Can the wet suction technique change the efficacy of EUS-FNA for diagnosing autoimmune pancreatitis type 1? A prospective single-arm study

Mitsuru Sugimoto (kita335@fmu.ac.jp)
Fukushima Medical University, School of Medicine https://orcid.org/0000-0002-4223-613X
Tadayuki Takagi
Fukushma Medical University
Rei Suzuki
Fukushima Medical University
Naoki Konno
Fukushima Medical University
Hiroyuki Asama
Fukushima Medical University
Yuki Sato
Fukushima Medical University
Hiroki Irie
Fukushima Medical University
Ko Watanabe
Fukushima Medical University
Jun Nakamura
Fukshima Medical University
Hitomi Kikuchi
Fukushima Medical University
Mika Takasumi
Fukushima Medical University
Minami Hashimoto
Fukushima Medical University
Tsunetaka Kato
Fukushima Medical University
Takuto Hikichi
Fukushima Medical University
Kenji Notohara
Kurashiki Central Hospital
Hiromasa Ohira

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Abstract

Background: Other than surgical biopsy, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the only method for histologically diagnosing autoimmune pancreatitis (AIP). However, adequate specimens are difficult to obtain. Recently, more adequate specimens were reported to be obtained with a wet suction technique (WEST) of EUS-FNA than with the conventional method of EUS-FNA. This study aimed to histologically diagnose AIP by EUS-FNA with a WEST.

Methods: Eleven patients with possible type 1 AIP between February 2016 and August 2018 underwent WEST EUS-FNA (WEST group) with four punctures with 19 or 22 G needles. As a historical control, 23 type 1 AIP patients who underwent no fewer than four punctures with 19 or 22 G needles were selected (DRY group). Patient characteristics and histological findings were compared between the two groups.

Results: Three histopathological items of the International Consensus Diagnostic Criteria were significantly greater in the WEST group than the DRY group (n (%), lymphoplasmacytic infiltrate without granulocytic infiltration: 9 (81.8) vs 6 (26.1), p value=0.003, storiform fibrosis: 5 (45.5.) vs 1 (4.3), p value=0.008, abundant (>10 cells/HPF) IgG4-positive cells: 7 (63.6) vs 5 (21.7), p value=0.026). Level 1 or level 2 histopathological findings were observed more in the WEST group than in the DRY group (n (%) 8 (72.7) vs 3 (13.0), p value=0.001).

Conclusions: WEST EUS-FNA was more useful than standard EUS-FNA for histologically diagnosing AIP.

Trial registration: UMIN000019768

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Background

Autoimmune pancreatitis (AIP) was defined by Yoshida et al. [1] as pancreatitis caused by pancreatic swelling, irregular narrowing of the pancreatic duct, or infiltration and fibrillation of the lymphocytes, with such events related to autoimmune mechanisms. Hamano et al. [2] reported increased levels of serum IgG4 in patients with AIP. The 2010 International Consensus Diagnostic Criteria (ICDC) for AIP defined pancreatitis as “type 1” when there was elevated serum IgG4 and other organs were involved; lymphoplasmacytic sclerosing pancreatitis (LPSP) was the most prominent histological characteristic [3]. Four items were mentioned as being important for diagnosing LPSP, namely, periductal lymphoplasmacytic infiltrate without granulocytic infiltration, obliterative phlebitis, storiform fibrosis, and abundant (> 10 cells/HPF) IgG4-positive cells. If three of those four items are observed, that is defined as level 1 histological findings. If two items are observed, it is defined as level 2 histological findings.

AIP can be diagnosed by imaging and elevated serum levels of IgG4 or by other methods. However, histological diagnosis of AIP requires level 1 pancreatic histological findings. Apart from surgical biopsy, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the only method used to histologically

diagnose AIP. Nevertheless, it is very difficult to obtain an adequate specimen [4–6]. In the ICDC, EUS-FNA was recommended for ruling out malignancy before a diagnostic steroid trial [3]. In fact, Sugimoto et al. [7]reported that the clinical characteristics of pancreatic cancer differed from those of AIP and that EUS-FNA could be used to rule out malignancy in AIP patients.

However, recently, with a wet suction technique (WEST) of EUS-FNA, more adequate specimens were reported to be obtained than by the conventional method of EUS-FNA [8]. Therefore, we hypothesized that more AIP patients could be histopathologically diagnosed by WEST EUS-FNA.

