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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Differentiation between autoimmune pancreatitis and pancreatic carcinoma based on endoscopic retrograde cholangiopancreatography findings

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Abstract
Objective We have reviewed the endoscopic retrograde cholangiopancreatography (ERCP) images of patients with autoimmune pancreatitis (AIP) and pancreatic carcinoma (Pca) in an attempt to identify findings that would facilitate making a differential diagnosis between AIP and Pca.
Methods The study cohort consisted of 39 patients diagnosed with AIP and 62 patients diagnosed with Pca. The ERCP findings in the pancreatic duct and biliary tract were compared between the two groups.
Results The ERCP images revealed that AIP patients had a higher prevalence of narrowing of the main pancreatic duct (MPD) for ≥3 cm of its length and a higher prevalence for the presence of side branches in the narrowed portion of the MPD than Pca patients ($p < 0.001$ and $p < 0.001$, respectively). In contrast, the prevalence of an upstream MPD having a maximal diameter ≥4 cm was significantly higher in the Pca patient group ($p < 0.001$). The discriminant analysis identified three significant factors: (1) whether or not side branches were present; (2) total length of the narrowed portion of the MPD; (3) maximal diameter of the upstream MPD. It was impossible to differentiate Pca from AIP in the two Pca patients in whom ERCP revealed both narrowing of the MPD for >5 cm of its length and the presence of side branches.
Conclusions Among our patient cohort, the ERCP findings in terms of the length of the narrowed portion of the MPD, the presence of side branches, and maximal diameter of the upstream MPD enabled differential diagnosis between AIP and Pca in most of the cases. However, it must be borne in mind that some Pca patients have ERCP findings similar to those of AIP patients.

Keywords Autoimmune pancreatitis · ERCP · Pancreatic carcinoma

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Introduction

Recent proposals have led to autoimmune pancreatitis (AIP) being recognized as a disease entity characterized by the following unique clinical, diagnostic imaging, and pathological features: (1) highest incidence in elderly men; (2) pancreatic enlargement; (3) irregularly narrowed main pancreatic duct (MPD) as revealed by endoscopic retrograde cholangiopancreatography (ERCP); (4) increased serum immunoglobulin (Ig) G and IgG4 levels; (5) presence of autoantibodies; (6) lymphoplasmacytic infiltration with fibrosis of the pancreas; (7) responsiveness to steroid therapy [1–9]. Many new clinical aspects of AIP have been identified during the last 10 years, and AIP is now recognized as a distinct entity worldwide [10–12].

In 2006, the Japan Pancreas Society proposed clinical diagnostic criteria for AIP [12] based on [1] typical

radiological imaging findings [2], laboratory data suggesting an autoimmune mechanism, and [3] the histological findings. These criteria state that typical radiological imaging findings—in particular, observation of a diffusely or segmentally narrowed MPD with an irregular wall by ERCP—are essential to making the diagnosis of AIP. Nakazawa et al. [13] recently reported difficulty in diagnosing AIP due to the presence of atypical imaging findings, and it is well known that it is occasionally difficult to differentiate AIP from pancreatic carcinoma (Pca) [14, 15]. Here, we have we attempted to identify findings that would facilitate making a differential diagnosis between AIP and Pca on the basis of ERCP findings.

Patients and methods

The study cohort consisted of 39 patients (average age 65 years, male:female 27:12) diagnosed with AIP between 1991 and 2007 on the basis of the revised diagnostic criteria for AIP proposed by the Research Committee of Intractable Diseases of the Pancreas in 2006 (38/39) or the histological findings (1/39). We compared the ERCP findings of these patients with those of 62 Pca patients (average age 63 years, male:female 40:22) who were diagnosed during the same period as the AIP patients on the basis of imaging methods, such as ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI), and in whom the diagnosis was confirmed by the intraoperative and/or histological findings.

The diagnostic criteria used for AIP were: (1) diffuse or segmental narrowing of the MPD and an irregular wall on ERCP images and evidence of diffuse or localized pancreatic enlargement on imaging studies, such as abdominal US, CT, and MRI; (2) an elevated serum gamma-globulin level and/or IgG level and/or IgG4 level, or the presence of serum autoantibodies, such as antinuclear antibodies and rheumatoid factor; (3) marked interlobular fibrosis and prominent infiltration of the pancreas by lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles. Fulfillment of criterion 1 plus criterion 2 and/or 3 was required to make the diagnosis of AIP (12).

