A History of Acute Pancreatitis in Intraductal Papillary Mucinous Neoplasms of the Pancreas Is a Potential Predictive Factor for Malignant Papillary Subtype

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Key Words
Intraductal papillary mucinous neoplasm • Acute pancreatitis

Abstract
Background/Aims: There are several reports regarding intraductal papillary mucinous neoplasms (IPMNs) detected after the occurrence of acute pancreatitis. Although the presence of symptoms is regarded as a factor for predicting malignant IPMNs, there have been few reports demonstrating whether a history of acute pancreatitis is a predictor of malignancy. The aim of this study was to evaluate the relationship between a history of acute pancreatitis and clinicopathological features of IPMNs including the papillary subtype.

Methods: The data of 150 IPMNs resected between 1990 and 2009 were retrospectively reviewed. They were classified into IPMNs with or without history of acute pancreatitis, and then the clinicopathological features were compared between the 2 groups.

Results: Nineteen (13%) of the 150 patients had a history of acute pancreatitis. Nine of them had repeated episodes of pancreatitis; however, severe pancreatitis was uncommon. The diameter of the main pancreatic duct of the pancreatitis group was significantly larger than that of the nonpancreatitis group (p = 0.04). The pancreatitis group had a significantly higher frequency of carcinoma derived from IPMNs than the nonpancreatitis group (p = 0.03). The incidence of intestinal-type IPMNs in the pancreatitis group was significantly higher than that in the non-pancreatitis group (p < 0.001).

Conclusion: Acute pancreatitis associated with IPMNs could predict malignant intestinal-type tumor.

Introduction
Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are characterized by hypersecretion of mucin that leads to cystic dilatation of the involved pancreatic ducts. Acute pancreatitis often develops in patients with IPMNs, regardless of its morphological, main duct and branch duct type [1–3]. IPMNs have a broad spectrum of dysplasia ranging from adenoma to borderline neoplasm, carcinoma in situ, and further to invasive carcinoma, progressing sequentially in a stepwise fashion [4]. Based on morphological features and immunohistochemical findings of mucin expression, IPMNs are also...
classified into several subtypes including gastric, intestinal, pancreatobiliary, and oncocytic types [5, 6].

According to the International Consensus Guidelines, presence of symptoms, dilatation of the main pancreatic duct (MPD), presence of mural nodules, cyst size of more than 30 mm, and positive cytology findings were considered as factors to predict malignant IPMNs [7]. Symptoms associated with IPMNs usually include abdominal pain, jaundice, recent new onset or deterioration of diabetes, weight loss, acute pancreatitis, and other nonspecific symptoms [8, 9]. Regarding acute pancreatitis-associated IPMNs, we could imagine that pancreatitis might develop due to obstruction of the MPD with a tumor itself or secreted mucin, and this situation might predict the possibility of malignancy. However, there have been few reports addressing whether a history of acute pancreatitis would really be a predictor of malignant IPMN.

The aims of the present study were to investigate the frequency of malignancy in patients with IPMNs with acute pancreatitis and the clinicopathological characteristics of acute pancreatitis associated with IPMN.

**Patients and Methods**

The medical records of 150 patients with IPMNs who underwent surgical resection at the Department of Surgery and Oncology, Kyushu University, between 1990 and 2009 were retrospectively reviewed. According to diagnostic criteria in the Japanese (JPN) guidelines for the management of acute pancreatitis [10], the diagnosis of acute pancreatitis was made if the patients fulfilled at least two of the following three criteria: (1) acute abdominal pain and tenderness in the upper abdomen; (2) elevated pancreatic enzymes levels in blood or urine, and (3) the presence of imaging findings associated with acute pancreatitis. The severity of acute pancreatitis was determined according to the JPN scoring system [11–13]. Acute pancreatitis associated with endoscopic retrograde cholangiopancreatography (ERCP) was excluded. Ultrasoundography (US), computed tomography (CT), and magnetic resonance cholangiopancreatography were performed preoperatively in all patients to determine the type of IPMN, size of cyst, and diameter of the MPD. Histopathological findings were reviewed by two pathologists (Y.O. and S.A.) experienced in the histopathological classification of IPMNs. According to the World Health Organization (WHO) histological classification [14], IPMNs were categorized as adenoma (IPMA), borderline neoplasm (IPMB), carcinoma in situ (CIS), and invasive carcinoma derived from IPMN (invasive IPMC). IPMA and IPMB were considered as nonmalignant IPMNs, whereas CIS and invasive IPMC were classified as malignant. IPMNs were also divided into four subgroups based on the subclassification system recently suggested by Furukawa et al. [5], including gastric, intestinal, pancreatobiliary, oncocytic, and unclassified type, and then classified into intestinal-type and nonintestinal-type (gastric, pancreatobiliary, oncocytic, and unclassified) IPMNs.

Statistical analyses were performed with JMP statistical software (version 6.0.3; SAS, Inc., Cary, N.C., USA). Data were analyzed by the Mann-Whitney U test or Fisher’s exact probability test. Statistical differences were considered significant when p was <0.05.

**Results**

**Clinical Characteristics of Acute Pancreatitis Associated with IPMNs**

There were 19 patients (13%) with IPMNs with a preoperative history of acute pancreatitis (fig. 1). Nine of the 19 patients had repeated events and the average number of attacks was 3.4 times (range 1–10). The severity of acute pancreatitis was mild (stage 0) in 16, moderate (stage 1) in 1, and severe (stage 2) in the remaining 2 patients, based on the JPN score [13]. Severity scores were 2 and 7 points in the 2 patients with severe pancreatitis, and both indicated a milder form of severe pancreatitis (severe acute pancreatitis 1).

