45 Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. *Semin Arthritis Rheum* 2013; **43:** 806–17.

46 Ohno K, Sato Y, Ohshima K, et al. IgG4-related disease involving the sclera. *Mod Rheumatol* 2014; **24:** 195–98.

47 Wallace ZS, Khosroshahi A, Jakobiec FA, et al. IgG4-related systemic disease as a cause of "idiopathic" orbital inflammation, including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol* 2012; **57:** 26–33.

48 Inoue D, Zen Y, Sato Y, et al. IgG4-related perineural disease. *Int J Rheumatol* 2012; **29:** 212–18.

49 Takahira M, Ozawa Y, Kawano M, et al. Clinical aspects of IgG4-related orbital inflammation in a case series of ocular adnexal lymphoproliferative disorders. *Int J Rheumatol* 2012; published online April 2. DOI:10.1155/2012/635473.

50 Baer AN, Gourin CG, Westra WH, Cox DP, Greenspan JS, Daniels TE, and the Sjögren's International Collaborative Alliance. Rare diagnosis of IgG4-related systemic disease by lip biopsy in an international Sjögren syndrome registry. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **115:** e34–39.

51 Hermet M, André M, Kémény JL, et al. Is IgG4-related disease a cause of xerostomia? A cohort study of 60 patients. *Int J Rheumatol* 2012; published online Oct 16. DOI:10.1155/2012/303506.

52 Geyer JT, Ferry JA, Harris NL, et al. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010; **34:** 202–10.

53 Yao Q, Wu G, Hoschar A. IgG4-related Mikulicz's disease is a multiorgan lymphoproliferative disease distinct from Sjögren's syndrome: a Caucasian patient and literature review. *Clin Exp Rheumatol* 2013; **31:** 289–94.

54 Himi T, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012; **39:** 9–17.

55 Fatemi G, Fang MA. IgG4-related pharyngitis-an addition to the nomenclature of IgG4-related disease: comment on the article by Stone et al. *Arthritis Rheum* 2013; **65:** 2217.

56 Hu EK, Parrish C, Wrobel B, Deshpande V, Stone JH. Immunoglobulin G4-related disease presenting as an ethmoid and maxillary mass. *Ann Allergy Asthma Immunol* 2013; **111:** 75–77.

57 Schiffenbauer AI, Gahl WA, Pittaluga S, et al. IgG4-related disease presenting as recurrent mastoiditis. *Laryngoscope* 2012; **122:** 681–84.

58 Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 2010; **62:** 1312–18.

59 Deshpande V, Huck A, Ooi E, Stone JH, Faquin WC, Nielsen GP. Fibrosing variant of Hashimoto thyroiditis is an IgG4 related disease. *J Clin Pathol* 2012; **65:** 725–28.

60 Pusztaszeri M, Triponez F, Pache JC, Bongiovanni M. Riedel's thyroiditis with increased IgG4 plasma cells: evidence for an underlying IgG4-related sclerosing disease? *Thyroid* 2012; **22:** 964–68.

61 Watanabe T, Maruyama M, Ito T, et al. Clinical features of a new disease concept, IgG4-related thyroiditis. *Scand J Rheumatol* 2013; **42:** 325–30.

62 Cheuk W, Chan JK. Lymphadenopathy of IgG4-related disease: an underdiagnosed and overdiagnosed entity. *Semin Diagn Pathol* 2012; **29:** 226–34.

63 Kasashima S, Zen Y, Kawashima A, et al. A clinicopathologic study of immunoglobulin G4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* 2010; **52:** 1587–95.

64 Stone JH, Patel VI, Oliveira GR, Stone JR. Case records of the Massachusetts General Hospital: case 38-2012, a 60-year-old man with abdominal pain and aortic aneurysms. *N Engl J Med* 2012; **367:** 2335–46.

65 Zen Y, Kasashima S, Inoue D. Retroperitoneal and aortic manifestations of immunoglobulin G4-related disease. *Semin Diagn Pathol* 2012; **29:** 212–18.

66 Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; **23:** 88–94.

67 Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. *Radiology* 2011; **261:** 625–33.

68 Inokuchi G, Hayakawa M, Kishimoto T, Makino Y, Iwase H. A suspected case of coronary periarteritis due to IgG4-related disease as a cause of ischemic heart disease. *Forensic Sci Med Pathol* 2014; **10:** 103–08.

69 Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine (Baltimore)* 2013; **92:** 82–91.

70 Zen Y, Onodera M, Inoue D, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; **33:** 1833–39.

71 Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology* 2009; **251:** 260–70.

72 Saeki T, Nishi S, Imai N, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; **78:** 1016–23.

73 Saeki T, Kawano M, Mizushima I, et al. The clinical course of patients with IgG4-related kidney disease. *Kidney Int* 2013; **84:** 826–33.

74 Alexander MP, Larsen CP, Gibson IW, et al. Membranous glomerulonephritis is a manifestation of IgG4-related disease. *Kidney Int* 2013; **83:** 455–62.

75 Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361:** 11–21.

76 Khosroshahi A, Ayalon R, Beck LH Jr, Salant DJ, Bloch DB, Stone JH. IgG4-related disease is not associated with antibody to the phospholipase A2 receptor. *Int J Rheumatol* 2012; published online May 10. DOI:10.1155/2012/139409.

77 Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344:** 732–38.

78 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:** 140–48, quiz e12–13.

79 Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut* 2013; **62:** 1771–76.

80 Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and Type 2. *Gut* 2013; **62:** 1373–80.

81 Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* 2010; **7:** 401–09.

82 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.

83 Ozaki Y, Oguchi K, Hamano H, et al. Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. *J Gastroenterol* 2008; **43:** 144–51.

84 Pezzilli R, Vecchiarelli S, Di Marco MC, et al. Pancreatic ductal adenocarcinoma associated with autoimmune pancreatitis. *Case Rep Gastroenterol* 2011; **5:** 378–85.

85 Gupta R, Khosroshahi A, Shinagare S, et al. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a retrospective analysis of pancreatic resections. *Pancreas* 2013; **42:** 506–10.

86 Maruyama M, Arakura N, Ozaki Y, et al. Type 1 autoimmune pancreatitis can transform into chronic pancreatitis: a long-term follow-up study of 73 Japanese patients. *Int J Rheumatol* 2013; published online May 16. DOI:10.1155/2013/272595.

87 Hirano K, Tada M, Isayama H, et al. Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. *Gastrointest Endosc* 2010; **71:** 85–90.

88 Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2006; **101:** 2070–75.

89 Oseini AM, Chaiteerakij R, Shire AM, et al. Utility of serum immunoglobulin G4 in distinguishing immunoglobulin G4-associated cholangitis from cholangiocarcinoma. *Hepatology* 2011; **54:** 940–48.

90 Kalaitzakis E, Levy M, Kamisawa T, et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2011; **9:** 800–03, e2.

91 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.

92 Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedures for IgG4-related sclerosing cholangitis. *J Hepatobiliary Pancreat Sci* 2011; **18:** 127–36.

93 Wallace ZS, Carruthers MN, Khosroshahi A, et al. IgG4-related disease and hypertrophic pachymeningitis. *Medicine (Baltimore)* 2013; **92:** 206–16.

94 Leporati P, Landek-Salgado MA, Lupi I, Chiovato L, Caturegli P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. *J Clin Endocrinol Metab* 2011; **96:** 1971–80.

95 Peikert T, Shrestha B, Aubry MC, et al. Histopathologic overlap between fibrosing mediastinitis and IgG4-related disease. *Int J Rheumatol* 2012; published online May 10. DOI:10.1155/2012/207056.

96 Salvarani C, Valli R, Boiardi L, Pipitone N, Nicoli F, Muratore F. IgG4-associated sclerosing mesenteritis. *Clin Exp Rheumatol* 2011; **29** (suppl 64): S79–80.

97 Ikeda T, Oka M, Shimizu H, et al. IgG4-related skin manifestations in patients with IgG4-related disease. *Eur J Dermatol* 2013; **23:** 241–45.

98 Hart PA, Smyrk TC, Chari ST. IgG4-related prostatitis: a rare cause of steroid-responsive obstructive urinary symptoms. *Int J Urol* 2013; **20:** 132–34.

99 Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M, and the Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol* 2010; **45:** 471–77.

100 Masaki Y, for the All-Japan Team for the Prospective Treatment Study of IgG4-RD. A trial of corticosteroids for IgG4-related disease. Second International Symposium on IgG4-related Disease & Associated Conditions, Honolulu, HA, USA, February 16–19, 2014.

101 Kamisawa T, Egawa N, Inokuma S, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas* 2003; **27:** 235–38.

102 Ito T, Kawabe K, Arita Y, et al. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. *Pancreas* 2007; **34:** 254–59.

103 Ko SB, Mizuno N, Yatabe Y, et al. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* 2010; **138:** 1988–96.

104 Shimizu Y, Yamamoto M, Naishiro Y, et al. Necessity of early intervention for IgG4-related disease–delayed treatment induces fibrosis progression. *Rheumatology (Oxford)* 2013; **52:** 679–83.

105 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.

106 Carruthers MN, Khosroshahi A, Topazian M, et al. Rituximab for IgG4-related disease: a prospective treatment trial. *Arthritis Rheum* 2013; **10:** 2649.

ORIGINAL ARTICLE

Gut and Liver, Published online June 18, 2014

Characteristic Findings of Endoscopic Retrograde Cholangiopancreatography in Autoimmune Pancreatitis

Susumu Iwasaki*, Terumi Kamisawa*, Satomi Koizumi*, Kazuro Chiba*, Taku Tabata*, Sawako Kuruma*, Go Kuwata*, Takashi Fujiwara*, Koichi Koizumi*, Takeo Arakawa*, Kumiko Momma*, Seiichi Hara*,†, and Yoshinori Igarashi†

**Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, and †Division of Gastroenterology and Hepatology, Omori Medical Center, Toho University School of Medicine, Tokyo, Japan*

Background/Aims: Diffuse or segmental irregular narrowing of the main pancreatic duct (MPD), as observed by endoscopic retrograde cholangiopancreatography (ERCP), is a characteristic feature of autoimmune pancreatitis (AIP). **Methods:** ERCP findings were retrospectively examined in 40 patients with AIP in whom irregular narrowing of the MPD was detected near the orifice. The MPD opening sign was defined as the MPD within 1.5 cm from the orifice being maintained. The distal common bile duct (CBD) sign was defined as the distal CBD within 1.5 cm from the orifice being maintained. Endoscopic findings of a swollen major papilla and histological findings of specimens obtained from the major papilla were examined in 26 and 21 patients, respectively. **Results:** The MPD opening sign was detected in 26 of the 40 patients (65%). The distal CBD sign was detected in 25 of the 32 patients (78%), which showed stenosis of the lower bile duct. The patients who showed the MPD opening sign frequently showed the distal CBD sign (p=0.018). Lymphoplasmacytic infiltration, but not dense fibrosis, was histologically detected in biopsy specimens obtained from the major papilla. **Conclusions:** On ERCP, the MPD and CBD adjacent to the major papilla are frequently maintained in patients with AIP involving the pancreatic head. These signs are useful for diagnosing AIP on ERCP. **(Gut Liver, Published online June 18, 2014)**

Key Words: Pancreatitis, chronic; Cholangitis, sclerosing

INTRODUCTION

Autoimmune pancreatitis (AIP) is a recently identified peculiar type of pancreatitis with a presumed autoimmune etiology. AIP is characterized serologically by elevated serum immunoglobulin G4 (IgG4) levels, histologically by abundant infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis, and therapeutically by a dramatic response to steroids. The most common presenting symptom of AIP is obstructive jaundice due to stricture of the bile duct. In many AIP patients, the causative stenosis is located in the lower part of the common bile duct (CBD). As AIP sometimes mimics pancreatic cancer, accurate differentiation of AIP from pancreatic cancer is important to avoid unnecessary surgery.[1,2]

Irregular narrowing of the main pancreatic duct (MPD) is a characteristic pancreatographic feature of AIP. Diffuse irregular narrowing of the MPD is rather specific to AIP; however, segmental narrowing of the MPD is sometimes difficult to differentiate from stenosis of the MPD caused by pancreatic cancer.[3-6] Given their utility in differentiating AIP from pancreatic cancer, pancreatographic findings play an important role in both the international consensus diagnostic criteria (ICDC)[7] and the Japanese diagnostic criteria 2011.[8] We have prospectively examined pancreatographic findings in AIP patients on endoscopic retrograde pancreatography (ERP). The current study retrospectively examined findings of endoscopic retrograde cholangiopancreatography (ERCP) for AIP patients in whom the pancreatic head was involved, focusing on the opening portion of the MPD and the distal portion of the CBD.