Our first step in evaluating the ERCP findings in the pancreatic duct was to determine whether there was obstruction, narrowing, or displacement in the MPD in the 39 AIP patients and 62 Pca patients. After excluding one AIP case and 24 Pca cases in which the ERCP findings showed obstruction or displacement of the MPD, we evaluated features of the MPD in the 38 AIP cases and 38 Pca cases whose pancreatogram revealed narrowing of MPD according to a modification of the criteria proposed by Wakabayashi et al. [14]. A scoring system was used to evaluate the features of MPD and side branches in which (1) side branches from the narrowed portion of the MPD were scored as 1 (present) or 0 (absent); (2) skipped narrowing of the MPD was scored as 0 (absent) or 1 (present); (3) total length of the narrowed portion of the MPD was scored as 1 (<30 mm), 2 (≥30 to <50 mm), or 3 (≥50 mm); (4) maximal diameter of the upstream MPD was scored as 1 (<4 mm), 2 ≥4 to <6 mm, or 3 (6 mm).

In terms of the biliary system, we compared all 39 AIP patients and 62 Pca patients according to the following findings: (1) whether or not stricture was present (yes or no); (2) whether or not stricture with deviation of the common bile duct (CBD) to the left in the lower portion was present (yes or no); (3) whether or not extrapancreatic bile duct (EPBD) stricture was present (yes or no). The ERCP findings were retrospectively assessed by T.N. and F.T. without prior knowledge of the patients' clinical or biochemical data.

After selecting the variables by the stepwise method, we performed a discriminant analysis using the pancreatic duct parameters of the 38 AIP patients and 38 Pca patients whose pancreatogram revealed a narrowed MPD.

Definitions

The irregular narrowing of the MPD was classified according to extent as 'diffuse' when the length of MPD involved was more than two-thirds of the length of the entire pancreas (Fig. 1), 'segmental' when the length of the MPD involved was between one-third and two-thirds of the length of the entire pancreas (Fig. 2), and 'focal' when the length of the MPD involved was less than one-third of the length of the entire pancreas (Fig. 3).

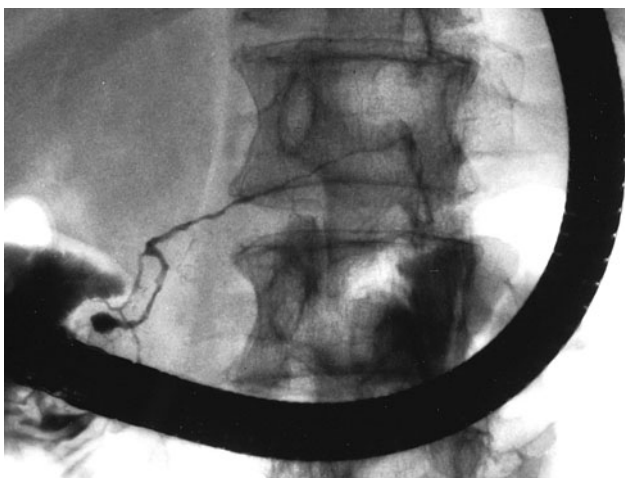

Fig. 1 Endoscopic retrograde pancreatography in a case of autoimmune pancreatitis (AIP). A diffusely narrowed main pancreatic duct with irregular lining was observed

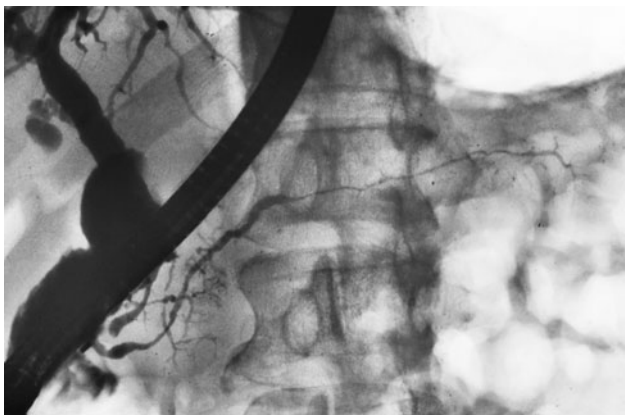

Fig. 2 Endoscopic retrograde pancreatography in a case of AIP. A segmental irregularly narrowed main pancreatic duct with an irregular lining was observed

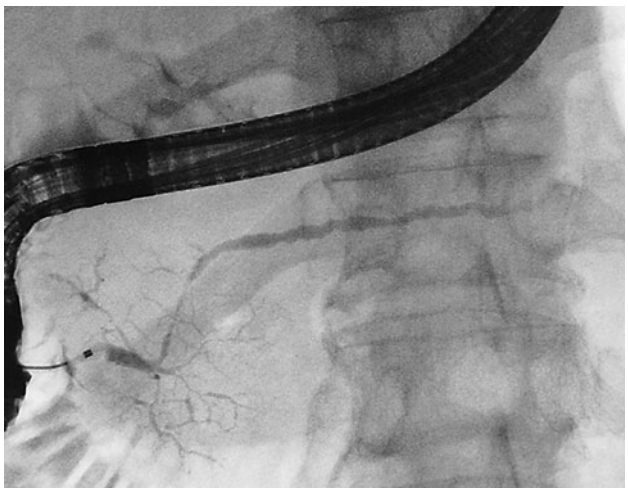

Fig. 3 Endoscopic retrograde pancreatography in a case of AIP. A focally narrowed main pancreatic duct with an irregular lining was observed

Statistical analysis

The data were statistically analyzed by the chi-square test with Yates' correction method or Fisher's exact test for non-parametric parameters and by Student's *t* test to compare parametric parameters. A p value <0.05 was considered to be statistically significant. The discriminant analysis was performed using pancreatic duct parameters after selecting the variables by the stepwise method.

