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Idiopathic Duct Centric Pancreatitis in Korea: A Clinicopathological Study of 14 Cases

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Background: Idiopathic duct centric pancreatitis (IDCP) is a subtype of autoimmune pancreatitis (AIP) that is histologically characterized by granulocytic epithelial lesion and scarce IgG4-positive cells. This subtype of AIP has not been documented in Asian countries. **Methods:** We reviewed 38 histologically confirmed AIP cases and classified them into lymphoplasmacytic sclerosing pancreatitis (LPSP) and IDCP. Then, clinicopathological characteristics were compared between LPSP and IDCP. **Results:** Fourteen cases (36.8%) were IDCP. IDCP affected younger patients more than LPSP. IDCP was associated with ulcerative colitis in 35.7% of cases, whereas LPSP was associated with IgG4-related sclerosing diseases such as cholangitis, retroperitoneal fibrosis or sialadenitis in 41.7% of cases. IDCP was microscopically characterized by neutrophilic ductoacinitis with occasional granulocytic epithelial lesions, whereas LPSP was characterized by storiform inflammatory cell-rich fibrosis and obliterative phlebitis. IgG4-positive cells were not detected in any IDCP case but more than 20 IgG4-positive cells per high-power-field were invariably detected in LPSP cases. All patients with IDCP responded dramatically to steroids without recurrence, whereas 33.3% of patients with LPSP developed recurrences. **Conclusions:** IDCP is clinicopathologically distinct from LPSP and can be diagnosed when neutrophilic ductoacinitis or granulocytic epithelial lesions are observed in a pancreatic biopsy under the appropriate clinical setting.

Key Words: Autoimmune pancreatitis; Idiopathic duct centric pancreatitis; Granulocytic epithelial lesion; Biopsy, Needle

Autoimmune pancreatitis (AIP) is a distinct form of chronic pancreatitis, which has several autoimmune features such as elevated serum immunoglobulin levels and heavy lymphoplasmacytic infiltration.[1] Two histological subtypes have been recently described: 1) lymphoplasmacytic sclerosing pancreatitis (LPSP) or type 1 AIP and 2) idiopathic duct centric pancreatitis (IDCP) or type 2 AIP. LPSP is characterized by periductal lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and associated IgG4-related systemic diseases. In contrast, IDCP is characterized by the presence of granulocyte epithelial lesions (GEL) and the absence of systemic involvement.[2,3] GEL is histologically defined by focal disruption and destruction of the duct epithelium resulting from invasion of mainly neutrophilic granulocytes.[4] Therefore, IDCP has also been called AIP with GEL, whereas LPSP has been called AIP without GEL. Similar to LPSP, IDCP is also associated with a periductal lymphoplasmacytic infiltration and storiform fibrosis but to a lesser extent than that of LPSP.[5] Although IDCP has been well described in Western countries, it remains poorly defined in Asian countries. To resolve this question, we identified IDCP cases among histologically documented AIP cases and described their clinicopathological characteristics.

MATERIALS AND METHODS

Patients and samples

We selected 38 patients diagnosed with AIP at Asan Medical Center, Seoul, Korea between 1995 and 2010. The diagnosis of AIP was based on the Asian diagnostic criteria.[6] Briefly, all patients presented with typical radiological features of AIP such as diffuse swelling of the pancreas and pancreatic duct stricture spanning the long segment.[7] Patients with a history of significant alcohol ingestion or radiographic features suggesting non-autoimmune chronic pancreatitis such as calculi and significant upstream pancreatic duct dilatation were excluded.[8] The mean age was 50 years (range, 18 to 72 years), and the male to female

ratio was 5.33 : 1. Five patients with LPSP and one patient with IDCP underwent surgical resection under the suspicion of pancreatic cancer. In the remaining patients, the diagnosis of AIP was confirmed by pancreatic core biopsy, and they were treated with corticosteroids. All patients were followed up with an emphasis on the radiological response to treatment.

