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Case Report

Primary hepatic mucosa-associated lymphoid tissue lymphoma: case report and literature review

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Abstract: Background: The prevalence of primary hepatic mucosa-associated lymphoid tissue (MALT) lymphomas is extremely low. Here, we describe a case of this disease misdiagnosed as hepatocellular carcinoma (HCC) and review relevant literature to prevent future misdiagnoses. Case presentation: a 58-year-old woman complained about abdominal pain for more than four months. About two months prior, she came to our hospital with elevated levels of HBV DNA and positive HBsAg and HBcAb. After two months of entecavir treatment, HBV DNA decreased to a normal level. She returned to the hospital with worsened abdominal pain for over a month. Magnetic resonance imaging and systemic positron emission tomography-computed tomography identified two nodes in the liver, and she was diagnosed with HCC. The patient then underwent a laparoscopic hepatectomy. Microscopic examination showed a diffuse infiltrate of small-to-medium-sized lymphocytes and lymphoepithelial lesions. Immunohistochemical staining showed that most of the lymphoid cells were strongly positive for CD20, CD79a, BCL2, IgM and weakly positive for IgD, while negative for CD3, CD10, BCL6, MUM1, CD43, CD5, cyclin D1, CD23, CD30, and PD1. The Ki-67 index of lymphoid cells was 5%. Further pathologic analysis confirmed the diagnosis of primary hepatic MALT lymphoma. The patient received antiviral treatment and recovered well with no sign of relapse for 17 months. Conclusions: Primary hepatic MALT lymphoma is an uncommon disease that is difficult to diagnose and has no widely accepted treatment. Surgical resection is a good choice for both diagnosis and local therapy, and strict follow-up of the patient is essential.

Keywords: Primary hepatic mucosa-associated lymphoid tissue lymphoma, hepatitis B virus, radiological image, misdiagnosis, liver hepatectomy, treatment modality

Introduction

Primary hepatic mucosa-associated lymphoid tissue (MALT) lymphoma, a subtype of hepatic malignant lymphoma, is rarely reported [1, 2]. Due to its unclear etiology and pathogenesis, absence of definite manifestations, and the lack of specific imaging features, the diagnosis of MALT lymphoma is difficult, and the misdiagnosis often happens prior to pathological examination [3]. Herein, we present a case of low-grade primary hepatic MALT lymphoma misdiagnosed as hepatocellular carcinoma (HCC) in a patient with a history of chronic infection with hepatitis B virus (HBV). The patient was treated by laparoscopic resection of the left lateral lobe of the liver and was followed for 17 months without relapse.

Case presentation

A 58-year-old female patient with positive HBsAg and HBcAb, fatty liver, gallstones, and hypertension complained of an on-and-off right upper abdominal dull pain, occasional fatigue, headache, and blurred vision for more than four months. No symptoms of fever, nausea, vomiting, loss of appetite, chest pain, diarrhea, constipation, and weight loss were present. She came to our hospital approximately two months

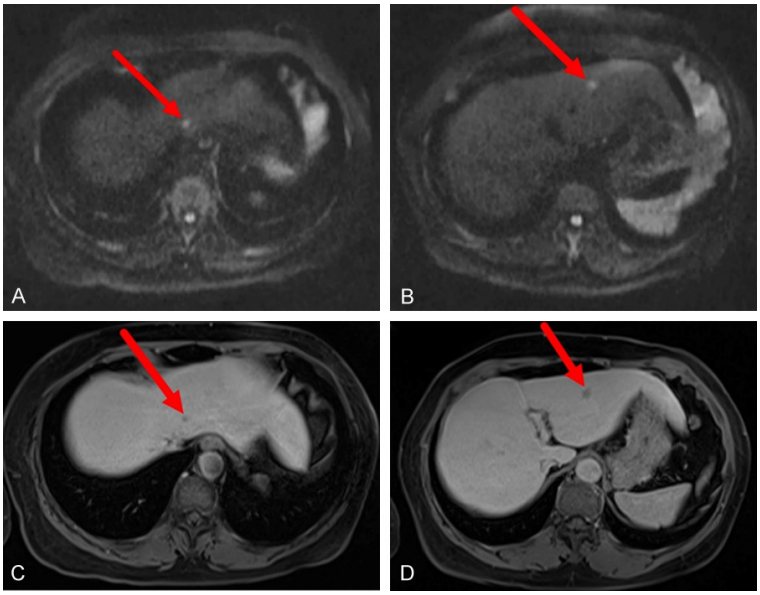

Figure 1. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI). Nodes exhibited low signal intensity in the hepatobiliary phase (A and B) and enhanced signal intensity in the delayed phase (C and D).

