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CASE REPORT

Multifocal Pancreatic Ductal Adenocarcinomas Concomitant with Intraductal Papillary Mucinous Neoplasms of the Pancreas Detected by Intraoperative Pancreatic Juice Cytology. A Case Report

Yasuhisa Mori, Takao Ohtsuka, Kosuke Tsutsumi, Takaharu Yasui, Yoshihiko Sadakari, Junji Ueda, Shunichi Takahata, Masafumi Nakamura, Masao Tanaka

Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University. Fukuoka, Japan

ABSTRACT

Context Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas have been detected with increasing frequency as a result of the progression of diagnostic modalities. Recently, invasive ductal carcinoma of the pancreas concomitant with IPMNs has been the focus of attention. **Case report** We report the case of a 57-year-old man with multifocal ductal carcinomas of the pancreas concomitant with IPMNs detected by intraoperative cytology. During a follow-up for branch duct IPMNs, a stenotic lesion of the main duct in the pancreatic body was found by ERCP, and brush cytology of the stenosis revealed an adenocarcinoma. A distal pancreatectomy was proposed; however, intraoperative pancreatic juice cytology from the pancreatic head also revealed adenocarcinoma, and a total pancreatectomy was finally carried out. Pathological examination of the resected specimen showed multifocal ductal carcinomas and IPMNs in the distal pancreas, and invasive ductal carcinoma in the pancreatic head which had not been detected by preoperative imaging studies. **Conclusions** Surgeons should be aware of the possibility of multifocal carcinomas in patients with concomitant IPMNs. Intraoperative pancreatic juice cytology should always be performed in order to confirm the absence of carcinoma in the pancreas to be left in place after planned resection.

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas were first reported in 1982 by Ohashi *et al*. [1] and have been detected with increasing frequency as a result of the progression of diagnostic modalities. Recently, invasive ductal carcinoma of the pancreas concomitant with IPMNs has been the focus of attention [2], and ductal carcinoma of the pancreas in addition to IPMN has been reported to develop in 9.2% of patients with IPMNs [3]. We herein report the case of a patient having multifocal ductal carcinomas concomitant with IPMNs which were detected by intraoperative pancreatic juice cytology and were treated by total pancreatectomy.

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Correspondence Masao Tanaka
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Fukuoka 812-8582, Japan
Phone: +81-92.642.5444; Fax: +81-92.642.5458
E-mail: masaotan@surg1.med.kyushu-u.ac.jp

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CASE REPORT

A 57-year-old man was admitted to our hospital in 2003 due to cystic lesions in the pancreas which had been detected by health screening ultrasonography. He had had a past history of diabetes mellitus but did not have a family history of malignancy. Laboratory tests including blood cell counts, blood chemistry and tumor markers, carcinogenic embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were all within normal limits. Enhanced computed tomography (CT) showed a low density mass measuring 10 mm in the tail of the pancreas. Magnetic resonance cholangio-pancreatography demonstrated two small cystic lesions, 10 mm in diameter in the pancreatic tail and 5 mm in the pancreatic head. Endoscopic retrograde cholangiopancreatography revealed a cystic dilatation of the branch duct measuring 10 mm in the tail of the pancreas without dilation of the main pancreatic duct. Cytologic examination of the pancreatic juice collected by the use of secretin (ChiRhoStim™, ChiRhoClin, Inc., Burtonsville, MD, USA) during ERCP demonstrated no malignant cells (Class II). Based on these results, a diagnosis of multiple benign branch duct IPMNs was made, and follow-up observations were scheduled for every 6 months. In 2006, CT and MRI revealed that the size of the IPMN in the