Histopathological analysis

All specimens were formalin-fixed and paraffin-embedded to prepare hematoxylin and eosin (H&E) stained slides. Histological features were carefully reviewed by two independent pathologists (KHJ and KJ). We recorded several important features such as periductal lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, neutrophilic ductoacinitis, and GEL. Based on the presence or absence of these histopathological features, we classified the 38 cases of AIP into two distinct subgroups: LPSP or AIP type 1 and IDCP or AIP type 2. The classification was based on descriptions from previous studies[6,9-14] with slight modifications. Briefly, we diagnosed cases as IDCP when they showed neutrophilic ductoacinitis, GEL, and the absence of or scarce IgG4-positive cells (< 10/high power field [HPF]), whereas we diagnosed cases as LPSP when they showed heavy lymphoplasmacytic infiltration, inflammatory cell-rich storiform fibrosis, obliterative phlebitis, and numerous IgG4-positive cells (> 20/HPF).

Immunohistochemistry

Immunochemical staining for IgG4 (monoclonal anti-mouse IgG4 antibody, Binding Site, Birmingham, UK) was conducted with 4 μm-thick paraffin embedded tissue sections, as described previously.[15] Briefly, antigen was retrieved by heating the tissue sections in pH 6.0 citrate buffer. Tissue sections were then incubated with primary anti-mouse IgG4 (1 : 400) for 37 minutes at 37℃. All procedures were performed using Benchmark XT and a Ventana Autostainer, and the primary antibody was detected using the UltraView Universal DAB Detection kit (Ventana, Rockland, IL, USA). The number of IgG4-positive cells was counted in 10 non-overlapping HPFs (×40 objective lens). The highest number was selected among the ten HPFs.

Statistical analysis

Comparisons between groups were performed using the χ^2 and Fisher's exact tests. All statistical analyses were performed using SPSS ver. 12.0K (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Histopathological characteristics

When we classified the 38 AIP cases histopathologically based on our criteria, 14 cases (36.8%) were IDCP and the remaining cases were LPSP. As summarized in Table 1, the histopathological characteristics of IDCP were distinct from those of LPSP. The most prominent histopathological feature of IDCP was neutrophilic ductoacinitis. Typically, many neutrophils, which were > 10 per HPF, were invariably observed in edematous lobules where ductoacinar units reside (Fig. 1A). Neutrophils were occasionally aggregated to form microabscesses (Fig. 1B). GEL, which is reportedly the most characteristic finding in IDCP, was seen in only one case (Fig. 1C). None of the cases showed IgG4-positive cells (Fig. 1D). In contrast, the most striking finding in LPSP was the inflammatory cell-rich storiform fibrosis. Numerous inflammatory cells, consisting mainly of lymphocytes and plasma cells, infiltrated as poorly defined aggregates or single files between dense whirling collagen bands (Fig. 2A). Obliterative phlebitis, one of the characteristic findings of LPSP, was noted in 12 cases (67%) (Fig. 2B). Some inconspicuous obliterative phlebitis foci on H&E stained slides were detected by elastic Van Gieson staining (Fig. 2C). All LPSP cases showed numerous IgG4-positive cells, which were > 20 per HPF (Fig. 2D). Interestingly, IgG4 was also strongly stained in

Table 1. Histopathological comparison between idiopathic duct centric pancreatitis (IDCP) and lymphoplasmacytic sclerosing pancreatitis (LPSP)

Histopathological features	IDCP (n = 14)	LPSP (n = 24)	p-value
Neutrophilic ductoacinitis[a]	14 (100)	0 (0)	< 0.001
Granulocytic epithelial lesion	1 (7.1)	0 (0)	0.368
Inflammatory cell-rich storiform fibrosis[b]	0 (0)	24 (100)	< 0.001
Obliterative phlebitis	0 (0)	16 (66.6)	< 0.001
Periductal lymphoplasmacytic infiltration	3 (21.4)	24 (100)	< 0.001
IgG4-positive cells (> 20/high-power-field)	0 (0)	24 (100)	< 0.001

Values are presented as number (%).
[a]Infiltration of more than 10 neutrophils per high magnification field (×40 objective lens) within lobules; [b]A peculiar type of fibrosis where many lymphocytes or plasma cells are infiltrated as poorly defined aggregates or as single files among dense whirling collagen fibers.