prior. Physical examination showed no jaundice, hepatosplenomegaly, or superficial enlarged lymph node, while the routine clinical laboratory values showed slightly increased serum total bilirubin (TBIL), direct bilirubin (DBIL), and HBV DNA. When abdominal ultrasonography was performed, gallstones were detected but without evident space-occupying lesions in the liver. The patient received entecavir treatment for two months, after which the HBV-DNA decreased to a normal level. She returned to our hospital, complaining of a worsened abdominal pain for over one month.

Laboratory test results showed that the complete blood cell count, including white blood cells, lymphocytes, neutrophils, eosinophils, basophils, monocytes, and platelets, was normal. Liver function test showed slightly increased levels of TBIL and DBIL whereas other values, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and albumin, were within the normal range. Tumor biomarkers, including alpha-fetoprotein (AFP), carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA), as well as lactate dehydrogenase (LDH) and C-reactive protein (CRP) were also in the normal range. The detection of autoantibodies for autoimmune hepatitis (AIH), including anti-smooth muscle antibodies (ASMA), anti-liver-kidney microsomal antibody (LKM), and anti-mitochondrial antibody (AMA), yielded negative results, except for weakly positive antinuclear antibodies (ANA).

Abdominal ultrasonography indicated one hypoechoic node, 11 × 9 mm in size, in the left lobe of the liver. The node had an unclear boundary and did not exhibit a blood flow signal. Other parts of liver parenchyma showed thickened echo and unevenly distributed signals. Strong echogenic foci of gallstones were clearly identified. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) revealed one long T1 and long or iso-T2 signal nodule, 10 × 6 mm in size, in the S2 segment of the liver. Diffusion was limited on diffusion-weighted imaging (DWI). The node was enhanced in the arterial phase and portal venous phase, and showed hypo-intensity from the delayed phase to the hepatobiliary phase (**Figure 1A-D**). This node corresponded to the foci found in abdominal ultrasonography and identified as a suspected tiny HCC. Another long T1 and long or iso-T2 signal node with a diameter of approximately 5 mm was found in segment II of the liver and near the second hepatic hilum. DWI showed limited diffusion. The node had suspiciously slight enhancement from the arterial phase to the delayed phase, and showed hypointensity in the hepatobiliary phase (**Figure 1A-D**). A distinction between a tiny HCC and a regenerative nodule based on MRI manifestations was difficult. Chronic liver changes, cirrhosis, cholestasis, and gallstones were also found. No evidence of intrahepatic or extrahepatic biliary duct dilatation or enlarged abdominal lymph nodes was observed. Systemic positron emission tomography/computed tomography (PET/CT) examination identified a small patchy low-density shadow with unclear borders in the S2 segment of the liver. Abnormal radioactivity concentration was not observed, while slight

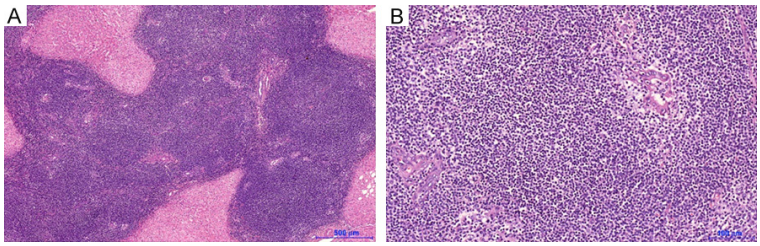

Figure 2. Histologic characteristics of the resected tumors. A. Diffuse lymphomatous infiltration of the hepatic lobule (× 50). B. Small- and medium-sized lymphoid cells infiltrating into the bile duct and forming lymphoepithelial lesions (× 200).

