

Subclassification of Autoimmune Pancreatitis: A Histologic Classification With Clinical Significance

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Abstract: Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of the pancreas. Examination of pancreatic resection specimens from patients with AIP has shown that there are 2 subclasses of this disease. However, there is no widely accepted pathologic classification scheme and the clinical significance of such a classification remains to be established. In this study, we revisited the subclassification of AIP and examine whether this provides clinically and prognostically meaningful information. We evaluated 29 pancreatic resection specimens from patients with AIP. Demographic, clinical, and imaging data were recorded, as was evidence of extrapancreatic manifestations. In addition to a detailed and semiquantitative histologic evaluation, immunohistochemistry for IgG4 was performed on pancreatic and extrapancreatic tissues. We also evaluated 48 consecutive cases of chronic pancreatitis, not otherwise specified. The resected specimens could readily be subclassified into 2 subtypes: type 1 ($n = 11$) and type 2 ($n = 18$). In comparison with patients with type 2 disease, patients with type 1 disease were significantly more likely to be males ($P = 0.09$), older ($P = 0.02$), and present with jaundice ($P = 0.01$), and less likely to be associated with abdominal pain ($P = 0.04$). On imaging, the pancreatic tail cut-off sign was exclusively seen in patients with type 2 disease (4 of 10 cases). Hypercellular inflamed interlobular stroma was unique to type 1 pattern (91%), whereas significant ductal injury in the form of microabscesses and ductal ulceration was almost exclusively seen in type 2 pattern (78%). Eight of 10 patients with a type 1 pattern had evidence of a systemic disease. Three patients with type 2 disease had recurrent episodes of pancreatitis after their pancreatic resection. In comparison with the cohort of chronic pancreatitis, not otherwise specified, type 2 AIP cases were less likely to be associated with a history of alcohol abuse, and showed significantly more foci of periductal inflammation and neutrophilic microabscesses. Our review of pancreatic resection specimens shows 2 histologically distinct forms of AIP. Our data support the concept that type 1 AIP is a systemic disease and is the pancreatic manifestation of IgG4-related systemic disease.

Type 2 disease is confined to the pancreas. The intensity of the periductal inflammatory infiltrate and the presence of ductal neutrophilic abscesses are features that assist in distinguishing type 2 AIP from chronic pancreatitis, not otherwise specified. Although imperfect, clinical and imaging features may help distinguish the 2 subtypes of AIP. On the basis of these significant differences between the 2 types of AIP, we advocate the position that all subsequent studies attempt to stratify their patients into these 2 groups.

Key Words: autoimmune pancreatitis, subclassification, IgG4

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Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of the pancreas, which was first recognized by Sarles et al. in 1961.^{18,19} However, wider appreciation of AIP came only in the 1990s in the form of case reports.^{12,25} In 2001, Hamano et al¹⁰ associated the presence of elevated levels of IgG4 with AIP, and subsequently this has emerged as a fairly robust marker of AIP, both at the serum and at the tissue level.^{6,11}

The disease that frequently mimics pancreatic adenocarcinoma, has led to frequent pancreatic resections, allowing pathologists to examine these surgical specimens.^{1,6,14,23,26} A thorough histopathologic analysis of these tissues has facilitated great progress in the field. Analyses of resection specimens suggest that AIP is not a homogenous disease. Indeed, 3 surgical series have suggested the possibility of 2 distinct classes of AIP.^{6,14,24,26} Yadav et al²⁴ recognized 2 forms of AIP: the “idiopathic ductcentric” and “lymphoplasmacytic sclerosing.” The former was characterized by periductal inflammation. In contrast, lymphoplasmacytic sclerosing pancreatitis was typified by an exuberant storiform type of inflammatory fibrosis with obliterative phlebitis.²⁴ In a subsequent study, Zamboni et al²⁶ focused their attention on neutrophilic infiltrates in the ducts, a lesion that they termed “granulocytic epithelial lesion.” These researchers linked the presence of granulocytic epithelial lesions to inflammatory bowel disease, both ulcerative colitis and Crohn’s disease. Data from our institution are consistent with the concept that 2 distinct forms of AIP exist.⁶ We have designated these variants the “ductocentric” and “lobulocentric” patterns.⁶ These terms refer to pathologic

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entities that are broadly similar to those described by Yadav et al.²⁴ In this study, we noted that the cohort of lobulocentric AIP was composed predominantly of male patients with obstructive jaundice, and were infrequently associated with inflammatory bowel disease.⁶ Significantly, 80% of ductocentric cases were associated with neutrophils within ducts. In comparison, only 17% of lobulocentric AIP showed similar neutrophilic infiltrates. Finally, when evaluated by immunohistochemistry, the lobulocentric variant showed significantly more IgG4-positive plasma cells than the ductocentric variant. A more recent study showed that the 2 forms of AIP have distinct clinical profiles with 47% of patients with “type 1” disease experiencing relapse, compared with none in the “type 2” group.¹⁷ Despite the emerging consensus that distinct subclasses exist within the spectrum of AIP, there is no widely accepted pathologic classification scheme for this disorder, and the clinical significance of such subtyping of AIP remains to be established.^{2,16,22}

The goal of this study was to illustrate a histologic subclassification scheme for AIP that unified current classification proposals and can serve as a model for subsequent studies on AIP. We proposed to address the following questions: (1) Can the 3 classification schemes of AIP be reconciled into a single system that is based on readily recognizable histologic features? (2) Is this classification clinically and prognostically meaningful? (3) In the absence of a pancreatic resection, can such a subclassification be performed solely on clinical and radiologic grounds? A broader presurgical recognition of the condition of AIP has led to the availability of fewer surgical resections. This clinical reality enhances the importance of clinicopathologic and radiopathologic correlations, because future classification is likely to be predicated on clinical, serological, and imaging findings.

