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[CASE REPORT]

A Case in which an Intraductal Papillary Neoplasm of the Bile Duct Was Surgically Resected 12 Years after the Initial Diagnosis

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Abstract:

A 66-year-old Japanese man was referred to our hospital with multiple giant liver cysts. The cysts had already been detected as multiple 3-cm cysts with small nodules at another hospital 12 years prior to this presentation. The cysts were diagnosed as an intraductal papillary neoplasms of the bile duct (IPNB) occupying the right lobe of the liver. Extended right lobectomy was performed. Based on the pathological findings, the tumor was diagnosed to be an oncocytic-type IPNB with minimal invasion. This experience suggests that the progression of IPNBs occur relatively slowly. The present case might provide important information for understanding the natural history of IPNBs.

Key words: intraductal papillary neoplasm of the bile duct, IPNB, natural history, prognosis

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Introduction

The term 'intraductal papillary neoplasms of the bile duct' (IPNBs) was originally used by Chen et al. in 2001 to describe hepatolithiasis-associated biliary tumors, which shared pathological features with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas (1). The 2019 World Health Organization (WHO) classification stated that IPNBs are pathologically characterized by dilated bile ducts filled with non-invasive papillary or villous neoplasms, which cover delicate fibrovascular stalks (2). However, there are some discrepancies among the previous reports about IPNBs with regard to the tumor site, the frequency of excess mucus production, and the incidence of associated invasive malignancies and their prognosis. These differences were

caused by confusion concerning the pathological features of IPNBs. In addition, the natural history of IPNBs, including their progression to malignancy, is still poorly understood. There have been few reports about patients with IPNBs who underwent long-term follow-up without any treatment. We herein report a case, in which an IPNB was surgically resected after being observed for 12 years.

Case Report

A 66-year-old Japanese man was referred to our hospital with multiple giant liver cysts. He exhibited tenderness in his epigastrium, and his enlarged liver could be touched at the right upper abdomen. Laboratory tests showed mildly elevated C-peptide immunoreactivity (CRP) levels (CRP: 5.88 mg/dL), and elevated biliary enzyme levels (γ -GTP: 78

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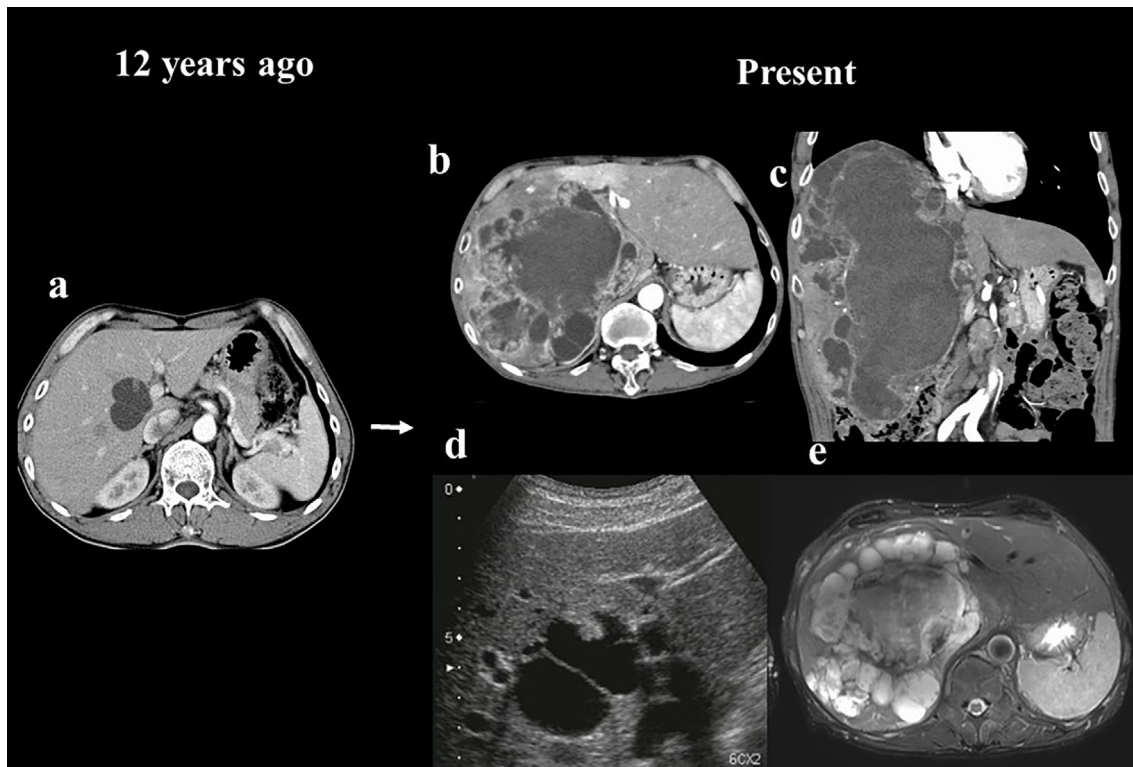


