The role of endoscopy in the diagnosis of autoimmune pancreatitis CME

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Autoimmune pancreatitis (AIP) is a unique type of chronic pancreatitis in which pathogenesis involves autoimmune mechanisms.[1,2] Contrary to ordinary chronic pancreatitis, AIP responds well to corticosteroids.[1,3,4] However, diagnostic uncertainty because of its mimicry of pancreatobiliary malignancies often has led to pancreatic resection for this benign disease.[5-8] If AIP is properly diagnosed, it can be treated without laparotomy or pancreatic resection. However, clinicians also must remain aware that AIP is still a very rare disease, compared with pancreatobiliary malignancy.[9] Overenthusiastic diagnosis of AIP should be avoided because of the potential risk of allowing malignant disease to progress untreated.[3,10,11]

AIP awareness is equally relevant to endoscopists. Not only pancreatologists but also endoscopists should know about AIP because the most frequent acute presentation of AIP is obstructive jaundice and/or a pancreatic mass/enlargement.[1,8] Endoscopists may be requested to perform ERCP to relieve cholestasis by biliary stenting and also undertake imaging and biopsies of the pancreatic lesions under EUS guidance.[1,8,12] Moreover, they have an important role in the integrated care of AIP patients during the evaluation of therapy.[12]

This technical review presents a systematic evaluation of the role of endoscopy in the diagnosis of AIP. We describe the performance characteristics of various endoscopic tests available for evaluating patients with suspected AIP, focusing particularly on the ability to differentiate AIP from pancreatic cancer, followed by a suggested endoscopic strategy that can help physicians identify AIP.

Abbreviations: AIP, autoimmune pancreatitis; ERC, endoscopic retrograde cholangiography; ERP, endoscopic retrograde pancreatography; EUS-FNA, EUS-guided FNA; EUS-TCB, EUS-guided trucut biopsy; ICDC, international consensus diagnostic criteria and algorithm; IDUS, intraductal US; IgG4, immunoglobulin G4; IgG4-SC, IgG4-associated sclerosing cholangitis; PSC, primary sclerosing cholangitis.

DISCLOSURE: *The authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 621.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2012.04.458

LITERATURE REVIEW METHODOLOGY

The PubMed database was used to search publications related to endoscopic tests for AIP by using the following keywords: *autoimmune pancreatitis, sclerosing pancreatitis, nonalcoholic duct-destructive chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis, duct-narrowing chronic pancreatitis, immunoglobulin G4 (IgG4)–associated sclerosing cholangitis (IgG4-SC), major duodenal papilla, endoscopic retrograde cholangiopancreatography, endoscopic retrograde pancreatography (ERP), endoscopic retrograde cholangiography (ERC), endoscopic ultrasonography, intraductal ultrasonography (IDUS),* and *IgG4 immunostaining*. Pertinent articles published in the English language literature were reviewed. All of the references were manually verified, and all reference lists in the retrieved articles were scrutinized to identify any additional articles that might have been missed by the PubMed search.

GRADE SYSTEM

Strength of recommendation

In accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[13,14] recommendations are classified as either strong or weak. The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms (the balance between desirable and undesirable effects, variability in values and preferences, and whether the intervention represents a wise use of resources). Weaker recommendations are indicated by phrases such as "we suggest," whereas stronger recommendations are typically stated as "we recommend."

Quality of evidence

The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[13,14]

INTERNATIONAL CONSENSUS DIAGNOSTIC CRITERIA AND ALGORITHM FOR AUTOIMMUNE PANCREATITIS

During the past decade, several different diagnostic criteria for AIP have been reported from Asia (Japan,

TABLE 1. Quality of evidence and definitions

Grade	Definition	Symbol
High	Further research is very unlikely to change our confidence in the estimate of effect.	ΦΦΦΦ
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	ΦΦΦ
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	ΦΦ
Very low	Any estimate of effect is very uncertain.	Φ

Adapted from Guyatt et al.[14]

Korea), Italy, Germany, and the United States.[8,15-17] Recently, a set of international consensus diagnostic criteria and algorithm (ICDC) for AIP has been proposed by a consensus of expert opinion.[1] The goals of the ICDC for AIP are to develop criteria that can be applied worldwide, taking into consideration the marked differences in clinical practice patterns, to nonsurgically diagnose AIP and avoid misdiagnosis of pancreatobiliary malignancies as AIP.[1] According to the ICDC, diagnosis of AIP usually is made on the basis of a combination of 5 cardinal features: (1) imaging (CT and direct pancreatogram), (2) serology (serum IgG4), (3) other organ involvement (bile duct, salivary gland, retroperitoneum, and kidney), (4) histology and IgG4 immunostaining of the pancreas, and (5) response to corticosteroids. However, the ICDC are not in complete concordance at present, and definite diagnosis sometimes continues to require pancreatic histology. In the ICDC, various endoscopic tools including ERCP and EUS are used to distinguish AIP from pancreatobiliary malignancies.[1]

Two subtypes of AIP

AIP can be classified readily into two subtypes. Although some overlap exists, a number of clinical, serologic, and histopathologic features distinguish the two subtypes of the disease (Table 2).[1,18-20] Type 1 AIP is considered as part of the spectrum of IgG4-related systemic disease, whereas type 2 disease is not.[21] Type 1 and type 2 AIP correspond roughly to lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic pancreatitis, respectively.[18,21] In terms of histopathology, type 1 AIP is typified by periductal lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis, whereas the hallmark of type 2 disease is the presence of granulocytic epithelial lesions.[18,21] This subtyping of AIP is more than just an academic exercise, because different diagnostic criteria and algorithms are applied in the ICDC, depending on the subtype of AIP.

