• BRIEF REPORTS •

Malignancies associated with intraductal papillary mucinous neoplasm of the pancreas

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Abstract

AIM: As intraductal papillary mucinous neoplasm (IPMN) has a favorable prognosis, associated malignancies have potential significance in these patients. We examined the incidence and characteristics of pre-existing, coexisting and subsequent malignancies in patients with IPMN.

METHODS: Seventy-nine cases of IPMN were diagnosed by detection of mucous in the pancreatic duct during endoscopic retrograde pancreatography. Histological diagnosis was confirmed in 30 cases (adenoma ($n = 19$) and adenocarcinoma ($n = 11$)). Other primary malignancies associated with IPMN, occurring in the prediagnostic or postdiagnostic period, were investigated. Postdiagnostic follow-up period was 3.3 ± 0.5 years (range, 0.2-20 years).

RESULTS: Other 40 malignancies occurred in 28 patients (35%). They were found before ($n = 15$), at ($n = 19$) and after ($n = 6$) the diagnosis of IPMN. Major associated malignancies were gastric cancer ($n = 12$), colonic cancer ($n = 7$), esophageal cancer ($n = 4$), pulmonary cancer ($n = 4$), and independent pancreatic cancer ($n = 3$). Pancreatic cancer was synchronous with IPMN in two patients and metachronous in one (3 years after diagnosis of IPMN). Thirty-one lesions were treated surgically or endoscopically. Fourteen patients died of associated cancers. Development of other malignancies was related to age (71.9 ± 8.2 vs 66.8 ± 9.3 , $P < 0.05$), but not to gender or site of the tumor.

CONCLUSION: IPMN is associated with a high incidence of other malignancies, particularly gastric and colonic cancers. Common genetic mechanisms between IPMN and other associated malignancies might be present. Clinicians should pay attention to the possibility of associated malignancies in preoperative screening and follow-up of patients with IPMN.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a distinct entity characterized by intraductal papillary growth and thick mucous secretion. Copious mucous fills the main and branch pancreatic ducts and causes ductal dilatation. IPMN histologically shows a broad spectrum ranging from adenoma to invasive carcinoma. IPMN is classified into two subtypes of main duct type and branch duct type based on the site of tumor involvement. IPMN is a slow-growing tumor and many cases of branch duct type IPMN have been followed. IPMN, even when malignant, is often resectable, and has a favorable prognosis, compared with that of pancreatic ductal adenocarcinoma^[1-3]. Prolonged postoperative survival can be anticipated in many IPMN cases. There are few papers reporting that IPMN is sometimes accompanied by malignant diseases of the other organs or pancreatic adenocarcinoma^[4,5]. This report thus evaluates the incidence and features of associated malignancies in patients with IPMN.

MATERIALS AND METHODS

Between 1980 and 2004, 79 patients with IPMN were treated in Tokyo Metropolitan Komagome Hospital. They were diagnosed by detection of mucous in the pancreatic duct during endoscopic retrograde pancreatography. These patients comprised 54 males and 25 females, with an age of 68.5 ± 9.2 (mean $\pm$ SD) years. Twenty-three patients underwent surgical resection. Thirteen patients became unclear during follow up (1-5 years). Histological examination of the surgical ($n = 23$), biopsied ($n = 2$), and autopsied ($n = 5$) specimens revealed adenoma in 19 patients, non-invasive adenocarcinoma in 6, and invasive adenocarcinoma in 5. They were classified into main duct type ($n = 30$) and branch duct type ($n = 49$) based on the site of tumor involvement. Postdiagnostic follow-up period was 3.3 ± 0.5 years (range, 0.2-20 years).

The inpatient records of these 79 patients were reviewed mainly for previous and coexisting nonpancreatic and

independent pancreatic neoplasms found at the time of diagnosis of IPMN. Furthermore, postdiagnostic follow-up data were obtained from outpatient charts.

Statistical analysis was performed using Student's *t*-test and Fisher's exact probability test. Differences were considered significant at $P < 0.05$.

RESULTS

Other 40 malignancies were diagnosed in 28 (35%) of 79 patients with IPMN. They were found before ($n = 15$), at ($n = 19$) and after ($n = 6$) the diagnosis of IPMN. Major associated malignancies were gastric cancer ($n = 12$), colonic cancer ($n = 7$), esophageal cancer ($n = 4$), pulmonary cancer ($n = 4$), and independent pancreatic cancer ($n = 3$) (Table 1). Three other organs were involved in three patients, and two organs in four patients (Table 2). Double gastric cancers occurred in two patients. All of 15 other malignancies occurring 1–10 years (3.7 ± 3.6 years) before the diagnosis of IPMN were resected surgically or endoscopically. Fifteen of nineteen other malignancies diagnosed simultaneously with IPMN were resected surgically or endoscopically. Only one other malignancy diagnosed after IPMN was surgically resected. Fourteen patients died of associated malignancies. Age at IPMN diagnosis in patients with other malignancies was significantly older than that in those without other malignancies ($P < 0.05$). However, gender, follow-up period, site of IPMN, and resection of IPMN did not differ

significantly between the two groups (Table 3).

