ALT after steroid therapy. (c) Changes in serum levels of ALP after steroid therapy.

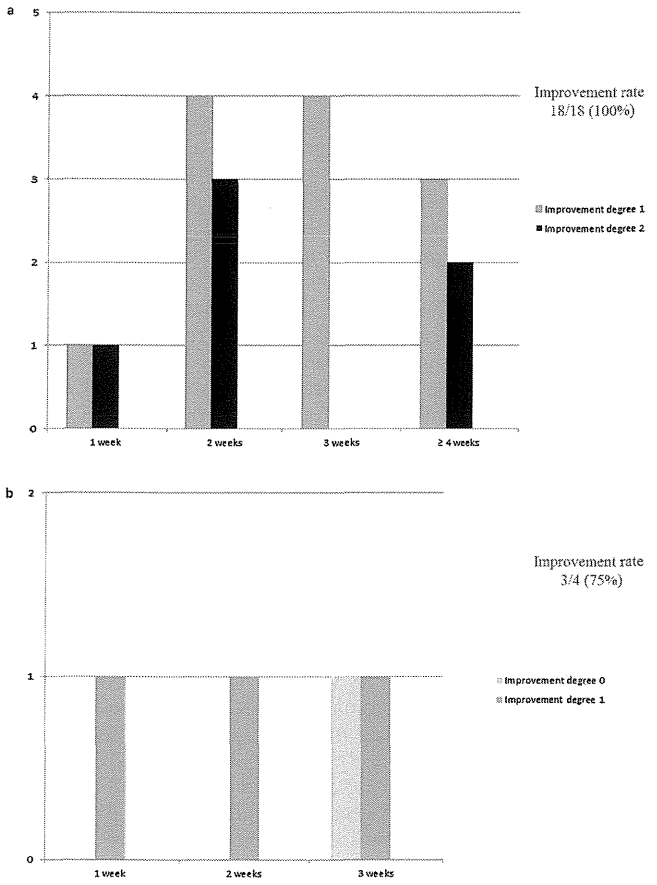

Fig. 2. Degrees of improvement on ERC after steroid therapy in IgG4-SC involving the lower bile duct (a) and the hilar/intrahepatic bile duct (b).

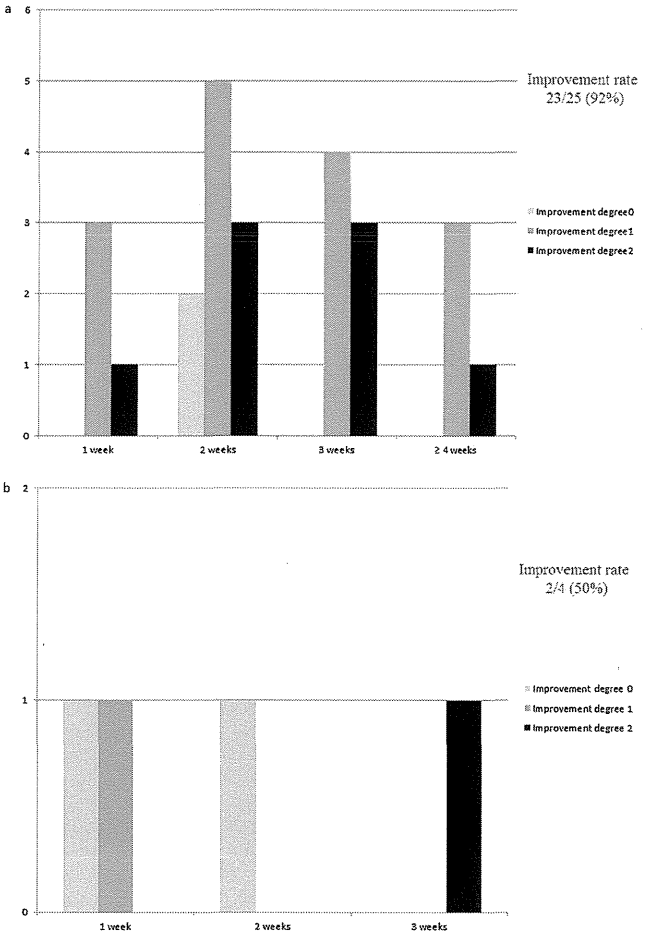

Fig. 3. Degrees of improvement on MRCP after steroid therapy in IgG4-SC involving the lower bile duct (a) and the hilar/intrahepatic bile duct (b).

in 2 patients (25%), and about 10 days in 3 (38%) (Fig. 1b). Time to halving of serum ALP level was about 5 days in 4 patients (44%), about 10 days in 4 (44%), and about 15 days in 1 (11%) (Fig. 1c).

3.2. ERC

The stenotic portion of the lower bile duct was improved in 100% (2/2) at about 1 week, in 100% (7/7) at about 2 weeks, in 100% (4/4) at about 3 weeks, and in 100% (5/5) at ≥4 weeks. Improvement by 2 degrees was observed in 1 patient at 1 week, 3 patients at 2 weeks, and 2 patients at ≥4 weeks (Fig. 2a). The stenotic portion of the hilar and/or intrahepatic bile duct was improved in 100% (1/1) at about 1 week, in 100% (1/1) at about 2 weeks, and in 50% (1/2) at about 3 weeks, and the degree of improvement was only 1 (Fig. 2b).

