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Prevention of Postoperative Pancreatic Fistula After Total Gastrectomy

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Abstract
Background Pancreatic fistula (PF) is still one of the serious complications after total gastrectomy (TG). The purpose of this study was to identify risk factors for PF after TG and to evaluate our attempts to prevent PF.
Methods From August 1992 to July 2006, 740 consecutive patients with gastric neoplasm underwent TG at the National Cancer Center Hospital East. Univariate and multivariate analyses of potential risk factors for the development of PF and the effectiveness of operative procedures to prevent PF were performed.
Results Postoperative PF was identified in 130 patients (18%). On multivariate analysis, body mass index ($P < 0.001$) and the operative procedure (TG with pancreaticosplenectomy) ($P = 0.001$) were independent risk factors. In TG with splenectomy (pancreas-preserving method), total preservation of the splenic artery was significantly correlated with a lower incidence of PF ($P < 0.001$). In TG with pancreaticosplenectomy, the use of a linear stapling device was an effective surgical technique for closure of the cut end of the pancreas, but there was no significant difference from conventional methods. Recently, the incidence decreased significantly for TG overall and TG with splenectomy.
Conclusions PF after TG is more likely to occur in obese patients undergoing TG with pancreaticosplenectomy. When TG with splenectomy (pancreas-preserving method) is performed, the splenic artery should be totally preserved. If TG with pancreaticosplenectomy is performed, the use of a linear stapling device for closure of the cut end of the pancreas should be suggested. These improvements in surgical techniques are useful to prevent PF.

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Introduction

Although gastric surgery has been performed with lower morbidity and mortality rates in recent years [1], pancreatic fistula (PF) remains a serious complication after total gastrectomy (TG) [2]. In a Japanese major clinical trial (JCOG9501) that included 523 patients with advanced gastric cancer, PF was the most frequent complication after gastrectomy [3]. The incidence of PF after TG has been reported to range from 9–19% [2, 4, 5].

Once PF develops, it sometimes contributes to other major complications, such as bleeding, anastomotic leakage, and intra-abdominal abscess. In fact, PF was the factor most strongly linked with death in most series [6, 7]. Therefore, every effort should be made to avoid the catastrophe of PF. The purpose of this study was to identify risk factors for PF after TG and to evaluate the effectiveness of our attempts to prevent PF.

Patients and methods

From August 1992 to July 2006, 740 consecutive patients with gastric neoplasm underwent TG at the National Cancer Center Hospital East. Of these patients, 512 were men and 228 were women (age range, 24–92 (median, 64) years). Among these 740 patients, 728 had gastric cancer and 12 had malignant lymphoma. Data for these patients were analyzed to identify risk factors for PF, using a multivariate logistic regression model.

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Operative procedures

At our institution, TG with splenectomy (so-called pancreas-preserving method [8]), Japanese-style D2 lymph node dissection, and reconstruction with Roux-en-Y esophagojejunostomy has been the standard surgical procedure for the treatment of advanced gastric cancer located in the upper third of the stomach. TG without splenectomy is performed for patients with early gastric cancer or far advanced gastric cancer that requires palliative resection. TG with pancreaticosplenectomy is performed for patients with direct invasion to the pancreas or evident macroscopic lymph node metastasis along the splenic artery.

Perioperative management

All patients received prophylactic antibiotics intraoperatively and for at least 1 day postoperatively. Prophylactic somatostatin analogues were not administrated to prevent PF. All drains were removed on postoperative day 7 or 8 when there was normal discharge. Preoperative total parenteral nutrition (TPN) was used only for patients who could not take a regular diet.

Pancreatic fistula

Postoperative PF was diagnosed when there was purulent discharge containing necrotic debris from the drainage tube for more than 7 days after operation. We included cases of intra-abdominal abscess that might have occurred from pancreatic juice leakage. On diagnosis, we referred to the amylase levels of drainage fluid measured on postoperative days 1, 3 or 4, and 7, but we had no diagnostic criterion for amylase concentration.

We usually treat PF by maintenance of the drains and intermittent irrigation. We need very little radiological guided drainage because we do not remove drains at an early postoperative day. If the patient's general condition is good, without signs of sepsis, oral food intake is continued and neither TPN nor enteral nutrition is adopted. Administration of somatostatin analogues is limited to the patient with large amount of pancreatic juice discharge. Thus, in our institution, the basic principle of treatment is adequate drainage.

Mortality

Mortality was defined as postoperative death due to any cause within 30 days, or death within the same hospital admission.

Statistical methods

Mann-Whitney U test and χ^2 test were used for univariate analyses. A multiple logistic regression model was used to determine the effect of all of the potential variables. Differences were considered significant at $P < 0.05$.

Results

Among 740 patients, TG without splenectomy was performed in 171 patients (23%), TG with splenectomy in 494 (67%), and TG with pancreaticosplenectomy in 75 (10%).

Postoperative complications were identified in 271 patients (37%) and PF in 130 patients (18%). Seven patients (1%) died as a result of serious postoperative complications (Table 1). Among these seven patients, three patients died as a result of PF and secondary hemorrhage, two as a result of acute renal failure, and two as a result of pneumonia.

Table 2 shows the results of 12 parameters subjected to univariate analysis as potential risk factors in the 130 patients with PF versus the 610 patients without PF. Three preoperative factors (sex, $P = 0.011$; body mass index (BMI), $P < 0.001$; diabetes, $P = 0.015$) and five perioperative factors (operative procedure, $P < 0.001$; operative time, $P < 0.001$; intraoperative bleeding, $P < 0.001$; curability, $P = 0.001$; lymph node dissection, $P < 0.001$) differed significantly between these two groups. There was no significant difference in pathological factors between these two groups.

Multivariate logistic regression analysis revealed that BMI ($P < 0.001$) and the operative procedure (TG with pancreaticosplenectomy; $P = 0.001$) were significant independent risk factors for PF (Table 3).

Figure 1 shows the sites of division of the splenic artery in the case of TG with splenectomy. The splenic artery was divided at the root in no patient (Group A), divided at the midpoint of the line between the root and the end in 98 patients (Group B), and totally preserved in 273 patients (Group C). Data were not available for 123 patients. There was a significant difference in the incidence of PF between group B and C ($P < 0.001$; Table 4).

Table 1 Operative morbidity and mortality (n = 740)

Morbidity	271 (37%)
Pancreatic fistula[a]	130 (18%)
Anastomotic leakage	42 (6%)
Wound abscess	26 (4%)
Pneumonia	20 (3%)
Paralytic ileus	20 (3%)
Cholecystitis	16 (2%)
Postoperative bleeding	10 (1%)
Anastomotic stenosis	10 (1%)
Mortality	7 (1%)

[a] Including intra-abdominal abscess

Table 2 Univariate analysis of risk factors influencing pancreatic fistula

	Pancreatic fistula		*P* value
	(+) (*n* = 130)	(−) (*n* = 610)	
Preoperative factors			
Sex			0.011
Male	102 (20%)	410 (80%)	
Female	28 (12%)	200 (88%)	
Age (yr)	64 (24–92)[a]	64 (27–88)[a]	0.521
Body mass index (kg/m^2)	22.7 (14.5–32.3)[a]	21.5 (14.3–32.4)[a]	<0.001
Diabetes			0.015
Yes	19 (28%)	48 (72%)	
No	111 (16%)	562 (84%)	
Neoadjuvant chemotherapy			0.474
Yes	9 (14%)	54 (86%)	
No	121 (18%)	556 (82%)	
Perioperative factors			
Operative procedure			<0.001
TG without splenectomy	9 (5%)	162 (95%)	
TG with splenectomy	85 (17%)	409 (83%)	
TG with pancreaticosplenectomy	36 (48%)	39 (52%)	
Operative time (min)	285 (154–678)[a]	245 (95–596)[a]	<0.001
Intraoperative bleeding (ml)	841 (213–4,750)[a]	598 (45–14,410)[a]	<0.001
Curability			0.001
Curative operation	124 (19%)	516 (81%)	
Palliative operation	6 (6%)	94 (94%)	
Lymph node dissection			<0.001
D0,1	11 (6%)	174 (94%)	
D2,3	119 (21%)	436 (79%)	
Pathological factors			
Primary tumor[b]			0.285
pT1	17 (14%)	103 (86%)	
pT2,3,4	113 (18%)	507 (82%)	
Regional lymph nodes[b]			0.968
pN0	46 (18%)	214 (82%)	
pN1,2,3	84 (18%)	396 (82%)	

TG—total gastrectomy

[a] Median value, with range in parentheses

[b] Japanese classification of gastric carcinoma

Figure 2 shows the surgical techniques for transection and closure of the cut end of the pancreas in the case of TG with pancreaticosplenectomy. The cut end of the pancreas was transected and closed by conventional methods in 50 patients (Group D) and using a linear stapling device in 12 patients (Group E). Data were not available for 13 patients. The incidence of PF in group E was lower than that in group D, but the difference was not significant (Table 4).

The incidence of PF is presented in Table 5. Recently, the incidence of PF decreased significantly for TG as a whole and TG with splenectomy. The ratio of cases with new operative procedures is presented in Table 6. We have adopted new operative procedures more frequently in second half period.

The postoperative outcomes of the patients with and without PF were compared (Table 7). The patients with PF had a longer postoperative hospital stay ($P < 0.001$) and higher postoperative mortality rate ($P = 0.001$).

