Chronic Pancreatitis Finding by Endoscopic Ultrasonography in the Pancreatic Parenchyma of Intraductal Papillary Mucinous Neoplasms Is Associated with Invasive Intraductal Papillary Mucinous Carcinoma

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Keywords

Chronic pancreatitis · Endoscopic ultrasonography · Intraductal papillary mucinous neoplasm · Pancreatic parenchyma

Abstract

Background/Objectives: The recent guideline for intraductal papillary mucinous neoplasms (IPMNs) focuses on morphological features of the lesion as signs of malignant transformation, but ignores the background pancreatic parenchyma, including features of chronic pancreatitis (CP), which is a risk factor for pancreatic malignancies. Endoscopic ultrasonography frequently reveals evidence of CP (EUS-CP findings) in the background pancreatic parenchyma of patients with IPMNs. Therefore, we investigated whether background EUS-CP findings were associated with malignant IPMN.

Methods: The clinical data of 69 consecutive patients with IPMNs who underwent preoperative EUS and surgical resection between April 2010 and October 2014 were collected prospectively. The association of EUS-CP findings (total number of EUS-CP findings; 0 vs. ≥ 1) with invasive IPMN was examined. The association of EUS-CP findings with pathological changes of the background pancreatic parenchyma (atrophy/inflammation/fibrosis) was also examined. **Results:** Among patients with EUS-CP findings, invasive intraductal papillary mucinous carcinoma (IPMC) was significantly more frequent than among patients without EUS-CP findings (42.5% [17/40] vs. 3.4% [1/29], $p = 0.0002$). In addition, patients with EUS-CP findings had higher grades of pancreatic

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atrophy and inflammation than patients without EUS-CP findings (atrophy: 72.5% [29/40] vs. 34.5% [10/29], $p = 0.003$; inflammation: 45.0% [18/40] vs. 20.7% [6/29], $p = 0.04$). **Conclusions:** In IPMN patients, detection of EUS-CP findings in the background pancreatic parenchyma was associated with a higher prevalence of invasive IPMC. Accordingly, EUS examination should not only assess the morphological features of the lesion itself, but also EUS-CP findings in the background parenchyma.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are a well-characterized group of intraductal mucin-producing cystic neoplasms of the pancreas with malignant potential [1, 2]. In the 2012 international consensus guidelines, high-risk IPMN included two clinical categories with “high-risk stigmata” and “worrisome features,” and different therapeutic strategies were recommended for both groups. It is recommended that patients with “high-risk stigmata” be treated by surgical resection [3–7]. Patients who have “worrisome features” and additional high-risk signs should also undergo resection, while patients with “worrisome features” alone should receive careful follow-up. The “high-risk stigmata” of IPMNs that can be detected by endoscopic ultrasonography (EUS) are an enhancing solid component inside the cyst and dilation of the main pancreatic duct (>10 mm) [3, 8–11]. Additional high-risk signs among the “worrisome features” are a definite mural nodule and suspected main duct involvement [12, 13]. Thus, the current guidelines focus on the morphological features of IPMN as revealed by EUS.

On the other hand, although not described in previous reports, clinical experience suggests that evidence of chronic pancreatitis (CP) is frequently identified in the background pancreatic parenchyma of IPMN patients by EUS (EUS-CP findings). CP is a well-known risk factor for pancreatic malignancy, including pancreatic ductal adenocarcinoma [14–16]. However, the relationship between malignant transformation of IPMNs and pathological changes of the pancreatic parenchyma, such as atrophy, inflammation, and fibrosis, remains unclear. Moreover, changes of the background parenchyma are not considered to be a high-risk sign for malignant IPMN in the current guideline. We hypothesized that EUS-CP findings might be associated with malignant IPMN.

To test this hypothesis, we utilized a database of 69 consecutive patients with IPMNs who underwent preopera-

tive EUS and surgical resection at Kobe University Hospital. We examined the association of EUS-CP findings with the incidence of malignant IPMN and with pathological changes of the background parenchyma in the resected specimens (atrophy, inflammation, and fibrosis).

