Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study CME

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Background and Aims: Histopathologic examination is critical for diagnosing autoimmune pancreatitis (AIP). However, specimens obtained using EUS-guided FNA (EUS-FNA) are not recommended for histopathologic diagnosis because of inadequate sample size volume. We evaluated EUS-FNA efficacy for AIP diagnosis using a 22G needle.

Methods: Seventy-eight patients exhibiting the imaging characteristics indicative of AIP in the pancreatic parenchyma and pancreatic duct underwent EUS-FNA with a 22G needle at 12 institutions between February 2013 and March 2014. Samples were evaluated for tissue sampling conditions, CD38- and IgG4-positive plasma cell counts, storiform fibrosis (SF), and obliterative phlebitis (OP).

Results: Tissue specimens containing >10, 5 to 10, and 1 to 4 high-power fields (HPFs) were obtained from 29 (37.2%), 18 (23.1%), and 15 (19.2%) of 78 patients, respectively. The mean ± standard deviation (SD) CD38- and IgG4-positive plasma cell counts were 23.2 ± 18.8/HPF and 5.1 ± 6.7/HPF, respectively. SF was detected in 49 of 78 patients (62.8%) and OP in 38 of 78 patients (48.7%). According to the International Consensus Diagnostic Criteria (ICDC), histopathologic levels corresponded to level 1 in 32, level 2 in 13, and unclassifiable in 17 patients. Hence, 45 of 78 patients (57.7%) could be diagnosed with lymphoplasmacytic sclerosing pancreatitis according to ICDC.

Conclusions: Pancreatic tissues with at least 1 HPF were obtained by EUS-FNA from approximately 80% of patients, and nearly 60% of patients were diagnosed with ICDC level 2 or higher. Our findings indicate that EUS-FNA with a 22G needle may be useful for the histopathologic diagnosis of AIP. (Clinical trial registration number: UMIN000010097.) (Gastrointest Endosc 2016;84:797-804.)

Abbreviations: AIP, autoimmune pancreatitis; HPF, high-power field; ICDC, International Consensus Diagnostic Criteria; IgG, immunoglobulin G; LPSP, lymphoplasmacytic sclerosing pancreatitis; OP, obliterative phlebitis; SF, storiform fibrosis; SD, standard deviation.

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Autoimmune pancreatitis (AIP) is a rare type of pancreatitis with a hypothesized autoimmune mechanism and distinctive clinical characteristics. AIP is currently regarded as a pancreatic manifestation of systemic immunoglobulin G (IgG)4-related disease[1] and has several distinct clinical, serologic, and morphologic characteristics. Histologically, lymphoplasmacytic sclerosing pancreatitis (LPSP) is a characteristic feature of type 1 AIP,[2] whereas idiopathic duct-centric chronic pancreatitis and granulocytic epithelial lesions are of type 2 AIP.[3-5] Compared with Western countries, type 2 AIP is extremely rare in Japan.[6-8] The world's first clinical diagnostic criteria for AIP were released by the Japan Pancreas Society in 2002.[9] Subsequently, diagnostic criteria for AIP have been proposed in several other countries.[10-14] To standardize the diagnostic criteria of AIP, the International Consensus Diagnostic Criteria (ICDC) were proposed in 2011.[15] EUS-guided FNA (EUS-FNA) is not included in ICDC as a method for histopathologic diagnosis of AIP because of the difficulty in obtaining adequate specimens for histopathologic analysis. However, several reports have suggested that EUS-FNA is useful for the diagnosis of AIP.[16-18] Therefore, we conducted a prospective multicenter study to investigate whether EUS-FNA is useful for the histopathologic diagnosis of AIP.