MATERIALS AND METHODS

The pathology reports of pancreatic resections between 1991 and 2009 diagnosed as chronic pancreatitis ($n = 168$), were retrieved from the surgical pathology files of the Massachusetts General Hospital. The existing reports were reviewed for evidence of AIP and slides from selected cases were reevaluated. Eighteen of these cases were reported in an earlier publication.⁶ The criteria used to establish a diagnosis of AIP are similar to those used in an earlier publication from the Massachusetts General Hospital, and the diagnosis was based primarily on histologic grounds.⁶ In brief, AIP was characterized by a robust periductal inflammatory infiltrate (Fig. 1B) with or without the additional features such as dense lymphoplasmacytic infiltrate in the interlobular septa and within the lobules of the pancreas, phlebitis, or obliterative phlebitis, and the presence of > 10 IgG4-positive plasma cells per high-power field (HPF). We hypothesized that there may be an overlap between AIP and other unspecified forms of chronic pancreatitis [chronic pancreatitis, not otherwise specified (CP-NOS)]. To address this issue, we evaluated 48 consecutive cases of CP-NOS

from our files. We excluded cases with a history of hereditary pancreatitis.

The clinical history was recorded with particular attention to demographic information, mode of presentation, and serological data. Radiologists who have a specific interest in pancreatic radiology and who had no knowledge of the patient's histologic type reviewed the imaging studies. On imaging, the pancreas was considered to be diffusely swollen when there was partial or complete obscuration of the lobular architecture. The focal mass-like swelling was defined as a focal enlargement without pancreatic or peripancreatic inflammatory changes. Involution of the pancreatic tail, or “tail cut-off,” was considered to be present when there was abrupt blunting and retraction of the tail. The peripancreatic region was evaluated for stranding (represented by streaking of peripancreatic fat), a hypoattenuating rim surrounding the pancreas (referred to as a “halo”), and any fluid collections. Follow-up information on these patients was obtained from the electronic medical records. We noted the development of any features within the extrapancreatic organs, which suggested the presence of the broader systemic illness known as IgG4-related systemic disease, and any recurrence of the disease within the pancreas.

The pancreatic resection specimens were reviewed and the following histologic features were recorded: number of ducts involved by periductal inflammation, grade of periductal lymphoplasmacytic inflammation (semiquantitatively graded as 0, 1, 2, 3), storiform pattern of inflammation, and number of foci of obliterative phlebitis. In addition, all forms of ductal injury including neutrophils within pancreatic ducts and ulcerative lesions were also noted, as were the number of abscesses. Neutrophils were frequently located adjacent to the pseudocyst, and these were disregarded. An elastic stain was performed on selected cases to facilitate the diagnosis of obliterative phlebitis. The histology available on any other organ at any time in the patient's clinical course was also reviewed, including the lymph nodes, stomach, liver, kidney, and colon.

Immunohistochemistry for IgG4 was also performed on the pancreatic and extrapancreatic lesions as described previously.⁶ In brief, immunohistochemical studies using antibodies to IgG4 (Zymed, 1:200 dilution) were carried out. Antigen retrieval was performed using protease digestion, and antigen detection was carried out using UltraView diaminobenzidine chromogen (Ventana Medical Systems, AZ). Three HPFs (area = 0.2375 mm^2) with the highest number of IgG4-positive cells were identified and the average was recorded.

Statistics

Statistics were calculated using SPSS version 15.0 (SPSS, Chicago, IL). Differences between groups were evaluated using the χ^2 test or the Fisher exact test for qualitative variables, and the Student t test was used for quantitative variables. A P value < 0.05 was considered significant.