Methods

Study Design

The clinical data of 69 consecutive patients with IPMNs in whom EUS was performed before surgical resection at Kobe University Hospital from April 2010 to October 2014 were collected prospectively. Patients with concomitant pancreatic carcinoma (defined by the presence of two discrete tumors) were excluded. We investigated various clinical and tumor characteristics, including age, sex, abdominal symptoms (presence vs. absence), serum CEA (<5 vs. ≥ 5 ng/mL), serum CA19-9 (<37 vs. ≥ 37 U/mL), diabetes mellitus (presence vs. absence), habitual drinking (none/sometimes/daily), alcohol consumption (<50 vs. ≥ 50 g/day), macroscopic type of IPMN (main duct, mixed, or branch duct type), cyst location (head vs. body/tail), main pancreatic duct diameter (<5 , 5–10, >10 mm), mural nodule in the cyst (presence vs. absence), cyst diameter (<30 , 30–40, >40 mm), and tumor mucin phenotype (intestinal, gastric, pancreatobiliary, or oncocytic). According to the 2012 international consensus guidelines [3], the macroscopic type of IPMN was classified as main duct type (MD-IPMN), mixed type (Mix-IPMN), or branch duct type (BD-IPMN) based on the results of imaging studies, mainly magnetic resonance cholangiopancreatography (MRCP). Tumors were histologically classified into four types (gastric, intestinal, pancreatobiliary, or oncocytic) according to the appearance on hematoxylin and eosin-stained sections and immunohistochemistry with antimucin antibodies (MUC1/MUC2/MUC5AC/MUC6). In patients with multiple morphologically distinct IPMNs, each neoplasm was classified depending on the type of the dominant component. Tumors were also classified into low-grade dysplasia, high-grade dysplasia, or invasive intraductal papillary mucinous carcinoma (IPMC). The diameter of the main pancreatic duct and the cyst size were measured by MRCP in most cases. In patients who did not undergo MRCP, measurement was done by an alternative method, such as endoscopic retrograde cholangiopancreatography or computed tomography. The presence of mural nodules was evaluated by EUS and magnetic resonance imaging. Abdominal symptoms were defined as including abdominal or back pain/discomfort, weight loss, appetite loss, and jaundice.

This study was conducted in accordance with the Declaration of Helsinki and its amendments (UMIN-CTR ID: 000021345). The study protocol was approved by the ethics committee of Kobe University School of Medicine (No. 1864). All authors had access to the study data and reviewed and approved the final manuscript.

Evaluation of the Pancreatic Parenchyma by EUS

Three echo-endoscopes (GF-UCT240, GF-UCT260, or GF-UE260; Olympus, Tokyo, Japan) were used in this study. EUS-CP findings refer to the parenchymal features of CP in the Rosemont classification recently proposed as EUS diagnostic criteria for this condition [17]. These findings included “hyperechoic foci with

Fig. 1. Typical EUS-CP findings based on the parenchymal features of CP according to the Rosemont classification. **a** Normal. **b** Hyperechoic foci with shadowing. **c** Lobularity with honeycombing. **d** Lobularity without honeycombing. **e** Hyperechoic foci without shadowing. **f** Stranding. CP, chronic pancreatitis; EUS, endoscopic ultrasonography.

shadowing,” “lobularity with honeycombing,” “lobularity without honeycombing,” “hyperechoic foci without shadowing,” and “stranding” (Fig. 1). “Cysts” is also a parenchymal feature of CP in the Rosemont classification, but it was excluded because IPMN itself affects cyst formation. For the same reason, ductal features of CP in the Rosemont classification were excluded, including “main pancreatic duct calculi,” “irregular main pancreatic duct contour,” “dilated side branches,” “main pancreatic duct dilation,” and “hyperechoic main pancreatic duct margin.”

EUS-CP findings were reviewed prospectively by an endosonographer (M. Takenaka) who was unaware of the other data. All cases were re-examined by a second endosonographer (H. Shiomi), who was also unaware of the other data, and there was a good correlation of EUS-CP findings between the two endosonographers ($\kappa = 0.80$ for score 0 vs. ≥ 1 , $p < 0.001$). Both endosonographers had experience with more than 1,000 EUS examinations.