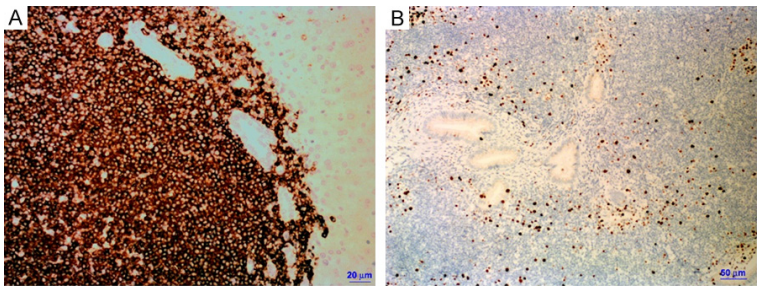

Figure 3. Immunohistochemical staining of the resected tumors. A. Lymphocytes were diffusely positive for CD20 (× 200). B. The fraction of Ki67-labeled cells was 5% (× 100).

concentration was found by delayed imaging with the maximum standardized uptake value (SUV) of 4.3, suggesting the possibility of HCC. Dot-shaped high-density shadow without abnormal radioactivity distribution in the gallbladder was noted, indicating the presence of gallstones. PET/CT imaging did not reveal any apparent changes. There was no enlargement of lymph nodes or spleen and no abnormal radioactivity distribution in bones and other areas, suggesting no secondary malignant lesions from other organs.

Based on the clinical and radiologic examinations, a diagnosis of primary tiny HCC without metastasis was made. A liver biopsy was not performed due to the small size of nodes and the risk of needle seeding. The results of the indocyanine green (ICG) clearance test, conducted to evaluate the hepatic functional reserve, were all within the normal level, including the ICG retention rate at 15 minutes (ICG R15) and the Child-Pugh grade A of 5 points. Considering that the nodes were localized and too tiny to perform radiofrequency ablation (RFA) even under the guidance of intraoperative ultrasound, as well as an acceptable liver reserve of the patient, laparoscopic resection of the left lateral lobe of the liver and cholecystectomy were performed.

Macroscopically, two grey-yellowish, soft and friable nodules, sized 10 × 8 mm and 8 × 4 mm were found. Microscopically, a diffuse and monotonous infiltration of typical centrocyte-like lymphoid cells, as well as lymphoepithelial lesions, were apparent (**Figure 2A**, **2B**). By immunohistochemistry, the nodules were positive for CD20, CD79a, BCL2, and IgM, and weakly positive for IgD, but negative for CD3, CD10, BCL6, MUM1, CD43, CD5, cyclin D1, CD23, CD30, and PD1. The Ki-67 index was 5% (**Figure 3A**, **3B**). Based on these pathologic findings, the patient was diagnosed with a low-grade primary hepatic MALT lymphoma. In situ hybridization for Epstein-Barr virus (EBV) was negative. The polymerase chain reaction (PCR) was performed to detect immunoglobulin heavy chain (IgH) rearrangements but failed due to the degradation of DNA. The non-tumorous hepatic tissue showed chronic hepatitis B with mild necroinflammatory activity and cirrhosis. No atypical hematolymphoid infiltrates were present in the remaining part of the liver. The patient refused bone marrow biopsy and gastric endoscopy due to financial considerations.

The postoperative course of the patient was uneventful. Since, according to the Ann Arbor staging, the tumor was indolent and confined without extrahepatic involvement (classified as stage IE), adjuvant chemotherapy or radiotherapy were not performed. The patient was treated with entecavir and was strictly followed-up for 17 months, including routine CT and MRI every 3 months. No signs of relapse were present.

A written informed consent was obtained from the patient for hepatectomy and publication of this case report. This research was approved by the Ethical Review Committee of the Tongji Medical College, and informed consent was obtained from the study participant.

Discussion

Primary hepatic MALT lymphoma is a rare extranodal low-grade B cell lymphoma developing in and restricted to the liver. It was first reported by Isaacson in 1995 [4], and its etiology remains poorly understood. Lymphoma at the liver arising from MALT was acquired as a result of HBV or hepatitis C virus (HCV) infection, prolonged immunogenic stimulation of primary biliary cirrhosis (PBC), hepatitis of other etiology, synchronous liver tumors, cirrhosis, ascariasis, gastric MALT lymphoma related to *H. pylori* infection [5, 6], rheumatoid arthritis, and multiple biliary unilocular cysts, although cases without any known disease were reported [7-9]. Some studies suggested the pathogenic role of HCV in the development of primary lymphoma of the liver due to HCV-stimulated indirect malignant transformation, chronic expansion of B cells, and overexpression of anti-apoptotic protein Bcl-2 [10-12]. In our case, the patient had a history of HBV infection for more than 20 years and HBV-related liver cirrhosis. This history is consistent with the reports that most hepatic MALT lymphoma patients suffered chronic liver inflammation due to HBV or HCV infection. It was also found that hepatic MALT lymphoma typically develops in the chronic inflammatory background of specific immune reactions or autoimmune disorders, such as PBC. However, a meta-analysis demonstrated that the association between PBC and non-Hodgkin lymphoma (NHL) is inconclusive [13]. One possible reason for the absence of correlation is that both hepatic MALT lymphoma and PBC are relatively rare diseases. In our patient, the tests for AIH were negative, and pathologic examination confirmed an absence of of PBC. The liver is rarely the primary site of NHL, while it is commonly a secondary site of the extranodal involvement in NHL. The most frequent site of the primary involvement of NHL is the stomach, with *H. pylorus* infection as the most common etiology. Additionally, Helicobacter species and related organisms colonizing the hepatobiliary system are considered as pathogenic factors for the development of both MALT lymphoma and hepatobiliary cancer [6, 9]. For non-gastric MALT lymphomas, bowel, lung, and parotid and salivary glands are the most frequent sites [14]. In the presented patient, PET examination was performed and did not provide evidence of other sites of lymphoma or other primary and secondary carcinomas. Also, the tests for *H. pylori* and EBV were negative in our patient.

