

REVIEW

Go KOBAYASHI · Naotaka FUJITA · Yutaka NODA
Kei ITO · Jun HORAGUCHI

Autoimmune pancreatitis: with special reference to a localized variant

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Abstract In 2006, the Japan Pancreas Society revised the diagnostic criteria for autoimmune pancreatitis (AIP) so as to more clearly define its morphological, pathological, and immunological features, as follows: (1) diffuse or segmental narrowing of the main pancreatic duct with an irregular wall and diffuse or localized enlargement of the pancreas recognized by imaging studies; (2) high serum gamma globulin, IgG, or IgG4 levels, or the presence of autoantibodies; and (3) marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas. Establishing a diagnosis of AIP has become easier with knowledge of its immunological abnormalities, including serum IgG4 levels. However, the localized form of AIP sometimes mimics pancreatic cancer. The rate of focal mass formation in patients with AIP is reportedly 24%–43%; however, there have been few reports on the histological findings of localized AIP, in contrast to mass-forming pancreatitis (MFP). Our review of patients who had undergone resection due to a preoperative diagnosis of MFP with possible cancer revealed 72% to be patients with localized AIP. For the discrimination of these conditions, it is important to recognize the characteristic ultrasonographic findings of AIP, i.e., (1) diffuse or localized enlargement and hypoechogenicity of the pancreas; (2) rarity of calcification, cystic lesions, and peripancreatic fluid collection; (3) thickened layer structure of the bile duct wall; (4) iso/hypervascularity in the swollen portion of the pancreas; (5) attenuation of pancreatic swelling and bile duct wall thickening after steroid therapy; and (6) multiple hypoechoic masses in various organs, including the pancreas. Contrast-enhanced endoscopic ultrasonography is potentially a useful tool in the differential diagnosis and for assessment of the efficacy of steroid therapy by enabling evaluation of the vascularity

of the lesions. Along with the presence of IgG4-positive plasma cells, verification of obliterative phlebitis is highly specific for the histological diagnosis of AIP.

Keywords autoimmune pancreatitis · mass-forming pancreatitis · obliterative phlebitis · IgG4 · contrast-enhanced ultrasonography

Introduction

The characteristic features of autoimmune pancreatitis (AIP) have been described by many researchers.^{1–6} Diffuse enlargement of the pancreas along with diffuse narrowing and irregularity of the main pancreatic duct are prominent morphological characteristics (Fig. 1),^{7,8} which are sometimes accompanied by narrowing of the bile duct.^{9–12} The lack or rarity of calcification or cystic dilatation of branch ducts and a good response to steroid therapy are other characteristics.^{1,9} Serologically, the elevation of serum gamma globulin, IgG, or IgG4,¹³ or autoantibody level is recognized as a characteristic manifestation of AIP. When the above-mentioned findings are present, establishing a diagnosis of AIP is easy. Recently, it has become known that IgG4-related inflammatory pseudotumors associated with elevated serum IgG4 level can develop in various organs in patients with AIP.^{14,15} Kamisawa et al.¹⁶ proposed a new clinicopathological entity for this condition, i.e., systemic IgG4-related autoimmune disease. In addition, the existence of a subentity of AIP, characterized by formation of a localized mass, has become accepted.^{17,18}

Concept and histology of AIP

Since the report by Sarles et al.¹ on pancreatitis associated with hypergammaglobulinemia, diagnostic criteria for AIP have been proposed by researchers from several countries.^{2,3,6} In the TIGAR-O system,¹⁹ the importance of the distinction of this entity from ordinary chronic pancreatitis

G. Kobayashi (✉) · N. Fujita · Y. Noda · K. Ito · J. Horaguchi
Department of Gastroenterology, Sendai City Medical Center, 5-22-1
Tsurugaya, Miyagino-ku, Sendai 983-0824, Japan
Tel. +81-22-252-1111; Fax +81-22-252-9431
e-mail: go-koba@mua.biglobe.ne.jp

