Intracholecystic papillary neoplasm of the gallbladder protruding into the common bile duct: A case report

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Abstract. The current study indicates the case of intracholecystic papillary neoplasm (ICPN) protruding into the common bile duct (CBD) without superficial spread. A 58-year-old woman presented to hospital with a fever that lasted for three days. Laboratory tests revealed elevated hepatobiliary enzyme levels. CT, MRI and endoscopic ultrasonography revealed a polypoid, papillary tumor inside the gallbladder cavity, which also extended to the CBD. On peroral cholangioscopy, a papillary tumor with mucin production was found at the middle bile duct. Biliary biopsy and bile cytology indicated adenocarcinoma. Based on a diagnosis of ICPN extending to the CBD, the patient underwent subtotal stomach-preserving pancreaticoduodenectomy and gallbladder bed resection. However, pathological examination revealed that the ICPN was confined to the gallbladder and cystic duct, whereas the CBD was tumor-free. The present case indicates that when ICPN increases in size, it may protrude into the CBD due to an increased intracholecystic pressure, which increases the risk of overestimation of tumor extension and may result in unnecessary additional bile duct resection.

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Abbreviations: ICPN, intracholecystic papillary neoplasm; CBD, common bile duct; IPMN, intraductal papillary mucinous neoplasm; IPNB, intraductal papillary neoplasm of the bile duct; CT, computed tomography; MRI, magnetic resonance imaging; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; EUS, endoscopic ultrasonography; ERC, endoscopic retrograde cholangiography; IDUS, intraductal ultrasound; POCS, peroral cholangioscopy

Key words: intracholecystic papillary neoplasm of the gallbladder, gastric-type, oncocytic-type, mucin-producing tumor, intraductal papillary mucinous neoplasm, intraductal papillary neoplasm of the bile duct

Introduction

Intracholecystic papillary neoplasm (ICPN) of the gallbladder is a relatively new concept and suspected to share clinicopathologic features with intraductal papillary mucinous neoplasm (IPMN) of the pancreas and intraductal papillary neoplasm of the bile duct (IPNB) (1,2). Because of its rarity, the imaging characteristics of ICPN have not yet been definitively standardized. Herein, we report a unique case of ICPN of the gallbladder extending to the common bile duct (CBD) without superficial spread.

Case report

A 58-year-old woman with no significant medical history presented with fever lasting for three days. Her physical examination was unremarkable. Laboratory analysis showed elevations in C-reactive protein (2.1 mg/dl; normal range: <0.2 mg/dl), aspartate aminotransferase (44 IU/l; 13-33 IU/l), alanine aminotransferase (169 IU/l; 8-42 IU/l), alkaline phosphatase (1675 IU/l; 115-359 IU/l), and gamma-glutamyl transpeptidase (757 IU/l; 8-42 IU/l). Her leukocyte count and serum levels of total bilirubin, carcinoembryonic antigen, and carbohydrate antigen 19-9 were within normal ranges. Contrast-enhanced computed tomography (CT) and T2-weighted magnetic resonance imaging (MRI) showed an enlarged gallbladder filled with a polypoid, papillary lesion. The CBD was also dilated with a similar intraluminal papillary tumor, suggesting superficial spread of the gallbladder neoplasm (Figs. 1 and 2). Endoscopic ultrasonography showed the polypoid lesion spreading from the gallbladder into the CBD without signs of stromal invasion (Fig. 3). She also underwent endoscopic retrograde cholangiography, which showed filling defects within the CBD, but the gallbladder and cystic duct could not be visualized (Fig. 4A). Endoscopic examination with intraductal ultrasound revealed a papillary lesion extending from the cystic duct orifice to the lower CBD (Fig. 4B). Furthermore, peroral cholangioscopy demonstrated a mucin-producing papillary tumor at the same site, while the confluence of hepatic ducts was tumor-free (Fig. 4C). The biopsy specimen taken from the papillary tumor and bile cytology showed atypical glandular cells consistent with adenocarcinoma. Based on the diagnosis of ICPN with spread into the CBD, she underwent subtotal stomach-preserving