ERCP

Endoscopic retrograde pancreatography

The typical pancreatographic appearance of AIP has been reported as a diffusely attenuated duct with irregular wall (Fig. 1; Table 3).[2,22-26] In contrast, the typical pancreatographic appearance of pancreatic cancer is a single localized stricture associated with marked upstream duct dilatation.[27,28] An international multicenter study has identified 4 specific endoscopic retrograde pancreatography (ERP) features of AIP that are useful in the differential diagnosis between AIP and pancreatic cancer: (1) a long (>1/3 the length of the pancreatic duct) stricture, (2) lack of upstream dilatation from the stricture (<5 mm), (3) multiple strictures, and (4) side branches arising from the stricture site.[24] In the cited study,[24] it was found that ERP had poor sensitivity in centers not routinely performing ERP to diagnose AIP. Interestingly, the ability to diagnose AIP based on ERP features alone could be improved by awareness of some key features described earlier. In a recent study,[29] the typical pancreatographic abnormalities seen in type 1 AIP also were seen in type 2 AIP with similar frequencies. Type 2 AIP potentially benefits the most from diagnostic ERP because patients with type 2 AIP typically have normal levels of serum IgG4 and negative tissue IgG4.[30]

Substantial disparity has been noted between the Asian and Mayo Clinic's HISORt criteria in the use of ERP to diagnose AIP.[4] The former mandate the use of an ERP to diagnose AIP, whereas the latter does not.[8,16,23,31] According to a recent study,[26] when patients with AIP were divided into two subgroups according to CT features (typical vs atypical), little incremental benefit was gained from additional ERP if findings on CT imaging were typical of AIP (diffuse pancreatic enlargement ± rim with homogeneous enhancement). On the contrary, when CT features were atypical (segmental/focal enlargement, dilatation/cutoff of the main pancreatic duct, or pancreatic mass), additional ERP increased the sensitivity and specificity in distinguishing between AIP and pancreatic cancer. In the setting of suspected AIP, therefore, the use of ERP may be tailored depending on CT features (typical vs atypical).[26] Actually, when CT findings are typical for AIP, the ICDC do not use ERP at all for differentiating AIP from pancreatic cancer.[1] In the ICDC, ERP is recommended when CT findings are not typical or when there is no collateral evidence to support the diagnosis (seronegative patients without other organ involvement).[1]

TABLE 2. Differences between clinicopathologic profiles of type 1 and type 2 AIP

	Type 1 AIP	Type 2 AIP
Synonym	Lymphoplasmacytic sclerosing pancreatitis	Idiopathic duct-centric chronic pancreatitis
Epidemiology	Asia > United States, Europe	Europe > United States > Asia
Clinical presentation	Obstructive jaundice (painless)	Obstructive jaundice/acute pancreatitis
Age at diagnosis	Old	Young
Serum IgG4 level	Elevated	Normal
Histologic hallmarks	Periductal lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis	Granulocytic epithelial lesion
Tissue IgG4 stain	Many IgG4 (+) cells	None or very few IgG4 (+) cells
Other organ involvement	Bile duct, salivary gland, kidney, retroperitoneum	Not seen
Steroid responsiveness	Excellent	Excellent
Recurrence	Common	Rare

AIP, Autoimmune pancreatitis; *IgG4,* immunoglobulin G4.

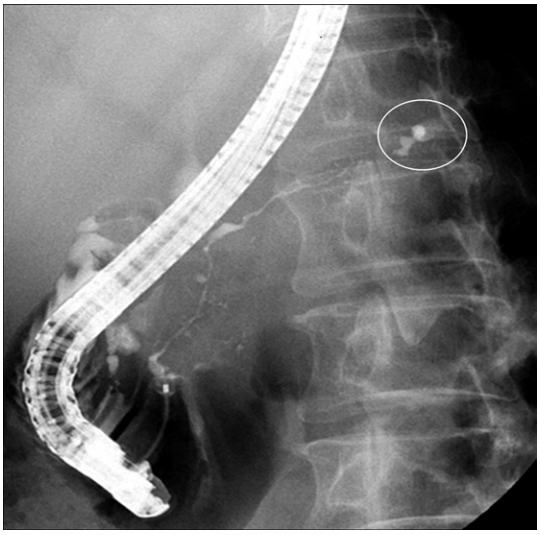

Figure 1. Endoscopic retrograde pancreatography shows diffusely attenuated duct with irregular wall in a patient with autoimmune pancreatitis. Upstream duct dilatation at the pancreatic tail (*circle*) is relatively mild.

Western endoscopists generally avoid injecting the pancreatic duct in patients with obstructive jaundice for fear of causing pancreatitis.[1] According to the literature,[22,26,32] however, no complication of ERCP-induced pancreatitis was reported in patients with AIP. One plausible explanation is that AIP is a unique form of chronic pancreatitis, and that ERCP-induced pancreatitis is rare in patients with chronic pancreatitis.[33] This may reflect a protective effect of chronic pancreatitis against ERCP-induced pancreatitis, due perhaps to fibrosis and decreased enzymatic activity.[26,33]

MRCP is not equivalent to ERCP for demonstrating pancreatic ductal narrowing in AIP patients.[34-37] MRCP showed moderate accuracy (22/34; 65%) in a study evaluating its accuracy in depicting the pancreatic ductal morphology of AIP, using ERP as the reference standard.[37] Currently, MRCP cannot wholly replace ERCP for the diagnostic evaluation of AIP,[34,37] although it might have the potential to serve as an alternative to ERCP because it is noninvasive and because diagnostic ERCP is not routinely performed in the setting of suspected AIP in some centers.[24,38] Secretin-stimulated MRCP may improve visualization of the pancreatic duct and may be useful in examining suspected AIP patients.[39]