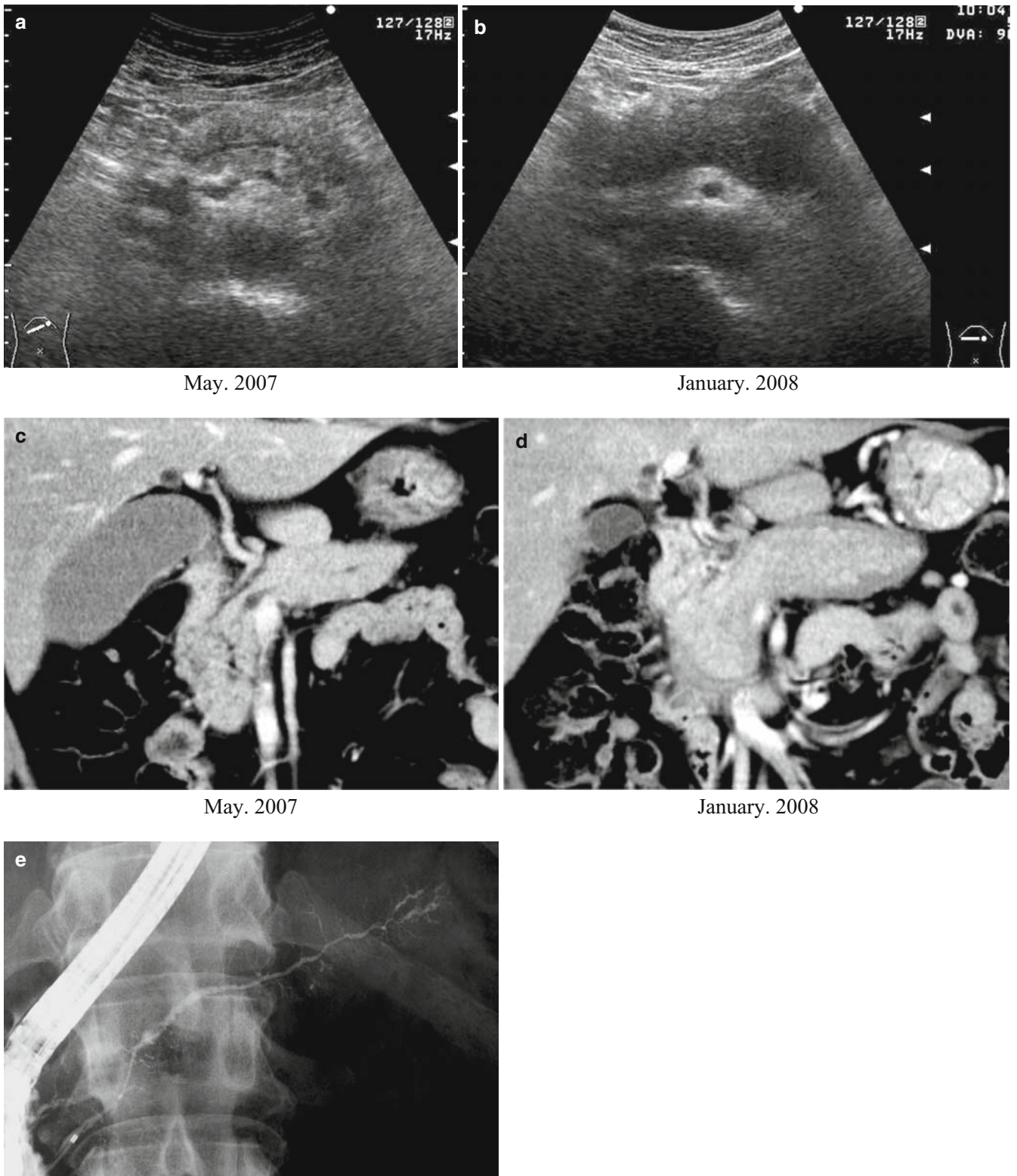


Fig. 1. A 49-year-old man with diffuse type autoimmune pancreatitis in the nonactive stage (transabdominal ultrasonography: US) (a). US showed a diffuse enlargement and hypoechoogenicity of the pancreas in the active stage (b). Contrast-enhanced computed tomography (CT)

showed a diffuse swelling and enhancement of the pancreas with rim sign in the active stage (d) compared with inactive stage (c). Endoscopic retrograde cholangiopancreatography (ERCP) showed a diffuse narrowing and irregularity of the main pancreatic duct (e)

Table 1. The Japanese Pancreatic Society clinical diagnostic criteria of autoimmune pancreatitis, as revised 2006²⁰

1. Diffuse or segmental narrowing of the main pancreatic duct with an irregular wall and diffuse or localized enlargement of the pancreas recognized by imaging studies
2. High serum gamma globulin, IgG or IgG4 level, or the presence of autoantibodies
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criterion 2 or 3, or both

Table 2. Histological and immunohistological findings of mass-forming pancreatitis¹⁸

Group	Patient no.	Age (years)	Sex	Location	Size (mm)	Branch dilatation	Protein plugs	Obliterative phlebitis	IgG4-LI mass (%)	IgG4-LI other (%)	CD4	CD8
A	1	69	M	H	30	±	–	++	46.4	7.2	±	++
	2	68	F	BT	30	–	–	++	26.0	5.8	+	++
	3	62	M	B	25	–	–	++	29.1	6.8	++	++
	4	72	F	T	34	–	–	++	31.7	0	+	++
	5	75	F	H	30	±	±	++	32.8	0	++	++
	6	79	F	B	20	–	–	++	11.6	0	++	++
	7	65	F	H	15	–	–	++	1.7	0	±	++
	8	75	M	T	70	–	–	++	0.3	0	+	++
B	9	58	M	H	60	++	++	–	2.3	1.1	±	++
	10	62	M	H	30	++	++	–	11.1	4.6	+	++
	11	39	F	H	35	++	++	–	8.0	1.0	++	++

Eight cases met the histological criteria of the Japanese Pancreas Society for autoimmune pancreatitis (Group A) while the other three did not (Group B). Two cases were added to those given in Kobayashi et al.¹⁸

Branch dilatation, protein plugs, obliterative phlebitis: (–) absent, (±) slight, (+) moderate, and (++) severe