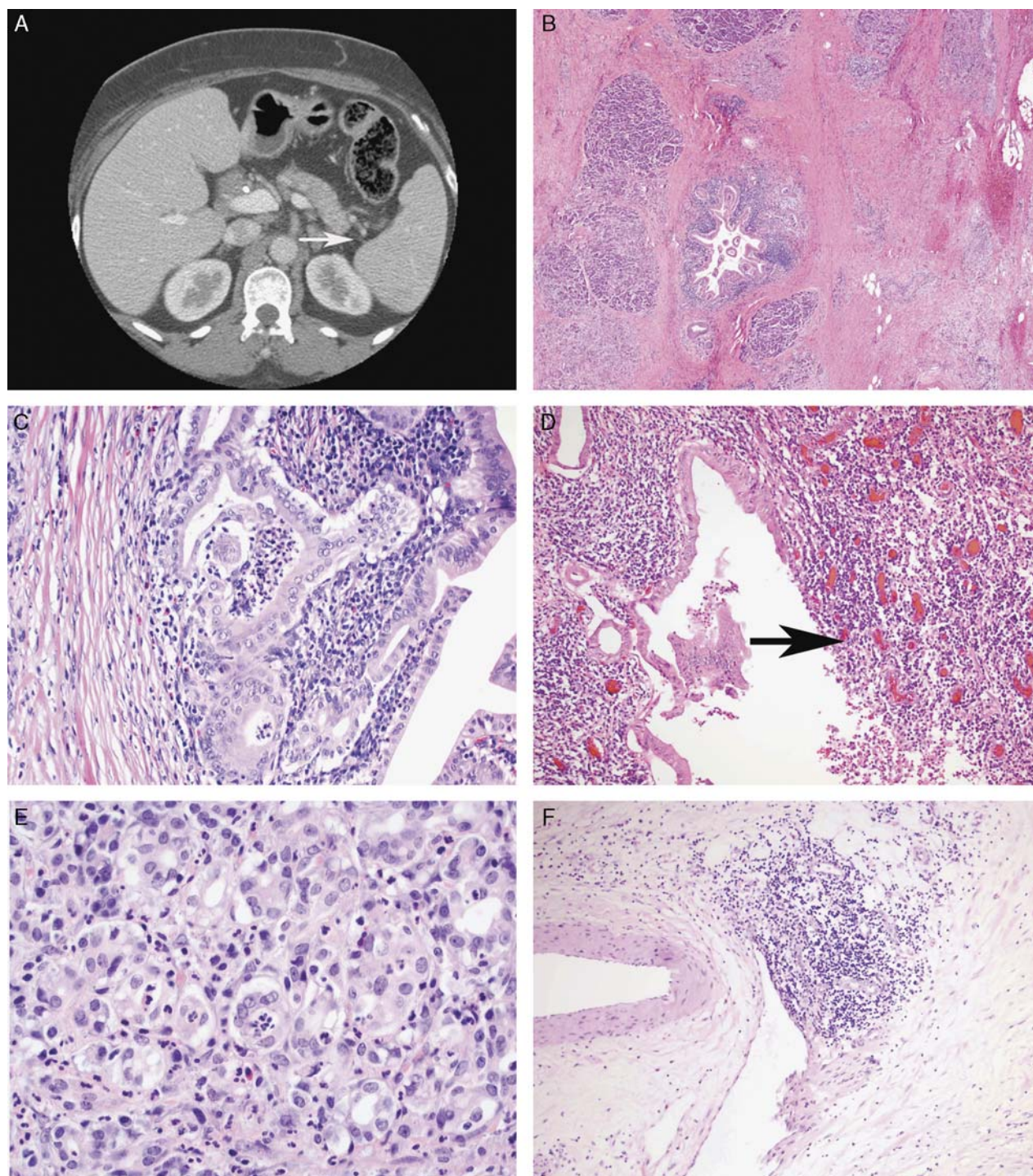


FIGURE 1. Type 2 autoimmune pancreatitis. computed tomography image showing a swollen pancreas that is truncated distally (arrow). We refer to this as the pancreatic tail cut-off sign (A). Type 2 autoimmune pancreatitis (AIP) with a robust periductal inflammatory infiltrate. The interlobular stroma lacks inflammation and is fibrotic (B). Type 2 AIP with intraductal abscess (granulocytic epithelial lesion) and a robust periductal inflammatory infiltrate (C). Type 2 AIP with ductal ulceration (arrow) and duct partially lined by granulation tissue (D). AIP with granulocytic epithelial lesion within a lobule (E). Focal nonobliterative phlebitis is a frequent finding in type 2 AIP (F).

RESULTS

We identified 2 histologic categories (see below for specific histologic features), termed type 1 and type 2 forms of AIP. Eleven patients had lesions consistent with type 1 pattern, and 18 patients had lesions consistent with the type 2 pattern.

Demographic and Clinical Findings

Remarkably, cases of type 1 AIP were composed almost exclusively of male patients, with only a single female patient (Table 1). In stark contrast with this, the ratio of male to female patients among patients with type 2 disease was 8:10 ($P = 0.09$). Patients with type 1 AIP were significantly older than those with type 2 disease, with a mean age of 65 and 52 years, respectively ($P = 0.02$). Abdominal pain, while uncommon in type 1 disease (20%), was seen in 67% of patients with type 2 disease ($P = 0.04$). Jaundice was more frequently seen in type 1 disease (70%) than in type 2 disease (17%) ($P = 0.01$).

Imaging

Four cases of type 1 AIP and 12 cases of type 2 disease were available for review (Table 2). In general, the radiologic features were not helpful in distinguishing type 1 from the type 2 pattern. Diffuse swelling of the pancreas, pancreatic stranding, halo sign, and common bile duct strictures were identified in both the subgroups, and with a considerable overlap. However, the pancreatic tail cut-off sign was exclusively seen in type 2 disease ($n = 4$, 40%) (Fig. 1A).

TABLE 1. Clinical Features of Type 1 and Type 2 Autoimmune Pancreatitis

	Type 1*	Type 2	P
Mean age, y (range)	65 (50-73)	52 (20-80)	0.017
Sex (F:M)	1:10	8:10	0.09
Weight loss	5/10 (50%)	5/18 (28%)	NS
Fatigue	5/10 (50%)	4/18 (22%)	NS
Jaundice	7/10 (70%)	3/18 (17%)	0.01
Abdominal pain	2/10 (20%)	12/18 (67%)	0.04
Nausea and vomiting	2/10 (20%)	6/18 (33%)	NS
No alcohol use or social use	10	14	NS
Alcohol abuse	0	1	
Inflammatory bowel disease	1	2	NS
Extrapancreatic manifestations	8 (80%): sclerosing cholangitis (2), lymphadenopathy (2), salivary gland (1), gastric mucosa (2), kidney (1)	0	0.001

*Data not available for 1 case.

F indicates female; M, male; NS, not significant.