Endoscopic retrograde cholangiography

Although most pancreatologists focus their attention on the morphologic changes in the pancreatic duct, the diagnostic importance of ERCP is not limited to the pancreatogram. Type 1 AIP often involves organs other than the pancreas, with the biliary tree most commonly affected.[40,41] ERCP typically reveals strictures of the biliary tree as well as the pancreatic duct. The most common finding is intrapancreatic common bile duct involvement, but biliary strictures can be observed anywhere in the biliary tree including hilar and intrahepatic bile ducts (Fig. 2).[40,42] Biliary involvement of AIP or IgG4-related systemic disease, referred to as IgG4-SC, presents radiographically as bile duct strictures with ductal wall thickening.[42-44] The differential diagnosis of IgG4-SC, which depends on the location and characteristics of the biliary stricture, includes primary sclerosing cholangitis (PSC), cholangiocarcinoma, and pancreatic cancer.[40,45]

In patients with isolated intrapancreatic common bile duct strictures, differential diagnosis includes pancreatic cancer and distal common bile duct cancer, whereas hilar cholangiocarcinoma and PSC should be differentiated

Table 3. Diagnostic performances of ERP in the differential diagnosis of AIP and pancreatic cancer

Study 1st author, y	Setting	Design	No. patients with AIP	No. patients with pancreatic cancer	ERP features	Sensitivity for AIP (%)	Specificity for AIP (%)
Kamisawa 2008[23]	Japan	Retrospective, blinded*	17	40	1. Long stricture (>30 mm)	76	75
					2. Lack of upstream dilatation (<5 mm)	94	79
					3. Multiple strictures	55	100
					4. Side branches†	65	67
Nishino 2010[25]	Japan	Retrospective, blinded	39	62	1. Long stricture (>30 mm)	95	87
					2. Lack of upstream dilatation (<4 mm)	89	87
					3. Multiple strictures	9	100
					4. Side branches	97	64
Kim 2012[26]	Korea	Retrospective, blinded	84	73	1. Long stricture (>1/3)	40	100
					2. Lack of upstream dilatation (<5 mm)	82	71
					3. Multiple strictures	43	100
					4. Side branches	61	73
Sugumar 2011[24]	USA, UK, Japan, Korea	Randomized, blinded, by expert panel	20	10	1. Long stricture (>1/3)	38	97
					2. Lack of upstream dilatation (<5 mm)	62	89
					3. Multiple strictures	26	98
					4. Side branches	66	73
					1 and 2	47	100
					1 or 2	78	91
					2 or 3	89	91
					1, 2, 3, and 4	52	91
					1, 2, 3, or 4	100	66

ERP, Endoscopic retrograde pancreatography; *AIP,* autoimmune pancreatitis; *USA,* United States; *UK,* United Kingdom.
*Blinded to clinical data or final diagnosis.
†Side branches arising from the stricture site.

in cases with intrahepatic and/or hilar bile duct strictures.[4,25,43-46] Intrahepatic and/or hilar bile duct strictures are important clues for distinguishing AIP from pancreatic cancer.[4,8] An international multicenter survey reported that proximal bile duct strictures were detected in 20% to 79% of AIP patients,[47] whereas cholangiograms did not reveal proximal bile duct strictures in pancreatic cancer.[8,23] Characteristic cholangiographic features may allow discrimination of IgG4-SC from PSC; short annular or band-like strictures, diverticulum-like outpouching, and beaded or pruned-tree appearance that are typical for PSC are rarely observed in IgG4-SC.[43,45,46,48] In contrast, IgG4-SC has longer stricture and more prestenotic dilatation.[43] In IgG4-SC, one hepatic segment or lobe can be saved from involvement, whereas intrahepatic strictures in PSC are typically diffusely distributed throughout both hepatic lobes. Strictures of the lower common bile duct are more common in IgG4-SC.[43,48] According to a Japanese study,[43,48] the sensitivity and specificity of endoscopic retrograde cholangiography findings to differentiate between IgG4-SC and PSC were 93% to 96% and 96% to 100%, respectively. Although characteristic cholangiographic features may aid in differentiating IgG4-SC from PSC, several clinical features deserve special mention. PSC is more commonly found in young and middle-aged patients, whereas IgG4-SC typically