CD4, CD8: (–): $0/10^4 \mu\text{m}^2$, (±): $<5/10^4 \mu\text{m}^2$, (+): <10 , $\geq 5/10^4 \mu\text{m}^2$, (++): $\geq 10/10^4 \mu\text{m}^2$

H, head; B, body; T, tail; LI, labeling index; IgG4-LI, IgG4-positive plasma cell/mononuclear cell ratio

(CP) is stressed, because AIP patients appear to respond well to steroid therapy. The Japan Pancreas Society (JPS) proposed diagnostic criteria for AIP in 2002² to more clearly define its morphological, pathological, and immunological features; a revised version of the criteria was released in 2006.²⁰ The revised criteria consist of (1) diffuse or segmental narrowing of the main pancreatic duct with an irregular wall and diffuse or localized enlargement of the pancreas recognized by imaging studies; (2) high serum gamma globulin, IgG, or IgG4 level, or the presence of autoantibodies; and (3) marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas. For diagnosis, criterion 1 must be present, together with criterion 2 or 3, or both (Table 1). Establishing a diagnosis of AIP has become easier with knowledge of its immunological abnormalities, including serum IgG4 levels.¹³

The recently recognized concept of AIP is based on the pathological findings of lymphoplasmacytic sclerosing pancreatitis (LPSP). The histological characteristics of LPSP, first described by Kawaguchi et al.,⁹ are that the entire pancreas is affected by primary sclerosing cholangitis-like change of the biliary tree. Histological changes in the pancreas include (1) diffuse lymphoplasmacytic cell infiltration with pronounced acinar atrophy and marked interstitial fibrosis affecting the total pancreas and extending to the contiguous soft tissue, (2) obliterative phlebitis in and around the pancreas, (3) rather well preserved ductal epithelium, and (4) the same inflammatory process affecting the common bile duct and gallbladder.

Idiopathic CP forming a mass in the pancreas with lymphocyte/plasma cell infiltration has been referred to by various names such as chronic inflammatory sclerosis of the pancreas, AIP,¹ LPSP,⁹ inflammatory pseudotumor,²¹ non-alcoholic duct-destructive CP,²² and idiopathic duct-centric CP.²³ Whether all these names describe the same pathological condition is unclear.

Since the report by Hamano et al.,¹³ the presence of IgG4-positive plasma cells has been regarded as an important indicator of AIP. Thus far, the pathogenesis of AIP has not been well understood,²⁴ and the IgG4 antibody is regarded as a mere pathological antibody that combines with IgG4 in the cytoplasm of plasma cells without causing tissue damage by immunocomplex.

The most prominent finding observed in all cases of mass-forming pancreatitis (MFP) due to AIP in our case series was the presence of obliterative phlebitis (Table 2)¹⁸ (Fig. 2). In contrast, obliterative phlebitis was not observed in cases of MFP showing histological features of alcoholic CP, regardless of its stage. Immunohistologically, the IgG4 labeling index (LI) was 25% or over in 63% of the patients with localized AIP, but the other patients (37%) showed a low IgG4-LI, similar to that of patients with alcoholic pancreatitis (Table 2). These observations suggest that the presence of prominent obliterative phlebitis along with marked fibrosis and lymphoplasmacytic infiltration is crucial in the diagnosis of AIP.¹⁸

The prevalence of AIP has been reported to be between 5% and 6% of all patients with CP.^{6,25} Pearson et al.² reported that 11% of patients (27/254) with CP