**Comparison of Demographic and Imaging Features between IPMNs with and without Pancreatitis**

Table 1 shows that there was no difference in the demographic characteristics between the pancreatitis and the nonpancreatitis groups of IPMN patients. The pancreatitis group consisted of 8 main duct IPMNs and 11 branch duct IPMNs, while the nonpancreatitis group comprised 32 main duct IPMNs and 99 branch duct IPMNs (p = 0.09). In the main duct IPMNs, the diameter of the MPD in the pancreatitis group was not different from that in the nonpancreatitis group. In branch duct IPMNs, there was no difference in cyst size between the two groups. However, when analyzing all the resected IPMNs, the diameter of the MPD in the pancreatitis group was significantly larger than that in the nonpancreatitis group (fig. 2, p = 0.04).

**Comparison of the Histopathological Features between Patients with IPMN with and without Pancreatitis**

The pancreatitis group included 4 IPMAs (21%), 4 IPMBs (21%), 5 CISs (26%), and 6 invasive IPMCs (32%), while the nonpancreatitis group consisted of 64 IPMAs (49%), 25 IPMBs (19%), 17 CISs (13%), and 25 invasive IPMCs (19%) (fig. 3a). The frequency of malignant IPMNs in the pancreatitis group was significantly greater than that in the nonpancreatitis group (p = 0.03, fig. 3b). Regarding papillary subtype, the pancreatitis group consisted of 3 cases of gastric type (16%), 15 cases of intestinal...
Acute Pancreatitis in IPMNs

Fig. 1. Flow diagram of the study population. Nonintestinal-type IPMNs consist of gastric type, pancreatobiliary type, oncocytic type, and unclassified type. Nonmalignant IPMNs include adenomas and borderline lesions.

Table 1. Demographic characteristics between the pancreatitis and nonpancreatitis groups of IPMN patients

<table>
<thead>
<tr>
<th></th>
<th>Pancreatitisc group (n = 19)</th>
<th>Nonpancreatitis group (n = 131)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>70.0 ± 8.2</td>
<td>66.0 ± 8.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>11/8</td>
<td>82/49</td>
<td>0.44</td>
</tr>
<tr>
<td>Ductal type (main duct/branch duct)</td>
<td>8/11</td>
<td>32/99</td>
<td>0.09</td>
</tr>
<tr>
<td>MPD diameter of main duct IPMNs, mm (n = 40)</td>
<td>17.0 ± 7.4 (n = 8)</td>
<td>12.0 ± 10.2 (n = 32)</td>
<td>0.21</td>
</tr>
<tr>
<td>Cystic size of branch duct IPMNs, mm (n = 110)</td>
<td>40.0 ± 9.7 (n = 11)</td>
<td>35.0 ± 13.4 (n = 99)</td>
<td>0.71</td>
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type (79%), and 1 case of pancreatobiliary type (5%),
while the nonpancreatitis group included 81 cases of gas-
tric type (62%), 31 of intestinal type (24%), 11 of pancrea-
tobiliary type (8%), 4 of oncocytic type (3%), and 4 of
unclassified type (3%) (fig. 4a). As shown in figure 4b, the
frequency of intestinal-type IPMNs in the pancreatitis
group was significantly higher than that in the nonpan-
creatitis group (p < 0.001).

**Discussion**

This is the first report demonstrating the relationship
between IPMNs with a history of acute pancreatitis and
the pathological subtype of the IPMNs. The findings in
this study have the following implications: (1) acute pan-
creatitis occurred in 13% of IPMNs, which was not severe
but often repeated. (2) The frequency of carcinoma de-
rived from IPMNs in the pancreatitis group was signifi-
cantly higher than that in the nonpancreatitis group. (3)
A history of acute pancreatitis was noted more frequent-
ly in patients with the intestinal-type IPMNs.

We found that acute pancreatitis occurred in 13% of
resected IPMNs and that such pancreatitis was mild in
severity and often repeated. A Japanese multi-institu-
tional study reported that the frequency of acute pancrea-
titis associated with IPMNs was 7.1% (99 of 1,379 IPMNs)
[15]. That study population included both resected and
not resected IPMNs and, therefore, the prevalence of
acute pancreatitis in IPMNs might well be lower than that
in our study. In contrast, a recent report from France showed that 64 (34.6%) of 185 resected IPMNs had a history of acute pancreatitis [3]. Another report from the USA showed that about 25% of the patients with IPMNs have pancreatitis-like symptoms such as epigastric pain and hyperamylasemia [16]. These differences in the incidence of IPMN-associated pancreatitis might be due to the difference in race and/or selection of study population.

Pelletier et al. [3] demonstrated that acute pancreatitis associated with IPMNs was not severe and often recurrent, and it was speculated that such recurrent episodes of pancreatitis might be caused by hypersecretion of mucus and temporary obstruction of the MPD [17]. Conven-
intestinal-type IPMNs might have a feature of hypersecretion and high consistency of mucin, and might cause obstruction of the MPD and subsequent development of acute pancreatitis. This hypersecretion of mucin would reflect the dilated MPD in the pancreatitis group, as shown in figure 2. We previously demonstrated that intestinal-type IPMNs seem to be frequently found as borderline neoplasm or carcinoma, but have a favorable prognosis compared with nonintestinal-type IPMNs [21]. Therefore, a history of acute pancreatitis in IPMNs would become a predictive factor for application of surgical resection to improve the prognosis as well as the symptoms.

In conclusion, in view of the significantly higher frequency of carcinoma derived from IPMNs and intestinal-type IPMNs in patients with a history of acute pancreatitis, the history of acute pancreatitis would be an indicator for surgical resection of IPMNs, possibly having a malignant potential.

**Disclosure Statement**

No competing financial interests exist.
References