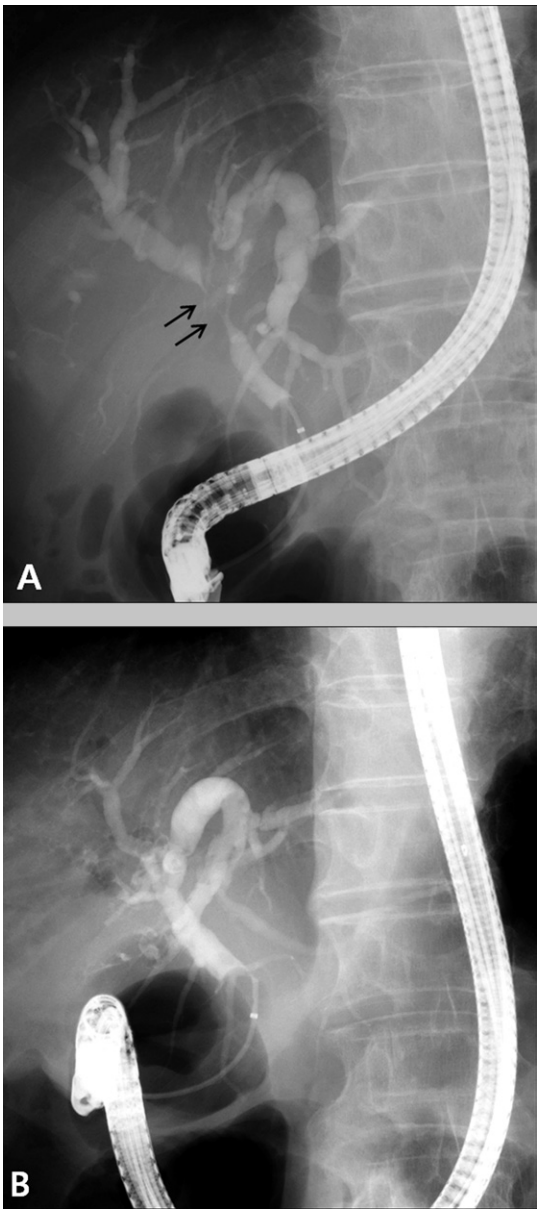

Figure 2. A, Serial images from a patient with autoimmune pancreatitis. Balloon-occluded cholangiogram shows hilar bile duct strictures (*arrows*) mimicking hilar cholangiocarcinoma. **B,** After a 2-week steroid trial, hilar bile duct strictures improved to almost normal.

Table 4. Differentiation between IgG4-SC and cholangiocarcinoma based on ERC/IDUS findings

IgG4-SC	Cholangiocarcinoma
Symmetric (concentric) wall thickening	Asymmetric (eccentric) wall thickening
Thickening of the bile duct wall (>1 mm) on IDUS in a nonstenotic bile duct on ERC	Thickening of the bile duct wall on IDUS only in a stenotic bile duct on ERC
Smooth luminal surface and preservation of wall layer structure	Irregular luminal surface and disruption of wall layer structure
Multifocal strictures (skipped lesions)	A single, localized stricture
Mild proximal duct dilatation despite a long stricture	Marked proximal duct dilatation

IgG4-SC, IgG4-associated sclerosing cholangitis; *ERC,* endoscopic retrograde cholangiography; *IDUS,* intraductal US.

presents in the sixth and seventh decades of life.[40,43] In addition, unlike PSC, IgG4-SC is not usually associated with inflammatory bowel disease.

Characteristic cholangiographic features that are useful in differentiating IgG4-SC from hilar cholangiocarcinoma are listed in Table 4.[40,42-44] Multifocal strictures and mild proximal duct dilatation despite prominent bile duct wall thickening are more common in IgG4-SC.[46] Some clinical and radiologic characteristics other than biliary imaging also aid in differentiating IgG4-SC from hilar cholangiocarcinoma.[40,46] The coexistence of concurrent pancreatic lesions (eg, pancreatic enlargement/mass) and other organ involvement (eg, salivary gland, kidney, or retroperitoneum) can further support the diagnosis of IgG4-SC.

Endobiliary biopsy for bile duct stricture may be performed in the setting of suspected AIP/IgG4-SC to exclude malignancy, especially when ERCP is performed to relieve biliary obstruction.[3,46] However, the sensitivity for detection of malignancy may be low in some cases, and other methods of tissue acquisition, such as EUS-guided FNA cytology (EUS-FNA) and biopsy, often are needed to establish the diagnosis and provide the rationale for steroid therapy. Endobiliary biopsy can be performed easily during endoscopic decompression of obstructive jaundice. Although the resulting specimen is generally too small to observe the full spectrum of lymphoplasmacytic sclerosing pancreatitis histology, IgG4 immunostaining may provide further histologic support for the diagnosis of AIP/IgG4-SC.[32,46,49] The sensitivity and specificity for IgG4 immunostaining of endobiliary biopsy specimens to differentiate AIP/IgG4-SC from malignancy were 18% to 88% and 9% to 100%, respectively (Table 6).[32,40,46,50] Positive IgG4 immunostaining of endobiliary biopsy specimens was found, independently of the presence of elevated serum IgG4 levels.[51] Endobiliary biopsy for diagnosing AIP/IgG4-SC is included in the ICDC.[1]

Ampullary biopsy for IgG4 immunostaining

The ampulla (major duodenal papilla) is often involved in AIP because this structure corresponds anatomically to the junction of the common bile duct and the main pancreatic duct.[52,53] Kamisawa et al[54] first reported that IgG4-positive infiltration in ampullary biopsies was specific for AIP. When positive IgG4 immunostaining is defined as more than 10 IgG4-positive cells in at least one high-

Table 5. Diagnostic yields of pancreatic biopsies in patients with AIP*

Study first author, y	Setting	No. patients with AIP	Sampling technique	Specimens†	Adverse event
Levy 2006[67]	United States	14	EUS-TCB	Diagnostic 57% (8/14) Suggestive 29% (4/14) Inconclusive 14% (2/14)	Abdominal pain 7% (1/14)
Hirano 2009[49]	Japan	15	Percutaneous	Diagnostic 47% (7/15) Suggestive 20% (3/15) Inconclusive 33% (5/15)	None
Mizuno 2009[84]	Japan	8	EUS-TCB	Diagnostic 50% (4/8) Suggestive 50% (4/8) Inconclusive 0% (0/8)	None
Detlefsen 2009[91]	Germany, Denmark	26	Percutaneous Intraoperative EUS-TCB	Diagnostic 81% (21/26) Suggestive 19% (5/26) Inconclusive 0% (0/26)	N/A
Iwashita 2012[88]	Japan	44	EUS-guided‡ (19-gauge needle)	Diagnostic 43% (19/44) Suggestive 43% (19/44) Inconclusive 7% (3/44) Histologic analysis impossible 7% (3/44)	Abdominal pain 2% (1/44)
Song 2012[29]	Korea	54	EUS-TCB Percutaneous	Diagnostic 72% (39/54) Suggestive 0% (0/54) Inconclusive 28% (15/54)	N/A