MATERIALS AND METHODS

From 1991 to 2013, a total of 94 patients with type-1 AIP (68 males, 26 females; median age, 64 years) were diagnosed according to the ICDC[7] in Tokyo Metropolitan Komagome Hospital. Enlargement of the pancreas on computed tomography (CT)

Correspondence to: Terumi Kamisawa
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: kamisawa@cick.jp
Received on December 26, 2013. Revised on January 17, 2014. Accepted on February 5, 2014.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl13473

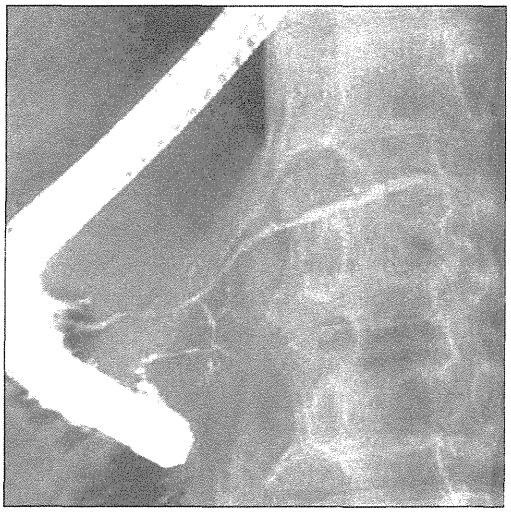

Fig. 1. Endoscopic retrograde pancreatography finding of diffuse narrowing of the main pancreatic duct involving the orifice in the major papilla.

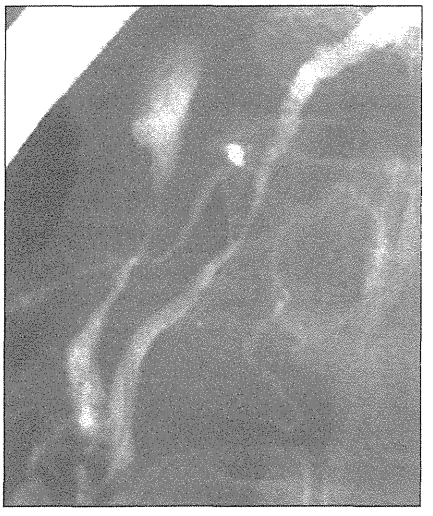

Fig. 2. Endoscopic retrograde pancreatography findings of excluded cases showing no irregular narrowing of the main pancreatic duct within 2 cm from the orifice.

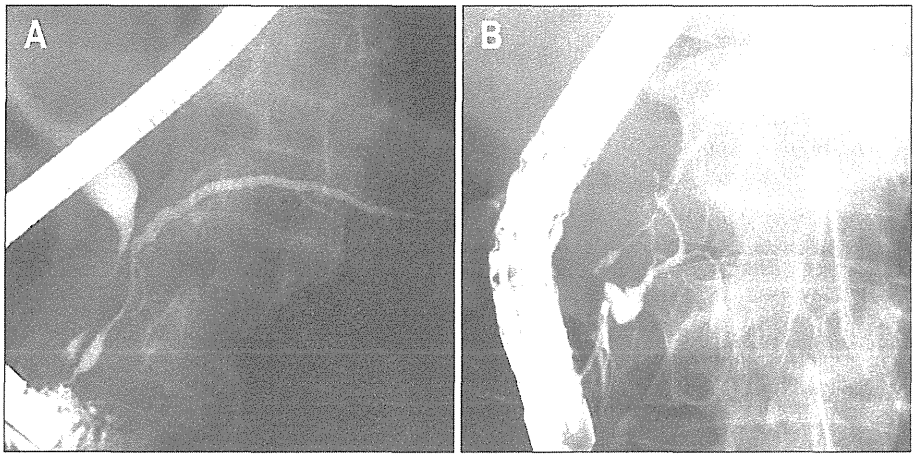

Fig. 3. Main pancreatic duct opening sign showing that the main pancreatic duct within 1.5 cm from the orifice is maintained without irregular narrowing. The preserved main pancreatic duct is either (A) spindle-shaped or (B) cystic-shaped.

and irregular narrowing of the MPD on ERP were detected in all patients (Fig. 1). ERCP findings were retrospectively examined for 48 patients in whom the pancreatic head was enlarged on CT, and satisfactory imagings from pancreatography were obtained. To achieve the best possible visualization, several pancreatograms of the head of the pancreas were taken in a prone or slightly oblique position. Four patients with pancreas divisum (complete, n=2; incomplete, n=2) and four patients in whom the MPD within 2 cm from the orifice was not involved in irregular narrowing were excluded from the study (Fig. 2). Forty type-1 AIP patients in whom irregular narrowing of the MPD was detected near the orifice were enrolled in this study. Pancreatic enlargement of the pancreas was diffuse (n=22) and segmental in the pancreatic head (n=18). Irregular narrowing of the MPD was diffuse (n=19), skipped in the pancreatic head and body (n=4), and segmental in the pancreatic head (n=17).

ERCP findings were examined in all 40 patients, focusing on

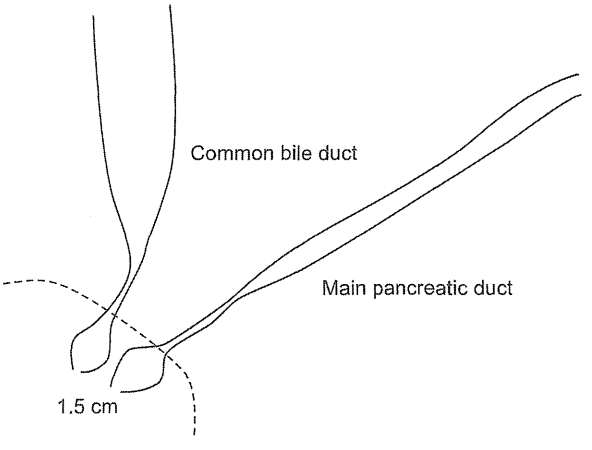

Fig. 4. Schematic illustration of the main pancreatic duct opening and distal common bile duct signs.

the opening portion of the MPD and the distal portion of the CBD. Endoscopic retrograde cholangiography (ERC) was not performed in six patients. Stenosis of the lower bile duct was observed in 32 patients on ERC. MPD opening sign was defined as the MPD within 1.5 cm from the orifice being maintained without irregular narrowing. The preserved MPD showed a spindle (Fig. 3A) or cystic shape (Figs. 3B and 4). Distal CBD sign was likewise defined as the distal CBD within 1.5 cm from the orifice being maintained without involvement of stenosis (Figs. 4 and 5).

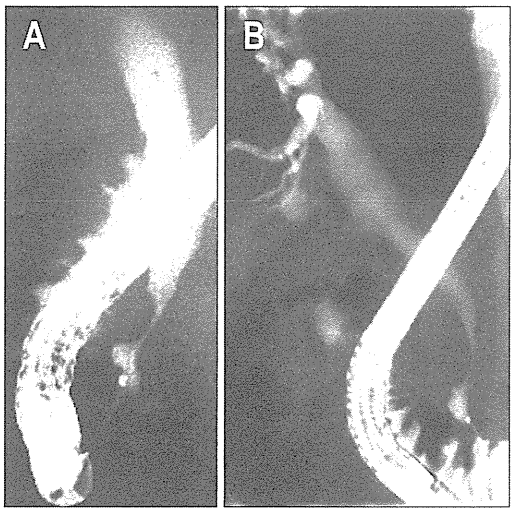

Fig. 5. (A, B) Distal common bile duct (CBD) sign showing that the distal CBD within 1.5 cm from the orifice is maintained without involvement of stenosis.

We examined endoscopic findings of the major papilla in 26 of the 40 AIP patients during ERCP. Swelling of the major papilla was judged during ERCP and/or from photographs of the papilla. A swollen major papilla was diagnosed based on observation of an indistinct border between the major papilla and oral protrusion.[9-11] At the end of ERCP, we obtained one or two specimens from the major papilla of 21 patients using biopsy forceps. To avoid biopsy-related acute pancreatitis, biopsy specimens were not obtained near the orifice of the pancreatic duct. Sections cut from paraffin-embedded blocks were stained with hematoxylin and eosin and immunostained using anti-IgG4 antibody (The Binding Site, Birmingham, UK) with avidin-biotin-peroxidase complex. Positive IgG4 immunostaining was defined as >10 IgG4-positive plasma cells in at least one high-power field.[11,12]

Statistical analysis was performed using chi-square test. A $p<0.05$ was considered statistically significant.

This 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.

RESULTS

MPD opening sign was detected in 26 of 40 patients (65%). Distal CBD sign was detected in 25 of the 32 patients (78%) who showed stenosis of the lower bile duct on ERC. Patients showing MPD opening sign frequently also showed distal CBD sign ($p=0.018$) (Table 1).

Table 1. Main Pancreatic Duct Opening Sign and Distal Common Bile Duct Sign in Autoimmune Pancreatitis

	Distal CBD sign (+)	Distal CBD sign (-)	No stenosis of the lower bile duct	No cholangiogram	Total
MPD opening sign (+)	20*	2	2	2	26
MPD opening sign (-)	5	5	0	4	14
Total	25	7	2	6	40

CBD, common bile duct; MPD, main pancreatic duct.
*p=0.018 comparing MPD opening sign and distal CBD sign.

Table 2. Relationship between the Main Pancreatic Duct Opening Sign and Endoscopic Findings of a Swollen Major Papilla in Autoimmune Pancreatitis

MPD opening sign	Swelling of the major papilla	
	(+)	(-)
(+)	9 (60)*	6 (40)
(-)	5 (45)	6 (55)

Data are presented as number (%).
MPD, main pancreatic duct.
*p=0.69.

Table 3. Relationship between the Main Pancreatic Duct Opening Sign and Histological Findings of Abundant Infiltration of IgG4-Positive Plasma Cells in the Major Papilla in Autoimmune Pancreatitis

MPD opening sign	Abundant infiltration of IgG4-positive plasma cells in the major papilla	
	(+)	(-)
(+)	8 (62)*	5 (38)
(-)	3 (38)	5 (62)

Data are presented as number (%).
MPD, main pancreatic duct.
*p=0.38.

