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【 CASE REPORT 】

A Biliary Mucinous Cystic Neoplasm with Intrahepatic and Lymph Node Metastases

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Abstract:
A 51-year-old woman who presented with a large cystic liver tumor with mural nodules in the lateral segment developed Trousseau's syndrome. A mural nodule directly invaded her liver parenchyma. Metastatic nodules were detected in the right lobe and portal/paraaortic lymph nodes. The pathological findings showed mucin-producing adenocarcinoma cells to have invaded the fibrous stroma forming a micropapillary cluster. She developed obstructive jaundice due to tumor progression and subsequently died of hepatic failure. Invasive biliary mucinous cystic neoplasm (MCN) is a rare form of a malignant tumor with a relatively favorable prognosis. This is a very rare case biliary MCN with invasive carcinoma that showed intrahepatic and lymph node metastases.

Key words: biliary mucinous cystic neoplasm, intrahepatic metastasis, lymph node metastasis

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Introduction

Biliary mucinous cystic neoplasms (MCNs) are rare cystic tumors of the liver. This type of cystic tumor was originally reported as cystadenoma with mesenchymal stroma by Wheeler et al. in 1985 (1). Biliary MCNs are defined and classified under the concept of the biliary counterpart of pancreatic MCNs by the World Health Organization (WHO) in 2010, which is a cyst-forming epithelial neoplasm with no communication with the bile ducts, composed of cuboidal to columnar cells, variably mucin-producing epithelium, associated with an ovarian-like stroma (2). The origin of the tumor cells is considered to derive from ectopic ovarian tissue (3). Biliary MCNs are divided into non-invasive MCNs and invasive MCNs. Invasive biliary MCNs are a very rare form of malignant hepatic tumor that comprise as low as 0.41% of primary epithelial malignant liver tumors (3, 4). Biliary MCNs usually show a slow progression and thereafter become invasive types over a period of years. Although invasive, biliary MCNs mostly remain at the primary site and rarely develop metastases (2). In this report, we present a very rare case of biliary MCN with invasive carcinoma showing intrahepatic and lymph node metastases.

Case Report

A 51-year-old woman who developed a high fever and right hypochondriac pain was admitted to our hospital with a diagnosis of multiple liver abscesses and pneumonia in July 2017. Abdominal computed tomography (CT) of the patient demonstrated multiple round lesions with rim enhancement in the medial segment and a large cystic lesion in the lateral segment of the liver. Her chest CT showed air bronchograms and consolidation in the right posterobasal lung indicating pneumonia. A thrombus in the right pulmonary artery was also detected. The intravenous administration of antibiotics was started as flomoxef sodium 2 g/day for 10 days followed by oral sitafloxacin hydrate 1 mg/day for 7 days in the division of infectious disease in our hospi-

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Table. Clinical Characteristics.

White blood cells (/μL)	11,600
Red blood cells (/μL)	2,550,000
Hemoglobin (g/dL)	7.5
Platelet (/μL)	222,000
Prothrombin time (%)	86.9
Total bilirubin (mg/dL)	0.6
Direct bilirubin (mg/dL)	0.1
AST (IU/L)	72
ALT (IU/L)	30
LDH (IU/L)	435
ALP (IU/L)	767
γ-GTP (IU/L)	356
Total protein (g/dL)	6.3
Albumin (g/dL)	3.3
Total cholesterol (mg/dL)	217
Triglyceride (mg/dL)	121
Urea nitrogen (mg/dL)	7.0
Creatinine (mg/dL)	0.6
Sodium (mEq/L)	141
Potassium (mEq/L)	3.8
Chloride (mEq/L)	104
CEA (ng/mL)	3.3
CA19-9 (IU/mL)	<2.0
γ-fetoprotein (ng/mL)	5.1
DCP (mAU/mL)	28.8

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH lactate dehydrogenase, ALT: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase: CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, DCP: des-γ-carboxy prothrombin

tal. Continuous intravenous infusion of heparin 10,000 unit/day was administered for the treatment of pulmonary thrombosis followed by the oral administration of the anticoagulant edoxaban. The patient's fever resolved and an elevation of white blood cells (WBC) count and c-reactive protein (CRP) returned to normal, however, her abdominal pain continued. Follow-up CT images indicated a huge cystic tumor with multiple intrahepatic metastases and lymph node metastases and then the patient was finally referred to our division.