Discussion

Until recently, there had been no universally acknowledged definition of PF. The incidence of PF after TG has been reported to range from 9–19% according to the different definitions applied [2, 4, 5]. Because these different definitions could lead to misleading discrepancies on the basis of only differences in terminology, a unifying definition of PF was necessary for us to compare the different surgical

Table 3 Multivariate analysis of risk factors influencing pancreatic fistula

	P value	Odds ratio	95% confidence interval
Sex : Male	0.118	1.475	0.906–2.402
Body mass index (continuous)	<0.001	1.142	1.063–1.227
Diabetes	0.06	1.836	0.974–3.459
Operative procedure			
TG with splenectomy	0.288	2.07	0.541–7.929
TG with pancreaticosplenectomy	0.001	10.06	2.506–40.381
Operative time (continuous)	0.163	1.002	0.999–1.005
Intraoperative bleeding	0.381	1	1–1
Curability: curative operation	0.355	1.564	0.248–1.65
Lymph node dissection: D2,3	0.585	1.43	0.396–5.169

TG—total gastrectomy

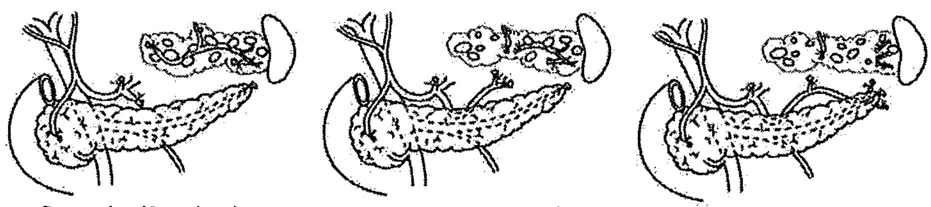

Fig. 1 Sites of division of splenic artery in cases of splenectomy. Group A (0 patient): the splenic artery was divided at the root. Group B (98 patients): the splenic artery was divided at the midpoint of the line between the root and the end. Group C (273 patients): the splenic artery was totally preserved

Table 4 Effectiveness of preservation of splenic artery and use of linear stapling device

	Pancreatic fistula		*P* value
	(+)	(−)	
TG with splenectomy[a]			<0.001
Group A ($n = 0$)	–	–	
Group B ($n = 98$)	36 (37%)	62 (63%)	
Group C ($n = 273$)	32 (12%)	241 (88%)	
TG with pancreaticosplenectomy[b]			0.124
Group D ($n = 50$)	29 (58%)	21 (42%)	
Group E ($n = 12$)	4 (33%)	8 (67%)	

TG—total gastrectomy

[a] Data were not available for 123 patients

[b] Data were not available for 13 patients

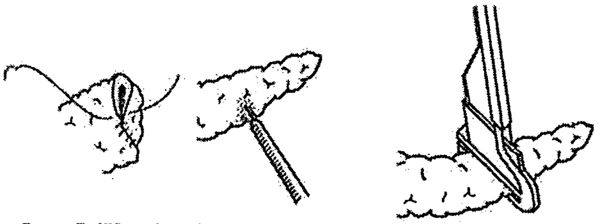

Fig. 2 Surgical techniques for transection and closure of cut end of pancreas in cases of pancreaticosplenectomy. Group D (50 patients): closure by conventional methods; the pancreas was transected with a knife and sutured, or transected with an ultrasonically activated scalpel. Group E (12 patients): closure using a stapling device; the pancreas was transected with a linear stapling device

experiences accurately. In July 2005, the International Study Group on Pancreatic Fistula (ISGPF) developed and published a universal definition and clinical grading for postoperative PF, as follows: an all-inclusive definition of PF is a drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content >3 times the serum amylase activity [9]. At our institution, we have made a diagnosis of PF mainly by the appearance of drainage fluid. In this study, the incidence of PF in patients in which TG without splenectomy, TG with splenectomy, and TG with pancreaticosplenectomy were performed was 5%, 17%, and 48%, respectively. The incidence must be lower if the ISGPF definition is used. However, the purpose of this study was to evaluate the operative procedures and the surgical techniques to reduce postoperative complications associated with the pancreas. Therefore, we included intra-abdominal abscess that might have resulted from pancreatic juice leakage as PF. Katai et al. [4] used the term "pancreas-related abscess" for the condition that was similar to ours.

Table 5 Incidence of pancreatic fistula

	No. of patients (%) with PF			*P* value
	First half (during 1992–1999)	Second half (during 2000–2006)	Total	
Overall	79/359 (22)	51/381 (13)	130/740 (18)	0.002
TG without splenectomy	2/ 62 (3)	7/109 (6)	9/171 (5)	0.368
TG with splenectomy	54/252 (21)	31/242 (13)	85/494 (17)	0.011
TG with pancreaticosplenectomy	23/ 45 (51)	13/ 30 (43)	36/75 (48)	0.509

PF—pancreatic fistula, TG—total gastrectomy

Table 6 Ratio of cases with new operative procedures

	No. of patients (%) with new operative procedures		*P* value
	First half (during 1992–1999)	Second half (during 2000–2006)	
Splenic artery preservation (Group C) in the case of TG with splenectomy	107/169[a] (63)	166/202[b] (82)	<0.001
Transection with a stapling device (Group E) in the case of TG with pancreaticosplenectomy	0/34[c] (0)	12/28[d] (43)	<0.001

TG—total gastrectomy

[a] Data were not available for 83 patients

[b] Data were not available for 40 patients

[c] Data were not available for 11 patients

[d] Data were not available for 2 patients

Table 7 Relationship of postoperative outcomes to pancreatic fistula

	Pancreatic fistula		*P* value
	(+) ($n = 130$)	(−) ($n = 610$)	
Postoperative hospital stay (days)	43 (21–114)[a]	20 (11–173)[a]	<0.001
Mortality	5 (4%)	2 (0.3%)	0.001

[a] Median value, with range in parentheses

A previous report confirmed that risk factors for PF after TG were age, BMI, and dissection of lymph nodes along the distal splenic artery [4]. Especially, being overweight increases the risk of surgical complications in patients undergoing gastrectomy [10]. Our study also showed that obesity and pancreatic transection were correlated with the risk of PF.

Maruyama et al. [8] reported that when performing splenectomy, the splenic artery should be divided at the root for complete removal of lymph nodes along this artery. At our institution, we formerly ligated and divided the splenic artery at the midpoint of the line between the root and the end. To preserve the blood supply to the pancreatic tail and to prevent PF, we have totally preserved the splenic artery in recent years. Maruyama et al. demonstrated that the preserved pancreas received a good blood supply through the dorsal pancreatic artery and the transverse pancreatic artery, even after removal of the splenic artery; however, we think that blood supply is insufficient with the Maruyama method, and the great pancreatic artery and caudal pancreatic artery should be preserved, too. With advanced surgical skill, we can perform complete lymph node dissection along the upper border of the pancreas, even preserving the splenic artery. We demonstrated that preserving the splenic artery was effective in preventing PF after splenectomy in this study.

When performing pancreaticosplenectomy, we formerly used a knife or ultrasonically activated scalpel (Harmonic Scalpel; Johnson & Johnson Medical, Ethicon, Tokyo, Japan) for transection of the cut end of the pancreas. In an attempt to reduce the incidence of PF, we have used a linear stapling device in recent years. Our study suggested that closure of the cut end of the pancreas with a stapler may have reduced the incidence of PF, whereas a previous study suggested that it was associated with a significantly higher PF rate [11]. It is important that the indications for use of a linear stapling device might be limited to soft and thin pancreatic parenchyma. A randomized, controlled trial to determine the best closure technique is now being planned [12], and we are awaiting the results.

Conclusions

PF after TG is more likely to occur in obese patients undergoing TG with pancreaticosplenectomy. When splenectomy is performed, the splenic artery should be totally preserved. When pancreaticosplenectomy is performed, the use of a linear stapling device for closure of the cut end of the pancreas is suggested. It has been shown that these improvements in surgical techniques for TG are useful to prevent PF.

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Low Serum Level of Cholinesterase at Recurrence of Pancreatic Cancer Is a Poor Prognostic Factor and Relates to Systemic Disorder and Nerve Plexus Invasion

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Objectives: Systemic disorder is a characteristic of advanced pancreatic cancer. Clinical prognostic factors in earlier disease state than terminal stage are expected to be sensitive markers for the foresight of systemic disorder. This study aimed to find the associations between these sensitive markers and morphological factors of primary tumor that may indicate finding a way of pathogenesis of systemic disorder.

Methods: The current study examined 75 patients who received macroscopic curative resection for pancreatic cancer in our institution as follows: (1) identification of clinical prognostic factors at initial recurrence after resection of primary tumor and (2) analysis of correlations between clinical prognostic factors and histological findings in primary tumor.

Results: Important prognostic factors were peritoneal dissemination and serum levels of carbohydrate antigen 19-9 and cholinesterase. Only low levels of serum cholinesterase correlated to nerve plexus invasion in histological findings of primary tumor. Patients with low cholinesterase levels show systemic disorder, including poor performance status, anemia, and hypoalbuminemia.

Conclusions: Nerve invasion may thus result in low functional state of the liver followed by systemic disorder. This mechanism may be useful for elucidating cancer cachexia in future studies.

Key Words: pancreatic cancer, cholinesterase, nerve plexus invasion, nerve invasion, systemic disorder, cachexia

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Systemic disorder is a characteristic of patients with invasive ductal carcinoma (IDC) of the pancreas[1] and includes anemia, worsened performance status, hypoalbuminemia, and weight loss,[1–3] all of which represent prognostic factors for end-stage cancer patients.[2–4] Predictive recognition of systemic disorder may be useful for judgement of suitable treatment and prevention of rapid general deterioration. This foresight for patients' conditions needs sensitive clinical markers for systemic disorder, and these markers are expected to be prognostic factors in earlier disease state than terminal stage. On analysis of clinical data, choosing clinical points to extract clinical data is important. Preoperative clinical condition of patients with IDC of the pancreatic head is affected by obstruction of the bile and pancreatic ducts.[5,6] Conversely, patients who undergo pancreatectomy for IDC of the pancreatic head are released from those obstructions by the reconstruction. After surgery for pancreatic IDC, recurrence is a common event that most patients experience.[7] Initial recurrence is thus considered a suitable point to investigate clinical data. Patients after surgery give us resected specimen as histological information of tumor. Many studies report morphological findings of pancreatic IDC as predictive of prognosis. Some histological factors in pancreatic IDCs may relate to systemic disorder. Sensitive histological factor for systemic disorder may be important tumoral information for choice of appropriate treatment and elucidation of pathogenesis. On the basis of the above context, the present study was planned to identify important clinical factors for predicting prognosis at initial recurrence and correlations to histological factors in patients with pancreatic IDC.

