Pancreatic Disorders & Therapy
ISSN: 2165-7092

Kimura and Tezuka, Pancreat Disord Ther 2015, 5:1
DOI: 10.4172/2165-7092.1000148

Review Article Open Access

Acute Pancreatitis is a Predictive Factor for Malignancy in Mixed or Main Duct Intraductal Papillary Mucinous Neoplasms

Wataru Kimura* **and Koji Tezuka**

First Department of Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan

***Corresponding author:** Wataru Kimura, First Department of Surgery, Department of Gastroenterological, Breast, Thyroid and General Surgery, Yamagata University Faculty of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan, Tel: +81-023-628-5336; Fax: +81-023-628-5339; E-mail: wkimura@med.id.yamagata-u.ac.jp

Rec date: Nov 24, 2014, **Acc date:** Feb 16, 2015, **Pub date:** Feb 18, 2015

Abstract

Objectives: It is still unclear whether acute pancreatitis (AP) is a predictor of malignancy. Using patients enrolled from a single institution, the objective of this study was to determine whether AP as a complication of intraductal papillary mucinous neoplasm (IPMN) predicts malignancy, and to clarify the clinicopathological characteristics of IPMN with AP.

Methods: The clinicopathological features of 87 patients who underwent surgical resection for IPMN between October 1998 and May 2010 were investigated. In this study, malignancy was defined as high-grade dysplasia (non-invasive carcinoma) and invasive carcinoma. Macroscopic classification was based on the 2012 international consensus guidelines and IPMN with a main pancreatic duct size of >5 mm was classified as either mixed or main duct IPMN.

Results: Among the patients, who underwent surgical resection for IPMN, AP was present in 18% (16/87) and malignancy was present in 43% (37/87). The median period from the first AP episode until surgery was 5.5 months (range: 1.0-116.3 months). There was no significant difference in the frequency of malignancy between IPMN patients with and without AP [63% (10/16) vs. 38% (27/71); p=0.096]. In mixed or main duct IPMN, malignancy was more frequent in patients with AP than in those without AP [91% (10/11) vs. 48% (22/46); P=0.016]. Comparison of the clinicopathological features between malignant IPMN with and without AP showed that the frequency of high-grade dysplasia (non-invasive carcinoma) was significantly higher in the former [80% (8/10) vs. 37% (10/27); P=0.029].

Conclusions: AP itself may not be a predictive factor for malignancy in IPMN, but may be such a predictor in mixed or main duct IPMN. AP is also an important clinical sign that must not be overlooked, as it may indicate the presence of malignant lesions at an earlier stage.

Keywords: IPMN; Acute pancreatitis; Malignancy; High-grade dysplasia; Non-invasive carcinoma; Mixed type; Main-duct type

Abbreviations

IPMN: Intraductal Papillary Mucinous Neoplasm; WHO: World Health Organization; AP: Acute Pancreatitis; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; MHLW: Ministry of Health, Labour and Welfare; ERCP: Endoscopic Retrograde Cholangiopancreatography; MRCP: Magnetic Resonance Cholangiopancreatography; MPD: Main Pancreatic Duct; BMI: Body Mass Index; SD: Standard Deviation; vs.: versus.

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a neoplasm arising from the pancreatic duct epithelium characterized morphologically by papillary growth and cystic dilation of the main pancreatic duct and its branches as a result of mucus production [1-4]. IPMN was first described in 1982 by Ohhashi et al. as a mucus-secreting pancreatic cancer [5], and thereafter gradually became more widely recognized, the international consensus guidelines for management of IPMN and mucinous cystic neoplasms of the pancreas being formulated in 2006 [6]. In the 2010 edition of the World Health Organization (WHO) classification, IPMN is classified according to pathological grade as IPMN with low- or intermediate-grade dysplasia, high-grade dysplasia, or an associated invasive carcinoma [7]. Recently, in 2012, the international consensus guidelines were newly established [8].

The prognosis of IPMN is good compared with that of ordinary ductal adenocarcinoma, and organ-sparing surgery such as spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein (Kimura's method [9,10]) may be performed [11-13] in carefully selected patients. However, the prognosis for IPMN with an associated invasive carcinoma is poor, and surgery at the high-grade dysplasia (non-invasive carcinoma) stage before the start of invasion is important for improving the outcome [14-16]. In 1994, Kimura et al. first classified carcinoma of the papilla of Vater into intestinal and pancreatobiliary types, reporting that these differed in prognosis and invasion pattern [17]. IPMN is also classified into gastric, intestinal, pancreatobiliary, and oncocytic histological subtypes according to factors such as the histological features of the tumor and immunohistochemical reactivity for human mucins [7], and the

prognosis and frequency of malignancy have been reported to differ between these subtypes [15].

