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Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens

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Abstract *Background and Aims:* Autoimmune pancreatitis seems to be a disease with a heterogeneous appearance. Our intention was to establish key diagnostic criteria, define grades of severity and activity, identify features of potential subtypes and evaluate the diagnostic relevance of biopsy specimens. *Methods:* Histopathological criteria and clinical features were recorded in pancreatic resection specimens from 53 patients who were found to have chronic pancreatitis lacking pseudocysts, calculi, irregular duct dilatations, pancreas divisum and/or duodenal wall inflammation. The severity of the chronic inflammation was graded, and the activity of the acute inflammatory component and the granulocytic epithelial lesion (GEL) were determined. Additionally, pancreatic biopsy specimens from 9 patients with suspected AIP were assessed. *Results:* Periductal lymphoplasmacytic

infiltration was identified in all cases, followed in order of frequency by periductal fibrosis and venulitis. These changes were absent in 147 pancreatic specimens that showed chronic pancreatitis associated with pseudocysts, calculi, pancreas divisum and/or duodenal wall inflammation. In 90% of the cases, these chronic changes were graded as 3 or 4. In 81%, the inflammatory process resided in the head of the pancreas and involved the common bile duct. GELs were present in 42% of the patients, who had a mean age of 40.5 years, an almost equal male–female ratio and a high coincidence of ulcerative colitis or Crohn's disease. Patients without GELs were older (mean age 64 years), showed a male preponderance, commonly had Sjögren's syndrome and often developed recurrent bile-duct stenosis. Diagnostically relevant lesions were present in two of five wedge biopsy specimens and three of four fine-needle specimens. *Conclusions:* Periductal lymphoplasmacytic infiltration and fibrosis, preferential occurrence in the pancreatic head and venulitis characterize autoimmune pancreatitis. GELs predominantly occur in a subset of patients who are younger, more commonly have ulcerative colitis and Crohn's disease and seem to have fewer recurrences than patients without GELs. Pancreatic biopsy material proved to be a very helpful adjunct for establishing the diagnosis.

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Introduction

In recent years, a special type of chronic pancreatitis has increasingly been recognized, the clinicopathological features of which suggest an autoimmune etiology [19, 26, 32, 43]. The disease has been referred to by various names, depending on whether it was studied by pathologists, clinicians or radiologists. The most widely used names are chronic sclerosing pancreatitis [37], lymphoplasmacytic sclerosing pancreatitis [18], duct-destructive

chronic pancreatitis [9] and autoimmune pancreatitis (AIP) [43]. Here, we will use the term AIP, although the evidence for an autoimmune pathogenesis is, so far, only circumstantial [19, 26, 28].

Recent reviews have described the currently available clinical, immunological, radiological and morphological features [19, 26, 28, 30]. Clinically, it is a heterogeneous disease that can present with either the classical symptoms of acute or severe pancreatitis or with obstructive jaundice due to a mass in the head of the pancreas mimicking pancreatic ductal carcinoma [6, 16, 28]. Immunologically, some patients show elevated levels of serum gamma globulin and particularly IgG₄ [12]. IgG positive plasma cells were also demonstrated in the pancreatic inflammatory infiltrate of patients with AIP [17]. Morphologically, AIP displays a lymphoplasmacellular and sclerosing inflammation that is particularly associated with the pancreatic ducts and may also involve the common bile duct as well as the gallbladder [1, 18, 34]. These features and the lack of calculi, pseudocysts and focal autodigestive necrosis distinguish it from alcoholic chronic pancreatitis, the most frequent type of chronic pancreatitis seen in western countries [9].

Recently, a number of articles have appeared that emphasized AIP as a mimicker of pancreatic ductal carcinoma [3, 14, 25, 41]. It was also reported that some cases show a conspicuous eosinophilic component [2]. Moreover, in a study performed by a group at the Mayo Clinic, it was demonstrated that there may be two morphological types of AIP, which were called lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric chronic pancreatitis (IDCP) [25]. Finally, the disease seems to unevenly involve the pancreas with preferential occurrence in the head or tail [9]. So far, it is not known whether these variable changes are all part of the spectrum of one disease, depending on its duration and progression, or whether they reflect subtypes of AIP with different etiologies, different clinical courses and different associations with other autoimmune diseases.

Because AIP is responsive to steroid therapy [15, 21], surgical treatment may be required in only a minority of cases. The decision to give steroid therapy, however, requires a precise tissue diagnosis based on a pancreatic biopsy [28]. Yet little information is available about the value of this method for establishing the diagnosis of AIP [41].

In this study, we investigated the histopathology of a series of cases of chronic pancreatitis that were treated surgically and were lacking pseudocysts, calculi, irregular duct dilatations, pancreas divisum and duodenal wall inflammation. On the basis of this selection process, we were able to identify 53 cases in which we suspected AIP. In addition, we studied 9 biopsy specimens from patients whose clinical, radiological and laboratory features were suggestive of AIP. Our special aims were (1) to identify histopathological features that distinguish AIP, (2) to grade the severity and activity of the inflammatory changes, in order to characterize AIP in the individual patient, (3) to search for biologically relevant morpho-

logical subgroups of AIP, and (4) to study the diagnostic value of pancreatic biopsy.

Materials and methods

Patients

We reviewed the pancreatic pathology of a series of 200 surgically treated patients with chronic pancreatitis and retained those cases that had neither pseudocysts, calculi, irregular duct dilatation, pancreas divisum, duodenal wall cysts with associated pancreatitis nor a history of alcohol abuse, cholelithiasis or choledocholithiasis. We identified 53 patients who met these criteria. Clinical information was obtained from each patient's medical and surgical records and by direct consultation with the clinician in charge. The presence of autoimmune antibodies was recorded in a few cases; they failed to show a consistent pattern. Hypergammaglobulinemia and IgG₄ levels were not available for this retrospective study. Particular attention was paid to whether the patient had evidence of autoimmune or autoimmune-related diseases, such as Sjögren's syndrome, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis, primary biliary cirrhosis, retroperitoneal fibrosis, rheumatoid arthritis, Hashimoto's thyroiditis and asthma. Follow-up data was available in 22 patients. It ranged from 6 months to 23 years (mean 3 years). Pancreatic biopsy specimens were available from 9 patients with strong evidence of AIP and detailed clinical and follow-up data. These patients met the same selection criteria as the above cohort of 53 patients.

