Case Report
Primary hepatic follicular lymphoma: a case report and literature review

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Abstract: Background: Extranodal lymphomas commonly occur in the spleen, but the likelihood of primary hepatic lymphomas is low. As such, studies on the diagnosis and treatment of primary hepatic follicular lymphoma are limited. Case presentation: Two liver space-occupying lesions were found in a 53-year-old female patient through magnetic resonance imaging (MRI). This patient was preoperatively diagnosed with a malignant tumor of the liver without a liver biopsy. The patient underwent a hepatectomy, a cholecystectomy, and microwave ablation. A definitive diagnosis of follicular lymphoma was confirmed by the pathological examination. Postoperative rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were administered. The patient survived without a recurrence of the tumor during the two years of follow-up. Conclusions: Primary hepatic follicular lymphoma is a rare malignant tumor of the liver. Surgical resection of the lesions followed by adjuvant chemotherapy might prevent recurrence in cases of hepatic follicular lymphoma.

Keywords: Primary hepatic lymphoma, follicular lymphoma, operation, chemotherapy

Introduction
Liver tumors are common, but the likelihood of hepatic lymphoma—including primary hepatic lymphoma (PHL) and secondary hepatic lymphoma—is low. Most hepatic lymphoma patients have secondary hepatic lymphoma due to the systemic spreading of the disease. Most extranodal lymphomas occur in the spleen. PHL is an extremely rare disease, but primary hepatic follicular lymphoma (FL) is even rarer due to its multiple classifications. The definitive diagnosis of hepatic FL requires a histopathological evaluation. Studies on the diagnosis and treatment of primary hepatic FL are rare. Herein, we describe a case of primary hepatic FL with two nodules in the liver.

Case presentation
A 53-year-old female patient with no history of hepatitis B- or C-virus infection complained of occasional right upper abdominal pain and eczema on her extremities. Biochemical tests confirmed that the levels of total bilirubin, direct bilirubin, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase were in the normal range. In addition, a decline in white blood cells (2.67 G/L) and lymphocytes (0.69 G/L) were discovered by a routine blood examination. No abnormal increase in the levels of known tumor markers was evident. Magnetic resonance imaging (MRI) scans revealed the presence of two round liver masses of varying sizes. The largest lesion was approximately 3.6 cm × 3.4 cm in size and located in the left inside lobe. All the lesions were hypointense on the T1-weighted images and hyperintense on the T2-weighted MRI images. The intrahepatic lesions showed marked diffusion limitations in the diffusion-weighted images and the apparent diffusion coefficients declined in the lesions. Ring-shaped enhancements were found in response to contrast agents. In the hepatobiliary phase of gadoxetic acid-enhanced MRI, the lesions were mainly hypointense (Figure 1). Systemic PET-CT examinations showed no suspicious tumor lesions other than in the liver. This patient was preoperatively diagnosed with
a malignant liver tumor. The patient underwent a hepatectomy, a cholecystectomy, and microwave ablation but did not undergo a preoperative biopsy. The patient received postoperative rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

**Pathological findings**

The mass was tough, the sections were gray (Figure 2A), and the gallbladder was infiltrated (Figure 2C). A definitive diagnosis of follicular lymphoma was confirmed by postoperative pathological examination (Figure 2B) and positive CD20, CD21, CD10, HGAL, BCL-2, BCL-6 and Ki-67 (low proliferation, LI: 5%) staining (Figure 3). The patient belonged to Ann Arbor stage IV and had an intermediate-risk prognosis according to the international prognostic index scoring system [1]. Consequently, the patient was postoperatively diagnosed with FL (Grade 1). The patient survived without any recurrence of the tumor during the two years of follow-up.