Methods

Study design and ethics

This study was a single arm prospective study intended to clarify the efficacy of WEST EUS-FNA for diagnosing type 1 AIP. This study was performed at Fukushima Medical University. This study was approved by the Institutional Review Board of Fukushima Medical University. All patients agreed to participate in this study. This trial was registered in UMIN (ID: 000019768).

Patients

We recruited 11 patients who were suspected to have type 1 AIP at Fukushima Medical University between February 2016 and August 2018. They showed diffuse or focal pancreatic swelling on abdominal enhanced CT with elevated serum IgG4 levels (> 135 mg/dl). To prove the efficacy of WEST EUS-FNA for diagnosing AIP, historical controls were used. These historical controls included 42 AIP patients who were diagnosed at Fukushima Medical University before this study began. Among these 42 patients, 35 had elevated IgG4 levels (≧ 135 mg/dl). In this study, WEST EUS-FNA was performed with four punctures using 19 or 22 G needles. The gauge of needle used during EUS-FNA was randomly chosen by each endoscopist. Therefore, 23 type 1 AIP patients who underwent procedures with no fewer than four punctures with 19 or 22 G needles were selected as the control group (Figure 1). The targets of this study were termed the WEST group. On the other hand, historical controls were termed the DRY group. The targets and historical controls were all diagnosed with type 1 AIP according to the ICDC.

The method of WEST EUS-FNA

All procedures were performed under the guidance of a professional endoscopist who was well versed in EUS-FNA (TT) and who had performed no less than 1500 EUS-FNA procedures. After a patient was well sedated with intravenous midazolam, an echoendoscope was inserted. The swollen pancreas was viewed on the monitor, and the vessels along the puncture line were confirmed by color doppler echo imaging. Then, the puncture needle was prepared for WEST. The WEST EUS-FNA was performed according to the

methods in a previous report by Attam et al [8]. First, the stylet was removed from the needle, and saline solution was injected into the needle (Figure 2A). After a suction syringe was loaded to 20 ml of suction in a locked position, the syringe was set at the edge of the needle without an extension tube (Figure 2B). The needle was inserted into the target lesion, and the lock of the suction syringe was opened. Saline solution flowed into the suction syringe because of the negative pressure (Figures 2C and D), and the needle was moved back and forth 20 times per puncture. The punctures were performed 4 times according to the instructions in the past report by Suzuki et al [9].

In the WEST group, the echoendoscope used was GF-UC240AL–5 or GF-UCT260 (Olympus Medical Systems, Tokyo, Japan). The ultrasonography equipment was EU-ME2 (Olympus Medical Systems). The biopsy needles were Expect 22 or 19 G (Boston Scientific, MA, USA). The biopsy needles were randomly selected by the endoscopists.

In the DRY group, the echoendoscope used was GF-UC240AL–5, GF-UCT240AL–5, or GF-UCT260 (Olympus Medical Systems, Tokyo, Japan). The ultrasonography equipment used was EU-ME1, EU-ME2 (Olympus Medical Systems) or SSD5000 (ALOKA, Tokyo, Japan). The biopsy needles were Expect 22 or 19 G (Boston Scientific, MA, USA); EZ Shot 22 G or NA11J-KB (Olympus Medical System); or EchoTip 19, 22, EchoTip ProCore 19 G, or Quick-Core 19 G (Cook Medical Inc., NC, USA).

Examination items

The primary endpoint was the level 1 or level 2 histopathological finding according to the ICDC [3]. Biopsy of the pancreatic duct by EUS-FNA is difficult; therefore, an item on the ICDC such as “periductal lymphoplasmacytic infiltrate without granulocytic infiltration” was replaced with “Lymphoplasmacytic infiltrate without granulocytic infiltration” according to the Clinical Diagnostic Criteria for AIP 2011 of Japan [10]. The secondary outcomes were each of the four items involved in the ICDC histopathological findings, namely, lymphoplasmacytic infiltrate without granulocytic infiltration, obliterative phlebitis, storiform fibrosis, and abundant (> 10 cells/HPF) IgG4-positive cells).

Patient characteristics (age, sex, type of pancreatic swelling, serum level of IgG4), items related to EUS-FNA (19 or 22 G needle, number of needle passes, histology, or adverse events), primary outcome and secondary outcomes were compared between the WEST group and the DRY group.