Tissues

The histopathological material from the 53 selected cases was obtained from 43 pancreaticoduodenectomy specimens, 8 distal pancreatectomy and 2 total pancreatectomy specimens. The pancreatic biopsies consisted of 5 intraoperative biopsy specimens and 4 ultrasound (US)-guided percutaneous fine-needle core specimens, including cytological material. Tissue blocks were retrieved from the files and consultation files of the Department of Pathology of the University of Kiel, Germany (patients 1–38), the Department of Pathology of Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA (patients 39, 40) and the Department of Pathology of the University of Verona, Italy (patients 41–62). Eight patients included in the series (patients 1, 2, 5–9, 11) had been reported on previously [9]. Additional histopathological material, retrieved from the files of the Department of Pathology, Kiel, was obtained from 147 resection specimens showing chronic pancreatitis characterized by one or more of the following criteria: presence of pseudocysts, calculi, irregular duct dilatation, pancreas divisum and duodenal wall inflammation associated heterotopic pancreatic tissue.

All tissue samples were routinely fixed in formalin or Bouin's fixative and embedded in paraffin. Multiple samples were obtained from the surgical specimens. The number of blocks available in each case ranged from 2 to 18. In the group of biopsied patients, only a single block was available in each case. Deparaffinized sections 4-µm thick were stained with hematoxylin and eosin and periodic acid-Schiff, both with and without diastase pretreatment.

Immunohistochemical analysis was carried out on serial sections in 20 of the 53 selected cases and 10 of the remaining 147 cases, using the alkaline phosphatase-anti-alkaline phosphatase (APAAP) or peroxidase-anti-peroxidase (PAP) method. The antibodies used for the immunohistochemical stains included CD3 (Dako, Glostrup, Denmark, polyclonal), CD4 (Novocastra, Newcastle, UK, 1F6), CD8 (Dako, C8/144B), CD20 (Dako, clone 26), CD57 (Immunotech, Marseille, France, polyclonal), CD79α (Dako, JCB117), kappa and lambda chains (Dako, A8B5, N10/2), CD68 (Dako, 3MA134), S100 (Dako, polyclonal), HLA-DR (Biotest-Seralc, Brussels, Belgium, Tu34), vimentin (Dako, V9) and smooth muscle actin (Dako, 1A4).

Table 1 Grading of severity of autoimmune pancreatitis

Grade 1	Scattered periductal lymphoplasmacytic infiltrates; mild duct narrowing; almost no interlobular and acinar involvement
Grade 2	Multiple periductal lymphoplasmacytic infiltrates; mild periductal fibrosis and duct narrowing; mild interlobular and acinar involvement; focal inflammatory storiform fibrosis; occasional, mild venulitis
Grade 3	Diffuse periductal lymphoplasmacytic infiltrates; marked periductal fibrosis and duct obstruction; moderate interlobular and acinar involvement; moderate focal inflammatory storiform fibrosis; frequent venulitis; scattered lymphoid follicles
Grade 4	Diffuse periductal lymphoplasmacytic infiltrates; severe periductal fibrosis and duct obstruction/disappearance; severe interlobular and acinar involvement; severe inflammatory storiform fibrosis and diffuse sclerosis; frequent venulitis and occasional arteritis; scattered and occasionally prominent lymphoid follicles

Grading of severity and activity index

The detailed histopathological features of AIP were assessed according to a standardized protocol. Briefly, the following features were considered: focal involvement (i.e. if the sections contained affected and unaffected pancreatic tissue next to each other) and diffuse involvement (i.e. if the sections contained only affected tissue); periductal lymphoplasmacytic infiltration, ductal narrowing and obstruction, periductal fibrosis, "granulocytic epithelial lesions" [GELs (i.e. granulocytic periductal and ductal infiltration with or without rupture and destruction of ductal epithelium)], acinar lymphoplasmacytic infiltration, acinar granulocytic infiltration, periacinar fibrosis and acinar atrophy, inflammatory storiform fibrosis (myofibroblastic cells intermingled with some lymphocytes, plasma cells, macrophages and collagen bundles), venulitis, obliterative arteritis, presence of lymphoid follicles, bile-duct involvement, and involvement of the major and/or minor papilla. All features were graded according to their severity and extent as mild/moderate or severe. On the basis of this evaluation, the grade of severity of the entire inflammatory process was determined, as outlined in Table 1. Since the "GELs" were only found in a limited number of cases and appeared to be active changes, differing in severity from patient to patient, an activity index was determined in every affected patient. The activity was considered low if there were only sparse GELs affecting one or multiple ducts and sometimes associated with a few intralobular granulocytes. High activity, in contrast, was characterized by prominent GELs affecting one or multiple ducts, forming "duct abscesses," occasionally leading to duct destruction and commonly associated with inter- and intralobular granulocytes.

Results

Surgically treated patients

Clinical features

Table 2 summarizes the detailed clinical features of the 53 selected patients. They included 35 men and 18 women ranging in age from 14 years to 77 years (mean 56 years; men 56 years; women 55.5 years). Of the patients, 40 (75%) presented with jaundice. Abdominal discomfort and pain were the main symptoms in 16 patients. Since, radiologically, 51 patients were found to have either a mass-forming lesion, the preoperative diagnosis in these patients was pancreatic carcinoma. In two patients the radiological findings were suggestive of chronic pancreatitis, but a carcinoma could not be excluded. Of the patients, 43 were treated by pancreaticoduodenectomy, 8 by distal pancreatectomy and 2 patients by total pancreatectomy. At the time of diagnosis, 10 of the 53 patients (19%) had associated autoimmune or autoimmune-related diseases (Table 2), Sjögren's syndrome being most fre-

quent (4 of 53 patients). During follow-up, 4 other patients also developed autoimmune diseases. Apart from these diseases, one patient had had Hodgkin's disease, another suffered from bronchial asthma and a third patient had diabetes which was already present before the symptoms of pancreatitis started. In all patients, the short-term postoperative course was uneventful. Among 22 of 53 (41%) patients who were followed for a mean of 3 years (range 6 months to 23 years), 5 (24%) developed an inflammatory stenosis of the bile-duct remnant at an average of 2.5 years (range 1–4 years) after pancreaticoduodenectomy. Of these patients, 2 were treated by liver transplantation, the others by stenting the bile-duct stenosis. One of the transplant patients died of sepsis. Histopathological examination of the explanted livers revealed a stenosing fibroinflammatory process showing many lymphocytes and plasma cells and surrounding the common hepatic duct and its hilar branches. The portal tracts were expanded by periportal and periductal fibrosis and contained scattered lymphocytes, findings consistent with a diagnosis of unspecific chronic cholangitis and excluding primary sclerosing cholangitis. Another patient suffered from relapsing pancreatitis and additionally developed Sjögren's syndrome after 8 years. None of the patients received steroid treatment for the pancreatic disease before or after pancreatic resection.

