Int J Clin Exp Med 2019;12(7):9473-9477
www.ijcem.com /ISSN:1940-5901/IJCEM0090624

Case Report

An uncommon diagnosis and treatment challenge in a patient with primary hepatic lymphoma: a case report

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Received December 29, 2018; Accepted May 7, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: Primary hepatic lymphoma (PHL) is a rare condition that is likely to pose a diagnostic challenge. Here is reported a 71-year-old man with PHL who presented with a history of night sweats, low-grade fever, dizziness, nausea, and weight loss in 1 month. The patient was initially misdiagnosed as a case of liver abscess. A histopathological examination of a percutaneous ultrasound-guided liver biopsy specimen revealed that the pathologic diagnosis of the tissue was diffuse large B cell lymphoma (NOS, non-GCB); and did not exclude follicular lymphoma.On immunohistochemical examination, the tumor tested positive for CD20, BCL-6, MUM-1, BCL-2, and c-myc; CD3, CD10, CD23, CyclinD1, AE1/AE3, but CD56 were negative.The Ki-67 labeling index was approximately 70%. He was treated with six cycles of the R-CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab injection). As of the 2-year follow-up, there were no signs of relapse or metastasis. Based on this experience and review of relevant literature, due caution should be exercised with respect to the diagnosis of PHL. Chemotherapy is the main treatment option for these patients.

Keywords: Primary hepatic lymphoma, misdiagnosis, liver biopsy, immunohistochemistry, chemotherapy

Introduction

Primary hepatic lymphoma (PHL) is an unusual type of lymphoma characterized by no evidence of lymphomatous involvement of the other lymphoid structures. Extra-nodal lymphomas account for 10-25% of non-Hodgkin lymphoma cases [1]. PHL represents 0.016% of all non-Hodgkin lymphomas and 0.4% of all extra-nodal lymphomas [2]. Therefore, PHL is a rare malignancy. In patients with multiple liver lesions, discriminating between primary and secondary is a key diagnostic challenge in the context of PHL. PHL is considered an early stage disease. However, secondary hepatic involvement indicates that the disease has developed into an advanced stage. Therefore, a diagnosis of primary non-Hodgkin disease is not straightforward in patients with a solitary liver lesion. PHL is frequently diagnosed intra-or-post operatively or based on a liver biopsy, therefore it is liable to be misdiagnosed as some other disease, such as liver abscess, liver cancer, or hepatic tuberculosis. No large studies have described a treatment for PHL. Surgery, chemotherapy and local radiotherapy are often chosen. This is the report of a PHL case that was difficult to discriminate from liver abscess. In addition, a review of the literature is presented, including studies on the clinical, radiological, histological, and therapeutic features of this disease. Written informed consent from the patient was obtained for the publication of this case report.

Case presentation

A 71-year-old man presented with a history of fever and night sweats, he had experienced the previous two weeks. The fever typically occurred in the afternoon, and his body temperature fluctuated between 37.1-37.3°C. He sometimes experienced dizziness and nausea, but there was no history of vomiting. He had lost 4 kg weight in the last month. He was hypertensive but had no history of hepatitis. Therefore, he was admitted to our Department of Respiratory Medicine. His general physical examination was unremarkable. His superficial lymph nodes were not palpable. The routine blood investiga-