3.3. MRCP

The stenotic portion of the lower bile duct was improved in 100% (4/4) at about 1 week, in 80% (8/10) at about 2 weeks, in 100% (7/7) at about 3 weeks, and in 100% (4/4) at ≥4 weeks. Improvement of 2 degrees was observed in 1 patient at 1 week, 3 patients at 2 week, 3 patients at 3 weeks, and 1 patient at ≥4 weeks (Fig. 3a). The stenotic portion of the hilar and/or intrahepatic bile duct was improved in 50% (1/2, 1 degree) at about 1 week, in 0% (0/1) at about 2 weeks, and in 100% (1/1, 2 degrees) at ≥4 weeks (Figs. 3b and 4a, b).

4. Discussion

The most important factor in the diagnosis of IgG4-related disease is to differentiating this pathology from malignancy. As definitive diagnostic markers for IgG4-related disease are lacking, diagnosis is made using a combination of clinical, imaging, serological, and histopathological features. However, differentiation between IgG4-related disease and malignancy is still difficult in some cases [1].

As IgG4-related disease responds well to steroid, rapid response to steroids is reassuring and confirms the diagnosis. As steroid trial should not be used as a substitute for a thorough search for an etiology and should only be started in patients showing a negative work-up for known etiologies, including cancer. Furthermore, two major points need to be considered in steroid trials for IgG4-related disease. First, as steroids have anti-inflammatory effects, including improvement in clinical symptoms, steroid responsiveness should be assessed objectively. Second, as cancer may progress in resectable patients during a steroid trial, steroid responsiveness should be assessed within a short duration as possible.

Moon et al. [9] conducted a 2-week steroid trial for 22 patients with clinically suspected AIP showing atypical findings on imaging after an initial negative investigation for malignancy. Steroid responsiveness was assessed based on a marked improvement of narrowing of the main pancreatic duct and a reduction in the size of the pancreatic mass. All 15 patients who responded to steroids

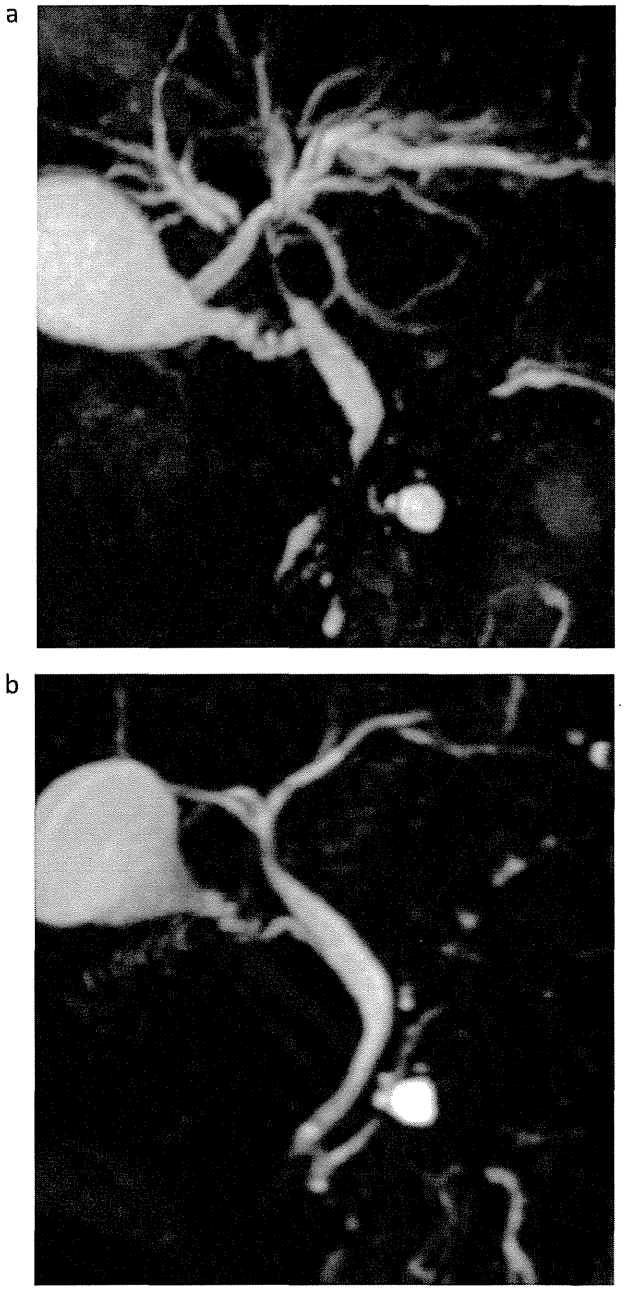

Fig. 4. MRCP findings of IgG4-SC showing a 2-degree improvement in the lower bile duct and a 1-degree improvement in the hilar bile duct after steroid therapy. (a) Before, and (b) 1 week after starting steroid therapy.