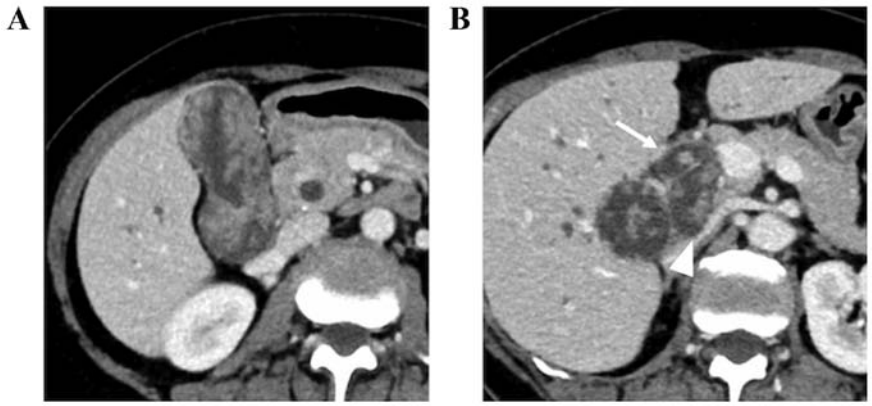

Figure 1. Findings of contrast-enhanced CT. (A) Contrast-enhanced CT revealed that the gallbladder was almost completely filled with papillary lesions. (B) The tumor extended to the common bile duct (arrow) through the cystic duct (arrow head). CT, computed tomography.

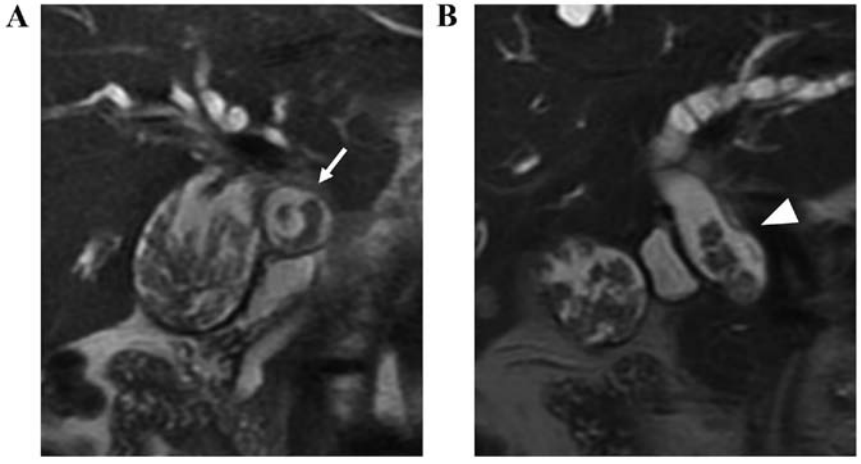

Figure 2. Findings of T2-weighted MRI. (A) T2-weighted MRI (coronal image) showed the papillary tumors filling the gallbladder and spreading to the cystic duct (arrow). (B) The tumors protruded into the common bile duct (arrow head). MRI, magnetic resonance imaging.

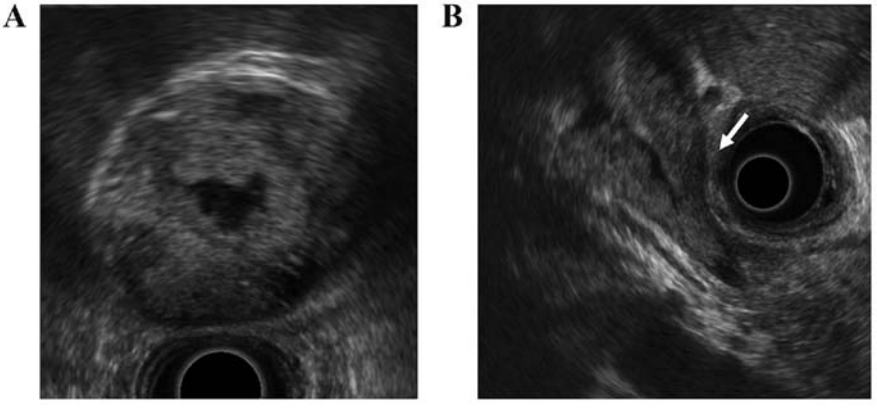

Figure 3. Findings of EUS. (A) EUS demonstrated polypoid lesions (B) extending from the gallbladder into the common bile duct (arrow) without invasion of the gallbladder wall or the bile duct. EUS, endoscopic ultrasonography.

pancreaticoduodenectomy (SSPPD) and gallbladder bed resection.