Swelling of the major papilla was detected endoscopically in 9 of 15 patients (60%) with MPD opening sign, but no significant relationship was apparent between MPD opening sign and a swollen major duodenal papilla (p=0.69) (Table 2).

Lymphoplasmacytic infiltration was histologically detected in the biopsy specimen taken from the major papilla of 11 of 21 patients (52%), but dense fibrosis was not detected in any patients. Abundant infiltration of IgG4-positive plasma cells in the major papilla was detected histologically in 8 of the 13 patients (62%) with MPD opening sign, but no significant relationship was found between MPD opening sign and abundant infiltration of IgG4-positive plasma cells (p=0.38) (Table 3).

DISCUSSION

In our previous studies comparing ERP findings between AIP and pancreatic cancer, a narrowed MPD longer than 3 cm, skipped MPD lesions, side branch derivation from the narrowed MPD, and upstream dilatation of the MPD less than 5 mm were all more frequent in AIP.[3,6] However, several AIP cases were encountered in which differentiation from pancreatic cancer using ERP findings was difficult.

The present study examined ERCP findings focusing on the opening portion of the MPD and the distal portion of the CBD in 40 patients. The MPD within 1.5 cm from the orifice was maintained without irregular narrowing in 65% of AIP patients with irregular narrowing of the MPD in the pancreatic head. The maintained portion of the MPD showed a spindle or cystic shape. Distal CBD within 1.5 cm from the orifice was also maintained without stenosis in 78% of patients with stenosis of the lower bile duct. We termed these findings as MPD opening sign and distal CBD sign, respectively. Patients showing MPD opening sign also frequently showed distal CBD sign.

The characteristic histological pattern of AIP was designed as lymphoplasmacytic sclerosing pancreatitis with abundant infiltration of Ig4-positive plasma cells and lymphocytes, acinar atrophy, interlobular fibrosis and obliterative phlebitis in the pancreas.[1,2] The pancreatic duct is narrowed by nonocclusive fibrosis with lymphoplasmacytic infiltration within the existing periductal elastic fiber layer, and the epithelium of the pancreatic duct is well preserved.[1,2,13]

Lymphoplasmacytic infiltration is detected around the major papilla continuing from an inflammatory pancreatic head;[14] however, dense fibrosis is not seen in biopsy specimens taken from the major papilla of AIP patients. The opening portion of the MPD and the distal CBD are both located inside the duodenal wall and are surrounded by the sphincter of Oddi.[15,16] The sphincter of Oddi consists of sphincter choledochus, sphincter pancreaticus, and sphincter ampullae.[15,16] As radiological length of the sphincter pancreaticus in autopsy specimens is reported to be 11.4±4.1 mm,[17] we defined MPD opening sign as the MPD within 1.5 cm from the orifice being maintained. Although the exact pathophysiological mechanisms underlying MPD opening sign and distal CBD sign remain unknown, we suspect that the opening portion of the MPD and the distal CBD are maintained in AIP patients, as lymphoplasmacytic infiltration occurs, but dense fibrosis does not, in the periductal portions of the MPD and CBD surrounded by the sphincter muscle. The major papilla has been reported to be swollen in 41% to 65%[9-11] of AIP patients, resulting directly from an inflammatory pancreatic head; however, no relationship was identified between MPD opening sign and a swollen major duodenal papilla.

There are several limitations in this study. First is a retrospective design which was not subsequently tested in a blinded fashion in cohort of AIP patients. Secondly, comparative study of pancreatograms between AIP and pancreatic cancer could not be done, as pancreatograms of pancreatic head cancer involving the major papilla are rarely obtained. Thirdly, histological examination of the pancreatic head of AIP patients was not done comparing to cholangiopancreatograms. Forth is small sample size due to the rarity of the disease. Although it is preliminary, this is the first report about new characteristic features of ERCP in autoimmune pancreatitis.

In conclusion, the MPD and CBD adjacent to the major papilla are frequently preserved in patients with AIP involving the pancreatic head on ERCP. These signs are useful for diagnosing AIP on ERCP.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010;7:401-409.
2. Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and type 2. Gut 2013;62:1373-1380.
3. Kamisawa T, Imai M, Yui Chen P, et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. Pancreas 2008;37:e62-e67.
4. Nishino T, Oyama H, Toki F, Shiratori K. Differentiation between autoimmune pancreatitis and pancreatic carcinoma based on endoscopic retrograde cholangiopancreatography findings. J Gastroenterol 2010;45:988-996.
5. Sugumar A, Levy MJ, Kamisawa T, et al. Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: an international multicentre study. Gut 2011;60:666-670.
6. Takuma K, Kamisawa T, Tabata T, Inaba Y, Egawa N, Igarashi Y. Utility of pancreatography for diagnosing autoimmune pancreatitis. World J Gastroenterol 2011;17:2332-2337.

7. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40:352-358.
8. 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;41:1341-1342.
9. Unno H, Saegusa H, Fukushima M, Hamano H. Usefulness of endoscopic observation of the main duodenal papilla in the diagnosis of sclerosing pancreatitis. Gastrointest Endosc 2002;56:880-884.
10. Kubota K, Iida H, Fujisawa T, et al. Clinical significance of swollen duodenal papilla in autoimmune pancreatitis. Pancreas 2007;35:e51-e60.
11. Kim MH, Moon SH, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. Dig Surg 2010;27:110-114.
12. Kamisawa T, Tu Y, Egawa N, Tsuruta K, Okamoto A. A new diagnostic endoscopic tool for autoimmune pancreatitis. Gastrointest Endosc 2008;68:358-361.
13. Kamisawa T, Funata N, Hayashi Y, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut 2003;52:683-687.
14. Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A. Usefulness of biopsying the major duodenal papilla to diagnose autoimmune pancreatitis: a prospective study using IgG4-immunostaining. World J Gastroenterol 2006;12:2031-2033.
15. Boyden EA. The anatomy of the choledochoduodenal junction in man. Surg Gynecol Obstet 1957;104:641-652.
16. Suda K, Miyano T, Hashimoto K. The choledocho-pancreaticoductal junction in infantile obstructive jaundice diseases. Acta Pathol Jpn 1980;30:187-194.
17. Flati G, Flati D, Porowska B, Ventura T, Catarci M, Carboni M. Surgical anatomy of the papilla of Vater and biliopancreatic ducts. Am Surg 1994;60:712-718.

Major and Minor Duodenal Papillae in Autoimmune Pancreatitis

Kazuro Chiba, MD, Terumi Kamisawa, MD, PhD, Sawako Kuruma, MD, Susumu Iwasaki, MD, Taku Tabata, MD, Satomi Koizumi, MD, Yuka Endo, MD, Go Kuwata, MD, Takashi Fujiwara, MD, Takeo Arakawa, MD, Koichi Koizumi, MD, and Kumiko Momma, MD

Objective: The objective of this study was to evaluate picture of the major and minor duodenal papillae in patients with autoimmune pancreatitis (AIP).

Methods: Endoscopic features of the major and minor papillae were examined in 59 and 13 patients with AIP. After steroid therapy, changes of the major and minor papillae were observed in 5 and 6 patients. The major and minor papillae were observed with narrow band imaging in 24 and 6 patients. Biopsy specimens from the major (n = 50) and minor (n = 13) papillae were immunostained using an anti-IgG4 antibody.

Results: Endoscopic features of the major and minor papillae were abnormal in 26 patients (44%; swelling [n = 20] and redness [n = 14]) and 5 patients (38%; swelling [n = 5]). Swelling of the pancreatic head, irregular narrowing of the main pancreatic duct of the pancreatic head, stenosis of the lower bile duct, and abundant infiltration of IgG4-positive plasma cells were more frequent in the patients with an abnormal major papilla compared with those with a normal major papilla. On narrow band imaging, dilated vessels were observed in abnormal papillae. After therapy, swelling of the major and minor papillae improved in all 4 and 2 patients.

Conclusions: Endoscopic features of the major and minor papillae were abnormal in 44% and 38% of the patients with AIP.

Key Words: autoimmune pancreatitis, major duodenal papilla, minor duodenal papilla, IgG4

(*Pancreas* 2014;43: 1299–1302)

Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis with a presumed autoimmune etiology. It is characterized clinically by frequent presentation with obstructive jaundice and dramatic response to steroids, radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, serologically by elevation of serum IgG4 levels, and histologically by abundant infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis in the pancreas. Because AIP sometimes mimics pancreatic cancer, accurate diagnosis is important to avoid unnecessary surgery. Currently, AIP is considered a pancreatic manifestation of IgG4-related systemic disease.[1,2] Affected organs typically have an infiltrate of IgG4-positive plasma cells with fibrosis.[1]

The major duodenal papilla corresponds anatomically to the junction of the common bile duct and the main pancreatic duct. Because the major papilla conducts bile and pancreatic juice between the duodenum and the pancreaticobiliary system, duodenoscopic features of the major papilla may reflect underlying pancreatobiliary disorders. Unno et al[3] first reported in 2002 that the major papilla is frequently swollen in patients with AIP. We first reported in 2006 our findings of abundant infiltration of IgG4-positive plasma cells in the major papilla of 5 patients with AIP and the usefulness of IgG4 immunostaining of biopsy specimens taken from the major papilla for diagnosing AIP.[4] Although similar case studies have been conducted, the number of patients with AIP has been small in most of the studies.[5–10]

We examined the endoscopic features of the major papilla of 59 patients with AIP in relation to clinical findings including pancreatic location involved in AIP and histological findings as well as their changes after steroid therapy. We also observed the major papilla of the patients with AIP using narrow band imaging (NBI). The minor duodenal papilla of the patients with AIP was also examined endoscopically and histologically.

MATERIALS AND METHODS

From 2000 to 2013, we prospectively observed the major papilla of 59 patients with AIP (41 males and 18 females; average age, 64.2 years) under duodenoscopy during endoscopic retrograde cholangiopancreatography (ERCP) before any treatment, including steroid therapy. All the patients were diagnosed as having type 1 AIP according to international consensus diagnostic criteria.[11]

Two experienced endoscopists judged the swelling of the major papilla and the redness of its orifice before cannulation during ERCP and/or from photographs of the papilla. Final judgment was made with consensus of the 2 endoscopists. A swollen major papilla was diagnosed on the basis of the observation of an indistinct border between the major papilla and the oral protrusion. Changes in the endoscopic features of the major papilla without endoscopic sphincterotomy were observed in 5 patients approximately 1.5 months after starting steroid therapy (0.6 mg/kg per day). The 5 patients with AIP responded well to steroid. We observed the major papilla of 24 AIP patients with NBI from 2009.

At the end of the ERCP, we obtained 1 or 2 specimens from the major papilla of 50 patients with biopsy forceps from 2004. To avoid biopsy-related acute pancreatitis, the biopsy specimens were not obtained near the orifice of the pancreatic duct. Sections cut from paraffin-embedded blocks were immunostained using anti-IgG4antibody (The Binding Site, Birmingham, United Kingdom) with avidin-biotin-peroxidase complex. *Positive IgG4 immunostaining* was defined as more than 10 IgG4-positive plasma cells in at least 1 high-power field.