Primary hepatic MALT lymphoma affects both genders equally. The age of patients ranges from 36 to 85 years, with a median of 62 years [15]. The majority of patients present with a solitary tumor and lack specific clinical features and biomarkers. Liver lesions were always found during examination or surgery. Serum levels of AFP, CA19-9, and CEA were almost within normal values, while evaluated AFP and liver enzymes were only found in a few cases with concurrent liver disease, such as cirrhosis and HCC [16]. In our case, the patient complained of an on-and-off right upper abdominal dull pain, which might have been caused by gallstones. Serum levels of TBIL, DBIL, and HBV DNA were slightly elevated, but tumor markers and liver enzymes were almost within the normal range.

Although radiologic imaging has been considered an essential and convenient tool for diagnosis and optimizing treatment, there are no distinctive radiologic features for the identification of primary hepatic MALT lymphoma [17]. The majority of primary hepatic MALT lymphoma lesions were described as homogeneous hypoechoic nodes by ultrasound imaging [15], hypoattenuating with no or faint peripheral enhancement in the early arterial phase in CT imaging, and were hypo- or iso-intense on T1-weighted images and moderately high hyperintense on T2-weighted images in MRI imaging [18]. Gd-EOB-DTPA-enhanced MRI has been recommended for the diagnosis and differential diagnosis of liver cancer less than 1 cm in diameter. However, the above-indicated features are also present in the imaging of HCC, intrahepatic cholangiocellular carcinoma, or metastatic tumors, frequently leading to misjudgment, as was the case in our patient who was misdiagnosed with a tiny HCC. A heterogeneous aspect or hyperechoic lesions on ultrasound and an intense arterial enhancement with washout on the portal or delayed phases on CT scanning were used to discriminate between primary liver tumors and primary hepatic MALT lymphoma [19, 20]. However, the distinction between primary hepatic MALT lymphoma and other benign and malignant tumors of the liver based on imaging characteristics

remains challenging. In our case, images of two nodes with different sizes were slightly different on Gd-EOB-DTPA-enhanced MRI, suggesting a possible correlation between the enhanced image with the size and biologic behavior of the lesion. Primary hepatic MALT lymphoma has an extremely low incidence and, in most cases, its diagnosis would not be initially considered before histologic examination. Hence, differential images obtained with distinct imaging modalities are preferred over an evaluation by a single technique. Recently, angiography, dynamic CT, and fluorodeoxyglucose-PET (FDG-PET) examination integrated with CT scanning or sonazoid-enhanced ultrasound were also recommended as effective and accurate methods to diagnose and distinguish primary hepatic MALT lymphoma [8, 21, 22].

The gold standard for the diagnosis of MALT lymphoma is based on pathologic examination. In our case, the patient did not undergo a liver biopsy to make a definite diagnosis due to the presence of HBV and HBV-related cirrhosis, imaging results, the possibility to excise the limited nodes with a diameter of less than 2 cm, and potential needle dissemination. This decision was in accordance with the Chinese guidelines for diagnosis and treatment of primary liver cancer (2019 edition). Then, surgical resection was performed, and primary hepatic MALT lymphoma was diagnosed based on the morphological and immunohistochemical features. Some differential diagnoses should be considered. Hepatic lymphoepithelioma-like (LEL) carcinoma (HLELC), including LEL HCC and LEL intrahepatic cholangiocarcinoma (ICC), was first excluded given the absence of histologic evidence of undifferentiated carcinoma cells or different grades of glandular differentiated adenocarcinoma, and the prominent presence of infiltrating lymphocytes [23]. Other B cell lymphomas involving the liver, such as diffuse large B cell lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), and small lymphocytic lymphoma (SLL), were also considered in the differential diagnosis for expression of CD20 in most atypical lymphoid cells. Diffuse large B-cell lymphoma, which represents the most common primary hepatic lymphoma, was easily excluded by the lack of characteristic large-sized lymphoid cells and lymphoepithelial lesions [24]. In addition, specific immunophenotypes are useful for the distinction of other low-grade small B-cell lymphomas from MALT lymphoma. MCL was excluded due to negative CD5 and cyclin D1 expression, FL was ruled out by negative CD10 and Bcl-6 expression, and SLL was excluded due to negative CD5 and CD23 expression [24].