Blood studies showed a slight elevation of liver enzymes and a decrease of hemoglobin and red blood cell count caused by abnormal menstrual bleeding due to the anticoagulant edoxaban (Table). No tumor markers were elevated such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), alpha-fetoprotein (AFP), and des-γ-carboxy prothrombin (DCP). There were no abnormalities which indicated chronic liver diseases including viral hepatitis and autoimmune liver diseases.

The patient's abdominal CT showed a large cystic tumor in the left lobe of the liver measuring 15×11 cm in size (Fig. 1A-C). The cystic lesion had at least four mural nodules with slight enhancement in the arterial phase (Fig. 1C, Supplementary material 1). The medial segment was occupied with a tumorous lesion, which was consist of multiple nodules (Fig. 1D). One of the mural nodules was connected to this tumorous lesion, which indicates that the mural nodule directly invaded the medial segment (Fig. 1C). The intrahepatic bile duct in the left lobe was dilated due to the volume effect of the cystic lesion (Fig. 1A, B). Small multiple nodules ware detected in the right lobe of the liver which indicated intrahepatic metastases (Fig. 1A). Enlarged portal lymph nodes (Fig. 1C) and multiple paraaortic lymph nodes were also detected which indicated lymph node metastases. Another cystic lesion measuring 8 cm in diameter was in segment 8 that had septae inside but no mural nodules. Similarly, abdominal ultrasonography showed mural nodules in the cystic lesion (Fig. 2A). Abdominal magnetic resonance imaging (MRI) detected debris inside the cystic tumor that indicated precipitated blood clots (Fig. 2B). There were no findings indicating any communication between the cystic tumor and bile ducts. The patient underwent a diagnostic workup, including physical examination, whole-body CT, upper gastrointestinal endoscopy, total colonoscopy, and pelvic ultrasound, however, we could not identify any tumors that appeared to be a primary tumor.

Liver biopsy was performed targeting the tumorous lesion in the medial segment of the left hepatic lobe because targeting the cystic wall of the tumor posed a high risk of bleeding and peritoneal dissemination. Adenocarcinoma cells that had irregular nuclei with increased chromatin invaded fibrous stroma and vessels forming micropapillary and small tubular clusters (Fig. 3A). The clusters of cells were surrounded by pools of mucin positive for alcian blue and periodic acid-Schiff (PAS) staining, indicating mucin-production by the tumor cells. (Fig. 3B, C). The tumor cells expressed cytokeratin 7 and cytokeratin 19, but not cytokeratin 20. Tumor cells slightly expressed MUC5AC and MUC6. We could not detect any expression of carcinoembryonic antigen, carbohydrate antigen19-9, estrogen receptor, progesterone receptor, human epidermal growth factor type2, GATA3, cancer antigen 125, Wilms tumor gene-1, calretinin or glypican 3. No structure was found that indicated an ovarian-like stroma in the biopsy tissue specimens.

Although we could not prove ovarian-like stroma in the biopsy tissue specimens, we concluded that the tumor could be an invasive biliary MCN at an advanced stage. The patient demonstrated all the typical features of biliary MCNs which were a middle-aged woman, left lobe tumor location, tumor morphology, and lack of bile duct communication. As a differential diagnosis, we considered intraductal papillary neoplasms of the bile duct (IPNB), cholangiocarcinoma with a specific invasive form, and a cystic degeneration due to necrotic changes of hepatic malignancies such as an intrahepatic cholangiocarcinoma. If this case had been an IPNB, then the cystic morphology would be the result of significant bile duct dilatation due to excessive mucus production