The minor papilla was also examined endoscopically in 13 patients and using NBI in 6 patients. A minor papilla that was seen endoscopically being larger than the general size (<5 mm)[12] was judged as swollen. Biopsy specimens taken from the minor papilla of 6 patients were IgG4-immunostained. Changes in the minor papilla were observed in the 6 patients after steroid therapy.

From the Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.
Received for publication November 21, 2013; accepted April 9, 2014.
Reprints: Terumi Kamisawa, MD, PhD, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113–8677, Japan (e-mail: kamisawa@cick.jp).
This study was supported in part by the Research Committee of Intractable Diseases provided by the Ministry of Health, Labour, and Welfare of Japan.
The authors declare no conflict of interest.

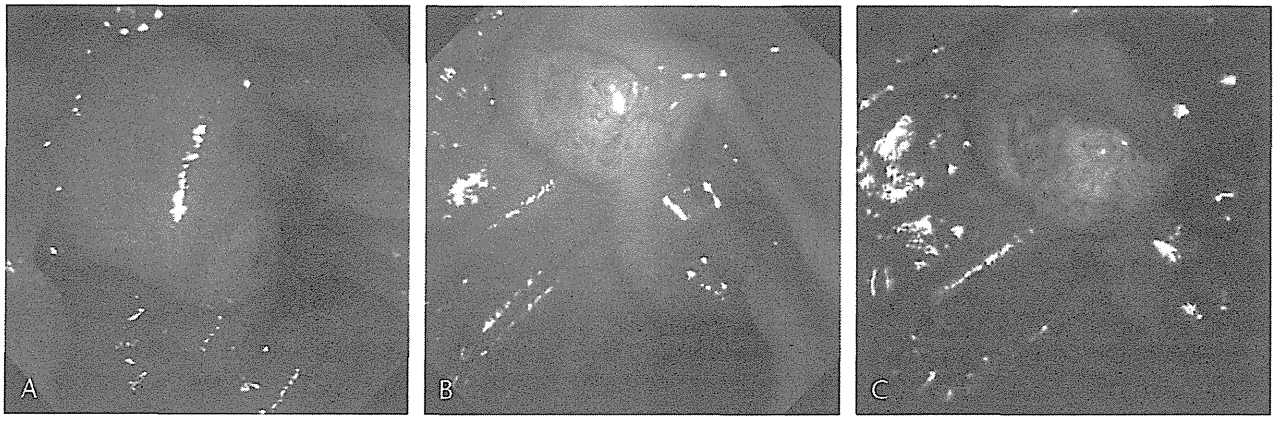

FIGURE 1. Endoscopic view of the major papilla in a patient with autoimmune pancreatitis. A, Swollen major papilla. B, Reddish major papilla. C, Dilated vessels in the reddish major papilla on NBI. **Editor's note:** A color image accompanies the online version of this article.

This study was approved by the institutional review board of our institution, and informed consent was obtained from each patient.

Continuous variables were compared using the Student *t* test and the Mann-Whitney *U* test. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Major Duodenal Papilla

Endoscopic features of the major papilla were abnormal in 26 (44%) of the 59 patients with AIP. The observations consisted of swelling alone (n = 12, Fig. 1A), swelling and redness (n = 8), as well as redness alone (n = 6, Fig. 1B). No abnormal findings were endoscopically detected in the duodenum near the major papilla.

There were no significant differences in age at diagnosis, sex, serum IgG4 levels, and other organ involvement (sialadenitis, retroperitoneal fibrosis, or hilar sclerosing cholangitis) between the 26 patients with an abnormal major papilla and the 33 patients with a normal major papilla (Table 1).

Swelling of the pancreatic head, irregular narrowing of the main pancreatic duct of the pancreatic head, and stenosis of the lower bile duct were more frequent in the patients with an abnormal major papilla than in the patients having a normal major papilla (24/26 [92%] vs 20/33 [61%], $P = 0.002$; 24/26 [92%] vs 21/33 [64%], $P = 0.013$; and 23/26 [88%] vs 19/33 [58%], $P = 0.019$, respectively). Abundant infiltration of IgG4-positive plasma cells was more frequently detected in the abnormal papillae (18/24 [67%]) than in the normal papillae (3/26 [12%], $P < 0.001$) (Table 2). Abundant infiltration of IgG4-positive plasma cells was detected in 8 (73%) of 11 swollen papillae, in 6 (86%) of 7 swollen and reddish papillae, and in 4 (67%) of 6 reddish papillae.

On NBI, dilated vessels were observed in all 10 abnormal papillae (Fig. 1C).

After the steroid therapy, swelling improved in all 4 patients with swelling of the major papilla, but redness persisted in 2 of 3 patients with redness of the major papilla.

Minor Duodenal Papilla

Swelling of the minor papilla was detected in 5 (38%) patients (Fig. 2). On NBI, dilated vessels were observed in both patients with an abnormal minor papilla but not in any of the 4 patients with a normal minor papilla. Swelling of the pancreatic head and irregular narrowing of the accessory pancreatic duct were detected in all 5 patients with an abnormal minor papilla. Abundant infiltration of IgG4-positive plasma cells was detected in 2 of 3 abnormal minor papillae (Table 3). After the steroid therapy, swelling improved in all 2 patients with swelling of the minor papilla.

In an AIP patient with complete pancreas divisum,[13] irregular narrowing of the pancreatic duct was detected only in the dorsal pancreatic duct, showing no communication with the normal short ventral pancreatic duct. The minor papilla was swollen with redness, but the major papilla appeared normal. Abundant infiltration of IgG4-positive plasma cells was detected in the biopsy specimen taken from the minor papilla but was not detected in the biopsy specimen from the major papilla. The swollen minor

TABLE 1. Differences in Clinical Features of Patients With Autoimmune Pancreatitis Having Abnormal and Normal Major Papilla

	Abnormal Major Papilla (n = 26)	Normal Major Papilla (n = 33)	*P*
Male:female	17:9	24:9	0.569
Age, mean (SD), y	67.0 (12.8)	62.0 (15.6)	0.133
Serum IgG, mean (SD), mg/dL	1993 (842)	1860 (946)	0.501
Serum IgG4, mean (SD), mg/dL	551 (453)	407 (487)	0.308
Other organ involvement	9 (35%)	10 (30%)	0.573
Sialadenitis	1	4	0.340
Retroperitoneal fibrosis	7	6	0.528
Hilar sclerosing cholangitis	3	1	0.300

TABLE 2. Differences in Imaging and Histological Features of Patients With Autoimmune Pancreatitis Having Abnormal and Normal Major Papilla

	Abnormal Major Papilla (n = 26)	Normal Major Papilla (n = 33)	*P*
Swelling of the pancreas			
Diffuse	14 (54%)	10 (30%)	0.109
Segmental head	10 (38%)	10 (30%)	0.579
Segmental body/tail	2 (8%)	13 (40%)	0.002
Swelling of the pancreatic head	24 (92%)	20 (61%)	0.002
Narrowing of the MPD in the pancreatic head	24 (92%)	21 (64%)	0.013
Stenosis of the lower bile duct	23 (88%)	19 (58%)	0.019
Abundant infiltration of IgG4-positive plasma cells	18/24 (67 %)	3/26 (12 %)	<0.001

MPD, main pancreatic duct.

papilla and irregular narrowing of the dorsal pancreatic duct improved after the steroid therapy.

There was no significant bleeding or acute pancreatitis related to endoscopic biopsy of the major or minor papilla in any of the study patients.

DISCUSSION

It has been reported that the major papilla is swollen in 41% to 65% of patients with AIP.[3,5,10] Abundant infiltration of IgG4-positive plasma cells is reportedly detected in the biopsy specimens taken from the major papilla in 53% to 80% of patients with AIP.[5,6,8–10] It was also reported that positive IgG4 immunostaining of the major papilla is rarely seen in other pancreatobiliary diseases and that IgG4 immunostaining of the biopsy specimens from the major papilla may offer the ability to advance a diagnosis of AIP.[5,6,8–10] However, the number of examined patients with AIP in most studies has been small and the precise picture of the major papilla in patients with AIP has not been fully assessed.

Papillitis is an acute inflammatory disorder of the major papilla and sometimes reflects an underlying biliary or pancreatic disease. Swelling of the major papilla and redness of the orifice are major endoscopic features of papillitis.[14] Therefore, we examined endoscopic features of the major papilla of patients with AIP focusing on its swelling and redness. In the present study, an abnormal major papilla was detected in 26 (44%; swelling [n = 20] and redness [n = 14]) of the 59 patients with AIP. The frequency was similar to the reported data. There were no differences in the clinical and serological features of AIP patients with or without an abnormal major papilla.

The pathogenic nature of the abundant infiltration of IgG4-positive plasma cells into the major papilla of patients with AIP is unclear. On pancreatography, pancreatic head was seen to be involved in 96% of the AIP patients with an abnormal major papilla and abundant infiltration of IgG4-positive plasma cells was detected in 67% of the patients with an abnormal major papilla, compared with 58% and 12% of the patients with a normal major papilla. Kubota et al[5] also reported that, in patients with AIP, 77% of 13 major papillae containing abundant IgG4-positive plasma cells were swollen, whereas only 1 of 4 major papillae without IgG4-positive plasma cell infiltration was swollen. On the other hand, in the international diagnostic criteria for AIP,[11] positive IgG4 immunostaining in the major papilla was added as a histological criterion of extrapancreatic organs and ampullary biopsy was regarded as a useful adjunctive method for the diagnosis of AIP. A resected lymphoplasmacytic granuloma with abundant IgG4-positive plasma cells localized to the major papilla (IgG4-related ampullary lesion) without the coexistence of AIP was reported.[15] However, in consideration of our experience of 3 resected AIP specimens showing inflammation of AIP in the pancreatic head spreading to the major papilla,[4] abnormal major papilla and infiltration of increased numbers of IgG4-positive

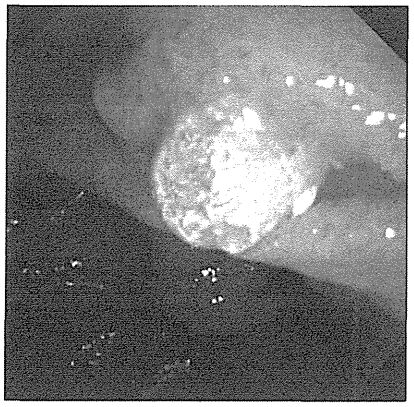

FIGURE 2. Endoscopic view of a swollen minor papilla in a patient with autoimmune pancreatitis. **Editor's note:** A color image accompanies the online version of this article.

TABLE 3. Differences in Imaging and Histological Features of Patients With Autoimmune Pancreatitis Having Abnormal and Normal Minor Papilla

	Abnormal Minor Papilla (n = 5)	Normal Minor Papilla (n = 8)	*P*
Swelling of the major papilla	2 (40%)	4 (50%)	0.731
Swelling of the pancreatic head	5 (100%)	4 (50%)	0.063
Narrowing of the MPD in the head	4 (80%)	4 (50%)	0.291
Narrowing of the accessory pancreatic duct	5 (100%)	4 (50%)	0.063
Abundant infiltration of IgG4-positive plasma cells	2/3 (67%)	0/3 (0%)	0.0832

MPD, main pancreatic duct.

plasma cells seem to result directly from an inflammatory pancreatic head in many AIP cases.