Sample size

The results of conventional EUS-FNA for AIP type 1 patients in our hospital indicated that level 1 or level 2 histopathological findings were observed in 13% (3/23) of patients. The results of WEST EUS-FNA were expected to be 60%, which was better than a previous multicenter study [11]. Eleven patients were needed in this study for an α error of 0.05 and statistical power of 0.8.

Statistical analysis

Age was compared by Student's t test. Serum IgG4 level and the number of needle passes were compared using the Mann-Whitney U test. Nominal variables were compared by Fisher's exact test. A *p* value <0.05 was defined as statistically significant. All statistical analyses were performed using the EZR platform (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander that was designed to perform functions that are frequently used in biostatistics [12].

Results

Patient characteristics were not significantly different between the WEST and DRY groups except for sex (Table 1). Females were significantly more common in the WEST group than in the DRY group (male/female, WEST group 6/5, DRY group 21/2, *p* value = 0.024).

Regarding the comparison of procedures and results related to EUS-FNA, several items were significantly different between the two groups (Table 2). The number of needle passes was significantly lower in the WEST group than in the DRY group (median (range), 4 (4–4) vs 5, [4–9] *p* value < 0.001). In terms of the histopathological findings according to the ICDC, three items were observed to be significantly greater in the WEST group than in the DRY group (n (%), lymphoplasmacytic infiltrate without granulocytic infiltration: 9 (81.8) VS 6 (26.1), *p* value = 0.003, storiform fibrosis: 5 (45.5.) vs 1 (4.3), *p* value = 0.008, abundant (> 10 cells/HPF) IgG4-positive cells: 7 (63.6) vs 5 (21.7), *p* value = 0.026). Level 1 histopathological findings were observed more in the WEST group than in the DRY group (n (%), 4 (36.4) vs 1 (4.3), *p* value = 0.029). Level 1 or level 2 histopathological findings were observed more often in the WEST group than in the DRY group (n (%) 8 (72.7) vs 3 (13.0), *p* value = 0.001). Adverse events were not observed in either group.

In Figure 3, a representative case of a patient diagnosed with AIP by WEST EUS-FNA is shown.

Discussion

In this study, we investigated the efficacy of WEST EUS-FNA for diagnosing AIP. Three histopathological items according to the ICDC were observed more frequently in the WEST group than in the DRY group. Level 1 histopathological findings and level 2 histopathological findings were observed more in the WEST group than in the DRY group.

Regarding EUS-FNA for AIP, the results of procedures performed with standard needles and more complex needles were reported. Regarding previous reports using standard needles, Iwashita et al. [13]reported that performing EUS-FNA with a 19 G needle resulted in a diagnosis of AIP in 17 of 44 cases. The reports using a 22 G needle are described below. Ishikawa et al.[4]diagnosed LPSP in 9 of 47 AIP patients. Imai et al. [5]could not histopathologically diagnose AIP. Interestingly, a multicenter study found that the

diagnosability of AIP by EUS-FNA was poor [6], and another multicenter study reported that 57.7% of patients were diagnosed with level 2 or higher based on the histopathological findings [14].

Second, some previous reports involved more complex needles. Mizuno et al. [15]reported that 45.5% of AIP patients were diagnosed with LPSP using EUS Tru-Cut biopsy (EUS-TCB) needles. In a report by Kanno et al.[11], level 1 and 2 histological findings were observed in 56% and 24% of AIP patients, respectively, by EUS-FNA using 22 G automated spring-loaded PowerShot needles. The histopathological diagnosability of EUS-FNA for AIP was improved by needle choice; however, it was difficult to statistically compare the sensitivity and accuracy between the standard needles and more complex needles.

On the other hand, the histopathological accuracy by WEST EUS-FNA was statistically superior to that by the standard EUS-FNA method or EUS-TCB in this study (seven historical control cases underwent EUS-TCB). Moreover, the positive result of this study was achieved with standard needles. Though the reasons underlying the increased size of the specimens collected by WEST are not clear, it is thought that the saline solution coating the lining of the needle leads to better transmission of the applied suction or that the saline solution acts as a stylet, reducing the contamination from GI tissue [8].

Recently, the efficacy of EUS-FNA using a 22 G SharkCore needle was reported for the diagnosis of AIP [16, 17]. By the development of puncture methods such as WEST or special puncture needles, the diagnosability of AIP by EUS-FNA will be improved.