TABLE 2. Radiologic Features of Type 1 and Type 2 Autoimmune Pancreatitis

	Type 1	Type 2
Diffuse swelling	3/4 (75%)	7/10 (70%)
Peripancreatic stranding	1/2 (50%)	1/6 (17%)
Halo sign	1/4 (25%)	3/10 (30%)
Focal enlargement	2/4 (50%)	6/12 (50%)
Pancreatic tail cut-off sign	0/4 (0%)	4/10 (40%)
Common bile duct stricture	1/3 (33%)	3/4 (75%)

Histology

Type 1 AIP

The hallmark of type 1 AIP was changes in the interlobular stroma. The most striking of these changes was the cellular stromal reaction composed of lymphocytes, plasma cells, and reactive fibroblasts/myofibroblasts (Fig. 2A). The stroma frequently showed a swirling/storiform pattern of growth (Fig. 2D). Within these zones of inflamed fibrous tissue, obliterated veins were frequently found (10 of 11 cases) (Fig. 2E) (Table 3). Obliterative phlebitis was almost exclusively seen in type 1 cases and was generally obvious on hematoxylin and eosin stain (mean foci of obliterative phlebitis per case = 8) as these were located adjacent to their accompanying artery. Three cases also showed evidence of arteritis. Eosinophils were frequently noted interspersed in this infiltrate. In contrast, the interlobular stroma in type 2 disease was relatively acellular with only a few lymphocytes and plasma cells (Fig. 1B). Ten of 11 cases showed grade 3 periductal inflammation. The mean number of ducts with periductal inflammation in type 1 AIP ($n = 10$) was significantly less than those seen in type 2 AIP ($n = 26$). However, this may be a reflection of the lower number of slides available from type 1 cases (5 vs 10, $P = 0.0001$).

Type 2 AIP

The hallmark of type 2 disease was the presence of overt ductal injury. Although a minority of cases with type 1 disease showed evidence of ductal injury, this pattern of injury was seen in the majority of cases with type 2 disease (Figs. 1B–D and Table 3). Granulocytic epithelial lesions were identified in 89% ($n = 16$) of cases with type 2 pattern and 27% ($n = 3$) of cases with type 1 pattern ($P = 0.001$). When granulocytic epithelial lesions were identified in type 1 pattern, they consisted only of rare intraepithelial neutrophils. Both frank ductal ulceration and neutrophilic abscesses were almost exclusively seen in cases classified as type 2 AIP. These abscesses were relatively easily visualized, and the mean number of ducts/lobules with such lesions was 8.6 (per case). Ulcers were typically noted in large-caliber pancreatic ducts and these ducts were lined by inflammatory granulation tissue that was rich in neutrophils (Fig. 1D). The granulocytic epithelial lesions were more commonly recognized within ducts, although some cases showed neutrophilic infiltrates