were finally diagnosed with AIP, whereas all 7 patients who did not show a response to steroids were later confirmed as having pancreatic cancer. Improvements in clinical symptoms or normalization of elevated levels of serum IgG4 may be seen in response to steroids, but were excluded as a criterion for steroid responsiveness because they might be induced by the anti-inflammatory effect of steroids. Pancreatic enlargement resulting from obstructive pancreatitis associated with pancreatic cancer may also be relieved by steroid therapy, again due to the anti-inflammatory effect of steroids. Therefore, their study defined steroid responsiveness not simply as improvement of pancreatic swelling, but more strictly as relief of narrowing of the main pancreatic duct and resolution of the pancreatic mass.

In the international consensus diagnostic criteria for AIP [10], response to steroids is used as an optional criterion. This criterion involves use of prednisolone at 0.6–1 mg/kg/day with reassessment of imaging findings and CA19.9 levels after 2 weeks of treatment, based on the Moon's study. Response to steroid therapy is also used as an optional criterion in the clinical diagnostic criteria of IgG4-related SC 2012 [7]. Although evaluation of the effectiveness by imaging modalities is recommended, precise methods were not assessed in the criteria. We undertook this study to assess how to appropriately conduct a steroid trial for IgG4-related SC.

Resolution of stenosis of the lower bile duct after steroid therapy was observed in all 18 ERC series. The resolution was also detected in 23 MRCP series, but was not observed in 2 patients on MRCP performed about 2 weeks after starting steroids. This might be due to lower spatial resolution on MRCP. On the other hand, resolution of hilar/intrahepatic bile duct stenosis was not observed in 1 patient on ERC at about 3 weeks, and in 2 patients on MRCP at about 1 and 2 weeks, respectively. Responsiveness to steroids can be evaluated at 1–2 weeks on ERC or MRCP, but responsiveness was less apparent in the hilar/intrahepatic bile duct than in the lower bile duct. Reasons for the differences of steroid responsiveness between hilar/intrahepatic and lower bile duct were unknown.

Response to steroids can be evaluated using tests of blood chemistry in IgG4-SC patients without biliary drainage. In our 19 patients without biliary drainage, elevated serum levels of T. Bil, ALT, and ALP were decreased in 100%, 75%, and 100% at about 10 days after starting steroid. They were halved in 50%, 25%, and 44% at about 5 days, and in 17%, 38%, and 44% at about 10 days.

Steroid trials for IgG4-SC should be undertaken for patients in whom a response can be assessed objectively after possible negative work-ups. To avoid cancer progression in resectable patients during a steroid trial, steroid responsiveness should be judged using blood chemistry at 5 and 10 days and on MRCP and/or ERC at 1–2 weeks after starting steroid. However, as slight responsiveness may be seen by the anti-inflammatory effect of steroids even in cases of cholangiocarcinoma, the judgment of steroid responsiveness should be done carefully by both findings.

Limitations of this study that must be considered on interpreting the results include the retrospective design and the small number of cases of IgG4-SC involving the hilar/intrahepatic bile duct. However, this represents the first study to assess appropriate steroid trials for IgG4-SC.

5. Conclusions

Steroid responsiveness in steroid trials for IgG4-SC is recommended to be assessed using blood biochemistry tests at 5 and 10 days and on MRCP and/or ERC at 1–2 weeks after starting steroid.

Conflict of interests

None declared.

Financial disclosure

None declared.

References

[1] Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2014. http://dx.doi.org/10.1016/S0140-6736(14)60720-0. pii:S0140-6736(14)60720-0 [in press, Epub ahead of print].

[2] Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010;7:401–9.
[3] Okazaki K, Kawa S, Kamisawa T, Ito T, Inui K, Irie H, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013. I. Concept and diagnosis of autoimmune pancreatitis. J Gastroenterol 2014;49: 567–88.
[4] Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedure for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci 2011;18: 127–36.
[5] Tabata T, Kamisawa T, Hara S, Kuruma S, Chiba K, Kuwata G, et al. Differentiating immunoglobulin G4-related sclerosing cholangitis from hilar cholangiocarcinoma. Gut Liver 2013;7:234–8.
[6] Erdogan D, Kloek JJ, ten Kate FJ, Rauws EA, Busch OR, Gouma DJ, et al. Immunoglobulin G4-related sclerosing cholangitis in patients resected for presumed malignant bile duct strictures. Br J Surg 2008;95:727–34.
[7] Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 2012;19:536–42.
[8] Kamisawa T, Okazaki K, Kawa S, Ito T, Inui K, Irie H, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013. III. Treatment and prognosis of autoimmune pancreatitis. J Gastroenterol 2014;49: 961–70.
[9] Moon SH, Kim MH, Park DH, Hwang CY, Park SJ, Lee SS, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. Gut 2008;57:1704–12.
[10] Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40: 352–8.