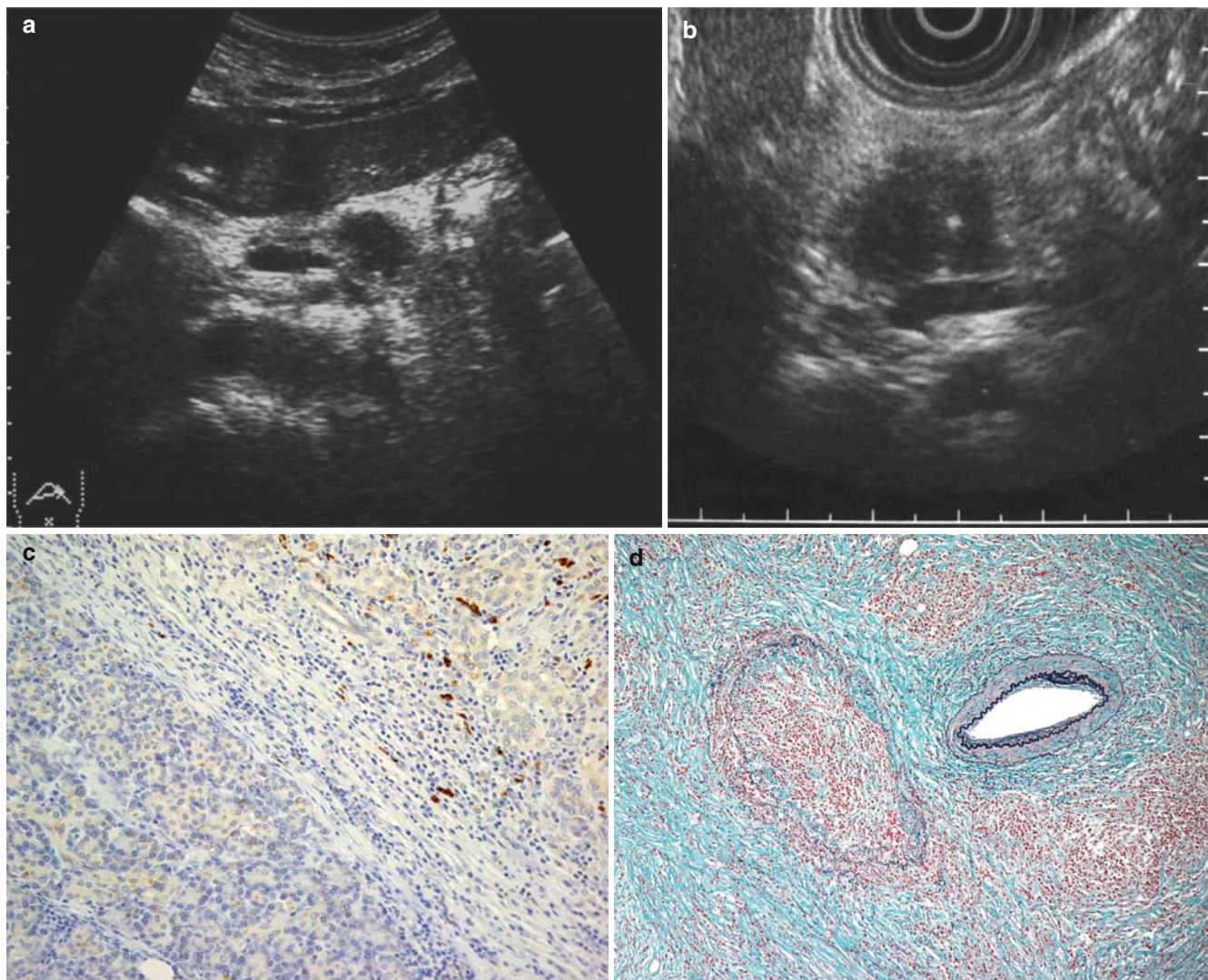


Fig. 2a-d. A 62-year-old man with autoimmune pancreatitis forming a localized mass. US (a) and endoscopic ultrasonography (EUS) showed a hypoechoic mass in the pancreatic body with a comet echo (b). IgG4 staining ($\times 50$). IgG4-positive plasma cells were seen in the

mass portion but were undetectable in the remaining portion (c). Elastica-Masson staining ($\times 25$). In the mass portion, veins of various sizes were highly affected by obliterative phlebitis (d)

received a diagnosis of AIP based on histologic findings. In a previous surgical series, MFP accounted for 7.6%, 19.5%, and 23.4% of patients in whom benign diseases were found after pancreatic resection for presumed malignancy before knowledge of AIP had become widespread.^{18,26,27} The rate of focal mass formation in patients with AIP has been reported to be 24%–43%.^{28,29} In our institute, the prevalence of localized AIP was 38% of all patients with AIP (10/26). There have been few reports on the histological findings of localized AIP, in contrast to MFP. The frequency of AIP among resected patients histologically diagnosed with MFP has been reported to be 20%.³⁰ Our review of 11 patients (in addition to two patients in our previous report¹⁸) who had undergone resection due to a preoperative diagnosis of MFP with possible cancer revealed 72.2% to be patients with localized AIP (Fig. 3).

Ultrasonographic findings of AIP

The ultrasonographic characteristics of MFP are described in the ultrasonographic diagnostic criteria of pancreatic cancer published by the Japan Society for Medical Ultrasonics to facilitate its differentiation from pancreatic cancer.³¹ Although an irregular boundary and relatively homogeneous hypoechoic internal echo of the mass are listed as characteristic findings, they unfortunately are not so specific for MFP. Recent studies have reported difficulties in the differential diagnosis of MFP from pancreatic cancer by ultrasonography alone.^{32–37}

The characteristic ultrasonographic findings of AIP are as follows: (1) diffuse or localized enlargement and hypochoogenicity of the pancreas; (2) rarity of calcification, cystic lesions, and peripancreatic fluid collection; (3)