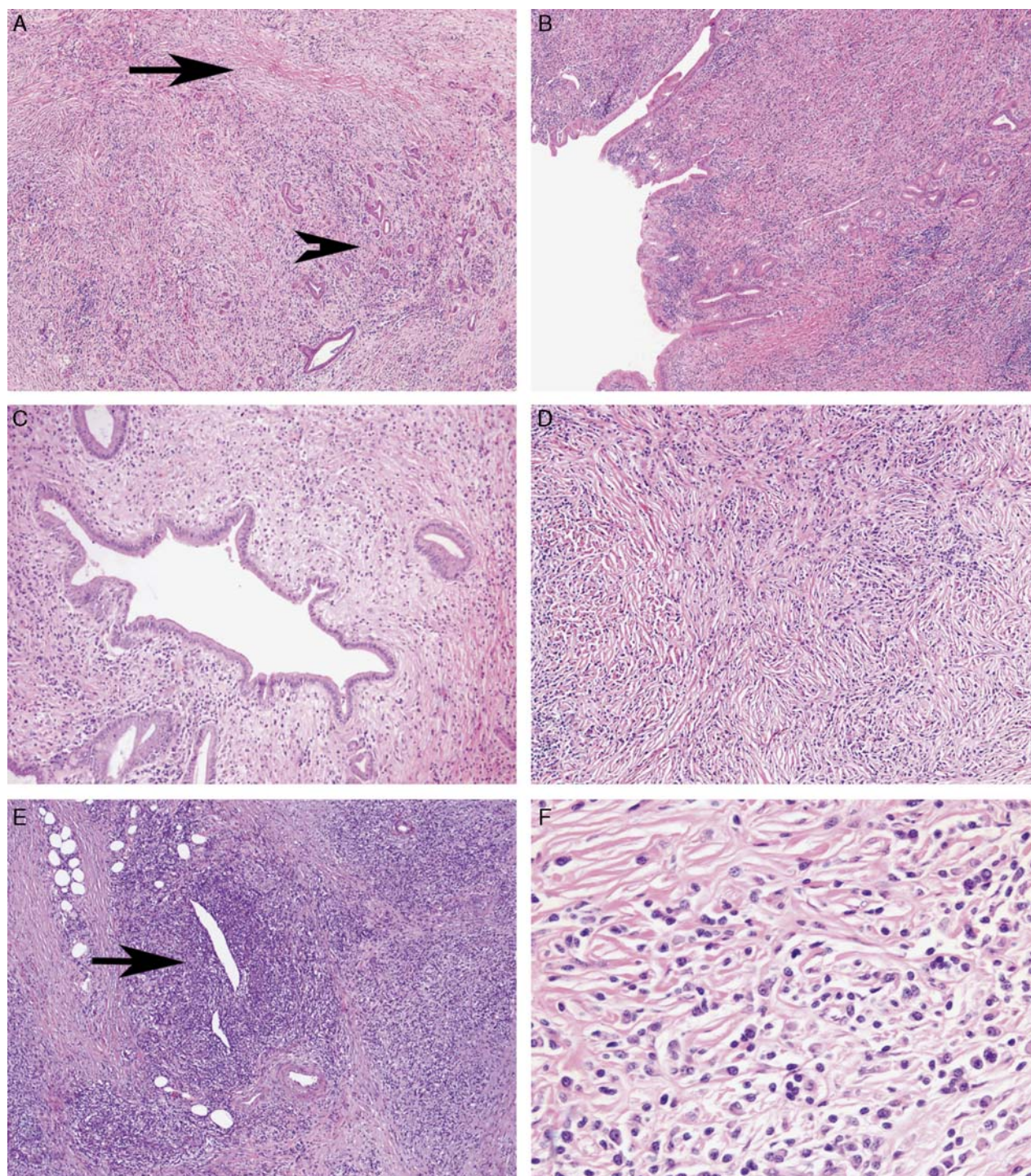


FIGURE 2. Type 1 autoimmune pancreatitis. Low-power image shows fibroinflammatory tissue involving an interlobular septum (arrow), replacing acinar tissue within the pancreatic lobule (arrowhead) (A) and infiltrating the intrapancreatic bile duct (B). Mild (1+) periductal inflammation (C). Type 1 disease tended to show a relatively sparse periductal inflammatory infiltrate. Storiform pattern of fibrosis (D). Obliterative phlebitis (arrow) (E). Note the accompanying artery, a feature that frequently helps uncover obliterative phlebitis. Plasma cell-rich infiltrate with fibrosis (F).

in the lobules as well (Fig. 1E). Although phlebitis was evident in type 2 cases (Fig. 1F), obliterative phlebitis was noted in only 1 case.

Type 2 AIP Versus CP-NOS

A history of alcohol abuse was more frequently noted in the CP-NOS cohort, although 1 case of AIP was

TABLE 3. Histologic Features of Type 1 and Type 2 Autoimmune Pancreatitis

	Type 1 (n = 11)	Type 2 (n = 18)	P
Mean number of foci of periductal inflammation	10	26	0.04
Grade of periductal inflammation			NS
1	0	0	
2	1	8	
3	10	10	
Obliterative phlebitis	10 (91%)	1 (6%)	0.03
Mean number of foci of obliterative phlebitis (range)	8 (0-18)	< 1 (0-5)	0.03
Storiform pattern	10/11 (91%)	0/18 (0%)	0.0001
GEL	3 (27%)	16 (89%)	0.001
GEL location			
Duct	1	11	
Lobule	1	0	
Both	1	5	
Duct/lobular microabscess	1 (9%)	14 (89%)	0.001
Mean number of abscesses per case	1.6	8.6	0.05
Duct ulceration	0 (0%)	7 (39%)	0.05
Granulomas	1 (9%)	2 (11%)	NS

NS indicates not significant.

associated with alcohol abuse (Table 4); this latter case showed both marked (3+) periductal inflammation and ductal neutrophilic abscesses. Although foci of periductal inflammation were identified in 9 cases of CP-NOS, these were both fewer in number and the density of the lymphoplasmacytic infiltrate was less than that seen with type 2 AIP. Furthermore, ductal/lobular abscesses were

TABLE 4. Clinical and Histologic Features of Type 2 Autoimmune Pancreatitis and Chronic Pancreatitis, Not Otherwise Specified

	Type 2 AIP N = 18	Chronic Pancreatitis, NOS N = 48	P
Mean age, y (range)	52 (30-80)	48 (27-74)	NS
Sex (F:M)	10:8	22:26	NS
No alcohol use or social use	14	14	0.06
Alcohol abuse	2	15	
Pancreatic divisum	0	9	
Mean number of ducts with periductal inflammation (range)	26 (6-89)	0.6 (0-7)	0.0001
Degree of inflammation			
0	0	39	0.0001*
1	0	5	
2	8	4	
3	10	0	
Number of cases with duct/lobular abscesses	14 (78%)	1 (2%)†	0.0001
Mean number of duct/lobular abscesses‡ (range)	8.6 (0-37)	0.4 (0-21)†	0.004

*0.1 vs 2.3.

†Single case with ductal abscesses lacked periductal inflammation.

‡Neutrophils in the vicinity of cysts were not included.

NOS indicates not otherwise specified.

seen in only a single case of CP-NOS. In addition, significantly, the abscesses in this case were not associated with periductal lymphocytic infiltration. In contrast, such abscesses were effortlessly identified (mean of 11/case) in 78% of type 2 AIP cases. Significantly, there was no difference in the number of slides evaluated between the AIP (mean, 11) and CP-NOS cohort (mean, 10) ($P =$ not significant).

Tissue IgG4 Stain

We stained the pancreatic resection samples and the peripancreatic lymph nodes for IgG4. Type 1 AIP showed significantly more IgG4-positive plasma cells within the pancreas than the type 2 variant (Table 5). Although all 8 cases with type 1 disease showed > 10 IgG4-positive plasma cells per HPF, only half of the type 2 cases showed a similar number of immunoreactive plasma cells ($P = 0.02$). Furthermore, although 88% of type 1 cases showed > 50 IgG4-positive cells per HPF, only a single case with type 2 disease (7%) showed similar numbers of IgG4-positive plasma cells ($P = 0.001$). This latter case of type 2 disease lacked other stigmata of type 1 disease, that is, obliterative phlebitis and storiform fibrosis.