Figure 1. Image findings of the tumor. (a) Twelve years prior to this presentation, a CT scan showed 3 cm multiple cysts with an enhanced small nodule at the right hepatic lobe. (b) A CT scan (axial view) showed multilocular cysts with enhanced nodules. (c) A CT scan (coronal view) showed a massive multilocular cystic tumor occupying the entire right lobe of the liver. (d) A multilocular cyst was also observed by ultrasound, and a nodule was found inside. (e) MRI also suggested the presence of multiple cysts with papillary nodules. However, the lumen was not clear due to mucus.

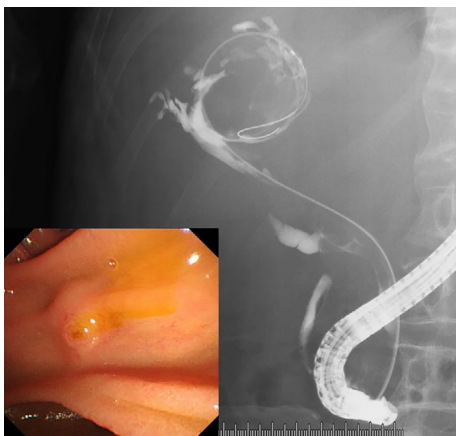


Figure 2. ERC findings. In endoscopic retrograde cholangiopancreatography, mucus flowed out of the duodenal papilla. Because of the mucus in the bile duct, there was little information available on the bile duct. ERC: endoscopic retrograde cholangiography

U/L, ALP: 571 U/L). His bilirubin level was normal. The tumor markers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and alpha-fetoprotein (AFP), were within the normal ranges. No blood count abnormalities were detected. He had smoked half a pack of cigarettes per day for 46 years, but had never drunk alcohol.

Twelve years prior to this presentation, a cystic liver tumor had been detected during a medical check-up at another hospital. A computed tomography (CT) scan showed multiple 3-cm cysts with small contrast-enhanced nodules in the right hepatic lobe (Fig. 1a). Although careful observation was recommended, the patient stopped going to the hospital of his own will. Twelve years later, he visited the hospital because of tenderness in his epigastrium and was referred to our hospital with multiple giant liver cysts. A CT scan demonstrated massive multilocular cysts with contrast-enhanced nodules occupying the entire right lobe of the liver (Fig. 1b, c). Abdominal ultrasonography (US) and magnetic resonance imaging (MRI) also revealed multiple cysts with multiple papillary nodules (Fig. 1d, e). No metastasis or vascular invasion was suspected based on these imaging examinations. Then, endoscopic retrograde cholangiography (ERC) was performed. The extrusion of mucus from the duodenal papilla was observed. ERC showed a filling defect in the common bile duct, which was suspected to have been caused by mucus (Fig. 2). Evaluating the intrahepatic bile ducts was difficult due to the large amount of mucus present. There was no tumor invasion into the common bile duct. Although the bile juice cytology findings were not conclusive, the cysts were diagnosed to be an IPNBs occupying the right lobe of the liver. Extended right lobectomy was performed. A macroscopic examination of the resected