This study had some limitations. First, this study was performed with a small sample size in a single institution. Second, historical controls were used as a control group. In the future, a multicenter randomized controlled trial (RCT) with more cases is needed. However, AIP patients are rare, rending an RCT difficult to conduct. Third, we used EUS-TCB needles such as ProCore 19 G or Quick-Core 19 G (Cook Medical Inc., NC, USA) in the historical control patients. Although these needles have been reported to increase the yield of samples [18, 19], these needles were not used in the WEST group. Therefore, they were not a factor in the superiority of the WEST technique.

Conclusion

WEST EUS-FNA was more useful for histologically diagnosing AIP than was standard EUS-FNA.

Abbreviations

AIP: autoimmune pancreatitis; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; WEST: wet suction technique; ICDC: International Consensus Diagnostic Criteria; LPSP: lymphoplasmacytic sclerosing pancreatitis; EUS-TCB: EUS Tru-Cut biopsy; RCT: randomized controlled trial.

Declarations

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Author Contribution

M. S. wrote the paper and designed and performed the research and laboratory work. T. T. wrote the paper and designed and oversaw the research. R. S., N. K., H. A., T. H., K. W., J. N., H. K., M. T., Y. S., H. I., M. H., and T. K. provided clinical advice. T. H. supervised the report. K. N. performed the pathological diagnoses. H. O. supervised the report and the writing of the paper. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All patients gave written informed consent. The study protocol was reviewed and approved by the Institutional Review Board of Fukushima Medical University (Number 2527).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1.Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 1995;40(7):1561–8.

2.Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732–8.

3.Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352–8.

4.Ishikawa T, Itoh A, Kawashima H, Ohno E, Matsubara H, Itoh Y, et al. Endoscopic ultrasound-guided fine needle aspiration in the differentiation of type 1 and type 2 autoimmune pancreatitis. World J Gastroenterol. 2012;18(29):3883–8.

5.Imai K, Matsubayashi H, Fukutomi A, Uesaka K, Sasaki K, Ono H. Endoscopic ultrasonography-guided fine needle aspiration biopsy using 22-gauge needle in diagnosis of autoimmune pancreatitis. Dig Liver Dis. 2011;43(11):869–74.

6.Morishima T, Kawashima H, Ohno E, Yamamura T, Funasaka K, Nakamura M, et al. Prospective multicenter study on the usefulness of EUS-guided FNA biopsy for the diagnosis of autoimmune pancreatitis. Gastrointest Endosc. 2016;84(2):241–8.

7.Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Watanabe K, et al. Endoscopic Ultrasonography-Guided Fine Needle Aspiration Can Be Used to Rule Out Malignancy in Autoimmune Pancreatitis Patients. J Ultrasound Med. 2017;36(11):2237–44.

8.Attam R, Arain MA, Bloechl SJ, Trikudanathan G, Munigala S, Bakman Y, et al. “Wet suction technique (WEST)“: a novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. Gastrointest Endosc. 2015;81(6):1401–7.

9.Suzuki R, Irisawa A, Bhutani MS, Hikichi T, Takagi T, Sato A, et al. Prospective evaluation of the optimal number of 25-gauge needle passes for endoscopic ultrasound-guided fine-needle aspiration biopsy of solid pancreatic lesions in the absence of an onsite cytopathologist. Dig Endosc. 2012;24(6):452–6.

10.Naitoh I, Nakazawa T, Hayashi K, Miyabe K, Shimizu S, Kondo H, et al. Clinical evaluation of international consensus diagnostic criteria for type 1 autoimmune pancreatitis in comparison with Japanese diagnostic criteria 2011. Pancreas. 2013;42(8):1238–44.

11.Kanno A, Masamune A, Fujishima F, Iwashita T, Kodama Y, Katanuma A, et al. Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study. Gastrointest Endosc. 2016;84(5):797–804 e1.

12.Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452–8.

13.Iwashita T, Yasuda I, Doi S, Ando N, Nakashima M, Adachi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol. 2012;10(3):316–22.

14.Kanno A, Ishida K, Hamada S, Fujishima F, Unno J, Kume K, et al. Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc. 2012;76(3):594–602.

15.Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol. 2009;44(7):742–50.

16.Runge TM, Hart PA, Sasatomi E, Baron TH. Diagnosis of autoimmune pancreatitis using new, flexible EUS core biopsy needles: report of 2 cases. Gastrointest Endosc. 2017;85(6):1311–2.

