Letter

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A case of hilar biliary cystadenoma with elevated IgG4 levels

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SUMMARY Cholangiocytic adenoma in the hilar bile duct is rare, and elevated IgG4 at the same time is extremely rare. This situation has not been reported in the literature. Nonetheless, the current case involved hilar biliary cystadenoma with elevated IgG4 levels. A 66-year-old man presented at this hospital with dark tea-colored urine. Preoperative imaging studies suggested hilar cholangiocarcinoma. This case demonstrates the difficulty of preoperative diagnosis of benign hilar lesions and the rarity of two combined benign lesions. A point of contention is whether this case should be treated with surgery or hormone therapy.

Keywords biliary cystadenoma, hilar cholangiocarcinoma, IgG4, immunoglobulin G4-related cholangitis, jaundice

Biliary cystadenoma is a rare benign cystic lesion of the liver originating from the bile duct epithelium, and it accounts for less than 5% of all hepatic cystic lesions (*1*). Its pathogenesis is still unclear; its congenital cause may be related to the abnormal development of the vagus bile duct in the embryonic stage (*2*), and its acquired causes are mainly related to liver cirrhosis and oral contraceptives (*3*). The symptoms of this disease are mostly atypical, and they often differ substantially depending on the location and size of the tumor. Moreover, there are no effective serological tumor markers. For special types of bile duct cystadenomas, the clinical features may even overlap with those of hilar cholangiocarcinoma and IgG4-related sclerosing cholangitis, which can easily lead to misdiagnosis. Here, a case of hilar bile duct cystadenoma with elevated IgG4 is reported to improve the understanding of this disease.

A 66-year-old man visited a local hospital in September 2019 due to "dark tea-colored urine for longer than a month." Imaging studies suggested hilar cholangiocarcinoma, and inflammatory lesions were not excluded. Total bilirubin was 96.1 umol/L, direct bilirubin was 67.8 umol/L, autoimmune-related antibodies were negative, and the serological tumor markers AFP, CA199, and CA125 were within the normal range. In July 2020, total bilirubin was 76.0 umol/L, and direct bilirubin was 44.1 umol/L. Afterwards, ERCP was performed and a common bile duct stent was placed. Biliary cytology pathology: (hilar bile duct) a small number of atypical glandular cells, no typical cancer cells. The patient visited this hospital in August, and bilirubin and serological tumor markers were checked as before. CT, MRI, and MRCP revealed stent shadows in the lumen of the common hepatic duct. The hepatic hilum ended abruptly, the left and right hepatic ducts were separated, the bile duct wall had thickened, and suspicious soft tissue masses were evident in the hepatic hilar region (Figure 1A).

Imaging studies could not rule out hilar cholangiocarcinoma. Autoimmune-related cholangitis was considered, but the serum IgG4 level was 1.670 g/L (Figure 1C), and imaging studies revealed no other organ lesions. A left hepatectomy with caudate lobe resection was performed on August 21, 2020. A postoperative histopathological examination revealed biliary cystadenoma and negativity for IgG4 (Figure 1B). The patient was discharged 14 days after surgery, and further testing revealed that IgG4 had returned to normal (Figure 1C).

Hilar bile duct cystadenoma and elevated IgG4 is a rare condition, and it has not been reported previously. Ghazale *et al*. reported that one-third of patients preoperatively diagnosed with hilar cholangiocarcinoma were diagnosed with IgG4-related cholangitis after surgery (*4*). At present, there are no accurate diagnostic criteria for IgG4-related cholangitis and obtaining a pathological diagnosis via a biopsy is difficult, causing a delay in diagnosis. The serum IgG4 level has certain limitations as a diagnostic criterion because some patients with IgG4-related cholangitis have only a slight increase (between 1 and 4 times the normal value); moreover, up to 15% of patients with cholangiocarcinoma also have elevated serum levels of IgG4 (*5*). According to the diagnostic criteria for

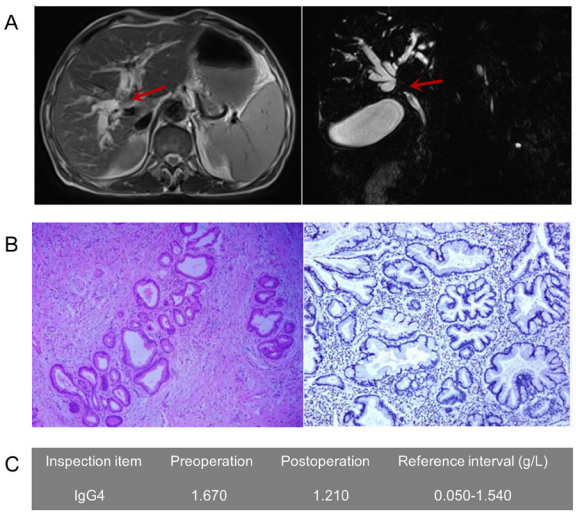

Figure 1. (A), MRI and MRCP showing the confluence of the left and right hepatic ducts and a left bile duct mass; (B), Postoperative pathology showing the dilated bile ducts and negativity for IgG4; (C), Level of IgG4 pre- and post-operatively.

IgG4-related cholangitis devised in Japan in 2012 (*6.7*): (*i*) characteristic changes in biliary imaging; (*ii*) serum IgG4 levels higher than the normal upper limit (≥1.35 g/L); (*iii*) lesions in other organs as well; and (*iv*) histopathological characteristics: ① infiltration of landmark lymphocytes or plasma cells; ② infiltration of IgG4-positive plasma cells (>10 IgG4-positive plasma cells per high-power field); ③ spoke-shaped fibrosis; and ④ obliterative phlebitis.

The current case involved a slight increase in serum IgG4, a histology revealing no infiltration of IgG4-positive cells, and no diffuse intrahepatic bile duct lesions. The lesions overlapped cystadenoma lesions, and both were located in the hilar bile duct. The postoperative decrease in IgG4 to normal is also a feature of this case that deserves attention. However, a postoperative pathological examination of the cystadenomas did not suggest that IgG4 was elevated in diseased tissue, indicating that this case may have little relationship to IgG4. Postoperatively, IgG4 decreased below the normal level, which may be related to the resection of the lesion and bile drainage. The local inflammatory reaction subsided, and it needs to be reviewed regularly after surgery. Previous studies have reported that slight elevation of IgG4 may occur in bile duct inflammation and bile duct malignancies (*2,6*), and this clinical feature was also evident in the current case. Imaging revealed no lesions in the pancreas, which is the most frequently infiltrated organ in IgG4-related cholangitis, or other organs, so a histological biopsy was not clinically indicated. The malignant transformation rate of intrahepatic bile duct cystadenoma is about 30% (*8*), and it is considered to be a precancerous lesion, so once it is found, it needs to be treated. Hilar invasion should be treated with gallbladder and extrahepatic bile duct resection. Even after local resection, extrahepatic bile duct cystadenoma still has a recurrence rate of 50%, and the tumor should be completely resected to achieve a negative resection margin before performing cholangioenterostomy (*9*).

In summary, hormone therapy is the treatment of choice for isolated IgG4-related cholangitis (*10,11*). When cystadenoma is also present, however, whether hormone therapy will delay or accelerate the malignant transformation of the cystadenoma is unclear. As corroborated by the literature, our center considers cystadenoma to be a precancerous lesion. Hilar cholangiocarcinoma could not be ruled out before surgery, so surgical resection was performed in the current case. This strategy warrants discussion, and it needs to be studied in large-scale studies with a follow-up.

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