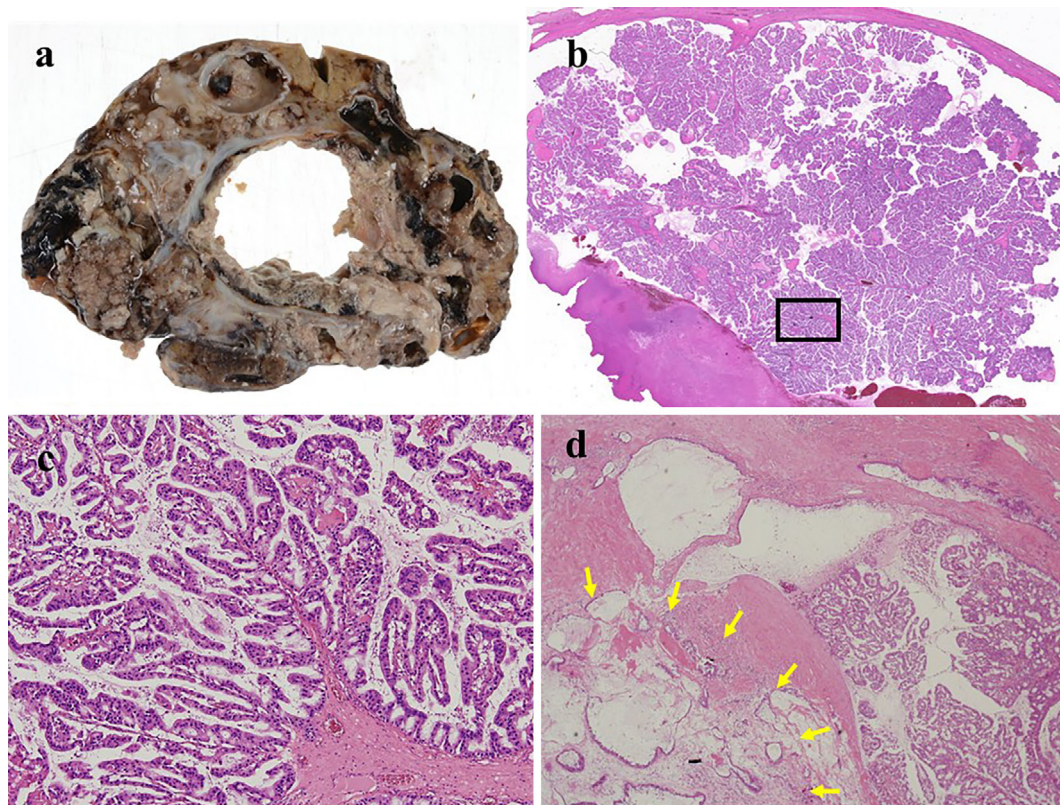


Figure 3. Pathological diagnosis. (a) Macroscopically, the cystic lesions with necrotic and mucus pools inside were identified. A tumor growing in a papillary shape was observed toward the lumen inside. (b, c) Histologically, the tumor cells showed well organized papillary growth with thin fibrovascular stalks. This finding was consistent with the findings characteristic of IPNB. (d) Microinvasion was detected within 10 mm (yellow arrows). IPNB: intraductal papillary neoplasms of the bile duct