Indications for Surgical Resection

Indications for surgical resection of IPMN at our hospital were decided according to the 2012 International Consensus Guidelines. According to the guidelines, resection is recommended for MD-IPMN. In the case of Mix-IPMN and BD-IPMN, resection is recommended if the patient has “high-risk stigmata.” In patients with “worrisome features” and additional high-risk signs, resection is also recommended.

Pathological Evaluation of Pancreatic Parenchymal Atrophy, Inflammation, and Fibrosis

Hematoxylin and eosin-stained tissue sections from all resected specimens of IPMN were reviewed by a pathologist (Y. Zen), who was blinded to all clinical features. Pancreatic parenchymal atrophy, infiltration of inflammatory cells, and fibrosis were evaluated in the background pancreatic parenchyma. The severity of parenchymal atrophy, inflammation, or fibrosis was graded as 0 (none), 1+ (mild), 2+ (moderate), or 3+ (severe). Representative examples are shown in Figure 2.

Statistical Analysis

All statistical analyses were conducted using JMP version 11 (SAS Institute, Cary, NC, USA), and all p values were two-sided. The χ^2 test (or Fisher exact test, if appropriate) was used to assess associations between categorical variables. To assess the association of the number of EUS-CP findings (0 vs. ≥ 1) with the incidence of invasive IPMN, we conducted multivariate logistic regression analysis. The binary categorical variable (presence and absence) of the incidence of invasive IPMN was used as an outcome variable. Multivariate binary logistic regression analysis was performed to adjust for potential confounders. The OR was adjusted for age, alcohol consumption, and macroscopic type of IPMN, the p value of which was < 0.2 in univariate analysis. Kappa coefficients were calculated to assess agreement of EUS-CP findings between the two observers. In all analyses, $p < 0.05$ was considered statistically significant.

Fig. 2. Pathological findings of the background pancreas parenchyma in intraductal papillary mucinous neoplasm patients. The figure shows the grading of parenchymal atrophy, inflammation, and fibrosis of the pancreas. **a–d** Parenchymal atrophy of grades 0–3. **a** Grade 0 (no atrophic change). **b** Grade 1 (focal atrophy). **c** Grade 2 (moderate atrophy). **d** Grade 3 (severe atrophy with few

residual acinar cells). **e–h** Inflammation of grades 0–3. **e** Grade 0 (no inflammation). **f** Grade 1 (mild inflammation). **g** Grade 2 (moderate inflammation with lymphoid aggregates). **h** Grade 3 (massive inflammation). **i–l** Fibrosis of grades 0–3. **i** Grade 0 (no fibrosis). **j** Grade 1 (mild fibrosis). **k** Grade 2 (moderate fibrosis). **l** Grade 3 (massive fibrosis).

Results

Association of EUS-CP Findings with Invasive IPMC

We categorized 69 IPMN patients by clinical features and factors associated with EUS-CP findings. There were 29 patients without EUS-CP findings and 40 patients with at least one EUS-CP finding. The clinical and morphological features of IPMN are summarized with respect to EUS-CP findings in Table 1. Patients with EUS-CP findings were older than those without EUS-CP findings (70.2 ± 1.4 vs. 65.0 ± 1.7 years, $p = 0.02$). Among the patients with EUS-CP findings, invasive IPMC was significantly more frequent than among those without EUS-CP findings (42.5% [17/40] vs. 3.4% [1/29], $p = 0.0002$) (Table 2). Multivariate analysis showed that detection of EUS-CP findings in the background pancreatic parenchyma was associated with a higher prevalence of invasive IPMC (multivariate OR = 21.9, 95% CI = 3.8–423.1,

$p = 0.0001$). Assessment of each EUS-CP finding showed that invasive IPMC was significantly more frequent in the patients with “stranding” than in those without (55% [11/20] vs. 14% [7/49], $p = 0.002$). In addition, invasive IPMC was significantly more frequent in the patients who had “lobularity without honeycombing” than in those without (83% [5/6] vs. 21% [13/63], $p = 0.004$) (Table 3).

