Diffuse Intracystic Papillary Neoplasm Indistinguishable from Gallbladder Cancer: A Case Report

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Case Report

Diffuse Intracystic Papillary Neoplasm Indistinguishable from Gallbladder Cancer: A Case Report

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This report describes a patient who underwent resection for an intracystic papillary neoplasm (ICPN) classified by the World Health Organization in 2010 as a pre-cancerous or early cancerous tumor of the gallbladder. The patient was a 70-year-old Japanese woman who was hospitalized for hepatic dysfunction and jaundice. Various imaging tests revealed multiple papillary tumors, present mainly in the gallbladder lumen as well as infiltrating the intra- and extra-hepatic bile ducts and the liver. Advanced gallbladder cancer was suspected. The patient underwent extended right hepatectomy and resection of the extrahepatic bile duct and regional lymph nodes along with hepatico-jejunostomy. However, the gallbladder tumor was diagnosed immuno-histopathologically as intestinal-type ICPN with high-grade dysplasia. ICPN has been described as a gallbladder papilloma (papillomatosis), comparable to benign gallbladder lesions. To date, however, there have been no reports of patients with multiple tumors in the gallbladder lumen resulting in an ICPN of large diameter. As ICPN is regarded as a pre-cancerous or early cancerous tumor of the gallbladder, the method of diagnosis and histopathological classification require standardization.

Key Words: intracystic papillary neoplasm (ICPN), intraductal papillary neoplasm of bile duct (IPNB), gallbladder papillomatosis, gallbladder cancer

Introduction

To date, most papilliform tumors growing in the intra- and extra-hepatic bile duct epithelium have been recognized as benign lesions[1)2)], although some tumors are regarded as borderline-low grade malignancies[3)]. Intracystic papillary neoplasms (ICPN) are papilliform growths of tumorous lesions in the gallbladder. These tumors include intrabiliary lesions, called intraductal papillary neoplasms of the bile duct (IPNB), classified by the World Health Organization in 2010 WHO as pre-cancerous/early cancerous lesions of the gallbladder[4)5)]. The pathologic morphology and clinical characteristics of IPNB are similar to those of intraductal papillary mucinous neoplasms (IPMN)[6)], which are regarded as a pancreatic disease. To date, however, little is known about the car-

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cinogenetic mechanisms and progression of ICPN.

We recently encountered a patient who underwent resection of diffuse ICPN in the gallbladder, accompanied by intra- and extra-hepatic bile duct infiltration. The lesion was found to be a papillomatous tumor indistinguishable from advanced gallbladder cancer. This report describes our findings in this patient.

Case Report

A 70-year-old Japanese woman was urgently admitted to our department in December 2012 for upper abdominal pain after eating. Her prior history included emphysema due to long-term smoking. Her family history was unremarkable. Blood tests showed a white blood cell (WBC) count of 18,700 /μl, and a serum C-reactive protein (CRP) concentration of 8.63 mg/dl, indicating a serious inflammatory reaction. Her serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin concentrations were 1,100 IU/*l*, 627 IU/*l*, 1,426 IU/*l*, and 6.3 mg/dl, respectively, indicating hepatic dysfunction, and jaundice was observed. Her carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) concentrations were 16.2 ng/ml and 369 U/ml, respectively, both of which were high. We determined that the inflammation was caused by mild acute cholangitis, but this gradually resolved with conservative treatment. Abdominal ultrasound (US) revealed swelling of the gallbladder, to 114 × 45 mm, and a papillomatous tumor with widespread growth in the lumen. In addition, the border between the gallbladder and liver was unclear, which is evidence of suspected liver invasion by the tumor (**Fig. 1**). Multi detector-row contrast-enhanced computed tomography (CT) revealed many multiple papilliform tumors in the swollen gallbladder. Coronal cross-sectional CT showed marked retraction of the right branch and right hepatic duct of the portal vein, along with enlargement of the secondary branches of the intrahepatic bile ducts at the periphery (**Fig. 2**). Magnetic resonance imaging (MRI) revealed that the tumor in the gallbladder lumen was of low inten-