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MATERIALS AND METHODS

Patients

This study reviewed 73 consecutive patients (32 women, 41 men) who displayed recurrent pancreatic IDC after macroscopic curative resection at National Cancer Center Hospital East. Inclusion criteria were as follows: (1) macroscopic curative resection for IDC of the pancreas performed between September 1992 and January 2004 in our institution; (2) pathologically confirmed pancreatic IDC from a resected specimen by 2 authors (S.M. and T.H.); (3) sufficient follow-up at our institution, comprising computed tomography (CT), complete blood cell counts, serum biochemistries, and physical examinations at intervals of at least once every 3 to 6 months after resection; and (4) clear recognition of date of initial recurrence on the basis of CT or cytology, enabling review. Median patient age at diagnosis of initial recurrence was 62 years (range, 25–81 years). None of the patients received neoadjuvant or adjuvant therapy. Pancreaticoduodenectomy (PD) had been performed for 55 patients, and distal pancreatectomy (DP) had been performed for 18 patients. Regional lymph node dissection had been performed in all patients. Median duration to recurrence after resection was 312 days (95% confidence interval [CI], 260–364 days).

Assessment of Initial Recurrence

Initial recurrence was diagnosed based on cytology in 4 patients and CT in 69 patients. Cytology revealed the presence of IDC of the pancreas in ascites of 2 patients and pleural effusion in 2 patients, and date of initial recurrence date was determined as the puncture date on the basis of cytology reports. Computed tomography was performed using a helical CT scanner (X-Vigor Laudator; Toshiba Medical, Tokyo, Japan). All helical CT scans were performed concomitantly with dynamic studies. Tumor recurrence on CT examination was defined as abnormal and/or increasing tissue or nodules depicted in the portal phase scanned 60 to 70 seconds after the start of contrast media administration. Date of initial recurrence was determined as the day when CT examination contributing to the confirmed diagnosis of the recurrence was performed. One author (S.M.) reviewed all CT reports and images and evaluated CT findings. According to CT review, 43 patients displayed local recurrence defined as locoregional recurrence, including lymph node metastases, 39 patients had hepatic metastases, and 10 patients showed peritoneal dissemination diagnosed as metastatic peritoneal nodules.

Clinical Parameters

The following clinical parameters at initial recurrence were evaluated (Table 1): (1) age; (2) sex; (3) operative method; (4) Eastern Cooperative Oncology Group performance status (PS)[8]; (5) weight loss ratio, calculated as (100 × [body weight at initial operation − body weight at recurrent]/ body weight at initial operation); (6) blood level of hemoglobin (Hgb); (7) blood platelet count (Plt); (8) serum level of total bilirubin (T.Bil); (9) serum level of albumin (Alb); (10) serum level of total cholesterol (T.cho); (11) serum level of pseudo-cholinesterase (ChE); (12) serum level of carcinoembryonic antigen (CEA); (13) serum level of carbohydrate antigen (CA) 19-9; (14) ascites confirmed on CT; and (15) site of initial recurrence. These 15 parameters were classified to 2 or more categories according to usual status, mean value, or reported values, as quoted from reports by Scott et al,[9] Gianotti et al,[2] and Tas et al,[3] National Cancer Institution–Common Toxicity Criteria (NCI-CTC) version 2.0,[10] and Child classification[11] for analysis of clinical prognostic factors (summarized in Table 2). All clinical data were obtained within 2 weeks from date of initial recurrence.

Histological Parameters

The only material appropriate for evaluating histological findings as to the invasiveness of the entire tumor is from primary tumor in pancreatic IDC because surgical treatment for metastatic or recurrent pancreatic IDC is not usually performed. The resected specimen of primary pancreatic IDC was thus evaluated histologically. Methods of the histological examination have been described in our previous report.[7] Briefly, pathological diagnosis and findings were evaluated and confirmed by 2 authors (S.M. and T.H.). Pathological parameters were categorized as follows: (1) tumor size (≤3.0 or >3.0 cm), (2) predominant differentiation of tumor (well/moderately or poorly differentiated), (3) least differentiation of tumor (well/moderately or poorly differentiated), (4) retroperitoneal invasion (0/1 or 2/3), (5) lymphatic invasion (0/1 or 2/3), (6) vascular invasion (0/1 or 2/3), (7) intrapancreatic neural invasion (0/1 or 2/3), (8) Japanese pathological N category (JpN) (JpN0/1/2 or JpN3),[12] (9) International Union Against Cancer (UICC) pathological T category (pT) (pT1/2 or pT3),[13] (10) UICC pathological stage (UICC pStage; IA/IB/IIA or IIB/IV),[13] (11) tumor necrosis (absent or present),[7] (12) nerve plexus invasion (absent or present), (13) fibrotic focus (absent or present),[7] (14) UICC pathological N category (pN) (pN0 or pN1),[13] and (15) UICC R classification (R0 or R1).[13] The above categorizations of 15 pathological factors reflected prognostic impact in our previous study.[7] Predominant and least differentiation were estimated according to World Health Organization classifications.[14] Retroperitoneal invasion, lymphatic invasion, vascular invasion, and intrapancreatic neural invasion were classified into 0, 1, 2, and 3 according to the following: 0, not observed; 1, slightly seen; 2, occasionally seen; and 3, frequently seen.

TABLE 1. Patient Characteristics at Initial Recurrence After Curative Resection for IDC of the Pancreas

Age (median/range), yrs	62/25–81
Sex (male/female), n	41/32
Operation (PD/DP), n	55/18
PS (0/1/2/3), n	5/33/19/16
Ascites (absent/present), n	50/23
Weight loss ratio (mean [95% CI]), %	5.8 (3.3–8.3)
Hgb (mean [95% CI]), g/dL	11.1 (10.6–11.5)
Plate (mean [95% CI]), $\times 10^4$/dL	21.3 (19.0–23.6)
T.Bil (mean [95% CI]), mg/dL	0.9 (0.7–1.2)
Alb (mean [95% CI]), g/dL	3.5 (3.4–3.6)
T.cho (mean [95% CI]), IU/mL	150.2 (140.6–160.0)
ChE (mean [95% CI]), IU/dL	205.0 (188.8–221.3)
CEA (mean [95% CI]), ng/mL	38.3 (14.2–62.4)
CA19-9 (mean [95% CI]), U/mL	2945.5 (570.3–5320.8)
Duration to recurrence (d)	311.7 (259.5–363.9)
Diagnostic modality for recurrence (n)	
CT	69
Cytology	4
Initial recurrent site (n)	
Local recurrence	43
Liver metastasis	39
Peritoneal dissemination	12
Initial therapy for recurrence (n)	
Chemotherapy	22
Radiotherapy	6
Resection	6
Palliative therapy	39

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation. Palliative therapy meant best support care, and the patients with palliative therapy did not receive any antitumor treatments.

Statistical Analysis

Survival was calculated from the date of initial recurrence. Median duration of follow-up was 1921 days (95% CI, 1670–2283 days). Parameters with 3 or more grades such

TABLE 2. Summary of Categories Tested to Determine Cutoffs for Predicting Prognosis in Each Clinical Parameter

Parameter	Tested Category	Reference for Tested Category
Age (yrs)	≤62, >62	Mean value
Sex	Male, female	
Operation	PD, DP	
PS	0, 0–1, 0–3, 1–2, 3	
Ascites	Absent, Present	
Weight loss ratio (%)	<0, 0 to <5, 5 to <10, ≥10	Gianotti et al,[2] Scott et al[9]
Hgb (g/dL)	<8.0, 8.0 to <10.0, 10.0 to <12.0, ≥12.0	Tas et al,[3] NCI-CTC version 2.0[10]
Plt ($\times 10^4$/dL)	<10.0, 10.0 to <15.0, 15.0 to <40.0, ≥40.0	NCI-CTC version 2.0[10]; upper limit of normal value; lower limit of normal value
T.Bil (mg/dL)	<1.2, 1.2 to <2.0, ≥2.0	Upper limit of normal value; Child classification[11]
Alb (g/dL)	<2.0, 2.0 to <3.0, 3.0 to <3.5, ≥3.5	NCI-CTC version 2.0[10]; Child classification[11]
T.cho (IU/mL)	<100, 100 to <150, 150 to <200, ≥200	Mean value; mean value ±50
ChE (IU/dL)	<150, 150 to <200, 200 to <250, >250	Mean value; mean value ±50
CEA (ng/mL)	<5, 5 to <10, 10 to <40, 40 to <100, ≥100	Upper limit of normal value; 2× upper limit of normal value; mean value; 100
CA19-9 (U/mL)	<38, 38 to <100, 100 to <500, 500 to <1000, 1000 to <3000, 3000 to <10,000, ≥10,000	Upper limit of normal value; mean value; 100; 500; 1000; 10,000
Duration to recurrence (d)	<180, ≥180	Mean value
Peritoneal dissemination	Absent, present	

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation.

as PS were classified into 2 groups according to the significant cutoff to assign patient survival data using the log-rank test (significant cutoff shown in Table 3). Clinical parameters that significantly associated with survival rates in univariate analyses were further analyzed together in multivariate analyses using the Cox proportional hazard regression model to identify independent clinical prognostic parameters. Survival curves were drawn using the Kaplan-Meier method. To investigate relationships between important clinical parameters and histological findings, the frequency of patients with each important clinical prognostic factor was calculated for each pathological parameter and evaluated using Fisher exact test. Noncategorical data were compared using a 2-tailed Student t test. Values of $P < 0.05$ were considered statistically significant. All analyses were performed using Statview-J 5.0 software, Windows version (SAS, Cary, NC).