Gross examination showed an enlarged gallbladder and dilated cystic duct, which were filled with significant amounts of mucus as well as the papillary neoplasm. However, the mucosa of the CBD was unremarkable with no tumor identified (Fig. 5). Microscopically, the gallbladder neoplasm consisted of atypical glandular epithelium arranged in a highly papillary architecture along fibrovascular stalks. The tumor showed extensive superficial spread along the gallbladder mucosa, and also into the Rokitansky-Aschoff sinus. Most tumor cells had gastric-type features such as intracytoplasmic mucus, round nuclei, and clear cytoplasms. Small foci consisting of highly eosinophilic cells with centrally located

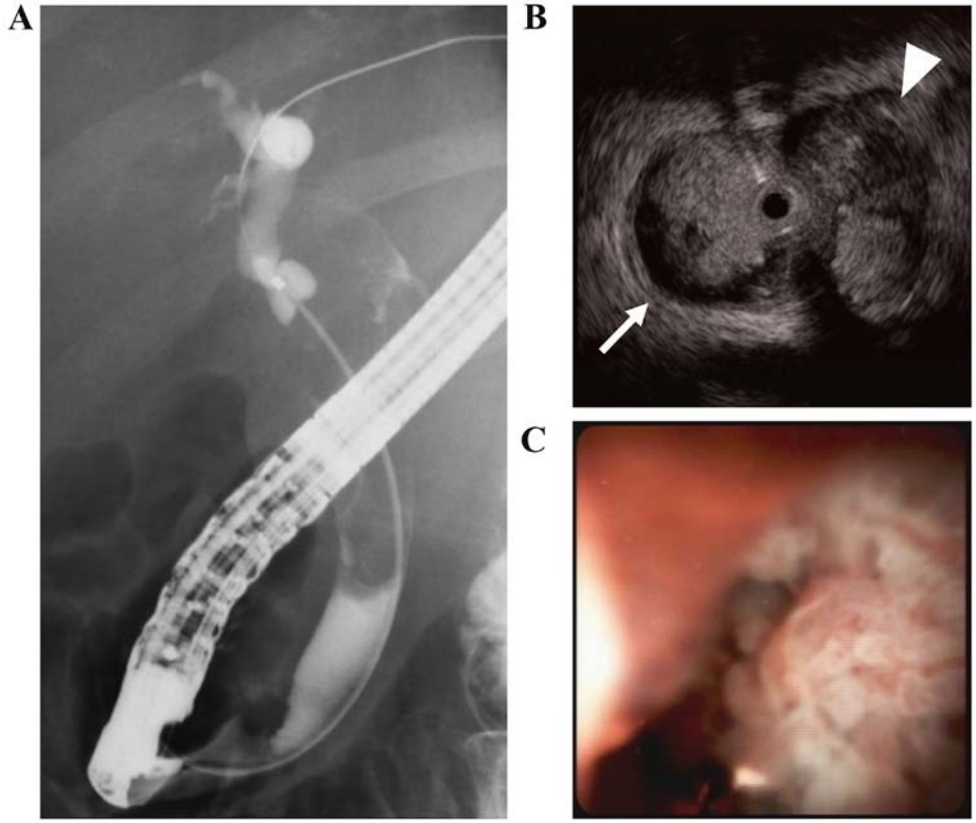

Figure 4. Findings of ERC, IDUS and POCS. (A) ERC showed filling defects within the common hepatic duct, but the gallbladder and cystic duct could not be visualized. (B) IDUS revealed papillary lesions protruding into the common bile duct (arrow) through the cystic duct (arrow head). (C) POCS revealed mucin-producing papillary tumors around the cystic duct orifice and extending to the lower common bile duct. ERC, endoscopic retrograde cholangiography; IDUS, intraductal ultrasound; POCS, peroral cholangioscopy.