We endoscopically observed the major papilla using NBI, which provides imaging superior to that of conventional white-light imaging. Dilated vessels were observed in all 10 abnormal papillae observed using NBI. In our peroral cholangioscopic study of IgG4-related sclerosing cholangitis by using NBI, dilated and/or tortuous vessels were frequently observed.[16] Proliferation of vessels seems to be a characteristic feature of the biliary tract in patients with IgG4-related sclerosing pancreatitis and cholangitis.

We believe that we are the first in the world to assess the minor papilla of patients with AIP endoscopically and histologically. Embryologically, the accessory pancreatic duct is the main duct of the dorsal pancreatic primordium in the embryo and enters the duodenum through the minor papilla. The accessory pancreatic duct usually becomes the less-constant pancreatic duct, and the minor papilla is usually smaller than the major papilla.[12,17] In the present study, swelling of the minor papilla was detected in 5 (38%) of 13 patients with AIP. Although there was no relationship between swelling of the major and minor papillae, swelling of the pancreatic head and irregular narrowing of the accessory pancreatic duct were detected in all 5 patients with an abnormal minor papilla. Abundant infiltration of IgG4-positive plasma cells was detected in the biopsy specimen taken from the minor papilla in 2 of 3 patients with an abnormal minor papilla. Inflammation of the minor papilla in patients with AIP seems to occur via a mechanism similar to the major papilla. However, in the presented patient who had complete pancreas divisum, the patient's AIP involved only the dorsal pancreas; we would call this case autoimmune dorsal pancreatitis.[13]

A limitation of this study is that the criteria of swollen major and minor papillae are too observer dependent.

In conclusion, the endoscopic features of the major and minor papillae were abnormal in 44% and 38% of the patients with AIP. The findings seemed to result directly from an inflammatory pancreatic head in many cases.

REFERENCES

1. Kamisawa T, Takuma K, Egawa N, et al. Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol.* 2010;7:401–409.
2. Kamisawa T, Chari ST, Lerch MM, et al. Recent advances in autoimmune pancreatitis: type 1 and type 2. *Gut.* 2013;62:1373–1380.
3. Unno H, Saegusa H, Fukushima M, et al. Usefulness of endoscopic observation of the main duodenal papilla in the diagnosis of sclerosing pancreatitis. *Gastrointest Endosc.* 2002;56:880–884.
4. Kamisawa T, Tu Y, Nakajima H, et al. Usefulness of biopsying the major duodenal papilla to diagnose autoimmune pancreatitis: a prospective study using IgG4-immunostaing. *World J Gastroenterol.* 2006;12:2031–2013.
5. Kubota K, Iida H, Fujisawa T, et al. Clinical significance of swollen duodenal papilla in autoimmune pancreatitis. *Pancreas.* 2007;35:e51–e60.
6. Kamisawa T, Tu Y, Egawa N, et al. A new diagnostic endoscopic tool for autoimmune pancreatitis. *Gastrointest Endosc.* 2008;68:358–361.
7. Sepehr A, Mino-Kenudson M, Ogawa F, et al. IgG4+ to IgG + plasma cells ration of ampulla can help differentiate autoimmune pancreatitis from other "mass forming" pancreatic lesions. *Am J Surg Pathol.* 2008;32:1770–1779.
8. Hirano K, Fukushima N, Tada M, et al. Diagnostic utility of biopsy specimens for autoimmune pancreatitis. *J Gastroenterol.* 2009;44:765–773.
9. Moon SH, Kim MH, Park DH, et al. IgG4 immunostaining of duodenal papillary biopsy specimens may be useful for supporting a diagnosis of autoimmune pancreatitis. *Gastrointest Endosc.* 2010;71:960–966.
10. Kim MH, Moon SH, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. *Dig Surg.* 2010;27:110–114.
11. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas.* 2011;40:352–358.
12. Kamisawa T, Tu Y, Egawa N, et al. Size, location and patency of the minor duodenal papilla as determined by dye-injection endoscopic retrograde pancreatography. *Dig Endosc.* 2001;13:82–85.
13. Hara S, Kamisawa T, Tabata T, et al. Embryological aspects in autoimmune pancreatitis, proposal of autoimmune dorsal pancreatitis. *Scand J Gastroenterol.* 2013;48:856–861.
14. Park JS, Kim MH, Lee SK, et al. The clinical significance of papillitis of the major duodenal papilla. *Gastrointest Endosc.* 2002;55:877–882.
15. Hisa T, Ohkubo H, Shiozawa S, et al. Lymphoplasmacytic glanuloma localized to the ampulla of Vater: an ampullary lesion of IgG4-related systemic disease? *Gastrointest Endosc.* 2008;68;1229–1232.
16. Itoi T, Kamisawa T, Igarashi Y, et al. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. *J Gastroenterol.* 2013;48:504–514.
17. Adda G, Hannoun L, Loygue J. Development of the human pancreas: variations and pathology. A tentative classification. *Clin Anat.* 1984;5:275–283.

Digestive Endoscopy 2014; **26**: 627–635 doi: 10.1111/den.12289

Review

Role of endoscopy in the diagnosis of autoimmune pancreatitis and immunoglobulin G4-related sclerosing cholangitis

Terumi Kamisawa,[1] Hirotaka Ohara,[2] Myung Hwan Kim,[6] Atsushi Kanno,[4] Kazuichi Okazaki[3] and Naotaka Fujita[5]

[1]*Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo,* [2]*Department of Community-Based Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya,* [3]*Department of Gastroenterology and Hepatology, Kansai Medical University, Hirakata,* [4]*Division of Gastroenterology, Tohoku University Graduate School of Medicine,* [5]*Department of Gastroenterology, Sendai City Medical Center, Sendai, Japan, and* [6]*Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Autoimmune pancreatitis (AIP) must be differentiated from pancreatic carcinoma, and immunoglobulin (Ig)G4-related sclerosing cholangitis (SC) from cholangiocarcinoma and primary sclerosing cholangitis (PSC). Pancreatographic findings such as a long narrowing of the main pancreatic duct, lack of upstream dilatation, skipped narrowed lesions, and side branches arising from the narrowed portion suggest AIP rather than pancreatic carcinoma. Cholangiographic findings for PSC, including band-like stricture, beaded or pruned-tree appearance, or diverticulum-like outpouching are rarely observed in IgG4-SC patients, whereas dilatation after a long stricture of the bile duct is common in IgG4-SC. Transpapillary biopsy for bile duct stricture is useful to rule out cholangiocarcinoma and to support the diagnosis of IgG4-SC with IgG4-immunostaining. IgG4-immunostaining of biopsy specimens from the major papilla advances a diagnosis of AIP. Contrast-enhanced endoscopic ultrasonography (EUS) and EUS elastography have the potential to predict the histological nature of the lesions. Intraductal ultrasonographic finding of wall thickening in the non-stenotic bile duct on cholangiography is useful for distinguishing IgG4-SC from cholangiocarcinoma. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is widely used to exclude pancreatic carcinoma. To obtain adequate tissue samples for the histological diagnosis of AIP, EUS-Tru-cut biopsy or EUS-FNA using a 19-gauge needle is recommended, but EUS-FNA with a 22-gauge needle can also provide sufficient histological samples with careful sample processing after collection and rapid motion of the FNA needles within the pancreas. Validation of endoscopic imaging criteria and new techniques or devices to increase the diagnostic yield of endoscopic tissue sampling should be developed.

Key words: autoimmune pancreatitis, chronic pancreatitis, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), immunoglobulin (Ig)G4, sclerosing cholangitis

INTRODUCTION

AUTOIMMUNE PANCREATITIS (AIP) and immunoglobulin (Ig)G4-related sclerosing cholangitis (SC) are recently recognized pancreatobiliary manifestations of IgG4-related disease.[1,2] AIP and IgG4-SC are both rarer diseases than pancreatobiliary malignancies, but clinically mimic them. AIP must be differentiated from pancreatic carcinoma. IgG4-SC involving the intrahepatic or hilar bile duct should be differentiated from hilar cholangiocarcinoma or primary sclerosing cholangitis (PSC). As both diseases respond dramatically to steroid therapy, accurate diagnosis is important to avoid unnecessary surgical intervention.[1,3,4]

Endoscopists play an integral role in the evaluation and treatment of these diseases. Endoscopic retrograde cholangiopancreatography (ERCP) is frequently carried out to relieve cholestasis by biliary stenting, and to undertake imaging and biopsies. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) plays an important role in confirming the diagnosis and excluding malignancy.

An international session 'IgG4-related disease and endoscopy' was held during the 86th Annual Meeting of the Japan Gastroenterological Endoscopy Society (President: Naotaka Fujita). Several hot topics about the role of endoscopy in the

Corresponding: Terumi Kamisawa, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. Email: kamisawa@cick.jp

Received 7 January 2014; accepted 19 February 2014.

diagnosis of AIP and IgG4-SC were discussed. The present review about the role of endoscopy in the diagnosis of AIP and IgG4-SC was cowritten by two modulators and three panelists in the session.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

IRREGULAR NARROWING OF the main pancreatic duct (MPD) is a characteristic pancreatographic feature of AIP. Diffuse irregular narrowing of the MPD is rather specific to AIP, but segmental narrowing of the MPD is sometimes difficult to differentiate from stenosis of the MPD caused by pancreatic carcinoma. The typical pancreatographic appearance of pancreatic carcinoma is a single localized stricture of the MPD associated with marked upstream duct dilatation. In contrast, pancreatographic findings such as no obstruction of the MPD, a long narrowing (exceeding one-third the length of the MPD), lack of upstream dilatation from the narrowing (<5 mm), skipped lesions of narrowing in the MPD, and side branches arising from the narrowed portion are more common in AIP (Fig. 1).[5,7] In AIP, lymphoplasmacytic infiltration is primarily subepithelial and the ductal epithelium is usually preserved, whereas pancreatic carcinoma typically infiltrates and destroys the epithelium of the pancreatic duct, resulting in ductal obstruction. These differences in periductal histopathological features likely account for the variance in pancreatographic findings between AIP and pancreatic carcinoma.[5,7] Given their utility in differentiating AIP from pancreatic carcinoma, pancreatographic findings play important roles in both the International Consensus Diagnostic Criteria (ICDC)[8] and the Japanese Diagnostic Criteria 2011.[9] However, as little incremental benefit was gained from additional endoscopic retrograde pancreatography (ERP) in cases with typical findings of diffuse delayed-enhanced pancreatic enlargement with or without capsule-like rim on computed tomography (CT), these criteria do not use ERP in such typical cases. Cytology of pancreatic juice with or without brushing is also useful to differentiate AIP from pancreatic carcinoma.

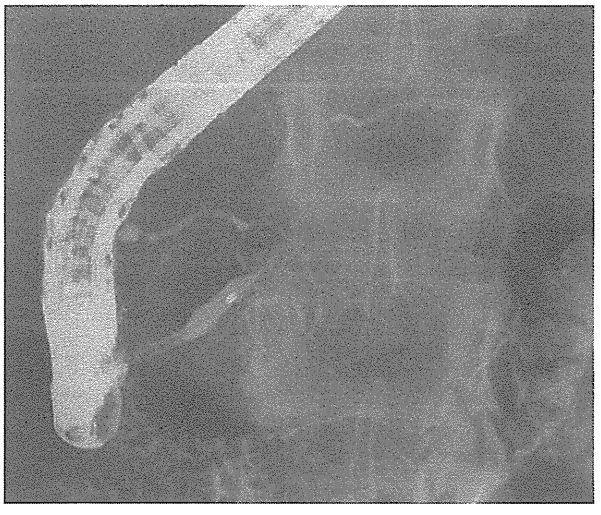

Figure 1 Endoscopic retrograde pancreatography showing irregular narrowing of the main pancreatic duct in a patient with autoimmune pancreatitis. Santorini's duct arose from the narrowed portion and upstream dilatation from the narrowed portion was less.