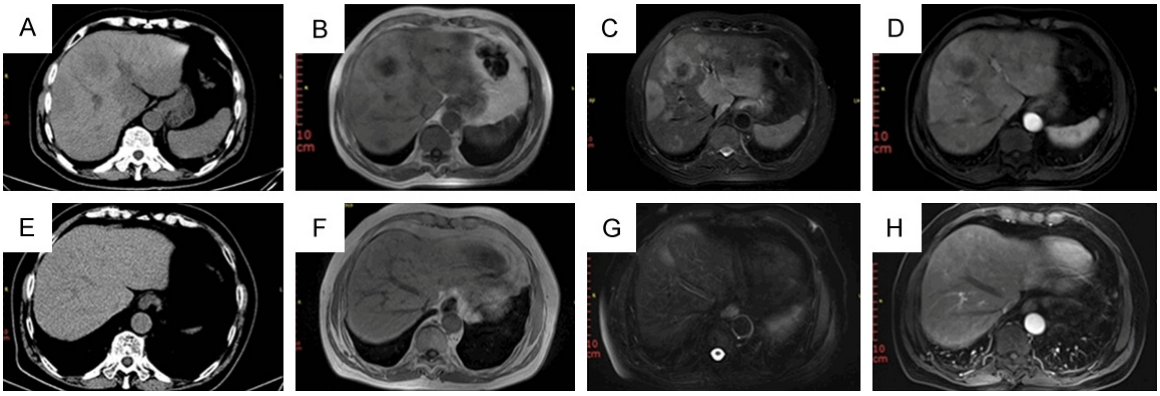

Figure 1. Before chemotherapy: (A) Plain abdominal CT showing multiple hypodense areas in the liver. (B) T1-weighted MRI image showing multiple diffuse slightly hypo-intense lesions. (C) T2-weighted MRI image showing slightly hyper-intense lesions. (D) T2-weighted MRI image showing enhancement in the arterial phase after injection. After chemotherapy: (E-H) Corresponding images showing a complete resolution of the tumor.

tions, including blood and bone marrow culture, were normal. The serology results were negative for hepatitis B and C viruses. The serum levels of alfa fetoprotein (AFP), carcinoembryonic antigen (CEA), and other tumor markers were normal. However, serum lactate dehydrogenase (LDH) (243 U/L; reference range, 135-226 U/L), hypersensitive C-reactive protein (hs-CRP) (75.91 mg/L; reference range, 0-5 mg/L), erythrocyte sedimentation rate (41 mm/h; reference range, 0-20 mm/h), and procalcitonin levels (0.08 ng/mL; reference range, 0-0.05 ng/mL) were elevated. Elevated inflammatory indices were indicative of infection. A computed tomography (CT) of the chest, brain, and pelvis revealed no abnormalities. Three-dimensional CT imaging of the liver showed multiple hypodense lesions with unclear boundaries. The size of the largest lesion was approximately 58 × 53 mm, and the CT value was about 45 HU (**Figure 1A**). Magnetic resonance imaging (MRI) of the liver showed multiple diffuse slight hypo-intense lesions on T1-weighted images (**Figure 1B**) and slight hyper-intense on T2-weighted images enhanced in the arterial phase after contrast injection. No significant lesion enhancement was observed in the venous and delayed phases (**Figure 1C**, **1D**). There were no signs of lymphadenopathy on the MRI. Collectively, the radiographic characteristics were consistent with potential inflammatory lesions. On the basis of these findings, liver abscess or hepatocellular carcinoma was suspected. Based on a presumptive diagnosis of liver abscess, the patient was initially treated with amoxicillin sulbactam, imipenem, and cilastatin sodium for twenty days. However, the patient did not respond to antibiotic therapy; his body temperature rose to 38.2-38.8°C, accompanied by sweating, fatigue, and a poor appetite. Therefore, a percutaneous, ultrasound-guided liver biopsy was performed. Histopathological examination showed that the pathologic diagnosis of the tissue was diffuse large B cell lymphoma (NOS, non-GCB) and did not exclude follicular lymphoma. On immunohistochemical examination, CD20, BCL-6, MUM-1, BCL-2, and c-myc were positive; CD3, CD10, CD23, CyclinD1, AE1/AE3, CD56 were negative. Ki-67 labeling index was approximately 70% (**Figure 2**). Subsequently, the patient was transferred to the department of hematology for further treatment. He was treated with six cycles of a R-CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab injection). His body temperature returned to a normal level after 1 cycle. The low-density lesions disappeared after 6 chemotherapy cycles (**Figure 1E-H**). As of his 2-year follow-up, no new lesions have been noted, and the patient has survived with no signs of recurrence.

Discussion

Owing to the non-specific clinical manifestations, patients with PHL are liable to be misdiagnosed. This patient was initially misdiagnosed as a case of liver abscess. Currently, there is no consensus on the precise definition of PHL. In some reports, cases were considered as primary if the disease was confined to the liver at presentation. Edgardo et al [3]. proposed the following criteria for diagnosis: symp-