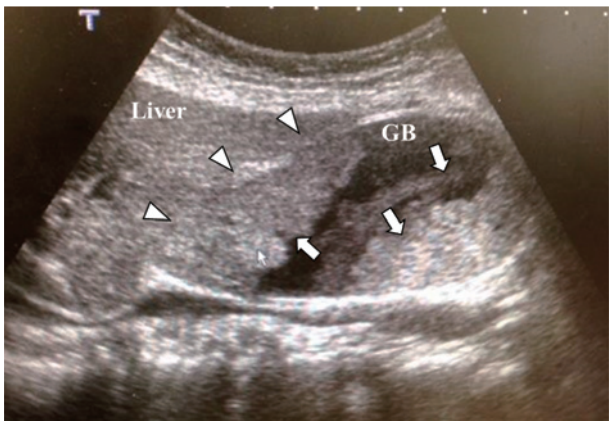

Fig. 1 Abdominal ultrasonography
Abdominal ultrasonography, showing multiple papilliform tumors at mixed echo level in the gallbladder lumen (arrows). The border between the gallbladder and liver was unclear, which was evidence of liver infiltration by the tumors (arrowheads).
GB, gallbladder.

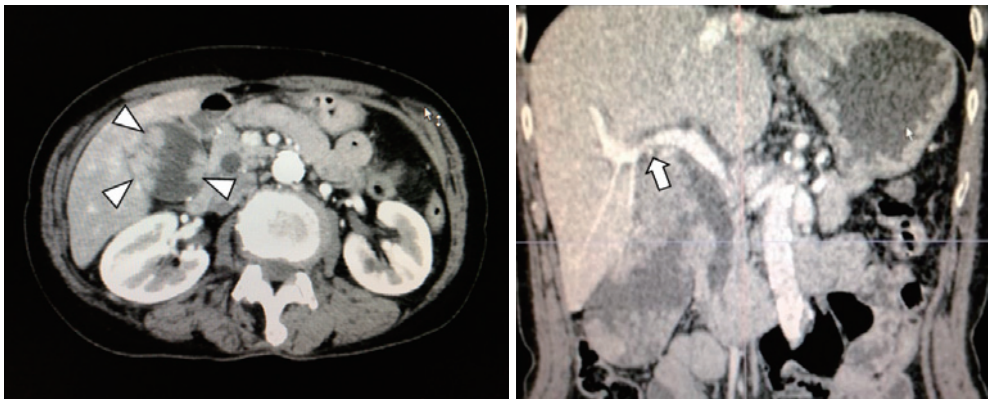

Fig. 2 Multi detector-row computed tomography
Multi detector-row computed tomography (CT), showing the growth of multiple tumors in the lumen due to the contrast effect in the gallbladder (arrowheads). The coronal cross-sectional CT shows that the right primary branch of the portal vein was stenosed, a finding suggesting direct tumor infiltration (arrow).