specimen revealed that the resected liver was markedly enlarged, and multiple cystic lesions were confirmed (Fig. 3a). A cauliflower-like tumor with multiple cysts was found, and each cyst had formed from an expanded bile duct. The tumor was located in an intrahepatic bile duct, but no obvious tumor was found in the common bile duct. The tumor exhibited a papillary proliferation and had produced excessive amounts of mucus. Histologically, the tumor cells displayed a well-organized papillary growth with thin fibrovascular stalks (Fig. 3b, c). The tumor cells demonstrated a relatively uniform growth pattern. Most of the tumor cells exhibited high-grade dysplasia; however, minimal invasion was noted (Fig. 3d; yellow arrows). On immunohistochemical (IHC) staining, the tumor cells were diffusely positive for MAC5 AC and MUC6, and negative for MAC1, MUC2, CK7, and CK20 (Fig. 4). Based on these pathological findings, we diagnosed the tumor to be an oncocytic-type IPNB with invasive carcinoma. The patient's postoperative course was uneventful. After one year of follow-up, he did not display any signs of recurrence.

Discussion

IPNBs are characterized by dilated intrahepatic bile ducts

filled with a papillary or villous biliary neoplasm that covers delicate fibrovascular stalks (2). Although a number of studies of IPNBs have been conducted, controversy remains, particularly regarding the standardization of the definition of IPNBs. Recently, to resolve the issues associated with the pathological diagnosis of IPNBs, expert Japanese and Korean pathologists have proposed a classification for IPNBs. In this system, Nakamura et al. divided IPNBs into two categories, namely, types 1 and 2 (3). The most representative type 1 IPNB is called "classical IPNB," which commonly arises in the intrahepatic bile ducts, whereas the most representative type 2 IPNB is called "papillary carcinoma or cholangiocarcinoma" and has a more complex histological papillary architecture and typically arises in an extrahepatic bile duct. Type 1 IPNBs are largely composed of low-grade to high-grade dysplasia. On the other hand, most type 2 IPNBs have invasive components and are known to be similar to the non-invasive and minimally invasive papillary carcinoma of the extrahepatic bile ducts reported by Albores-Saavedra et al. (4). According to this classification, the present case was therefore considered to be a typical case of type 1 IPNB.

Based on the histological findings, IPNBs are classified into four subtypes. The present case was diagnosed with