Until now, there is no therapeutic consensus on the treatment of primary hepatic MALT lymphoma. Surgery, chemotherapy, radiotherapy alone, and combined therapy are all commonly used. Resection is preferred in patients with the local solitary node, preserved liver function, and no metastasis, and most of these cases had a favorable outcome [15]. RFA is usually chosen for a small local lesion with a diameter of less than 3 cm in a primary hepatic malignant lesion along with severe cirrhosis [25]. Radiotherapy alone for a local lesion was also reported with long-lasting remission of 6 years [26]. Since the recurrence rate of non-gastric MALT lymphoma, including hepatic lymphoma, is higher than that of gastric MALT lymphoma, surgical treatment combined with chemotherapy or immunotherapy were recommended. R-CHOP-based regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), effective treatment of B-cell lymphoma [27, 28], has also been used for hepatic MALT lymphoma. Rituximab is an anti-CD20 monoclonal antibody that was reported to be safe and provide a significant effect in MALT lymphoma [14]. The overall response rate (ORR) to rituximab treatment for MALT lymphoma is 73%, and in the case of chemotherapy-naive patients the ORR is 87% [14]. Rituximab is also effective in relapsed patients and diffuse or unresectable hepatic MALT lymphoma [29]. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase (PI3K), is an appropriate choice for relapsed primary hepatic MALT lymphoma after the failure of rituximab treatment [30]. However, a patient that received only resection without any further treatment also remained without any evidence of disease for 34 months [31]. Treatment options should be selected according to the stage of the disease [32]. The low-grade MALT lymphomas are often indolent and are characterized by late recurrence and prolonged survival [32]. Low-grade hepatic MALT with limited status can be treated by resection, and some authors have concluded that additional chemotherapy is not required for low-grade hepatic MALT [3], although longer follow-

up and a higher number of cases should be analyzed to strengthen this notion. In addition, HCV infection was reported to play an important role in lymphomagenesis. Thus, in low-grade lymphoma patients with HCV-infection, antiviral therapy has been proposed as an alternative to surgery or chemotherapy, or their combination. This concept is based on the fact that the infection with *H. pylori* plays a pathogenic role in the development of gastric MALT lymphoma, and eradication of the infection constitutes effective treatment. However, the demonstration of the effectiveness of this approach requires epidemiologic studies in a large cohort with longer follow-up. Antiviral treatment using interferon and ribavirin resulted in the regression of splenic lymphoma in a patient with villous lymphocytes and HCV infection [33]. In the hepatic MALT lymphoma staged as IE and complicated with hepatitis C, patients treated by the combination of interferon β and ribavirin instead of surgery followed by chemotherapy had no recurrence for 27 months [3]. In our case, surgical resection was performed instead of RFA as the size of the node was too small, and, in the treatment of tiny HCC, surgical resection correlates with higher overall survival and recurrence-free survival rate than RFA [34]. Since the lung is the most frequent site of recurrence of hepatic MALT lymphoma [7], the patient received routine follow-up including a CT scan of the lung and was free from relapse.

Conclusion

Here, we describe a case of primary hepatic MALT lymphoma in a patient with chronic HBV infection and HBV-related cirrhosis. Due to the absence of characteristic clinical manifestations and laboratory biomarkers, and variable features by radiologic imaging, an accurate diagnosis of this disease before histologic confirmation is very difficult, and misdiagnosis often happens. Liver biopsy is not suitable or recommended for patients with hepatitis and hepatitis-related cirrhosis, because of the small size of nodes, and potential needle dissemination. We conclude that surgical resection is a better choice for both diagnosis and therapy in patients with low-grade hepatic MALT lymphoma.

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Disclosure of conflict of interest

None.

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