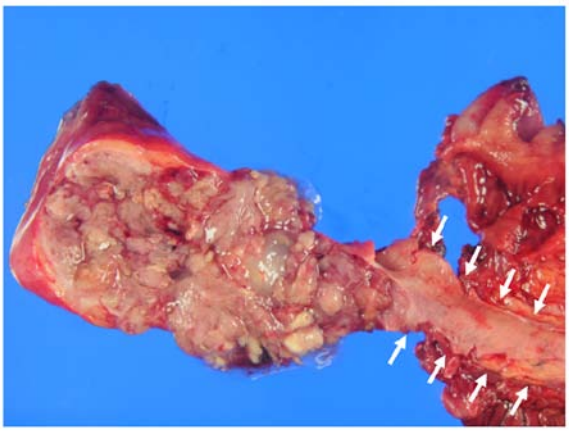

Figure 5. Macroscopic findings in the intracholecystic papillary neoplasm. Macroscopically, the papillary tumor was present in the gallbladder along with a large amount of mucin spreading to the cystic duct. No tumors were observed in the common bile duct (arrows).

round nuclei, consistent with the oncocytic-type, were also present. The tumor was mostly non-invasive, but there was a small focus (<1 cm) of stromal invasion in the subserosal layer (Fig. 6).

On immunostaining, the cells were diffusely positive for MUC1, MUC5AC, and MUC6, and negative for MUC2. On the basis of the histologic findings, the tumor was diagnosed as a gastric-type ICPN with an associated adenocarcinoma. Although the patient refused adjuvant chemotherapy, the post-operative course was uneventful with no recurrence observed at 6 months of follow-up.

Discussion

ICPN is a comparatively new entity, first described in the 2010 World Health Organization classification (1). Adsay *et al* (2) defined ICPN as an exophytic intramucosal gallbladder mass (>1.0 cm) composed of dysplastic cells forming a lesion distinct from the adjacent mucosa. However, this definition is suspected of being excessively lax, and papillary invasive carcinomas or intraductal tubular neoplasms (e.g., pyloric gland adenoma) may also meet the criteria.

It has been reported that ICPNs are more common in women older than 60 years and that they are present in <0.5% of gallbladders removed for cholelithiasis or chronic cholecystitis (2,3). These rare tumors present with an intramucosal papillary or polypoid mass, often associated with overproduction of mucin. ICPN is suspected to share characteristics with IPMN and IPNB; however, they differ in some aspects. Low-grade lesions and *GNAS* mutations were markedly less common in IPNBs and ICPNs than in IPMNs of the pancreas (4-6).

Although 50% of patients with ICPN have invasive malignant components, the prognosis of ICPN is reportedly favorable. The 1-, 3- and 5-year survival rates of patients with noninvasive ICPN were 90, 90 and 78%, respectively.