AIP, Autoimmune pancreatitis; *EUS-TCB,* EUS-guided trucut biopsy; *N/A,* not available.
*Retrospective design.
†Specimens were categorized as diagnostic for AIP (adequate for diagnosis of AIP, sometimes supported by immunoglobulin G4 immunostaining), suggestive of AIP (showing part of the features for lymphoplasmacytic sclerosing pancreatitis or idiopathic duct-centric chronic pancreatitis), or inconclusive.
‡EUS-guided tissue acquisition by using a conventional 19-gauge needle.

power field at a magnification of ×400, the sensitivity and specificity of positive IgG4 immunostaining of the ampulla were 52% to 80% and 89% to 100%, respectively (Table 6).[32,54-56] Significant bleeding and acute pancreatitis have not been reported in association with endoscopic biopsy of the ampulla.[32,52,56] Positive IgG4 immunostaining of the ampulla occurs irrespective of serum IgG4 levels, and the finding of IgG4 immunostaining in ampullary biopsies is in line with that of IgG4 immunostaining in pancreatic biopsies.[51,56,57] IgG4 immunostaining of biopsy specimens from the ampulla may, therefore, be particularly attractive when AIP is clinically suspected, whereas serum IgG4 levels are normal or pancreatic tissue is not available. The ICDC also recommend endoscopic biopsy of the ampulla at the time of ERCP because it is simple and safe.[1]

INTRADUCTAL US

In AIP cases with biliary involvement or IgG4-SC, thickening of the bile duct wall and enhancement on CT may be disguised as cholangiocarcinoma.[45,46,50,58,59] The evaluation of the thickening of the bile duct wall may include transpapillary intraductal US (IDUS), which can be performed during ERCP in a single session. IDUS provides high-resolution images of the layer structure of the bile duct wall, which normally has an inner hypoechoic and outer hyperechoic layer. The characteristic IDUS findings for AIP are concentric bile duct wall thickening with smooth configuration of the outermost layer and a smooth luminal surface (Table 4).[45,50,59] In contrast, IDUS findings for cholangiocarcinoma include eccentric wall thickening with an irregular luminal surface, disruption of the layer structure of the bile duct wall, and a hypoechoic mass with irregular margins.[45,50,60] The most specific IDUS finding for differentiating AIP from cholangiocarcinoma is thickening of the bile duct wall (exceeding 1 mm) in a bile duct that is dilated and/or nonstenotic on endoscopic retrograde cholangiography (Fig. 3).[45,50,58,61] This IDUS feature had 100% specificity and 85% sensitivity.[50] To distinguish benign versus malignant biliary strictures, IDUS may be used as a supplement to ERCP.

ENDOSCOPIC US

Patients who lack the typical features of AIP should first be investigated for pancreatic cancer, and a corticosteroid trial should be considered only if work-up for cancer is negative. For this purpose, EUS examination and EUS-FNA is highly recommended because (1) EUS has excellent negative predictive value and can detect a small pancreatic

Table 6. IgG4 immunostaining positivity of the endoscopically obtained biopsy specimens in patients with AIP and other pancreaticobiliary diseases

Sampling site	Study first author, y	No. patients with AIP	Positive IgG4 immunostaining*	Study first author, y	No. patients with other pancreaticobiliary diseases	Positive IgG4 immunostaining*
Pancreas	Zhang 2007[92]	29†	72% (21/29)	Zhang 2007[92]	9† (Alcoholic chronic pancreatitis)	11% (1/9)
	Detlefsen 2009[91]	29†	41% (12/29)		25† (Pancreatic cancer)	12% (3/25)
	Hirano 2009[49]	15†	47% (7/15)	Deheragoda 2007[51]	20† (Pancreatic cancer)	5% (1/20)
	Mizuno 2009[84]	8	88% (7/8)	Bang 2008[90]	8† (Alcoholic chronic pancreatitis)	25% (2/8)
	Iwashita 2012[88]	44	11% (5/44)		10† (Pancreatic cancer)	10% (1/10)
	Song 2012[29]	54†	41% (22/54)	Detlefsen 2009[91]	15† (Non-AIP chronic pancreatitis)	13% (2/15)
Bile duct	Ghazale 2008[40]	16	88% (14/16)	Naitoh 2009[50]	11 (Cholangiocarcinoma)	9% (1/11)
	Hirano 2009[49]	5	0% (0/5)	Kawakami 2010[32]	6 (PSC)	17% (1/6)
	Naitoh 2009[50]	17	18% (3/17)		27 (Pancreatobiliary cancer)	0% (0/27)
	Kawakami 2010[32]	29	52% (15/29)	Oh 2010[46]	13† (PSC)	0% (0/13)
	Oh 2010[46]	13	69% (9/13)		13† (Hilar cholangiocarcinoma)	0% (0/13)
Duodenal papilla	Kamisawa 2008[54]	10	80% (8/10)	Kamisawa 2008[54]	10 (Pancreatic cancer)	0% (0/10)
	Kubota 2008[55]	27	67% (18/27)	Kubota 2008[55]	12 (PSC)	0% (0/12)
	Moon 2010[56]	19	53% (10/19)	Moon 2010[56]	55 (Pancreatobiliary cancer)	0% (0/55)
	Kawakami 2010[32]	29	52% (15/29)		11 (Ampullary cancer)	0% (0/11)
				Kawakami 2010[32]	6 (PSC)	0% (0/6)
					27 (Pancreatobiliary cancer)	11% (3/27)

IgG4, Immunoglobulin G4; *AIP,* autoimmune pancreatitis; *PSC,* primary sclerosing cholangitis.
*Positive IgG4 immunostaining is defined as >10 IgG4-positive plasma cells in at least 1 high-power field at a magnification of ×400.
†The number included some percutaneous or surgical approaches.

mass not visible on a CT scan, and (2) EUS-FNA is the most reliable tool for excluding pancreatic cancer while avoiding pancreatic resection.[62-64] In most instances, EUS-guided trucut biopsy (EUS-TCB) does not offer advantages over EUS-FNA; however, EUS-TCB should be considered when details of tissue architecture and immunostaining are required to establish a specific diagnosis.[65] EUS elastography and contrast-enhanced EUS may provide information complementary to conventional EUS imaging.