Acute pancreatitis (AP) and obstructive chronic pancreatitis of varying severity are known to occur as complications of IPMN as a result of tumor mucus production and obstruction of the pancreatic duct due to intraductal proliferation [1,18-22]. Although some features of IPMN complicated by AP have been reported [18-20,23], many aspects including the issue of whether or not AP is a predictor of malignancy remain controversial.

In the present study, we retrospectively analyzed clinicopathological and imaging data from a cohort of patients treated at a single institution to determine whether or not AP complicated by IPMN predicts malignancy, and to clarify the clinicopathological characteristics of AP complicated by IPMN.

Materials and Methods

The subjects were 87 of 90 patients with IPMN who underwent surgical resection at Yamagata University Hospital between October 1998 and May 2010 for whom either preoperative computed tomography (CT) and/or magnetic resonance imaging (MRI) data were available.

AP was diagnosed according to the criteria formulated by the Ministry of Health, Labour and Welfare (MHLW) Research Committee for Intractable Pancreatic Disease [24]. AP was diagnosed if other pancreatic disorders and acute abdomen had been excluded, and at least two of the following three criteria were met: (1) acute episodes of abdominal pain and tenderness in the upper abdomen; (2) elevated levels of pancreatic enzymes in blood, urine, ascites, or other fluids; and (3) abnormal pancreatic signs associated with AP on abdominal ultrasonography, CT, or MRI [24]. Severity was similarly determined according to the MHLW severity assessment criteria [25]. Patients with AP following endoscopic retrograde cholangiopancreatography (ERCP), other treatments of the duodenal papilla, or biliary stones were excluded from this study. Surgical indications were basically determined according to the criteria set out in the 2006 international consensus guidelines, surgery being indicated for cases of main duct IPMN or branch duct IPMN with a dilated branch duct diameter of >30 mm, mural nodules, positive pancreatic juice cytology, and/or the presence of symptoms [6].

Contrast-enhanced CT, MRI, or magnetic resonance cholangiopancreatography (MRCP) was used to evaluate lesion location, main pancreatic duct (MPD) diameter, dilated branch duct diameter, mural nodules, and macroscopic classification. IPMNs were basically classified as either mixed or main-duct type, or branch-duct type according to the 2012 international consensus guidelines [8]. Main duct IPMN was defined as the presence of either diffuse or segmental dilation of the MPD of >5 mm without other causes of obstruction, or obvious mural nodule in the main pancreatic duct. Branch duct IPMN was defined as the presence of pancreatic cysts of >5 mm in diameter that communicated with the MPD. Mixed type IPMN was defined as the presence of characterization of both main duct and branch duct IPMN. In this study, mixed type IPMN was classified in combination with main duct IPMN [3,15]. Mural nodules were defined as enhanced lesions protruding into the dilated pancreatic duct on contrast-enhanced CT and/or MRI [26].

IPMN was classified histopathologically according to the 2010 WHO classification, and also by grade as IPMN with low- or intermediate-grade dysplasia, high-grade dysplasia (non-invasive carcinoma), or an associated invasive carcinoma [7]. In this study, high-grade dysplasia (non-invasive carcinoma) and invasive carcinoma were grouped into a malignant category, and low- or intermediate-grade dysplasia was grouped into a benign category.

Alcohol drinkers were defined as patients whose average alcohol intake was more than 50 g per day at the time of diagnosis of AP or IPMN.

Clinical information about the treatment of AP was obtained by visiting, and/or by request from, the hospital that had referred the patients. This study was approved by the Ethics Committee of Yamagata University.

Statistical Analysis

Numerical data are expressed as means ± standard deviation (SD) or median (range). Categorical variables were compared between groups using the $\chi 2$ test or Fisher's exact test. Continuous variables were compared between two groups using the Mann-Whitney U test. The statistical software used was JMP version 9.0.2 (SAS Institute Inc., Cary, NC), and differences at $p<0.05$ were regarded as significant.

