総　説

Endosonographic features of autoimmune pancreatitis

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Abstract：Autoimmune pancreatitis（AIP）has come to be increasingly recognized due to the evolving awareness about the disease and the possibility of making a correct diagnosis based on consensus diagnostic criteria. Diagnosis of AIP is no longer difficult, because of the existence of reliable international consensus guidelines. AIP is visualized as a diffuse swelling of the pancreas with a capsular rim on computed tomography, although it sometimes manifests as a focal mass lesion mimicking pancreatic cancer. Endoscopic ultrasonography（EUS）could play pivotal role in the diagnosis of AIP in that it can provide real-time imaging findings of early chronic pancreatitis, including features such as foci/stranding, lobularity and a hyperechoic pancreatic duct margin, and also features of advanced pancreatitis such as cyst formation, dilatation of the side branches of the pancreatic duct and calcification. EUS-guided fine-needle aspiration biopsy（EUS-FNA）also allows tissue specimens to be obtained, which could be processed for histopathology and immunohistochemistry for the diagnosis of type 2 AIP. EUS-elastography and contrast-enhanced EUS are also promising techniques.

要　旨：自己免疫性膵炎は，最近その存在が注目されている疾患であり，正確な診断は確立された国際診断基準による．超音波内視鏡（EUS）はその中で，診断に重要な役割を担っている－早期慢性膵炎の診断基準項目であるfoci，stranding，loburality，hyperechoic pancreatic duct margins，そして非代償期を示すcyst，dilatation of the side branch duct and calcificationにより，AIPの診断に寄与する．さらにEUS－FNAによる組織診断も免疫染色を付加することで可能であり，２型AIPを診断できる可能性もある．EUS－elastographyや造影EUSの有用性も期待できるが発展段階である．

Key words: autoimmune pancreatitis, EUS, EUS-FNA

Introduction

Sarles et al described autoimmune pancreatitis（AIP）for the first time in 1961[1)], and AIP was established as a clinical entity by Yoshida et al in 1995[2)]. Typical AIP is a reversible inflammatory disease of the pancreas associated with other organs involvements such as the biliary system, retroperitoneal organs, lacrimal/salivary glands and mediastinal/abdominal lymphoadenopathy[3)]. However, AIP is sometimes misdiagnosed as pancreatic cancer and treated mistakenly by surgical resection. AIP is becoming increasingly well recognized due to the evolving awareness about the disease and possibility of making the correct diagnosis based on consensus diagnostic criteria criteria[4)]. Diagnosis of typical AIP is no longer difficult, because of the existence of reliable international consensus guidelines[5)]. AIP is visualized as a diffuse swelling of the pancreas with a capsular rim on computed tomography（CT）, although it sometimes manifests as a focal mass lesion mimicking pancreatic cancer[6)]. In addition, focal type AIP patients often

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show negative test results for serum IgG4, which may also make the diagnosis difficult[7]. Some patients with focal type 1 and/or type 2 AIP may undergo unnecessary surgery because of the difficulty in differentiating this condition from cancer based on the symptoms and imaging findings without histopathological evidence. Under this circumstance, Endoscopic ultrasonography (EUS) could be a useful tool to diagnose AIP in that it can provide real-time images useful for the diagnosis and also allow specimens to be obtained for histopathological and immunohistochemical analysis[8]. This review is aimed at highlighting the roles of EUS in the diagnosis of AIP.

