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ORIGINAL ARTICLE

Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria

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Abstract Autoimmune pancreatitis (AIP) has been established as a special entity of chronic pancreatitis (CP). However, its clinical distinction from pancreatic cancer and other types of CP is still difficult. The aim of this study was to evaluate the efficacy of pancreatic core needle biopsy for the diagnosis of AIP. In 44 core needle biopsy specimens, we assessed the following microscopic features: granulocytic epithelial lesions (GELs), more than ten IgG4-positive plasma cells/HPF, more than ten eosinophilic granulocytes/HPF, cellular fibrosis with inflammation, lymphoplasmacytic infiltration, and venulitis. All biopsies that showed four or more of the six features (22 of 44) were obtained from 21 of 26 patients whose clinical diagnosis and follow-up were consistent with AIP. All non-AIP CP patients (n=14) showed three or less than three of the features in their biopsies. GELs were only observed in biopsy specimens from AIP patients. In conclusion, our data indicate that the six criteria we applied were able to recognize AIP in 76% of biopsy specimens using a cut-off level of four. When the specimens that revealed only three features but showed GELs were added, the sensitivity rose to 86%. Pancreatic core needle biopsy can therefore make a significant contribution to the diagnosis of AIP.

Keywords Autoimmune pancreatitis · Diagnosis · Pancreatic biopsy · Granulocytic epithelial lesion · IgG4

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Introduction

Autoimmune pancreatitis (AIP) has been established as a special entity of chronic pancreatitis (CP) that is responsive to steroid treatment. However, its clinical distinction from pancreatic cancer and other entities of CP is difficult because of the similarity of these diseases and the lack of a reliable marker of AIP [1].

According to the criteria of the Japan Pancreas Society, AIP can be diagnosed on the basis of imaging findings together with *either* laboratory findings (elevated levels of serum gammaglobulin and/or IgG or presence of autoantibodies) or histopathological findings (marked lymphoplasmacytic infiltration and fibrosis) [2, 3]. The criteria of the Korean working group include imaging, laboratory findings, histological findings, and response to steroid treatment. For the diagnosis of AIP, the imaging criterion is required along with any one of the other three features [4]. The criteria of the Mayo Clinic (HISORt criteria) are histopathology (marked lymphoplasmacytic infiltration and infiltration of more than ten IgG4-positive plasma cells per high power field (HPF)), imaging, serology, presence of other organ involvement, and response to steroid treatment [5]. In contrast to the other working groups, the Mayo Clinic group already diagnoses AIP if only the histology is positive. The fact that with the HISORt criteria AIP can be diagnosed on the basis of typical histopathological features alone gives pancreatic core needle biopsy a special significance. However, the role of pancreatic

core needle biopsy in the diagnosis of AIP is still controversial because the available data are sparse and its usefulness is not generally accepted. In a previous study, we found diagnostically relevant lesions in three of four core needle biopsy specimens [6]. In other studies, the effectiveness of core needle biopsy in diagnosing AIP was less significant [5, 7, 8]. This also held for fine-needle aspiration cytology, which was even thought to be barely suggestive of or even inadequate for the diagnosis of AIP [9–13].

We studied 44 pancreatic core needle biopsy specimens from 40 patients, which were obtained to establish the diagnosis of AIP or pancreatic cancer or alcoholic chronic pancreatitis. Most of the histopathological features we used for the diagnosis of AIP were recently established in resection specimens [6, 13–15]. Using six microscopic features of AIP, we wanted to know how many of these features are needed in a biopsy specimen to enable the diagnosis of AIP. In addition, we attempted to identify features whose presence in a biopsy enables the diagnosis of AIP also in those cases that lack significant infiltration with IgG4-positive plasma cells.