TABLE 3. Univariate Analyses and Survival Outcome in Patients With Recurrence Who Underwent Curative Resection for IDC of the Pancreas

Parameter	Category	P
Age (yrs)	≤62/>62	0.859
Sex	Male/female	0.986
Operation	PD/DP	0.092
PS	0, 1/2, 3*	<0.001
Ascites	Absent/present*	0.002
Weight loss ratio (%)	<0/≥0	0.555
Hgb (g/dL)	<12.0*/≥12.0	0.004
Plt ($\times 10^4$/dL)	<10.0*/>10.0	0.015
T.Bil (mg/dL)	<1.2/≥1.2*	0.031
Alb (g/dL)	<3.5*/≥3.5	0.003
T.cho (IU/mL)	<150*/≥150	0.013
ChE (IU/dL)	<200*/≥200	<0.001
CEA (ng/mL)	<40/≥40*	<0.001
CA19-9 (U/mL)	<100/≥100*	0.003
Duration to recurrence (d)	<180/>180	0.515
Peritoneal dissemination	Absent/present*	<0.001

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation.

*Factor displayed significant prognostic impact in univariate analysis and was used for multivariate analysis in Table 4. Univariate analysis was performed using the log-rank test. Level of significance was set at $P < 0.05$.

RESULTS

Patient Characteristics

Clinical data for 73 pancreatic IDC patients at initial recurrence are summarized in Table 1. Performance status 3 was present in 22% of patients. Weight loss was observed in 77% of patients, and mean weight loss ratio was 5.8%. No obvious jaundice was observed, and mean T.Bil was 0.9 mg/dL. Local recurrence, liver metastasis, and peritoneal dissemination were identified in 43, 39, and 12 patients, respectively. Chemotherapy (30%) and palliation (53%) were mainly chosen for the treatment of initial recurrence.

Survival and Prognostic Factors

The cumulative survival curve after initial recurrence is shown in Figure 1A. Median survival time and 1-year cumulative survival rate were 140 days and 22%, respectively. Univariate analysis produced the following candidates for predicting prognosis: PS, ascites, Hgb, Plt, T.Bil, Alb, ChE, CEA, CA19-9, and peritoneal dissemination (Table 3). Multivariate analysis (Table 4) revealed the following independent prognostic factors: PS, 2 or 3 (n = 35; hazard ratio [HR], 2.2; $P = 0.007$); ChE less than 200 IU/dL (n = 35; HR, 3.2; $P < 0.001$) (Fig. 1B); CEA, 40 ng/mL or greater (n = 10; HR, 2.7; $P = 0.026$); CA19-9 greater than 100 U/mL

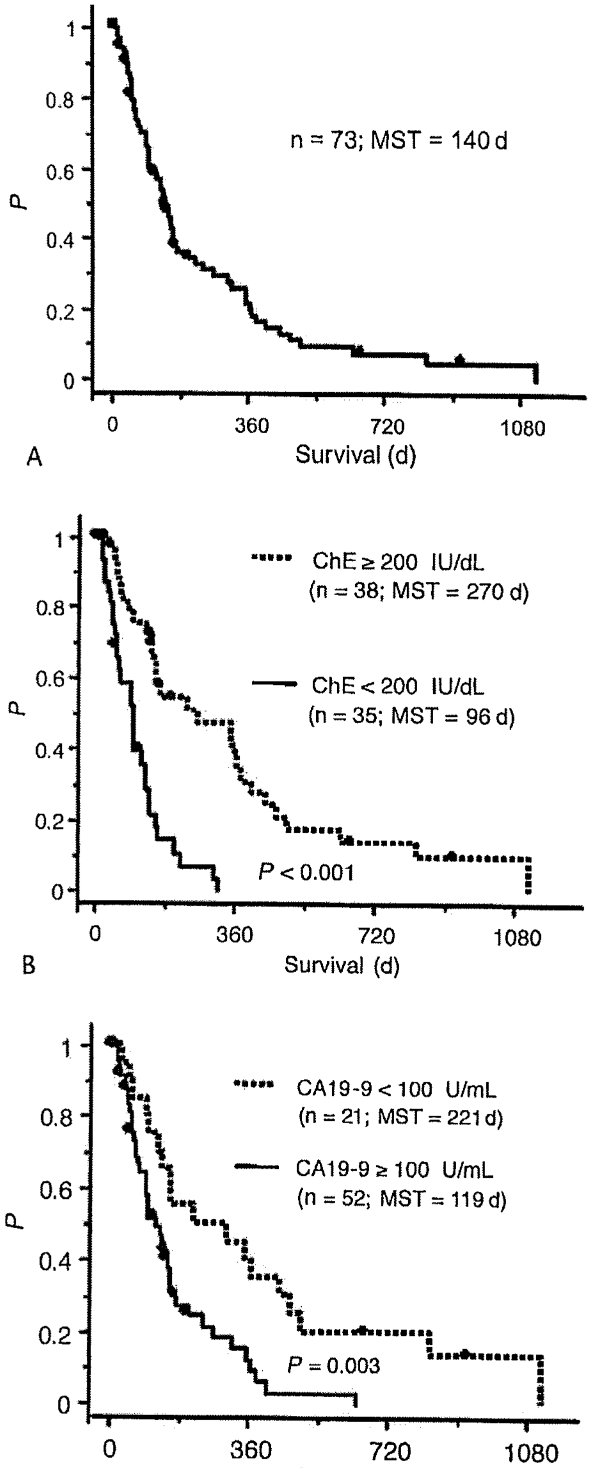

FIGURE 1. Survival curves after initial recurrence. A, Survival curve for all patients. B, Survival curve assigned by serum ChE level. Prognosis was significantly worse in patients with low ChE than in those with high ChE levels. C, Survival curve assigned by serum CA19-9 level. Survival was significantly shorter in patients with high CA19-9 than in those with low CA19-9 levels. Values of $P < 0.05$ were considered statistically significant.

TABLE 4. Multivariate Analyses in Patients With Recurrence Who Underwent Curative Resection for IDC of the Pancreas

Parameter	Tested Factor	N	HR	95% CI	P
PS	2,3	35	2.2	1.2–3.9	0.007
ChE (IU/dL)	<200	35	3.2	1.7–6.1	<0.001
CEA (ng/mL)	≥40	10	2.7	1.1–6.4	0.026
CA19-9 (U/mL)	≥100	52	1.9	1.0–3.6	0.038
Peritoneal dissemination	Present	12	5.0	2.1–11.6	<0.001
Group without peritoneal dissemination					
ChE (IU/dL)	<200	26	3.5	1.8–6.9	<0.001
CA19-9 (U/mL)	≥100	44	2.8	1.4–5.5	0.003

Multivariate analysis was performed using the Cox hazard regression model. Level of significance was set at $P < 0.05$.

(n = 52; HR, 1.9; $P = 0.038$) (Fig. 1C); and peritoneal dissemination (n = 12; HR, 5.0; $P < 0.001$). Peritoneal dissemination is a parameter predictive of poor prognosis in general, and prognostic factors in patients without peritoneal dissemination are also important. Additional multivariate analysis was therefore performed in patients without peritoneal dissemination, demonstrating that ChE less than 200 IU/dL (n = 26; HR, 3.5; $P < 0.001$) and CA19-9 100 U/mL or greater (n = 44; HR, 2.8; $P = 0.003$) showed independent prognostic value from peritoneal dissemination (Table 4).

Correlation Between Clinical Parameters and Histological Findings

Patients showing nerve plexus invasion in primary tumors displayed ChE less than 200 IU/dL (65% vs 35%; $P = 0.031$) and CA 19-9 100 U/mL or greater (74% vs 26%; $P = 0.003$) at initial recurrence significantly more frequently than patients without plexus invasion (Table 5). No other histological factors showed significant associations with ChE and CA19-9. Furthermore, patients with nerve plexus invasion showed significantly lower ChE levels than patients without nerve plexus invasion (mean, 180 vs 219 IU/dL; $P = 0.023$; Table 6), but CA19-9 levels did not differ significantly between patients with and without nerve plexus invasion (mean, 2166 vs 3377 U/dL; $P = 0.630$; Table 6). In the view of other clinical data, the patients with nerve plexus invasion in primary tumor showed anemia significantly ($P = 0.030$; Table 6). On the basis of these results, only nerve plexus invasion as a histological factor of primary tumor correlated with the important clinical factor of ChE at initial recurrence.

Clinical Characteristics of Patients With Lower ChE

To identify patient characteristics associated with ChE less than 200 IU/dL, clinical data were compared between patients with serum ChE level at initial recurrence less than 200 or greater than or equal to 200 IU/dL (Table 7). Surprisingly, patients with ChE less than 200 IU/dL showed significant cachexia compared with patients with ChE 200 IU/dL or greater as follows: poor performance status (mean PS, 2.1 vs 1.2; $P < 0.001$), anemia (mean Hgb, 10.2 vs 11.9 g/dL; $P < 0.001$), hypoalbuminemia (mean Alb, 3.1 vs 3.9; $P < 0.001$), hypocholesterolemia (mean T.cho, 125.4 vs

TABLE 5. Correlation Between Pathological Factors and Independent Clinical Prognostic Factors in Patients With Recurrence After Curative Resection for IDC of the Pancreas

Pathological Parameter	Category	CA19-9 (U/mL)			ChE (IU/dL)		
		<100	≥100	*P*	<200	≥200	*P*
Tumor size (cm)	≤3.0/>3.0	12/9	21/31	0.207	15/20	18/20	0.815
Predominant differentiation	Well, mod/poor	16/5	48/4	0.109	31/4	33/5	>0.999
Least differentiation	Well, mod/poor	12/9	27/25	0.797	21/14	18/20	0.350
Retroperitoneal invasion	0, 1/2, 3	5/16	25/27	0.069	13/22	17/21	0.635
Lymph vessel invasion	0, 1/2, 3	15/6	39/13	0.774	25/10	29/9	0.790
Blood vessel invasion	0, 1/2, 3	2/19	6/46	>0.999	6/29	2/36	0.142
Intrapancreatic neural invasion	0, 1/2, 3	5/16	15/37	0.777	9/26	11/27	0.798
Nerve plexus invasion	Absent/present	19/2	28/24	0.003	18/17	29/9	0.031
JpN	JpN0, 1/JpN2, 3	16/5	39/13	>0.999	25/10	30/8	0.588
UICC pT	1, 2/3	2/19	2/50	0.574	0/35	4/34	0.116
UICC pN	0/1	2/19	9/43	0.494	4/31	7/31	0.519
UICC pStage	≤IIA/≥IIB	1/20	8/44	0.432	3/32	6/32	0.483
UICC R	R0/R1	17/4	43/9	>0.999	29/6	31/7	>0.999
Tumor necrosis	Absent/present	14/7	33/19	>0.999	22/13	25/13	0.812
Fibrotic focus	Absent/present	8/13	21/31	>0.999	16/19	13/25	0.347

Categorical analysis was performed using Fisher exact test. Level of significance was set at $P < 0.05$.