Results

Extent of the irregular narrowing of the MPD in the AIP cases

The extent of the irregular narrowing of the MPD in our series is shown in Table 1. Of the 38 AIP patients, the extent of irregular narrowing of the MPD was assessed to be diffuse in 14 patients and segmental in 20 patients. Three of the latter 20 patients showed skipping in the narrowed region (narrowing of the head and tail only) of the MPD (Fig. 4). The remaining four AIP patients had focal irregular narrowing of the MPD (Table 1).

Table 1 Characteristics of the extent of pancreatic duct narrowing in patients with AIP according to the ERCP findings

Extent and region of irregular narrowing of the main pancreatic duct	Upstream dilatation	Number of cases ($n = 38$)
Diffuse (≥2/3)		14 (37%)
Segmental (≥1/3 to <2/3)		20 (53%)
Head and body	+	2 (5%)
	−	4 (11%)
Body and tail	+	1 (3%)
	−	11 (29%)
Head and tail		3 (8%)
Focal (<1/3)		4 (11%)
Head	+	0 (0%)
	−	2 (5%)
Body	+	1 (3%)
	−	0 (0%)
Tail	+	0 (0%)
	−	1 (3%)

AIP autoimmune pancreatitis, *ERCP* endoscopic retrograde cholangiopancreatography

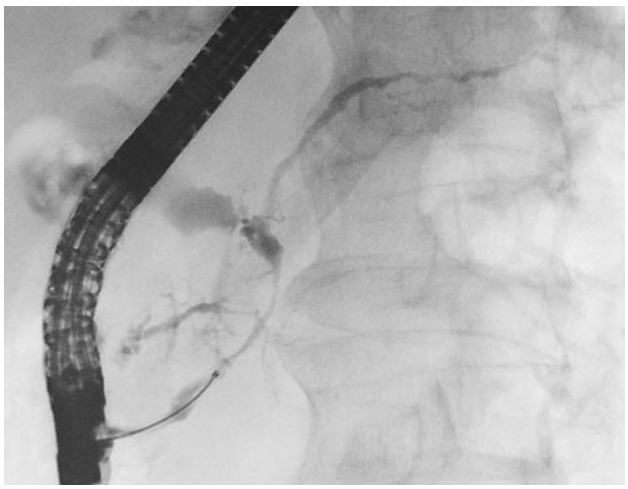

Fig. 4 Endoscopic retrograde pancreatography in a case of AIP. A narrowed main pancreatic duct region with skipping (narrowing in the head and tail only) and an irregular lining was observed

Table 2 Clinical features differentiating patients with AIP from those with Pca based on the pancreatography findings

Clinical features	AIP ($n = 39$)	Pca ($n = 62$)	p value
MPD			
Obstructed	1 (3%)	22 (35%)	0.0003
Narrowed	38 (97%)	38 (61%)	0.0001
Displaced	0 (0%)	2 (5%)	
Characteristics of the narrowed MPD	AIP ($n = 38$)	Pca ($n = 38$)	p value
Side branches present (yes/no)	37/1	10/28	<0.001
Skipped region of MPD (yes/no)	3/35	0/38	ns
Total length of the narrowed portion of the MPD			
<30 mm	2 (5%)	33 (79%)	
≥30 to <50 mm	3 (8%)	3 (8%)	
≥50 mm	33 (87%)	2 (5%)	<0.001
Maximal diameter of the upstream MPD			
<4 mm	34 (89%)	5 (13%)	
≥4 to <6 mm	1 (3%)	5 (13%)	
≥6	3 (9%)	28 (74%)	<0.001

Pca pancreatic carcinoma, *MPD* main pancreatic duct, *ns* not significant

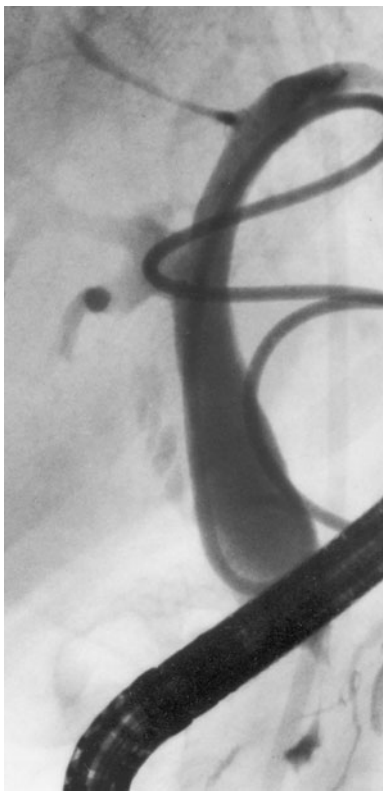

Fig. 5 Endoscopic retrograde cholangiography in a case of AIP. Stricture of a straight distal third of the common bile duct was observed