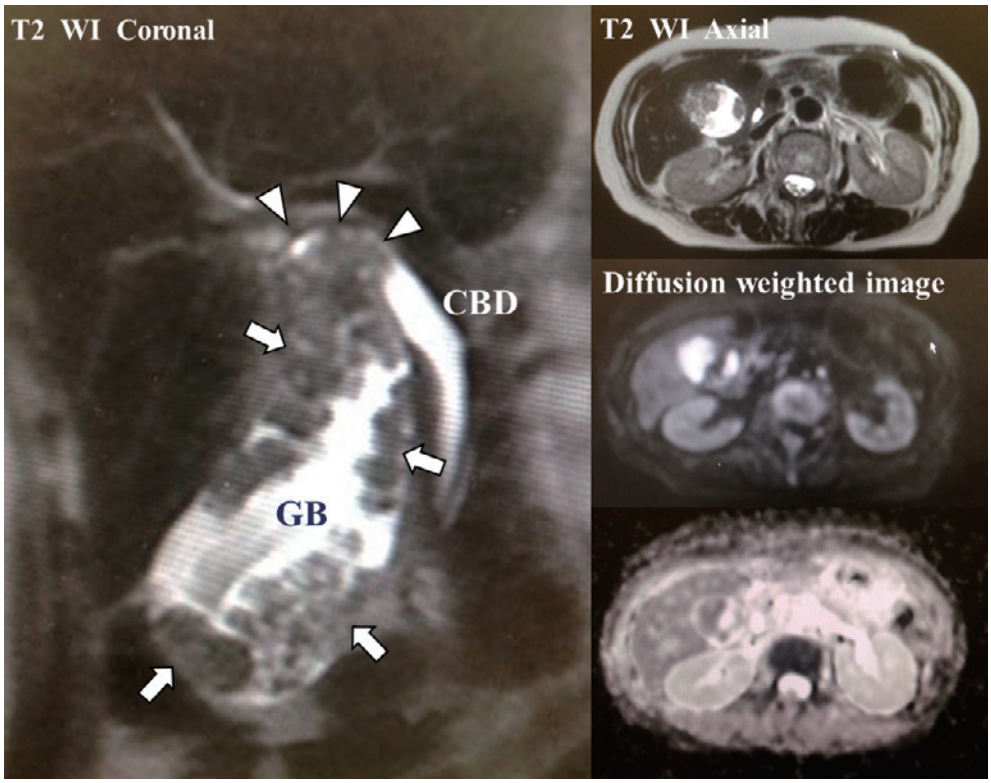

Fig. 3 Abdominal magnetic resonance imaging
T2 weighted image (WI) showing shrinkage of the common hepatic duct and right hepatic duct (arrowheads) due to retraction by the multiple tumors (arrows) in the gallbladder lumen. Diffusion weighted imaging (DWI) of the gallbladder tumors yielded high signals, and the apparent diffusion coefficient (ADC) was low.
CBD, common bile duct; GB, gallbladder.

sity in T1 and high intensity in T2 and diffusion weighted images. On the latter, however, the apparent diffusion coefficient (ADC) map was decreased, resulting in the diagnosis of a tumor with malignant potential (**Fig. 3**). Endoscopic retrograde cholangiography (ERC) showed enlargement of the extrahepatic bile duct diameter to 12 mm, as well as stenosis due to retraction in the downwards direction from the right hepatic bile duct through the common hepatic bile duct. Because the cystic duct was interrupted behind the common bile duct, imaging of the gallbladder was not feasible. Cytologic assessment showed that the bile sampled from the bile duct interior was class IIb, with no malignant cells detected. Finally, we strongly suspected that the tumor was gallbladder cancer of papillary infiltrating type from these findings. And the liver function just before operation was within liver damage A.

After obtaining written informed consent from the patient, surgery was performed in January 2015. Operative findings included a markedly swollen gallbladder with whitened serosa. Perioperative US revealed that the border between the gallbladder and liver was unclear. The right side of the hepatic portal area was strongly adherent to the neck region of the gallbladder making it impossible to visualize the gallbladder. These operative findings suggested gallbladder cancer and direct invasion of the right hepatic lobe. Therefore, extended right hepatectomy and resection of the extrahepatic bile duct and regional lymph nodes with hepatico-jejunostomy were performed. The operative time was 382 min and the volume of blood lost was 1,015 ml.

Macroscopic examination of the resected specimen revealed irregular thickening of the gallbladder wall and the aggregation of multiple pedunculated-semipedunculated papillomatous tumors in the lumen. These tumors were confined to the gallbladder neck and strongly adhered to the right hepatic bile duct (**Fig. 4**). However, microscopic examination showed that the tu-

mor cells had cuboid or cylindrical nuclei, with no evidence of nucleolar enlargement. The part thought to be direct invasion from the gallbladder cancer was strong benign inflammatory findings. Moreover, the Ki-67 proliferation-index (MIB-1) of one area was higher than those of the other areas; although mixed with areas of high neoplastic ducts, there was no evidence of vascular, lymph duct or lymph node metastasis. On immunostaining, the cells were focally positive for mucin core protein (MUC) 1, diffusely positive for cytokeratin (CK) 20, and negative for MUC2, MUC6, and CK7. Based on these findings, the tumor was diagnosed as intestinal-type ICPN with high-grade dysplasia (**Fig. 5**). Her postoperative course was uneventful, with no complications, and the patient was discharged on day 22. To date, 5 years and 4 months after surgery, the patient has shown no recurrence of symptoms. Her high preoperative CEA and CA 19-9 concentrations decreased rapidly after surgery and have since remained in their normal ranges.