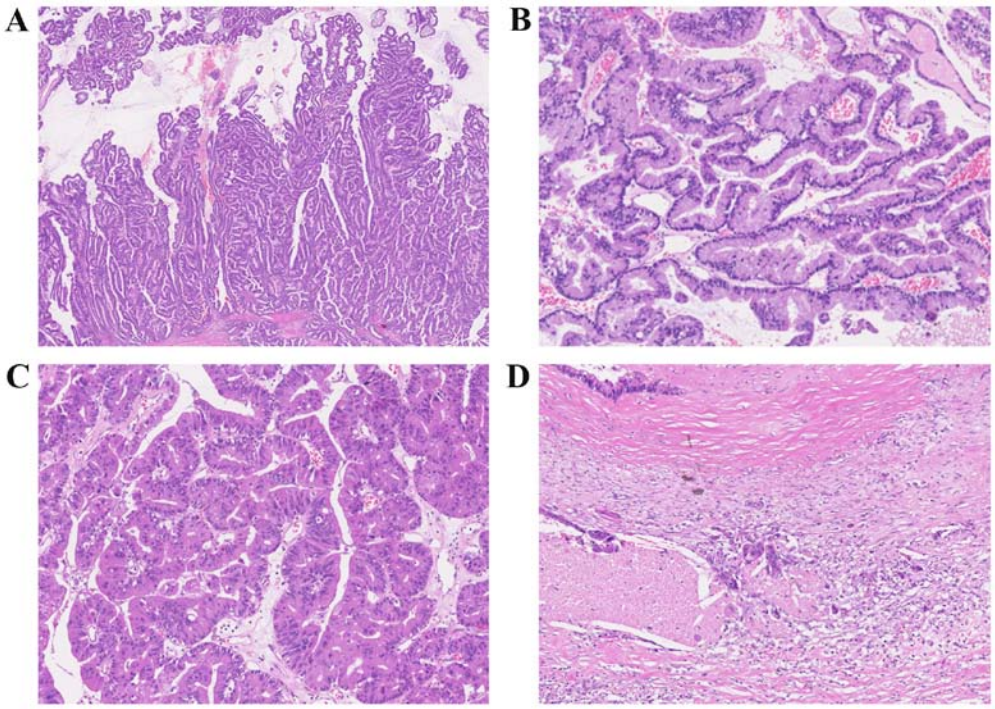

Figure 6. Microscopic findings in the intracholecystic papillary neoplasm. (A) The tumor consisted of atypical glandular epithelium arranged in a high papillary architecture along thin fibrovascular stalks (hematoxylin and eosin staining; magnification, x40). (B) Most tumor cells showed a gastric-type morphology (magnification, x200). (C) Small lesions consistent with the oncocytic-type were also present (magnification, x200). (D) Focal invasion of the subserosa was observed (magnification, x200).

Even patients with associated invasive carcinoma have a significantly better clinical outcome than those with ordinary invasive gallbladder cancer (2). The difference in prognosis can be at least partly explained by the exophytic growth of ICPN, which increases the chances of diagnosis at an early stage and curative resection.

In the present case, multimodality imaging studies suggested superficial spread to the CBD, requiring SSPPD. However, no tumor was found in the CBD, suggesting that the papillary mass observed inside the bile duct was a prolapsed gallbladder neoplasm. This discrepancy highlights the challenge in determining the degree of lateral extension of ICPNs. Distinguishing tumor protrusion without surface invasion from ordinary tumor extension is difficult. Repeated CT and/or MRI may play an important role in telling them apart in the case of a tumor moving easily between the gallbladder and the CBD. Intraoperative ultrasonography may also be useful for determining the degree of lateral tumor extension. Another discrepancy between the imaging interpretations and pathological diagnosis was the presence of stromal invasion. Small foci of stromal invasion are difficult to identify on imaging, as in the case of IPNB and IPMN of the pancreas. Considering this limitation of the imaging studies, gallbladder bed resection was performed.

Almost 50% of patients with ICPN present with right upper outer quadrant pain, whereas the remaining 50% are found to have a tumor incidentally without any associated symptoms (2). The fever in our patient was likely due to cholangitis, suggesting that prolapsed ICPN can cause cholangitis even without true bile duct involvement. In addition to the tumor, the large amount of thick mucus might have also caused the cholangitis. In contrast, obstructive jaundice is unusual in the context of ICPN with only 2 reported cases presenting with biliary obstruction to our knowledge (7,8). In both cases, the tumors were present in the CBD mucosa as well. To the best of our knowledge, this is the first study to suggest that ICPN may protrude into the CBD without superficial spread.

In conclusion, when ICPNs increase in size, they may protrude into the CBD due to the increased intracholecystic pressure, which increases the risk of overestimation of tumor extension and may result in unnecessary additional bile duct resection.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MY acquired the data and wrote the manuscript. KH, AS, TM, RH, TA and HA acquired the data and contributed clinical advice. SY and YZ interpreted the pathological data. YZ revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

A written consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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