Differences between the ERCP findings in AIP and Pca

Pancreatography

Pancreatography revealed irregular narrowing of the MPD in 38 of the 39 (97%) AIP patients and an obstructed MPD in the remaining patient (3%) as opposed to narrowing of the MPD in 38 (61%) of the 62 Pca patients and an obstructed MPD in 22 (32%) Pca patients ($p = 0.001$ and $p = 0.003$, respectively) (Table 2).

Of the 38 AIP patients with a narrowed MPD, the total length of the narrowed portion was ≥50 mm in 33 patients (87%), ≥30 to ≤50 mm in three (8%) patients, and <30 mm in the remaining two patients (5%); in comparison, the total length of the narrowed portion was <30 mm in 33 (87%) of the 38 Pca patients with a narrowed MPD. The prevalence of the total length of the narrowed portion of the MPD detected by pancreatography being ≥30 mm was significantly higher in the AIP patients than in the Pca patients ($p < 0.001$). The total length of the narrowed portion in the AIP patients was 93 ± 35 mm [mean ± standard deviation (SD)] as opposed to 19 ± 10 mm in the Pca patients ($p < 0.001$). The percentage of patients with side branches present was significantly higher in the AIP group than in the Pca group ($p < 0.001$). A maximal diameter of the upstream MPD of <4 mm was observed in 34 of the 38 (89%) AIP patients but

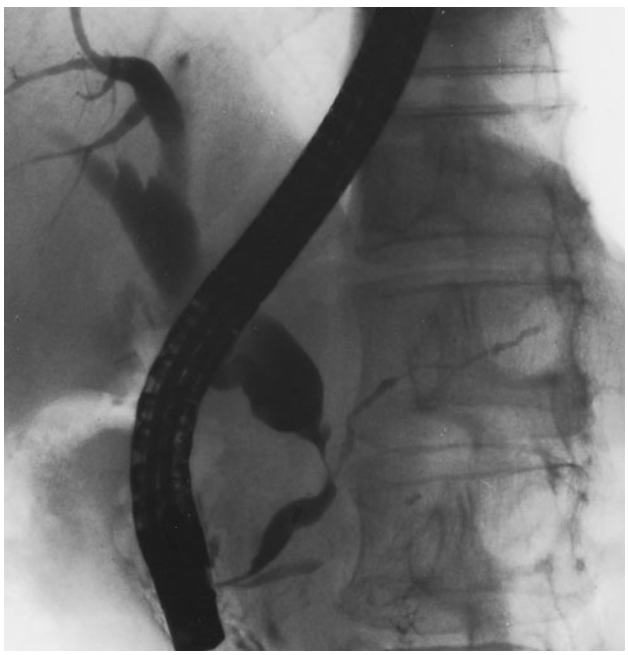

Fig. 6 Endoscopic retrograde cholangiography in a case of AIP. Deviation to the left side and stricture of the distal third of the common bile duct were observed

Table 3 Features differentiating AIP from Pca based on the cholangiographic findings

Clinical features	AIP ($n = 39$)	Pca ($n = 62$)	p value
Biliary tract			
Common bile duct			
Stricture present	$n = 29$	$n = 30$	
Smooth/irregular	24/5	10/20	0.0001
Stricture with deviation to the left (yes/no)	4/25	19/11	0.0003
Length of the stricture ≥20 mm (yes/no)	20/9	19/11	ns
EPBD stricture present (yes/no)	8/33	0/38	0.01

EPBD extrapancreatic bile duct

Table 4 Discriminant analysis between AIP and Pca based on the pancreatography findings

Variables	Discriminant coefficients	Odds ratio	95% Confidence interval	p value
Side branches present	1.074	20.7	1.23–349	0.036
Total length of the narrowed portion of the MPD	1.289	4.45	1.31–14.1	0.016
Maximal diameter of the upstream MPD	−0.447	0.22	0.05–0.91	0.037

Discriminant function formula constant = −2.359

$Z = 1.074 \times$ (whether or not side branches were present: 1 or 0) + $1.289 \times$ (total length of narrowed portion: 1–3) − $0.447 \times$ (maximal diameter of the upstream MPD: 1–3) − 2.359

in only five of the 38 (21%) Pca patients ($p < 0.001$) (Table 2).

Cholangiography

Stricture of the distal third of the CBD was observed in 29 of the 39 AIP patients and in 30 of the 62 Pca patients. In most of the 29 AIP cases the stricture was straight (Fig. 5). CBD stricture with deviation to the left (Fig. 6) was present in a significantly higher proportion of Pca patients than AIP patients ($p = 0.003$). The difference between the length of the CBD stricture in the AIP group and Pca group was not significant. Extrapancreatic bile duct stricture was observed only in the AIP patients ($p = 0.04$) (Table 3).