Association of EUS-CP Findings with Pathological Changes of the Pancreatic Parenchyma

Table 4 shows the association between the total number of EUS-CP findings and the pathological findings (atrophy/inflammation/fibrosis) in the background pancreatic parenchyma of the IPMN patients. Among patients with EUS-CP findings, higher grades of pancreatic atrophy and inflammation were observed than in those without EUS-CP findings (atrophy: 72.5% [29/40]

Table 1. Characteristics of the patients and the IPMNs (number of EUS-CP findings 0 vs. ≥1)

	Number of EUS-CP findings		<i>p</i> value
	0	≥1	
Patients, <i>n</i>	29	40	
Age, years	65.0±1.7	70.2±1.4	0.02
Sex, male/female	17/12	20/20	0.50
Abdominal symptoms	5 (17%)	11 (28%)	0.32
CEA ≥5 ng/mL	8 (28%)	13 (33%)	0.66
CA19-9 ≥37 U/mL	8 (28%)	7 (18%)	0.32
Diabetes mellitus	10 (35%)	13 (33%)	0.86
Habitual drinking (none/sometimes/daily)	14/7/8	22/9/9	0.84
Alcohol consumption ≥50 g/day	1 (3%)	5 (13%)	0.19
<i>Clinical features of IPMN</i>			
Macroscopic type (main duct/mixed/branch duct)	0/16/13	5/24/11	0.08
Location of cyst (head/body-tail)	18/11	24/16	0.86
Diameter of main pancreatic duct (<5/5–10/≥10 mm)	12/10/7	10/14/16	0.26
Mural nodule in cyst	11 (38%)	18 (45%)	0.56
Cyst size (<30/30–40/≥40 mm)	14/8/7	23/3/14	0.08
Mucin phenotype (intestinal/gastric/pancreatobiliary/oncocytic)	8/16/4/1	12/24/4/0	0.64
Invasive IPMC	1 (3%)	17 (43%)	0.0002

Values are presented as *n*, *n* (%), or mean ± SD. *p* < 0.05 was considered statistically significant. CP, chronic pancreatitis; EUS, endoscopic ultrasonography; IPMC, intraductal papillary mucinous carcinoma; IPMN, intraductal papillary mucinous neoplasm.

Table 2. Frequency of invasive IPMC in relation to the number of EUS-CP findings

Univariate analysis	Patients, <i>n</i>	Invasive IPMC		<i>p</i> value
		present	absent	
Total	69	18 (26%)	51 (74%)	
EUS-CP findings				
≥1	40	17 (43%)	23 (57%)	0.0002
0	29	1 (3%)	28 (97%)	
Multivariate analysis	Invasive IPMC (outcome variable) ¹			<i>p</i> value
EUS-CP findings (≥1)	21.9 (3.8–423.1)			0.0001

p < 0.05 was considered statistically significant. ¹ Presented as OR (95% CI). The score presents as follows: 0 (absent), 1+ (present). The OR was adjusted for age, alcohol consumption, macroscopic type of IPMN, of which *p* was <0.2 in Table 1 (univariate analysis). CP, chronic pancreatitis; EUS, endoscopic ultrasonography; IPMC, intraductal papillary mucinous carcinoma.

Table 3. Prevalence of invasive IPMC in relation to each EUS-CP finding

	Patients, <i>n</i>	Invasive IPMC		<i>p</i> value
		present	absent	
Total	69	18 (26%)	51 (74%)	
Hyperechoic foci with shadowing				
Present	10	4 (40%)	6 (60%)	0.44
Absent	59	14 (24%)	45 (76%)	
Lobularity with honeycombing				
Present	2	1 (50%)	1 (50%)	0.46
Absent	67	17 (25%)	50 (75%)	
Lobularity without honeycombing				
Present	6	5 (83%)	1 (17%)	0.004
Absent	63	13 (21%)	50 (79%)	
Hyperechoic foci without shadowing				
Present	27	10 (37%)	17 (63%)	0.16
Absent	42	8 (19%)	34 (81%)	
Stranding				
Present	20	11 (55%)	9 (45%)	0.002
Absent	49	7 (14%)	42 (86%)	

p < 0.05 was considered statistically significant. CP, chronic pancreatitis; EUS, endoscopic ultrasonography; IPMC, intraductal papillary mucinous carcinoma.