METHODS

This multicenter study was prospectively conducted between February 2013 and March 2014 at 12 tertiary care referral centers. The inclusion criteria included patients exhibiting the imaging characteristics, such as diffuse or segmental/focal enlargement with delayed enhancement and diffuse or segmental/focal or multiple irregular narrowing of the main pancreatic duct without marked upstream dilatation, indicative of AIP in the pancreatic parenchyma and pancreatic duct according to the ICDC. These findings were detected by cross-sectional images via CT and/or magnetic resonance imaging techniques. Exclusion criteria were as follows: (1) patients less than 20 years old, (2) patients in whom EUS-FNA is difficult (eg, cases with surgically altered anatomy), (3) patients with a performance status > 2 as defined by the Eastern Cooperative Oncology Group, (4) patients with malignant tumors, and (5) patients who declined to participate. Patients with surgically altered anatomy were excluded because it was difficult to acquire clear EUS images from the stomach or duodenum in such cases. All patients who participated in this study provided written informed consent. The study was approved by the institutional review board at all participating institutions and was registered on February 22, 2013 at the University Hospitals Medical Information Network (UMIN000010097).

A linear echoendoscope with an Expect 22G needle (Boston Scientific Japan, Tokyo, Japan) was used to perform EUS-FNA. EUS-FNA processing of histologic samples and immunostaining were performed as previously described.[18] Endosonographers punctured the enlarged region in segmental or focal type AIP. In patients with a diffusely enlarged pancreas, the endosonographer determined the puncture site. Endosonographers did not change the pancreatic region for puncture in each session of EUS-FNA. After the puncture, a needle was moved up and down 10 to 20 times within the enlarged pancreas by pulling the needle stylet slowly and steadily (slow-pull method) or by aspiration under 20 mL of negative pressure (aspiration method). The endosonographer at each institution decided whether to use the slow-pull or aspiration method.

The number of punctures was 3.4 ± 1.3 (mean ± standard deviation [SD]; range, 1-7). Tissue samples were fixed in formalin and embedded in paraffin, and several thin serial sections were prepared at each institution. The sliced sections were subsequently sent to the Tohoku University Hospital for histologic examination. Hematoxylin and eosin, Masson's trichrome, and Elastica-Masson staining were performed on each section. Immunohistochemical staining was performed using antibodies against IgG4 (Invitrogen, Gaithersburg, Md) and CD38 (Novocastra, Newcastle upon Tyne, UK).

An expert pathologist (F.F.), who was blinded to all clinical information, reviewed the histopathologic specimens. An average of >10 IgG4- and CD38-positive plasma cells per high-power field (HPF, 400×) was defined as IgG4-positive and lymphocyte-plasma cell infiltration, respectively. Tissue samples were also examined for the presence of storiform fibrosis (SF), obliterative phlebitis (OP), and granulocytic epithelial lesions. OP was diagnosed by Elastica-Masson staining. Because the arteries and veins are usually found next to each other in the pancreas, OP unaccompanied by arteries was judged to be a suspected diagnosis.

Statistics

Statistical analysis was performed using SPSS, version 20.0 (SPSS Inc., Chicago, Ill). A P value < .05 was considered to be statistically significant.

RESULTS

Clinical findings

Eighty-one patients were assessed for eligibility, and 3 patients were excluded because of pancreatic cancer (n = 1) or surgically altered anatomy (n = 2). Table 1 summarizes the clinical characteristics of the 78 enrolled patients. A male-to-female ratio of 60:18 and a mean ± SD age of 65.8 ± 11.1 years were observed. Seventy-seven of the 78 patients (98.7%) showed pancreatic enlargement; 39.7% (31/78), 33.3% (26/78), and 25.6% (20/78) had diffuse, segmental, and focal enlargement, respectively. Only 1 patient did not exhibit pancreatic enlargement. In this patient the endosonographer