Histopathological findings

The frequency of occurrence of the investigated criteria is summarized in Fig. 1. The most significant and frequent finding was an intense inflammatory cell infiltration around medium-sized and large interlobular ducts (Fig. 2). Smaller ducts were also involved, but usually only in advanced cases. The periductal infiltrates were composed mainly of lymphocytes and plasma cells, but also contained some macrophages. Mast cells were detected in almost all cases, but were only occasionally abundant. The affected ducts were narrowed by an infolding of their epithelium, often giving their lumen a slit-like or star-like appearance. In most cases, the infiltrated duct walls were further thickened by cuff-like fibrosis and this change was usually accompanied by an extension of the inflammatory infiltrate and fibrosis into the interlobular and often also the intralobular areas. The intralobular fibrosis showed a periacinar pattern and was associated with atrophy of the acinar cells and encasement of the islets. In about half of the patients, a special type of fi-

Table 2 Clinical features of patients with diagnosis of autoimmune pancreatitis on surgical specimens. *CA* carcinoma, *CP* chronic pancreatitis, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *SS* Sjögren's syndrome, *UC* ul-

cerative colitis, *CD* Crohn's disease, *RA* rheumatoid arthritis, *RF* retroperitoneal fibrosis, *TH* thyroiditis, *NED* no evidence of disease, *NA* not available, *A* alive, *CBD* common bile duct, *DOD* dead of disease

Case no.	Age (years)	Sex	Jaundice	Pain	Autoimmune disease	Site	Clinical diagnosis	Surgical procedure	Follow-up (years)
1	29	Male	+	–	SS	Head	CA	PD	
2	17	Female	–	+		Tail	CA	DP	
3	50	Male	+	–		Head	CA	PD	
4	69	Male	+	–		Head	CA	PD	
5	77	Male	+	–		Head	CA	PD	A, 2, CBD stenosis
6	59	Male	+	–	CD and RA	Head	CA	PD	
7	20	Female	+	–		Diffuse	CA	TP	
8	59	Male	+	–	CD	Head	CA/CP	PD	
9	67	Female	+	–		Head	CP	PD	
10	28	Male	+	–		Head	CA	PD	
11	76	Male	+	–		Head	CA	PD	NED, 7
12	71	Male	–	+		Tail	CA	DP	
13	24	Female	–	+		Tail	CA/CP	DP	
14	64	Male	+	–		Head	CA	PD	
15	73	Male	+	–		Head	CA	PD	A, 4, CBD stenosis
16	62	Male	+	–		Head	CA	PD	DOD, 1, CBD stenosis
17	56	Male	+	–		Head	CA	PD	
18	24	Female	+	–		Head	CA	PD	
19	70	Male	+	–		Head	CA	PD	
20	64	Female	+	–		Head	CA	PD	NED, 3
21	69	Female	+	–		Head	CA	PD	
22	60	Male	+	–		Head	CA	PD	
23	71	Female	+	–		Head	CA	PD	
24	66	Male	+	–		Head	CA	PD	NED, 9
25	36	Male	–	+	SS and TH	Tail	CA	DP	A, 1, CBD stenosis
26	69	Male	+	–	SS and RF	Head	CA	PD	A, 3, recurrence
27	40	Female	–	+		Tail	CA	DP	
28	40	Male	–	+		Tail	CA	DP	
29	66	Female	+	–		Head	CA	PD	
30	56	Male	+	–		Head	CA	PD	A, 3, CBD stenosis
31	65	Female	+	+		Head	CA	PD	NED, 2
32	59	Male	+	–		Head	CA	PD	
33	52	Male	+	–		Head	CA	PD	
34	67	Male	+	–		Head	CA	PD	
35	41	Female	+	–		Head	CA	PD	
36	30	Male	+	–		Head	CA	PD	
37	40	Male	+	–		Head	CA	PD	
38	62	Male	+	–		Head	CA	PD	NED, 7
39	64	Female	–	+		Diffuse	CA	TP	NED, 11
40	14	Female	–	+		Head	CA	PD	
41	36	Male	–	+	CD	Head	CA	PD	NED, 8
42	56	Male	+	–	UC	Head	CA	PD	NED, 16
43	52	Male	–	+		Tail	CA	DP	
44	62	Female	+	+	UC	Head	CA	PD	NED, 1
45	66	Male	+	–		Head	CA	PD	NED, 3
46	32	Male	+	–	UC	Head	CA	PD	NED, 6
47	41	Male	–	+		Head	CA	PD	
48	46	Female	+	–		Head	CA	PD	NED, 2
49	54	Female	–	+		Tail	CA	DP	NED, 23
50	26	Male	+	–		Head	CA	PD	NED, 3
51	49	Male	+	–	SS	Head	CA	PD	A, 8, recurrence
52	48	Male	–	+		Head	CA	PD	
53	57	Female	+	+		Head	CA	PD	NED, 0.5

brotic changes was encountered, characterized by the presence of inflammatory cells and plump myofibroblasts intermingled with collagen bundles, some of which were arranged in a storiform pattern (Fig. 3). In 10% of the cases, this type of fibrosis occupied a large area, giving it a tumorous appearance. Scattered lymphoid follicles, mainly located at the periphery of the fibrotic areas, were

found in two-thirds of the cases. In 7 cases, however, they were restricted to periductal areas (Fig. 4). Another frequent finding was venulitis, which was mainly present in fibrotic areas (Fig. 5). Obliterative arteritis was less common and was usually seen together with advanced fibrosis. Focal involvement of the resected tissue (i.e. involvement of a small group of lobes, leaving the adja-