Table 4. Association between the number of EUS-CP findings and pathological changes in the background pancreatic parenchyma of IPMN patients

	Patients, <i>n</i>	Atrophy		<i>p</i> value	Inflammation		<i>p</i> value	Fibrosis		<i>p</i> value
		high	low		high	low		high	low	
Total	69	39 (57%)	30 (43%)		24 (57%)	45 (43%)		32 (46%)	37 (54%)	
Total number of EUS-CP findings										
≥1	40	29 (73%)	11 (27%)	0.003	18 (45%)	22 (55%)	0.04	21 (53%)	19 (47%)	0.33
0	29	10 (34%)	19 (66%)		6 (21%)	23 (79%)		11 (38%)	18 (62%)	

Atrophy, inflammation, and fibrosis were divided into two groups based on the grade of pathological findings (high, moderate, or severe; low, none, or mild). $p < 0.05$ was considered statistically significant. CP, chronic pancreatitis; EUS, endoscopic ultrasonography; IPMN, intraductal papillary mucinous neoplasm.

Table 5. Association between each EUS-CP finding and pathological changes in the background pancreatic parenchyma of IPMN patients

	Patients, <i>n</i>	Atrophy		<i>p</i> value	Inflammation		<i>p</i> value	Fibrosis		<i>p</i> value
		high	low		high	low		high	low	
Total	69	39 (57%)	30 (43%)		24 (57%)	45 (43%)		32 (46%)	37 (54%)	
Hyperechoic foci with shadowing										
Present	10	8 (80%)	2 (20%)	0.17	6 (60%)	4 (40%)	0.09	6 (60%)	4 (40%)	0.50
Absent	59	31 (53%)	28 (47%)		18 (31%)	41 (69%)		26 (44%)	33 (56%)	
Lobularity with honeycombing										
Present	2	2 (100%)	0 (0%)	0.50	0 (0%)	2 (100%)	0.54	2 (100%)	0 (0%)	0.21
Absent	67	37 (55%)	30 (45%)		24 (36%)	43 (64%)		30 (45%)	37 (55%)	
Lobularity without honeycombing										
Present	6	5 (83%)	1 (17%)	0.22	4 (67%)	2 (33%)	0.17	5 (83%)	1 (17%)	0.09
Absent	63	34 (54%)	29 (46%)		20 (32%)	43 (68%)		27 (43%)	36 (57%)	
Hyperechoic foci without shadowing										
Present	27	18 (67%)	9 (33%)	0.22	11 (41%)	16 (59%)	0.45	11 (41%)	16 (50%)	0.47
Absent	42	21 (50%)	21 (50%)		13 (31%)	29 (69%)		21 (50%)	21 (50%)	
Stranding										
Present	20	18 (90%)	2 (10%)	0.0004	11 (55%)	9 (45%)	0.03	15 (75%)	5 (25%)	0.003
Absent	49	21 (59%)	28 (41%)		13 (27%)	36 (73%)		17 (35%)	32 (65%)	

Atrophy, inflammation, and fibrosis were divided into two groups based on the grade of pathological findings (high, moderate to severe; low, none to mild). $p < 0.05$ was considered statistically significant. CP, chronic pancreatitis; EUS, endoscopic ultrasonography; IPMN, intraductal papillary mucinous neoplasm.

vs. 34.5% [10/29], $p = 0.003$; inflammation: 45.0% [18/40] vs. 20.7% [6/29], $p = 0.04$). Assessment of the pathological correlates with each EUS-CP finding revealed higher grades of pancreatic atrophy, inflammation, and fibrosis in patients with “stranding” than in those without (atrophy: 90% [18/20] vs. 43% [21/49], $p = 0.0004$; inflammation: 56% [11/20] vs. 27% [13/49], $p = 0.03$; fibrosis: 75% [15/20] vs. 35% [17/49], $p = 0.003$) (Table 5).