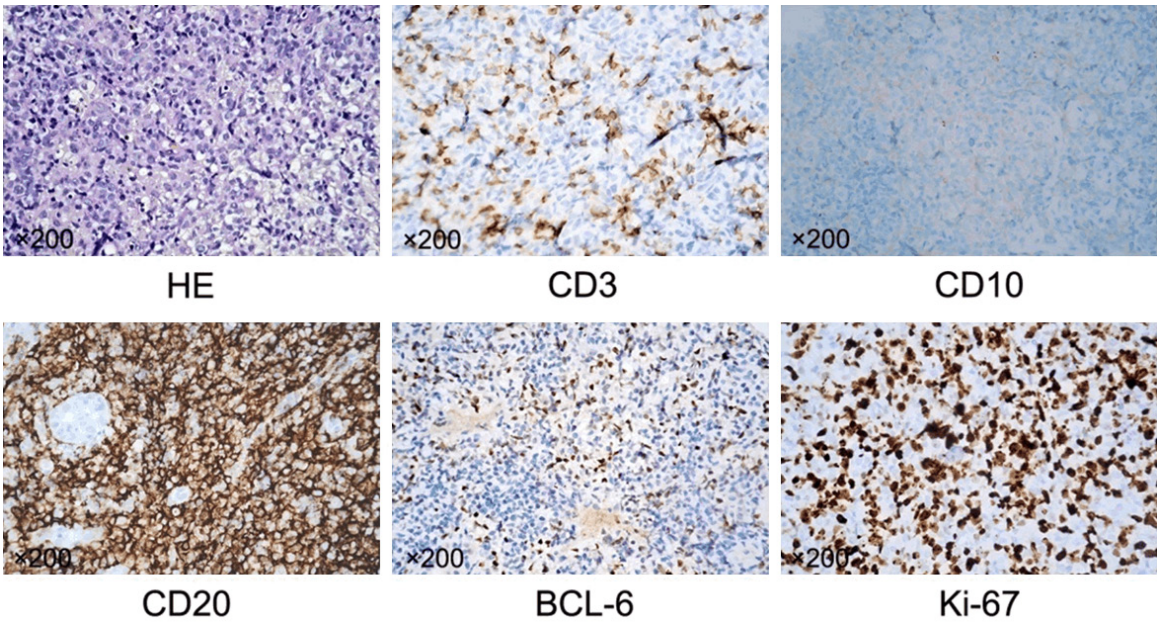

Figure 2. Histopathological examination showing diffuse large B-cell lymphoma (H&E); On the immunohistochemistry examination, the tumor cells tested positive for CD20 and Bcl-6; the tumor cells were negative for CD3 and CD10. The Ki-67 index is 70% (magnification × 200).

toms explained predominantly by liver involvement, an absence of lymph node involvement, normal hematological parameters, and no spleen or bone marrow involvement for at least 6 months since the appearance of the hepatic lesion. Accordingly, this definition is cited in some cases. In the present case, the diagnosis of PHL was made after exclusion of other sites of disease by imaging studies, bone marrow biopsy, and liver biopsy.

PHL can occur at any age, and the average age of the reported patients is 55 years old. The condition is more common in males (male to female ratio, 3:1) [4]. The etiology of PHL is uncertain, and it may be associated with HIV, AIDS, hepatitis B and C, the Epstein-Barr virus, liver cirrhosis, primary biliary cirrhosis, immunosuppressive therapy, and autoimmune diseases. Its mechanism potentially involves loss of inherent immune surveillance by T lymphocytes and impaired function after viral infection or the use of immunosuppressive agents. This may result in unrestrained lymphopoiesis, thereby forming lymphoma [5].

The clinical manifestations of PHL are usually non-specific and include hepatomegaly, gastrointestinal symptoms (abdominal pain, vomiting, loss of appetite), typical lymphoma symptoms (such as fever, night sweats), and weight loss. Other rare clinical manifestations include pleural effusion, jaundice, thrombocytopenia, metabolic acidosis, and hypercalcemia [4]. Patients with PHL tend to have abnormal liver enzymes (elevation of aspartate aminotransferase, alanine aminotransferase, bilirubin, gamma glutamyl transferase, alkaline phosphatase, and LDH). In particular, elevated LDH and ALP levels are more frequently encountered. Tumor markers such as AFP and CEA are typically normal in patients with PHL [6]. In this case, the patient experienced weight loss, night sweats, and a sustained fever, which are typical lymphoma symptoms. The patient's LDH level was increased, but his AFP and CEA levels were normal. The clinical characteristics were consistent with those of primary hepatic non-Hodgkin lymphoma. In a previous study, LDH levels in patients with PHL were normal or significantly decreased after surgery or chemotherapy. The recurrence of PHL was associated with an increase in the LDH level again. Dynamic changes in serum LDH levels may serve as a marker of diagnostic and prognostic relevance [7].

