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Pancreatobiliary fistula associated with intraductal papillary mucinous carcinoma accompanying obstructive jaundice: A case report

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ABSTRACT

INTRODUCTION: Intraductal papillary mucinous neoplasms (IPMNs) occasionally involve formation of fistulas with other adjacent organs. Pancreatobiliary fistulas associated with IPMNs are rare, but affected patients often develop obstructive jaundice and cholangitis.

PRESENTATION OF CASE: A 79-year-old man was referred to our hospital for evaluation of abnormal biliary enzymes. Contrast-enhanced computed tomography and endoscopic retrograde cholangiopancreatography demonstrated multiple cystic lesions with septa in the pancreatic head and fistulas between the cystic lesions and common bile duct. The clinical diagnosis was pancreatobiliary fistula associated with a mixed-type IPMN and accompanying obstructive jaundice. The patient underwent subtotal stomach-preserving pancreaticoduodenectomy. The resected specimen showed fistulas between the cystic lesions and common bile duct. Histopathological examination showed that the main and branch ducts of the pancreatic head were dilated and filled with mucus. The epithelia of the pancreatic ducts revealed papillary proliferation and an invasive adenocarcinoma arising from an intraductal neoplasm. Immunohistochemistry examination showed CDX2- and MUC2-positive reactions. The final diagnosis was an intraductal papillary mucinous carcinoma of the intestinal-type. The patient remained disease-free for 9 months postoperatively.

DISCUSSION: The causes of death in patients who have pancreatobiliary fistulas associated with IPMNs without resection are cholangitis or hepatic insufficiency. Nonoperative treatment is limited for cases with obstructive jaundice. It is necessary to prevent obstructive jaundice and cholangitis due to a large quantity of mucinous material.

CONCLUSIONS: Surgical resection should be considered, if possible, in patients with pancreatobiliary fistulas associated with IPMNs. A better prognosis is expected with prevention of obstructive jaundice or cholangitis.

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1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by intraductal papillary growth and mucin secretion in the

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; IPMC, intraductal papillary mucinous carcinoma; CT, computed tomography; PET, positron emission tomography; FDG, fludeoxyglucose; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; ENBD, endoscopic nasobiliary drainage; UICC, The International Union Against Cancer; TNM, tumor-node-metastasis.

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dilated pancreatic ducts [1]. IPMNs were first reported in 1982 [2], and international consensus guidelines for the management of IPMNs and mucinous cystic neoplasms (MCNs) of the pancreas were published in 2012 [3]. According to the World Health Organization classification [4], IPMNs can be histologically classified into the following four groups: IPMN with low-grade dysplasia, IPMN with intermediate-grade dysplasia, IPMN with high-grade dysplasia, and IPMN with an associated invasive carcinoma. IPMNs are the most important precursors of pancreatic ductal adenocarcinomas [5]. Generally, IPMNs progress slowly, and occasionally involve formation of fistulas with adjacent organs [6]. Pancreatobiliary fistulas associated with IPMNs are rare and are often associated with the development of obstructive jaundice and cholangitis. It has been reported that the incidence of obstructive jaundice or cholangitis in