Variable	**IPMN (n=87)**
Age at surgery, years±SD	66.8 ± 9.7
Sex, n (%)	
Male	66 (76%)
Female	21 (24%)
Body mass index, kg/m^2±SD	22.4 ± 3.3
Alcohol drinkers, n (%)	27 (31%)
Main tumor location, n (%)	
Head	48 (55%)
Body	24 (27%)

Tail	11 (13%)
Whole pancreas	4 (5%)
Macroscopic type, n (%)	
Branch-duct type Mixed/main-duct type	30 (34%) 57 (66%)
Dilated branch duct diameter, mm±SD	35.4 ± 14.4
MPD diameter, mm±SD	8.0 ± 7.7
Mural nodule, n (%)	27 (31%)
Acute pancreatitis	16 (18%)
Number of AP episodes per patient, mean±SD	1.4 ± 0.9
Recurrence rate of AP, %	25% (4/16)
Periods from first AP episode until surgery, months, median (range)	5.5 (1-116.3)
Severity of AP*	
Mild, %	85% (17/20)
Severe, %	15% (3/20)
Operative procedure	
Pancreaticoduodenectomy	50 (58%)
Distal pancreatectomy with splenectomy	20 (23%)
Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein	14 (16%)
Total pancreatectomy	3 (3%)
Malignancy	37 (43%)
Pathology, n (%)	
Benign category	
IPMN with low- or intermediate-grade dysplasia	50 (57%)
Malignant category	
IPMN with high-grade dysplasia (non-invasive carcinoma)	18 (21%)
IPMN with invasive carcinoma	19 (22%)
IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct. * Among 23 episodes of AP in 16 patients, severity was determined for 20 episodes in 14 patients.	

Table 1: Clinicopathological characteristics of the 87 patients who underwent surgical resection for IPMN

Results

Clinical characteristics of 87 patients who underwent surgical resection for IPMN

Table 1 shows the clinical characteristics of 87 patients who underwent surgical resection for IPMN. The mean age of the patients at the time of surgery was 66.8 ± 9.7 years (range: 25-87 years). AP occurred in 18% (16/87) of these patients. The average number of AP episodes per patient was 1.4 ± 0.9, and AP recurred in 25% (4/16) of the AP patients. The median period from the first AP episode until surgery was 5.5 months (range: 1.0-116.3 months). Among 23 episodes of AP in 16 patients, severity was determined for 20 episodes in 14 patients. Of these cases, 85% (17/20) were mild, and 15% (3/20) were severe. Malignancy was present in 43% (37/87) of the patients who underwent surgical resection of IPMN.

Comparison of the frequency of malignancy between IPMN patients with and without AP

Table 2 shows a comparison of the frequency of malignancy between IPMN patients with and without AP, Malignancy was present

in 63% (10/16) of IPMN patients with AP, and in 38% (27/71) of those without AP. There was no significant difference in the frequency of malignancy between IPMN patients with and without AP (p=0.096), but the frequency tended to be higher in the IPMN patients with AP.

Variable	IPMN with AP (n=16)	IPMN without AP (n=71)	P value
Malignant, n (%) Benign, n (%)	10 (63%) 6 (37%)	27 (38%) 44 (62%)	0.096
IPMN, intraductal papillary mucinous neoplasm; AP, acute pancreatitis.			

Table 2: Comparison of the frequency of malignancy of IPMN patients with and without AP

Comparison of clinicopathological characteristics between IPMN patients with and without AP

Table 3 shows a comparison of the clinicopathological characteristics between IPMN patients with and without AP. No significant difference was observed between these patient groups in terms of age at surgery, sex, body mass index (BMI), proportion of alcohol drinkers, main tumor location, macroscopic type, dilated branch duct diameter, MPD diameter, and presence of mural nodules.

Variable	IPMN with AP (n=16)	IPMN without AP (n=71)	P value
Age at surgery, years±SD	62.5 ± 12.2	67.6 ± 9.0	0.152
Sex, n (%)			0.751
Male	13 (81%)	53 (75%)	
Female	3 (19%)	18 (25%)	
Body mass index, kg/m^2±SD	21.6 ± 2.7	22.5 ± 3.4	0.473
Alcohol drinker, n (%)	4 (25%)	23 (32%)	0.766
Main tumor location, n (%)			0.750
Head	7 (44%)	41 (58%)	
Body	5 (31%)	19 (27%)	
Tail	3 (19%)	8 (11%)	
Whole pancreas	1 (6%)	3 (4%)	
Macroscopic type, n (%)			1.000
Branch-duct type	5 (31%)	25 (35%)	
Mixed/main-duct type	11 (69%)	46 (65%)	
Dilated branch duct diameter, mm±SD	32.6 ± 16.1	36.1 ± 15.9	0.669
MPD diameter, mm±SD	7.7 ± 5.9	8.1 ± 8.1	0.742
Mural nodule, n (%)	5 (31%)	22 (31%)	1.000
IPMN, intraductal papillary mucinous neoplasm; AP, acute pancreatitis; MPD, main pancreatic duct.			