Discriminant analysis

Discriminant analysis based on the pancreatic duct findings of the patients with narrowing of the MPD correctly identified 36 of the 38 AIP patients and 36 of the 38 Pca patients. Three factors, namely, (1) whether or not side branches were present in the narrowed portion of the MPD ($p = 0.036$), (2) total length of the narrowed portion of the MPD ($p = 0.016$), and (3) maximal diameter of the upstream MPD ($p = 0.037$), were significant discriminant factors based on the results of our stepwise approach (Table 4), and these three factors were used in the discriminant analysis. The discriminant analysis scores (Z) were calculated by using the formula: $Z = 1.074 \times$ (whether or not side branches were present: 1 or 0) + $1.289 \times$ (total length of narrowed portion: 1–3) − $0.447 \times$ (maximal diameter of the upstream MPD: 1–3) − 2.359. When the discriminant function formula was applied to all cases with narrowing of the MPD, the median value, 5th percentile value, and 95th percentile value were 2.136, 0.073, and 2.136, respectively, for AIP and −2.411, −2.411, and 1.012, respectively, for Pca.

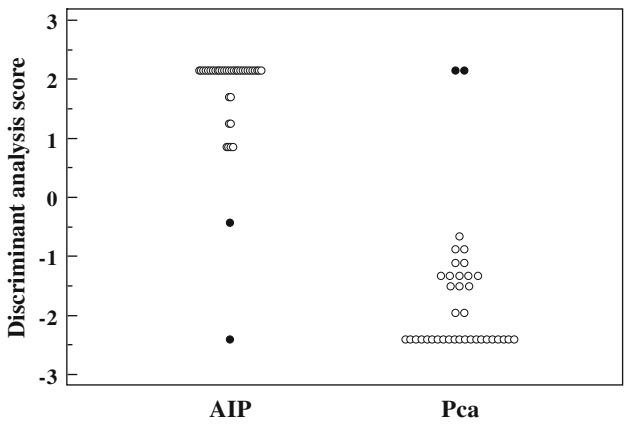

Fig. 7 Distribution of discriminant analysis scores in the AIP and pancreatic carcinoma (*Pca*) cases. *Closed circles* cases misdiagnosed according to the discriminant analysis

The distribution of the discriminant analysis scores of both the AIP patients and Pca patients are shown in Fig. 7.

Characteristics of the ERCP images in the cases misdiagnosed according to the discriminant analysis

Two AIP patients were misdiagnosed as having Pca according to the discriminant analysis. The discriminant score calculated by the discriminant function formula was −0.443 in case 1 and −2.411 in case 2, and both values are

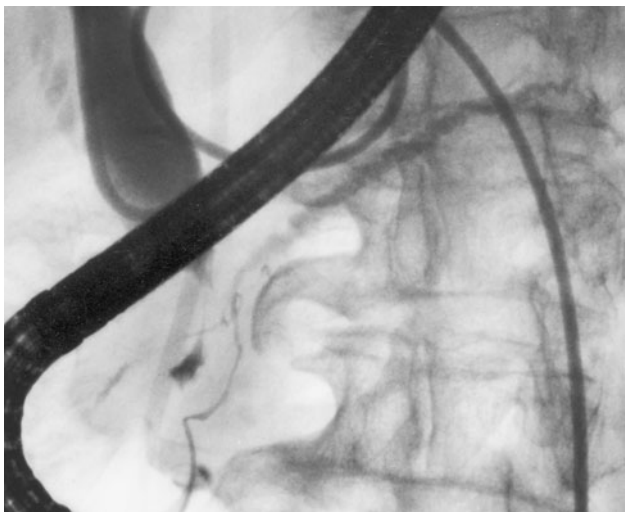

Fig. 8 Endoscopic retrograde pancreatography in a case of AIP. A focally narrowed main pancreatic duct with an irregular lining in the head and the presence of side branches were observed. Differentiation from Pca was difficult

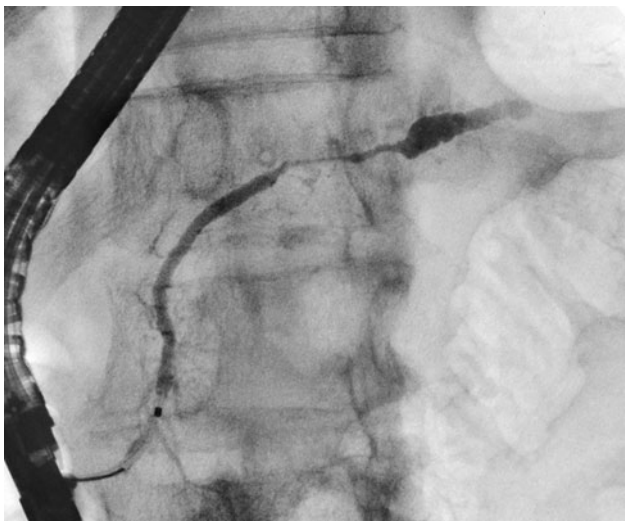

Fig. 9 Endoscopic retrograde pancreatography in a case of AIP. A focally narrowed main pancreatic duct with irregular lining in the body of the pancreas and no side branches and dilatation of the pancreatic duct upstream were observed. Differentiation from Pca was difficult