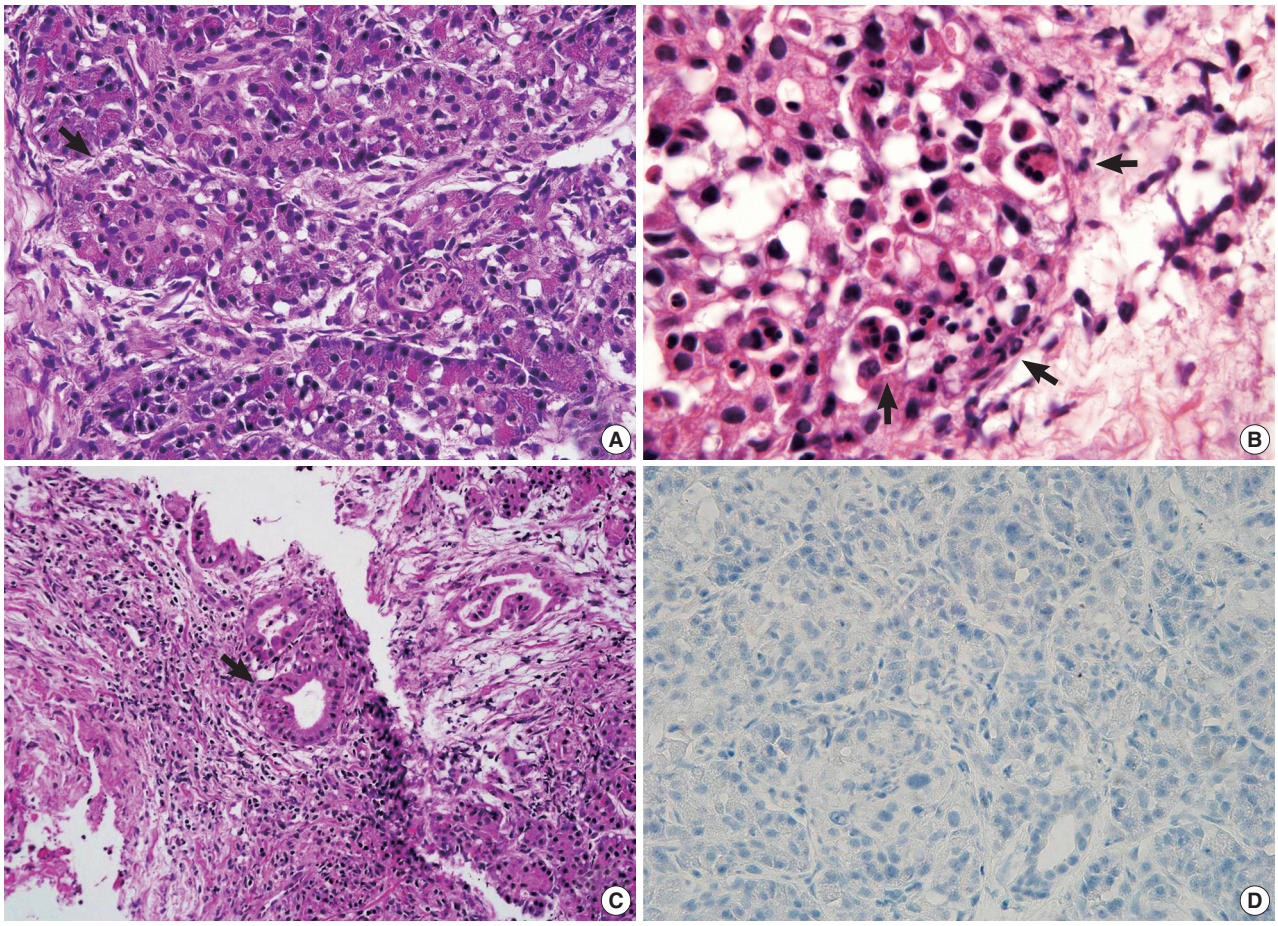

Fig. 1. Representative microscopic images of idiopathic duct centric pancreatitis. (A) Neutrophils accumulated mainly within the ductoacinar unit, namely neutrophilic ductoacinitis (arrow). (B) Infiltrated neutrophils occasionally make acinar microabscess (arrows). (C) In one case, pancreatic ducts are destroyed by neutrophils, which is called a granulocytic epithelial lesion (arrow). (D) No IgG4-positive cells are found (IgG4 immunohistochemical stain).

the stroma in most cases. Some eosinophils were occasionally observed in LPSP cases, but a significant number of neutrophils was not detected. Periductal lymphoplasmacytic infiltration was also seen in some IDCP cases but, even in those cases, it was confined to the periductal area, and the interlobular septa lacked inflammatory cell-rich storiform fibrosis.