Materials and methods

Core needle biopsies

Forty-four pancreatic core needle biopsy specimens with CP were reviewed from 40 patients whose history, symptoms, and imaging criteria were suggestive of either AIP, pancreatic cancer, or alcoholic CP. Thirty-one specimens were retrieved from the consultation files of the Department of Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Germany, and 13 from the files of the Department of Pathology, Aalborg Hospital, Denmark. The core needle biopsy specimens were obtained by transabdominal ultrasound (US)-guided core needle biopsy (n=33), intraoperative core needle biopsy (n=7), endoscopic US-guided core needle biopsy (n=3), and transabdominal computed-tomography-guided core needle biopsy (n=1). The biopsies were obtained from lesions localized in the pancreatic head (n=37), the pancreatic head–body (n=3), the pancreatic body (n=1), the pancreatic tail (n=2), and the entire pancreas (n=1). The mean length of the biopsy cylinders (with a width of approximately 1.2 mm) was 16.5 mm (range 4 to 48 mm). All biopsy specimens were fixed in formalin and embedded in paraffin. The sections were stained with hematoxylin and eosin. The mean number of slides evaluated per biopsy was 2.1 (range 1 to 11).

Immunohistochemistry

One slide from every biopsy specimen was immunostained for IgG4 using a monoclonal mouse antibody (The Binding Site, Birmingham, UK, clone HP6025) and the EnVision staining technique (Dako A/S, Glostrup, Denmark) with a working dilution of 1:100. The slides were first pretreated by boiling in citrate-buffered saline for 3.5 min. Endogenous phosphatase activity was blocked with 1 mM levamisole in the substrate solution. Normal tonsillar tissue served as controls.

Patients

Clinical information was obtained from either the medical and surgical records of the patients, from a questionnaire answered by the clinician and/or pathologist in charge, and/or by direct consultation with the clinician in charge.

During follow-up, 26 of the 40 patients fulfilled the criteria of the Mayo Clinic (HISORt criteria) and were diagnosed with AIP (16 men and ten women; mean age 51.2 years; range 10 to 79 years; Table 1) [5]. None of these patients developed malignant disease or had evidence of pancreatic pseudocysts or calculi. The mean follow-up period was 24 months, range 3 to 48 months. Eight of the 26 patients had other autoimmune-related diseases. Nineteen of the 26 patients were later treated with steroids, 18 of whom showed a clear-cut response. IgG4 serum levels were available in 12 patients (they were elevated in three and normal in nine).

Fourteen of the 40 patients (seven men and seven women; mean age 53.1 years; range 29 to 72 years) had non-AIP CP. These patients were diagnosed with alcoholic CP (n=7) or tumor-associated, obstructive CP (n=7; Table 2). In none of the seven tumor-associated core needle biopsy specimens, there was malignant cell infiltration. They derived from the margin of the tumor showing only fibrosis and inflammation. The mean follow-up period was 22.9 months, range 4 to 48 months.

Histopathological examination

Each core needle biopsy was evaluated for the presence of six microscopic AIP features [6, 13, 15–19]:

1. Granulocytic epithelial lesion (GEL): Focal disruption and destruction of the duct epithelium resulting from invasion of neutrophilic granulocytes into the lumen of medium- or large-sized interlobular ducts and/or invasion of neutrophilic granulocytes into the lumen of three or more small intralobular ducts together with neutrophilic infiltration between acinar cells (Fig. 1a).
2. IgG4-positive plasma cell infiltration: more than ten IgG4-positive plasma cells in at least one HPF at a magnification of ×400 (0.2 mm^2; Fig. 1b).
3. Eosinophilic infiltration: more than ten eosinophilic granulocytes in at least one HPF at a magnification of ×400 (0.2 mm^2; Fig. 2a).

Table 1 Clinicopathological features of 26 patients whose pancreatic core needle biopsy specimen was suggestive of AIP and whose follow-up was consistent with this diagnosis

