Puzzle and Challenge in Differentiating Immunoglobulin G4-related Cholangitis from Hilar Cholangiocarcinoma

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Immunoglobulin G4 (IgG4)-related cholangitis (IAC) is one of the IgG4-related immune-mediated diseases. Although a study has provided a preliminary insight into its pathological mechanisms, the specific pathogenesis is unknown and the incidence of IAC remains unclear.[1]

Under normal conditions, IAC is often misdiagnosed as cholangiocarcinoma because these two diseases share almost the same clinical features. Importantly, IAC is a benign disease that can be treated by steroids, while hilar cholangiocarcinoma is a malignant disease that requires curative surgery. Research has revealed cases of misdiagnosis of IAC with biliary carcinoma who underwent unnecessary invasive surgery.[2] Thus, currently, it is a challenge to differentiate IAC accurately from carcinomas preoperatively and choose the appropriate treatment.

In terms of clinical manifestation and imaging, hepatic portal-occupying lesions tend to be biliary duct malignancies. For IAC, the main clinical symptom is obstructive jaundice, and magnetic resonance cholangiopancreatography (MRCP) shows bile duct narrowing or occupation accompanied by bile duct wall thickening. Thus, it is difficult to discriminate IAC from biliary duct malignancy merely from clinical manifestation and preoperative MRCP findings because of the low clinical specificity and occasionally elevated tumor markers.

According to the HISOR (Histology, Imaging, Serology,Other organ involvement, Response to therapy) classification,[1] IAC is always associated with elevated serum IgG4 levels and the involvement of organs, such as the pancreas, lacrimal, or salivary glands. In addition, the obstructive jaundice of IAC may disappear after glucocorticoid treatment, while biliary duct malignancies do not respond to steroids.[3] Final pathological diagnosis is the gold standard for diagnosing IAC, which is characterized as dense lymphoplasmacytic infiltration, marked increase of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. However, the above diagnostic criterion cannot be applicable to all the IAC patients, causing diagnostic difficulties.

We encountered a case of an IAC patient misdiagnosed as hilar cholangiocarcinoma who nearly underwent curative surgery. A 59-year-old woman presented with laboratory data comprising carcinoembryonic antigen, 5.13 ng/ml; carbohydrate antigen 19-9 (CA19-9), 149.90 U/ml; serum IgG4, 3.21 g/L; and total bilirubin, 354.90 μmol/L. MRCP showed a mass-occupying lesion in the hilar bifurcation, combined with proximal bile duct dilatation [Figure 1a]. Initially, hilar cholangiocarcinoma was suspected and IAC was retained as a differential diagnosis. Percutaneous transhepatic cholangial drainage was performed to relieve jaundice. During this period, steroid treatment was conducted in accordance with the standard treatment of IAC, with the initial prednisolone dosage of 30 mg/d for the first 4 weeks and was gradually tapered by 5 mg/d every 2 weeks. After 2 months, tumor markers, serum IgG4 level, and bilirubin levels were within the normal range. MRCP showed no specific stricture of the bile duct [Figure 1b]. She continued the maintenance steroids for 1 year and followed up for 18 months, during

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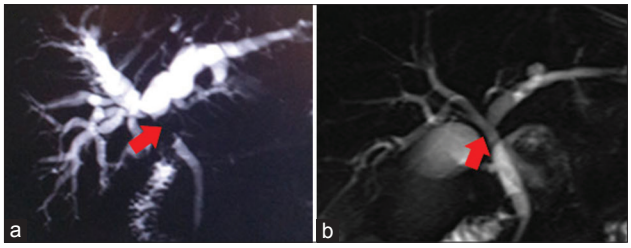

Figure 1: Representative images of the patient. (a) Magnetic resonance cholangiopancreatography showing a mass-occupying lesion in the hilar bifurcation, combined with the proximal bile duct dilatation (arrow); (b) magnetic resonance cholangiopancreatography showing that there was no specific stricture of bile duct after the steroid treatment (arrow).

which time the bile duct obstruction was completely relieved, without any indications of tumor involvement. This case provided an example that elaborated the problem in differentiating malignant and benign biliary stenosis to avoid unnecessary surgery. Further effort is needed to better fulfill this identification system and improve the diagnostic accuracy because of the distinct therapeutic strategies.

Although elevated IgG4 levels have certain values in differentiating IAC from hilar cholangiocarcinoma, some problems still exist. Not all IAC patients have elevated IgG4 levels. In addition, some scholars have reported elevated serum IgG4 levels in patients with primary sclerosing cholangitis and other hepatobiliary diseases.[4,5] Consequently, elevation of IgG4 levels can only be considered as an indication for the diagnosis of IAC and cannot be regarded as a reliable factor in certain specific patients. Thus, more sensitive diagnostic tests and multicenter research based on pathogenesis are urgently required.

It was reported that 90% of IAC patients have autoimmune pancreatitis (AIP), which can help to diagnose IAC; however, a diagnosis of AIP is also burdensome and the ultimate diagnosis relies on a biopsy. Moreover, in IAC cases without pancreatic or other organ involvement, just like the one in our series, diagnosis is extremely difficult because IAC mimics the characteristics of cholangiocarcinoma. Therefore, elevated serum IgG4 levels and other organ involvement can only be used as an indicator to identify whether the lesion is IAC or bile duct carcinoma. For cases with high suspicions of IAC, short-term glucocorticoid treatment can be used. Bile duct stenosis or lesions caused by IAC might be relieved by glucocorticoid treatment. If the glucocorticoid treatment is ineffective, endoscopic biopsy or surgical exploration should be performed such that timely surgery for bile duct cancers can be scheduled.

Pathological diagnosis is the most precise criterion to differentiate IAC from bile duct cancers. However, in most cases, endoscopic retrograde cholangiopancreatography (ERCP) is hard to access hepatic portal areas and perform the biopsy makes preoperative histological diagnosis and discrimination of IAC from malignancy difficult. In addition, ERCP can only take a limited tissue sample that might not be sufficient for histopathological evaluation. Furthermore, endoscopic biopsy might also result in tumor seeding. Therefore, it is difficult to discriminate the two diseases by using endoscopic biopsy for its' own limitations; in this current study, we did not adopt the endoscopic biopsy. However, with the progress in molecular biology and endoscopic technology, a breakthrough is expected to be made in the preoperative identification of IAC and tumors, which will guide subsequent treatment in the future.

In summary, precise diagnosis of IAC without other organ involvement is still difficult. The elevation of IgG4 levels can only be considered as an indication of IAC. This paper aimed to enhance awareness of IAC in the context of hepatobiliary surgery, especially in female patients. Not all patients with obstructive jaundice have carcinomas. In cases highly suspected of IAC, short-term treatment with glucocorticoids can be adopted. If the glucocorticoid treatment is ineffective and endoscopic biopsy is difficult, surgical exploration and intraoperative frozen sections should be taken to determine whether curative surgery is required. More importantly, multicenter studies based on the mechanisms of IAC are required. Further developments in molecular biology and endoscopic technology are expected to prevent misdiagnosis and the risk of unnecessary surgery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient/patient's guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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