Fig. 3. Relationship of mass-forming pancreatitis and autoimmune pancreatitis

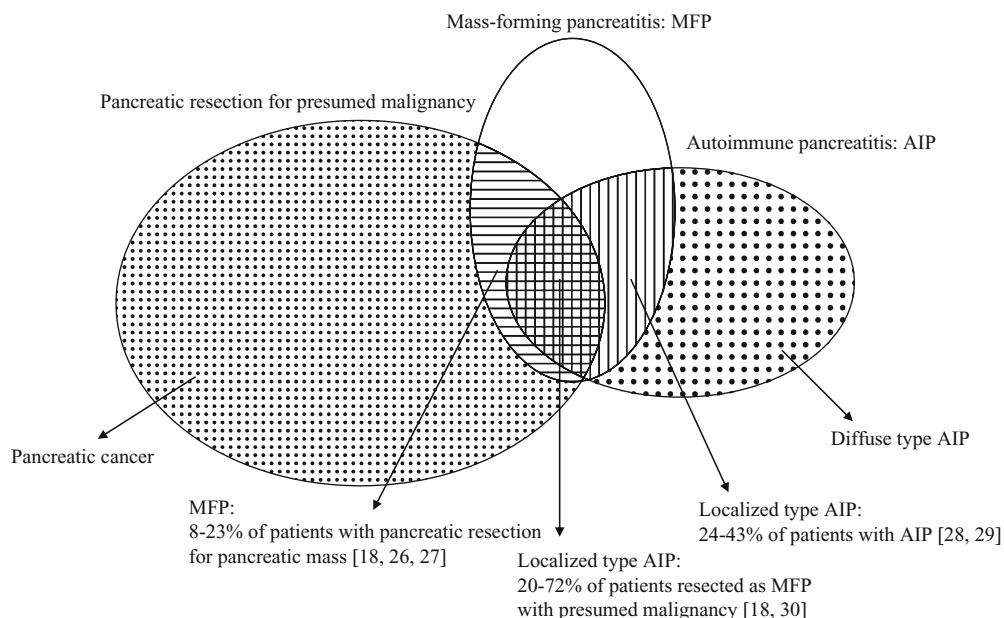


Table 3. Ultrasonographic findings of autoimmune pancreatitis

Diffuse or localized enlargement and hypoechogenicity of the pancreas ^a
Rarity of calcification, cystic lesions, and peripancreatic fluid collection ^b
Thickened layer structure of the bile duct wall ^c
Iso/hypervascularity in the swollen portion of the pancreas
Attenuation of pancreatic swelling and bile duct wall thickening after steroid therapy
Multiple hypoechogenic masses in various organs, including the pancreas ^d

^a Diffuse, sausage-like; localized, mass-forming pancreatitis 24%–43%^{17,18,28,29}

^b Calcification, 8%; cyst, 7%^{28,40,41}

^c Secondary sclerosing cholangitis^{9–12,28,42,51}

^d IgG4-related inflammatory pseudotumors,^{15,16} retroperitoneum,^{52,53} salivary gland,⁵⁴ lung,⁵⁵ liver,^{56,57} gallbladder,⁵⁸ prostate⁵⁹

thickened layer structure of the bile duct wall; (4) iso/hypervascularity in the swollen portion of the pancreas; (5) attenuation of pancreatic swelling and bile duct wall thickening after steroid therapy; and (6) multiple hypoechoic masses in various organs, including the pancreas (Table 3).

Enlargement and hypoechogenicity

The JPS diagnostic criteria for AIP² include an abdominal ultrasonographic (US) finding of hypoechoic swelling of the pancreas, sometimes with scattered echogenic spots. Although Irie et al.³⁸ reported that on computed tomography (CT), AIP appears with a capsule-like rim, which is thought to correspond to an inflammatory process involving peripancreatic tissues, no low-echoic zone indicating a capsule is delineated by US. Other peripancreatic fluid collections are not likely to be common features of AIP either.

Endoscopic ultrasonography (EUS) is reportedly not superior to CT, magnetic resonance imaging, or endoscopic retrograde cholangiopancreatography (ERCP) for the differentiation of AIP from pancreatic neoplasia. EUS-guided fine-needle aspiration (EUS-FNA), however, has a high

accuracy of 85%–96% for differentiating benign from malignant pancreatic masses.³⁹ EUS-FNA contributes to establishment of the diagnosis of AIP by providing histological proof of the presence of IgG4-positive plasma cells or obliterative phlebitis.

Rarity of calcification and cystic lesions

The absence of calcification and pancreatic cysts is considered to be a characteristic feature of AIP.^{1,9,18} Recently, however, an increasing number of reports have documented cases of AIP complicated by calcification or pseudocysts in the pancreas.^{40,41} These pathological changes may be demonstrated as hyperechoic foci and comet-like echoes by US (Fig. 2). Nakazawa et al.²⁸ reported a total of 37 patients with AIP, with three showing calcification of the pancreas and two with pancreatic cysts. They speculated that calcification is a rare finding at the onset of AIP and that relapses of AIP prior to an initial diagnosis may be the reason why calcification develops. They also speculated that severe stenosis of the pancreatic duct was responsible for pancreatic cyst formation and considered these cysts to be retention cysts.