CASE no.	Age	Sex	Other autoimmune disease	Total no. of AIP features in the specimen	GELs present in the specimen	>10 IgG4-positive plasma cells/HPF in the specimen	Serum IgG4	Steroid therapy
1	62	M	No	3	No	No	ND	ND
2	10	M	Chronic glomerulonephritis, Evan's syndrome	4	Yes	No	N	EF
3	46	M	No	5	No	Yes	ND	EF
4	50	M	Chronic parotitis	4	No	No	ND	EF
5	40	F	No	4	No	Yes	ND	EF
6	73	F	No	4	Yes	No	N	EF
7	46	F	No	5	Yes	No	ND	ND
8	75	M	No	4	No	Yes	E	NCE
9	64	M	No	4	No	Yes	ND	ND
10	72	F	No	4	Yes	No	ND	EF
11	51	M	Inflammatory subcutaneous pseudotumor	5	Yes	No	ND	ND
12	59	M	No	3	No	No	E	EF
13a[a]	36	F	No	4	Yes	No	N	EF
13b[a]	36	F	No	5	Yes	No	N	EF
14	32	M	No	3	Yes	No	N	EF
15	26	M	Suspected autoimmune hepatitis	6	Yes	Yes	ND	EF
16	53	M	Ulcerative colitis, Hashimoto's thyroiditis	5	No	Yes	N	EF
17	58	M	No	3	No	Yes	E	EF
18	79	F	No	4	No	Yes	N	EF
19	53	M	No	5	Yes	No	N	EF
20	19	F	No	3	Yes	No	N	EF
21	54	F	Hashimoto's thyroiditis	4	Yes	No	N	EF
22a[a]	57	M	No	3	No	Yes	ND	ND
22b[a]	57	M	No	5	No	Yes	ND	ND
23a[a]	38	M	Intrahepatic cholangiogram with PSC-like changes	3	Yes	No	ND	EF
23b[a]	38	M	Intrahepatic cholangiogram with PSC-like changes	4	Yes	No	ND	EF
24	60	F	Wegener's granulomatosis	4	No	Yes	ND	EF
25	53	F	No	4	No	Yes	ND	ND
26	65	M	No	4	No	No	ND	ND

F female, *M* male, *PSC* primary sclerosing cholangitis, *E* elevated, *N* normal, *ND* not determined, *EF* effective, *NCE* no clear-cut effect

[a] Patients from whom two biopsy specimens were obtained at an interval of several weeks.

4. Cellular fibrosis with inflammation: Fibrotic tissue usually arranged in a perilobular pattern and intermingled with myofibroblasts and at least 20 lymphocytes and/or plasma cells, if present in at least one field of view at a magnification of ×200 (0.6 mm^2; Fig. 2b).
5. Lymphoplasmacytic infiltration: two patterns were distinguished, periductal lymphoplasmacytic infiltration and diffuse infiltration. The diffuse infiltrate covered >30% of the total area of the biopsy specimen (Fig. 3a).
6. Venulitis: Dense lymphocytic infiltration in the tissue surrounding one or several venules, often accompanied by vessel obliteration and endothelial damage (Fig. 3b).

Statistical analysis

Statistical analysis was carried out using SigmaStat 3.0. Results obtained in core biopsy specimens from AIP patients and core biopsy specimens from patients diagnosed

Table 2 Clinicopathological features of 14 patients whose pancreatic core needle biopsy specimen met three or less features for the diagnosis of autoimmune pancreatitis and whose follow-up was consistent with the diagnosis of either alcoholic chronic pancreatitis (CP) or tumor-associated obstructive CP

CASE no.	Age	Sex	No. of AIP features observed per specimen	Main clinical features	Treatment	Diagnosis
1	50	M	2	Intake of >80 g alcohol/day for at least 10 years/recurrent acute bursts of CP	Conservative	Alcoholic CP
2[a]	57	M	1	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP	Conservative	Alcoholic CP
3	29	M	0	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP	Cholecystectomy/stenting of bile duct/pain treatment with opioids	Alcoholic CP
4	48	F	0	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP	Percutaneous drainage of pseudocysts/ gastrocystostomy/oral antidiabetics	Alcoholic CP
5	46	F	0	Intake of >80 g alcohol/day for several years/ERCP with short stenoses of the main pancreatic duct	Subcutaneous insulin/choledocho-duodenostomy	Alcoholic CP
6a[b]	47	F	3	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP/abdominal US: intrapancreatic calcifications	Percutaneous drainage of pseudocysts/ subcutaneous insulin/enzyme substitution/ pain treatment with opioids	Alcoholic CP
6b[b]	50	F	2	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP/abdominal US: intrapancreatic calcifications	Percutaneous drainage of pseudocysts/ subcutaneous insulin/enzyme substitution/ pain treatment with opioids	Alcoholic CP
7	51	F	3	Intake of >80 g alcohol/day for several years/recurrent acute bursts of CP/abdominal US: pseudocysts	Pain treatment with opioids	Alcoholic CP
8	60	M	3	Pancreatic mucinous cystadenoma[c]	Whipple resection/reoperation for intraabdominal abscesses with poor overall outcome	Obstructive CP
9	53	F	2	Metastasizing pancreatic ductal adenocarcinoma	Palliation	Obstructive CP
10	71	F	1	Metastasizing pancreatic ductal adenocarcinoma	Palliation	Obstructive CP
11	72	M	0	Metastasizing pancreatic ductal adenocarcinoma[c]	Gastroenterostomy/palliation	Obstructive CP
12	56	F	0	Pancreatic solid-pseudopapillary tumor[c]	Whipple resection/good outcome	Obstructive CP
13	38	M	3	Metastasizing pancreatic ductal adenocarcinoma	Chemotherapy	Obstructive CP
14[a]	69	M	2	Advanced pancreatic ductal adenocarcinoma w. infiltration of superior mesenteric vein[c]	Cholangio- and gastrojejunostomy/palliation	Obstructive CP