JpN indicates classification of lymph node metastasis according to Japan Pancreas Society criteria; JpN0/JpN1/JpN2/JpN3, parameters showing the range of lymph node metastasis according to classifications of the Japanese Pancreas Society; mod, moderately differentiated; poor, poorly differentiated; UICC, classification according to International Union Against Cancer criteria; 0, none; 1, slightly seen; 2, occasionally seen; 3, frequently seen; well, well differentiated.

173.2 IU/mL), and ascites (70% vs 30%; $P = 0.025$) (Table 6). Elevation of bilirubin and a high frequency of liver metastasis were not associated with ChE less than 200 IU/dL.

Clinical and Histological Characteristics in Patients With Liver Metastasis

Serum ChE is synthesized in and released from the liver. The serum level of ChE may be affected by liver metastasis. To evaluate the association between serum ChE and liver metastasis, the distribution of clinical parameters at initial recurrence was analyzed according to the presence of liver metastasis (Table 8). Hepatic metastasis is common distant spreading manner of pancreatic cancer, and the associated histological factors with hepatic metastasis may be useful information for clinicians to predict clinical course and choose the treatment. Therefore, the distribution of histological findings of primary tumor was analyzed according to the presence of liver metastasis in addition (Table 8). Large tumor size (P = 0.010), poor differentiation on least differentiation of tumor (P = 0.002) and the presence of tumor necrosis

TABLE 6. Distribution of Clinical Parameters at Initial Recurrence According to the Presence of Nerve Plexus Invasion in Primary Tumor

Parameter	Category	Nerve Plexus Invasion in Primary Tumor		*P*
		Absent	Present	
PS	Mean (95% CI)	1.62 (1.39–1.86)	1.48 (1.0–1.9)	0.520
Hgb (g/dL)	Mean (95% CI)	11.5 (10.9–12.0)	10.4 (9.7–11.1)	0.030
Plt ($\times 10^4$/dL)	Mean (95% CI)	21.4 (18.6–24.2)	21.1 (17.1–25.1)	0.883
T.Bil (mg/dL)	Mean (95% CI)	1.0 (0.6–1.3)	0.8 (0.6–1.1)	0.645
Alb (g/dL)	Mean (95% CI)	3.6 (3.4–3.7)	3.4 (3.1–3.6)	0.216
T.cho (IU/mL)	Mean (95% CI)	152.9 (140.7–165.0)	145.5 (128.5–162.6)	0.473
ChE (IU/dL)	Mean (95% CI)	218.7 (197.9–239.5)	180.3 (155.6–205.0)	0.023
CEA (ng/mlL)	Mean (95% CI)	25.0 (2.5–47.6)	62.3 (6.7–117.9)	0.141
CA19-9 (U/mL)	Mean (95% CI)	3376.7 (−286.0 to 7039.3)	2166.1 (816.0–3516.3)	0.630
Weight loss ratio (%)	Mean (95% CI)	6.7 (4.1–9.4)	4.5 (−0.8 to 9.8)	0.403
Duration to recurrence (d)	Mean (95% CI)	330.6 (257.0–404.1)	277.6 (211.6–343.6)	0.336
Ascites (n)	Absent/present	33/14	17/9	0.794
Local recurrence (n)	Absent/present	22/25	8/18	0.220
Liver metastasis (n)	Absent/present	23/24	11/15	0.631
Peritoneal dissemination (n)	Absent/present	40/7	21/5	0.744

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation. Analysis was performed using 2-tailed Student t test or Fisher exact test. Level of significance was set at $P < 0.05$.

TABLE 7. Patient Characteristics Classified According to Serum Cholinesterase Level

Parameter		ChE <200 (IU/dL)	ChE ≥200 (IU/dL)	*P*
PS	Mean (95% CI)	2.1 (1.7–2.4)	1.2 (1.0–1.5)	<0.001
Hgb (g/dL)	Mean (95% CI)	10.2 (9.5–10.9)	11.9 (11.5–12.4)	<0.001
Plt (×104/dL)	Mean (95% CI)	19.6 (16.0–23.2)	22.9 (20.1–25.7)	0.145
T.Bil (mg/dL)	Mean (95% CI)	1.1 (0.7–1.4)	0.8 (0.4–1.1)	0.235
Alb (g/dL)	Mean (95% CI)	3.1 (2.9–3.2)	3.9 (3.8–4.0)	<0.001
T.cho (IU/mL)	Mean (95% CI)	125.4 (113.8–137.0)	173.2 (161.9–184.5)	<0.001
ChE (IU/dL)	Mean (95% CI)	146.3 (135.8–156.8)	259.2 (243.4–275.0)	
CEA (ng/mL)	Mean (95% CI)	41.6 (9.0–74.1)	35.3 (−1.4 to 72.1)	0.798
CA19-9 (U/mL)	Mean (95% CI)	2639.6 (974.8–4304.3)	3227.3 (−1181.6 to 7636.3)	0.807
Weight loss ratio (%)	Mean (95% CI)	6.2 (2.0–10.4)	5.5 (2.2–8.9)	0.809
Duration to recurrence (d)	Mean (95% CI)	328.4 (247.9–408.9)	296.3 (225.6–367.1)	0.544
Ascites (n)	Absent/present	19/16	31/7	0.025
Local recurrence (n)	Absent/present	12/23	18/20	0.351
Liver metastasis (n)	Absent/present	19/16	15/23	0.168
Peritoneal dissemination (n)	Absent/present	26/9	35/3	0.065

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation. Analysis was performed using 2-tailed Student *t* test or Fisher exact test. Level of significance was set at $P < 0.05$.

($P = 0.015$) in histological findings of primary tumor and high serum CEA level ($P = 0.012$), and short duration to recurrence ($P = 0.004$) in clinical parameters of initial recurrence were significantly associated with the presence of liver metastasis. Serum ChE level was not affected by the presence of liver metastasis significantly.

DISCUSSION

Low serum level of ChE at initial recurrence after resection was identified as an important clinical prognostic factor of pancreatic IDC in this study. The prognostic impact of serum ChE level has been reported in patients with liver cirrhosis[15] and advanced solid cancer.[16] In the present study, the prognostic value of serum ChE level was identified through multivariate analysis using all patients. In further multivariate analysis using patients without peritoneal dissemination, serum ChE level maintained its prognostic value. The prognostic power of serum ChE level was thus validated through 2 multivariate analyses in this study. Cholinesterase is formed in the liver and released into plasma immediately after synthesis.[17] Serum ChE level shows good correlation to Child-Pugh score,[15] a superior index of liver function.[18] Low serum level of ChE is thus regarded as indicative of hepatic impairment.[15,17] Significant characteristics of patients with low serum level of ChE at initial recurrence were worsened PS, anemia, hypoalbuminemia, hypocholesterolemia, and the presence of ascites. Because low serum level of ChE is associated with low functional state of the liver,[15,17] hepatic impairment might result in hypoalbuminemia, hypocholesterolemia, and the presence of ascites. Worsened PS[1] and anemia[9] have been reported as prognostic factors in patients with advanced cancer and are prevalent in patients with cancer cachexia.[9,15] Hypoalbuminemia is also indicated as a characteristic of cancer cachexia.[15] Conversely, body weight loss is an important finding in cancer cachexia[15] and was not a significant finding in our patients with low serum levels of ChE. These data might mean that body weight loss seems subsequent to worsened PS, anemia, hypoalbuminemia, and low serum levels of ChE. If body weight loss is necessary to fulfil the criteria for cancer cachexia and appears in more advanced states of disease progression, this study might indicate serum levels of ChE as a sensitive marker of cancer cachexia. Cholinesterase and the associated factors with low serum ChE level, PS, Hgb, Alb, and T.cho are the index of malnutrition. Cholinesterase shows the strongest predictive power of prognosis in nutritional parameters. This result may indicate that life-threatened nutritional factor is a hepatic impairment that is well indexed by ChE. This hypothesis needs further clinical and experimental studies to evaluate liver function, hematogenesis, digestive absorption, and appetite in pancreatic cancer patients, to find the molecule resulting in abnormality of hepatocyte function, and to reveal ChE as the most sensitive marker to abnormal hepatocyte.