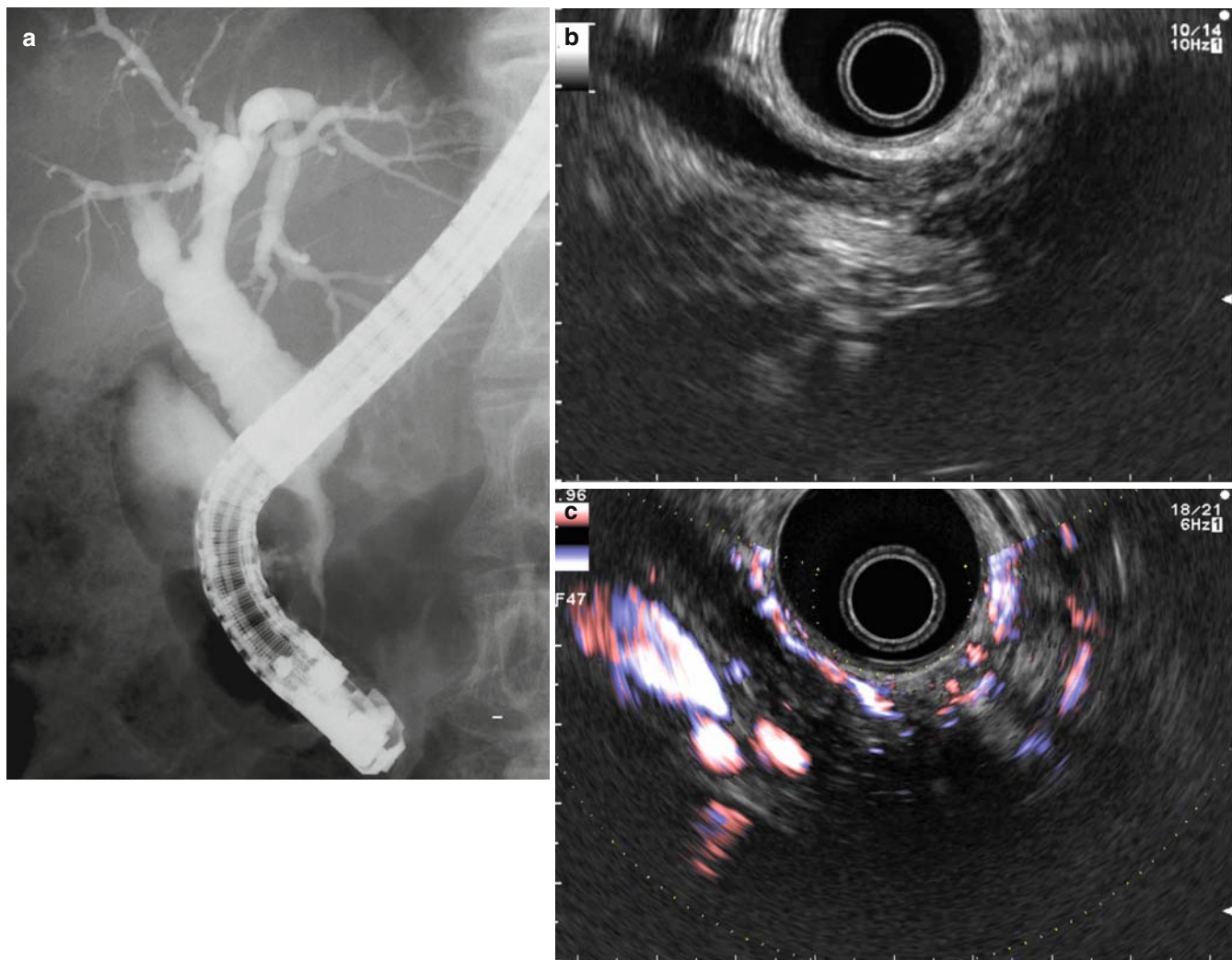


Fig. 4a-c. A 77-year-old man with autoimmune pancreatitis in the nonactive stage. ERCP showed a smooth stricture of the lower bile duct (**a**). EUS (GF UE260-AL5, OLYMPUS, Tokyo, Japan) showed a hypoechoic mass in the pancreatic head and a thickened bile duct

wall (**b**). Contrast-enhanced EUS obtained 50 s after injection of Sonoazoid (0.7 ml/body) revealed the architecture of the pericholedocal vessels to be hypervascular in the D-eFLOW mode (ProSound α 10, ALOKA, Tokyo, Japan) (**c**)

Sclerosing cholangitis

AIP is frequently associated with sclerosing cholangitis, which makes up a distinct clinical entity that is different from primary sclerosing cholangitis (PSC) due to its good response to steroid therapy, clinical manifestations, cholangiographic findings, associated diseases, and levels of IgG4, among others.⁹⁻¹² Nakazawa et al.²⁸ reported that 16 of 37 patients (43%) with AIP had stenosis of the bile duct in the hepatic hilar region, in the intrahepatic duct, or in both. They classified bile-duct changes on Endoscopic retrograde cholangiography into four types: Type I, common bile duct stricture in the pancreas (49%); Type II, common bile duct stricture in the pancreas and multiple strictures in the intrahepatic ducts (24%); Type III, stricture in the hepatic hilar region (11%); and Type IV, stricture in both the hepatic hilar region and common bile duct (8%).

The characteristic ultrasonographic finding of sclerosing cholangitis associated with AIP is a layer structure or con-

centric wall thickening of the bile duct (Fig. 4).⁴² Hyodo et al.⁴³ reported that contrast-enhanced intraductal ultrasonography (IDUS) was useful in differentiating bile duct carcinoma from inflammatory diseases such as primary/secondary sclerosing cholangitis: long-lasting enhancement starting in the early phase (about 30 s) was seen in inflammatory disease, but enhancement was poor in bile duct carcinoma.