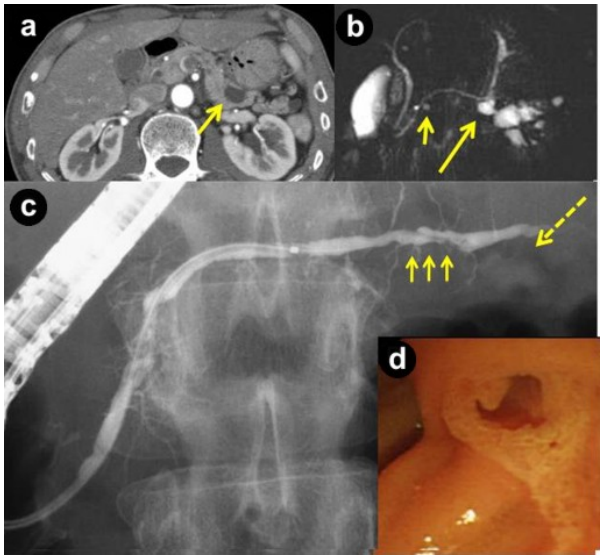

Figure 1. a. Computed tomogram showing a low density mass in the tail of the pancreas, the size of which had slightly increased to 15 mm in diameter (arrow). **b.** Magnetic resonance cholangio-pancreatogram demonstrating two small cystic lesions; 10mm in diameter in the pancreatic tail (long arrow) and 5mm in the pancreatic head (short arrow). **c.** ERCP showing a cystic lesion measuring 10 mm in the tail of the pancreas (arrow with broken line), and stenotic lesions in the main duct of the pancreatic body (arrows). **d.** Endoscopic photograph of the dilated orifice of the duodenal papilla with mucin excretion.

pancreatic tail had slightly increased to 15 mm in diameter; however, cytology of the pancreatic juice during ERCP showed no atypical cells (Class II) and, therefore, the patient continued to be followed up.

The findings of CT and MRI in 2009 showed no remarkable change; however, ERCP demonstrated dilatation of the orifice of the duodenal papilla with mucin excretion and a irregular stenotic lesion measuring 5 mm in the main pancreatic duct of the pancreatic body (Figure 1). Both brush cytology from the stenotic lesion and subsequent pancreatic juice cytology collected by a balloon catheter placed in the pancreatic head demonstrated adenocarcinoma (Class V). At this time, the serum CEA level was normal while the CA 19-9 level was slightly elevated to 38.4 U/mL (reference range: 37.0 U/mL). A distal pancreatectomy was proposed with a diagnosis of pancreatic ductal carcinoma concomitant with branch duct IPMNs. Hypersecretion of mucin was considered to be from the IPMN in the pancreatic tail, and was expected to be resected. However, to avoid the possibility of co-existent pancreatic cancer in the remnant pancreas, intraoperative pancreatic juice cytology in the remnant pancreas was also planned.

During surgery, there was neither peritoneal dissemination nor liver metastasis. The pancreas was cut above the portal vein, and then a 4 French tube was inserted into the main pancreatic duct of the remnant pancreas about 2 cm from the cut margin. Fluid for cytology was obtained by saline irrigation through the tube with a syringe. Although the surgical cut margin was pathologically negative for cancer cells, cytologies of the pancreatic juice obtained 3 times from the remnant pancreas proved to be positive. Therefore, a total pancreatectomy was performed, followed by hepaticojejunostomy and duodenojejunostomy in the Billroth-II fashion. Operating time was 10 hours and blood loss was 1,185 g.

Pathological examination of the resected specimen revealed that there were two invasive carcinomas in the head and tail of the pancreas, and two non-invasive ductal carcinomas as shown in Figure 2. The sizes of the two invasive carcinomas in the pancreatic head and tail were 12 mm and 3 mm, respectively. Those lesions had no definitive communication with each other. There were two cystic dilations of the branch ducts in the body and tail of the pancreas, both of which were intraductal papillary mucinous adenomas. A regional lymph node on the posterior surface of the pancreatic head contained carcinoma cells. The postoperative course was uneventful, and the patient has received chemotherapy using gemcitabine for 6 months to date without any sign of recurrence. The patient had also been treated to control pancreatic diabetes with a satisfactory nutrient status and quality of life.