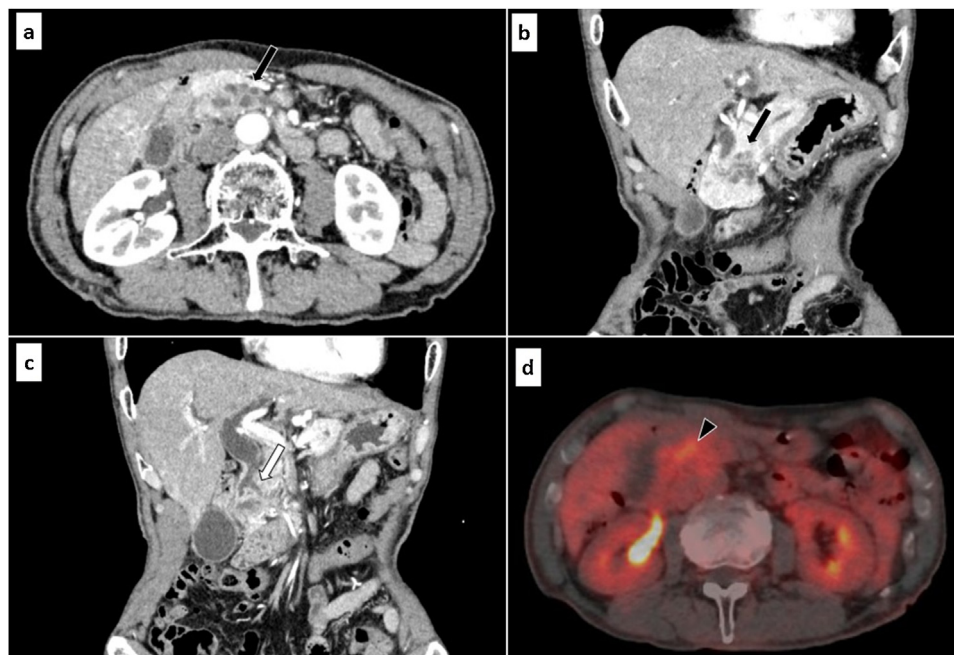


Fig. 1. Contrast-enhanced CT showed multiple cystic lesions with septa in the pancreatic head (black arrow) (a, b) and fistulas between the cystic lesions and common bile duct (white arrow) (c). PET-CT showed increased FDG accumulation (SUVmax: 4.1) in the multiple cystic lesions in the pancreatic head (black arrowhead) (d).

patients with pancreatobiliary fistulas associated with IPMNs was 97.1% [7]. However, which treatment is most appropriate remains controversial for patients with pancreatobiliary fistulas. We report herein a case of pancreatobiliary fistula associated with intraductal papillary mucinous carcinoma (IPMC). The present work has been reported in line with the SCARE criteria [8].

2. Presentation of case

A 79-year-old man was referred to our hospital for evaluation of abnormal biliary enzymes. The patient had no symptom. Laboratory analysis revealed the following: hemoglobin, 13.8 g/dL; white blood cell count, $6.11 \times 10^3/\mu\text{L}$; platelets, $21.4 \times 10^4/\mu\text{L}$; serum total protein, 7.3 g/dL; serum albumin, 4.5 g/dL; total bilirubin, 1.7 mg/dL; aspartate aminotransferase, 94 IU/L; alanine aminotransferase, 154 IU/L; alkaline phosphatase, 699 IU/L; and serum amylase, 84 IU/L; lactic acid dehydrogenase, 232 IU/L; γ -glutamyl transpeptidase, 419 IU/L. The serum levels of various tumor markers, including carcinoembryonic antigen (5.0 ng/ml) and carbohydrate antigen 19–9 (20.2 U/mL), were normal. Contrast-enhanced computed tomography (CT) demonstrated multiple cystic lesions with septa in the pancreatic head and fistulas between the cystic lesions and common bile duct (Fig. 1a–c). Positron emission tomography (PET)-CT showed increased fludeoxyglucose (FDG) accumulation (SUVmax: 4.1) in the multiple cystic lesions in the pancreatic head (Fig. 1d). Endoscopic retrograde cholangiopancreatography (ERCP) showed dilated duodenal papilla with mucin extrusion and segmental dilation of the main pancreatic duct (7 mm in diameter) and a pancreatic cyst (6 mm in diameter) that communicated with the main pancreatic duct. ERCP and intraductal ultrasonography (IDUS) showed a pancreatobiliary fistula and dilated common bile duct containing mucinous material (Fig. 2). The patient's common bile duct was drained with an endoscopic nasobiliary drainage (ENBD) tube because the patient had obstructive jaundice. It was improved after the fistula drainage. The patient, who was diagnosed as having a pancreatobiliary fistula associated with the mixed-type IPMN and accompanying obstructive jaundice, underwent subtotal stomach-

preserving pancreaticoduodenectomy and regional lymph node dissection (SSPPD-II-A-1, D2, R0). The resected specimen showed fistulas between the cystic lesion and common bile duct (Fig. 3). The tumor in the pancreatic head was $46 \times 25 \times 24$ mm in diameter. Histopathological examination showed the pancreatobiliary fistula and found that the main and branch pancreatic ducts of the pancreatic head were dilated and filled with mucus (Fig. 4a). The epithelia of the pancreatic ducts revealed papillary proliferation arising from an intraductal neoplasm (Fig. 4b). Immunohistochemistry examination showed CDX2- and MUC2-positive reactions (Fig. 4c,d). The patient was diagnosed as having an IPMC of the intestinal type, Stage III (pT3N0M0), based on the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification. There was no regional lymph node metastasis, and the tumor was not invasive into the common bile duct. The patient's postoperative course was complicated by a pancreatic fistula (ISGPF grade B), but he was discharged on postoperative day 42. He did not hope for chemotherapy. He was followed once in three months and remained disease-free for 9 months after surgery.

3. Discussion

IPMNs were first reported in 1982 [2], and are defined as intraductal papillary mucin-producing neoplasms, arising in the main pancreatic duct or branch pancreatic duct [9]. IPMNs of the pancreas are potentially malignant cystic lesions, and are incidentally detected with increasing frequency, largely due to the widespread use of CT during the evaluation of patients for other reasons [10].

International consensus guidelines for the management of IPMNs and MCNs of the pancreas were published in 2006 [11], and were revised in 2012. These updated guidelines stratified the management of IPMNs based on the presence or absence of high-risk stigmata or worrisome features [3]. IPMNs progress slowly, and they occasionally involve formation of fistulas with surrounding organs, including bile ducts [6]. Some investigators have reported that the incidence of fistulas to adjacent organs associated with IPMNs was 1.9–6.6% [6,12]. It has been reported that these fistulas involved the duodenum (65.4%), stomach (19.2%), common

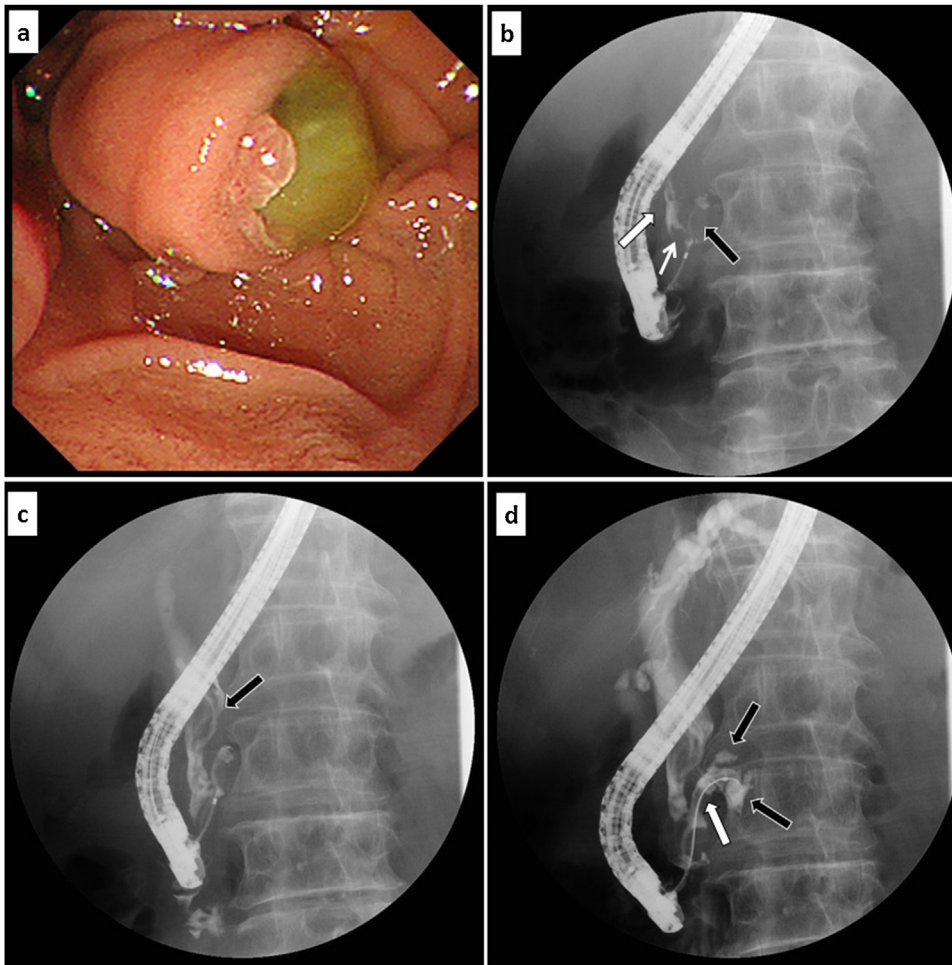


Fig. 2. ERCP showed dilated duodenal papilla with mucin extrusion (a), a pancreaticobiliary fistula (thin white arrow) between the cystic lesion (thick black arrow) and common bile duct (white arrow) (b), the dilated common bile duct containing mucinous material (thick white arrow) (c), and segmental dilation of the main pancreatic duct of 7 mm in diameter (thick white arrow) and a pancreatic cyst of 6 mm in diameter that communicated with the main pancreatic duct (thick black arrow) (d).

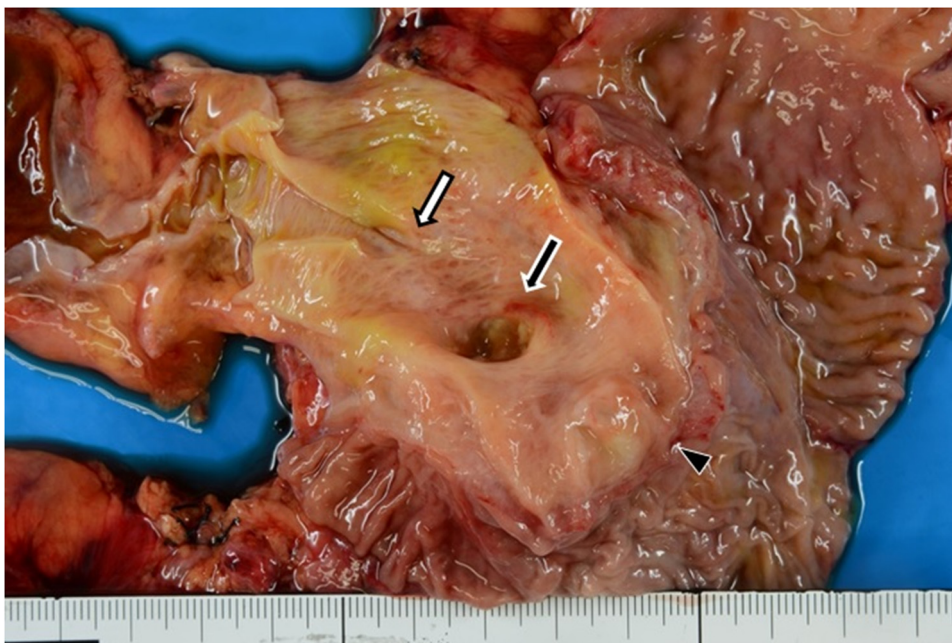


Fig. 3. The resected specimen showed fistulas between the cystic lesions and common bile duct. Common bile duct: thick white arrow; fistulas: thick black arrow; and duodenal papilla: black arrowhead.

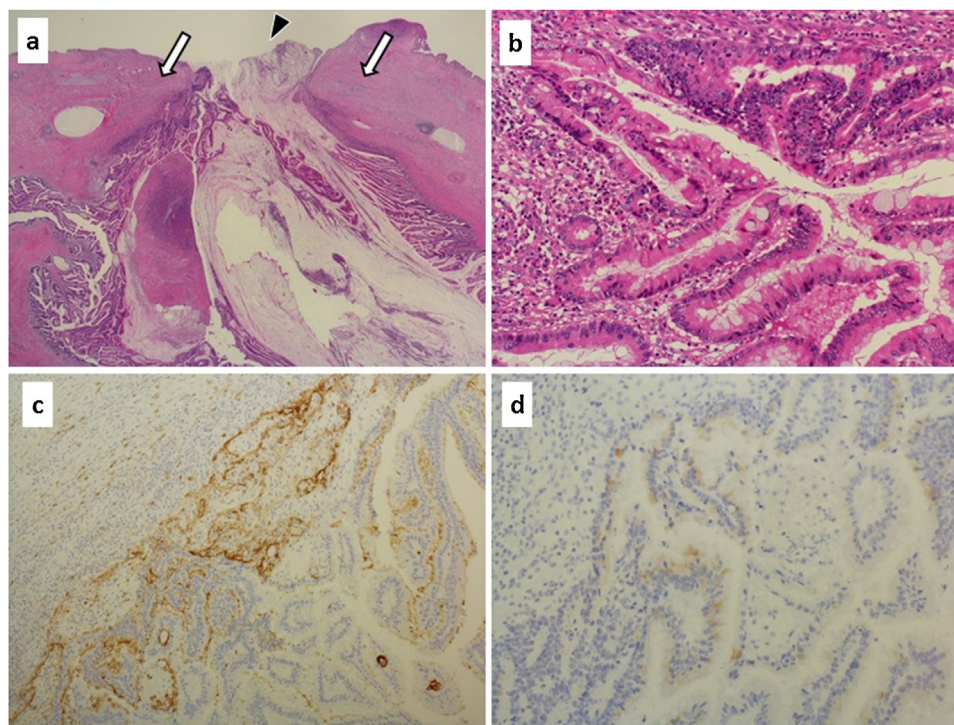


Fig. 4. Histopathological examination showed the pancreatobiliary fistula (Common bile duct: thick white arrow; fistula: black arrowhead) (a). The epithelia of the pancreatic ducts revealed papillary proliferation arising from an intraductal neoplasm (b). Immunohistochemistry examination showed CDX2- and MUC2-positive reactions (c, d).

bile duct (11.5%), and colon (3.8%) [12]. Pancreatobiliary fistulas associated with IPMNs are extremely rare, and only 22 cases have been reported in the English literature. Patients with pancreatobiliary fistulas associated with IPMNs often develop obstructive jaundice and cholangitis. The incidence of obstructive jaundice due to the mucinous material of pancreatobiliary fistulas associated with IPMNs was 97.1% [7]. Kurihara et al. [13] reported that the factors associated with fistula formation between the pancreatic duct and adjacent organs are pancreatic perforation due to inflammatory stimulation and high pressure in the pancreatic ducts or direct invasion of IPMNs into adjacent organs. Furukawa et al. [14] classified IPMNs into 4 subtypes based on the morphological phenotypes: the intestinal, gastric, pancreatobiliary, and oncocyctic-subtypes. Kobayashi et al. [6] reported that 94% of IPMNs with the penetration to adjacent organs were intestinal-type IPMNs, and 67% of them showed mechanical penetration. Most pancreatobiliary fistulas associated with IPMNs are identified with cholangiography or CT. Intestinal-type IPMNs show CDX2 and MUC2 positive. Intestinal-type IPMNs can have invasive carcinoma, typically of the colloid type and with relatively indolent behavior [15]. In the present case, it was thought that the factor associated within fistula formation between the pancreas and common bile duct was pancreatic perforation due to high pressure in the pancreatic ducts by mucinous material because the tumors did not invade into the common bile duct and intestinal-type IPMNs have a higher degree of viscosity of the mucinous material in the cyst than other subtypes of IPMNs (Fig. 4a,c,d). Noninvasive IPMNs are classified into 3 categories depending on the degree of dysplasia: low-grade, intermediate-grade, or high-grade. IPMN-associated invasive carcinoma is detected in approximately 30% of resected IPMNs. The postoperative 5-year survival rate in patients with benign tumors and noninvasive carcinomas is nearly 100%, compared with approximately 60% in patients with invasive carcinomas [16]. Yamaguchi et al. [7] reported that mean survival times in patients with pancreatobiliary fistulas associated with IPMNs who underwent surgical resection versus those who did not undergo surgical resection

were 47.9 and 10.4 months, respectively. The causes of death in patients without resections were cholangitis or hepatic insufficiency. Obstructive jaundice due to a large quantity of mucinous material was treated with ENBD or percutaneous transhepatic biliary drainage (PTBD). Intermittent lavage is usually effective to improve obstructive jaundice [7]. A metallic stent often fails to drain due to obstruction and deviance [17]. However, ENBD and PTBD tubes may not be suitable for long-term placement. Therefore, surgical procedures should be considered in patients with obstructive jaundice and cholangitis. Fortunately, as the elderly patient in this case kept a good performance status, a subtotal stomach-preserving pancreatoduodenectomy could be performed.

However, surgical resection is sometimes difficult. Elderly patients with operable IPMNs often cannot undergo surgical resection due to poor performance status. Even if the diagnosis of IPMN-associated invasive carcinoma is doubted, the patient has a favorable prognosis in comparison with a patient diagnosed with pancreatic ductal adenocarcinoma. In order to maintain the patient's quality of life, choledochojejunostomy alone is sometimes performed to allow adequate drainage and to prevent obstructive jaundice and cholangitis caused by a large quantity of mucinous material.

Surgical resection, including a choledochojejunostomy, should be considered as early as possible in the patients with pancreatobiliary fistulas associated with IPMNs to provide a better prognosis and to prevent obstructive jaundice or cholangitis.

4. Conclusions

We report herein a case of pancreatobiliary fistula associated with IPMC. There are no guidelines for the optimal management strategy for pancreatobiliary fistulas associated with IPMNs. Surgical resection should be considered as early as possible in patients with pancreatobiliary fistulas associated with IPMNs though this condition is extremely rare. Additional case reports and long-term follow-up data will help to define optimal treatment regimens.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical approval

The study such as this case report was exempted from ethical approval by the Institutional Review Board of Hiroshima City Asa Citizens Hospital.

Consent for publication

When obtaining informed consent for surgical procedures, general consent for publication and presentation was obtained from the patient.

Authors' contributions

TK drafted the manuscript. TK and KO reviewed and edited the manuscript. TK, KO, TK, MK, and AN participated in the care of the patients. MK provided the histopathological examination and diagnosis. TK, JH, HM, and NH participated in critical revision of the manuscript. All authors read and approved the final manuscript.

Registration of research studies

None.

Guarantor

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