Endosonographic features

Endosonograhic findings of chronic pancreatitis can be divided into parenchymal (foci/stranding, lobularity, cyst) and ductal (hyperechoic main pancreatic duct margin, dilated side branches) features[9]. Correlations between the endosonographic findings and histopathologic features in patients with AIP are shown in Table 1. These findings can aid in the diagnosis of AIP[10]. Hyperechoic foci are defined as hyperechoic structures measuring more than 2 mm in length and width that produced shadow. Histopathologically, these foci correspond to focal fibrosis. Stranding is defined as the presence of at least three hyperechoic lines measuring more than 3 mm in length and corresponds histopathologically to bridging fibrosis. Lobularity on endosonography is defined as the presence of well-circumscribed structures measuring more than 5 mm in diameter, with rims that are hyperechoic relative to the echogenicity of the central area. At least three lobules in the body/tail of the pancreas must be present to define lobularity. Honeycomb lobularity refers to the presence of at least three lobules that are contiguous with each other. Cysts indicate abnormal anechoic round or oval structures, corresponding histopathologically to retention cysts or pseudocysts. A hyperechoic main pancreatic duct margin is defined as a relatively hyperechoic duct wall in greater than 50% of the entire length of the main pancreatic duct in the body and tail, and corresponds to periductal fibrosis. Dilated side branches are defined as the presence of three or more tubular anechoic structures measuring more than 1 mm in width each and communicating with the main pancreatic duct. Endosonographic images can increase the diagnostic accuracy of AIP in patients with negative workup for atypical AIP[10]. The prevailing diagnostic criteria for AIP include CT, magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) findings, but not endosonographic findings. While EUS provides high-definition imaging of the pancreas, EUS features alone are not sufficient for the diagnosis of AIP because EUS couldn't reveal the focal narrowing irregular pancreatic duct stricture for focal type AIP, which can be shown on ERCP or magnetic resonance cholangiopancreatography (MRCP)[5,10]. In addition to providing endosonographic images, EUS is also useful for obtaining tissue specimens for histopathology and immunohistochemistry. The endosonographic features of AIP include diffusely enlarged sausage-liked hypoechoic swelling of the pancreas. Cysts and/or calcification are not recognized in the reversible phase which is responsive to corticosteroid treatment (CST) (Figure 1). AIP can be classified into early-stage disease (characterized by good response to corticosteroid therapy), and advanced-stage disease (characterized by stone and cyst formation, similar to the findings in chronic alcoholic pancreatitis)[10]. Advanced chronic pancreatitis is associated with irregular dilatation of the main pancreatic duct and calculi and/or cyst formation. We suggested that lobularity and a hyperechoic pancreatic duct margin were characteristic EUS features of early AIP, which had a more favorable prognosis, with a higher frequency of spontaneous remission and preservation of acinar cells than advanced AIP[10]. Focal type AIP may be difficult to differentiate from pancreatic cancer in the absence of histopathological evidence.

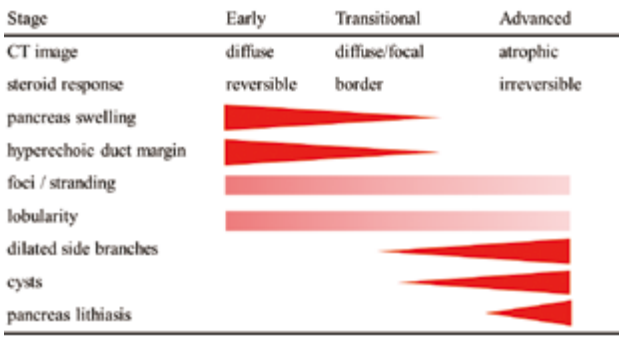

Figure 1. Endosonographic features in patients of autoimmune pancreatitis.

Endosonographic finding	Histopathology
hyperechoic foci/stranding	focal or bridging lesions of fibrosis
	3mm>:foci, more than 3mm:stranding
lobularity	focal edema surrounded by lobular fibrosis
hyperechoic duct margin	periductal fibrosis
dilated side branches	dilated side branches due to stenosis
cysts	cyst/ cystic side branches
pancreas lithiasis	stones

Table 1. Correlation between endosography and histopathology in autoimmune pancreatitis.

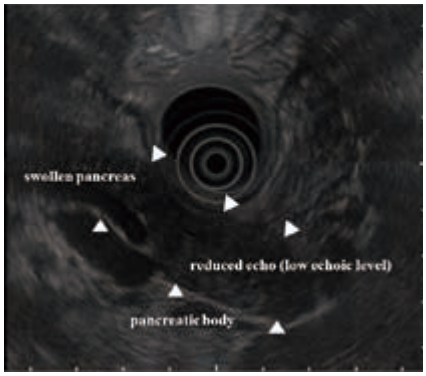

Figure 2 . Sausage like swollen pancreas(arrow head) with reduced echo in patien with autoimmue pancreatitis.