DISCUSSION

It is well known that an IPMN is often accompanied by malignant diseases including gastric, colon and lung cancers [4]. In addition to such extrapancreatic cancers, we previously stated that attention should be paid to the possible presence of ductal carcinoma of the pancreas because 7 of the 76 (9.2%) patients of our series of patients with IPMNs had ductal carcinoma of the pancreas [5]. Using the latest technology, we have recently reported that concomitant ductal carcinoma was detected synchronously or metachronously in 22 of 236 patients with IPMN (9.3%) [3]. Of note, all of these 22 patients had a benign branch duct IPMN, and our patient also had two branch duct IPMNs. We have also demonstrated that a worsening of diabetes mellitus and elevated serum CA 19-9 levels are indicators for coexisting ductal carcinoma during a follow-up of IPMNs, although these were not observed in the current patient. The precise mechanisms of the coexistence of ductal carcinoma with branch duct IPMNs of the pancreas remains unknown. In addition, multifocal ductal carcinomas concomitant with IPMNs are a very rare condition, and, in our experience, this is first case to date. Further clinical and molecular-based investigations are necessary to elucidate the mechanism of the development of ductal carcinoma and an IPMN in the same pancreatic organ. However, an IPMN could be an indicator of coexisting pancreatic ductal carcinoma, and careful attention should be paid to the possibility of concomitant malignant diseases including pancreatic ductal carcinoma, even when the existing IPMN is diagnosed as benign.

Eguchi *et al.* and Ishikawa *et al.* [6, 7] demonstrated that intraoperative pancreatic juice cytology as well as frozen-section histology during resection of an IPMN are necessary to detect continuous or skip lesions. They collected the pancreatic juice from the pancreatic head, body and tail by the use of a balloon catheter, in