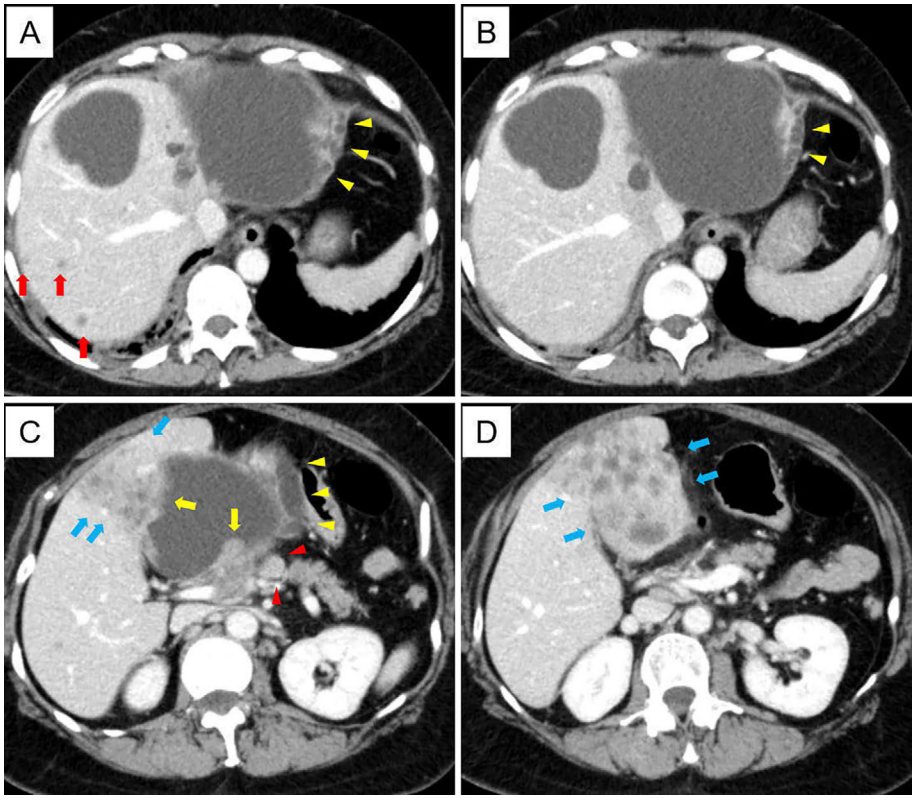

Figure 1. **Abdominal CT images at referral to our division. A large cystic tumor was in the left lobe of the liver measuring 15×11 cm in size (A, B, C). The cystic lesion had mural nodules (yellow arrows in C). The medial segment was occupied with a tumor consisting of multiple nodules (blue arrows in C, D). A mural nodule seemingly directly invaded the medial segment (left yellow arrow). The left lobe bile duct was dilated due to the volume effect of the cystic lesion (yarrow arrowheads in A, B, C). Small multiple nodules in the right lobe indicated intrahepatic metastasis (red arrows in A). An enlarged portal lymph node indicated lymph node metastasis (red arrowheads in C).**

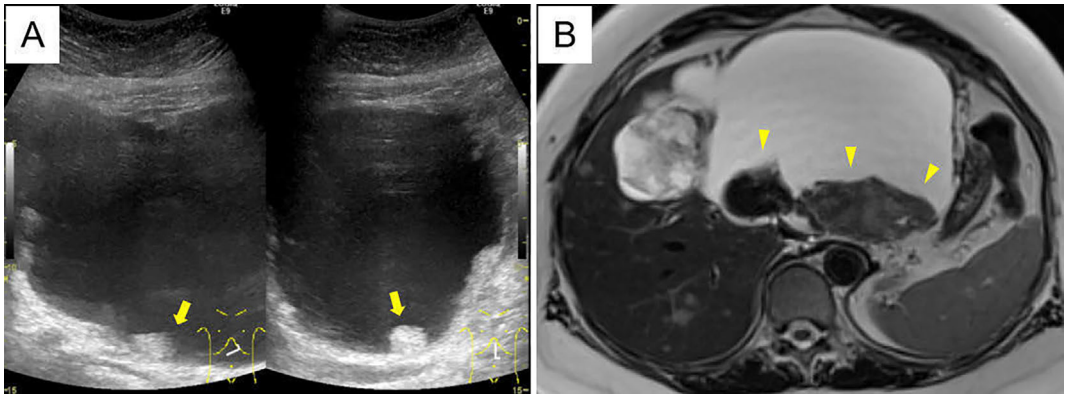

Figure 2. **Abdominal ultrasound and MRI-T2. (A) A cystic tumor in the lateral segment of the liver with mural nodules (arrows). (B) A structure in the cystic tumor indicated the presence of precipitated blood clots (arrowheads).**

in the bile ducts of the tumor cells. Alternatively, it could be that an IPNB with invasive carcinoma invaded and obstructed the central biliary tract, resulting in the development of a cyst-like morphology. Similarly, if cholangiocarcinoma showed a specific form of invasion, then the cystic change would be the result of the central biliary tract obstruction due to invasion. However, based on the CT imaging (Supplementary material 2), the intrahepatic bile ducts and common bile duct were observed to be a normal form except for the dilated intrahepatic bile ducts in the lateral segment that were at the peripheral site of the cystic tumor. There were no findings to suggest that part of the bile duct had become extremely dilated and formed a cyst-like morphology. Therefore, we considered that this case was unlikely to be IPNB