A significant correlation was identified between nerve plexus invasion by the primary tumor and low serum ChE level in this study. Nerve plexus invasion is a common behavior of primary pancreatic IDC and has been identified as an important prognostic factor in our own[7,19] and other studies.[20] When nerve plexus invasion at initial recurrence is mentioned, 2 important issues should be clarified: (1) the presence of nerve plexus invasion at initial recurrence and (2) alteration of tumor characteristics from primary tumor to tumor recurrence. First, whether nerve plexus invasion exists at initial recurrence after resection is important. According to recent reports, nerve plexus invasion is observed in 79% of autopsies for patients who died of recurrence after resection for pancreatic IDC.[21] Median survival after initial recurrence was 4.7 months in this study compared with 3 to 7 months in another study.[22] In the very short duration between initial recurrence and death, some discrepancies may exist between frequency of nerve invasion at autopsy and at initial recurrence. We thus suspect that nerve plexus invasion is prevalent at initial recurrence after resection, appearing in up to almost 80% of patients according to Hishinuma et al.[21]

TABLE 8. Distribution of Clinical and Histological Parameters According to the Presence of Liver Metastasis

Parameter	Category	Liver Metastasis at Initial Recurrence		*P*
		Absent	Present	
Histological in primary tumor				
Tumor size (cm)	<3.0/>3.0	21/13	12/27	0.010
Predominant differentiation	Well, mod/poor	32/2	32/7	0.162
Least differentiation	Well, mod/poor	25/9	14/25	0.002
Retroperitoneal invasion	0, 1/2, 3	13/21	17/22	0.812
Lymph vessel invasion	0, 1/2, 3	28/6	26/13	0.182
Blood vessel invasion	0, 1/2, 3	6/28	2/37	0.135
Intrapancreatic neural invasion	0, 1/2, 3	8/26	12/27	0.602
Nerve plexus invasion	Absent/present	23/11	24/15	0.631
JpN	JpN0, 1/JpN2, 3	24/10	31/8	0.424
UICC pT	pT1, 2/pT3	4/57	0/12	>0.999
UICC pN	pN0/pN1	5/29	6/33	>0.999
UICC pStage	<IIA/>IIB	4/30	5/34	>0.999
UICC R	R0/R1	28/6	32/7	>0.999
Tumor necrosis	Absent/present	27/7	20/19	0.015
Fibrotic focus	Absent/present	18/16	11/28	0.054
Clinical at initial recurrence				
PS	Mean (95% CI)	1.7 (1.3–2.0)	1.5 (1.2–1.8)	0.462
Hgb (g/dL)	Mean (95% CI)	11.1 (10.5–11.8)	11.1 (10.4–11.7)	0.921
Plt (× 104/dL)	Mean (95% CI)	20.2 (16.4–24.0)	22.3 (19.5–25.1)	0.348
T.Bil (mg/dL)	Mean (95% CI)	1.1 (0.6–1.6)	0.8 (0.6–0.9)	0.261
Alb (g/dL)	Mean (95% CI)	3.5 (3.2–3.7)	3.6 (3.4–3.7)	0.463
T.cho (IU/mL)	Mean (95% CI)	144.3 (130.0–158.6)	155.5 (142.0–169.0)	0.251
ChE (IU/dL)	Mean (95% CI)	197.8 (175.6–220.0)	211.3 (187.1–235.6)	0.411
CEA (ng/mL)	Mean (95% CI)	6.1 (3.6–8.7)	66.4 (22.4–110.4)	0.012
CA19-9 (U/mL)	Mean (95% CI)	555.5 (−61.8 to 1172.8)	5029.1 (630.9–9427.3)	0.061
Weight loss ratio (%)	Mean (95% CI)	6.7 (2.4–11.2)	5.2 (2.0–8.3)	0.541
Duration to recurrence (d)	Mean (95% CI)	391.2 (312.2–470.2)	242.4 (177.9–307.0)	0.004
Ascites (n)	Absent/present	24/10	26/13	0.803

Weight loss ratio was calculated as 100 × (body weight at initial operation − body weight at recurrence)/body weight at initial operation. Analysis was performed using 2-tailed Student *t* test or Fisher exact test. Level of significance was set at $P < 0.05$.

JpN indicates classification of lymph node metastasis according to Japan Pancreas Society criteria; JpN0/JpN1/JpN2/JpN3, parameters showing the range of lymph node metastasis according to classifications of the Japanese Pancreas Society; mod, moderately differentiated; poor, poorly differentiated; UICC, classification according to International Union Against Cancer criteria; 0, none; 1, slightly seen; 2, occasionally seen; 3, frequently seen; well, well differentiated.

Another important problem that should be described is the alteration of tumor characteristics between primary and recurrent tumor. Tumor cells evolve through a process analogous to Darwinian natural selection aided by genetic instability, resulting in the acquisition of growth advantages, and clonal progression of selected tumor cells contributes to tumor development.[23] Primary pancreatic IDCs evolve until clinical recurrence and are expected to possess a high ability for nerve invasion at initial recurrence compared with that at resection. Patients with nerve plexus invasion in primary tumor might thus display more severe nerve invasion at initial recurrence compared with patients without nerve plexus invasion in primary tumor. On the basis of this context, a significant relationship may exist between severe nerve invasion and low functional state of the liver. Mechanisms underlying such a relationship are unknown. Anatomically, the pancreatic nerve plexus is a part of a neural network connecting the spine and abdominal organs, and this network innervates the liver.[24] Sympathetic and parasympathetic hepatic nerve reportedly regulate hepatocyte metabolism.[25] Carreno and Seelaender[26] showed that liver denervation led the reduction of liver noradrenergic nerve, hepatic noradrenalin, hepatocyte mitochondrial fatty acid transport capacity, and fatty acid oxidation. In the view of the above reports, it is possible that the modulated hepatic nerve by nerve invasion via neural network changes hepatocyte metabolism. Low serum ChE level may indicate abnormal hepatic metabolism itself or hepatocyte impairment due to chronic abnormal hepatic metabolism. Relationships between nerve invasion and alteration of hepatic function may be a good target for further study.

Patients with peritoneal dissemination in pancreatic IDC show extremely poor prognosis, and survival time is reportedly 30 days or less.[27] This study revealed peritoneal dissemination as an important prognostic factor through multivariate analysis using all patients. When multivariate analysis was performed using patients without peritoneal dissemination, independent prognostic factors were high serum level of CA19-9 and low serum level of ChE. Carbohydrate antigen 19-9 has been reported as an important prognostic factor in previous studies.[28,29] Although the frequency of patients with high serum level of CA19-9 level was significantly higher in patients with nerve plexus invasion of the primary tumor, mean CA19-9 level of patients with nerve plexus invasion was not significantly higher than that of patients without nerve plexus invasion. Carbohydrate antigen 19-9 level at initial recurrence was thus not significantly associated with histological factors in the primary tumor.

In summary, this study found that (1) peritoneal dissemination, low serum levels of ChE, and high serum levels of CA19-9 are important prognostic factors at initial recurrence after macroscopic resection for pancreatic IDC; (2) patients with low serum levels of ChE show a cachexia-like systemic condition; and (3) nerve plexus invasion and low serum levels of ChE at initial recurrence are significantly associated. This study may indicate an association between nerve invasion and hepatic impairment, and such a relationship warrants further study.

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Autoimmune pancreatitis with multifocal lesions

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Abstract
Two cases of a focal type of autoimmune pancreatitis (AIP) with distinct double mass lesions within the pancreas are described. In both patients, computed tomography (CT) showed localized pancreatic masses with delayed enhancement, and magnetic resonance cholangiopancreatography (MRCP) revealed localized stenoses of the main pancreatic duct (MPD) with mild upstream dilatation. Fluorodeoxyglucose positron emission tomography (FDG-PET) examination, performed in one patient, showed intense uptake concordant with tumors. Both patients received pancreatic resection with a presumptive diagnosis of pancreatic carcinoma. Histologic evaluation of the tumors showed marked lymphoplasmacytic infiltration and fibrosis around the large and medium pancreatic ducts, without any evidence of malignancy. Serum IgG4 concentration, measured postoperatively, was elevated in both patients. The characteristic morphological features of AIP are diffuse swelling of the pancreatic parenchyma and diffuse narrowing of the MPD. Recently, a focal type of AIP, which mimics pancreatic carcinoma, has been recognized. Considering the favorable response of AIP to steroid therapy, it is clinically important to differentiate the focal type of AIP from pancreatic carcinoma and to know that AIP sometimes exhibits multiple lesions within the pancreas.

Key words Autoimmune pancreatitis · Multifocal lesions · IgG4 staining

Introduction

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis associated with an autoimmune inflammatory process.[1] Although diffuse swelling of the pancreatic parenchyma and diffuse irregular narrowing of the pancreatic duct system are morphologically characteristic of AIP, a focal type of this clinical entity has been recently recognized.[2–4]

The focal type of AIP exhibits a localized mass lesion in the pancreas, similar to pancreatic carcinoma, and it often exhibits obstructive jaundice,[5] which is also characteristic of pancreatic carcinoma, when the lesion involves the head of the pancreas. Consequently, some patients with these features have been subjected to surgical exploration with a presumed diagnosis of pancreatic carcinoma.[6] Considering that AIP shows a favorable response to steroid therapy, the differentiation of these two entities is clinically important.

Although patients with AIP sometimes show multifocal or skipped narrowing of the main pancreatic duct (MPD), there have been only a few cases of AIP with multifocal lesions.[7] In this report, we describe the clinical, radiological, and histopathological features of two patients with AIP who exhibited distinct double masses in the pancreas; the masses were resected on the suspicion of pancreatic carcinoma.