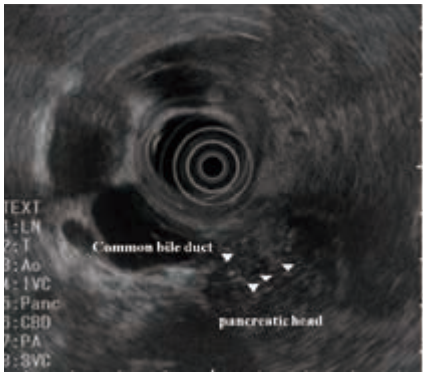

Figure 3 . Non shadowing hyperechoic foci(arrow head) in patient with autoimmune pancreatitis..

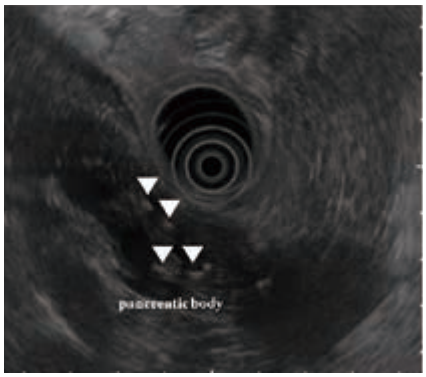

Figure 4 . Stranding(arrow head) was recognized in patient with autoimmune pancreatitis.

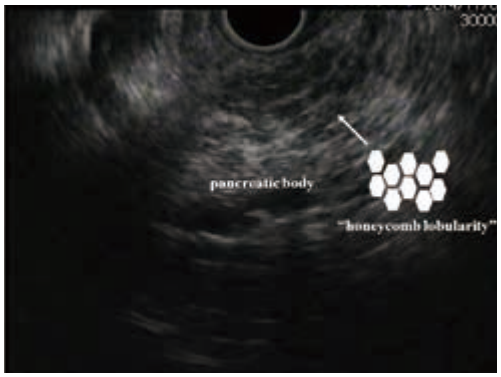

Figure 5 . Pancreatic parenchyma demonstrating honeycomb lobularity(arrow) in patient with autoimmune pancreatitis.

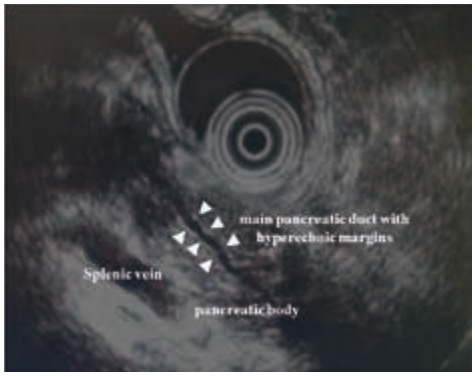

Figure 6 . The pancreatic duct is tortuous with hyperechoic duct margins(arrow head) in patient with autoimmune pancreatitis.

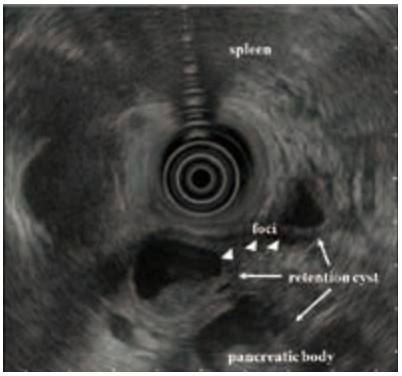

Figure 7 . Retention cysts recognized in patient with autoimmune pancreatitis, foci also noted.