17.Bhattacharya A, Cruise M, Chahal P. Endoscopic ultrasound guided 22 gauge core needle biopsy for the diagnosis of Autoimmune pancreatitis. Pancreatology. 2018;18(2):168–9.

18.Thomas T, Kaye PV, Ragunath K, Aithal G. Efficacy, safety, and predictive factors for a positive yield of EUS-guided trucut biopsy: a large tertiary referral center experience. Am J Gastroenterol. 2009;104(3):584–91.

19.Mukai S, Itoi T, Yamaguchi H, Sofuni A, Tsuchiya T, Tanaka R, et al. A retrospective histological comparison of EUS-guided fine-needle biopsy using a novel franseen needle and a conventional end-cut type needle. Endosc Ultrasound. 2018:doi: 10.4103/eus.eus_11_18.

Tables

Table 1 Comparisons of patient characteristics between the WEST group and the DRY group.

	WEST group (n = 11)	DRY group (n = 23)	*P* value
Age (years, means ± SD)	62.9 ± 12.4	61.0 ± 9.6	0.626
Sex, male/female	6/5	21/2	0.024
Pancreatic swelling type, diffuse/focal	6/5	11/12	1.0
Serum IgG4 level (mg/dl, median (range))	568 (177-2100)	447 (149-1480)	0.663

Table 2 Comparisons of the procedures and results between WEST and DRY techniques for EUS-FNA.

	WEST group (n = 11)	DRY group (n = 23)	*P* value
EUS-FNA needle (19 G/22 G)	1/10	8/15	0.214
Number of needle passes (median (range))	4 (4-4)	5 (4-9)	< 0.001
Histopathological findings			
Lymphoplasmacytic infiltrate without granulocytic infiltration, n (%)	9 (81.8)	6 (26.1)	0.003
Obliterative phlebitis, n (%)	2 (18.2)	0 (0)	0.098
Storiform fibrosis, n (%)	5 (45.5)	1 (4.3)	0.008
Abundant (> 10 cells/HPF) IgG4 positive cells, n (%)	7 (63.6)	5 (21.7)	0.026
Level 1 histopathological findings, n (%)	4 (36.4)	1 (4.3)	0.029
Level 1 or level 2 histopathological findings, n (%)	8 (72.7)	3 (13.0)	0.001
Adverse events, n (%)	0 (0)	0 (0)	