ERCP endoscopic retrograde cholangio-pancreaticography, *US* ultrasound

[a] Specimens showing IgG4 positivity (more than ten IgG4-positive plasma cells/HPF) as one criterion

[b] Patient from whom two biopsy specimens were obtained at an interval of 3 years

[c] Final diagnosis in resection specimen

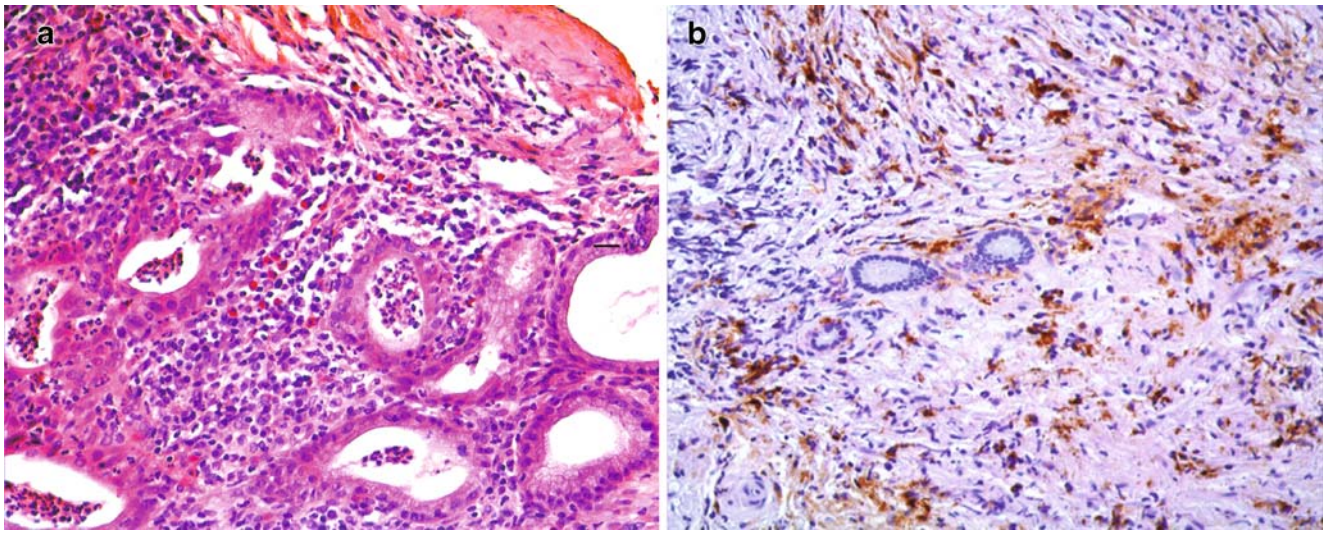

Fig. 1 Pancreatic core needle biopsy specimens from AIP patients. **a** Granulocytic epithelial lesions (hematoxylin and eosin, ×200). **b** Increased numbers of IgG4 immunopositive plasma cells (×200)

with other types of CP were evaluated using Fisher's exact test (Table 3) and the χ^2 test for tabulated data (Table 4). The level of significance was set at $p<0.05$.