Significantly, this pattern of IgG4 reactivity was also noted in the peripancreatic lymph nodes (Figs. 3A, B). Peripancreatic lymph nodes in cases with type 1 disease (mean, 168/HPF) showed more IgG4-positive plasma cells than those with type 2 disease (mean, 14/HPF) ($P = 0.08$).

Serology

Patients with type 1 disease [mean, 1613 mg/dL (SD 336)] showed a higher serum IgG level than those with type 2 disease [mean, 1056 mg/dL (SD 331)] ($P = 0.05$). The IgG4 level of only a single case with type 1 disease was available, and was measured at 211 mg/dL. The mean serum IgG4 level of patients (available in 7 cases) with type 2 disease was 258 mg/dL (range, 7 to 1310 mg/dL).

Patients with type 1 AIP [mean, 244 U/mL (SD 623)] showed a higher serum CA19.9 than patients with type 2 disease [mean, 20 U/mL (SD 11)] ($P =$ not significant).

Systemic Manifestations/Recurrences and Outcome

The overall mean follow-up in the AIP cohort was 50 months (range, 12 to 160 mo). Two patients were lost to follow-up immediately after surgery. There were 4 recorded deaths, 2 of which seemed to be related to AIP: 1 case each of hepatic failure and pancreatic carcinoma. The adenosquamous carcinoma was identified in a distal pancreatectomy specimen from a 73-year-old male patient. Ten years before the diagnosis of carcinoma a Whipple resection showed histologic evidence of type 1 AIP. Review of this specimen showed storiform fibrosis, obliterative phlebitis, and > 50 IgG4-positive plasma cells per HPF. The other 2 patients died of unrelated causes: cerebrovascular accident and amyotrophic lateral sclerosis.

TABLE 5. IgG4 Counts in Pancreas and Peripancreatic Lymph Nodes

	Type 1 AIP	Type 2 AIP	P
Pancreas IgG4 > 50 per HPF	7/8 (88%)	1/14 (7%)	0.001
Pancreas IgG4 > 10 per HPF	8/8 (100%)	7/14 (50%)	0.02
Peripancreatic lymph nodes > 50 per HPF	3/3 (mean, 168; SD, 47)	0/9 (mean, 14; SD, 5)	0.08

AIP indicates autoimmune pancreatitis; HPF, high-power field; SD, standard deviation.

Type 1 AIP

The mean follow-up in this group was 54 months (range, 26 to 95 mo). Eight of the 10 patients with type 1 AIP on whom clinical information was available developed at least 1 extrapancreatic manifestation. Two patients showed clinical and radiologic evidence of sclerosing cholangitis. The histologic findings in 1 of these cases showed portal-based nodules composed of lymphocytes and plasma cells and showed 123 IgG4-positive plasma cells per HPF.⁷ One patient showed enlargement of both the submandibular salivary glands. Two patients presented with clinical and/or radiologic evidence of lymphadenopathy, cervical in 1 case and mediastinal in the other; the former lesion was biopsied. A single case showed renal involvement and this patient has been reported previously.⁵ A single case with ulcerative colitis was also present in this cohort.

Both cases of AIP with type 1 disease, in which gastric fundic mucosa was available for review, showed marked chronic inactive gastritis. The infiltrate was present predominantly in the lower half of the mucosa, and the inflammatory infiltrate was composed predominantly of lymphocytes and plasma cells. Mild-to-moderate atrophy and pyloric-type metaplasia were also seen. Both the cases showed > 200 IgG4-positive plasma cells per HPF. The gastric mucosa from 9 type 2 AIP cases was essentially devoid of inflammation (mean, 1 IgG4 plasma cells/HPF).

Type 2 AIP

The mean follow-up in this group was 41 months (range, 12 to 160 mo). Two patients with type 2 pattern of disease developed ulcerative colitis and 1 patient had rheumatoid arthritis. In addition, after pancreatic resection 3 cases developed recurrent episodes of acute pancreatitis that required hospitalization. Similar recurrence of acute pancreatitis was not seen with type 1 disease.

DISCUSSION

Our data support the concept that AIP can be readily classified into 2 clinically relevant categories. Patients with type 1 AIP, show a storiform type of interlobular fibrosis with obliterative phlebitis. In contrast, ductal lesions that include neutrophilic microabscesses and ulcerated ductal lesions characterize type 2 disease. Of note, this scheme incorporates all 3 earlier attempts at classifying AIP and does not contradict these studies.^{6,26,27} The classification is also supported by the larger number of IgG4-positive plasma cells in type 1 disease within the pancreas, peripancreatic lymph nodes, and gastric mucosa. Although the nodal form of IgG4-related disease has been studied extensively,^{4,20} the relationship of IgG4 plasma cells in the peripancreatic lymph nodes with subtypes of AIP has not been analyzed. As these lymph nodes may be targeted on EUS-guided fine needle aspiration biopsy, this observation may have diagnostic value in cases of suspected type 1 disease.