IgG4-SC is the most common other organ involvement (OOI) of AIP.[1] IgG4-SC associated with AIP frequently shows as stricture of the lower bile duct; however, biliary strictures can occur anywhere in the biliary tree. Characteristic cholangiographic findings may allow differentiation between IgG4-SC and PSC. The dominant cholangiographic findings of PSC, including band-like stricture, beaded or pruned-tree appearance, and diverticulum-like outpouching, are rarely observed in patients with IgG4-SC, whereas dilatation after a long stricture of the bile duct is common in IgG4-SC.[4,10,11] Cholangiography cannot distinguish IgG4-SC from hilar cholangiocarcinoma. Although transpapillary biopsy for bile duct stricture can be carried out during ERCP, interpreting the results is sometimes difficult as a result of the small specimen size. IgG4 immunostaining may provide further histological support for the diagnosis of IgG4-SC. The sensitivity of IgG4 immunostaining for transpapillary biopsy specimens to differentiate IgG4-SC from malignancy was reported as 18–88%,[12–15] but abundant infiltration of IgG4-positive plasma cells was detected in biopsy specimens from the bile duct of one case with cholangiocarcinoma[13] and one with PSC.[15] The sensitivity of transpapillary biopsy for hilar cholangiocarcinoma was reported as 53%,[16] and biopsy might be useful to rule out cholangiocarcinoma from IgG4-SC. The most frequent findings on peroral cholangioscopy in patients with IgG4-SC were dilated and tortuous vessels, and absence of partially enlarged vessels; therefore, cholangioscopy is useful to differentiate IgG4-SC from PSC and cholangiocarcinoma.[17]

BIOPSY OF THE MAJOR PAPILLA FOR IgG4 IMMUNOSTAINING

BECAUSE THE MAJOR duodenal papilla corresponds anatomically to the junction of the common bile duct and the MPD, the major papilla is often involved in AIP, resulting directly from inflammation of the pancreatic head in many cases. The major papilla has been reported as

swollen in 41–65% of AIP patients.[18 20] Abundant infiltration of IgG4-positive plasma cells is reportedly detected in biopsy specimens taken from the major papilla in 53–80% of AIP patients.[19 22] As positive IgG4 immunostaining of the major papilla is rarely seen in other pancreatobiliary diseases, IgG4 immunostaining of biopsy specimens from the major papilla offers the ability to advance a diagnosis of AIP.[19 22] Endoscopic biopsy of the major papilla is also recommended in the ICDC[8] as an easy and safe method.

EUS, CONTRAST-ENHANCED EUS, AND EUS ELASTOGRAPHY

THE TYPICAL EUS findings in AIP patients are a relatively diffuse pancreatic enlargement with a homogeneous hypoechoic pattern and linear or reticular hyperechoic inclusions.[23 27] In most cases, dilatation of the MPD is not observed. The characteristic pancreatic parenchymal and ductal features observed in patients with chronic pancreatitis (such as heterogeneous texture, lobular outer gland margin, calcification, and hyperechoic ductal margin) are rarely observed.[26,28]

AIP patients show a localized mass with hypoechoic patterns along with linear or reticular hyperechoic inclusions. Duct penetration is useful for differentiation of AIP from pancreatic carcinoma.[26] Hoki *et al.*[28] reported that diffuse hypoechoic areas, diffuse enlargement, bile duct wall thickening, and peripancreatic hypoechoic margins occurred more frequently in AIP patients than in those with pancreatic carcinoma. Focal hypoechoic areas and focal enlargement were more commonly observed in pancreatic carcinoma than in AIP. However, on occasion, similar findings are observed in AIP patients as well as those with other pancreatic disorders including pancreatic carcinoma.[23,25] Consequently, new EUS diagnostic techniques have been developed to ensure safe and accurate diagnosis of AIP.[25,29] The recently developed contrast-enhanced EUS and EUS elastographic techniques may satisfy these requirements.[25,29,30]

Contrast-enhanced EUS provides more information on the vascularity and blood flow in normal and pathological tissues.[30 32] As contrast agents increase the Doppler signal and enable visualization of microvessels, contrast-enhanced EUS has proven to be more useful in discriminating between various pancreatic disorders than conventional EUS imaging.[25,29,31 33] Contrast-enhanced EUS findings showed that AIP resulted in lesions along with hypervascularization of the surrounding pancreas. In contrast, pancreatic carcinoma caused hypovascularized lesions.[31,33]

Elastography is an imaging technique that reveals differences in tissue hardness, which facilitates the estimation of elasticity distribution in normal and pathological areas.[29,34 36] Several published studies evaluating the accuracy of EUS elastography in diagnosing solid pancreatic masses have revealed a sensitivity ranging from 85% to 100% and a specificity ranging from 33% to 93%.[29,32,34 37] A meta-analysis revealed that the sensitivity, specificity, and diagnostic odds ratio of EUS elastography in the differentiation of benign masses 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, 0.94–0.97), respectively.[38] Dietrich *et al.*[34] reported that AIP patients presented with a characteristic stiff elastographic pattern not only of the mass lesion but also of the surrounding pancreatic parenchyma, which was not detected in pancreatic carcinoma. However, further study is needed to examine whether elastography is useful for differentiation between localized AIP and small pancreatic cancer.

INTRADUCTAL ULTRASONOGRAPHY

IN PATIENTS WITH IgG4-SC, thickening of the bile duct demonstrating enhancement on CT and various cholangiographic features may be disguised as cholangiocarcinoma.[13,14,26,39,40] Accurate diagnosis of IgG4-SC not associated with AIP is particularly difficult.[41 43] Endoscopic intraductal ultrasonography (IDUS) which provides high-resolution images of the layer structure of the bile duct wall is a reliable procedure for evaluation of thickening of the bile duct wall and it can be done during ERCP in a single session.[13] An IDUS survey should be carried out before endoscopic biliary drainage because biliary drainage frequently induces thickening of the bile duct wall.[44]

The characteristic IDUS findings for IgG4-SC are circular-symmetrical wall thickness, a smooth outer margin, a smooth inner margin, and a homogeneous internal echo in the stricture[13,26,27,40] (Fig. 2). In contrast, IDUS findings for cholangiocarcinoma include circular-asymmetrical wall thickening, a notched outer margin, a rigid or papillary inner margin, and a heterogeneous internal echo in the stricture.[13,26,45] Hyodo and Hyodo[40] reported that the thickened bile duct wall in IgG4-SC was markedly enhanced with Levovist® (Bayer, Leverkusen, Germany) on IDUS.

The most characteristic IDUS finding in cases of IgG4-SC was wall thickness in the bile duct that appeared normal on the cholangiogram[13,26,27,39,46] (Fig. 2). The wall thickness predominantly spread from the intrapancreatic bile duct to the upper bile duct continuously. This characteristic IDUS finding is useful for distinction of IgG4-SC from cholangiocarcinoma. Naitoh *et al.*[13] reported that a bile duct wall thickness >0.8 mm in regions of non-stricture on a cholangiogram is highly suggestive of IgG4-SC (sensitivity 95.0%, specificity 90.9%, accuracy 93.5%).

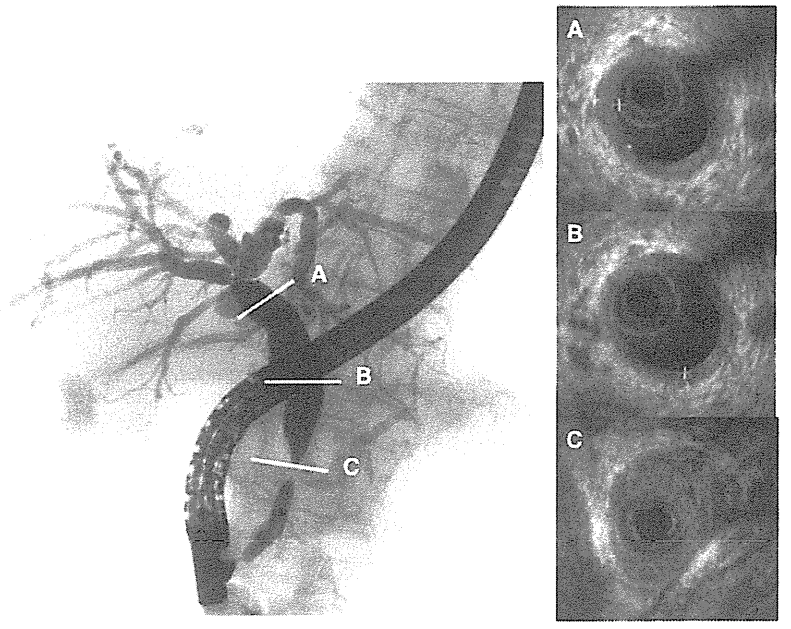

Figure 2 Intraductal ultrasonography (IDUS) in a patient with immunoglobulin G4-related sclerosing cholangitis showing a lower bile duct stricture. IDUS reveals wall thickness (1.0–1.2 mm) of the common bile duct in non-stenotic lesions whereas cholangiography shows normal findings (lines A, B), and wall thickness (3.0 mm) in the lower common bile duct stricture (line C). Symmetry was circular-symmetrical. Outer and inner margins were smooth. Internal echo was homogeneous.

ENDOSCOPIC ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION

HISTOLOGICAL EXAMINATION IS very important for the diagnosis of AIP based on the ICDC.[8] EUS-FNA has become widely used to diagnose pancreatic diseases. According to the ICDC, EUS-FNA is not recommended for the histological diagnosis of AIP because of difficulty in collecting an adequate amount of tissue samples for evaluation including the assessment of obliterative phlebitis.[47] Only tissue samples obtained by EUS-Tru-cut biopsy (TCB) have been considered suitable.[25,48,49] EUS-FNA using a 19-gauge (G) needle is also useful for the diagnosis of AIP.[50] However, EUS-TCB and EUS-FNA using large-gauge needles have the potential risk of complications and are difficult in manipulation.[51,52] Kanno *et al.*[53] reported the usefulness of EUS-FNA with a 22-G needle for the histopathological diagnosis of AIP. EUS-FNA with a 22-G needle provided an adequate amount of tissue samples for histological evaluation and could be used to diagnose >80% of AIP patients based on the ICDC. Obliterative phlebitis was identified in 40%. To obtain sufficient histological samples by EUS-FNA, they emphasized careful sample processing after collection and rapid motion of the FNA needles within the pancreas. After pushing out the pieces of tissue onto a glass slide, tubifex-like pieces of tissue in the blood are picked up and transferred to a formalin-filled dish. These tubifex-like pieces of pancreatic tissue consist mainly of blood clots and some whitish pancreatic tissues. The pancreatic tissues are trimmed with disposable 18-G needles and transferred to another formalin-filled container, which is then submitted to pathologists for examination. Another important point in obtaining sufficient histological samples is the speed of needle insertion; that is, how fast the needle is motioned in the pancreas. As it is difficult to gain sufficient speed of needle insertion manually, they recommended the use of a spring-loaded biopsy needle. Several new EUS-FNA needles are expected to improve sample collection of pancreatic tissue. EUS-FNA would be a powerful tool for the ICDC-based diagnosis of AIP by improving the histological diagnosis of this disease.