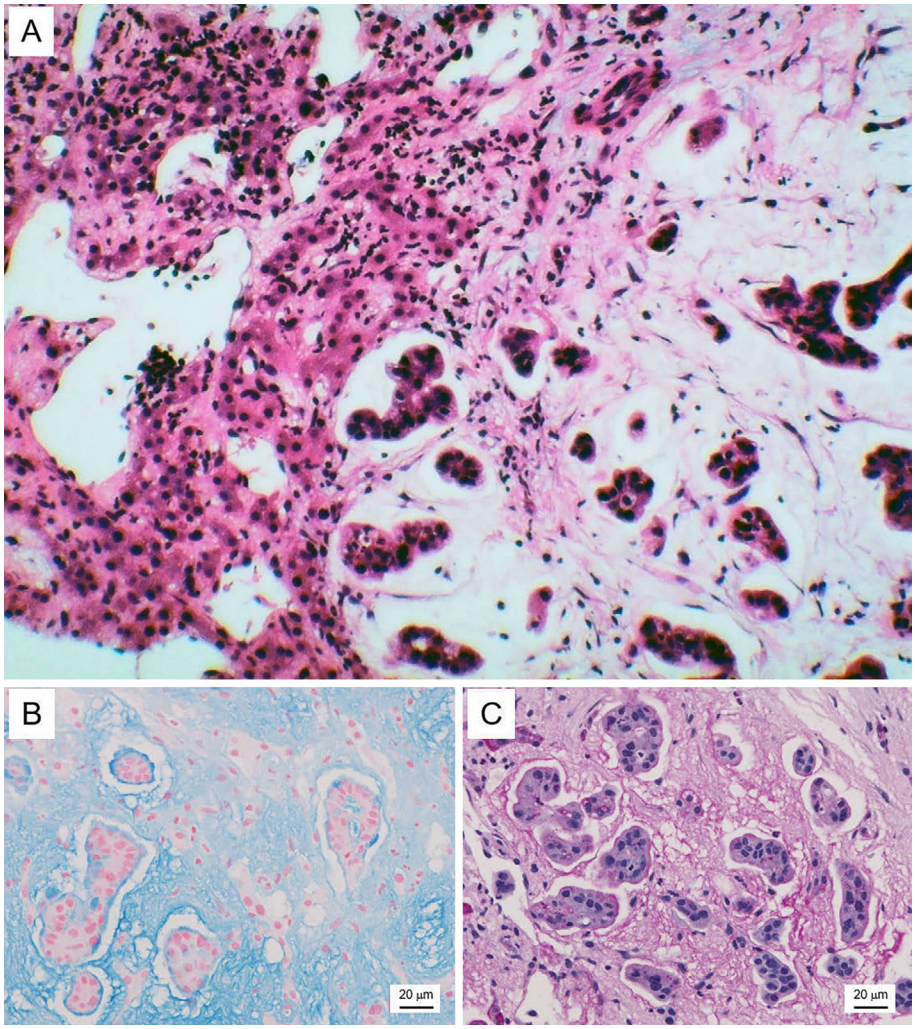

Figure 3. **Pathological images of the tumor in the medial segment. A biopsy tissue specimen obtained from the tumor in the medial segment. (A) Hematoxylin and Eosin staining. Adenocarcinoma cells that had irregular nuclei invaded fibrous stroma. (B) Alcian blue staining, (C) Periodic acid-Schiff (PAS) staining. The clusters of cells were surrounded by pools of mucin positive for alcian blue and PAS staining, indicating mucin-production by the tumor cells.**

and cholangiocarcinoma with a specific invasive form. If it the patient had cystic degeneration due to necrotic changes of hepatic malignancies, then a cystic cavity would have formed due to liquefactive necrosis of the tumor tissue. However, according to the diagnostic images of CT and ultrasound, the cystic cavity was formed with a consistent thickness of the cystic wall except for the mural nodules, thus making the hypothesis that the cystic morphology was formed by liquefactive necrosis unlikely. According to the WHO revised classification in 2010, the case did not meet the diagnostic criteria of biliary MCN due to lacking proof of an ovarian-like stroma. However, the case presented all typical features of biliary MCN, and among the hepatobiliary malignancies that could form cyst-like morphology, IPNB, cholangiocarcinoma with a specific invasive form, and other hepatic malignancies forming liquefactive necrosis were unlikely, so we comprehensively diagnosed the case to have biliary MCN. The patient's thrombosis indicated Trousseau's syndrome associated with extreme mucin-producing from the tumor cells.

In the clinical course, the patient developed jaundice due to obstruction of the common bile duct by the progression of a mural nodule of the cyst in the medial segment according to magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 4). When ERCP was performed, there was no mucus discharge from the papila of Vater, and no luminal communication between the bile ducts and the cystic tumor was detected even the cholangiography was performed with a certain amount of pressure. Cholangiography indicated no suspected defects such as stones in the bile ducts. The stenosis was smooth and appeared to be due to external compression (Fig. 4). On the CT findings before the patient developed jaundice, a mural nodule of the cyst in the medial segment came in contact with the common bile duct and there was a slight space between them (Supplementary material 2A, B). However, on the MRI at jaundice, the nodule had expanded and compressed the common bile duct

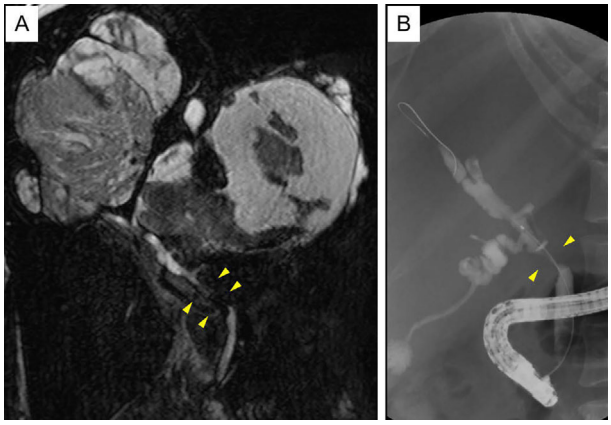

Figure 4. MRCP and ERCP. (A) Stenosis of the common bile duct due to the progression of the tumor (arrowheads). (B) A biliary stent was endoscopically placed over the stenosis in the common bile duct. MRCP: magnetic resonance cholangiopancreatography, ERCP: endoscopic retrograde cholangiopancreatography

(Supplementary material 3). The patient developed acute cholangitis with diffuse intravascular coagulation and a biliary stent was endoscopically placed for drainage of the common bile duct. The patient subsequently died of hepatic failure.

Discussion

Hepatic mucinous cystic tumors are one of the rare neoplasms in the liver. Cystic tumors of the liver have been previously called hepatic (biliary) cystadenoma/cystadenocarcinoma. Mucin-producing biliary tumors macroscopically include two types including cyst-forming type and duct-ectatic type, however, these two tumor types had not been distinguishably described for decades. In 2010, these types of tumors were defined as biliary MCN and IPNB as counterparts of the pancreas in the WHO revised classification (1). Biliary MCN is defined as a cyst-forming and mucin-producing epithelial neoplasm lacking communication with the bile ducts, and demnstrating an ovarian-like stroma with the expression of estrogen receptors in the cyst wall. Most of the biliary MCNs arise in the left lobe of the liver in middle-aged women (5, 6). These features of biliary MCNs indicate a common developmental pathway between pancreatic MCNs. Both the biliary system and the pancreas develop from the ventral endoderm of the foregut in mammals. Extrahepatic peribiliary glands can produce pancreatic enzymes such as amylase, trypsin, and pancreatic lipase (7). Sumazaki et al. reported that the biliary epithelium has a potential for pancreatic differentiation regulated by a transcription factor Hes1 (8). These findings suggest that common genetic and molecular oncologic pathways exist in the development of biliary and pancreatic neoplasms (6).

IPNB is characterized by a lesion with bile duct extension due to excessive mucin production. The progression of such extension due to extreme mucin-production bends the bile duct, which could make the bile duct look like a cystic lesion. For this reason, distinguishing biliary MCN from IPNB by imaging is sometimes difficult (9). In the present case, the hepatic tumors developed in a middle-aged woman, the primary cystic tumor was located in the left lobe, and the MRCP/ERCP images showed no evidence of communication with the normal bile ducts. These features of biliary MCN could distinguish it from IPNB.

