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ORIGINAL ARTICLE–GASTROENTEROLOGY

Association between hyperechogenic pancreas and pancreatic ductal adenocarcinoma concomitant with intraductal papillary mucinous neoplasms

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Abstract

Purpose Pancreatic ductal adenocarcinoma (PDAC) may independently occur in the pancreas separate from an intraductal papillary mucinous neoplasm (IPMN). Therefore, identifying the characteristics of patients with IPMN who will likely develop PDAC is clinically important. Although a recent study found that fatty pancreas correlated with PDAC, no reports have examined this matter in patients with IPMN. A previous study showed that fatty pancreas increased the echogenicity; hence, this study aimed to investigate the association between hyperechogenic pancreas and PDAC in patients with IPMN.

Methods We retrospectively collected data of patients with IPMN who underwent endoscopic ultrasonography (EUS) between January 2012 and November 2018. A case–control analysis was performed between patients with IPMN concomitant with PDAC (cases) and those without PDAC (controls). We identified controls by matching age and sex with cases. The echogenicity of the pancreas was determined using EUS by comparing it with the left kidney or spleen. Echogenicity was determined using transabdominal ultrasonography by comparison with that of the liver when it was difficult to determine using EUS.

Results Among 400 patients with IPMN, 23 cases and 92 controls were identified. The proportion of patients with hyperechogenic pancreas was significantly greater in cases than in controls (91.3% vs. 65.2%, $P=0.02$). Multivariate analysis, including family history of pancreatic cancer, multifocal cysts, and hyperechogenic pancreas, showed that hyperechogenic pancreas was correlated with PDAC concomitant with IPMN (odds ratio = 7.07; 95% confidence interval = 1.48–33.80; $P=0.01$).

Conclusion Our analysis demonstrated that hyperechogenic pancreas was associated with concomitant PDAC in patients with IPMN.

Keywords IPMN · Hyperechogenic pancreas · Fatty pancreas · Pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) may independently occur in the pancreas separate from intraductal papillary mucinous neoplasms (IPMNs) [1]. The cancer-specific survival of patients with PDAC concomitant with IPMN was found to be significantly poorer than that of patients with invasive IPMN [2]. Therefore, identifying the characteristics of patients with IPMN who will likely develop PDAC is clinically important.

Patients with the gastric subtype of IPMN are considered to be at high risk for the development of concomitant PDAC [3]. This is important for the follow-up of surgically resected IPMN. IPMN subtypes are difficult to diagnose without resection, and subtyping may be less useful during IPMN surveillance without resection. Moreover, because the vast majority of branch duct IPMN is of the gastric type [4], it is difficult to narrow down the high-risk category associated with concomitant PDAC.

Fatty pancreas is associated with hyperechogenic pancreas [5] and correlated with pancreatic intraepithelial neoplasm (PanIN) and PDAC [6, 7]. Although this was not examined in previous reports in patients with IPMN, we hypothesized that hyperechogenic pancreas may be

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associated with the development of PDAC concomitant with IPMN. The present study aimed to examine the association between hyperechogenic pancreas and concomitant PDAC in patients with IPMN.

Materials and methods

We used a retrospective case–control design. Cases consisted of patients with IPMN concomitant with PDAC, whereas controls consisted of those without PDAC. At our institution, endoscopic ultrasonography (EUS) was performed for IPMN at the initial detection, even when the cyst size was small, to accurately evaluate mural nodules of IPMN and to prevent overlooking PDAC concomitant with IPMN [8]. To identify cases, data of patients with IPMN who had undergone EUS between January 2012 and November 2018 at our institution were collected. Among these patients, 400 with a medical history concerning risk factors for pancreatic cancer, such as a family history of pancreatic cancer, were selected. The study was reviewed and approved by the Kyoto Second Red Cross Hospital Institutional Review Board. All study participants provided informed consent.

IPMN was diagnosed when the pancreatic cystic lesions communicated with the main pancreatic duct and/or showed a grape-like cyst. According to the histological analysis or imaging findings, pancreatic cancer distant from IPMN was classified as PDAC, whereas pancreatic cancer continuous with IPMN was classified as malignant IPMN.

The echogenicity of the pancreas was determined using EUS by comparing the pancreatic body and tail with the left kidney or the spleen. Echogenicity was determined using transabdominal ultrasonography (US) when it was difficult to judge using EUS. First, we compared the liver to the right kidney. If the liver had the same echogenicity as the right kidney, the former was compared to the pancreatic body. If the liver seemed hyperechoic relative to the right kidney, the right kidney was compared to the pancreatic body [9, 10]. When the pancreas was identified retrospectively as hyperechoic by more than three of four experts with experience performing more than 800 EUS and more than 6000 US examinations (K. Mandai, K. Nakase, T. Kawamura, K. Uno), a diagnosis of hyperechogenic pancreas was made. In patients with PDAC concomitant with IPMN, the echogenicity of the pancreas was determined based on EUS or US performed at more than 6 months prior to the diagnosis of PDAC. We excluded patients who had undergone EUS or US for the first time to diagnose PDAC.

Four controls were determined for each case by matching sex and age. A matched case–control analysis using a Mantel–Haenszel test was performed for univariate analysis and a conditional logistic-regression model for multivariate analysis. The following parameters were evaluated: risk factors for pancreatic cancer, family history of pancreatic cancer, history of smoking, current smoking, diabetes mellitus, obesity (body mass index [BMI] of ≥ 30 kg/m^2), multifocal cysts, cyst size, diameter of the main pancreatic duct, and hyperechogenic pancreas. Multifocal cysts were located at the head and body, head and tail, body and tail, or head and body and tail in the pancreas [11]. Matching and all statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [12]. A P value of < 0.05 was considered to indicate a statistically significant difference.

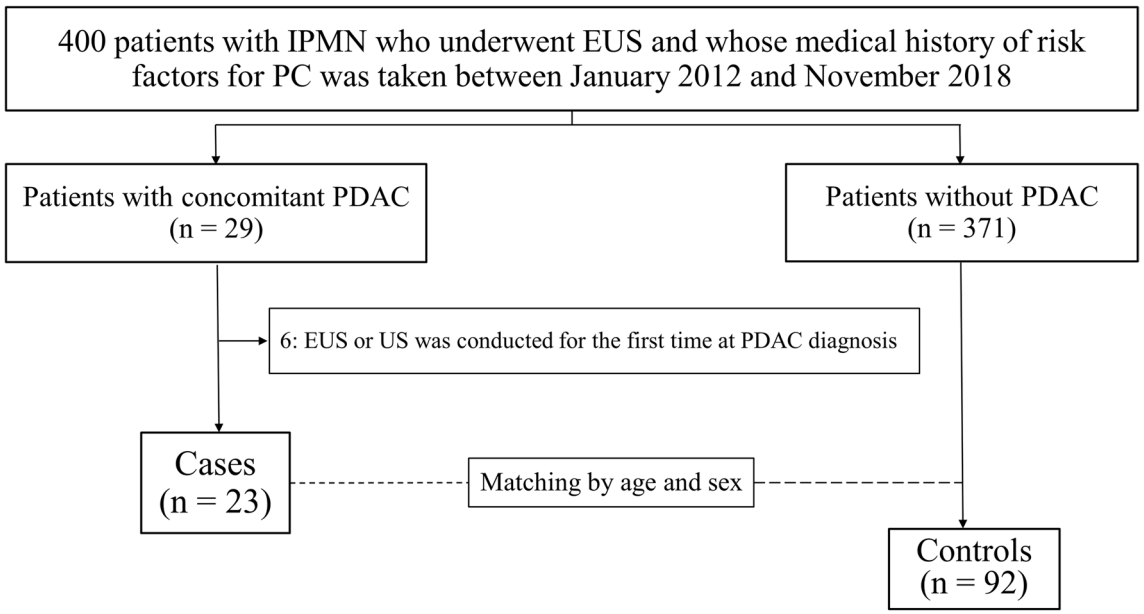
Results

Characteristics of cases

We identified 29 patients with PDAC concomitant with IPMN during the study period. After excluding patients who had undergone EUS or US for the first time at PDAC diagnosis, 23 remained (Fig. 1). The characteristics of cases are shown in Tables 1 and 2. The cohort consisted of 10 men and 13 women. The median age was 73 (interquartile range 69–79) years. Ten PDACs were located at the pancreatic head, seven were at the body, and six were at the tail. Surgical resection was performed in 15 patients, and chemotherapy in eight patients; 13 patients had multifocal cysts. None of the 23 patients had mural nodules in IPMNs. Among the 21 patients with hyperechogenic pancreas, 12 had homogeneous and nine had heterogeneous parenchyma. The periods between the diagnosis of echogenicity and the detection of PDAC were 6–91 months. In 14 patients who had undergone US or EUS more than twice before PDAC detection, the pancreatic echogenicity did not change.

Case–control analysis

Among the 371 patients with IPMN without PDAC, 92 controls were obtained by matching their sex and age with cases. None of the 92 patients had mural nodules in IPMNs. Median follow-up periods in cases and controls were 33 and 48 months, respectively. In the univariate analysis, the proportion of patients with hyperechogenic pancreas was significantly higher in cases than in controls (91.3% vs. 65.2%, $P = 0.02$), although a family history of pancreatic cancer in a first-degree relative, obesity, smoking, diabetes mellitus, multifocal cysts, cyst size, and diameter of the main pancreatic duct were not related to PDAC concomitant with IPMN (Table 3). In the multivariate analysis including a family history of pancreatic cancer, multifocal cysts, and hyperechogenic pancreas, hyperechogenic pancreas was associated



IPMN, intraductal papillary mucinous neoplasm; EUS, endoscopic ultrasonography; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; US, transabdominal ultrasonography

Fig. 1 Flowchart of the study. We selected 400 patients with IPMN who underwent EUS and whose medical history of risk factors for pancreatic cancer was obtained between January 2012 and November 2018. We identified 29 patients with IPMN concomitant with PDAC and 371 patients with IPMN without PDAC. After excluding six patients who underwent EUS or US for the first time at PDAC diagnosis, 23 were finally recruited. Among the 371 patients without PDAC, 92 controls were obtained by matching their sex and age with cases

Table 1 Clinical characteristics of 23 cases

Sex (male), *n*	10
Median age, years (IQR)	73 (69–79)
Location of PDAC (Ph:Pb:Pt), *n*	10:7:6
Treatment	
Surgical resection, *n*	15
Chemotherapy, *n*	8
Multifocal cysts, n	13
Hyperechogenic pancreas	21

PDAC, pancreatic ductal adenocarcinoma; IQR, interquartile range; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail

with PDAC concomitant with IPMN (odds ratio = 7.07, 95% confidence interval = 1.48–33.80, $P = 0.01$) (Table 4).

Discussion

This study investigated the association between hyperechogenic pancreas and concomitant PDAC in patients with IPMN. A retrospective case–control analysis was performed between patients with IPMN concomitant with PDAC (cases) and those without PDAC (controls). Because age, sex, and BMI may influence fatty infiltration in the pancreas [9], controls were identified by matching age and sex with cases. As the number of patients with obesity (BMI ≥ 30 kg/m^2) was small, BMI was not included as a matching factor. Multivariate analysis showed that hyperechogenic pancreas was associated with concomitant PDAC in patients with IPMN.

A previous study found that fatty pancreas increased echogenicity [5]. A recent study in patients who had undergone pancreatoduodenectomy showed that pancreatic fatty infiltration was a possible risk factor for PDAC [7], and another study of surgically resected specimens demonstrated a correlation of pancreatic fatty infiltration with PanINs known as precancerous lesions [6]. Although the mechanisms of carcinogenesis in the pancreas remain controversial, an imbalance of adipokines due to increased pancreatic adipose tissues may induce chronic local inflammation and lead to cell injury and cancer development [13]. Based on these studies, hyperechogenic pancreas may be related to PDAC. Although there have been no reports regarding this matter in patients with IPMN, our study showed that the proportion of patients with hyperechogenic pancreas was significantly higher in the group with IPMN concomitant with PDAC.

Among the patients with PDAC without IPMN diagnosed in the same period at our institution, 35 had undergone US

Table 2 Characteristics of 23 cases

No.	Age/sex	Location		Periods between the diagnosis of echogenicity and PDAC, months	Hyperechogenic pancreas	Treatment
		IPMN	PDAC			
1	79/M	Ph	Pt	6	–	Resection
2	79/M	Ph > Pb,Pt	Ph	12	–	Ct
3	54/F	Ph	Ph	6	+	Resection
4	55/M	Pb > Pt	Ph	23	+	Resection
5	62/F	Pb	Ph	12	+	Resection
6	64/M	Pt	Pb	91	+	Resection
7	69/F	Pb > Pt	Ph	18	+	Resection
8	69/F	Ph > Pb,Pt	Ph	6	+	Resection
9	69/F	Pb	Pb	40	+	Ct
10	69/F	Pb > Ph	Pb	33	+	Resection
11	70/M	Ph > Pt	Ph	18	+	Resection
12	71/M	Pt	Pb	6	+	Resection
13	73/F	Ph	Pb	6	+	Ct
14	73/F	Pb	Ph	6	+	Resection
15	74/F	Pb > Pt	Pb	44	+	Resection
16	74/F	Ph > Pb,Pt	Pt	21	+	Resection
17	76/M	Ph	Pt	22	+	Resection
18	81/M	Pb > Pt	Ph	40	+	Resection
19	79/F	Pb > Pt	Pt	72	+	Ct
20	81/F	Pt > Ph,Pb	Ph	72	+	Ct
21	82/M	Ph > Pb,Pt	Pb	36	+	Resection
22	82/M	Ph	Pt	48	+	Ct
23	82/F	Ph > Pb	Pt	28	+	Ct

IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; Ct, chemotherapy

Table 3 Comparison of characteristics between cases and controls

	Cases ($n=23$)	Controls ($n=92$)	Two-tailed P value	Odds ratio	95% CI
Sex (male), *n* (%)	10 (43.4)	40 (43.5)	–	–	–
Median age, years (IQR)	73 (69–79)	73 (69–79)	–	–	–
Median FU period, months (IQR)	33 (18–60)	48 (21–66)	–	–	–
Risk factors for PC, *n* (%)	13 (56.5)	61 (66.3)	0.49*	0.64	0.24–1.69
FH of PC, *n* (%)	2 (8.7)	11 (12.0)	0.94*	0.66	0.12–3.61
History of smoking, *n* (%)	9 (39.1)	36 (39.1)	1*	1	0.35–2.80
Current smoking, *n* (%)	3 (13.0)	18 (19.6)	0.66*	0.60	0.15–2.31
Diabetes mellitus, *n* (%)	5 (21.7)	22 (23.9)	0.83*	0.88	0.30–2.60
BMI ≥ 30 kg/m^2, *n* (%)	1 (4.3)	3 (3.3)	0.80*	1.33	0.13–12.81
Multifocal cysts, *n* (%)	13 (56.5)	42 (45.7)	0.50*	1.5	0.61–3.63
Cyst size ≥ 30 mm, *n* (%)	2 (8.7)	6 (6.5)	0.70*	1.4	0.24–8.03
MPD diameter > 5 mm, *n* (%)	1 (4.3)	4 (4.3)	1*	1	0.07–12.55
Hyperechogenic pancreas, *n* (%)	21 (91.3)	60 (65.2)	0.02*	4.42	1.09–17.91

CI, confidence interval; IQR, interquartile range; FU, follow-up; PC, pancreatic cancer; FH, family history of pancreatic cancer in a first-degree relative; BMI, body mass index; MPD, main pancreatic duct

*Mantel–Haenszel test

Table 4 Risk factors for concomitant PDAC in patients with IPMN

	Two-tailed *P* value	Odds ratio	95% CI
Risk factors for PC	0.13	0.44	0.15–1.29
Multifocal cysts	0.67	1.23	0.47–3.16
Hyperechogenic pancreas	0.01	7.07	1.48–33.80

PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; CI, confidence interval; PC, pancreatic cancer

at more than 6 months prior to the diagnosis of PDAC. Of these patients, 31 (88.5%) had hyperechogenic pancreas. Because this is almost the same proportion as in "cases", hyperechogenic pancreas was considered to be unrelated to IPMN itself, but related to PDAC.

Multifocal cysts were not correlated with concomitant PDAC in our study, although a recent study found a correlation between multifocal cysts and the incidence of PDAC concomitant with IPMN [11]. Both in our study and this recent study, not all IPMNs were diagnosed in the resected specimen, and it was sometimes difficult to distinguish between IPMN and non-IPMN cysts, especially in patients with smaller pancreatic cysts. This may be the reason why the results were different.

Our study has several limitations. This was a retrospective study in a single center. The number of cases was small; therefore, the echogenicity added with parenchymal heterogeneity could not be evaluated. Further studies with a large number of patients, such as comparative studies between a hyperechogenic plus heterogeneous group and a hyperechogenic plus homogeneous group, are needed. Selection bias might have occurred as patients with a medical history of risk factors for PDAC had been collected and patients who had undergone EUS or US for the first time at PDAC diagnosis were excluded. Whether the echogenicity was similar in the whole pancreas remains to be evaluated, because the degree of echogenicity of the pancreatic head was not identified.

Nevertheless, we believe that the results are meaningful, because narrowing down the high-risk category of patients with PDAC concomitant with IPMN is clinically important. This is the first study to investigate the association between hyperechogenic pancreas and concomitant PDAC in patients with IPMN.

Conclusion

Our analysis demonstrated that hyperechogenic pancreas was related to PDAC concomitant with IPMN. Our results should be evaluated by conducting a prospective cohort study with a large number of patients.

Compliance with ethical standards

Conflict of interest Koichiro Mandai, Koji Uno, Kojiro Nakase, Takuji Kawamura, and Kenjiro Yasuda declare that they have no conflicts of interest associated with this study.

Ethical statements All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from patients included in this study.

References

1. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
2. Kang MJ, Lee KB, Jang JY, et al. Disease spectrum of intraductal papillary mucinous neoplasm with an associated invasive carcinoma invasive IPMN versus pancreatic ductal adenocarcinoma-associated IPMN. Pancreas. 2013;42:1267–74.
3. Ideno N, Ohtsuka T, Kono H, et al. Intraductal papillary mucinous neoplasms of the pancreas with distinct pancreatic ductal adenocarcinomas are frequently of gastric subtype. Ann Surg. 2013;258:141–51.
4. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738–53.
5. Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. Radiology. 1980;137:475–9.
6. Rebours V, Gaujoux S, d'Assignies G, et al. Obesity and fatty pancreatic infiltration are risk factors for pancreatic precancerous lesions (PanIN). Clin Cancer Res. 2015;21:3522–8.
7. Hori M, Takahashi M, Hiraoka N, et al. Association of pancreatic fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol. 2014;5:e53.
8. Mandai K, Uno K, Yasuda K. Does a family history of pancreatic ductal adenocarcinoma and cyst size influence the follow-up strategy for intraductal papillary mucinous neoplasms of the pancreas? Pancreas. 2014;43:917–21.
9. Choi CW, Kim GH, Kang DH, et al. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. World J Gastroenterol. 2010;16:4329–34.
10. Al-Haddad M, Khashab M, Zyromski N, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case–control study. Pancreas. 2009;38:672–5.
11. Ikegawa T, Masuda A, Sakai A, et al. Multifocal cysts and incidence of pancreatic cancer concomitant with intraductal papillary mucinous neoplasm. Pancreatology. 2018;18:399–406.
12. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
13. Lesmana CRA, Gani RA, Lesmana LA. Non-alcoholic fatty pancreas disease as a risk factor for pancreatic cancer based on endoscopic ultrasound examination among pancreatic cancer patients: a single-center experience. JGH Open. 2018;2:4–7.