DIAGNOSTIC ALGORITHM USING ENDOSCOPY

FOR THE DIAGNOSIS of AIP, the most sensitive ICDC[8] among the five major criteria (ICDC, JPS-2011,[9] Asian criteria,[54] revised-HISORt[55] and Korean criteria[56]) has proposed that the diagnostic algorithm (Fig. 3) can be tailored to individual institutions, depending on local expertise. In response to the ICDC, the JPS-2011[9] proposed the same diagnostic items (pancreas image on CT/magnetic resonance imaging (MRI), ductal image, serology, OOI, and steroid effect) as those of the ICDC without level 1 and 2 classifications. In contrast, for the diagnosis of IgG4-SC, the Japanese diagnostic criteria,[4] which contain similar diagnostic items (cholangiogram, serology, OOI and steroid effect) have been proposed. For the ductal images, magnetic

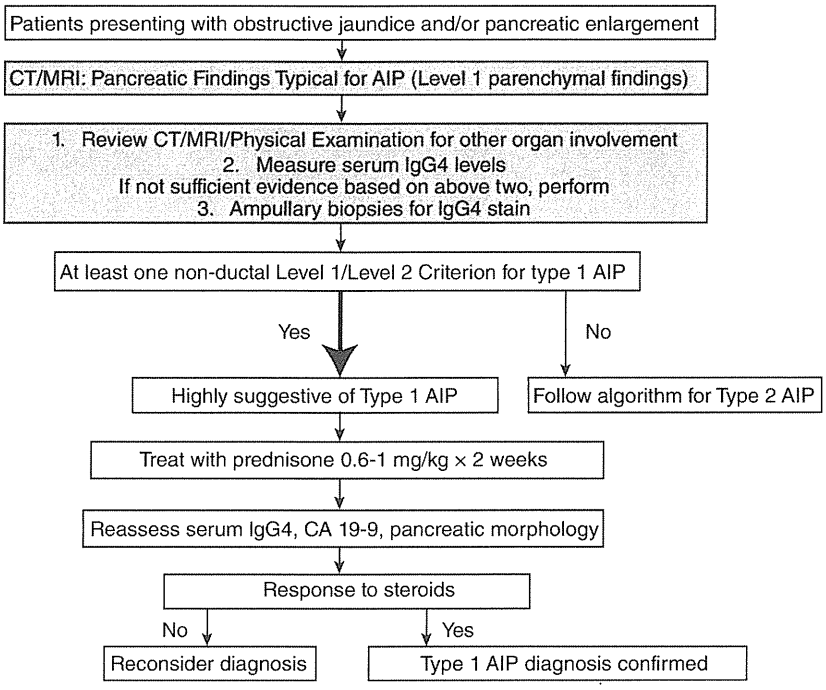

Figure 3 Diagnostic algorithm to diagnose type 1 autoimmune pancreatitis (AIP) by International Consensus Diagnostic Criteria (ICDC).[8] Algorithm to diagnose type 1 AIP in subjects presenting with obstructive jaundice and/or pancreatic enlargement. This schematic drawing shows a flow to diagnose type 1 AIP with typical diffuse enlargement of the pancreas on computed tomography (CT)/magnetic resonance imaging (MRI) (level 1 parenchymal findings). IgG, immunoglobulin G.

resonance cholangiopancreatography (MRCP) is applicable in the diagnosis of IgG4-SC, but less in AIP compared with ERCP because of low resonance, except for multiple obstructive pancreatograms or changes by steroid treatment. Different from Japan and Korea, diagnostic ERCP is rarely carried out in the West.[8] The JPS-2011[9] and Korean algorithm[27,56] (Fig. 4) for AIP and Japanese criteria for IgG4-SC[4] basically require ERCP in the atypical (segmental/focal) AIP and IgG4-SC, but not in the typical diffuse type of AIP. Different from stricture of the intrapancreatic bile duct usually observed in both AIP and pancreatic carcinoma, intrahepatic and/or hilar bile duct strictures suggesting association with IgG4-SC are important clues to the diagnosis of AIP.[10,57] PSC and hilar cholangiocarcinoma should be differentiated from IgG4-SC showing intrahepatic and/or hilar bile duct strictures.[10,57]

In addition to ductal images, brushing cytology of pancreatic or bile juice, ductal biopsy, and EUS-FNA/TCB with IgG4 immunostaining are useful, although they provide insufficient amounts for the diagnosis of AIP or IgG4-SC. The diagnostic accuracy of EUS-FNA in the diagnosis of pancreatic mass is superior to brushing cytology,[47,50,52,58 63] but not necessarily in bile duct lesions. Although affiliations available for EUS-FNA have been increasing in Japan,[47,50,59,60] ERCP procedures are more commonly carried out than EUS-FNA/TCB. Therefore, the JPS-2011[9] recommends carrying out ERCP in pancreatic masses, including segmental/focal type of AIP, following the first evaluation of pancreatic parenchymal images on CT/MRI, but this is not mandatory in the diffuse typical type of AIP. Similar to Western countries, a Japanese study[64] recently proposed a diagnostic algorithm (Fig. 5), which recommends an initial procedure of EUS-FNA/TCB prior to ERCP in the pancreatic body/tail mass, or head mass without obstructive jaundice. In contrast, it recommends initial procedures of diagnostic and therapeutic ERCP in cases of pancreatic head mass with obstructive jaundice or abnormal biliary enzymes. Additionally, a routine ampullary biopsy for IgG4 immunostaining[21] or IDUS at the time of ERCP procedure is recommended to assist diagnosing AIP and IgG4-SC.

FUTURE PERSPECTIVES

Definition and disease spectrum of IgG4-SC

THE CONCEPT AND role of endoscopy in diagnosing AIP and IgG4-SC continues to evolve. The inclusion of a distal biliary stricture isolated to the intrapancreatic portion in the definition of IgG4-SC is still under debate, but reaching a consensus on a clear definition is important, as it relates to the difference in epidemiological characteristics of IgG4-SC. Distal biliary strictures isolated to the intrapancreatic portion may be as a result of compression and extension of inflammation from a swollen and inflamed pancreas of AIP, or true IgG4-related cholangitic involvement.

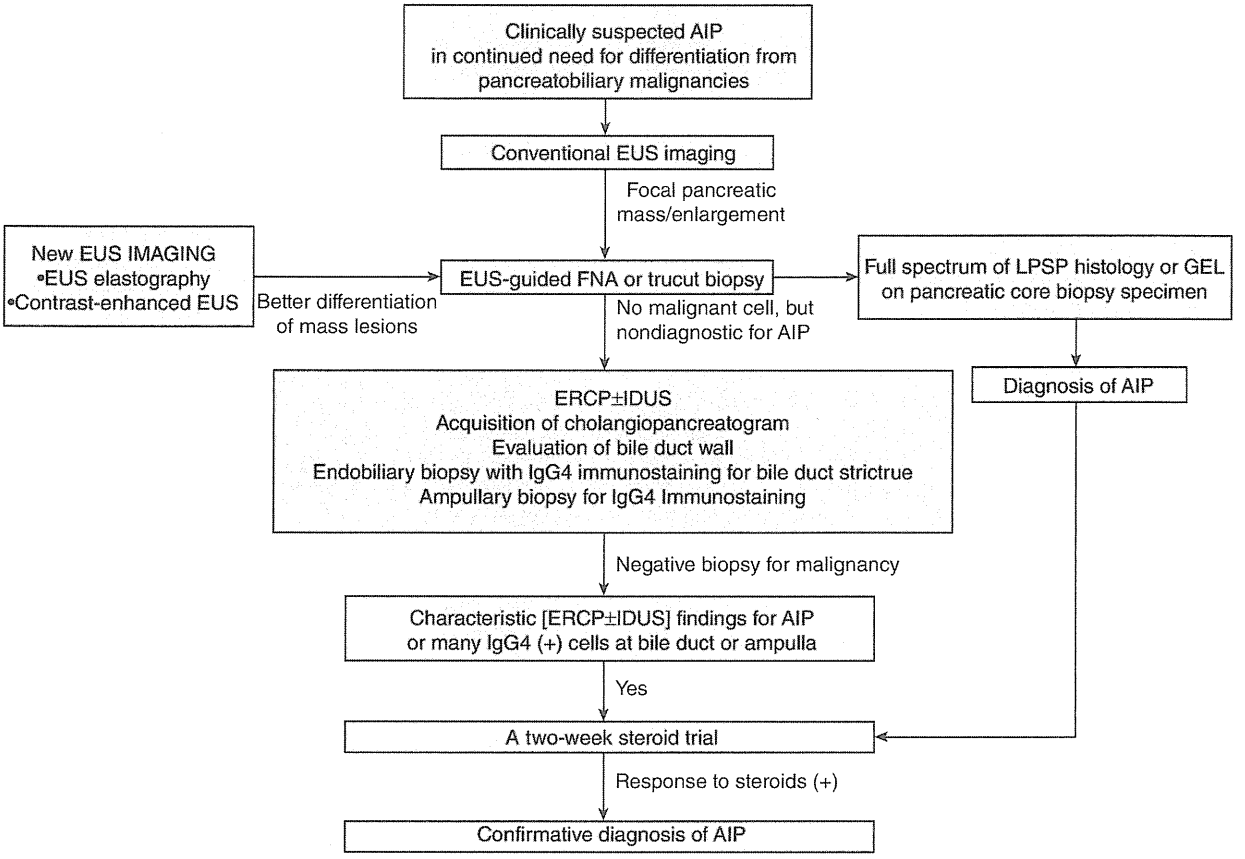

Figure 4 Korean endoscopic strategy to distinguish autoimmune pancreatitis (AIP) from pancreatobiliary malignancies.[27] ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; GEL, granulocytic epithelial lesion; IDUS, intraductal ultrasonography; LPSP, lymphoplasmacytic sclerosing pancreatitis.