TABLE 1. Clinical profiles of the enrolled patients

Characteristics	Values
Sex, male-to-female	60:18
Age, y (mean ± SD)	65.8 ± 11.1
Pancreatic imaging	
Enlargement	77/78 (98.7%)
Diffuse enlargement	31/77 (40.3%)
Segmental enlargement	26/77 (33.8%)
Focal enlargement	20/77 (26.0%)
MPD narrowing	70/78 (89.7%)
Diffuse (≥2/3)	24/70 (34.3%)
Segmental (1/3-2/3)	21/70 (30.0%)
Focal (<1/3)	24/70 (34.3%)
Serology	
IgG4 ± SD, mg/dL	421.0 ± 351.2
IgG4, ≥135 mg/dL	63/78 (80.8%)
Level 1, ≥270 mg/dL	43/78 (55.1%)
Level 2, ≥135 mg/dL <270 mg/dL	20/78 (25.6%)
OOI (including overlapping cases)	44/78 (56.4%)
Level 1	
Sclerosing cholangitis (hilar)	5
Sclerosing cholangitis (intrapancreatic lesion)	15
Retroperitoneal fibrosis	2
Level 2	
Sialadenitis, dacryoadenitis	28
Interstitial nephritis	3
OOI for type 2	
Inflammatory bowel disease (ulcerative colitis)	2
Others	7
Treatment	
Steroid administration	52/78 (66.7%)
Effective cases	52/52 (100%)

MPD, Main pancreatic duct; *IgG*, immunoglobulin G; *OOI*, other organ involvement.

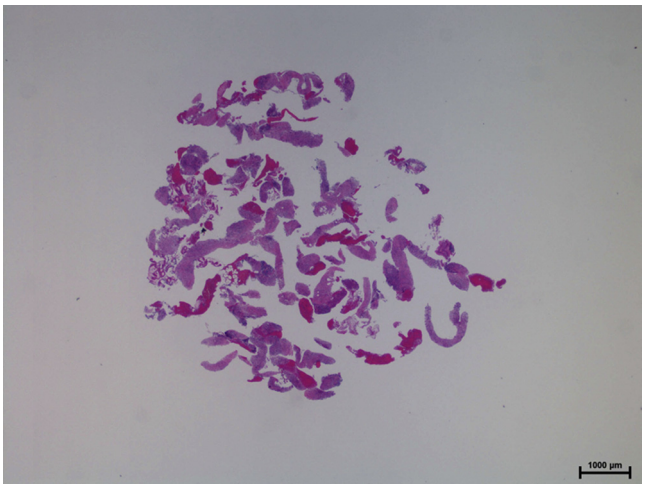

Figure 1. Macroscopic findings of the specimens obtained by EUS-FNA with a 22G needle demonstrated adequate specimens for histopathologic diagnosis (H&E, orig. mag. ×10).

TABLE 2. Tissue acquisition of the enrolled AIP patients

0	1-4 HPFs	5-10 HPFs	≥10 HPFs
16 (20.5%)	15 (19.2%)	18 (23.1%)	29 (37.2%)

AIP, Autoimmune pancreatitis; *HPFs*, high-power fields.

TABLE 3. Histopathologic findings of the enrolled AIP patients

Findings	Per-protocol
IgG4-positive plasma cells (mean ± SD)	5.1 ± 6.7/HPFs
IgG4 (≥10/HPFs)	19/78 (24.4%)
CD38-positive plasma cells (mean ± SD)	23.2 ± 18.8/HPFs
CD38 (≥10/HPFs)	43/78 (55.1%)
Storiform fibrosis	49/78 (62.8%)
Obliterative phlebitis	38/78 (48.7%)

AIP, Autoimmune pancreatitis; *IgG*, Immunoglobulin G; *HPFs*, high-power fields; *CD*, cluster of differentiation.

punctured the pancreatic body where the main pancreatic duct was irregularly narrowed.

Main pancreatic duct narrowing was observed in 70 patients (89.7%). Among them, approximately two thirds of the patients presented with segmental main pancreatic duct narrowing. Serum IgG4 was increased to ≥135 mg/dL (upper limit of normal range in Japan) in 63 of 78 patients (80.8%). The number of patients with levels 1 (IgG4 >270 mg/dL) and 2 (IgG4 ≥ 135 and <270 mg/dL) in the serologic criteria were 43 and 20, respectively. The involvement of other organs was detected in 44 of 78 patients (56.4%).

No patients had a history of steroid treatment, and steroids were administered to 52 patients (66.7%) after EUS-FNA. No patients had been treated with immunomodulating drugs.