Recognizing subclasses within AIP is equally relevant for pathologists, as diagnostic criteria for AIP will vary according to the subtype of the disease (Table 6). The diagnostic criteria of type 1 disease include a dense lymphoplasmacytic inflammation that is frequently organized in a storiform pattern, obliterative phlebitis, and elevated numbers of IgG4-positive cells. In contrast, in most instances, none of these features are seen in type 2 disease. Instead, the histologic diagnosis of type 2 disease

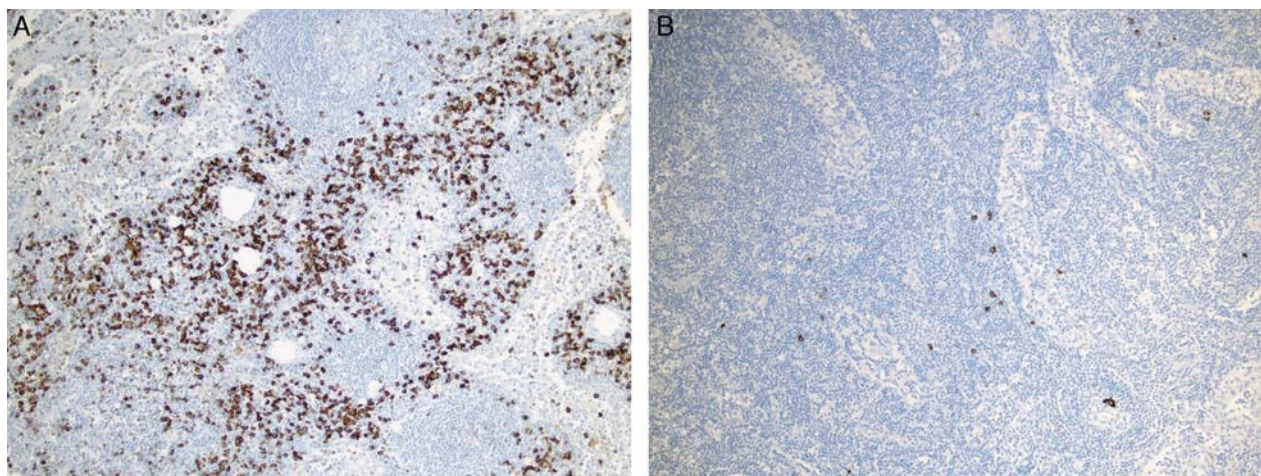


FIGURE 3. Immunohistochemical stain for IgG4 performed on periductal lymph nodes. Type 1 (A) and type 2 (B) patterns of autoimmune pancreatitis. [full color online](#)

TABLE 6. Impact of Subclassification on Pathologic Diagnostic Criteria for Autoimmune Pancreatitis

Type 1 AIP	Type 2 AIP
Periductal inflammation with 1 or more of these features	Periductal inflammation with 1 or more of these features
Interlobular inflammation and fibrosis (storiform pattern)	Ductal/lobular abscesses
Obliterative phlebitis	Ductal ulceration with neutrophils

AIP indicates autoimmune pancreatitis.

relies on documenting duct injury, including neutrophilic infiltration of ducts, neutrophilic abscesses, and ductal ulceration.

Significantly, the interobserver agreement for distinguishing AIP from chronic pancreatitis, even among pathologists with an expertise in the pancreas, is only moderate.³ One of the reasons for this difficulty is a general lack of recognition that AIP is morphologically a heterogeneous disease. The diagnostic criteria for the 2 groups of AIP (Table 6) are significantly different, and it is our hypothesis that acknowledgment of the 2 subtypes will significantly improve diagnostic accuracy.

In practice, an elderly man who presents with obstructive jaundice and lacks abdominal pain is significantly more likely to have type 1 than type 2 disease. In contrast, a middle-aged woman with abdominal pain would represent the prototypic type 2 patients. With the exception of the pancreatic tail cut-off sign, found in 40% of patients with type 2 disease, computed tomography findings could not unequivocally distinguish the 2 subtypes. Ductal injury in type 2 AIP results in pancreatic atrophy, and this may preferentially affect the tail of the pancreas, accounting for the distal shortening of the pancreas. In contrast, the diffusely inflamed and edematous pancreatic stroma of type 1 disease correlates with the absence of pancreatic cut-off sign on imaging. Larger series are required to confirm the significance of this finding.

The subtyping of AIP is more than just an academic exercise. Subtyping can be used to predict the likelihood and pattern of disease recurrence.^{2,6,22,26} Type 1 AIP is invariably associated with systemic involvement, and 8 of our 10 type 1 cases showed 1 or more extrapancreatic manifestations of this disease. The most common of these were sclerosing cholangitis and lymphadenopathy. All these are well-recognized sites of systemic involvement by AIP.^{5,7,9} Other sites of systemic involvement included the stomach, kidney, and salivary gland. Significantly, there was no difference in the length of follow-up between type 1 and type 2 AIP. The increase in the number of IgG4-positive plasma cells in the peripancreatic lymph nodes and the gastric mucosa in type 1 disease further support the hypothesis that these represent distinct forms of AIP.