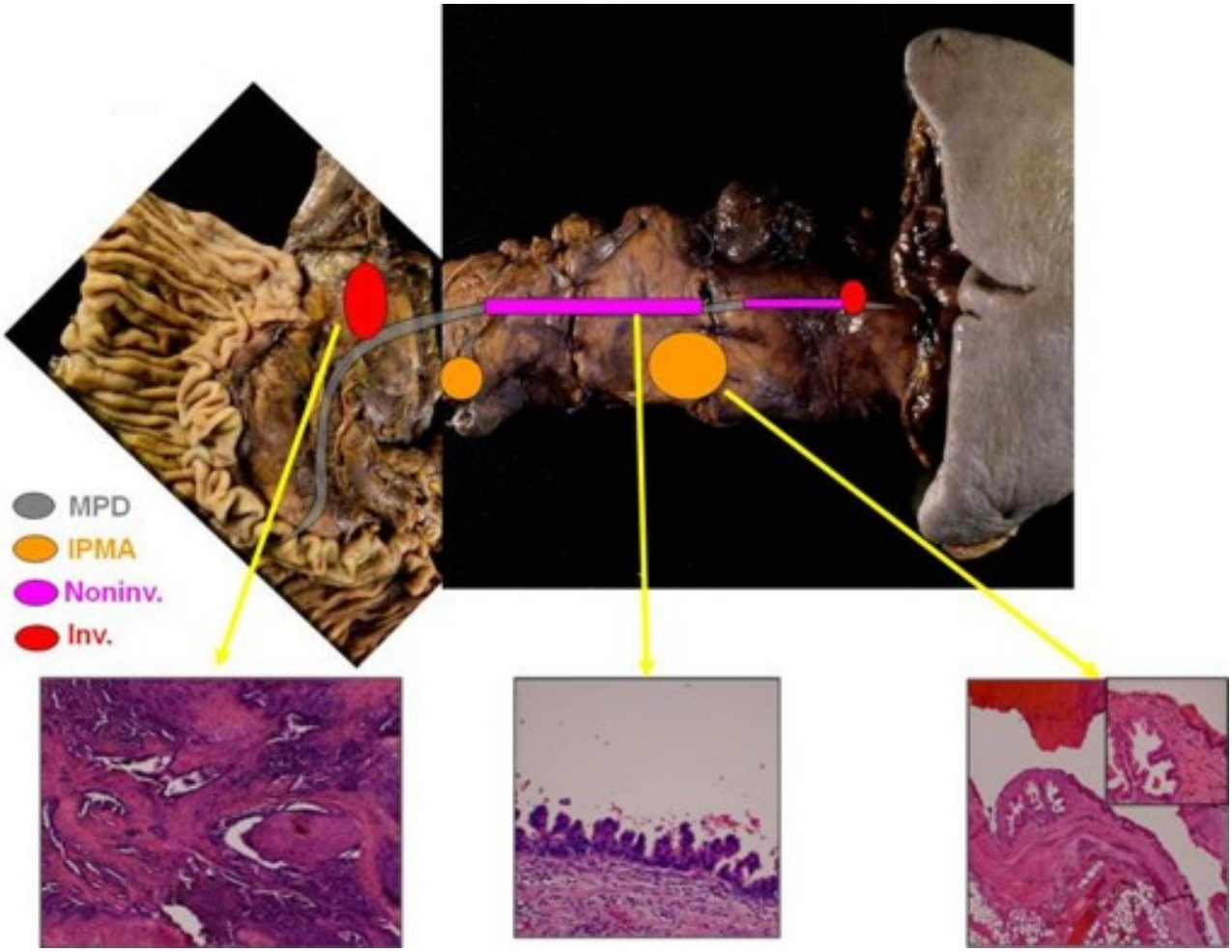

Figure 2. Upper panel. Schematic representation of the location of intraductal papillary mucinous neoplasms (IPMNs) and non-invasive and invasive ductal carcinomas. **Lower panel.** Microscopic photographs corresponding to the lesions are also shown (H&E; left x40; middle x200; right x40, insert x100).

addition to frozen-section histology of the surgical margin, during pancreatectomy for IPMNs, and showed that 42% of the patients required additional pancreatic resection for intraductal carcinomas. At our institution, intraoperative irrigation cytology is routinely performed three times during a pancreatectomy for IPMN, when there are IPMN(s) in the remnant pancreas or preoperative pancreatic juice cytology is positive for cancer cells. Although the two IPMNs were included in the initially resected side in our patient, preoperative pancreatic juice cytology was positive for cancer cells and, therefore, intraoperative cytology was also performed. As a result, we could detect the ductal carcinoma in the pancreatic head, which had not been detected by any preoperative imaging studies. We previously reported two patients having a branch duct IPMN with a concomitant carcinoma in situ which was likewise not detected by imaging studies but was diagnosed by pancreatic juice cytology preoperatively [8]. The reason for carrying out irrigation cytology three times is to negate the possibility of migration of the floating cancer cells in the resected side into the portion to be left unremoved. During collection of the pancreatic juice, operators should pay attention to leakage of the pancreatic juice into the abdominal cavity to prevent later possible dissemination.

Total pancreatectomy was first introduced in 1943 by Rockey [9]; however, the indication for such a procedure has been limited to date because of its high morbidity and mortality. Recently, several reports have shown the efficacy and safety of total pancreatectomy in selected patients [10, 11, 12, 13]. Reddy *et al*. [14] demonstrated that operative mortality after total pancreatectomy decreased over time from 40.0% to 1.9%. Our patient had an uneventful postoperative course and his postoperative nutrition and quality of life have been satisfactory due to the control of the pancreatic diabetes. Total pancreatectomy seems to have become a feasible procedure in selected patients, and should be considered when the oncological situation leaves no choice.

In conclusion, careful attention should be paid to the possible presence of ductal carcinoma in patients with IPMNs. During surgery for IPMN(s), intraoperative irrigation cytology from the remnant pancreas could be useful in detecting the lesions which were not observed in the preoperative imaging studies. If this is the case,

then total pancreatectomy should be considered when the oncological situation leaves no choice.

Conflict of interest The authors have no potential conflict of interest

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