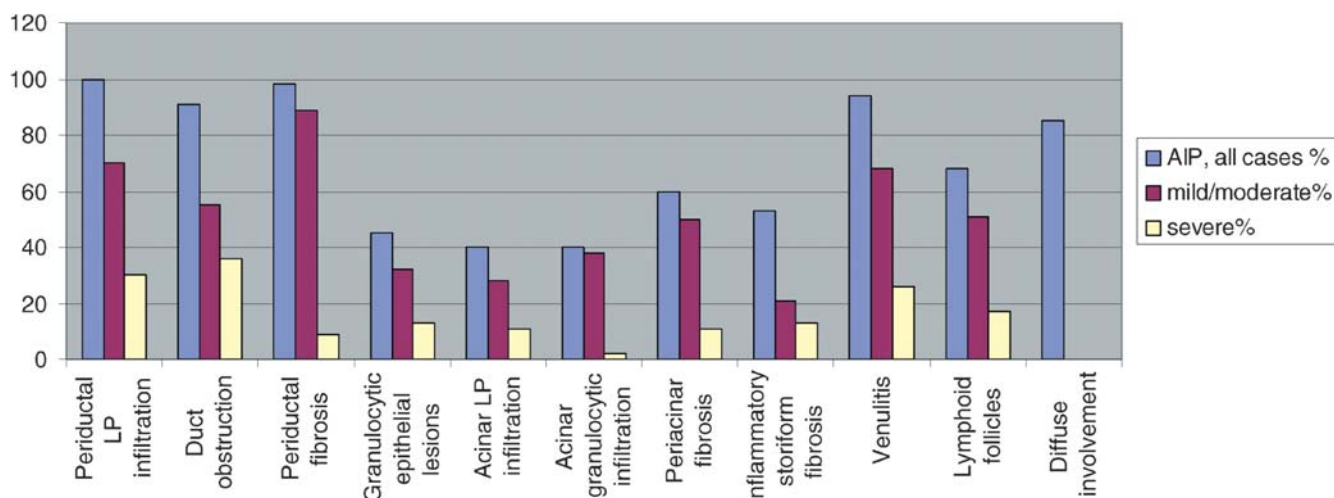


Fig. 1 Frequency (%) of histopathological features in 53 resected pancreatic specimens from patients with autoimmune pancreatitis (AIP)

cent ones unaffected) was seen in 8 patients (15%). The

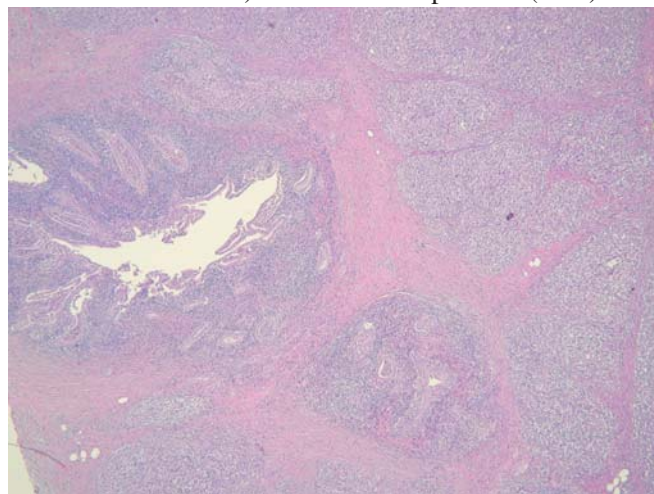


Fig. 2 Autoimmune pancreatitis showing periductal lymphoplasmacytic infiltration and fibrosis leading to duct narrowing (H&E $\times 120$)

distal bile duct was affected by the inflammatory process in 25 patients (47%) (Fig. 6). However, this figure is not representative, because it only refers to the cases with histologically documented involvement of the distal bile duct. If all patients with jaundice because of a bile-duct stenosis are considered, 75% of the patients were affected. In 18 of 53 (34%) patients, the inflammatory process involved the major papilla and in 6 of 53 (11%) the minor papilla was also involved. In 16 patients (30%), both the distal bile duct and the major and/or minor papilla were affected. When the severity of the disease was graded on the basis of the above findings (Table 1), only 4 cases proved to be in grades 1 (1 of 53) or 2 (3 of 53), while the majority (92%) showed grades 3 (25 of 53) and 4 (24 of 53).

In addition to the described chronic changes, GELs (Fig. 7) were observed in 24 of 53 (45%) patients. The

granulocytic infiltrate consisted mainly of neutrophils in

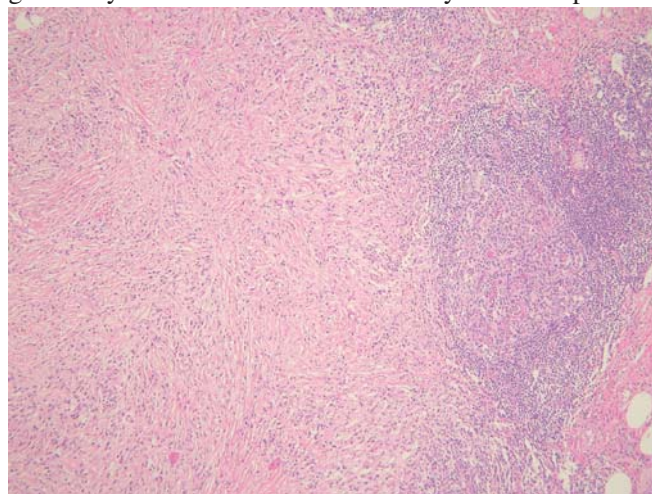


Fig. 3 Autoimmune pancreatitis showing complete replacement of acinar tissue by storiform fibrosis (H&E $\times 200$)

all cases. In 21 of 53 cases, it extended into the small intralobular ducts and the acini. The granulocytic infiltration was considered an acute inflammatory process and was classified into two grades of activity. In 17 of 24 (71%) patients, the activity was classified as low and in 7 of 24 (29%) patients as high. A predominantly eosinophilic infiltration that barely affected the ductal epithelium was observed in 3 cases.

When the activity index of the GELs was related to the severity grade of the chronic inflammatory process, it was found that high activity was mainly associated with grade 4 (4 of 7 patients, 57%), whereas low activity was mainly noted in grade 3 (12 of 17 patients, 70%).