Table 3: Comparison of clinicopathological characteristics between IPMN patients with and without AP

Variable	IPMN with AP		IPMN without AP	
	Malignant (n=10)	Benign (n=6)	Malignant (n=27)	Benign (n=44)
Age at surgery, years ± SD	63.2 ± 13.9	61.3 ± 9.8	68.6 ± 12.1	67.0 ± 6.5
Sex, n (%)				
Male	8 (80%)	5 (83%)	22 (82%)	31 (70%)
Female	2 (20%)	1 (17%)	5 (18%)	13 (30%)

Body mass index, kg/m^2±SD	22.2 ± 2.4	20.6 ± 3.1	22.6 ± 3.8	22.5 ± 3.1
Number of AP episodes per patient, meanSD	1.2 ± 0.4	1.8 ± 1.3		
Recurrence rate of AP, %	20 % (2/10)	33% (2/6)		
Period from first AP episode until surgery, months, median (range)	1.9 (1 - 116.3)	9.3 (1.7 - 107.3)		
Main tumor location, n (%)				
Head	5 (50%)	2 (33%)	15 (56%)	26 (59%)
Body	3 (30%)	2 (33%)	6 (22%)	13 (30%)
Tail	1 (10%)	2 (33%)	3 (11%)	5 (11%)
Whole pancreas	1 (10%)		3 (11%)	
Macroscopic type, n (%)				
Branch-duct type	0*	5 (83%)	5 (26%)**	20 (46%)
Mixed/ main-duct type	10 (100%)	1 (17%)	22 (74%)	24 (54%)
Dilated branch duct diameter, mmSD	33.8 ± 17.8	30.5 ± 14.1	41.0 ± 19.8**	33.1 ± 12.2
MPD diameter, mm ± SD	10.2 ± 6.3*	3.5 ±1.0	11.5 ±12.1**	5.9 ±2.7
Mural nodule, n (%)	3 (30%)	2 (33%)	17 (63%)**	5 (11%)
Pathology, n (%)				
IPMN with high-grade dysplasia (non-invasive carcinoma)	8 (80%)***		10 (37%)	
IPMN with invasive carcinoma	2 (20%)		17 (63%)	

IPMN, intraductal papillary mucinous neoplasm; AP, acute pancreatitis; *P<0.05 vs benign IPMN with AP. **P<0.05 vs benign IPMN without AP. ***P<0.05 vs malignant IPMN without AP.

Table 4: Comparison of clinical data among the 4 groups divided according to the presence or absence of AP and malignancy

Comparison of clinicopathological features among the four groups divided according to the presence or absence of AP and malignancy

Table 4 compares the clinicopathological features of the four groups divided according to the presence or absence of AP and malignancy. There were no significant differences among the four groups in terms of age at surgery, sex, BMI, or main tumor location, and there were no significant differences between malignant and benign IPMN with AP in terms of the number of AP episodes per patient, AP recurrence rate, and the period from the first AP episode until surgery.

Discussion

In this series, the occurrence rate of AP in patients who underwent surgery for IPMN was 18%, being similar to the rates of 10–43% reported previously [1,27-32]. The variation in the frequency of AP among the previous studies may be attributable to factors such as differences in race and in the definition of AP. In the present study, AP was defined according to the diagnostic criteria formulated by the MHLW Research Committee for Intractable Pancreatic Disease [24], and most cases of AP that occurred as a complication of IPMN were mild, a finding consistent with other reports [18,19].

It is still controversial whether AP predicts malignancy in IPMN [18, 19]. In the present study, there was no significant difference in the frequency of malignancy between IPMN patients with and without AP [63% (10/16) vs. 38% (27/71); p=0.096], which appears to support the results of some previous studies [19,28-35]. However, other studies have found significant differences in the frequency of malignancy between IPMN patients with and without AP [18, 29]. The reason for this difference in findings among studies is still unclear. In the present study, the frequency of the mixed/main-duct type in cases of malignant IPMN with AP was significantly higher than in cases of benign IPMN with AP [100% (10/10) vs. 17% (1/6); P=0.001] (Table 4). AP occurs even if there is no obvious main duct involvement of IPMN. Therefore, one of the reasons for the difference may be variations in patient background factors, including macroscopic type. In the 2012 international consensus guidelines, AP is classified under "worrisome features" and is considered an indication for surgery for relief of symptoms [8]. Careful follow-up without surgical intervention might be feasible for branch-duct type IPMN with a single AP episode where no macroscopic features predictive of malignancy, such as mural nodules, are evident.