Histopathologic examination

Tissue acquisition. The numbers of patients whose tissue specimens contained >10, 5 to 10, and 1 to 4 HPFs were 29 (37.2%), 18 (23.1%), and 15 (19.2%), respectively (Fig. 1, Tables 2 and 3). Pancreatic tissue specimens from 16 patients (20.5%) contained no HPFs. The following results are presented per protocol (n = 78).

IgG4-positive plasma cells. Abundant lymphoplasmacytic infiltration was observed in these specimens (Fig. 2). The mean ± SD IgG4-positive plasma cell count was 5.1 ± 6.7 per HPF (Fig. 3). Specimens from 19 patients (24.4%) contained >10 IgG4-positive plasma cells per HPF on an average.

CD38-positive plasma cells. The mean ± SD CD38-positive plasma cell count was 23.2 ± 18.8 per HPF

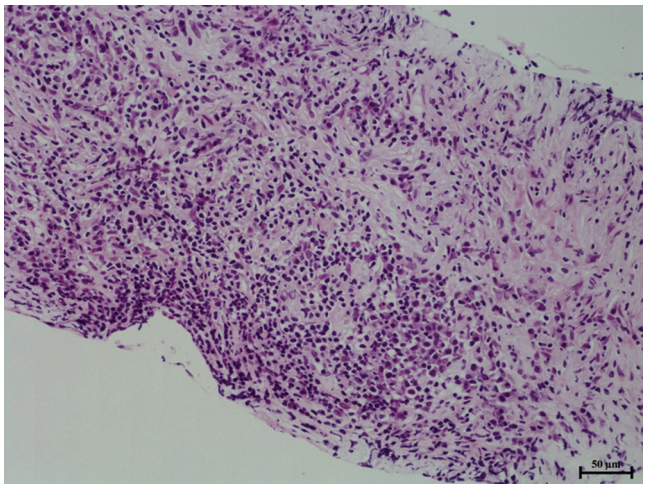

Figure 2. The findings in high-power fields (H&E, orig. mag. ×400) reveal abundant lymphoplasmacytic infiltration.

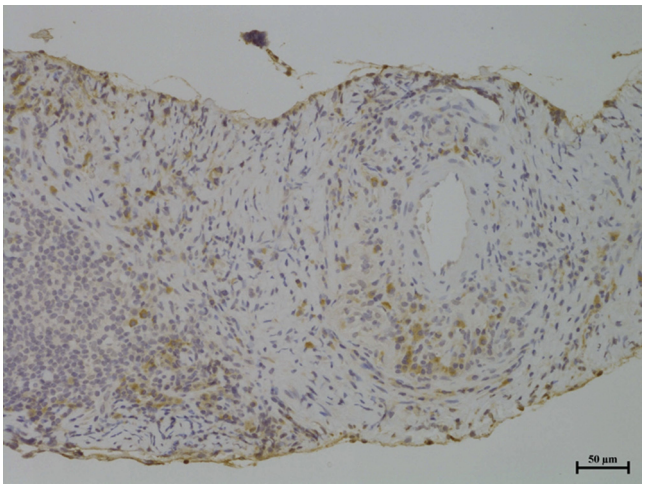

Figure 4. Immunohistochemical staining of CD38. Abundant CD38-positive plasma cells were found in the high-power field (orig. mag. ×400).

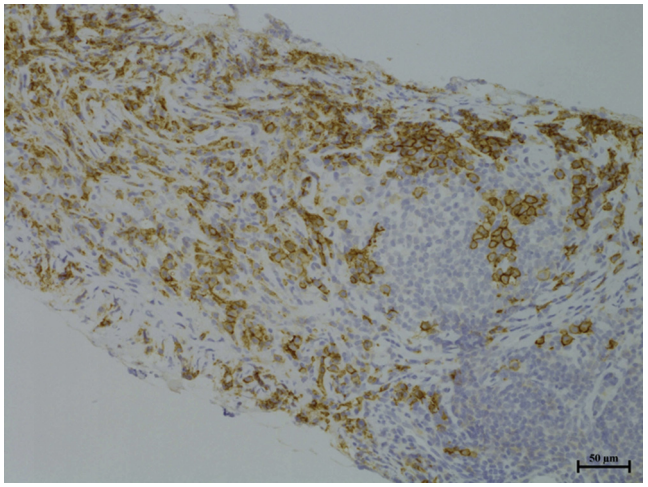

Figure 3. IgG4 immunostaining in the specimens obtained by EUS-FNA shows markedly increased numbers of IgG4-positive plasma cells (orig. mag. ×400).

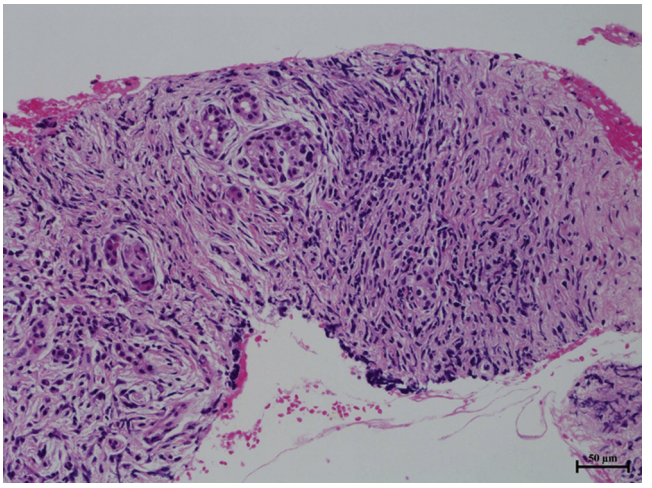

Figure 5. A specimen showing storiform fibrosis in high-power fields (H&E, orig. mag. ×400).

(Fig. 4). Specimens from 43 patients (55.1%) contained >10 CD38-positive plasma cells per HPF on average.

SF, OP, and granulocytic epithelial lesions. The presence of SF was observed in 49 patients (62.8%) (Fig. 5) and of OP in 38 patients (48.7%) (Fig. 6). Granulocytic epithelial lesions were not observed in any of the patients.

Histopathologic diagnosis according to the ICDC

Of the 62 patients whose specimens contained at least 1 HPF, 3 or 4 items were positively identified as level 1 in 32 patients and 2 items were positively identified as level 2 in 13 patients, indicating that 45 of 62 patients (70.5%) had LPSP according to the ICDC. Therefore, 45 of 78 patients (57.7%) undergoing EUS-FNA had LPSP according to the ICDC. Table 4 summarizes the histopathologic findings stratified by the number of HPFs acquired by EUS-FNA. The number of patients diagnosed as having LPSP were significantly higher in specimens containing >10 HPFs than in those containing ≤10 HPFs (28/29 vs 17/33; $P < .01$).

There were no patients with type 2 AIP in this study. This result was not unexpected because cases of type 2 AIP are extremely rare in Japan.[3] Our previous study demonstrated that type 2 AIP could be accurately diagnosed by EUS-FNA.[18]

Adverse events

There were no adverse events (eg, pancreatitis) during or after EUS-FNA in any of the 78 enrolled patients.

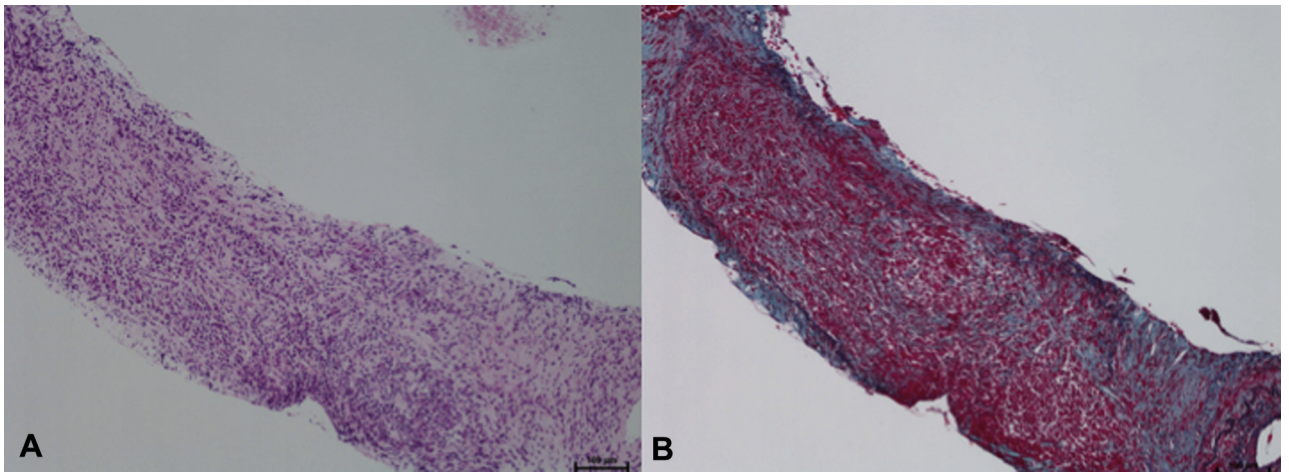

Figure 6. Obstructive phlebitis revealed by (**A**) H&E and (**B**) Elastica-Masson staining (orig. mag. ×200) shows that the infiltration of inflammatory cells obstructed the vein.

TABLE 4. Summary of the histopathologic findings according to the number of HPFs obtained via EUS-FNA

	No. of HPFs obtained by EUS-FNA			
	0	**1–4**	**5–10**	**>10**
No. of patients	16	15	18	29
IgG4 (≥10/HPFs)	—	0 (0%)	4 (22.2%)	15 (51.7%)
CD38 (≥10/HPFs)	—	3 (20.0%)	12 (66.7%)	28 (96.6%)
Storiform fibrosis	—	9 (60.0%)	15 (83.3%)	25 (86.2%)
Obliterative phlebitis	—	4 (26.7%)	7 (38.9%)	27 (93.1%)
No. of patients diagnosed as LPSP according to ICDC	—	7 (46.7%)	10 (55.6%)	28 (96.6%)

HPFs, High-power fields; *IgG*, immunoglobulin G; *LPSP*, lymphoplasmacytic sclerosing pancreatitis; *ICDC*, International consensus diagnostic criteria; —, not acquired data.

Contribution of histologic findings to the diagnosis of AIP according to the ICDC

According to the ICDC,[15] 25 patients could be diagnosed as having definitive type 1 AIP in the absence of histologic findings based on pancreatic imaging, serum IgG4, and other organ involvement (Fig. 7). Of these 25 patients, 9, 5, and 11 patients had histologic findings of level 1, level 2, and undiagnosed AIP in the specimens obtained by EUS-FNA, respectively. In contrast, 53 patients could not be diagnosed with definitive type 1 AIP based on pancreatic imaging, serum IgG4, and other organ involvement. Of these 53 patients, 23, 8, and 22 patients had histologic findings of level 1, level 2, and undiagnosed AIP, respectively. These 23 level 1 patients could be diagnosed as definitive type 1 AIP solely based on the histologic findings of EUS-FNA specimens (Fig. 7).

DISCUSSION

Histologic examination is important for the diagnosis of AIP. According to the ICDC, if 3 of 4 cardinal histopathologic findings are present (ie, LPSP), type 1 AIP can be definitively diagnosed without the need for any additional findings. The ICDC currently requires histologic specimens to be acquired by EUS-trucut biopsy sampling or operation but not EUS-FNA.[15,19-21] However, the needles for EUS-trucut biopsy sampling are not commercially available in several countries. EUS-trucut biopsy sampling or EUS-FNA using a large-gauge needle poses a risk of adverse events (eg, bleeding or perforation), and it is difficult to handle an endoscope with tight angulation.[22] We have previously reported that the histologic diagnosis of AIP according to the ICDC could be made in 20 of 25 patients (80%) using EUS-FNA with a 22G needle.[18] A 22G aspiration needle has been widely used in clinical examinations in Japan. To extend this finding, we conducted a multicenter, prospective study. In agreement with our previous study, pancreatic tissues with at least 1 HPF were obtained from approximately 80% of patients by EUS-FNA with a 22G needle. Nearly 60% of patients were diagnosed with ICDC level 2 or higher, supporting the notion that EUS-FNA with a 22G needle is useful for the histopathologic diagnosis of AIP. In line with this finding, studies, including a nationwide epidemiologic survey, showed that EUS-FNA has become the most widely used modality for obtaining pancreatic tissue specimens for the diagnosis of AIP.[16-18,23]