Association of Pathological Changes in the Pancreatic Parenchyma with Invasive IPMC

Figure 3 displays the relationship between pathological changes (atrophy, inflammation, and fibrosis) in the background pancreatic parenchyma and invasive IPMC. Higher grades of atrophy and inflammation were significantly associated with the presence of invasive IPMC (atrophy: $p = 0.002$; inflammation: $p = 0.002$). Higher grades of fibrosis were also associated with invasive IPMC, but the relationship was not significant ($p = 0.057$).

Fig. 3. Association of pathological changes in the pancreatic parenchyma of intraductal papillary mucinous neoplasm with invasive intraductal papillary mucinous carcinoma (IPMC). The figure displays the relationship between pathological changes (atrophy, inflammation, and fibrosis) in the background pancreatic parenchy-

ma and invasive IPMC. $p < 0.05$ was considered statistically significant. Atrophy, inflammation, and fibrosis were divided into two groups based on the grade of pathological findings (high, moderate to severe; low, none to mild). HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Discussion

In this study, we found that the frequency of invasive IPMC was significantly higher in patients with EUS-CP findings than in those without. In other words, IPMN patients with “normal background pancreatic parenchyma” on EUS had a significantly lower rate of malignancy. To the best of our knowledge, this is the first study to examine the association between EUS-CP findings and malignant transformation of IPMNs.

The Rosemont classification has been proposed as EUS criteria for diagnosing CP [17]. The EUS-CP findings used in this study corresponded to the parenchymal features of the Rosemont classification. However, the relationship between EUS findings and pathological findings in patients with CP has not been well characterized, even in the Rosemont classification. One of the reasons for this is that tissue specimens for evaluating the pancreatic parenchyma often cannot be obtained in patients with CP because they rarely undergo surgery. In this study, we were able to examine the relationship between EUS-CP findings and pathological changes of the background pancreatic parenchyma because we used the resected specimens from IPMN patients.

In the Rosemont classification, each EUS finding has a predictive value, and the findings are categorized into major or minor criteria. The major criteria of CP are “hyperechoic foci with shadowing” and “lobularity with honeycombing.” On the other hand, “stranding” and “lobularity without honeycombing” are classified as minor cri-

teria because of poor specificity. In the present study, “stranding” and “lobularity without honeycombing” were frequently observed in the background parenchyma of IPMN patients, which was a discrepancy between our results and the Rosemont classification. This difference might have arisen because the causes of CP were different. The Rosemont classification was mainly based on alcoholic CP. On the other hand, our study did not target alcoholic CP, but instead assessed CP caused by mucin stagnation in IPMN patients. It has been reported that hypersecretion of mucin by IPMNs causes obstruction of the main pancreatic duct, which may induce low-grade pancreatitis [2]. This difference in the pathogenesis of the parenchymal changes might be associated with the difference of major EUS findings.

Alcohol consumption is strongly associated with CP [18–20]. In our study, there were no significant differences in alcohol consumption between the groups with and without EUS-CP findings, but the presence of these findings was associated with pathological changes of the background parenchyma, such as atrophy and inflammation. This indicates that the EUS-CP findings we investigated were not associated with alcohol consumption and that an increase in mucin production with malignant transformation of IPMN might be associated with changes in the background parenchyma.

The present study has some limitations. First, it was difficult to demonstrate the association of each EUS-CP finding with specific pathological features. Even in the Rosemont classification, only “hyperechoic foci with

shadowing” and “cysts” (excluded from this study) have histological correlates such as calcification and pseudocyst, while other factors (including “stranding” and “lobularity with honeycombing”) are not associated with specific histological features. Further studies will be required to clarify the pathological correlates of these findings. Next, this was a retrospective single-center study, and the number of subjects was limited. Thus, larger studies will be necessary to confirm our results.

In conclusion, detection of EUS-CP findings in the pancreatic parenchyma of IPMN patients was associated with invasive IPMC. When EUS examination of IPMN is performed, the background parenchyma should be evaluated in addition to the morphological features of the tumor itself.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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