Case reports

Case 1

A 62-year-old male patient with mild epigastralgia was referred for further investigation of pancreatic masses. He had no medical history of autoimmune disease, but he had a history of hypertension. The results of laboratory examinations, including complete blood count, electrolytes, bilirubin, liver function tests, and pancreatic enzymes and tumor markers (carbohydrate antigen [CA] 19-9, and carcinoembryonic antigen [CEA]), were all within normal limits. Computed tomography (CT) showed irregular mass lesions in the head and body of the pancreas (Fig. 1a, b); the lesions were 30 mm and 25 mm in diameter, respectively. The tumors showed slight attenuation in the delayed phase with contrast

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a,c e
b,d

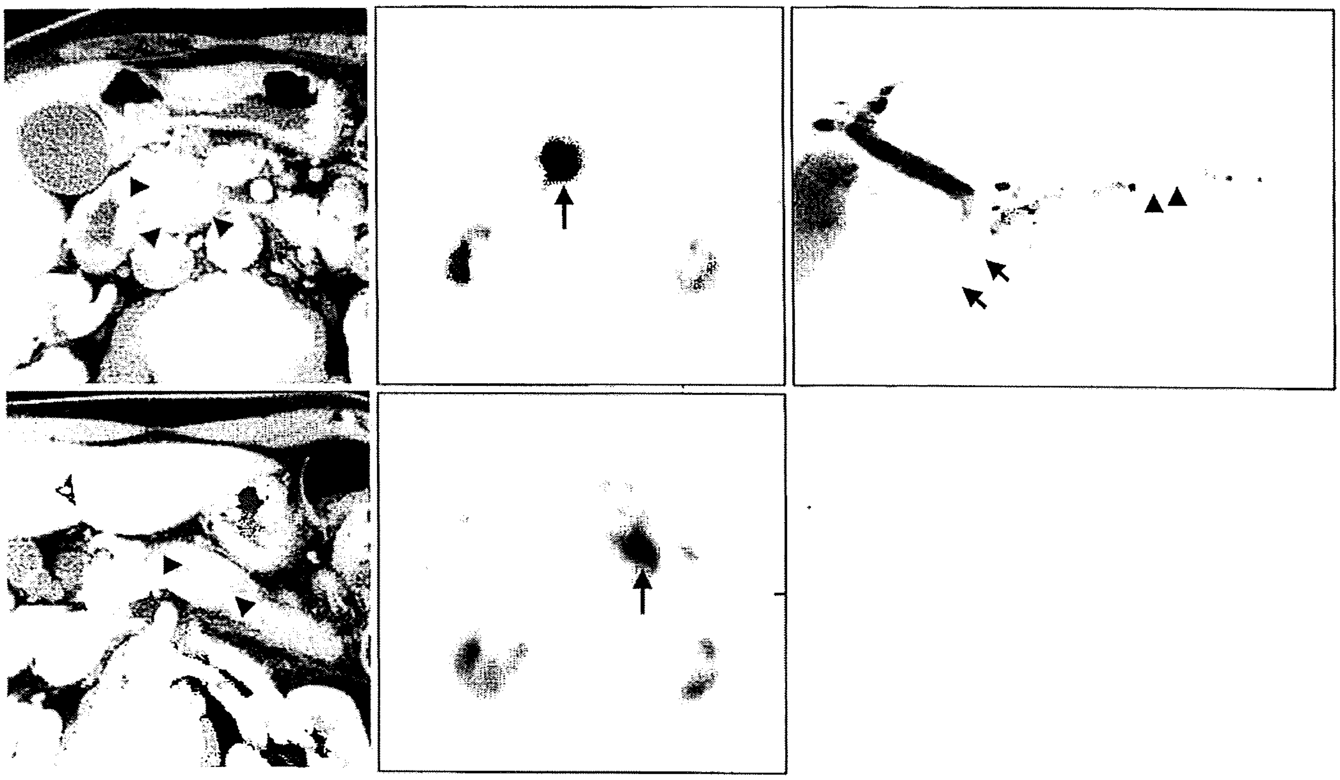


Fig. 1a–e. Case 1. Computed tomography (CT) revealed irregular mass lesions in the head (**a**) and body (**b**) of the pancreas (*arrowheads*); early phase. **c**, **d** Fluorodeoxyglucose positron emission tomography (FDG-PET) showed intense uptake in both lesions (*arrows*), and their standardized uptake values (SUVs) were 6.6 and 8.3, respectively. (**c**, head; **d**, body). **e** Magnetic resonance cholangiopancreatography (MRCP) revealed skipped stenoses in the main pancreatic duct (MPD) concordant with the tumors (head, *arrows*; body, *arrowheads*), and mild dilatation between the tumors and distally

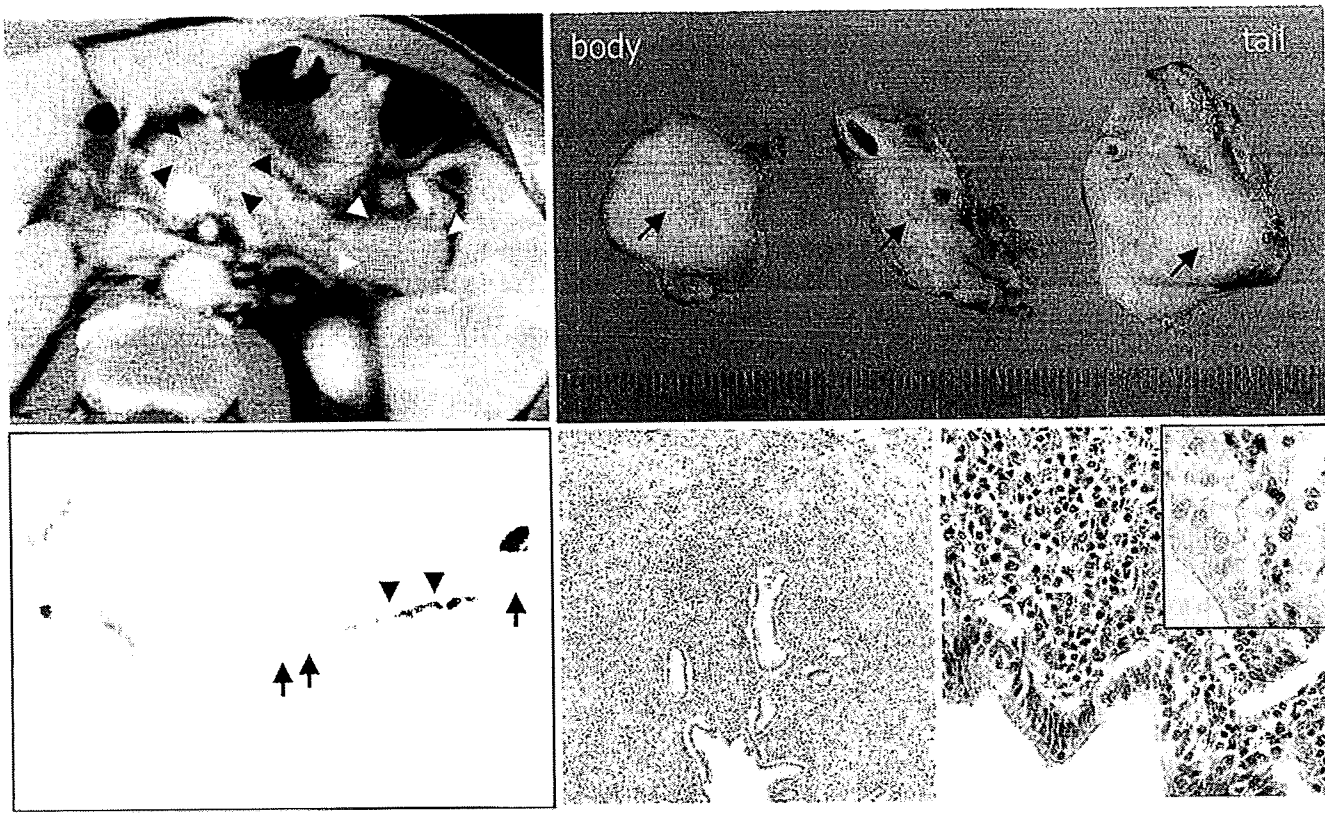
medium. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed intense uptake in both lesions, and their standardized uptake values (SUVs) were 6.6 and 8.3, respectively (Fig. 1c, d). Magnetic resonance cholangiopancreatography (MRCP) revealed skipped stenoses of the MPD, concordant with the tumors, and mild dilatation between the tumors and distally (Fig. 1e).

Case 2

A 64-year-old male patient without any symptoms or past medical history was admitted because of pancreatic masses that were picked up on a medical checkup. Laboratory tests showed slight elevation of blood glucose (126 mg/dl; normal, 69–104 mg/dl) and hepatic enzymes (aspartate aminotransferase, 41 IU/l [normal, 13–33 IU/l], alkaline aminotransferase, 75 IU/l [normal, 8–42 IU/l]). Dynamic CT showed two lesions, in the body and tail of the pancreas, 28 mm and 30 mm in diameter, respectively, and exhibited subtle delayed enhancement (Fig. 2a). MRCP revealed obstruction of the MPD in concordance with the tumors, and slight dilatation between the tumors (Fig. 2b).

The proximal lesions in both patients were considered to be pancreatic carcinomas because the finding of localized stenoses with upstream dilatation of the MPD was suggestive of pancreatic carcinoma. The distal lesions were deemed to be either obstructive pancreatitis demonstrating mass lesions because of severe inflammation, or other primary pancreatic carcinoma. In case 1, core needle biopsy of the tumor in the pancreatic body was performed during surgery, and this revealed parenchymal fibrosis and infiltration of inflammatory cells, including plasma cells, without any evidence of malignancy. Therefore, Whipple resection was performed to resect only the head lesion. In case 2, the patient received distal pancreatectomy.

The three resected tumors (case 1, head; case 2, body and tail) resembled each other on both macroscopic and microscopic examinations. On gross appearance, all cut surfaces of the tumors demonstrated swelling of the parenchyma, but the border between the tumor and the surrounding pancreatic tissue was unclear, while the existing lobular structure and narrowed MPD were clearly identified (Fig. 2c). Microscopic examination confirmed marked lymphoplasmacytic infiltration and fibrosis around the large and medium pancreatic ducts a,c



b,d e

Fig. 2a–e. Case 2. **a** CT showed two lesions, in the body and tail of the pancreas (*arrowheads*), and exhibited subtle delayed enhancement; delayed phase. **b** MRCP revealed obstruction of the MPD concordant with the tumors (*arrows*), and slight dilatation between the tumors (*arrowheads*). **c** On macroscopic examination, the cut surface of the tumors showed swelling of the parenchyma, and the border between the tumor and the surrounding pancreatic tissue was unclear. The parenchyma between the two lesions was markedly atrophic. The MPD was narrowed in the tumor lesions, but was normal in the area between the tumors (*arrows*). **d** Microscopic examination confirmed that the MPD was narrowed, with dense lymphoplasmacytic infiltration and severe periductal fibrosis around the MPD. **e** Lymphocytes and plasma cells around the MPD. *Inset* shows IgG4-positive plasma cells. **d** H&E, × 40; **e** H&E, × 200; *inset* in **e** IgG4 staining, × 400

(Fig. 2d, e). Lobular inflammation, atrophy of the parenchyma, and obliterative phlebitis were also observed. No cystic lesion or calcification was detected. On immunohistochemical staining, abundant plasma cells showing strong immunoreactivity for IgG4 were observed, predominantly around the pancreatic ducts (Fig. 2e, inset).

