

## Case Report

# Intrahepatic biliary papillomatosis associated with malignant transformation: report of two cases and review of the literature

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**Abstract:** Biliary papillomatosis (BP) is a rare disease characterized by multiple numerous papillary adenomas in both the intrahepatic and extrahepatic biliary tree. Due to its high recurrence rate and frequent transformation to malignancy, BP should not be considered a benign disease, and a radical resection with an adequate resection margin is advocated in cases of localized intrahepatic biliary papillomatosis. Since BP is a rare disease and its clinical features and outcomes are not well known, it's really difficult to diagnose the disease before operation. We encountered two cases diagnosed as intrahepatic biliary papillomatosis postoperatively, and herein present the diagnostic difficulties and therapeutic options for this rare disease.

**Keywords:** Biliary papillomatosis, cholangiocarcinoma, malignant transformation

## Introduction

Biliary papillomatosis (BP) is a very rare disease that is characterized by multiple papillary adenomas of the intra and extrahepatic biliary tree [1, 2]. In the past BP was considered to be a disease with low malignant potential. However, a current review of the English literature revealed a high rate of malignant transformation occurrence (approximately 41%) [3, 4]. The definitive cause and pathogenesis of this unusual lesion remain unknown and preoperative diagnosis is usually difficult. Here we report two cases of intrahepatic BP, and our data support the viewpoint that BP is a neoplasm with high malignant potential. Meanwhile, a discussion of the clinical manifestations, diagnostic modalities and therapeutic management of the disease is presented.

## Case presentation

### Case 1

A 45-year-old woman was admitted to our surgical department with a history of right upper

quadrant abdominal pain, nausea and weight loss experienced over a period of five months. Physical examination found no jaundice and revealed a mildly tenderness at the right upper quadrant of the abdomen without other abnormal signs. Laboratory test results showed a roughly normal liver function except for mildly elevated gamma glutamyltransferase (131 IU/L) and alkaline phosphatase (124 IU/L) levels. Serum alpha-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9 levels were within the normal range. Hepatitis B and C were negative. Abdominal ultrasonography demonstrated cholecystolithiasis and dilatation of the left intrahepatic duct without the presence of space-occupying lesions. Computerized tomography (CT) scan revealed vague lesions in the left lobe of the liver associated with intrahepatic ductal dilatation (**Figure 1**). Cholangiocarcinoma was highly suspected. Subsequently, the patient underwent exploratory laparotomy. The size and appearance of the liver were found to be normal and the diameter of the common bile duct (CBD) was 1.0 cm. No stone or tumor was found in CBD except cholecystolithiasis. After opening up the left hepatic duct at the



**Figure 1.** Computed tomography scan revealed vague lesions in the left lobe of the liver associated with intrahepatic ductal dilatation.

confluence of the hepatic ducts, a mass of gray sloughed-like tumor debris and mucus was vacated from the intrahepatic duct. Then intraoperative cholangioscopy was performed, which revealed a dilated left intrahepatic duct associated with proliferative lesions extending to the distal biliary tract. The right intrahepatic bile duct and common hepatic duct were found to be normal and had no tumor or stone. Intrahepatic BP was diagnosed on frozen sections of tumor debris and a left hemi-hepatectomy and cholecystectomy were carried out. All resection margins were proved to be clear and normal (**Figure 2**). The postoperative course was uneventful and the patient recovered well. However, the routine histopathological examination revealed a local well-differentiated adenocarcinoma of the left intrahepatic duct in the background of BP (**Figure 3**). The patient refused any further therapy and was discharged on the tenth postoperative day. Upon follow-up, the patient was asymptomatic and in good physical condition. No signs of recurrence or tumor metastasis have been observed at the time of writing (12 months after operation).

#### Case 2

A 58-year-old woman was presented to us in 2014 with a history of vague upper abdominal pain for 7 years. Physical examination and labo-

ratory studies were noncontributory. Abdominal ultrasound and CT scan revealed multiple space-occupying lesions in the left intrahepatic bile duct. Calculus of intrahepatic bile duct was suspected. Upon surgical exploration the liver was found to be sclerotic with mixed macronodular and micronodular cirrhosis. Choledochectasia was not obvious. The subsequent exploration of CBD revealed a 0.5 cm papillomatous lesion at the site of the left hepatic duct and some pale tumor debris associated with mucus bile was discharged from the left intrahepatic ducts. Frozen section examination of lesion showed a low grade malignant tumor. A left hepatectomy and cholecystectomy were

performed successfully. The postoperative histopathological analysis revealed papillomatosis in the left hepatic duct and the intrahepatic biliary duct. No malignant transformation was observed. The patient recovered well and was discharged 12 days after the operation. Later she did not visit the outpatient clinic and follow-up data was lost.

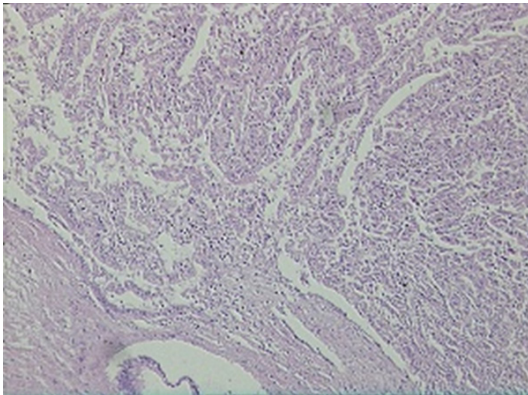
#### Discussion

The first case of BP was reported by Chappet in 1894 [5]. In 1959, Caroli gave the first detailed anatomic description of this rare pathologic condition. Up till now, approximately 200 cases have been published in the literature worldwide [6]. To our knowledge, no more than 20 cases have been reported in the mainland of China. Since it is often misdiagnosed as biliary stones or cholangiocarcinoma, the true incidence of this disorder is perhaps underestimated. BP is characterized by the presence of intraluminal papillary tumors of the intra- and/or extrahepatic bile ducts. It can arise from any site of the biliary tree, including the gall bladder arose from the extrahepatic ducts alone in 58% of the cases, both extra and intrahepatic ducts in 33% and intrahepatic ducts alone in 9% of the cases [7].