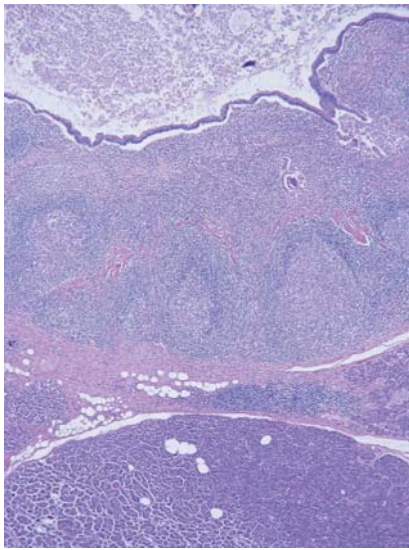


Fig. 4 Autoimmune pancreatitis showing lymphoid follicles within a dense mononuclear cell infiltration surrounding a large duct (H&E ×120)

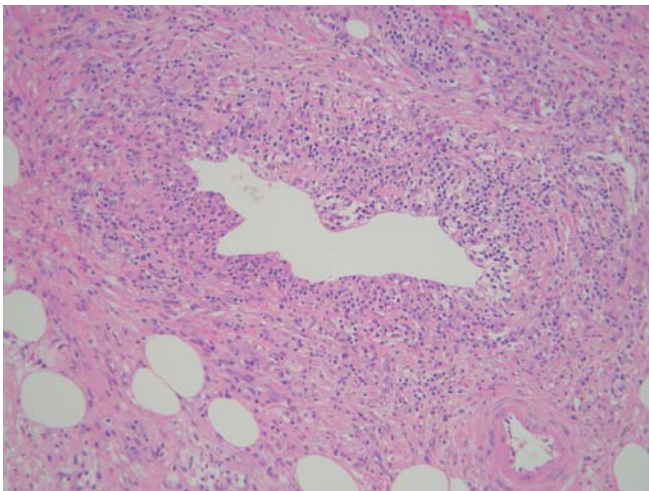


Fig. 5 Autoimmune pancreatitis showing an area with intense venulitis (H&E ×200)

Immunohistochemical findings

Immunohistochemical staining in the 20 selected cases revealed a predominance of CD3+, CD4+ and CD8+ T lymphocytes in the inflammatory infiltrates surrounding the medium-sized and large interlobular ducts. In addition, the infiltrates contained CD20+ B lymphocytes and CD68+ macrophages. The plasma cells showed a polyclonal pattern, expressing either kappa or lambda chains. T lymphocytes (CD4+>CD8+) occasionally invaded the duct epithelium. The lymphoid follicles that were found either scattered in sclerotic tissue or around ducts consisted mainly of B lymphocytes.

Analysis of the spindle cells that were found in areas with inflammatory storiform fibrosis revealed the ex-

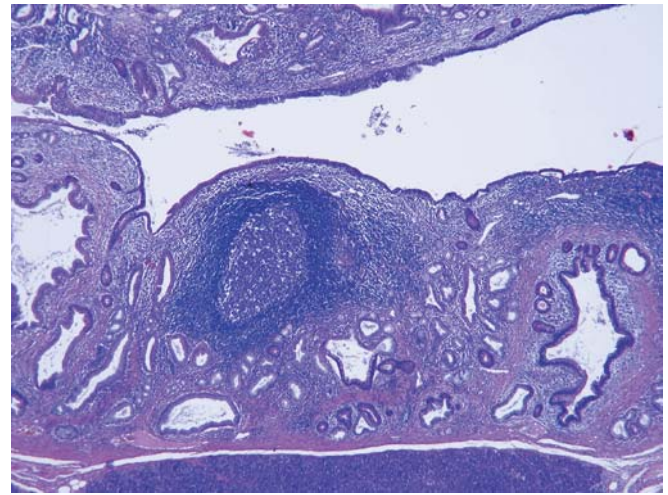


Fig. 6 Autoimmune pancreatitis with common bile duct involvement (H&E ×120)

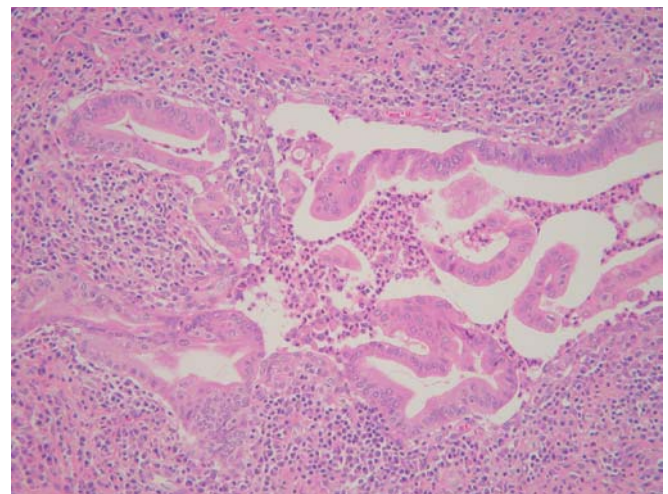


Fig. 7 Autoimmune pancreatitis showing granulocytic infiltration and destruction of the ductal epithelium (H&E ×200)

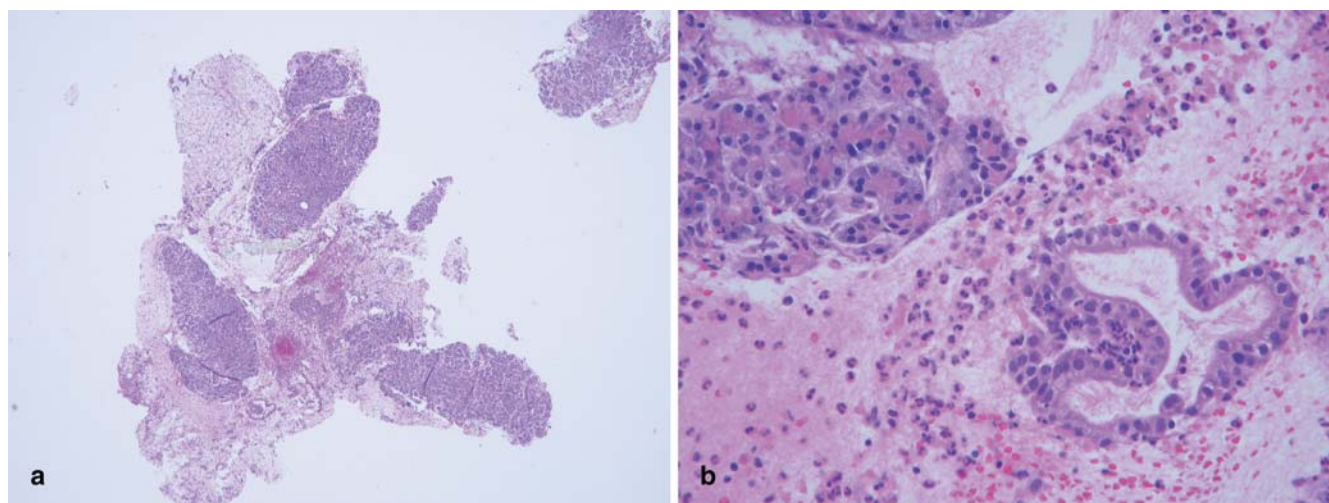
pression of smooth muscle actin and vimentin, whereas most of the intermingled mononuclear cells stained with CD68, characterizing them as macrophages. In addition, T lymphocytes and CD79+ plasma cells were identified. Scattered HLA-DR expression was found in duct cells, endothelial cells, inflammatory cells and myofibroblastic cells.