The parenchyma between the two lesions in case 2 was markedly atrophic, and the acinar cells were almost all replaced by fibrous tissue. The MPD was infiltrated with lymphoplasmacytes, including IgG4-positive plasma cells, as observed in the tumorous area.

The serum IgG4 level, measured postoperatively, was elevated in both patients (case 1, 149 mg/dl; case 2, 183 mg/dl [normal, 0–135 mg/dl[8]]).

Discussion

Since Yoshida et al.[1] proposed the term "autoimmune pancreatitis (AIP)" to describe a type of chronic pancreatitis with an autoimmune mechanism in 1995, the concept of AIP has been widely recognized. The characteristics of AIP are described as follows: mild symptoms, increased serum γ-globulin or IgG level and the presence of autoantibodies, diffuse enlargement of the pancreas, diffuse irregular narrowing of the MPD, fibrotic change with lymphoplasmacyte infiltration histopathologically, and a favorable response to steroid therapy.[1] In addition, an elevated concentration of serum IgG4 is reported to be supportive of the diagnosis of AIP.[8]

AIP is frequently associated with other autoimmune disorders such as inflammatory bowel disease and sclerosing cholangitis. Recently, IgG4-related sclerosing diseases of organs other than the pancreas have been documented.[9] Various organs, including the bile duct, gallbladder, salivary gland, and retroperitoneum are considered to be affected multifocally. These organs are characterized by dense infiltrations of IgG4-positive plasma cells.

With an increase of AIP cases being reported, some AIP patients have presented with focal involvement showing localized narrowing of the MPD and focal swelling of the pancreas.[2–4] As this focal variant of AIP sometimes shows clinical and radiological findings resembling those of pancreatic carcinoma, patients with such findings have frequently been treated surgically for suspected malignancy.[6] Although some diagnostic clues have been reported to differentiate the focal type of AIP from pancreatic carcinoma, such as a fluctuating course of jaundice,[3] homogeneous delayed enhancement on dynamic CT, longer stenosed MPD without upstream dilatation,[4] and raised concentration of serum IgG4,[8] definite discrimination is still difficult in spite of the advances in imaging technology. Even with FDG-PET examination, when the lesion is localized, it can be confused with pancreatic malignancy, because it has been reported to show increased uptake at the affected site of AIP.[10]

Our preoperative diagnosis in both the present patients was pancreatic carcinoma with obstructive pancreatitis demonstrating mass lesions, or double primary pancreatic carcinomas. However, the possibility of mass-forming pancreatitis should have been entertained, considering the fact that cases of double pancreatic carcinomas have seldom been encountered in clinical settings and considering the finding that the tumor markers in both patients were within normal limits. From a retrospective point of view, stenotic or obstructive findings of the MPD on MRCP are not only characteristic of pancreatic carcinoma but may also be suggestive of AIP, because of the low resolution of MRCP.

Interestingly, the parenchyma between the two lesions in case 2, which appeared almost normal on radiological images, was markedly atrophic, and the acinar cells were almost all replaced by fibrosis on microscopic examination. The MPD was infiltrated with lymphoplasmacytes, including IgG4-positive plasma cells. This suggested that this area had suffered from autoimmune inflammation previously and was almost burned out. In other words, the intensity of inflammation may be related to the degree of swelling of the pancreas, and parenchyma that appears normal on radiological examination may be either actually normal or mildly affected without clinical manifestation, or it may already be burned out as in our case 2.

Considering a reported case of AIP that started as a localized form and progressed to diffuse swelling of the pancreas,[11] the focal type of AIP may be regarded as part of the same clinical spectrum as the diffuse type of AIP. Whether the distribution is diffuse or focal may merely reflect the stage or extent of the disease.[12]

The serum IgG4 level, measured postoperatively, was elevated in both of our patients. However, a case of pancreatic cancer in a patient with a high serum IgG4 concentration was recently reported.[13] Without definite criteria, it is still difficult to discriminate the focal type of AIP from pancreatic carcinoma. Therefore, it is clinically important to know that AIP sometimes exhibits multiple lesions within the pancreas.

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ORIGINAL ARTICLE

Incidence of the focal type of autoimmune pancreatitis in chronic pancreatitis suspected to be pancreatic carcinoma: Experience of a single tertiary cancer center

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Abstract

Objective. With an increase in autoimmune pancreatitis (AIP) being reported, the focal type of AIP, which shows localized narrowing of the main pancreatic duct and focal swelling of the pancreas, has recently been recognized. Therefore, cases of focal-type AIP subjected to surgical intervention for presumptive malignancy might previously have been diagnosed as mass-forming chronic pancreatitis. The aim of this study was to elucidate the incidence of focal-type AIP in resected chronic pancreatitis at a single tertiary cancer center. The clinical and radiological features of focal-type AIP were also evaluated. ***Material and methods.*** We re-evaluated 15 patients who underwent pancreatic resection with a presumed diagnosis of pancreatic ductal adenocarcinoma, and who in the past had been diagnosed pathologically as having chronic pancreatitis. ***Results.*** Seven of 15 patients showed AIP, and the other 8 patients were diagnosed as having mass-forming chronic pancreatitis not otherwise specified by pathological retrospective examination. In other words, nearly half of the cases of resected chronic pancreatitis that were suspected to be pancreatic carcinoma preoperatively showed focal-type AIP. Regarding the characteristic findings of focal-type AIP, narrowing of the pancreatic duct on endoscopic retrograde pancreatography (ERP) might be diagnostic. ***Conclusions.*** Focal-type AIP is not a rare clinical entity and might be buried in previously resected pancreatic specimens that in the past were diagnosed simply as mass-forming pancreatitis.

Key Words: *Autoimmune pancreatitis, focal type, pancreatic carcinoma*

Introduction

Autoimmune pancreatitis (AIP) is a special type of chronic pancreatitis characterized by diffuse swelling of the pancreatic parenchyma and irregular narrowing of the pancreatic duct system, periductal lymphoplasmacytic infiltration and fibrosis, and a favorable response to steroid therapy [1].

With increasing recognition of AIP, however, AIP with focal involvement has recently been reported [2–7]. This focal type of AIP is considered to be in the same clinical category as the diffuse type of AIP, and only the extent of the disease may differ between them [8].

Regarding tertiary cancer centers, patients with so-called mass-forming chronic pancreatitis have been referred to our institute with a presumptive diagnosis of pancreatic ductal adenocarcinoma and subjected to surgical exploration. As focal-type AIP has not been well known in the clinical setting until only recently, patients with this category of disease who had received pancreatic resection for suspected malignancy might previously simply have been diagnosed with mass-forming chronic pancreatitis. Therefore, the frequency of focal-type AIP in patients with chronic pancreatitis who underwent surgical intervention has not been well documented.

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In this study, we retrospectively reviewed all resected specimens of chronic pancreatitis for presumed pancreatic carcinoma, and uncovered the incidence of focal-type AIP in a single tertiary cancer center. Moreover, the clinical and radiological features of focal-type AIP were also evaluated.

Material and methods

From July 1992 to December 2006, 15 patients underwent surgical exploration with a presumptive diagnosis of pancreatic ductal adenocarcinoma, and were diagnosed pathologically as having chronic pancreatitis in the past. We re-evaluated the pathological specimens of these 15 patients, and classified them as AIP or mass-forming pancreatitis not otherwise specified.

The pathological characteristics of AIP are: dense periductal lymphoplasmacytic inflammation, periductal and parenchymal fibrosis, and obliterative venulitis [9]. In an immumohistochemical study, dense infiltration of IgG4-positive plasma cells was also reported to be diagnostic [10–12].

The clinical manifestations and radiological findings for focal-type AIP were also reviewed. Each patient received dynamic computed tomography (CT) and either endoscopic retrograde cholangiopancreatography (ERCP) (4 patients) or magnetic resonance cholangiopancreatography (MRCP) (3 patients).

Results

Incidence of focal-type AIP

Seven (all male) of 15 patients showed AIP, and the other 8 patients (7 M, 1 F) were diagnosed as having mass-forming chronic pancreatitis not otherwise specified, pathologically. Immunohistochemical staining for IgG4 was positive in all AIP patients except one, whereas it was negative in all patients with mass-forming pancreatitis.

Distribution and number of mass lesions

Of the 7 AIP patients, 5 showed a single mass lesion, including 4 in the pancreatic head and one in the body–tail of the pancreas. The remaining 2 patients showed double lesions within the pancreas; one patient with tumors in the pancreatic head and body underwent pancreaticoduodenectomy, and the other patient with mass lesions in the body and tail was subjected to distal pancreatectomy for suspected pancreatic carcinoma (Table I).

Table I. Clinical, laboratory and CT findings in seven patients with resected AIP.

Case	Age/gender	Past history	Symptoms	CEA (ng/ml)	CA19-9 (U/ml)	IgG4 (mg/dl)	Location	Size (mm)	Operation	Delayed enhancement	Capsule-like rim
1	64/M	None	None	0.9	6.2	183	Body, tail	28, 30	DP	++	−
2	62/M	HT	Epigastralgia	2.8	11.1	149	Head, body	30, 25	SSpPD	+	−
3	59/M	None	Epigastralgia, jaundice	0.9	8	NA	Head (Uncus)	30	SSpPD	+++	−
4	51/M	None	None	1.8	5	NA	Body–tail	50	DP	++	+
5	60/M	DM	Epigastralgia, jaundice	3.8	228	NA	Head	23	PpPD	++	−
6	62/M	None	Epigastralgia, jaundice	3.2	98	NA	Head	40	PpPD	+	−
7	68/M	Ulcer, gout	Jaundice	1.6	14	NA	Head	45	PpPD	+	−

Abbreviations: AIP = autoimmune pancreatitis; CEA = carcinoembryonic antigen; NA = not available; HT = hypertension; DM = diabetes mellitus; DP = distal pancreatectomy; SSpPD = subtotal stomach-preserving pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy.