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Pancreatic inflammation and atrophy are not associated with pancreatic cancer concomitant with intraductal papillary mucinous neoplasm

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ABSTRACT

Background: Inflammation-induced carcinogenesis in pancreatic ductal adenocarcinoma (PDAC) has been reported; however, its involvement in PDAC with intraductal papillary mucinous neoplasm (IPMN) remains unclear. We herein investigated the relationship between pancreatic atrophy and inflammation and the incidence of PDAC concomitant with IPMN.

Methods: This study included 178 consecutive patients who underwent surgical resection for PDAC with IPMN (N = 21) and IPMN (N = 157) between April 2001 and October 2016. A multivariable logistic regression analysis was conducted to assess the relationship between pancreatic inflammation and atrophy and the incidence of PDAC concomitant with IPMN, with adjustments for clinical characteristics and imaging features. Pathological pancreatic inflammation and atrophy were evaluated in resected specimens.

Results: High degrees of pancreatic inflammation and atrophy were not associated with the incidence of PDAC with IPMN (multivariable odds ratio [OR] = 0.5, 95% confidence interval [CI] = 0.07 to 3.33, $P = .52$, adjusted by clinical characteristics, OR = 0.9, 95% CI = 0.10 to 5.86, $P = .91$, adjusted by imaging studies; OR = 0.2, 95% CI = 0.009 to 1.31, $P = .10$, adjusted by clinical characteristics, OR = 0.2, 95% CI = 0.01 to 1.43, $P = .12$, adjusted by imaging studies, respectively).

Conclusions: Pancreatic inflammation and atrophy were not associated with pancreatic cancer concomitant with IPMN.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IPMN, intraductal papillary mucinous neoplasm; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a mucin-producing cystic tumor with various cellular atypia, ranging from low grade dysplasia to invasive carcinoma [1]. Invasive IPMN is defined as pancreatic ductal adenocarcinoma (PDAC) originating from IPMN. On the other hand, PDAC concomitant with IPMN is defined as PDAC that develops independently of IPMN and there is no histological transition between PDAC and IPMN [2]. PDAC concomitant with IPMN developed in approximately 10% of IPMN in previous studies [3,4]. PDAC concomitant with IPMN exhibits aggressive tumor characteristics and has a significantly poorer prognosis than invasive IPMN [2,5]. It is clinically important to clarify the pathogenesis of PDAC concomitant with IPMN.

Chronic pancreatitis is a well-known risk factor for ordinal PDAC [6,7], and pancreatic inflammation and parenchymal atrophy may lead to PDAC [8,9]. In IPMN, inflammatory cell infiltration and pancreatic atrophy, similar to chronic pancreatitis, are frequently detected in surgically resected tissues. We previously reported that low serum levels of pancreatic enzymes, which are markers of advanced chronic pancreatitis, were associated with a higher incidence of invasive IPMN [10,11]. Furthermore, more severe inflammation and atrophy were associated with a higher incidence of invasive IPMN [10]. Inflammation and pancreatic atrophy may play an important role in the carcinogenesis of IPMN itself. However, the relationship between pancreatic inflammation and atrophy and the incidence of PDAC with IPMN remains unclear. Therefore, we hypothesized that PDAC concomitant with IPMN may occur due to inflammation-induced carcinogenesis, partly because of the stagnation of mucin produced by IPMN.

In the present study, we investigated whether pancreatic inflammation and atrophy are associated with the incidence of PDAC concomitant with IPMN. We analyzed a database of 178 consecutive patients who underwent surgical resection for PDAC with IPMN (N = 21) and IPMN (N = 157) at Kobe University Hospital, and assessed the relationship between pancreatic inflammation and atrophy and the incidence of PDAC concomitant with IPMN.

Methods

Study design

This study included 178 consecutive patients who underwent surgical resection for PDAC with IPMN (N = 21) and IPMN (N = 157) between April 2001 and October 2016. Indications for surgical resection were according to the international consensus guidelines for IPMNs [12] and the general rules of the Japanese Pancreatic Society for pancreatic cancer [13]. In this retrospective study, we prospectively collected the following information preoperatively: age, body mass index (BMI), sex, diabetes mellitus (presence, absence), alcohol consumption (more than 50 g/day, less than 50 g/day), smoking (presence, absence), main pancreatic duct diameter (less than 5 mm, 5 mm−10 mm, or more than 10 mm), presence of a nodule in the cyst (presence, absence), and cyst diameter (less than 30 mm, 30-40 mm, or more than 40 mm).

Tumors were histologically classified into four distinct types (gastric, intestinal, pancreatobiliary, or oncocytic) based on the results of hematoxylin and eosin staining and immunohistochemical reactivity for anti-mucin antibodies (MUC1/MUC2/MUC5AC/MUC6). A total of 178 IPMN cases were classified as follows: 44 gastric type, 109 intestinal type, 11 pancreatobiliary type, and 1 oncocytic type. IPMNs concomitant with PDAC (N = 21) comprised 17 cases of the gastric type and 1 of the pancreatobiliary type. In patients with multiple morphologically distinct tumors, each neoplasm was classified according to the most dominant component. IPMNs were also classified into low-grade dysplasia, intermediate-grade dysplasia, high-grade dysplasia, or invasive adenocarcinoma. Intraductal papillary mucinous adenoma (IPMA) comprises low-grade dysplasia, intermediate-grade dysplasia, and high-grade dysplasia. The diameter of the main pancreatic duct and the cyst size were measured using magnetic resonance cholangiopancreatography (MRCP) in most patients. In patients who did not undergo MRCP, measurements were performed using an alternative method such as endoscopic ultrasonography (EUS), ERCP, or computed tomography (CT). The presence of mural nodules was evaluated by EUS and magnetic resonance imaging (MRI). EUS and ERCP were mainly performed by three endoscopists (A. Masuda, M. Takenaka, and H. Shiomi) with experience of more than 1000 procedures. In cases of PDAC with IPMN, all PDACs were detected preoperatively using imaging modalities. This study was conducted in accordance with the Declaration of Helsinki and its amendments (UMIN-CTR ID: 000020140). The study protocol was approved by the Kobe University School of Medicine Ethics Committee (No.1864). All authors had access to the study data and reviewed and approved the final manuscript.

Pathological evaluation of pancreatic inflammatory cell infiltration and parenchymal atrophy

Hematoxylin and eosin-stained tissue sections from all PDAC with IPMN and IPMN patients were reviewed by Y. Zen who was blinded to their clinical features. All cases were re-examined by a second reviewer (A. Masuda) unaware of other data, and the consensus for inflammatory and atrophic scores between the two reviewers was good (inflammatory score; $\kappa = 0.77$ for score <3 vs. ≥3, $p < .0001$, atrophic score; $\kappa = 0.87$ for score <3 vs. ≥3, $p < .0001$). In each IPMN patient, pancreatic inflammatory cell infiltration and parenchymal atrophy were evaluated at a proximal site distant from the tumor. The evaluation at the distant site was performed in order to obtain information on background histological changes in the pancreas. In PDAC with IPMN, pancreatic inflammatory cell infiltration and parenchymal atrophy were evaluated at the proximal side of PDAC in order to avoid the influence of PDAC-associated pancreatitis, such as that shown in Supplemental Fig. 1. Pancreatic inflammation cell infiltration was categorized as grade 0 (none: no inflammatory cells observed), 1+ (mild: inflammatory cells were observed in 1%−10% of the area of the pancreatic parenchyma), 2+ (moderate: 11%−20%), 3+ (severe: >21%), and pancreatic parenchymal atrophy was categorized as grade 0 (none: 100%−90% of the normal pancreatic parenchyma remained), 1+ (mild: 89%−70%), 2+ (moderate: 69%−30%), 3+ (severe: <29%). Representative examples of these grades are shown in Fig. 1, according to a previous study [14]. In order to identify inflammatory cell types, we examined all cases using HE staining. Eight cases were randomly selected from all cases and CD3 (DAKO and M7254) and CD20 (DAKO and IR604) staining was performed.

Statistical analysis

All statistical analyses were conducted using JMP software (version 11, SAS Institute, Cary, NC), and all *P* values were two-sided. In order to assess the relationships between pancreatic inflammatory cell infiltration and parenchymal atrophy in resected pancreatic tissue and the clinical characteristics and morphological features of PDAC patients with IPMN and IPMN, the chi-squared test (or Fisher's exact test where appropriate) was performed (Tables 1 and 3). In order to compare mean age and body mass index (BMI), a *t*-test or ANOVA (analysis of variance), assuming equal variances, was performed (Tables 1 and 3).

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