Comparison of histopathological and immunohistochemical features

The most significant findings, i.e. periductal lymphoplasmacytic infiltration, cuff-like periductal fibrosis and venulitis, which were found in all or most of the 53 selected specimens (Fig. 1), were not detected in any of the other 147 pancreatic specimens showing chronic pancre-

Table 3 Clinical and radiological features in patients with suspected autoimmune pancreatitis who underwent pancreatic biopsy. *UC* ulcerative colitis, *BD* before diagnosis, *AD* after diagnosis, *NED* no evidence of disease

Case no.	Age (years)	Sex	Signs and symptoms	Radiological findings	Site	Autoimmune disease	Steroid therapy	Follow-up (years)
1	47	Male	Jaundice	Mass	Head	UC (3 years BD)		NED, 10
2	25	Female	Jaundice	Mass	Head	UC (1 week AD)		NED, 8
3	55	Male	Abdominal pain	Mass	Head	UC (10 years BD)		NED, 8
4	50	Male	Jaundice	Mass	Head	UC (4 years BD)		NED, 9
5	18	Male	Jaundice	Mass	Head	UC (3 years AD)		NED, 3
6	50	Male	Jaundice	Enlargement	Head-body	UC, sialadenitis	Yes	Recurrence, 6
7	60	Male	Jaundice	Enlargement	Head-body	Retroperitoneal fibrosis		NED, 6
8	29	Male	Abdominal pain	Mass	Body	UC (2 years BD)	Yes	Recurrence, 2
9	32	Female	Abdominal pain	Mass	Head	No	Yes	NED, 1

**Fig. 8** Biopsy specimen from a patient (no. 9, Table 5) with suspected autoimmune pancreatitis. **a** Low-power view showing perilobular fibrosis and lymphoplasmacytic infiltration. **b** High-power view showing a granulocytic epithelial lesion (H&E $\times 40$ and $\times 240$)

atitis associated with pseudocysts, calculi, irregular duct dilatation, pancreas divisum and/or duodenal wall inflammation. The immunohistochemical staining identified sparse T cell infiltrates and a few scattered B cells and macrophages. Plasma cells were very rare. Smooth muscle actin positive myofibroblasts were abundant in the fibrotic areas close to pseudocysts as well as in interlobular areas with high cellularity.

Biopsied patients

Clinical features

Table 3 summarizes the clinical features of 9 patients who were diagnosed on the basis of biopsy and radiological findings. They included 7 men and 2 women, whose mean age was 47 years (range 18–60 years). Of these patients, 6 had jaundice in association with pain; 3 patients had pain only. Ulcerative colitis had developed in 4 patients before the diagnosis of AIP and in 3 after or at the time of diagnosis of AIP; 1 patient had retroperitoneal fibrosis and another chronic sialadenitis. Radiologically, US and

computed tomography (CT) scans revealed a mass or enlargement in the pancreatic head in 8 patients and 1 had a mass in the body. All patients were followed up (mean period 6 years; range 1–10 years); 6 patients are alive and well without steroid treatment. Steroid treatment was given to 3 patients, starting with 50–75 mg tapered by 2.5–5 mg/week. Of these 3 patients, 2 are still on therapy because abdominal pain recurred when they reached a dose of 10–15 mg; 1 patient is doing well after withdrawal of the initial steroid therapy.

Histopathological findings

Intraoperative wedge biopsy was performed in 5 patients who had an explorative laparotomy to rule out malignancy. The biopsy specimens did not show any signs of any type of pancreatic malignancy. In 1 patient, the biopsy findings were diagnostic of AIP (Fig. 8 and Table 4). In another patient, the findings were suggestive of AIP, while in the remaining patients they were inconclusive. In 4 patients, a percutaneous US-guided, fine-needle-core biopsy was performed. Both the histological and the cy-

Table 4 Histopathological features of pancreatic biopsy specimens from patients with suspected autoimmune pancreatitis. *FNCB* fine-needle-core biopsy, *IWB* intraoperative wedge biopsy, *LP* lymphoplasmacytic, *GEL* granulocytic epithelial lesion

Case no.	Biopsy	LP infiltrate	Periductal LP infiltrate	GEL	Acinar granulocytic infiltrate	Venulitis	Storiform proliferation	Histopathology
1	IWB	++	++	+	+	+	–	Diagnostic
2	IWB	++	–	+	+	+	+	Suggestive
3	IWB	–	–	–	–	–	–	Inconclusive
4	IWB	–	–	–	–	–	–	Inconclusive
5	IWB	–	–	–	–	–	–	Inconclusive
6	FNCB	+	–	–	+	–	–	Suggestive
7	FNCB	++	–	–	–	+	+++	Suggestive
8	FNCB	–	–	–	+	–	–	Inconclusive
9	FNCB	+	+	+++	++	–	+	Diagnostic

Table 5 Patients with associated autoimmune diseases, distinguished by the absence or presence of granulocytic epithelial lesions (GELs). *CBD* common bile duct, *NED* no evidence of disease

Case no.	Age (years)	Sex	Site	Disorders	Follow-up	Recurrence (years)
AIP/GEL-neg						
1	29	Male	Head	Sjögren's syndrome	/	/
2	59	Male	Head	Crohn's disease, rheumatoid arthritis (before)	/	/
3	36	Male	Head	Sjögren's syndrome, thyroiditis (+1 yr)	1 year, CBD stenosis	1, CBD stenosis
4	69	Male	Head	Sjögren's syndrome, retroperitoneal fibrosis (+3 yrs)	3 years, recurrence	3, recurrence
5	49	Male	Head	Sjögren's syndrome (+2 yrs)	8 years, recurrence	8, recurrence
6	50	Male	Head-body	Ulcerative colitis (simultaneously), sialadenitis (+1 yr)	6 years, recurrence	6, recurrence
7	60	Male	Head-body	Retroperitoneal fibrosis (simultaneously)	6 years, NED	No
AIP/GEL-pos						
1	59	Male	Head	Crohn's disease (before)	/	/
2	36	Male	Head	Crohn's disease (before)	8 years, NED	No
3	56	Male	Head	Ulcerative colitis (–12 years)	16 years, NED	No
4	62	Female	Head	Ulcerative colitis (–1 year)	1 year, NED	No
5	32	Male	Head	Ulcerative colitis (+2 years)	6 years, NED	No
6	47	Male	Head	Ulcerative colitis (–3 years)	10 years, NED	No
7	25	Female	Head	Ulcerative colitis (+1 week)	8 years, NED	No

tological evaluation excluded a malignant pancreatic tumor and allowed the diagnosis of AIP in 1 patient, while it was suggestive in 2 others and inconclusive in 1 (Table 4).