AIP and early chronic pancreatitis

Early chronic pancreatitis is a reversible entity just like AIP[11]. Sahai described the endosonographic diagnostic criteria for the diagnosis of chronic pancreatitis using terms such as hyperechoic foci, stranding, lobilarity, hyperechoic duct margin, dilated side branches, cysts and pancreatic lithiasis[12] (Table 1). We showed that some of Sahai's criteria corresponded to the diagnostic criteria of AIP, because the endosonographic images of AIP are almost the same as those of early chronic pancreatitis. Sausage-like swollen pancreas with reduced echogenicity (Figure 2), foci (Figure 3), stranding (Figure 4), lobulation (Figure 5) and a hyperechoic duct margin (Figure 6) are frequently recognized in patients with early-stage AIP, which is often responsive to CST. CST can lead to rapid resolution of the clinical, imaging as well as histopathological abnormalities in patients with AIP. Figure 2 indicates the transition of the endosonographic findings of AIP: a hyperechoic duct margin, foci/stranding and lobularity are noted in the early phase, while all of these features become less pronounced in the advanced phase. On the other hand, dilated side branches, cyst formation (Figure 7) and

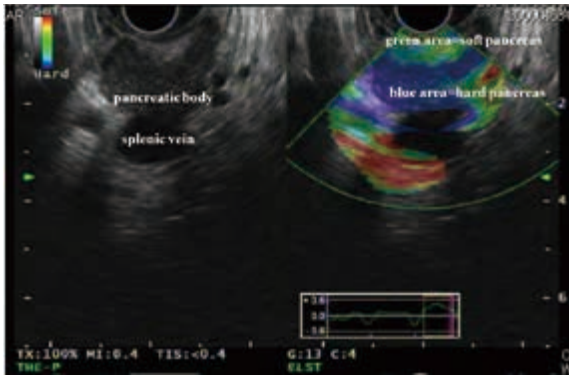

Figure 8. Elastography showed hard lesion (blue) in patient with autoimmune pancreatitis.

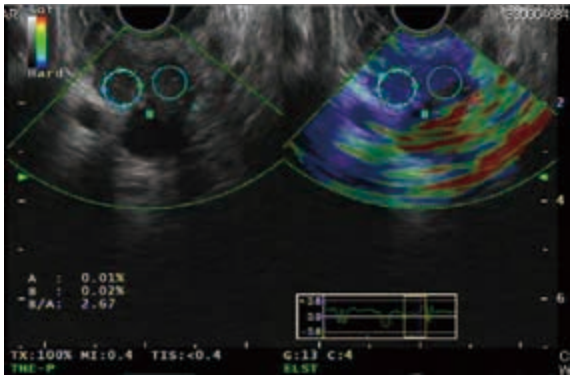

Figure 9. Elastography strain ratio indicated 2.67 in patient with autoimmune pancreatitis, which tended to be lower than that with in patient with pancreatic cancer(mean 18.12[13]).

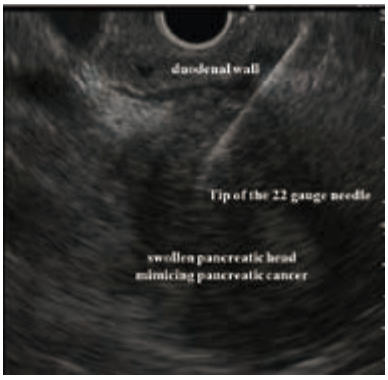

Figure10. EUS-FNA using 22 gauge needle.

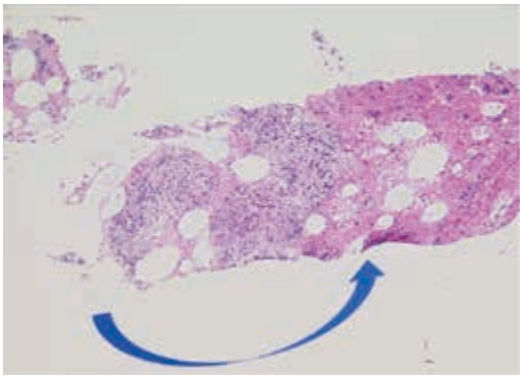

Figure11. FNA specimen(arrow) obtained by 22 gauge needle; autoimmune pancreatitis (reversible stage).

pancreatolithiasis are the landmarks of the late phase of AIP.

EUS elastography (EUS-ela)

The usefulness of EUS-elastography (EUS-ela) in differentiating AIP from pancreatic cancer has been under debate. EUS-ela is a non-invasive technique for measuring the elasticity of a tissue in real time. Quantitative elastography provides the ratio of the elasticity of a target tissue over that of a soft reference tissue (strain ratio)[13]. Different pathological features such as inflammation, fibrosis and cancer can change the tissue elasticity and confer distinct elastographic appearances[14]. Giovannini studied EUS-ela based on qualitative elastographic evaluation. The sensitivity and specificity for differentiating between benign and malignant pancreatic masses were 100% and 67%, respectively. EUS-ela is a state-of-the art technique to diagnose pancreatic cancer. It can provide characteristic elastographic features of both focal tumors and the surrounding areas[15]. Iglesias et al[13] evaluated the strain ratios of solid pancreatic masses in 86 patients, including 27 inflammatory masses. The strain ratios of malignant tumors were significantly higher as compared to those of inflammatory masses. The mean strain ratio of the normal pancreas was 1.68 (95% CI: 1.58-1.78), that of inflammatory masses was 3.28 (95% CI: 2.61-3.98), and that of pancreatic cancer was 18.12 (95% CI: 16.03-20.21). EUS-ela was useful for detecting the hard lesions in patients with AIP (Figure 8), (Figure 9). However, quantitative evaluation is subject-dependent, and further evidence needs to be accumulated.

Contrast-enhanced EUS (CE-EUS)

CE-EUS, which provides perfusion images is used to validate the vascularity of pancreatic mass lesions, including focal type AIP and pancreatic cancer[16]. This technique is considered useful as it provides images of contrast flow in the blood vessels without the burden of Doppler-related artifacts. Napoleon et al showed that the finding of a hypo-enhancing lesion on CE-EUS is associated with a sensitivity, specificity and accuracy for the diagnosis of malignancy of 89%, 88% and 88.5%, respectively[17]. Imazu et al[18] attempted to

differentiate AIP from pancreatic cancer on CE-EUS by carrying out quantitative analysis of the perfusion using a time-intensity curve. Recent data indicate that AIP can show hypervascularity, while pancreatic cancer can be hypovascular[19].

EUS-guided fine-needle aspiration biopsy (EUS-FNA)

The most important role of EUS-FNA is that it aids in the differentiation of focal-type AIP (Figure 10, 11) from pancreatic cancer, although EUS-FNA findings alone are not sufficient to exclude pancreatic cancer. As negative results of EUS-FNA do not confirm the benign nature of a disease, repeated EUS-FNA biopsies or short-term follow-up imaging is mandatory[20]. To diagnose AIP correctly, obtaining sufficient material for immunohistopathology is essential[21]. As AIP is characterized by patchy and/or focal involvement of the pancreas, sampling errors can occur, therefore, repeated EUS-FNA biopsies may be necessary to exclude malignancy[22] . True-cut needle might be the most reliable for the diagnosis of AIP[23], however, true-cut biopsy is technically challenging, and in addition, is associated with a high risk of complications and is particularly difficult for lesions in the head of the pancreas. Thinner 22/25 gauge needles are not always suitable to get sufficient tissue, while a 19-gauge needle is suitable for non-surgical diagnosis[24]. AIP is divided into two types, type 1 and type 2 . Typical type 1 AIP, an IgG 4 -related disease, can be diagnosed according to the International Consensus Diagnostic Criteria (ICDC) criteria[5], additionally, EUS-FNA could play an important role in the diagnosis of focal-type 1AIP. On the other hands, type 2 AIP needed histopathological evidences alone but cytology[25]. Recently, Kanno et al[26] showed that EUS-FNA with a 22-gauge needle using the quick motion method plus careful handling and processing of histological specimens is effective for the diagnosis.

Conclusion

EUS could play pivotal roles in the diagnosis of AIP in that it can provide real-time imaging findings of early chronic pancreatitis, including features such as foci/stranding, lobularity and a hyperechoic pancreatic duct margin, and also features of advanced pancreatitis such as cyst formation, dilatation of the side branches of the pancreatic duct and calcification. EUS-FNA also allows tissue specimens to be obtained, which could be processed for histopathology and immunohistochemistry for the diagnosis of type 2 AIP. EUS-elastography and contrast-enhanced EUS could be supplemental techniques in the different diagnosis for AIP.

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