Results

In 22 of the 44 pancreatic core biopsy specimens, four or more of the six features were present Table 3. There was no clear correlation between the length of the biopsy cylinder and the number of features observed in the tissue. The 22 specimens were obtained from 21 of 26 patients whose clinical diagnosis was consistent with AIP (Table 1). In the remaining 22 of 44 specimens, 11 showed three features. Seven of these were from seven of 26 patients with the clinical diagnosis of AIP. Only four of 11 specimens with three features were associated with non-AIP CP (Table 2). All biopsy specimens with two or fewer features were from non-AIP CP patients (Table 3). Among the 29 biopsy specimens from the 26 AIP patients, there were 14 biopsy specimens that revealed GELs, a feature that was not observed in any of the 15 non-AIP CP biopsy specimens (Table 1; Fig. 1a). If the three biopsy specimens that showed only three features, including GELs, were added to the 22 specimens showing four or more criteria, all of which came from 21 of 26 AIP patients, a total of 25 of 29

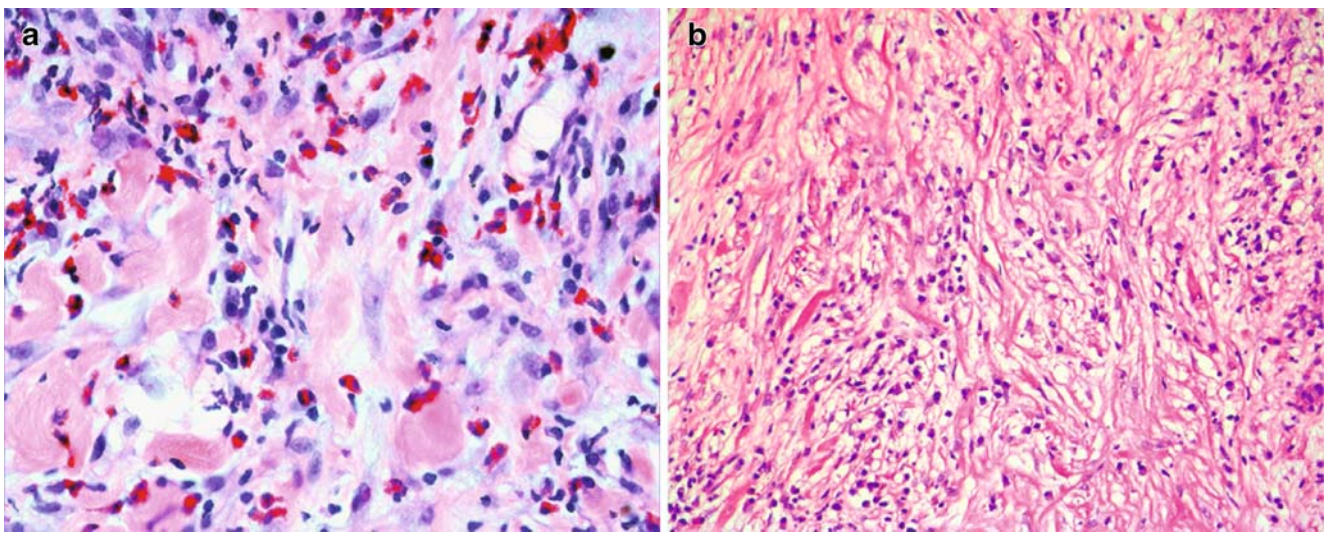

Fig. 2 Pancreatic core needle biopsy specimens from AIP patients. **a** Infiltration by eosinophilic granulocytes (hematoxylin and eosin, ×400). **b** Cellular fibrosis with an inflammatory infiltrate replacing acinar tissue (hematoxylin and eosin, ×200)