far lower than those in the other AIP cases. The characteristics of the ERCP images of these two patients are as follows. One patient (case 1) was an 83-year-old woman whose pancreatogram showed a narrowed MPD in the head of the pancreas. The narrowed portion was <3 cm long and had side branches, and the maximal diameter of the upstream MPD was <4 mm (Fig. 8). Her serum IgG4 level had not been determined. The inflamed pancreas was resected, and histological examination revealed lymphoplasmacytic infiltration with storiform fibrosis and obliterative phlebitis. The other patient (case 2) was a 73-year-old man whose pancreatogram showed narrowing of <3 cm of the MPD in the body of the pancreas and no side branches, and the maximal diameter of the upstream MPD was approximately 8 mm (Fig. 9). The patient's serum IgG4 level was 505 mg/dl. After steroid therapy, the narrowing of the MPD was reversed.

Two Pca patients were misdiagnosed as having AIP according to the discriminant analysis. The discriminant score calculated by the discriminant function formula was 2.136 in both of these cases (cases 3 and 4), which is far higher than those in the other Pca cases. The characteristics of the ERCP images of these patients are as follows. One patient (case 3) was a 68-year-old woman whose pancreatogram showed a narrowed MPD with side branches in the body and tail of the pancreas. The length of the narrowed portion was about 5 cm, and its side branches showed mild dilatation (Fig. 10). Brush cytology of the pancreatic duct revealed pancreatic adenocarcinoma. The pancreatic phase CT images showed a pancreas that was homogeneously enhanced and a slight enlargement of the pancreatic body and tail; in the hepatic phase, the tail of the

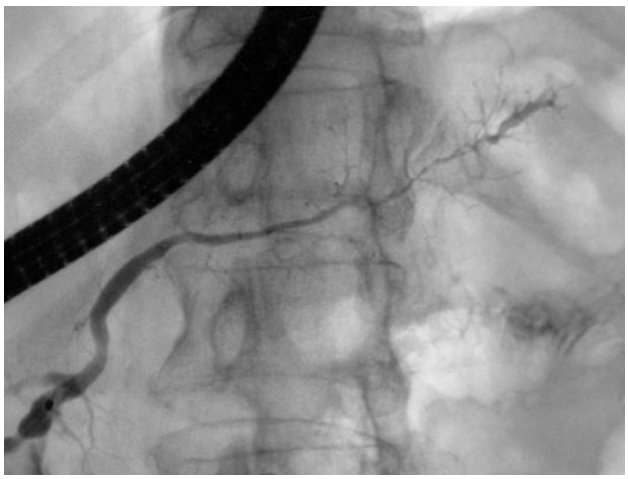

Fig. 10 Endoscopic retrograde pancreatography in a case of Pca. A segmentally narrowed main pancreatic duct with side branches that mimicked the findings in AIP was observed. Brush cytology of the pancreatic duct revealed pancreatic cancer cells. Differentiation from AIP was difficult

pancreas contained a low-density area (Fig. 11a, b). Differentiation between Pca and chronic pancreatitis was very difficult. The patient subsequently died of pancreatic cancer. The other patient (case 4) was a 66-year-old woman whose pancreatogram showed a narrowed MPD with side branches, as in case 3. Brush cytology of the pancreatic duct revealed pancreatic adenocarcinoma. The length of the narrowed MPD was about 5 cm (Fig. 12). CT of the pancreas revealed atrophy, and there was no evidence of a pancreatic tumor in either the pancreatic or the hepatic phase (Fig. 13a, b). The serum IgG4 level had not been