**Discussion**

Extranodal non-Hodgkin lymphomas (NHL) in the spleen and PHL account for less than 1% of cases [2]. Follicular lymphoma is the most common inactive lymphoma in Europe and the United States, accounting for ~20% to 30% of NHL incidence. Asia, including China, has a low incidence of NHL (less than 10%). Primary hepatic FL is thus extremely rare. PHL lesions are confined to the liver without invasion and metastasis from other locations [3]. It has been reported that hepatitis B- or hepatitis C-virus infections are related to the occurrence of hepatic lymphoma [4, 5]. The majority of PHL patients complain of abdominal pain and are diagnosed during imaging. However, the clinical presentation of PHL is often non-specific. When the volume and lesion number increase, the space-occupying effect increases tension in the liver capsules leading to abdominal pain. When the main vascular system of the liver is compressed, abnormal liver function results, leading to systemic fatigue, a loss of appetite and nausea. When liver enlargement is obvious, it is sufficiently enlarged to be touched under the ribs. When the main bile duct is compressed and blocked by a mass, the skin and sclera turn yellow. Eczema in the patient is also associated with immune dysfunction and tumor development. During the active stage of non-Hodgkin’s lymphoma, blood sedimentation and lactate dehydrogenase levels increase, suggesting a poor prognosis. Intrahepatic space-occupying lesions or diffuse infiltration are the most common radiological findings. These features resemble other intrahepatic neoplasms, including liver metastases. These characteristics on MRI scans, including hypointense T1-weighted images, and hyperintense T2-weighted images, non-specific dynamic enhancement after contrast agent administration, diffusion limitation in diffusion-weighted imaging and hypointensity in the hepatobiliary phase of gadoxetic acid-enhanced MRI.
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may help to differentiate PHL from other hepatic malignant lesions. However, the definitive diagnosis of follicular lymphoma still requires a histopathologic evaluation [6]. Consequently, pathological examinations and immunohistochemistry remain the standard methods of diagnosis for lymphoma and treatment guidance.

FL is a type of indolent B cell lymphoma, originating from follicular center B-cells [1]. FL is highly sensitive to chemotherapy, but complete curative effects are difficult. It is known that the course of FL is both long and repetitive, and conversion to invasive lymphoma can occur [1]. Immunohistochemistry is important for diagnosis and treatment guidance. Rituximab is effective in B cell lymphoma patients with positive CD20 staining [7], but the reactivation of the hepatitis B virus may complicate rituximab chemotherapy [8]. Liver biopsy is not routinely used for the diagnosis of liver lesions as the operation may fail or carry a risk of bleeding and tumor metastasis. However, the correct use of liver biopsies is advocated to confirm the diagnosis of atypical liver lesions in patients with increased serum lactate dehydrogenase and blood sedimentation [3]. There remains no consensus on the timing of surgery and chemotherapy for PHL. Studies have reported that chemotherapy without surgery after liver biopsy, surgical resection with postoperative chemotherapy, and surgical resection with preoperative and postoperative chemotherapy are effective [3, 9, 10]. Early postoperative chemotherapy is recommended to avoid recurrence [11]. Surgical

Figure 2. Pathological findings: (A) Postoperative, gross, tough gray specimens; (B) The histopathological section of the liver mass showing follicular lymphoma (HE × 100); (C) The histopathological section of the gallbladder showing follicular lymphoma infiltrating the gallbladder (HE × 40).

Figure 3. Immunohistochemical staining: Positive CD20 (A), CD21 (B), CD10 (C), BCL-6 (D), BCL-2 (E) and HGAL (F) (× 200).
resection can remove the liver lesions and reduce the tumor burden. Preoperative chemotherapy can reduce the tumor size, allowing surgeons to remove otherwise unresectable tumors [10].

Due to the rarity of PHL, prospective trials and retrospective studies that have compared treatment modalities are difficult to perform in a single center. Consequently, large-scale multicenter prospective cohort studies are required to confirm optimal surgical timing, methods, and chemotherapy for PHL. Nevertheless, this case report of an effective treatment for hepatic lymphoma still holds value.

Conclusion

Primary hepatic FL is an extremely rare hepatic malignant tumor. The surgical resection of lesions followed by adjuvant postoperative chemotherapy might prevent recurrence in patients with hepatic FL.

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Disclosure of conflict of interest

None.

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