Clinical characteristics

Clinical characteristics of patients with IDCP, particularly associated diseases, age of onset, and serum immunoglobulin levels, were also distinct from those of patients with LPSP (Table 2). First, the extrapancreatic manifestation was strikingly different between the two categories. Ulcerative colitis was exclusively observed in the IDCP cases (five of 14, 35.7%), whereas a variety of systemic IgG4-related sclerosing diseases were found (10 of 24, 41.7%) in the LPSP cases. The extrapancreatic IgG4-related sclerosing diseases consisted of sclerosing cholangitis (four cases), retroperitoneal fibrosis (four cases), sclerosing sialadenitis (two cases), and renal pseudotumors (three cases). Three patients had two concurrent extrapancreatic manifestations. Patients with IDCP were significantly younger than patients with LPSP (mean ± standard deviation, 35.29 ± 14.37 vs 58.54 ± 9.09, $p < 0.001$). As expected, serum IgG and IgG4 levels in patients with LPSP were frequently elevated (45.8% and 75.0%, respectively), whereas those of all patients with IDCP were within normal limits. Serum autoantibody levels were obtained in nine patients with IDCP and 20 with LPSP, but the number of patients with any significant level of autoantibodies was not different between the groups. The radiological findings of the patients with IDCP were indistinguishable from those of patients with LPSP on abdominal computed tomography, endoscopic retrograde cholangiopancreatography, and magnetic resonance cholangiopancreatography (Fig. 3).