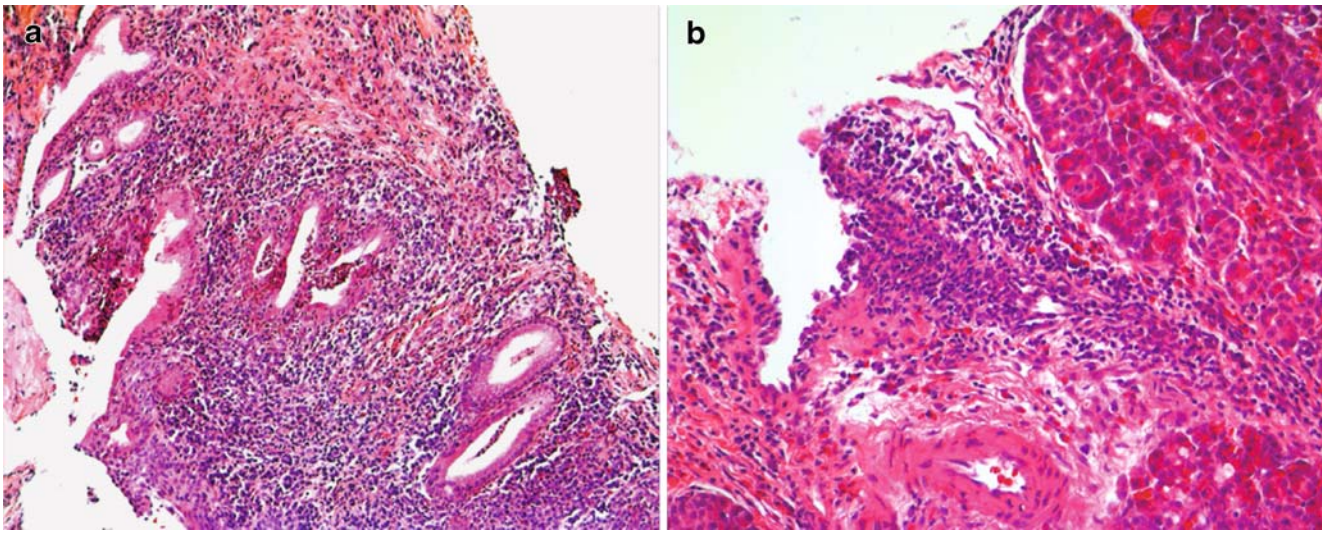

Fig. 3 Pancreatic core needle biopsy specimens from AIP patients. **a** Periductal lymphoplasmacytic infiltration (hematoxylin and eosin, ×100). **b** Venulitis (hematoxylin and eosin, ×200)

(86%) biopsy specimens (from 23 of 26 AIP patients) were associated with AIP.

More than ten IgG4-positive cells were found in 14 of 44 biopsy specimens (Fig. 1b), of which 12 of 29 were from 11 of 26 AIP patients (Table 4). These 12 of 29 specimens were negative for GELs and eosinophilic granulocytes (>10/HPF), except for one case that revealed both IgG4-positive plasma cells and GELs (Table 1). Of the 17 IgG4-negative AIP specimens, on the other hand, 11 revealed positivity for eosinophils and 13 for GELs. Among the seven AIP specimens that showed only three features, five showed either GELs (three of seven) or more than ten IgG4-positive plasma cells (two of seven). In the remaining two of seven specimens, other features were present. Cellular fibrosis was found in almost all AIP specimens (28 of 29; Table 4; Fig. 2b). However, it was also found in six of 15 specimens from non-AIP CP patients (Table 4). Next in frequency were lymphoplasmacytic infiltration (27 of 29; Fig. 3a) and venulitis (19 of 29; Fig. 3b), but both features were also recorded in biopsy specimens from non-AIP CP patients, though only in a few instances (Table 4). The number of AIP features noted in the AIP core needle biopsy specimens was significantly higher than the frequency recorded in the biopsy specimens from the non-AIP CP patients ($p<0.001$).

In 11 of the 44 pancreatic core needle biopsy specimens, two or fewer of the six features were present (Tables 2 and 3). All 11 specimens were obtained from 11 of 14 patients whose clinical diagnosis was consistent with non-AIP CP. In addition, there were four specimens obtained from non-AIP CP patients that contained three of the features. Hence, none of the 15 core biopsy specimens from 14 patients diagnosed

Table 3 Number of microscopic features per specimen observed in 29 core needle biopsy specimens from 26 patients whose clinical diagnosis and follow-up were consistent with autoimmune pancreatitis (AIP) and in 15 core needle biopsy specimens from 14 patients with symptoms consistent with non-AIP chronic pancreatitis (non-AIP CP) consisting of alcoholic CP and tumor-associated, obstructive CP