Three patients had both IPMN and independent pancreatic cancer. Two patients had the two lesions synchronously, and pancreatic cancer occurred 3 years after the diagnosis of IPMN in one patient. All the three IPMNs were of branch type located in the pancreatic head and ranged from 1.5 to 3 cm. The lesion of IPMN was proximal to pancreatic cancer in two patients and distal in the other. Independence of IPMN and pancreatic cancer of two patients was proved histologically in the resected and autopsied pancreas, respectively. Two lesions were radiologically far from each other in the other patient (Figure 1). Although prognosis was poor in two patients in whom the presence of pancreatic cancer led to the diagnosis of IPMN, one patient with pancreatic cancer discovered during the follow-up of IPMN is doing well without any signs of recurrence, 36 mo after the operation (Table 4).

DISCUSSION

The incidence of occurrence of multiple primary malignant neoplasms occurring in different tissues has been reported

Table 1 Other malignancies in patients with IPMN

	Previous	At diagnosis	Post diagnosis	Total
Gastric cancer	4	7	1	12
Colonic cancer	4	3	0	7
Esophageal cancer	3	1	0	4
Pulmonary cancer	0	2	2	4
Pancreatic cancer	0	2	1	3
Breast cancer	2	0	0	2
Hepatocellular cancer	0	2	0	2
Uterine cancer	1	0	0	1
Pharyngeal cancer	1	0	0	1
Bile duct cancer	0	1	0	1
Prostatic cancer	0	1	0	1
Laryngeal cancer	0	0	1	1
Malignant lymphoma	0	0	1	1

Table 3 Clinicopathological findings of IPMN patients with and without other malignancies

	With other malignancies ($n = 28$)	Without other malignancies ($n = 51$)	<i>P</i>
Age (yr)	71.9±8.2	66.8±9.3	$P < 0.05$
Male/Female	8/20	34/17	NS
Follow-up period ¹	3.2±0.5	3.4±0.5	NS
Site of IPMN			NS
Main duct	13	17	
Branch duct	15	34	
Resection/Nonresection of IPMN	7/20	16/35	NS
Cause of death			
Invasive IPMN	1	4	
Gastric cancer	4	0	
Pulmonary cancer	3	0	
Pancreatic cancer	2	0	
Colonic cancer	2	0	
Esophageal cancer	1	0	
Hepatocellular cancer	1	0	
Malignant lymphoma	1	0	
Pneumonia	1	1	
Renal failure	0	1	

Table 2 Other malignancies of more than two organs in patients with IPMN

Case	Age (yr)	Sex	Previous	At diagnosis	Postdiagnosis
1	76	M	Gastric cancer (EMR, 1 yr ago) Esophageal cancer (EMR, 1 yr ago)		Pulmonary cancer (4 yr after)
2	74	F	Uterine cancer (ope, 10 yr ago)	Hepatocellular cancer Colonic cancer	
3	70	M		Gastric cancer Colonic cancer Pulmonary cancer	
4	83	F		Esophageal cancer	Malignant lymphoma (1 yr after)
5	78	M		Hepatocellular cancer	Gastric cancer (6 yr after)
6	78	M	Esophageal cancer (EMR, 1 yr ago)		Laryngeal cancer (6 yr after)
7	68	M	Esophageal cancer (EMR, 2 yr ago)		Pancreatic cancer (3 yr after)

EMR: endoscopic mucosal resection.

Table 4 IPMN concomitant with independent pancreatic cancer

Case	Age (yr)	Sex	Syn/Met	Other malignancies	IPMN location	Site	Therapy	Pancreatic location	Cancer therapy	Stage	Prognosis
1	71	M	Syn	None	Head	Branch	None	Body	DP	III	Died 7 mo after operation
2	75	M	Syn	None	Head	Branch	None	Head	None	IV	Died 8 mo after diagnosis
3 ¹	68	M	Met	Esophageal cancer	Head	Branch	PD	Head	PD	II	Alive now 3 yr after diagnosis of IPMN

Syn: synchronous, Met: metachronous, PD: pancreatoduodenectomy, DP: distal pancreatectomy. ¹: This case is the same as case 7 in Table 2.