Figures

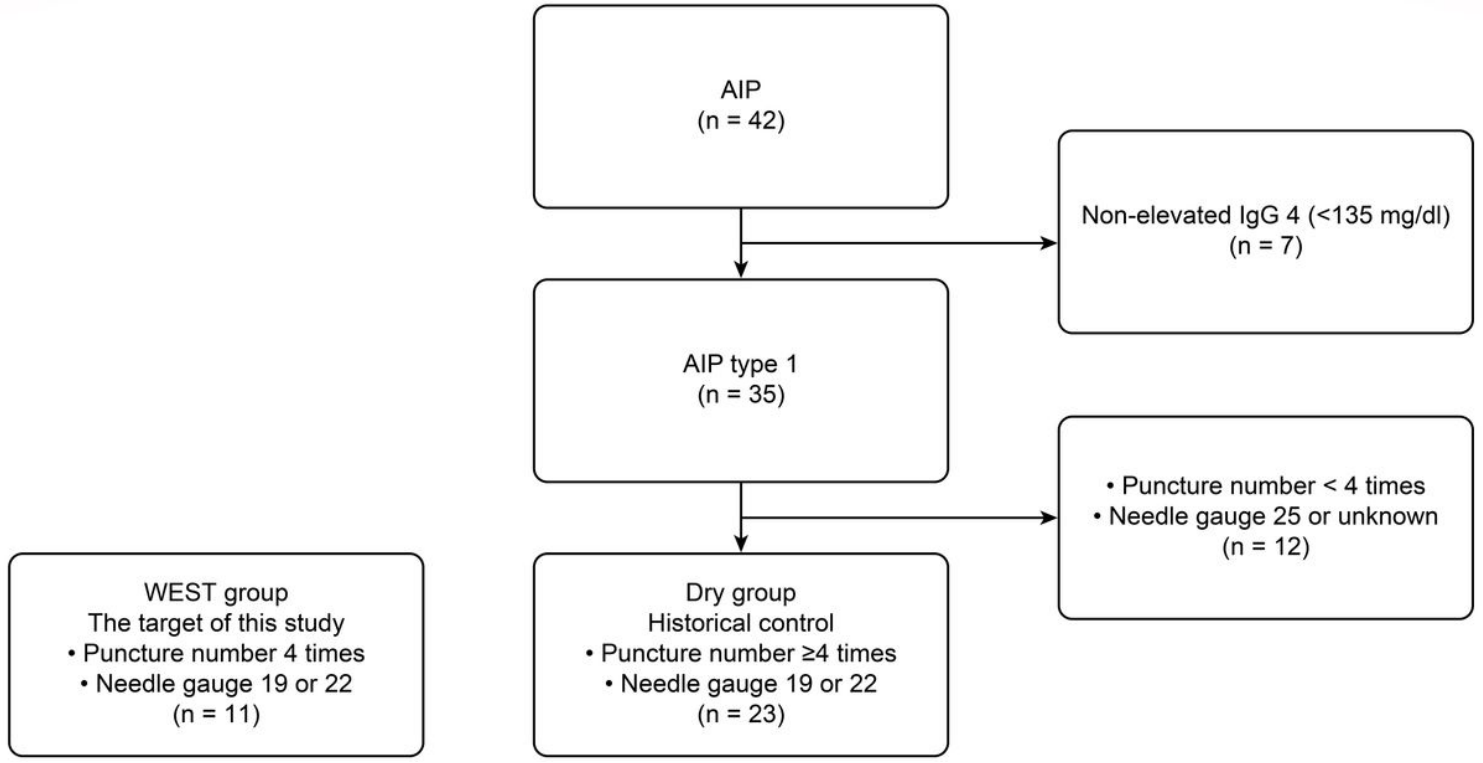

Figure 1

Target patients in this study and historical controls. The historical controls were 23 AIP patients who underwent EUS-FNA with no fewer than 4 punctures by 19 or 22 G needles. The target subjects in this study underwent wet suction technique (WEST) EUS-FNA. The historical controls were termed the DRY group.

Figure 2

The wet suction technique method of EUS-FNA. A, After the stylet of the needle was withdrawn, saline solution was injected into the needle. B, A locked suction syringe with 20 ml of negative pressure was set at the edge of the needle. C, The needle was used to puncture the target lesion, and D, then, the lock on the syringe was opened. Saline solution flowed into the suction syringe due to the negative pressure.

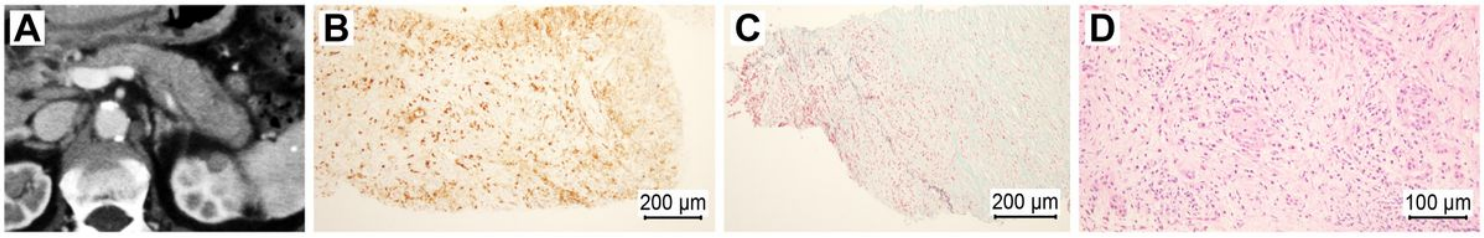

Figure 3

The case of a patient with autoimmune pancreatitis diagnosed by wet suction technique (WEST) EUS-FNA. A, The pancreatic tail is swollen with a capsule-like rim sign as observed on abdominal CT. B, Specimen acquired by WEST EUS-FNA (HE x200): IgG4-positive plasma cells were observed. C, Specimen acquired by WEST EUS-FNA (EM x200): obliterative phlebitis was observed. D, Specimen acquired by WEST EUS-FNA (HE x400): fibrosis with a storiform pattern of plasma cells was observed.

Supplementary Files

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- CONSORT2010Checklist2019.9.11.pdf