In mixed/main duct IPMN, malignancy was more frequent in patients with AP than in those without AP [91% (10/11) vs. 48% (22/46); P=0.016] (Table 5). In the 2012 international consensus guidelines, IPMN with either diffuse or segmental dilation of the MPD of >5 mm without other causes of obstruction classified as the main-duct type or the mixed type showing pancreatic cysts >5 mm in diameter that communicate with the MPD. MPD dilatation 5-9 mm is

considered to be "worrisome features" for which immediate resection is not indicated but further evaluation is recommended [8]. It is also stated that, to date, there have been no consistent predictive factors for malignancy in main duct IPMN, including the degree of MPD dilatation, presence of symptoms, or mural nodules [8]. Based on the 2012 international consensus guidelines [8], the presence of AP in mixed/main duct IPMN strongly predicts malignancy (Table 5).

Variable	Mixed/main duct IPMN with AP (n=11)	Mixed/main duct IPMN without AP (n=46)	P value
Malignant, n (%)	10 (91%)	22 (48%)	0.016
Benign, n (%)	1 (9%)	24 (52%)	
IPMN, intraductal papillary mucinous neoplasm; AP, acute pancreatitis			

Table 5: Comparison of the frequency of malignancy of mixed/main duct IPMN patients (n=57) with and without AP

In the IPMN patients with AP we studied, the median period from the first AP episode until surgery was 5.5 months (range: 1.0－116.3 months). The rate of recurrence of AP as a complication of IPMN and the number of AP episodes per patient have been reported to be 47-73% [18-20,33,34] and 2.5–3.4 times [18,19], respectively. However, in the present study, the corresponding figures were 25% (4/16) and 1.4 ± 0.9 times, respectively, both being lower than those reported previously [18-20,33,34]. These figures may reflect the fact that IPMN patients with AP in this study underwent surgery at a comparatively earlier stage than those in the other studies.

In the present series, the incidence of high-grade dysplasia (non-invasive carcinoma) was significantly higher in patients with malignant IPMN with AP than in those without AP [80% (8/10) vs. 37% (10/27); P=0.029] (Table 4), suggesting that AP is an important clinical indicator of possible malignancy at an earlier stage. Although the reasons are unclear, it has been reported that AP occurs more frequently in the intestinal subtype of IPMN than in the other subtypes [18,35], and that in the intestinal subtype, high-grade dysplasia (non-invasive carcinoma) is the most common pathological grade [15,36]. These observations may have been attributable to differences in the proportions of the various subtypes between malignant IPMN with and without AP.

The prognosis of IPMN with associated invasive carcinoma is poor, and surgery at the high-grade dysplasia (non-invasive carcinoma) stage before the start of invasion is important for improving the outcome [14-16]. In 4 of 10 patients with malignant mixed/main duct IPMN with AP, the MPD size was 5-9 mm, which alone is categorized as a "worrisome feature". Therefore, surgery may be indicated for mixed/main duct IPMN with AP. It will be necessary to be more mindful of this issue in the future.

In conclusion, although AP itself may not be a predictive factor for malignancy in IPMN, it may be such a factor in mixed/main duct IPMN. AP is also an important clinical sign that must not be overlooked, as it may indicate the presence of malignant lesions at an earlier stage.

Acknowledgments

This work was supported in part by the Research Committee for Intractable Pancreatic Diseases (Principal Investigator: Tooru Shimosegawa) of the Ministry of Health, Labour, and Welfare of Japan. The authors declare no conflicts of interest. The authors thank the following hospitals for their contributions to the collection of the clinical data at the onset of AP: Tsuruoka Kyoritsu Hospital, Kitamurayama Hospital, Yamagata Prefectural Shinjo Hospital, Yamagata Prefectural Kahoku Hospital, Nihonkai Hospital, Yonezawa City Hospital, Sanyudo Hospital, Okitama Public General Hospital, Misawa Clinic, Kojirakawa Shiseido Hospital, and Tohoku Central Hospital. We also appreciate the advice of our colleagues, Ichiro Hirai, Shuichiro Sugawara, Toshihiro Watanabe, and Naoki Takasu.

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