Figure 1 Endoscopic retrograde pancreatography showing branch-type intraductal papillary mucinous tumor of the pancreatic head and tapering obstruction of the main pancreatic duct involved with the concomitant pancreatic cancer of the body.

as 5.1%^[6]. The incidence of other malignant neoplasms preceding, following or occurring simultaneously with the diagnosis of pancreatic cancer was reported to be 7%^[4]. The present study revealed a high incidence of other malignancies (35%) in patients with IPMN. Other 40 malignancies were found before ($n = 15$), at ($n = 19$) and after ($n = 6$) the diagnosis of IPMN. Major associated malignancies were gastric cancer ($n = 12$) and colonic cancer ($n = 7$). Sugiyama and Atomi^[4] reported that 15 (32%) of 42 patients with IPMN had nonpancreatic malignancies, including colonic cancer ($n = 5$) and gastric cancer ($n = 4$). Yamaguchi *et al.*^[5] also reported that 13 (27%) of 48 patients with IPMN had malignant diseases, including gastric cancer ($n = 5$) and colonic cancer ($n = 2$). Incidence and associated other malignancies were similar to our results. In the present series, 14 patients died of associated malignancies. As IPMN is a slow-growing tumor with a relatively favorable prognosis, associated malignancies have potential prognostic significance. Systemic surveillance at the diagnosis of IPMN and careful follow-up is necessary for early detection of associated malignancies in patients with IPMN.

Interestingly, three patients with IPMN had also independent pancreatic cancer. All these IPMNs were of branch type located in the pancreatic head. The lesion of IPMN was proximal to pancreatic cancer in two patients and distal in the other. Pancreatic cancer occurred during the follow-up of IPMN could be diagnosed in relatively early stage. There is only one report describing the relationship between IPMN and pancreatic cancer^[7]. In this report, independent pancreatic cancer was detected in 7 (10%) of 69 patients with IPMN, suggesting that the entire ductal epithelium of the pancreas with IPMN might already be in the premalignant condition.

The cause of frequent development of other malignancies in patients with IPMN is unknown. In the present study, age at IPMN diagnosis in patients with other malignancies was significantly older than the age in those without other malignancies. As elderly patients are more susceptible to neoplasms in most organs than younger patients and IPMN mainly affects elderly men, patients with IPMN have increased risk for other malignancies due to their age. Furthermore, oncogenetic changes of various organs of patients with IPMN might induce frequent development of other malignancies. Recent study has suggested that IPMN might form part of the spectrum of lesions encountered in attenuated familial adenomatous polyposis^[8]. Common underlying genetic etiology might be present between IPMN and other associated malignancies. Further investigations focusing on this field are necessary in future.

In conclusion, IPMN is associated with a high incidence of other malignancies including pancreatic cancer. As IPMN has a relatively favorable prognosis, associated malignancies have potential prognostic significance. Clinicians should pay attention to the other associated malignancies in patients with IPMN.

REFERENCES

- 1 Obara T, Maguchi H, Saitoh Y, Itoh A, Arisato S, Ashida T, Nishino N, Ura H, Namiki M. Mucin-producing tumor of the pancreas: natural history and serial pancreatogram changes. *Am J Gastroenterol* 1993; **88**: 564-569
- 2 Kimura W, Sasahira N, Yoshikawa T, Muto T, Makuuchi M. Duct-ectatic type of mucin producing tumor of the pancreas—new concept of pancreatic neoplasia. *Hepatogastroenterology* 1996; **43**: 692-709
- 3 Sugiyama M, Atomi Y, Kuroda A. Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. *Surgery* 1997; **122**: 617-625
- 4 Sugiyama M, Atomi Y. Extrapancratic neoplasms occur with unusual frequency in patients with intraductal papillary mucinous tumors of the pancreas. *Am J Gastroenterol* 1999; **94**: 470-473
- 5 Yamaguchi K, Yokohata K, Noshiro H, Chijiwa K, Tanaka M. Mucinous cystic neoplasm of the pancreas or intraductal papillary-mucinous tumor of the pancreas. *Eur J Surg* 2000; **166**: 141-148
- 6 Moertel CG, Dockerty MB, Baggettoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. *Cancer* 1961; **14**: 221-230
- 7 Yamaguchi K, Ohuchida J, Ohtsuka T, Nakano K, Tanaka M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. *Pancreatol* 2002; **211**: 484-490
- 8 Chetty R, Salahshor S, Bapat B, Berk T, Croitoru M, Gallinger S. Intraductal papillary mucinous neoplasm of the pancreas in a patient with attenuated familial adenomatous polyposis. *J Clin Pathol* 2005; **58**: 97-101