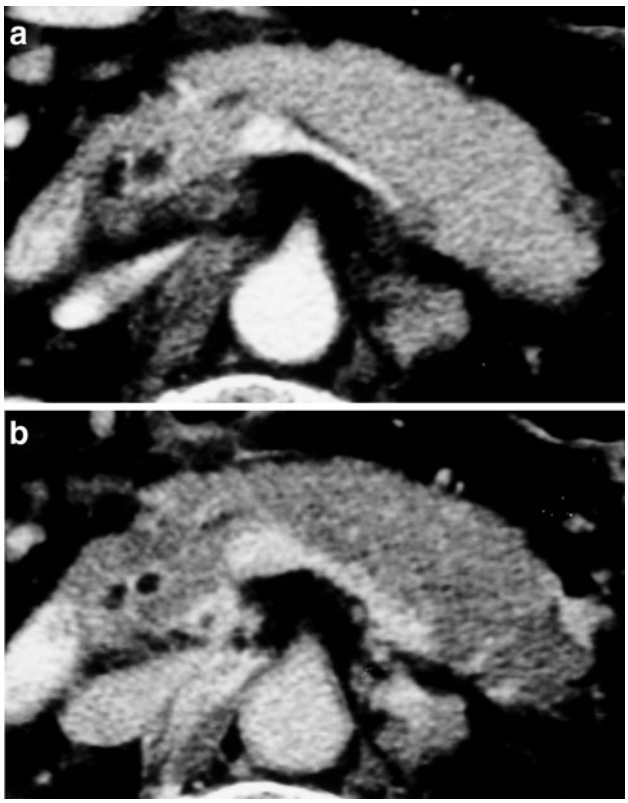

Fig. 11 Computed tomography (CT) in a case of Pca. CT images in the pancreatic phase showed that the pancreas was homogeneously enhanced and there was slight enlargement of the pancreatic body and tail (**a**) and that in the hepatic phase the tail of the pancreas contained a low-density area (**b**)

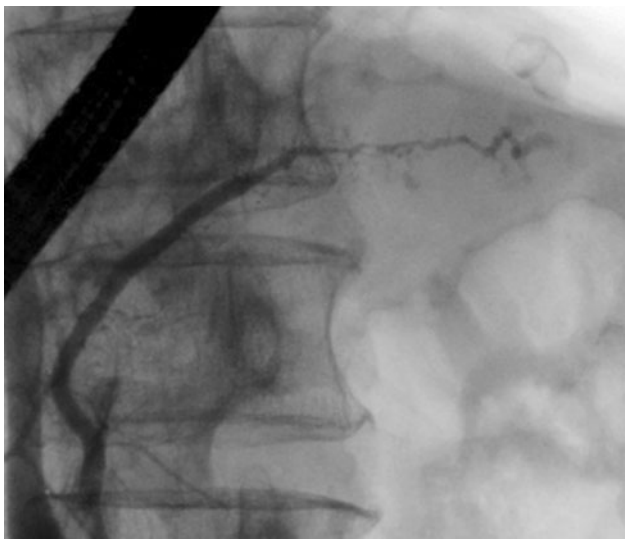

Fig. 12 Endoscopic retrograde pancreatography in a case of Pca. A segmentally narrowed main pancreatic duct with side branches that mimicked the findings in AIP was observed. Brush cytology of the pancreatic duct revealed pancreatic cancer cells. Differentiation from AIP was difficult

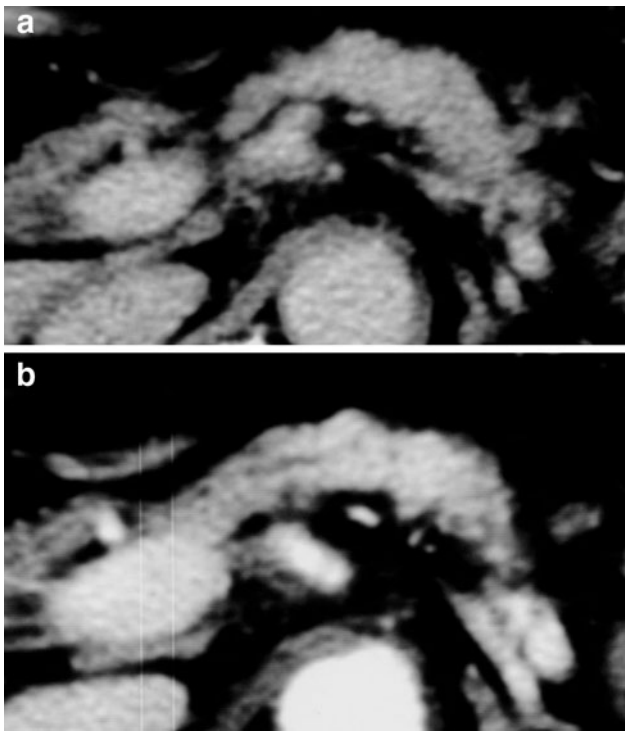

Fig. 13 Computed tomography in a case of Pca. CT examination of the pancreas revealed an atrophic pancreas and no evidence of a pancreatic tumor in the pancreatic phase (**a**) or the hepatic phase (**b**)

determined in either patient. Distal pancreatectomy was performed, and the histological diagnosis was tubular adenocarcinoma of the pancreas.

Discussion

Autoimmune pancreatitis is a new category of pancreatitis, and the diagnosis is based on a combination of clinical, laboratory, imaging, and histological findings. ERCP findings are the key imaging findings for making the diagnosis. In a recent study of 37 AIP patients, Nakazawa et al. [13] reported a variety of ERCP imaging findings, including segmental (focal according to our definition) narrowing of the MPD (nine patients) and a skipped narrowed region (narrowing in the head and tail of the pancreas only; six patients). In our study of 38 AIP patients, ERCP showed a diffusely irregularly narrowed MPD (narrowing of more than two-thirds of the length of the entire pancreas) MPD in only 14 patients, a skipped narrowed region (narrowing in just the head and tail of the pancreas) in four patients, and a focal irregularly narrowed MPD in four patients.

It is very important that AIP be differentiated from Pca because their treatment is different [14–18]. Wakabayashi et al. [14] were the first to demonstrate several ERCP

features that differentiated focal AIP from Pca. They found that obstruction of the MPD is much more suggestive of Pca than of focal AIP and that when the ERCP reveals a narrowed MPD, a longer narrowed portion of the MPD and a thinner MPD upstream from the narrowed portion are much more suggestive of AIP than of Pca. The differences between our AIP and Pca patients in terms of pancreatography findings can be summarized as follows. An obstructed MPD was significantly more common in Pca patients than in AIP patients. When the MPD was narrowed, the narrowed portion of the MPD was significantly longer and the prevalence of side branches in the narrowed portion was significantly higher in the AIP patients than in the Pca patients. The diameter of the MPD upstream from the narrowed portion was significantly smaller in AIP patients than in Pca patients. Skipping of the narrowed regions was observed only cases of AIP. Consequently, the pancreatographic findings in our study are consistent with those described by Wakabayashi et al. [14]. Histological examination showed that the pancreatic duct of the AIP patients was narrowed by peripancreatic nonocclusive fibrosis and lymphoplasmacytic infiltration [5, 19], which were usually extensive and present throughout the entire pancreas, although the degree of inflammation varied according to location in the affected pancreas [19]. This fibrosis and infiltration is why pancreatography showed a longer narrowed portion of the MPD and skipping of the narrowed regions of the MPD more frequently in the AIP patients than in the Pca patients. Although side branches arising from narrowed MPD were rarely seen in the Pca patients because of obstruction by invasive cancer cells, several side branches frequently arose from the narrowed portion of the MPD in the AIP patients because the infiltrate was primarily subepithelial and the ductal epithelium was usually preserved. We therefore conclude that these characteristic pancreatographic features will allow clinicians to differentiate between AIP and Pca.

Sclerosing cholangitis is the most common extrapancreatic lesion associated with AIP, and in most cases the resulting stricture is located in the distal third of the CBD [20, 21]. The bile duct stricture in most of the AIP patients in our study was straight rather than deviated to the left, whereas bile duct stricture with a deviation to the left was observed in >60% of the Pca cases. Stricture of the intrahepatic bile duct was found in some AIP patients, but not in any of the extrapancreatic stricture Pca patients. This finding favors the diagnosis of AIP over Pca.

In our study, the discriminant analysis of the patients with narrowing of the MPD correctly identified 36 of the 38 AIP patients and 36 of the 38 Pca patients and demonstrated that the length of the narrowed portion, the presence/absence of side branches in the narrowed portion, and maximal diameter of the upstream MPD were significant factors. Although our discriminant function formula can be expected to facilitate differentiation between these two diseases, it was impossible to differentiate Pca from AIP in two patients in whom ERCP showed both an MPD that was narrowed in the body and tail of the pancreas for >5 cm of its length and the presence of side branches. Thus, it should be pointed out that there are cases of pancreatic cancer in which the ERCP findings mimic those of AIP because of the presence of a long narrowed MPD with side branches.

An elevated serum IgG4 level is characteristic of AIP [3, 16, 19]. However, the authors of one study reported observing a mild (<2-fold) serum IgG4 elevation in about 10% of the patients who did not have AIP, including pancreatic cancer patients, and that an elevated IgG4 level alone cannot be used to distinguish AIP from Pca [16]. The diagnosis of AIP should be made based on the IgG4 level in combination with clinical, laboratory, imaging, and histological findings. We therefore consider detailed analysis and interpretation of the ERCP findings to be important as well as essential to making the differential diagnosis between AIP and Pca.

The limitation of the discriminant analysis in our study is that it failed when ERCP showed MPD obstruction. In our study, brush cytology was positive for malignant cells in 82% (18/22) of the 22 Pca cases in which ERCP showed MPD obstruction, while a focal defect in the MPD with upstream MPD dilatation, which strongly suggested Pca, was observed in 83% (15/18), and there was no serum IgG4 elevation in any of the Pca cases in which it was measured (data were not shown). We therefore conclude that brush cytology of the pancreatic duct must be performed in such cases and that the results must be interpreted in combination with the magnetic resonance cholangiopancreatography findings and serum IgG4 levels.

Based on four specific ERCP findings, namely, the presence/absence of side branches, length of the narrowed portion of the MPD, maximal diameter of the upstream MPD, and character of the bile duct stricture, we were able to make the differential diagnosis between AIP and Pca in most of the cases evaluated. However, it should be borne in mind that some Pca patients have ERCP findings similar to those of AIP patients.

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