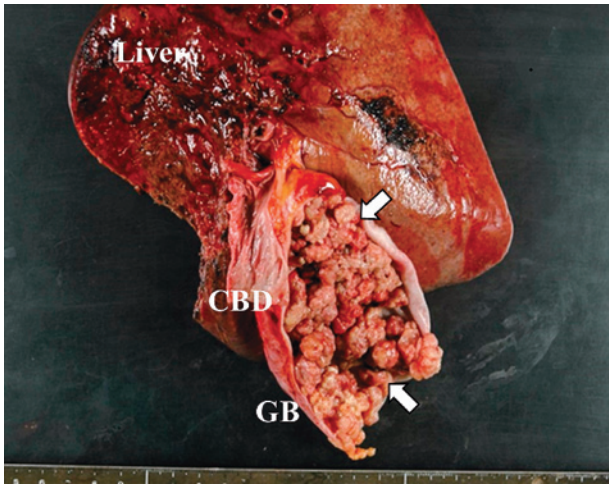

Fig. 4 Macroscopic analysis of the resected specimen.
Macroscopic analysis of the resected specimen, showing that the gallbladder lumen was packed with swollen papilliform growth (arrows). The gallbladder cervix showed extensive adherence from the common hepatic duct to the right porta hepatis, forming a tumor mass.
CBD, common bile duct; GB, gallbladder.

Discussion

Most gallbladder cancers are diagnosed at an advanced stage, with few patients being candidates for surgical resection. Therefore, diagnosis at an early or preneoplastic stage can enhance treatment outcomes. Lesions with pa-

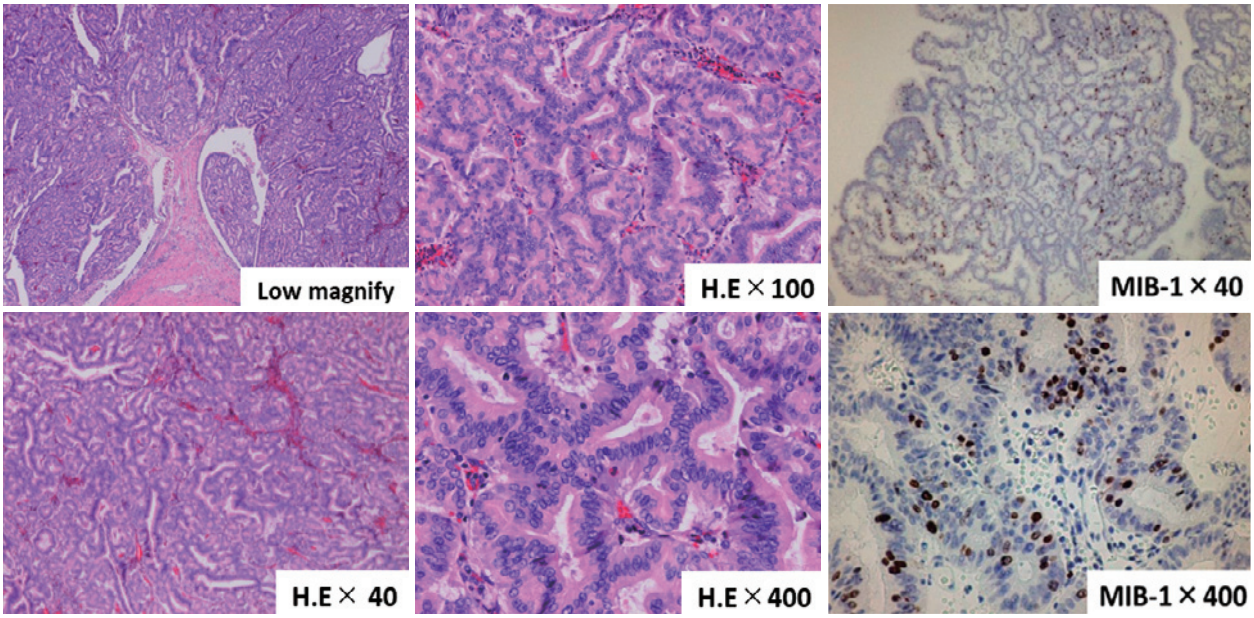

Fig. 5 Histopathological findings in our patient.
Histoimmunopathologic findings, showing that most cells retained polarity and the nuclei and chromatin showed no clear evidence of malignancy on hematoxylin-eosin (HE) staining (× 40, × 100, × 400). The tumor consisted mainly of non-invasive, highly deformed papillotubular mucosal epithelium. Ki-67 proliferation-index (MIB-1) staining showed that the density of the neoplastic duct was low (× 40, × 400). The tumor was diagnosed as an intracystic papillary neoplasm with high-grade intraepithelial neoplasia.