Number of features per specimen	AIP	Non-AIP CP
0	0% (0/29)	33.3% (5/15)
1	0% (0/29)	13.3% (2/15)
2	0% (0/29)	26.7% (4/15)
3	24.1% (7/29)	26.7% (4/15)
4	48.3% (14/29)	0% (0/15)
5	24.1% (7/29)	0% (0/15)
6	3.5% (1/29)	0% (0/15)

Table 4 Frequency of the individual features in pancreatic core needle biopsy specimens

Feature	AIP	Non-AIP CP
Granulocytic epithelial lesion (GEL)	48.3% (14/29)	0% (0/15)
>10 IgG4 positive plasma cells/HPF	41.4% (12/29)	13.3% (2/15)
>10 eosinophilic granulocytes/HPF	62.1% (18/29)	33.3% (5/15)
Cellular fibrosis with inflammation	96.6% (28/29)	40.0% (6/15)
Lymphoplasmacytic infiltration	93.1% (27/29)	33.3% (5/15)
Venulitis	65.5% (19/29)	26.7% (4/15)

Twenty-nine specimens derived from 26 patients whose clinical diagnosis and follow-up were consistent with autoimmune pancreatitis (AIP). The remaining 15 specimens were from 14 patients with symptoms consistent with non-AIP chronic pancreatitis (non-AIP CP), consisting of alcoholic CP and tumor-associated, obstructive CP

with other types of CP showed more than three of the features or GELs (Table 3). Infiltration by more than ten IgG4-positive plasma cells/HPF was observed in two of the non-AIP CP specimens (Table 4). Cellular fibrosis and lymphoplasmacytic infiltration were seen in six of 15 and five of 15 cases, respectively. The latter feature was lacking a periductal association, but instead showing a diffuse pattern. Infiltration by more than ten eosinophilic granulocytes/HPF and changes compatible with venulitis were recorded in five of 15 and four of 15 specimens, respectively. The difference in frequency of each of the six features between AIP and non-AIP CP specimens was not statistically significant (p=0.8; Table 4).

Discussion

AIP shows distinct histopathological features that allow it to be diagnosed in pancreatic resection specimens without great difficulty and that distinguish it clearly from other types of CP and also from ductal adenocarcinoma [6, 15, 20, 21]. However, in pancreatic biopsy specimens, AIP seems to be difficult to recognize [5, 7, 9, 22]. Hence, the usefulness of pancreatic biopsy for the diagnosis of AIP has been debated [23]. In this study, we reviewed 44 pancreatic core needle biopsy specimens from 40 patients. These specimens were obtained to establish the diagnosis of AIP or alcoholic CP or pancreatic cancer. Most of the histopathological AIP features that we used in this study had been recently defined in pancreatic specimens obtained by surgical resection [6]. Our data show that with the six chosen microscopic features, we were able to recognize AIP in 76% (22 of 29) of core needle biopsy specimens from 21 of 26 patients whose clinical diagnosis was compatible with AIP, when we used a cut-off level of four features. Moreover, this figure rose to 86% (25 of 29), when we added those specimens that showed three features but contained GELs. On the other hand, all cases that showed two or fewer features came from non-AIP CP patients. The number of features observed was not clearly correlated to the length of the biopsy cylinder.

Few data exist on the usefulness of pancreatic core needle biopsy for the diagnosis of AIP. In 2004, we evaluated five wedge biopsy specimens and four core needle biopsy specimens [6]. Among the core needle biopsy specimens, one was regarded as diagnostic, two as "suggestive of AIP", and one as "inconclusive" [6]. In a series of five core needle biopsy specimens, Deshpande found only one to be diagnostic because the two histological hallmarks of AIP, periductal collar of inflammation and venulitis, were only present in this specimen [8]. Levy reported on three AIP cases for which trucut biopsy specimens were available. They were able to establish the diagnosis of AIP in two of the three cases [24]. In another study including 16 pancreatic core needle biopsy specimens deriving from AIP patients, seven showed the "full spectrum" of characteristic histological changes [5]. The largest survey of core biopsy specimens so far came from 22 Japanese AIP patients [7]. In this study, which relied on the presence of periductal lymphoplasmacytic infiltrates, cellular fibrosis and venulitis as well as the demonstration of more than ten IgG4-positive plasma cells per HPF as a diagnostic criterion of AIP, the diagnosis was only made in six of 22 (27%) cases.