Clinicopathological correlations

Clinicopathological correlation was only performed in the selected 53 surgically treated patients. When the 24 patients with GELs were compared with the 29 patients without this finding, it was found that the sex distribution was almost equal (57% men) in the AIP/GEL-positive group, whereas males predominated (77%) in the AIP/GEL-negative group. Moreover, the AIP/GEL-positive patients were considerably younger (mean age 40.5 years versus 64 years), had no Sjögren's syndrome and only ulcerative colitis or Crohn's disease and, finally, showed no recurrence of AIP (Table 5). In contrast, the AIP/GEL-negative group showed a strong association with Sjögren's syndrome and retroperitoneal fibrosis and were all males. In addition, all recurrent bile-duct stenoses were observed in the latter group of patients (Table 5), who in general also had more advanced AIP than the AIP/GEL-negative patients. There was no significant difference

between the two groups of patients regarding the main localization of the disease (i.e. pancreatic head versus body-tail).

Discussion

Periductal lymphoplasmacytic infiltration, cuff-like periductal fibrosis and venulitis were identified as the most characteristic histological lesions in pancreatic specimens that showed chronic pancreatitis lacking pseudocysts, calculi, irregular duct dilatations, pancreas divisum and/or duodenal wall inflammation associated with heterotopic pancreatic tissue. This spectrum of findings seems to define the pathology of AIP, since all chronic pancreatitis specimens in our series that showed one or more of the above-mentioned changes, such as pseudocysts or calculi, lacked lymphoplasmacytic duct changes and venulitis. Recent reports on the occurrence of calculi in otherwise typical cases of AIP do not contradict our findings, since the calculi obviously only appeared late in the course of AIP and were not present at the time of diagnosis [13]. Further help in distinguishing AIP from chronic pancreatitis of other causes is provided by the frequent occurrence of AIP in the head of the pancreas combined with

bile-duct stenosis and the abundant occurrence of plasma cells and CD4 and CD8 T lymphocytes around the ducts.

Reports of chronic interstitial pancreatitis and primary inflammatory sclerosis by Ball [5] and Sarles [32], respectively, were probably the first recorded cases of AIP. However, their histological descriptions are only suggestive of AIP—not conclusive. The first description that we regard as diagnostic of AIP was by Kawaguchi [18] and included prominent infiltration of the pancreas by lymphocytes and plasma cells combined with marked interstitial fibrosis, acinar atrophy and obliterating phlebitis. Subsequently, it became obvious that the lymphoplasmacytic infiltration concentrated around narrowed pancreatic ducts and was frequently associated with a “cuff” of periductal fibrosis. Moreover, it was noted that there were often granulocytes (some of them eosinophils), lymph follicles and an occasionally distinct patchy involvement [2, 3, 9, 14, 25, 41, 44]. Analysis of our 53 patients, none of them previously treated with steroids, revealed that periductal lymphoplasmacytic infiltration was present in each case, followed in order of frequency by periductal fibrosis and venulitis. In 80% of the patients, these changes were seen throughout the pancreatic tissue that was available for review. In the remaining patients, the involvement of the pancreatic tissue was patchy. Less frequent histopathological features, present in only 40–60% of cases, included involvement of the acinar tissue, fibrotic areas rich in myofibroblasts where acinar cells, ducts and islets were replaced by collagen bundles partly arranged in a storiform pattern, and inflammatory cells such as lymphocytes, plasma cells, neutrophils and occasionally also eosinophils. An impressive acute inflammatory component that we called GEL was detected in 42% of cases. This change, first described by Ectors [9] and later by Scully [33], was characterized by focal detachment, disruption and destruction of the epithelium of interlobular ducts due to invading neutrophilic and occasionally eosinophilic granulocytes, which were also in the duct wall, particularly under the duct epithelium, and in the duct lumen (duct abscesses). In the cases with the most severe GELs, the acute inflammatory infiltrate extended into the ductules, acini and interstitial spaces. Notohara [25] recently reported this finding in 31% of 35 AIP cases, a proportion similar to ours. Their diagnosis in these cases was IDCP, and they differentiated it from LPSP. Although we believe that the GEL is a distinctive biologically important finding, we refrain from using Notohara’s terminology since, in our study, the GELs were superimposed on the periductal lymphoplasmacytic infiltration and fibrosis and did not occur independently of these basic changes. We, therefore, prefer “AIP with GEL” to identify pancreases exhibiting this acute inflammatory component.

The severity of the chronic inflammatory process and the activity of the GELs varied from case to case. To quantify these differences in individual patients, we developed a grading system and an activity index, distinguishing four grades of severity and two levels of activity, respectively. Grading of the chronic inflammatory process

revealed that 92% of the cases were grades 3 and 4. We had only one grade-1 and three grade-2 cases. Grade-1 and grade-2 AIP may only rarely cause clinical symptoms (e.g. pain and jaundice) of such intensity that they become an indication for resection. Looking at the acute inflammatory component of AIP represented by the GELs, we noted that the grade of severity of AIP paralleled the activity index in 60–70% of the patients, suggesting that the two processes are to some extent interrelated.

Fibrosis of the pancreas in AIP predominantly shows a periductal and interlobular pattern [20], features that are characteristic of grade-3 AIP. If the fibrosis extended into the lobules, grade-4 AIP was assigned. In grade 4, there were also fibroinflammatory areas that share histological features with those described in inflammatory pseudotumors of the pancreas and the common bile duct [7, 8, 10, 11, 24, 27, 31, 38, 40, 42]. These features include smooth muscle actin-positive myofibroblasts admixed with lymphocytes and plasma cells and embedded between bundles of dense collagen with storiform foci. Additionally, venulitis and obliterative arteritis have also been mentioned in several cases [8, 40, 42]. Since the clinical features of patients with inflammatory pseudotumors are very similar, the possibility that inflammatory pseudotumors of the pancreas might represent grade-4 AIP in which the fibroinflammatory storiform fibrosis has acquired a tumor-like appearance should be considered [10].