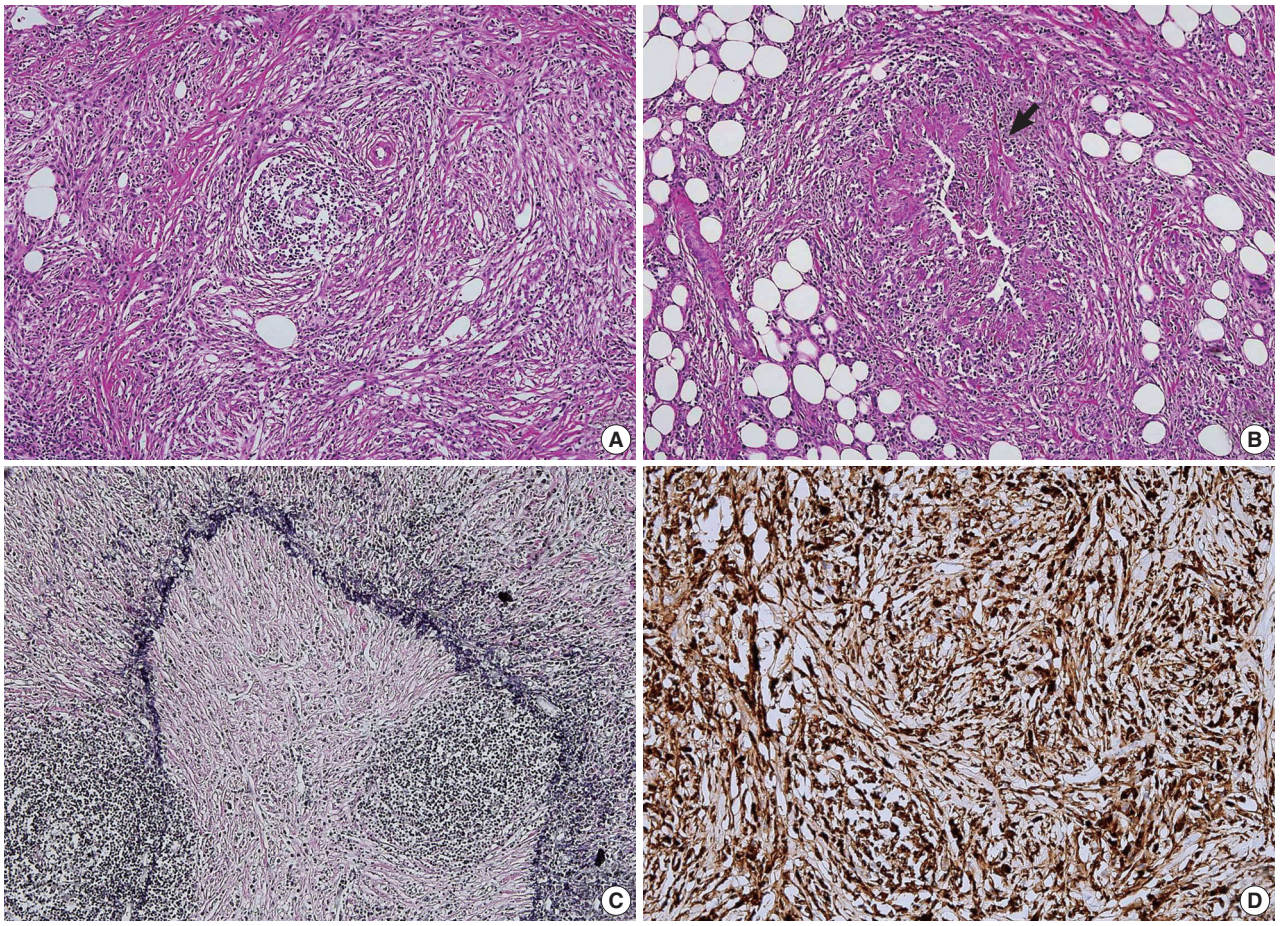

Fig. 2. Representative microscopic images of lymphoplasmacytic sclerosing pancreatitis (LPSP). (A) Numerous lymphocytes and plasma cells characteristically heavily infiltrated between whorling collagen fibers to form inflammatory cell-rich storiform fibrosis. (B) Some blood vessels are obliterated by the fibrosing inflammatory process called obliterative phlebitis (arrow). (C) Elastic Van Gieson staining is very useful for identifying completely obliterated blood vessels (Elastic Van Gieson stain). (D) Numerous IgG4-positive cells are observed in all LPSP cases (IgG4 immunohistochemical stain).

Response to steroid therapy

All patients with AIP who received steroid therapy showed a dramatic radiological response. However, some patients with LPSP (eight of 24, 33.3%) relapsed (Table 3). Among the eight recurrent cases, one patient received surgical treatment only and the others received steroid treatment only. Interestingly, patients who relapsed were all males and were significantly older than those who did not relapse (mean±standard deviation, 62.75±6.36 vs 46.57±16.01, $p<0.001$). In patient who had a recurrence after surgery, the recurrent lesion was retroperitoneal fibrosis, which was absent at the initial presentation. Among the seven patients who received steroid therapy, initial extrapancreatic involvement was observed in five (71.4%). Thus, the prevalence of extrapancreatic involvement in recurrent LPSP cases was significantly higher than that in non-recurrent cases (75% vs 25%, $p<0.001$). The patient who received surgical treatment relapsed relatively early (6.6 months), whereas most patients who received steroid treatment relapsed later (mean±standard deviation, 33.8±20.6 months). Radiological or histopathological findings of recurrent and non-recurrent cases were similar.

DISCUSSION

We successfully identified several IDCP cases that were clinicopathologically distinct from LPSP by analyzing clinicopathological features of pathologically documented AIP cases. IDCP was histologically characterized by neutrophilic ductoacinitis, acinar abscess, acinar edema, occasional GEL, and the absence of IgG4-positive cells, whereas LPSP was characterized by inflammatory cell-rich storiform fibrosis, obliterative phlebitis, and

Table 2. Clinical comparison between idiopathic duct centric pancreatitis (IDCP) and lymphoplasmacytic sclerosing pancreatitis (LPSP)