In our series of 44 core needle biopsy specimens from the pancreas, 22 showed four of the six features we had chosen. All of these 22 biopsy specimens were obtained from 21 patients whose clinical diagnosis and follow-up were consistent with AIP. In contrast, the specimens obtained from patients with non-AIP CP never displayed more than three of the six features, and seven of 15 (obtained from seven patients) revealed none or only one of them. This suggests that the presence of four or more of the microscopic features that we chose is highly diagnostic of AIP in a pancreatic core needle biopsy specimen.

Among the applied features, most crucial and discriminative were the presence of GELs and the demonstration of more than ten IgG4-positive plasma cells per HPF (Table 4). GELs were not noted in non-AIP CP cases, suggesting that GELs can be regarded as diagnostic of AIP. Apart from the AIP cases, more than ten IgG4-positive plasma cells were also seen in two of 15 non-AIP CP cases, implying that the abundance of IgG4-positive plasma cells is suggestive of, but not specific to, AIP. Although these two features, the presence of GELs and the abundance of IgG4-positive plasma cells, play a crucial role in the diagnosis of AIP, they also have their limitations in view of the two types of AIP that can be currently distinguished. As we and others have shown, GELs and IgG4 positivity are features that may distinguish two subgroups of AIP [6, 25, 26]. One subgroup displays GELs and seems to lack increased numbers of IgG4-positive plasma cells in the pancreas and probably also elevated serum IgG4 levels. This AIP subtype has also been called "ductocentric AIP" [27] or "idiopathic duct destructive pancreatitis" [25]. In our series of resection specimens, it accounted for almost 45% of the AIP cases [6]. In the present study, 13 of 29 (45%) AIP core needle biopsies from 11 of 26 patients were IgG4−/GEL+, while one of 29 AIP biopsies from ten of 26 patients were IgG4+/GEL+, and 11 of 29 AIP biopsies were IgG4+/GEL−. Importantly, we took into account GELs not only when present in medium- and large-sized interlobular ducts but also when seen in small intralobular ducts.

The second subtype, which was found to be GEL negative, appears to correspond to the AIP subtype that has been called "lymphoplasmacytic sclerosing pancreatitis"

[25] or "lobulocentric AIP" [27]. This subtype seems to present with abundant IgG4-positive plasma cells within the lymphoplasmacytic infiltrates [26]. These data provide an explanation why in our current study almost half of the AIP specimens were IgG4 negative, but at the same time GEL positive, or vice versa. The features IgG4 positivity and GEL may therefore be complementary to each other as they appear to characterize two different subtypes of AIP. It is interesting to note that the relative frequency of the two AIP subtypes in Europe and the US seems to differ from that in East Asia. While in Europe each subtype can be expected in about 40–50% of the cases (in our present biopsy series they amount to 38% and 45%, respectively), the GEL-positive AIP subtype seems to be rare in East Asia [1, 28–35].

Because the presence of GELs seems to be specific to one subtype of AIP, a diagnosis of AIP can be made if GELs are recognized in a biopsy specimen, regardless of the number of other features found. Among the microscopic features that were less discriminative were the demonstration of a lymphoplasmacytic infiltration, cellular perilobular fibrosis with inflammation, venulitis, and increased numbers of eosinophilic granulocytes because each of these changes were also identified in a small number of non-AIP CP cases. Therefore, it was necessary to set a cut-off level for the number of criteria that are required for the diagnosis of AIP in a pancreatic core needle biopsy specimen.

In conclusion, our microscopic criteria were able to recognize AIP in 22 of 29 (76%) core needle biopsy specimens from 21 of 26 AIP patients when using a cut-off level of four features and in 25 of 29 biopsies (86%) from 23 of 26 AIP patients when the GEL-positive cases were added. Core needle biopsy is therefore in many patients a useful adjunct for recognizing AIP and distinguishing it from other diseases such as alcoholic CP or obstructive CP secondary to pancreatic cancer. However, our criteria for the diagnosis of AIP in pancreatic core needle biopsies have to be tested on a larger number of patients in a prospective study before the utility of our findings can be fully appreciated.

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Conflict of interest statement The authors declare that they have no conflict of interest.

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