The biliary MCNs are diagnosed not only by imaging such as CT, MRI, and ERCP, but also based on the pathological findings, which include an ovarian-like stroma with the expression of estrogen receptors in the cystic wall of the tumor (2, 10). In the present case, we could not obtain tissue specimens from the cystic wall of the primary tumor. Hepatic resection was not an option because the patient's tumors had spread to the bilateral liver lobes and lymph nodes. A biopsy targeting at the wall of the cystic tumor posed a high risk of bleeding and peritoneal dissemination.

In the present case, there was no elevation of common tumor markers of adenocarcinomas such as CA19-9 and CEA. Serum CA19-9 has been reported as a predictive marker of invasive carcinoma in pancreatic MCN (11, 12). In biliary MCN, however, there have been no reports of certain trends in the association of serum or cyst fluid CA19-9 with invasive carcinoma; some invasive carcinomas without an elevation of CA19-9 have been reported (13). Although it remains rather unclear, even biliary MCN with invasive carcinoma may not show an elevation of the serum CA19-9 level. The present case seems to be one of these.

The biliary MCN has been reported to have an excellent prognosis if a complete surgical resection can be performed. Kubota et al. reported a 5-year survival rate of biliary MCN (adenoma, 7 cases; adenocarcinoma, 2 cases) was 100% (14). However, the prognosis of MCN in an advanced stage spreading to the liver parenchyma, lymph nodes or distant organs has not been reported yet. The definition of MCN requires the existence of an ovarian-like stroma. The patients in an advance stage rarely have a chance to receive hepatic resection that may make the diagnosis of MCN difficult. This case presented with the typical features of biliary MCN and had intrahepatic and distant metastases. It was unlikely that other hepatic malignancies developed cyst formation. We could not prove the existence of an ovarian-like stroma, but we made a diagnosis of biliary MCN overall. Among biliary MCNs, which is a rare form of liver tumor, a biliary MCN with invasive carcinoma is even rarer. It has been reported that intrahepatic metastases and lymph node metastases are very rare even in the case of biliary MCN with invasive carcinoma.

Before the biliary MCN was defined in WHO classification in 2010, several articles reported the treatment and prognosis of the hepatic (biliary) cystadenocarcinoma. Nakajima et al. reported the prognosis of patients with hepatic cystadenocarcinoma with extramural invasion who died from 5 to 12 months after the resection whereas the prognosis of

the patients with tumors confined in the cystic wall was a5-year survival of 100% (15).

Lauffer et al reported that 13% of the patients with hepatic (biliary) cyst adenocarcinoma who received hepatic resection showed lymph node metastases, and the survival of the patients with lymph node metastasis developed early recurrence whilst the others did not with a 5-year survival of 100% (16). The hepatic cystadenocarcinoma in these reports probably includes an invasive type of MCNs, IPNBs, or other neoplasms. According to the current classification of MCN defined by WHO in 2010, there may exist a certain number of patients with invasive biliary MCN in advanced stage whose diagnosis is not confirmed without the pathological proof of an ovarian-like stroma in the cystic wall because hepatic resection cannot be performed. The classification of biliary MCN may need to be revised to provide an appropriate diagnosis for patients in the advanced stage. Additional data are required to define the prognosis in patients with biliary MCN in advanced stage using a new classification.

The present case developed pulmonary artery thrombosis due to Trousseau's syndrome in the clinical course. The primary sites of cancer-related thrombosis, the more commonly known as Trousseau's syndrome, have been reported to include the lung 17%, pancreas 10%, colon 8%, kidney 8%, and prostate 7% (17). Reports of cholangiocarcinoma are rare, with a total of seven cases reported since 1991 (18). It is generally believed to be associated with mucus-producing adenocarcinoma, and there have been no reports of biliary MCN/IPNB or pancreatic MCN/IPMN. Thrombosis is thought to result from the release of mucin with an abnormal structure produced by cancer cells into the blood (19). Only three cases of Trousseau's syndrome due to benign tumors have been reported, which all included primary ovarian tumors (20). The reason for the absence of reports in biliary and pancreatic MCN which produce significant amounts of mucin may be that most of these are benign lesions producing normal mucin.

In conclusion, we herein described a rare case of biliary MCN with intrahepatic and lymph node metastases. Further investigations with a sufficient number of cases are necessary to clarify the biologic features and to establish a standard therapy for this malignant tumor with a poor prognosis.

The authors state that they have no Conflict of Interest (COI).

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