The imaging features of hepatic lymphoma are non-specific and difficult to distinguish from those of focal nodular hyperplasia, primary hepatic tumor, hepatic-metastases, or systemic lymphoma with secondary hepatic involve-

Table 1. Published case reports of primary hepatic lymphoma in the contemporary literature

	Corresponding author	Year	Diagnosis	Treatment
1	Vivian Resende	2013	Primary hepatic lymphoma	Chemotherapy (R-CHOP)
2	MeryemAitelhaj	2014	Primary hepatic lymphoma	Chemotherapy (R-CHOP)
3	Christoph J Zech	2014	Primary hepatic diffuse large b-cell lymphoma	Chemotherapy (R-CHOP)
4	D. Myoteri	2014	Primary hepatic lymphoma	Chemotherapy (R-CHOP)
5	Trupti S. Patel	2015	Primary non-Hodgkin lymphoma of the liver	CHOP
6	Z W. Liu	2016	Primary hepatic marginal zone B cell lymphoma	Surgery + interferon β and ribavirin
7	Jeong-Ik Park	2017	Primary hepatic lymphoma	Chemotherapy (R-CHOP)
8	Srinivasan Muthukrishnan	2018	Primary Hodgkin's lymphoma of liver	Chemotherapy (ABVD + HAART)

ABVD, Adriamycin, bleomycin, vinblastine and dacarbazine; HAART, highly active antiretroviral therapy.

ment [8]. PHL may appear as a solitary lesion (39-60%), multiple lesions (25-40%), or as a diffuse infiltration (rare) in the liver [9, 10]. Our patient exhibited multiple lesions on his imaging examination. PHL appears as a low-density lesion on CT and exhibits no enhancement or minimally patchy or ring-like enhancement on contrast-enhanced CT. On MRI, the lesion appears hypo-intense on T1-weighted and mildly hyper-intense on T2-weighted images. On diffusion weighted MRI, PHL lesions showed a signal restriction [11]. Contrast enhancement was higher in lesions with higher T2 signals in our patient. Furthermore, peripheral enhancement was occasionally seen. Similar to lymphoma at other sites, PHL also shows a diffuse restriction owing to its cellularity [12]. The imaging features of PHL may mimic those of hepatic tuberculosis or primary hepatic tumors among other conditions. Radiological and laboratory investigations are extremely useful in differentiating PHL from other diseases. Patients with hepatic tuberculosis typically have a history of pulmonary tuberculosis. In 80% of cases, primary hepatic tumor develops in the cirrhotic liver; these patients are HBV- or HCV-positive and often have elevated AFP levels. In addition, a primary hepatic tumor usually exhibits hyper-vascularity with marked enhancement in the arterial phase and washout in the delayed phase [13]. On CT images, hepatic miliary tuberculosis shows liver volume increased, diffuse miliary or nodular lesions with low density, uniform size, < 2 cm in diameter, with clear boundaries, calcification, and enhancement in the arterial and venous phases. Hepatic lymphoma lacks a blood supply and has no obvious enhancement ring.

This combination of clinical and laboratory features allows a speculative diagnosis of PHL. However, a definite diagnosis requires histological results (liver biopsy or surgical specimen) and the absence of lymphoproliferative disease outside the liver. An immunohistochemical examination is essential for the identification of the type and for the differential diagnosis of PHL. The currently reported PHL are all non-Hodgkin's lymphoma, and there are no Hodgkin lymphoma reports. Most PHL cases (46-68%) reported in the literature are diffuse large B-cell lymphoma. Other types have been described in less than 5% of cases including diffuse mixed large and small cell, lymphoblastic, diffuse immunoblastic, diffuse histiocytic, mantle cell, and small non-cleaved or Burkitt lymphoma [7].

PHL treatment options include surgery, chemotherapy and local radiotherapy; these options have been used alone or in combination. The treatment of similar diseases from recent years is enumerated in **Table 1**. However, with the continuous development of chemotherapeutic regimens, especially the application of targeted therapeutic drugs, chemotherapy combined targeted therapeutic drugs (rituximab) has become the first-line treatment of PHL [14]. In this case, a single course treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen to remarkable attenuation of low-density lesions.

Conclusion

Cases of primary hepatic lymphoma initially presenting with liver mass or liver infiltration with normal levels of alpha-fetoprotein and CEA are indeed rare. The clinical and imaging manifestations of PHL are non-specific. The diagnosis of PHL should be strictly based on histopathology and immunophenotype. Owing to the rarity of the disease, the diagnosis and management of PHL is typically challenging. Nevertheless, chemotherapy is still the main treatment option for PHL. The patient rapidly responded to 6 cycles of a R-CHOP chemother-

apy regimen. Therefore, a confirmation of the diagnosis and appropriate therapy is necessary for such a challenging case.

Disclosure of conflict of interest

None.

Abbreviations

AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamate transpeptidase; CEA, carcinoembryogenic antigen; LDH, lactate dehydrogenase; hs-CRP, hypersensitive c-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging.

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