Clinicopathological factors	IDCP (n=14)	LPSP (n=24)	p-value
Age (mean±standard deviation, yr)	35.29±14.37	58.54±9.09	<0.001
Sex			0.167
Male	10 (71.4)	22 (91.7)	
Female	4 (28.6)	2 (8.3)	
Extrapancreatic manifestations			<0.001
Systemic sclerosing disease	0 (0)	10 (41.7)[a]	
Ulcerative colitis	5 (35.7)	0 (0)	
Serum immunoglobulin levels			<0.001
Elevated serum IgG level (>1,600 mg/dL)	0 (0)	11 (45.8)	
Elevated serum IgG4 level (>1.214 g/L)	0 (0)	18 (75.0)	
Serum autoantibodies			0.351
Positive[b]	3 (33.3)[c]	9(45.0)[d]	
Negative	6 (66.6)	11(55.0)	
Abdominal computed tomography scan			0.175
Typical features[e]	11 (78.6)	13 (54.2)	
Atypical features[f]	3 (21.4)	11 (45.8)	
Endoscopic retrograde cholangiopancreatography			0.278
Typical features[g]	11 (78.6)	11 (57.9)	
Atypical features[h]	3 (21.4)	8 (42.1)	
Relapses	0 (0)	8 (33.3)	0.017

Values are presented as number (%).
[a]Sclerosing cholangitis 4 cases, retroperitoneal fibrosis 4 cases, sclerosing sialadenitis 2 cases, and renal pseudotumor 3 cases. Three patients had two concurrent lesions: retroperitoneal fibrosis+sclerosing sialadenitis, retroperitoneal fibrosis+sclerosing cholangitis, and sclerosing cholangitis+renal pseudotumor; [b]Rheumatoid factor (RF) level>20 IU/mL, antinuclear antibodies (ANA) titer>1:40, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) level>10 U/mL; [c]RF 1 case, ANA and MPO-ANCA 1 case, PR3-ANCA 1 case; [d]RF 1 case, ANA 6 cases, ANA and RF 2 cases; [e]Diffuse pancreatic enlargement with homogeneous attenuation and the peripheral hypoattenuated rim[10-13]; [f]Focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification, pancreatitis; [g]Diffuse or relatively long segmental narrowing of main pancreatic duct; [h]Normal or dilated main pancreatic duct.

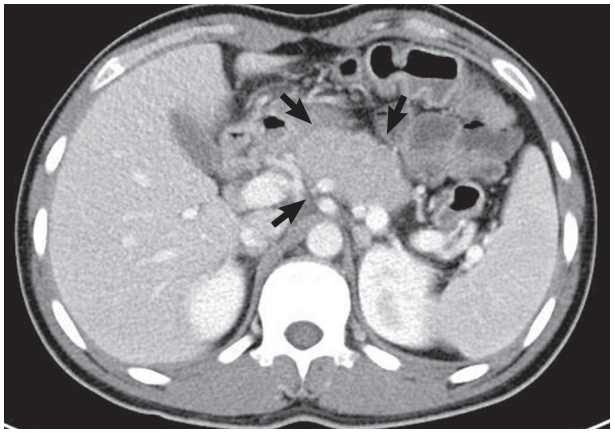

Fig. 3. A typical computed tomography image of idiopathic duct centric pancreatitis. The pancreas is diffusely swollen (arrows) and has a peripancreatic low attenuated rim. Significant ductal dilatation or calculus is not found.

numerous IgG4-positive cells. IDCP mainly affected young patients and was exclusively associated with ulcerative colitis. In contrast, LPSP affected elderly patients and was associated with a variety of IgG4-related sclerosing diseases. Additionally, patients with IDCP responded to steroid therapy very well without any recurrence, whereas those with LPSP experienced recurrences in about one-third of the cases. Therefore, IDCP, which is clinicopathologically distinct from LPSP, can be diagnosed reliably by histological examination, and IDCP constitutes a significant proportion of AIP in Korea.

GEL is one of the important features in the histopathological diagnosis of IDCP.[3-5] Although a core needle biopsy is useful for diagnosing AIP, the specimens are often too small to contain GEL. Consistent with this speculation, GEL was detected in only one of 14 IDCP cases. However, we reliably diagnosed IDCP, because its histopathological findings such as neutrophilic ductoacinitis, acinar abscess, the absence of inflammatory cell-rich storiform fibrosis, and scarce IgG4-positive cells were sufficiently distinct from those of LPSP. Collectively, we argue that GEL might be a diagnostic finding if present, but it is not a prerequisite for a histopathological diagnosis of IDCP.