pilliform growth have been described as papillary adenomas (adenomatosis) and papillomas (papillomatosis) of the gallbladder based on the degree of cellular atypia and morphological characteristics[7]. There is no international consensus on their histopathological category and its identification has therefore been chaotic. All tumors with papilliform development in the biliary lumen were found to be either highly differentiated papilliform adenocarcinomas or borderline lesions with a morphology and clinical condition similar to those of IPMN[8)9)]. This led to proposals that bile duct lesions be defined as IPNBs and gallbladder lesions as ICPN. The 2010 World Health Organization classification of tumors of the digestive system categorized ICPN as early or preneoplastic forms of biliary cancer[4)5)]. Therefore, the tumor in our patient corresponded to a gallbladder papillomatosis in western patients[7] or to an ICPN. Gallbladder papillomatoses reported to date are comparatively rare benign tumors[10)11)], although an ICPN was recently reported to be a borderline low-grade malignant lesion. Gallbladder lesions may develop into cancers via ICPN. The clinicopathological characteristics of ICPN include (a) an intramucosal location, (b) non-infiltrative properties, (c) a papilliform morphology, (d) size $\geq$10 mm, (e) a compact appearance, and (f) a clear surrounding mucosa and border. As in our patient, ICPN with abnormal findings in the intra- and extra-hepatic bile ducts occupying most of the gallbladder lumen are very rare[12]. ICPN usually arise from intrabiliary lesions and, in the absence of cholecystitis, patients appear asymptomatic during early stages, with cholestasis and jaundice usually not observed even on blood biochemistry tests. Tumor enlargement, as in our patient, can induce inflammation in the surrounding organs, with serum CEA and CA19-9 concentrations increasing due to cholestasis. The tumor may not always contribute to a diagnosis of malignant potential. Moreover, although imaging frequently shows characteristic papillomatous elevated lesions, as in our patient, most of the tumors are present in the gallbladder lumen. The occurrence of abnormal findings in the surrounding organs makes it very difficult to differentiate ICPN and gallbladder cancer. Positron emission tomography (PET)-CT and endoscopic US-fine needle aspiration (EUS-FNA)[13] will likely contribute in future to the preoperative diagnosis of ICPN.

The recommended treatment in patients with suspected ICPN is surgical resection, based on the malignant neoplasm of the gallbladder and the high potential for malignant transformation. Our patient underwent surgery due to the suspicion of advanced gallbladder cancer with invasion of the intra- and extra-hepatic bile ducts and liver infiltration. However, the extent of resection of large, multiform tumors is based on preoperative imaging[14]. In the future, for a similar case, there is scope for investigating how to avoid excessive invasive surgery, and considering the malignant potential of ICPN, perfect surgical resection aimed at total biopsy of the lesioned area is required. Curative surgical resection of ICPN in the absence of invasion has been associated with a 3-year overall survival rate of 90%, which is comparatively good[12].

Two carcinogenic pathways have been identified in gallbladder cancer, the adenoma-carcinoma sequence and de novo carcinogenesis[15]. The characteristics of gallbladder lesions, however, are similar to those of tumors derived from the epithelium of other organs[16]. However, characteristics that can lead to early diagnosis have not been determined. Assessment of additional patients with this condition will likely contribute to improvements in prognosis.

Conclusion

This report describes a patient with an ICPN indistinguishable from a gallbladder cancer. Histopathologically, ICPN are early or preneoplastic lesions of the gallbladder, suggesting a need for surgical treatment. Accumulation of data on patients diagnosed early and those with ICPN may improve treatment outcomes in patients with gallbladder cancer.

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Conflicts of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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