Iso/hypervascularity

On contrast-enhanced (ce) CT or US, the swollen portion of the pancreas with AIP shows isovascularity or hypervascularity due to inflammation. It is useful to examine the vascularity of a mass when making a differential diagnosis between mass-forming AIP and ductal carcinomas.⁴⁴⁻⁵⁰

Reports on the use of ceUS for MFP are shown in Table 4.⁴⁴⁻⁴⁹ Koito et al.⁴⁴ reported the results of 55 patients

Table 4. Reports on contrast-enhanced ultrasonography for mass-forming pancreatitis

Authors	Year	No. of patients	Contrast agent	Vascular image	Perfusion image enhancement	Sensitivity	Sensitivity of enhanced CT	
Koito et al. ⁴⁴	1997	20	CO ₂ microbubble		Isovascular	95%	73%	
Oshikawa et al. ⁴⁵	2002	4	Levovist		Slight	50%		
Ozawa et al. ⁴⁶	2002	3	Levovist		Moderate	50%		
					Mild	33%		
					Pronounced	77%		
Rickes et al. ⁴⁷	2002	41	Levovist			85%		
Kitano et al. ⁴⁸	2004	7	Levovist	Isovascular	100%	Isoperfusion	100%	95%
Sofuni et al. ⁴⁹	2005	5	Levovist	Isovascular	80%	Isoperfusion	100%	87%

CT, computed tomography

who had undergone ceUS using carbon dioxide microbubbles. On ceUS, 19 (95%) of the 20 inflammatory pancreatic masses were isovascular and 32 (91%) of the 35 ductal carcinomas were hypovascular. The contrast agent used in the ceUS examination was changed from carbon dioxide microbubbles during angiography to intravenous injection of (Levovist; Schering AG, Berlin, Germany) Rickes et al.⁴⁷ reported that pancreatitis-associated masses showed different patterns of vasculature, depending on the degree and phase of inflammation, fibrotic scarring, and necrosis, with acute edematous pancreatitis being hypervascular and chronic pancreatitis being hypovascular. In the differentiation of pancreatic masses, the rate of correct diagnosis by ceUS was 87%, while that by conventional US was 57%. In the diagnosis of carcinoma showing a hypovascular or hypoperfusion pattern, the sensitivity of ceUS (85%–87%) is reportedly superior to that of CT (73%–89%).^{44–49}

ceEUS is potentially a useful tool in the differential diagnosis and for assessment of the efficacy of steroid therapy by enabling evaluation of the vascularity of localized mass-forming AIP. Hyodo et al.⁴² reported that ceEUS showed diffuse strong enhancement of the thickened bile duct wall, possibly due to inflammation.

We evaluated the vascularity of masses due to AIP with an increase in serum IgG4 levels by ceEUS using Sonazoid; Daiichi-Sankyo, Tokyo, Japan. In patients with AIP in the active stage showing a localized mass, ceEUS performed at 10 s after injection of Sonazoid revealed hypervascularity of the masses. Perfusion images obtained at 20 s after injection showed hypervascular masses with a homogenous pattern in contrast to the rest of the pancreas. The architecture of the vessels in the mass was clearly observed in the late phase (40 s) (Fig. 5). In the assessment of the efficacy of steroid therapy, as well as for the differential diagnosis between pancreatic cancer and localized mass-forming AIP, ceEUS using the new contrast agent Sonazoid seems to be promising for the evaluation of lesion vascularity.

Morphological changes after steroid therapy

In patients with AIP, both pancreatic and extrapancreatic mass lesions can be treated effectively with steroid therapy. Numata et al.⁵⁰ evaluated the vascularity of AIP by comparing ceUS images with pathological findings. The grade

of vascularity of lesions on ceUS images correlated with the pathological grade of inflammation, and inversely correlated with the grade of fibrosis. The vascularity of all lesions decreased after steroid therapy. Hyodo et al.⁴² reported that ceEUS performed after initiation of steroid therapy showed reduced enhancement of the bile duct wall as well as attenuation of pancreatic swelling and bile duct thickening by conventional EUS. This likely reflects resolution of the inflammatory process as a result of treatment. Okaniwa et al.⁵¹ carried out IDUS examination of cases of AIP, which showed thickening of the wall of the main pancreatic duct and common bile duct, with a surrounding diffuse hypoechoic area including echogenic spots. Six weeks after steroid therapy, ERC findings returned to normal and the hypoechoic area had completely disappeared on IDUS.

Multisystemic disorder

AIP is often associated with systemic extrapancreatic lesions.^{14,15} IgG4-related inflammatory pseudotumors can develop in various organs in patients with AIP showing elevation of serum IgG4 levels.^{52–59} A new clinicopathological entity, systemic IgG4-related autoimmune disease, is proposed for this condition.¹⁶ Deheragoda et al.⁶⁰ evaluated the use of IgG4 immunostaining of extrapancreatic biopsy specimens, and concluded that it may allow a definitive diagnosis of AIP to be made in patients with evidence of pancreatic disease, without the necessity of pancreatic biopsy or surgical exploration. Occasional multiple masses in the pancreas associated with autoimmunity have also been reported.⁶¹