Conventional EUS imaging

The characteristic EUS morphologic finding for AIP is diffuse hypoechoic pancreatic enlargement, sometimes with hyperechoic inclusions.[45,66,67] EUS also may reveal a mass lesion mimicking pancreatic cancer.[66,67] Hoki et al[68] reported that the frequencies of diffuse hypoechoic areas, diffuse enlargement, bile duct wall thickening, and peripancreatic hypoechoic margins are significantly higher in AIP than in pancreatic cancer. In contrast, a focal hypoechoic area and focal enlargement are significantly more common in pancreatic cancer.[68] Because of the lack of pathognomonic features and the diverse spectrum of EUS morphologic findings, however, conventional EUS imaging cannot be used as the sole basis for differentiating between AIP and pancreatic cancer.[67]

EUS elastography/contrast-enhanced EUS

To limit shortcomings of conventional EUS imaging, researchers have used several techniques of image enhancement including the characterization of tumor vascularization and estimation of elasticity distribution in normal and pathologic areas in the pancreas.[69] These imaging techniques have the potential to make EUS less operator-dependent, improve the diagnostic yield of EUS-guided tissue sampling, and allow more reliable assessment of malignant infiltration.[69]

Elastography is a technology that has the potential for noninvasive gathering of information about the relative

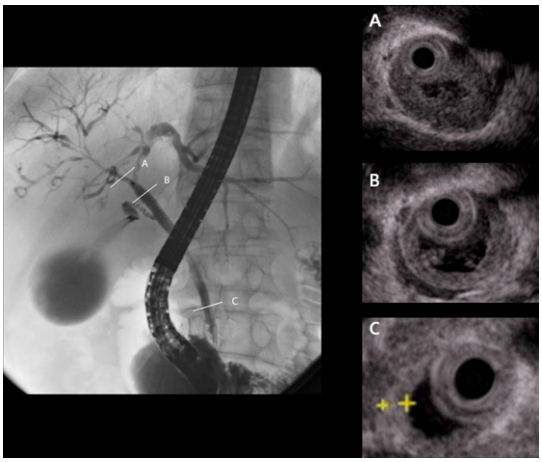

Figure 3. In a patient with IgG4-associated sclerosing cholangitis, cholangiography reveals hilar and intrahepatic bile duct strictures. **A,** In hilar stricture, intraductal US reveals bile duct wall thickening (thickness 2.9 mm), with a smooth configuration of the outermost layer and a smooth luminal surface. **B, C,** In the nonstenotic portions where the cholangiogram result is normal, intraductal US also reveals bile duct wall thickening in the proximal common hepatic duct (1 mm) and the intrapancreatic common bile duct (1.3 mm).

hardness of the examined lesions compared with the surrounding tissues.[70-73] The premise is that malignant tumors are of firmer consistency (harder) than benign ones. According to a study by Dietrich et al,[70] elastographic imaging of patients with pancreatic cancer showed a markedly hard area confined to the site of the low-echoic tumor area, whereas in patients with AIP, the hard (blue) area was not restricted to the mass lesion but included also the surrounding pancreatic parenchyma (Fig. 4).[70]

Contrast-enhanced EUS by using a contrast agent and Doppler mode provides perfusion imaging.[69,74,75] The contrast agent creates microbubbles and enhances the Doppler signal. Therefore, it can enable the depiction of microvessels and give imaging of vascularization.[74] Contrast-enhanced EUS has been shown to be superior to EUS with only B-mode imaging in discriminating neoplastic from nonneoplastic pancreatic lesions.[71,74,76] According to a study by Hocke et al,[74,76] who used contrast-enhanced EUS, the lesions of AIP typically appeared as hypervascularization, whereas hypoechoic tumors caused by pancreatic cancer appeared as hypovascular masses (Fig. 5).

EUS-FNA and trucut biopsy

When a pancreatic mass is detected during a diagnostic work-up, real-time EUS can guide cytology/biopsy, allowing distinction of benign from malignant masses. The addition of FNA improves the evaluation of pancreatic masses and provides sensitivity of about 80% to 90%, specificity of about 95% to 100%, and accuracy of about 90% to 95% in distinguishing benign pancreatic disease from pancreatic cancer.[67,73,77] These diagnostic sensitivities of EUS-FNA are much higher than the sensitivity

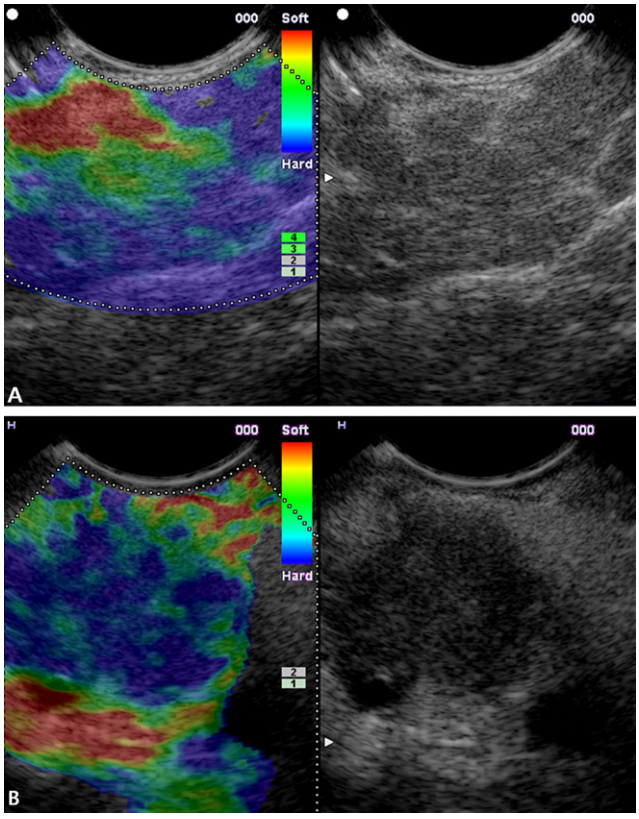

Figure 4. A, EUS elastography shows a characteristic blue (hard) elastographic pattern not only in the mass lesion but also in the surrounding pancreatic parenchyma in a patient with autoimmune pancreatitis. **B,** A blue area delimiting the low-echoic pancreatic tumor is seen in a patient with pancreatic cancer.