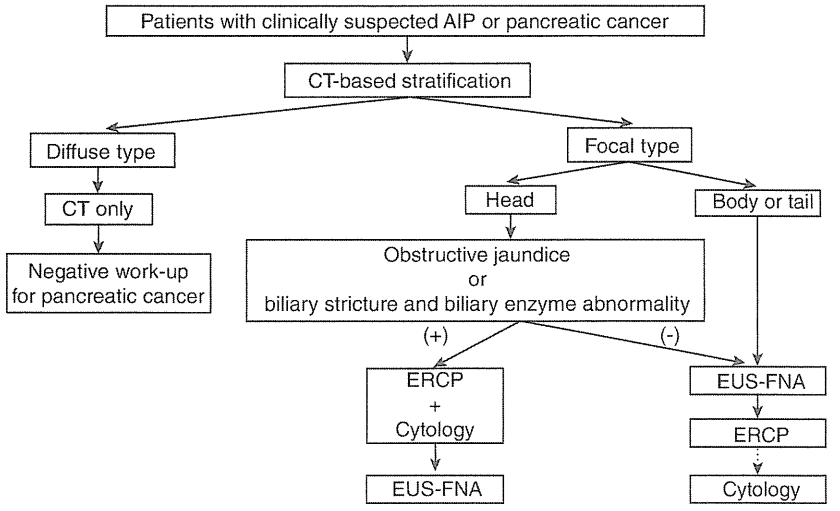

Figure 5 Modified Japanese diagnostic algorithm based on JPS-2011.[64] AIP, autoimmune pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

Recent research has shown that some patients with PSC have increased serum IgG4 levels and the resected livers from patients with PSC have positive IgG4 immunostaining.[65] Whether PSC with elevated serum/tissue IgG4 and IgG4-SC represent different ends of the same disease spectrum or are separate clinical entities is not yet clear.[66]

Diagnostic modality

Cholangiography is the gold standard for the diagnosis of PSC. Magnetic resonance cholangiography (MRC) is considered the first-line diagnostic modality for the diagnosis of PSC as it is non-invasive, uses non-ionizing radiation and can delineate the entire biliary anatomy in the presence of biliary obstruction.[67] However, ERCP has strengths over MRCP in acquiring tissue samples. In suspected IgG4-SC patients, MRC can be a potential first step for the evaluation of the biliary system, although magnetic resonance pancreatography (MRP) has not been accepted as a replacement for ERP because of its low spatial resolution. ERCP may be reserved for patients with atypical cholangiogram or who need endobiliary biopsy. In addition, new techniques or devices should be developed in order to increase the diagnostic yield of endoscopic tissue sampling.[27]

CONCLUSION

ENDOSCOPISTS PLAY AN important role in the management of AIP and IgG4-SC. ERCP and EUS are core procedures for the diagnosis of the two diseases. Validation of endoscopic imaging criteria and new techniques or devices to increase the diagnostic yield of endoscopic tissue sampling should be developed.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

REFERENCES

1 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.

2 Stone JH, Khosroshahi A, Deshpande V *et al.* Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum.* 2012; **64**: 3061–7.

3 Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: Type 1 and type 2. *Gut* 2013; **62**: 1373–80.

4 Ohara H, Okazaki K, Tsubouchi H *et al.* Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. *J. Hepatobiliary Pancreat. Sci.* 2012; **19**: 536–42.

5 Kamisawa T, Imai M, Chen PY *et al.* Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. *Pancreas* 2008; **37**: e62–e67.

6 Sugumar A, Levy MJ, Kamisawa T *et al.* Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: An international multicenter study. *Gut* 2011; **60**: 666–70.

7 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.

8 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.

9 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.

10 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.

11 Kamisawa T, Takuma K, Anjiki H *et al.* Sclerosing cholangitis associated with autoimmune pancreatitis differs from primary sclerosing cholangitis. *World J. Gastroenterol.* 2009; **15**: 2357–60.

12 Ghazale A, Chari ST, Zhang L *et al.* Immunoglobulin G4-associated cholangitis: Clinical profile and response to therapy. *Gastroenterology* 2008; **134**: 706–15.

13 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.

14 Oh HC, Kim MY, Lee KT *et al.* Clinical clues to suspicion of IgG4-associated sclerosing cholangitis disguised as primary sclerosing cholangitis or hilar cholangiocarcinoma. *J. Gastroenterol. Hepatol.* 2010; **25**: 1831–7.

15 Kawakami H, Zen Y, Kuwatani M *et al.* IgG4-related sclerosing cholangitis and autoimmune pancreatitis: Histological assessment of biopsies from Vater's ampulla and the bile duct. *J. Gastroenterol. Hepatol.* 2010; **25**: 1648–55.

16 Weber A, von Weyhern C, Fend F *et al.* Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. *World J. Gastroenterol.* 2008; **14**: 1097–101.

17 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.

18 Unno H, Saegusa H, Fukushima M, Hamano H. Usefulness of endoscopic observation of the main duodenal papilla in the

diagnosis of sclerosing pancreatitis. *Gastrointest. Endosc.* 2002; **56**: 880–4.
19 Kubota K, Iida H, Fujisawa T *et al.* Clinical significance of swollen duodenal papilla in autoimmune pancreatitis. *Pancreas* 2007; **35**: e51–e60.
20 Kim MH, Moon SH, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. *Dig. Surg.* 2010; **27**: 110–4.
21 Kamisawa T, Tu Y, Egawa N *et al.* A new diagnostic endoscopic tool for autoimmune pancreatitis. *Gastrointest. Endosc.* 2008; **68**: 358–61.
22 Hirano K, Fukushima N, Tada M *et al.* Diagnostic utility of biopsy specimens for autoimmune pancreatitis. *J. Gastroenterol.* 2009; **44**: 765–73.
23 Farrell JJ, Garber J, Sahani D *et al.* EUS findings in patients with autoimmune pancreatitis. *Gastrointest. Endosc.* 2004; **60**: 927–36.
24 Sahani DV, Kalva SP, Farrell J *et al.* Autoimmune pancreatitis: Imaging features. *Radiology* 2004; **233**: 345–52.
25 Levy MJ, Wiersema MJ, Chari ST. Chronic pancreatitis: Focal pancreatitis or cancer? Is there a role for FNA/biopsy? Autoimmune pancreatitis. *Endoscopy* 2006; **38** (Suppl 1): S30–35.
26 Kawa S, Okazaki K, Kamisawa T *et al.* Japanese consensus guidelines for management of autoimmune pancreatitis: II. Extrapancreatic lesions, differential diagnosis. *J. Gastroenterol.* 2010; **45**: 355–69.
27 Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. *Gastrointest. Endosc.* 2012; **76**: 645–56.
28 Hoki N, Mizuno N, Sawaki A *et al.* Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. *J. Gastroenterol.* 2009; **44**: 154–9.
29 Hirooka Y, Itoh A, Kawashima H *et al.* Diagnosis of pancreatic disorders using contrast-enhanced endoscopic ultrasonography and endoscopic elastography. *Clin. Gastroenterol. Hepatol.* 2009; **7**: S63–S67.
30 Fusaroli P, Saftoiu A, Mancino MG *et al.* Techniques of image enhancement in EUS (with videos). *Gastrointest. Endosc.* 2011; **74**: 645–55.
31 Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2011; **43**: 163–5.
32 Saftoiu A, Iordache SA, Gheonea DI *et al.* Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). *Gastrointest. Endosc.* 2010; **72**: 739–47.
33 Hocke M, Schulze E, Gottschalk P *et al.* Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J. Gastroenterol.* 2006; **12**: 246–50.
34 Dietrich CF, Hirche TO, Ott M *et al.* Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2009; **41**: 718–20.
35 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.
36 Zhang MM, Yang H, Jin ZD *et al.* Differential diagnosis of pancreatic cancer from normal tissue with digital imaging processing and pattern recognition based on a support vector machine of EUS images. *Gastrointest. Endosc.* 2010; **72**: 978–85.
37 Iglesias-Garcia J, Larino-Noia J, Abdulkader I *et al.* Quantitative endoscopic ultrasound elastography: An accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; **139**: 1172–80.
38 Mei M, Ni J, Liu D *et al.* EUS elastography for diagnosis of solid pancreatic masses: A meta-analysis. *Gastrointest. Endosc.* 2013; **77**: 578–89.
39 Hirano K, Tada M, Isayama H *et al.* Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. *Gastrointest. Endosc.* 2010; **71**: 85–90.
40 Hyodo N, Hyodo T. Ultrasonographic evaluation in patients with autoimmune-related pancreatitis. *J. Gastroenterol.* 2003; **38**: 1155–61.
41 Nakazawa T, Ohara H, Sano H *et al.* Difficulty in diagnosing autoimmune pancreatitis by imaging findings. *Gastrointest. Endosc.* 2007; **65**: 99–108.
42 Hamano H, Kawa S, Uehara T *et al.* Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: Part of a spectrum of autoimmune pancreatitis? *Gastrointest. Endosc.* 2005; **62**: 152–7.
43 Hayashi K, Nakazawa T, Ohara H *et al.* Autoimmune sclerosing cholangiopancreatitis with little pancreatic involvements by imaging findings. *Hepatogastroenterology* 2007; **54**: 2146–51.
44 Tamada K, Tomiyama T, Oohashi A *et al.* Bile duct wall thickness measured by intraductal US in patients who have not undergone previous biliary drainage. *Gastrointest. Endosc.* 1999; **49**: 199–203.
45 Pavey DA, Gress FG. The role of EUS-guided FNA for the evaluation of biliary strictures. *Gastrointest. Endosc.* 2006; **64**: 334–7.
46 Inui K, Yoshino J, Miyoshi H. Differential diagnosis and treatment of biliary strictures. *Clin. Gastroenterol. Hepatol.* 2009; **7**: S79–S83.
47 Imai K, Matsubayashi H, Fukutomi A *et al.* Endoscopic ultrasonography-guided fine needle aspiration biopsy using 22-gauge needle in diagnosis of autoimmune pancreatitis. *Dig. Liver Dis.* 2011; **43**: 869–74.
48 Mizuno N, Bhatia V, Hosoda W *et al.* Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: A comparison study with EUS-FNA. *J. Gastroenterol.* 2009; **44**: 742–50.
49 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.
50 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.

51 Binmoeller KF, Jabusch HC, Seifert H *et al.* Endosonography-guided fine-needle biopsy of indurated pancreatic lesions using an automated biopsy device. *Endoscopy* 1997; **29**: 384–8.
52 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.
53 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.
54 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.
55 Chari ST, Smyrk TC, Levy MJ *et al.* Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. *Clin. Gastroenterol. Hepatol.* 2006; **4**: 1010–6.
56 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.
57 Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. *Pancreas* 2006; **32**: 229.
58 Deshpande V, Mino-Kenudson M, Brugge WR *et al.* Endoscopic ultrasound guided fine needle aspiration biopsy of autoimmune pancreatitis: Diagnostic criteria and pitfalls. *Am. J. Surg. Pathol.* 2005; **29**: 1464–71.
59 Uchida N, Kamada H, Tsutsui K *et al.* Utility of pancreatic duct brushing for diagnosis of pancreatic carcinoma. *J. Gastroenterol.* 2007; **42**: 657–62.
60 Takahashi K, Yamao K, Okubo K *et al.* Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA. *Gastrointest. Endosc.* 2005; **61**: 76–9.
61 Raut CP, Grau AM, Staerkel GA *et al.* Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. *J. Gastrointest. Surg.* 2003; **7**: 118–26.
62 Tadic M, Kujundzic M, Stoos-Veic T, Kaic G, Vukelic-Markovic M. Role of repeated endoscopic ultrasound-guided fine needle aspiration in small solid pancreatic masses with previous indeterminate and negative cytological findings. *Dig. Dis.* 2008; **26**: 377–82.
63 Möller K, Papanikolaou IS, Toermer T *et al.* EUS-guided FNA of solid pancreatic masses: High yield of 2 passes with combined histologic-cytologic analysis. *Gastrointest. Endosc.* 2009; **70**: 60–9.
64 Sumimoto 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.
65 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.
66 Chapman R, Fevery J, Kalloo A *et al.* Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660–78.
67 Culver EL, Chapman RW. Systematic review: Management options for primary sclerosing cholangitis and its variant forms – IgG4-associated cholangitis and overlap with autoimmune hepatitis. *Aliment. Pharmacol. Ther.* 2011; **33**: 1273–91.