LPSP is so histologically unique that pathologists often diagnose LPSP even in the absence of clinical information, but this is not the case with IDCP. Neutrophilic ductoacinitis or an acinar abscess, which was recognized as the most striking histological finding in IDCP, is not specific to this type of AIP and can be observed in various conditions such as alcoholic chronic

Table 3. Details of recurrent cases

Age (yr)	Sex	Extrapancreatic manifestation at onset	CT	ERCP	Initial treatment	Recurrent lesion	TTR (mo)[a]
53	M	Retroperitoneal fibrosis, sclerosing sialadenitis	Atypical	Atypical	Steroid	Pancreatitis	72
58	M	None	Typical	Typical	Steroid	Pancreatitis	41.3
59	M	None	Typical	Typical	Steroid	Pancreatitis	15
70	M	Retroperitoneal fibrosis, sclerosing cholangitis	Typical	Typical	Steroid	Sclerosing cholangitis	34.4
61	M	Sclerosing sialadenitis	Typical	Atypical	Steroid	Pancreatitis	45.4
63	M	Sclerosing cholangitis	Typical	Atypical	Steroid	Pancreatitis	18.8
72	M	Renal pseudotumor	Atypical	Typical	Steroid	Renal pseudotumor	37
66	M	None	Atypical	Not done	Surgery	Retroperitoneal fibrosis	6.6

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; TTR, time to recurrence; M, male.

pancreatitis, hereditary pancreatitis, chronic pancreatitis associated with anatomic abnormalities, and obstructive chronic pancreatitis.[8] Given that the identification of typical GEL is limited in most core needle biopsies, the clinical context should be considered when diagnosing IDCP.

IDCP is reportedly associated with inflammatory bowel disease. Typically, ulcerative colitis is accompanied by IDCP more frequently than Crohn's disease.[16,17] Interestingly, patients with ulcerative colitis sometimes have primary sclerosing cholangitis too.[18,19] Indeed, one particular patient had IDCP, ulcerative colitis, and primary sclerosing cholangitis at the same time.[20] Although such a case was not observed in our study, it is worth investigating in the future. Meanwhile, the association between LPSP and systemic IgG4-related sclerosing disease is well known. These characteristic extrapancreatic manifestations of IDCP and LPSP were also confirmed in our study.

The diagnosis of AIP is clinically important because patients with AIP respond dramatically to steroid therapy.[21,22] Because AIP cases sometimes closely mimic pancreatic cancer, their responsiveness to steroid therapy is one of the important diagnostic criteria of AIP.[23] In our study, we used the AIP criteria published by Kim *et al.*[10,13,14] As reported previously,[3] both types of AIP responded to steroid initially but only patients with LPSP developed recurrences. Interestingly, LPSP cases with recurrences exhibited extrapancreatic involvement more frequently than those without recurrences. However, it is unclear whether these differences represent distinct biological pathways or different disease severity.

As AIP has been accepted as a distinct disease entity worldwide,[13,14] several groups have recognized two distinct groups of AIP: LPSP, which is also called AIP without GEL or type 1 AIP, and IDCP, which is also called AIP with GEL or type 2 AIP.[2] Between the two subtypes, IDCP has been recognized rather recently. Although IDCP has been well documented in Western populations, it has not been identified in Asian countries. In this sense, our clinicopathological data regarding IDCP made a contribution to identifying IDCP in an Asian population.

In the present study, we showed that IDCP is clinicopathologically distinct from LPSP and constitutes a significant proportion of AIP in Korea. Histologically, IDCP was characterized by neutrophilic ductoacinitis, acinar abscess, edema, and GEL and was easily distinguished from LPSP. IDCP mainly affected young men and was exclusively associated with ulcerative colitis, whereas LPSP affected older men and was associated with systemic IgG4-related sclerosing diseases. Furthermore, patients with IDCP did not experience any relapse, whereas approximately one-third of the patients with LPSP relapsed. Therefore, the differential diagnosis between IDCP and LPSP is important in the setting of tumefactive pancreatitis, and a careful pathological analysis of the core biopsy specimen is essential for the differential diagnosis.

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