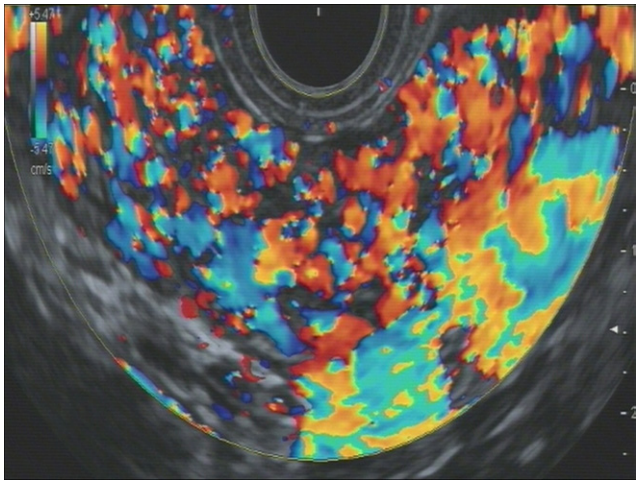

Figure 5. Contrast-enhanced EUS in color Doppler mode shows the characteristic rich vascularization of the pancreas in a patient with autoimmune pancreatitis.

(about 47%-67%) of transpapillary pancreatic-duct cytology/biopsy, although ERCP-guided approaches are well-established.[78-80] However, some of the difficulty in providing a diagnosis of pancreatic cancer may exist in cases

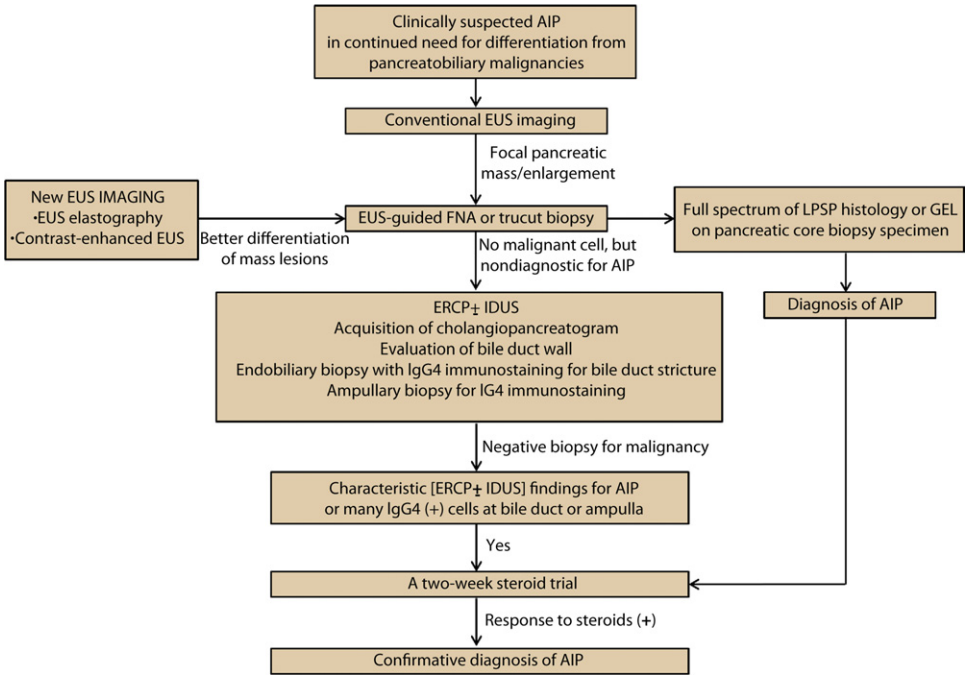

Figure 6. An endoscopic strategy to distinguish AIP from pancreatobiliary malignancies. *AIP,* autoimmune pancreatitis; *LPSP,* lymphoplasmacytic sclerosing pancreatitis; *GEL,* granulocytic epithelial lesion; *IDUS,* intraductal US.

with well-differentiated carcinoma, those with extensive necrosis, and those with a background of chronic pancreatitis.[81-83] Although EUS-FNA is sufficient for diagnosing pancreatic cancer, EUS-TCB is essential for the histologic diagnosis of AIP.[8,45,67,84] The primary role of EUS-FNA of the pancreas in patients with suspected AIP, therefore, may be to exclude malignancy rather than to provide definitive evidence for a diagnosis of AIP (Fig. 6).[85] We should keep in mind that a negative biopsy/cytology is not a guarantee of nonmalignancy; hence short-term follow-up imaging to assess corticosteroid responsiveness is needed.[3,8] If the patient does not respond to a diagnostic corticosteroid trial, a definitive diagnosis always should be pursued by surgical exploration or resection. In a recent study,[3] radiologic distinction between AIP and pancreatic cancer could be achieved by a 2-week steroid trial. The ICDC suggest that negative work-up for pancreatobiliary malignancies is a prerequisite for a corticosteroid trial.[1] It should be emphasized that repeat EUS-FNA is warranted in patients with continued suspicion of pancreatobiliary malignancies despite indeterminate or negative findings at initial EUS-FNA.[81] We should be aware that AIP is much less common than pancreatic cancer or cholangiocarcinoma.[9]