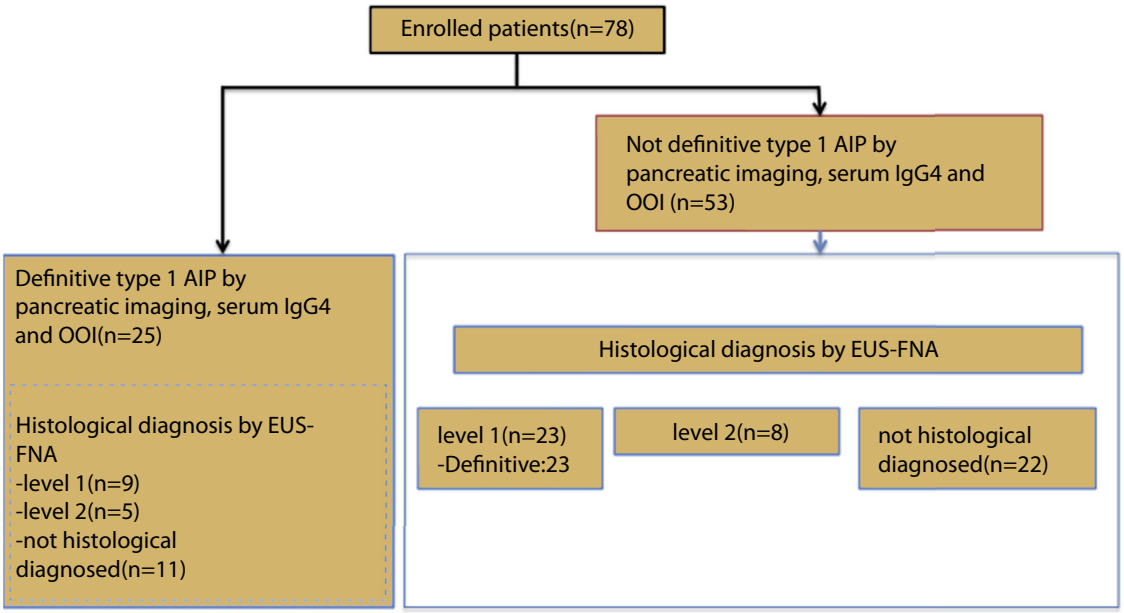

Figure 7. Flowchart illustrating the summary of this study focusing on the diagnosis according to the ICDC. *AIP,* autoimmune pancreatitis; *OOI,* other organ involvement; *ICDC,* International consensus diagnostic criteria.

TABLE 5. Comparison between the 2 groups of patients whose histologic samples were or were not obtained by EUS-FNA

	Sample obtained (n = 62)	Sample not obtained (n = 16)	*P* value
Sex (male/female)	48/14	12/4	.99
Age, y (mean ± SD)	65.6 ± 11.4	60.0 ± 10.2	.90
No. of punctures	3.5 ± 1.3	3.1 ± 1.1	.26
Region punctured (head/body/tail)	22/35/5	6/7/3	.40
Range of pancreatic enlargement (diffuse/other)	24/38	7/8	.57
MPD findings (narrowing/not narrowing)	55/7	15/1	.99

MPD, Main pancreatic duct.