Conclusions

AIP is now widely recognized, and the existence of a subentity of AIP characterized by the formation of a localized mass has become accepted. This localized form of AIP sometimes mimics pancreatic cancer. For the discrimination of these conditions, it is important to understand the characteristic ultrasonographic findings of AIP and their histological background. ceEUS has potential as a useful tool in

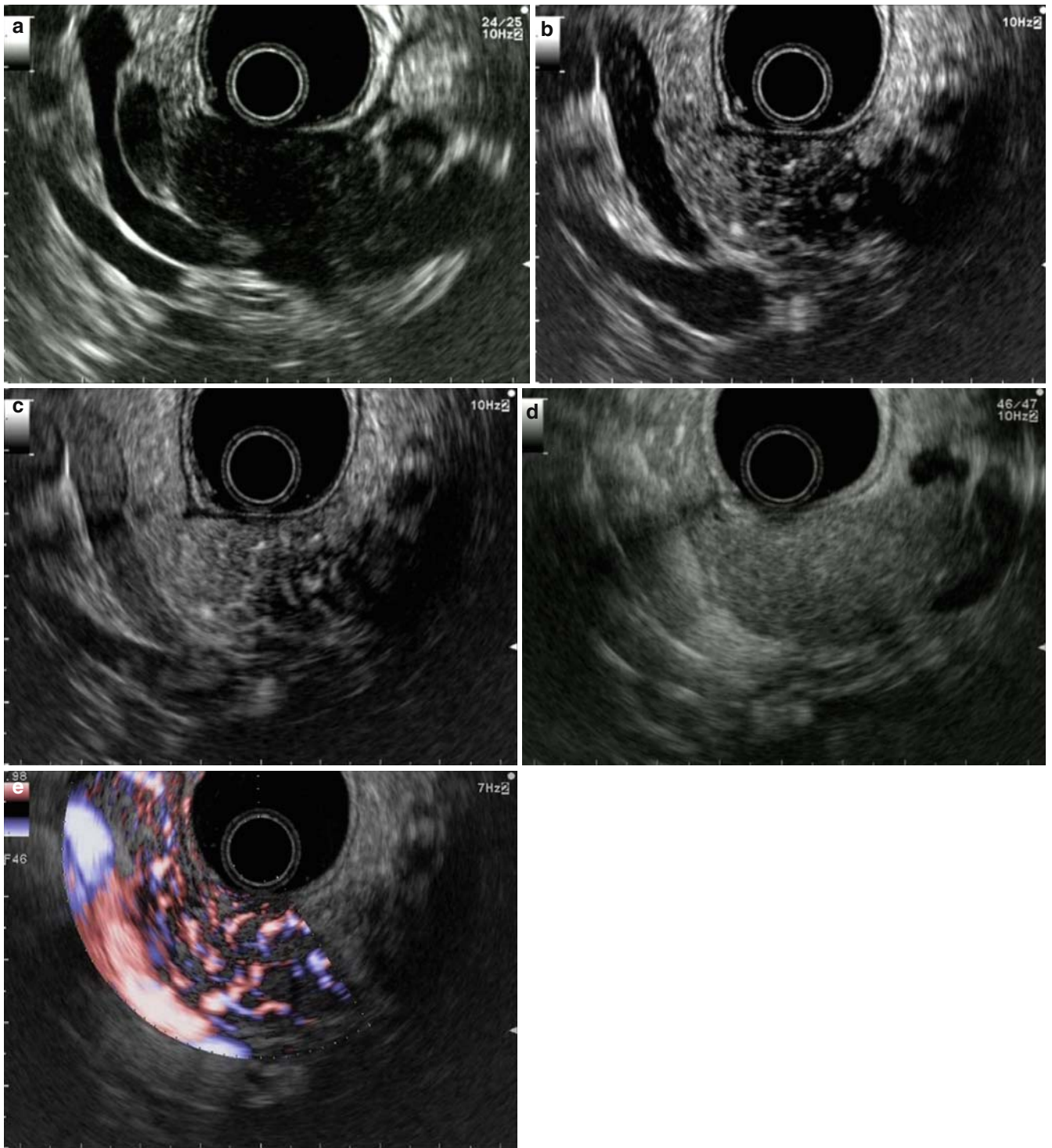


Fig. 5a–e. A 52-year-old man with autoimmune pancreatitis forming a localized mass in the active stage. EUS (GF UE260-AL5, OLYMPUS, Tokyo, Japan) showed a hypoechoic mass in the pancreas tail (**a**). Contrast-enhanced EUS images obtained at 10 s (**b**) and 15 s (**c**) after injection of Sonazoid (0.85 ml/body) revealed a hypervascular mass. A

perfusion image of contrast-enhanced EUS obtained at 20 s after injection revealed a hypervascular mass with a homogeneous pattern in contrast to the rest of the pancreas (**d**). The architecture of the vessels in the mass was clearly visualized in D-eFLOW (ProSound, α 10, ALOKA, Tokyo, Japan) mode at the late phase (40 s) (**e**)

the differential diagnosis of localized mass-forming AIP and for assessment of the activity of inflammation and the efficacy of steroid therapy by enabling evaluation of the vascularity of AIP.

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