Whereas FNA with a small caliber (22-gauge) provides material only for cytologic review, a trucut biopsy needle (19-gauge) acquires larger tissue samples while preserving tissue architecture, and so permits a nonoperative diagnosis of AIP.[8,67,84,86-88] EUS-TCB of the pancreas is required to look for unique histologic and immunochemical characteristics and therefore can lead to histologic confirmation of AIP (Table 5).[29,67,84,89] IgG4 immunostaining of biopsy specimens of the pancreas has a sensitivity of 11% to 88% and a specificity of 75% to 95% (Table 6).[29,49,51,84,88,90-92] EUS-TCB is particularly useful for diagnosing type 2 AIP because such patients are seronegative and lack other organ involvement. Until now, EUS-TCB is available in only a few specialized tertiary-care centers and is often not feasible as a result of location of mass/enlargement in the pancreas.[1,67,93] However, EUS-TCB is expected to become more widespread with the availability of a newly developed fine-needle biopsy needle (ProCore reverse bevel technology; Cook Endoscopy Inc, Winston-Salem, NC).[87] Further studies are required to assess the diagnostic performance of EUS-TCB from the perspective of consistency and reliability. Transabdominal US/CT-guided pancreatic tissue acquisition may be considered as an alternative to EUS guidance, especially in centers with limited EUS expertise.[49,91,94]

CONCLUSION

Various endoscopic tools are being used for the purpose of differential diagnosis between AIP and pancreatobiliary malignancies. EUS and ERCP are the cornerstone procedures of endoscopic evaluation for differentiation. It is important for endoscopists to be fully aware of the advantages, disadvantages, strengths, and weaknesses of the various endoscopic examinations and to use these tools properly for maximizing diagnostic yield and cost effectiveness. The role of endoscopy in the initial evalua-

tion and diagnosis of patients with suspected AIP continues to evolve.

RECOMMENDATIONS

We suggest that the use of ERP may be tailored to the findings (typical vs atypical) on CT scans in patients with suspected AIP. When CT findings are typical for AIP, diagnostic ERP may be omitted. ERP is recommended in cases where CT findings show "atypical" imaging for AIP (segmental/focal enlargement, dilatation/cutoff of the main pancreatic duct, or pancreatic mass) or when there is no collateral evidence to support the diagnosis of AIP. (ΦΦ) (See Table 1 for a description of the grading system.).

The key ERP findings highly suggestive of AIP in the differential diagnosis between AIP and pancreatic cancers are (1) a long (>1/3 the length of the main pancreatic duct) stricture, (2) lack of upstream dilatation from the stricture (<5 mm), and (3) multifocal strictures. (ΦΦΦ).

In the setting of suspected AIP, we recommend the diagnostic use of ERCP, when ERCP is performed to relieve biliary obstruction. Stricture of the intrapancreatic common bile duct is commonly observed in both AIP and pancreatic cancer. Associated intrahepatic and/or hilar bile duct strictures are important clues to the diagnosis of AIP because proximal bile duct strictures are not detected in pancreatic cancer. (ΦΦΦ). Hilar cholangiocarcinoma and primary sclerosing cholangitis should be differentiated in cases with intrahepatic and/or hilar bile duct strictures. (ΦΦ).

In cases of suspected AIP with obstructive jaundice associated with biliary strictures, we recommend that, at the time that ERCP is performed for biliary decompression, an endobiliary biopsy also may be performed, in order to exclude malignancy. IgG4 immunostaining of the bile duct biopsy specimen also is recommended to support a diagnosis of AIP. (ΦΦΦ).

To assist in making the diagnosis of AIP, we recommend routine ampullary biopsy for IgG4 immunostaining at the time of ERCP. (ΦΦΦ).

In the setting of suspected AIP, a concentric thickening of the bile duct wall exceeding 1 mm on IDUS in the regions of non-stricture on ERCP may suggest IgG4-SC rather than cholangiocarcinoma. (ΦΦΦ) To distinguish benign versus malignant strictures, we suggest IDUS, where available, as a supplement to ERCP. (ΦΦ).

AIP cannot be readily distinguished from pancreatic cancer on the basis of conventional EUS imaging alone, owing to significant morphological overlap. (ΦΦΦ) Emerging techniques in EUS imaging, such as EUS elastography and contrast-enhanced EUS, may provide further improvements over EUS with only B-mode imaging for discriminating inflammatory pseudotumor caused by AIP from pancreatic cancer. (Φ).

A negative work-up for cancer is a prerequisite for proceeding to a diagnosis of AIP. Especially in patients with atypical CT imaging for AIP, work-up for exclusion of pancreatic cancer including EUS-FNA should be performed before a corticosteroid trial. Repeat EUS-FNA is warranted in patients who demonstrate continued suspicion of pancreatobiliary malignancies despite indeterminate or negative findings at initial EUS-FNA. (ΦΦΦ).

EUS-TCB of the pancreas can allow histologic review of the specimens with their tissue architecture preserved. We recommend EUS-TCB in cases with suspected type 2 AIP or when no collateral evidence for AIP exists. (ΦΦ).

ACKNOWLEDGMENT

The authors thank Dr Michael Hocke (Meiningen Hospital, Germany) for providing figures of contrast-enhanced EUS, Dr Christoph Dietrich (Caritas Hospital, Germany) for providing figures of EUS elastography, and Dr Takahiro Nakazawa (Nagoya City University Graduate School of Medical Sciences, Japan) for providing figures of IDUS.

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Received February 9, 2012. Accepted April 17, 2012.

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