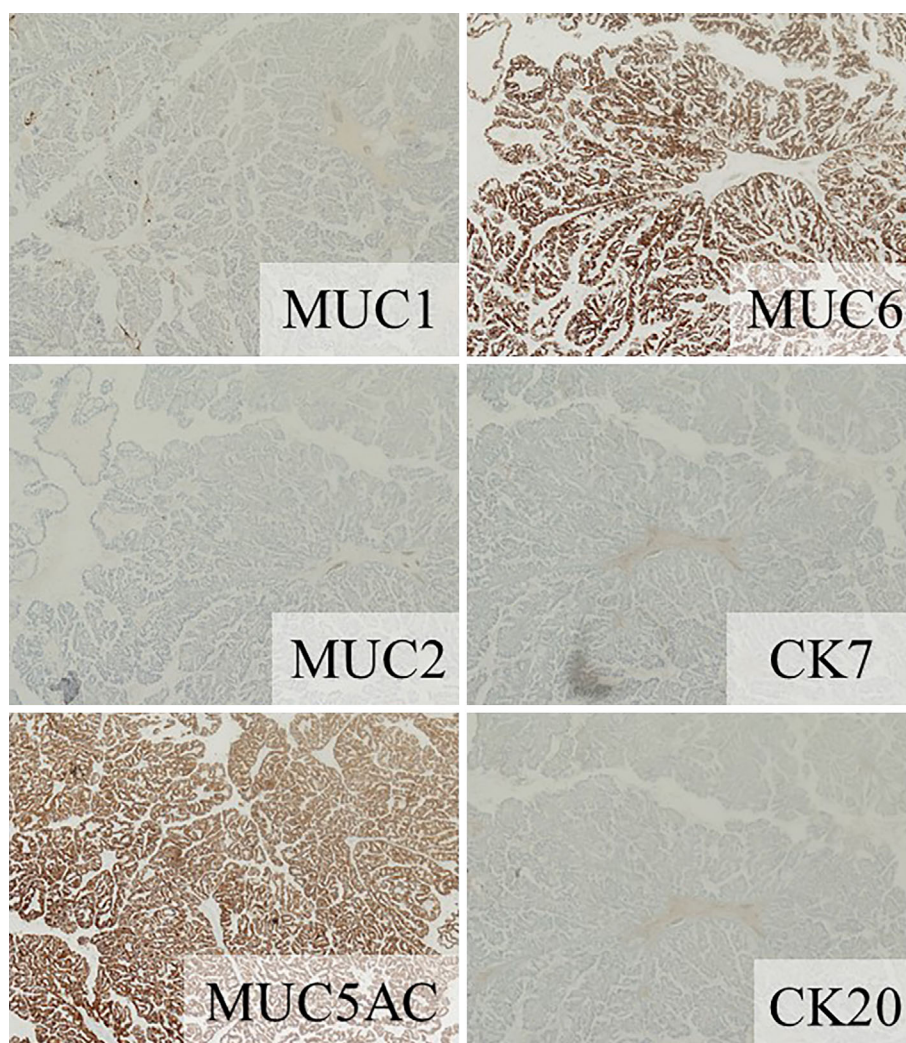


Figure 4. Immunostaining findings. The tumor cells were diffusely positive for MUC5AC and MUC6, but were negative for MUC1, MUC2, CK7 and CK20.

“Oncocytic-type IPNB,” which was considered to be a rare subtype. Nakanuma et al. reported that 11.6% of IPNBs were oncocytic-type, which is the rarest subtype. They described that this subtype usually has complex and arborizing papillae with delicate fibrotic and edematous stroma and the papillae are lined by one to several stratified layers of cuboidal to columnar cells with abundant eosinophilic granular cytoplasm and occasional hyaline globules with high-grade dysplasia. The nuclei are hyperchromatic, round, large and fairly uniform and typically contain a single and prominent nucleolus (5). The present case is considered to be valuable because the prognosis of oncocytic-type IPNB is still not well known.

Fujikura K et al. investigated the clinicopathological features, including the IHC staining patterns, of IPNBs and compared them with those of papillary cholangiocarcinomas. The IPNBs and papillary cholangiocarcinomas were comparable to type 1 and 2 IPNBs, respectively. Marked differences in IHC staining were seen between IPNBs and cholangiocarcinomas. The expression of MUC1 and CK20 was less common in IPNBs than in cholangiocarcinomas. On the other hand, MUC2 and MUC6 were often found in IPNBs,

while they were only rarely detected in papillary cholangiocarcinomas (6). Our case was clearly positive for MUC6, while IHC staining for both MUC1 and CK20 produced negative results. These immunostaining findings also indicate that our case was a type 1 IPNB.

Previously, *GNAS*, *KRAS*, and *RNF53* mutations have been identified in IPNBs (6-8). Fujikura et al. performed whole-exome sequencing and showed that *APC* or *CTNNB1* gene mutations were found in IPNBs, but not papillary cholangiocarcinomas, thus indicating that type 1 and type 2 IPNBs are both morphologically and genetically distinct diseases (9).

Most type 1 IPNBs are surgically resected because of their malignant potential. Hence, there are few reports about the natural course of type 1 IPNBs. Yamada et al. reported that they performed surgery after observing a mucin-producing IPNB, for 6 years (10). With regard to the prognosis, type 1 IPNBs have markedly better prognoses than type 2 IPNBs. Even the postoperative prognosis of invasive type 1 IPNBs tends to be better than that of type 2 IPNBs (11). In the present case, only minimal invasion was observed, even though the tumor was large. This experience

suggests that the progression of type 1 IPNBs occurs relatively slowly; thus, follow-up observation could be an option, especially for elderly patients with comorbidities.

In conclusion, we herein described a case in which a type 1 IPNB was surgically resected after being observed for 12 years. The present case might provide important information for understanding the natural history of IPNBs, which are slowly progressing tumors.

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

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