Because most of our patients presented with jaundice, pancreatic head resection specimens comprised almost 80% of the resected material. Although the inflammatory lesions in the resected tissue often extended up to the resection margin, it appeared that the major involvement was in the head of the pancreas since the corresponding CT images from these cases showed a mass-forming enlargement of the head. In 15% of our patients, the disease obviously focused on the tail of the pancreas, which was resected because of a mass. Primary involvement of the tail was supported by a disease-free pancreatic margin in these cases. These findings suggest that in most instances AIP is a focally accentuated disease that involves the head of the pancreas, including the distal common bile duct, four times more often than the remainder of the gland. However, the patchy pattern of involvement in some cases suggests that non-resected parenchyma may be involved even if the resection margins appear to be normal. Moreover, our series included two patients whose pancreases were totally removed because of suspected malignancies. In each of these patients, the entire pancreatic tissue was found to be affected by AIP, although unevenly. Similar conclusions can be drawn from ERCP images [15]. AIP, therefore, may involve the entire pancreas, but is usually focal, with strong preference for the head. Here, the fibroinflammatory process, if it shows grade-3 and grade-4 severity, affects the common bile duct and may also spread to the gallbladder, as has been noted in a number of reports [1, 18], and was also seen in some of our patients (data not shown).

Autoimmune diseases, notably autoimmune sialadenitis (Sjögren’s syndrome) [22, 36, 37, 39], Crohn’s disease

and ulcerative colitis [4, 23, 29, 35] and retroperitoneal fibrosis [31], have been reported in [38] between 8% and 25% of patients with AIP [3, 9, 14, 25, 41]. The incidence is higher if diseases such as Hashimoto thyroiditis, rheumatoid arthritis or asthma are added. The real incidence of autoimmune diseases in AIP, however, will only be ascertained if we consider not only the diseases that are present at the time of diagnosis, but also those that develop subsequently. Two of our patients developed Sjögren's syndrome or rheumatoid arthritis only after follow-up of several years. Autoimmune diseases occurred in 19% of our patients, Sjögren's syndrome being most frequent.

Notohara [25] noted that the two patients with Sjögren's syndrome in their series were among those who had LPSP, whereas the two patients with ulcerative colitis or Crohn's disease showed IDCP, what we call AIP with GELs. In addition, they found those in the group of patients with LPSP were older, on average (63.4 years), and contained more males than the group with IDCP (average age 48 years, male:female ratio 5:7). Our findings confirm and extend these observations. Our AIP patients without GELs were also considerably older (mean age 64 years), included relatively more men and had a stronger association with Sjögren's syndrome than the AIP patients with GELs, who were younger (mean age 40.5 years) and had an almost equal sex distribution and a strong association with inflammatory bowel disease. These observations suggest that AIP is a heterogeneous disease with two biologically different types, morphologically characterized by the presence or absence of GELs and clinically by the association either with sclerosing autoimmune disease (e.g. Sjögren) or with inflammatory bowel disease. The biological relevance of these observations is further underlined by the fact that all recurrent bile-duct stenoses and AIP recurrences, which were noted in 5 of 22 patients whose follow-up data were available to us, occurred in AIP patients without GELs. It seems, therefore, that these patients may have a higher risk of recurrent AIP after resection, either in the common bile duct or in the pancreas, than AIP patients with GELs. Whether this dichotomy also applies to the response of AIP patients to steroid therapy [26], which has an approximate response rate of 80% [15], is not yet known. It is of interest to note that the GELs in AIP share a number of histological features with ulcerative colitis, a disease that is known to respond to steroid treatment.

In view of the high success rate of corticosteroid therapy in AIP, it can be anticipated that, in the future, the AIP patients who will be treated surgically will be those who prove refractory to steroids and suspect for carcinoma. It is therefore essential to improve our ability to recognize AIP on the basis of clinical data, biopsy, imaging and laboratory findings [28]. Among five wedge biopsy specimens obtained during exploratory laparotomy and four percutaneous fine-needle-core biopsy specimens, the histological findings were diagnostic or suggestive of AIP in about half of the patients. More importantly, malignancy was excluded in all cases. The

diagnosis of AIP relied on its specific features discussed above. In the other half of the patients, the biopsy specimens showed inconclusive changes, such as perilobular fibrosis, that may also be seen in other types of pancreatitis. As a consequence of the biopsy results, which were supplemented by clinical, laboratory and radiological findings [28], none of the patients underwent pancreatic resection. Clearly, these preliminary results concerning the value of biopsies in AIP need to be confirmed in a prospective study, but we are more optimistic in this respect than other authors who, on the basis of the risk of complications and inconclusive results in preoperative fine-needle aspirations from six patients, did not recommend pancreatic biopsy [41].

In summary, we have shown that AIP is characterized by a spectrum of morphological features. These include the absence of pseudocysts and calculi, the preferential occurrence in the head of the pancreas, with frequent involvement of the distal bile duct, and the presence of a cuff-like lymphoplasmacytic infiltration and fibrosis and venulitis. Although these features are very distinctive, it should be kept in mind that, in individual cases of AIP, calculi or other alterations that are more characteristic of other types of pancreatitis may develop [13]. The histopathological features of AIP allow a diagnosis to be made on biopsy specimens but, because of the occasional focal accentuation of the disease, we have to expect some biopsies to be inconclusive. If the pancreatic changes that we considered as grade 1 are interpreted as the initial alteration in AIP, the disease starts as a duct-associated lymphoplasmacytic inflammation that may progress to duct narrowing, periductal fibrosis and finally duct obliteration and diffuse fibrosis, the hallmarks of grade-4 AIP. In addition to this chronic fibroinflammatory process, there may be an acute inflammatory component characterized by GELs that may cause rapid duct destruction. The initiating event(s) of this obviously heterogeneous disease, which is primarily oriented toward the duct system including the distal common bile duct, is totally unclear. However, the predominance of CD4- and CD8-positive lymphocytes, the selective demonstration of IgG₄-positive plasma cells [17], the oligoclonal pattern of T-cell receptor γ gene rearrangement [10] and the morphological features of the disease point to a specific immune process directed against antigens related to the pancreatic duct system, but also to the biliary duct system. Infectious agents that could trigger the disease and could explain its focality and often rapid onset have not yet been detected.

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