BP is classified as either mucin-hypersecreting type (MBP) or nonmucin-producing type (NM-



**Figure 2.** Surgical specimen of removed liver.



**Figure 3.** Histopathological examination showed a local well-differentiated adenocarcinoma in the background of BP (hematoxylin and eosin, original magnification,  $\times 100$ ).

BP), both MBP and NMBP show very similar macroscopic and microscopic findings. According to the degree of cytological and structural atypia, BP could be further classified into 5 classes: class 1 is defined as BP with low-grade dysplasia, showing mild nuclear atypia and no invasion; class 2 is BP with high-grade dysplasia, showing moderate nuclear atypia; class 3 as BP with carcinoma in situ (CIS); class 4 as CIS with microscopic foci of stromal invasion; and class 5 is defined as definite invasion into the hepatic parenchyma or a fibromuscular layer of the bile duct wall. The most advanced type was used for final classification when a lesion showed mixed types of BP. Class 1 and Class 2 were considered as benign adenoma while the other classes were regarded as adenocarcinoma.

BP is more common in men in the sixth to seventh decade of their life, the male/female ratio is 2:1 [3, 8]. The definite etiology and pathogenesis have not been well recognized. Recurrent

pyogenic cholangitis, congenital choledochal cysts, clonorchis infestation and chronic irritation by lithiasis, infection or pancreatic juice are considered to be possible factors that result in chronic biliary injury and papillary proliferation of the bile duct columnar epithelium cell [3, 9, 10].

The most common clinical manifestations are recurrent abdominal pain, repeated relapsing cholangitis with fever and jaundice due to intermittent and repeated obstruction caused by mucus secretion, enlarging papilloma or tumor fragments, which ultimately leads to biliary cirrhosis and death from hepatic failure [11]. Preoperative diagnosis is usually difficult. One of the greatest research on BP found that the level of CA 19-9 antigen was elevated in 40% of the subjects, and the mean level was much higher in MBP patients as compared to NMBP patients. Quite a few patients showed bile duct dilatation with cystic changes in intrahepatic bile duct. With recent developments in diagnostic technology, multiple modalities such as abdominal CT, ERCP, magnetic resonance cholangiopancreatogram, cholangioscopy and cholangiography have been used for clinical diagnosis of BP, but no special diagnostic or radiologic features has been described. ERCP might be a very useful diagnostic modality which has the additional advantage of obtaining tissue for histological analysis. The final diagnosis must be confirmed by histopathological examination.

In the past BP was regarded as a benign disease with low malignant potential. However, Lee SS reported that 48 (83%) out of 58 patients were diagnosed with BP that revealed papillary carcinoma (42 patients with adenocarcinoma and 6 patients with mucinous carcinoma) on cholangioscopic biopsy or surgically resected specimens. Then he proposed that BP should be considered as a premalignant disease with high malignant potential [4]. In the present study, the first patient also showed a localized malignant transformation. The treatment of BP is often controversial because of the associated high recurrence rate of local disease and frequent transformation to malignancy. Its multicentricity and diffuse nature explain the high recurrence rate after surgical resection of the underlying lesion. When the lesions are localized and the patient is able to tolerate major surgery, radical resection with an ade-



quate resection margin is advocated. During the operation, a combination of cholangioscopy and frozen sections is beneficial for a radical surgical resection. Although this procedure does not guarantee freedom from recurrence, it has proved to be efficient in prolonging the long-term survival of patients. In our current two cases, papillomatosis was predominantly localized in the left intrahepatic duct and left hepatectomy was carried out with a clear resection margin. For patients with diffused BP, liver transplantation represents the only potential curative hope. Dumortier J was the first to report a patient with BP treated with orthotopic liver transplantation [12]. In patients with superficial foci of malignancy or the whole biliary tree with high malignant potentiality and without a positive lymph node metastasis, liver transplantation could overcome the difficulty in BP treatment. So far, approximately 10 cases have been reported to be treated with liver transplantation. Patients recovered well and had no evidence of recurrence, degeneration and metastasis [13]. BP might become a new indication for liver transplantation. Since the extrahepatic biliary ducts are only partially removed in liver transplantation, a combination of liver transplantation with a Whipple operation probably represents the most effective treatment strategy for diffuse lesions. However, right now in China, liver transplantation is often restricted by donor shortage and high medical costs and radical surgical resection still remains the mainstay of therapeutic options for patients with BP. Due to insufficient knowledge about its clinical outcome and prognosis, an intensive long-term follow-up is strongly recommended.

### Conclusion

BP should be considered a premalignant disease with high malignant potential. Although preoperative diagnosis is difficult, elderly patients with biliary obstruction and a history of abdominal pain should be suspicious of this rare disease. Radical surgery is recommended considering the risk of malignant transformation and diffuse pattern of the disease, and this is the only treatment to achieve long-term survival. In patients with diffused lesions but without lymph node metastasis, liver transplantation is advocated to prolong survival.

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### Disclosure of conflict of interest

None.

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