In contrast, the recurrences in type 2 disease were restricted to the pancreas. In 3 of our type 2 cases, there were multiple episodes of acute pancreatitis, all of which

required hospitalization. Steroids were used to control recurrent episodes of pancreatitis in 1 case, but without success. The only extrapancreatic manifestation over-represented in type 2 disease is ulcerative colitis, an association that has been recognized earlier.^{6,26}

Our cohort, although largely in agreement with the data from earlier large series of AIP, differed in 1 significant aspect—our study had a higher proportion of type 2 disease, 62% in our study versus 42% and 41% in the 2 earlier series.^{26,27} One plausible explanation for this discrepancy is the extensive review of chronic pancreatitis cases we undertook in an attempt to uncover cases of AIP. Furthermore, with increasing clinical expertise in this area, there have been fewer resections for type 1 disease in this decade. Alternatively, one could argue that the larger number of cases with type 2 disease in our population raises the possibility that some forms of nonspecific chronic pancreatitis may have been mistakenly classified as AIP. We acknowledge the fact that periductal lymphoplasmacytic inflammation as an isolated finding is a nonspecific feature; a feature that we have noted in both alcohol-induced chronic pancreatitis and hereditary pancreatitis. To further clarify this issue, we examined 48 consecutive cases of CP-NOS and compared these cases with type 2 AIP. On the basis of these data, we believe that cases of AIP invariably show ducts with both a brisk periductal inflammatory infiltrate and neutrophilic infiltrates, typically in the form of an abscess. Occasional foci of periductal inflammatory infiltrates, typically paucicellular, are seen in other forms of pancreatitis, but these foci are not associated with neutrophilic infiltrates. Although there exists some morphologic overlap, we believe that based on a review of a pancreatectomy specimen, type 2 AIP can be readily distinguished from other forms of chronic pancreatitis. It is interesting to note that 1 published study also included 5 cases of AIP from Japan (a country in which type 2 disease is extremely rare), thus introducing a bias, and this may in part account for the preponderance of type 1 cases in the North American series.¹⁴ The absence of type 2 disease in Japan/Korea is intriguing, but an explanation for these geographic differences has yet to emerge.³

Although there seems to be a growing consensus that 2 subgroups of AIP exist, the terminology is in flux. A study from this institution suggested the terms “ductocentric” and “lobulocentric.”⁶ These subtypes roughly correspond to the idiopathic duct-centric pancreatitis and lymphoplasmacytic sclerosing pancreatitis, respectively, terminology suggested by Notohara et al.¹⁴ A European study recognized 2 patterns of AIP, defined by the presence or absence of granulocytic epithelial lesions.²⁶ One potential drawback of this terminology is the implication that the histologic subclassification of AIP relies primarily on granulocytic epithelial lesions. Notohara’s terminology provides a robust histologic description of the disease. However, the term “idiopathic” is not optimal as our understanding of both forms of the disease is only in its infancy. In fact, beyond the assumption that IgG4-bearing plasma cells may play some role in the

pathogenesis of type 1 disease, our understanding of AIP remains rudimentary. Furthermore, the term “lymphoplasmacytic sclerosing pancreatitis” has also been used as an alternate term for AIP.¹³

Our own terminology of ductocentric and lobulocentric is not precisely correct because the epicenter of the inflammation in the lobulocentric type is actually the interlobular stroma rather than the lobule. We therefore agree with a recent proposal to rename the subclasses of AIP as type 1 and type 2.^{2,22} The terminology avoids reference to both etiology and the pattern of pancreatic involvement.^{2,22}

Individuals with type 2 disease are significantly younger than those with type 1 disease; this raises the intriguing question as to whether these are 2 phases of the same disease. However, as this study shows, each disease shows distinct pathologic features and has unique patterns of recurrence, supporting related but independent entities, and not phases of the same disease.

Type 1 disease fits the prototypic description of AIP—an elderly man presenting with obstructive jaundice and markedly elevated serum and tissue levels of IgG4. In contrast, the clinical picture of type 2 disease shows significant overlap with conventional forms of chronic pancreatitis.¹⁷ These significant histologic and immunologic differences between type 1 and 2 disease raises the possibility that type 2 disease may eventually require reclassification as a new variant of pancreatitis and be deleted from the AIP category. Nonetheless, based on our current data we believe that the type 2 variant shares 2 important features with type 1 disease. The first of these is a robust periductal inflammatory infiltrate; a finding that we show is uncommon in other forms of chronic pancreatitis, but is invariably seen in both type 1 and type 2 disease. The second is the presence of IgG4 in both forms of the disease, albeit in significantly lesser numbers in type 2 disease. Furthermore, as this and earlier studies have shown, there is significant overlap between the clinical features of the 2 subtypes of AIP.¹⁷ Although these arguments support retaining type 2 disease within the category of AIP, we do recognize that future investigations may alter our views on this subject.

As the histology of the extrapancreatic manifestations of this disease, including those from the kidney, lung, liver, and salivary gland, all show a fibroinflammatory process that is remarkably similar to that seen in the pancreata of individuals with type 1 AIP. We believe that type 1 AIP should be considered as part of the spectrum of IgG4-related systemic disease, although type 2 disease does not.^{5,7,9,21} With this classification, one could explain why there has been so little progress in our understanding of the pathogenesis of AIP. Studies looking at different aspects of the pathogenesis of AIP (including identification of an autoantibody and the role of Th1 and Th2 populations) have been investigating not 1 homogenous disease, but instead 2 distinct but related diseases.^{8,15} We support the position that all subsequent studies on AIP stratify their patients using this subclassification¹⁷ while

simultaneously acknowledging the fact that clinical and imaging features may not distinguish type 1 from type 2 disease. There is a pressing need for a biomarker, preferably a serum marker that could assist in making this distinction.

To conclude, we have shown that a simple histologic classification can distinguish 2 unique variants of AIP. Type 2 disease is entirely restricted to the pancreas and does not involve the peripancreatic lymph nodes. In contrast, type 1 disease is a systemic disease. Recurrences are less common in type 2 disease, and these are confined to the pancreas. However, imperfect, clinical, radiologic, and serological features may distinguish the 2 subtypes of this disease.

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