In this study adequate tissue sampling was unsuccessful in 16 of 78 patients (20.5%). We compared the clinical features between patients whose tissue specimens contained at least 1 HPF (n = 62) and those with no HPF (n = 16). As shown in Table 5, there were no significantly different factors between the 2 groups. Our ability to obtain a sufficient histologic sample via EUS-FNA in each examination could be influenced by several factors (eg, individual technique of the endosonographer, hardness of the pancreas, and specific devices selected for EUS-FNA). Consequently, it is very difficult to clarify the optimal conditions for obtaining good-quality histologic samples by EUS-FNA. There are several important tips to optimize histopathologic sampling by EUS-FNA. We have emphasized the importance of quick movement of the FNA needle and selection of whitish pancreatic tissue from tubifex-like pieces.[18] We can collect many pancreatic tissue samples on 1 glass slide by trimming the aspirated specimens using a disposable 18G needle. Several studies have suggested that adequate processing of EUS-FNA specimens is important to obtain specimens suitable for histologic diagnosis.[18,24] However, it is difficult to standardize the processing of EUS-FNA specimens because the involvement of pathologic departments varied among the institutions. Iwashita et al[25] reported that macroscopic on-site quality assessment increases the diagnostic yield of EUS-FNA. Moreover, the presence of OP suggests AIP. OP was identified or suspected in 38 patients (48.7%). The diagnostic rate of OP in this study was excellent compared with that of OP in previous studies.[16,17,26] Elastica-Masson staining was useful to detect elastic fibers, which is also critical for diagnosing OP. On the other hand, the rate of IgG4-positive plasma cells was relatively low, in agreement with a previous study.[18] In this study some patients had serum IgG4 levels below 135 mg/dL. These results suggest that the existence of IgG4-positive plasma cells in histopathologic samples varies depending on the AIP activity. In the future, EUS-FNA may provide useful information regarding the function and behavior of IgG4-positive plasma cells in AIP.

There were no observed adverse events (eg, pancreatitis) during or after EUS-FNA in any of the 78 enrolled patients. In a systematic review by Wang et al,[27] of the 8246 patients undergoing EUS-FNA for pancreatic lesions, 36 (.44%) developed pancreatitis, which was mild to moderate in most cases. This rate is significantly lower than that after ERCP; in which a higher incidence of pancreatitis (3.5%) and pancreatitis-related mortality (3.1%) has been reported in a systematic review.[28]

Seventeen cases could not be diagnosed as LPSP, and in this study 28 of 29 patients whose specimen contained >10 HPFs could be diagnosed as LPSP. The number of patients diagnosed as LPSP were significantly higher in specimens containing >10 HPFs than in those containing ≤10 HPFs ($P < .01$). Therefore, most of these undiagnosed patients might have been diagnosed as LPSP if adequate sample material containing more HPFs was obtained. The development of specific needles for safe and adequate sampling for histopathologic analysis is urgently needed.

The ICDC uses the following 4 items for the histopathologic diagnosis of type 1 AIP: (1) infiltration of lymphocyte-plasma cells, (2) >10 IgG4-positive plasma cells in HPF, (3) SF, and (4) OP.[15] In this study, 13 patients satisfied all 4 items and 19 and 13 patients satisfied 3 and 2 items, respectively. Therefore, 32 patients were diagnosed as having level 1 and 13 patients as having level 2 in the histologic criteria according to the ICDC. In the ICDC, the diagnosis of definitive type 1 AIP could be made solely on the basis of a level 1 histologic finding (ie, LPSP). In these cases, ductal imaging on ERCP is not essential for the diagnosis of AIP and might be avoided. In addition, 53 patients could not be diagnosed as definitive AIP on the basis of pancreatic imaging, serology, and other organ involvement. Twenty-three of these 53 patients had level 1 histologic findings in EUS-FNA samples and could be diagnosed as definitive type 1 AIP without the aid of pancreatic imaging, serology, other organ involvement, and response to steroids. Therefore, further studies are required to clarify whether EUS-FNA should be included in the future diagnostic criteria of AIP as a method to obtain pancreatic samples for histologic evaluation.

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APPENDIX

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