Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(8) 1–7

DOI: 10.1177/0300060520938173
journals.sagepub.com/home/imr
SAGE

Jaundice may be the only clinical manifestation of primary hepatosplenic diffuse large B-cell lymphoma: a case report and literature review

Xue Shi[1,*], Tingting Zhang[1,*], Hong Xu[1], Xiaoying Zhang[2], Hongguo Zhao[1], Xiaodan Liu[1], Fang Hou[3], Guangjie Yang[4] and Zhihe Liu[5]

Abstract

A 64-year old Chinese male patient was admitted to our hospital because of severe jaundice that persisted for 2 months. No swollen lymph nodes or hepatosplenomegaly was detected on physical examination. His laboratory data indicated high levels of direct bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. No abnormality was revealed on abdominal computed tomography (CT). However, positron emission tomography (PET)-CT revealed diffuse hypermetabolism in the liver and spleen. Ultimately, liver biopsy guided by PET-CT was performed, revealing that atypical lymphocytes diffusely infiltrated the liver. The immunohistochemical analysis demonstrated that the tumor cells were positive for CD20, Bcl-2, Bcl-6, MUM1, and c-Myc but negative for CD3, CD4, CD8, and CD10. Based on these findings, this patient was diagnosed with primary hepatosplenic diffuse large B-cell lymphoma. After the definite diagnosis, he received chemotherapy and remained in good health as of September 2019.

[1]Department of Hematology, The Affiliated Hospital of Qingdao University, Qingdao, China
[2]Department of Emergency, The Affiliated Hospital of Qingdao University, Qingdao, China
[3]Department of Hematology Research Laboratory, The Affiliated Hospital of Qingdao University, Qingdao, China
[4]Department of PET/CT Center, The Affiliated Hospital of Qingdao University, Qingdao, China
[5]Department of Lymphoma, The Affiliated Hospital of Qingdao University, Qingdao, China

*These authors contributed equally to this work.

Corresponding author:
Zhihe Liu, Department of Lymphoma, The Affiliated Hospital of Qingdao University, No. 1677, Wutaishan Road, Qingdao 266555, Shandong, China.
Email: lzh19870109@163.com

Keywords
Diffuse large B-cell lymphoma, jaundice, liver, primary hepatosplenic lymphoma, positron emission tomography, computed tomography, R-CHOP

Date received: 4 January 2020; accepted: 9 June 2020

Introduction

Primary hepatosplenic lymphoma (PHSL) is a remarkably rare malignancy, accounting for 0.016% of all non-Hodgkin's lymphomas and 0.4% of all extranodal lymphomas.[1] It is highly heterogeneous, and it is characterized by an old age at presentation, female predominance, bone marrow involvement, advanced stage, a high international prognostic index (IPI), and the predominance of the γ/δ T-cell receptor type.[2] Although the pathogenesis of PHSL is uncertain, several etiological factors have been confirmed to increase the incidence of the disease, such as hepatitis virus infection (hepatitis A, B, and C) and autoimmune conditions.[3] Because this rare disease entity has neither a specific clinical manifestation nor significant tumor formation, liver biopsy is critical for clinical definite diagnosis.

In this article, we presented the case of a patient with PHS-DLBCL and severe skin jaundice. The clinical definite diagnosis was made after liver biopsy guided using positron emission tomography (PET)-computed tomography (CT). This patient achieved complete remission after four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Encouragingly, the general condition of this patient has remained good as of September 2019.

Case report

A 64-year-old Chinese male patient presented to our medical center with a chief complaint of skin jaundice that had persisted for 2 months. The patient denied any significant medical history, medication history, family history, and occupational exposure history. The patient also stated that he was not using any herbal supplements before hospital admission. After admission, physical examination did not identify surface lymphadenopathy or hepatosplenomegaly excluding severe skin jaundice. Routine blood testing revealed the following results: hemoglobin, 9.9 g/dL; leukocytes, 9.5×10^9/L; neutrophils, 7.1×10^9/L; and platelets, 73×10^9/L. His serum levels of direct bilirubin (DBil), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase were 165.24 mg/dL, 273 IU/mL, 156 IU/mL, 44 IU/mL, and 1000 IU/mL, respectively. The results of infectious disease-related tests, such as hepatitis A, B, and C, Epstein-Barr virus, and cytomegalovirus, were negative. The results of autoimmune hepatitis workups, such as anti-smooth muscle antibody, anti-liver kidney microsomal antibody, anti-soluble liver antigen antibody, were also negative. Abdominal CT was conducted to explore the cause of jaundice, but it failed to produce any meaningful results. During this period, the patient's serum DBil levels patient deteriorated further. To determine the cause of jaundice as quickly as possible, PET-CET was performed, and the results indicated diffuse hypermetabolism in the liver and spleen (Figure 1).

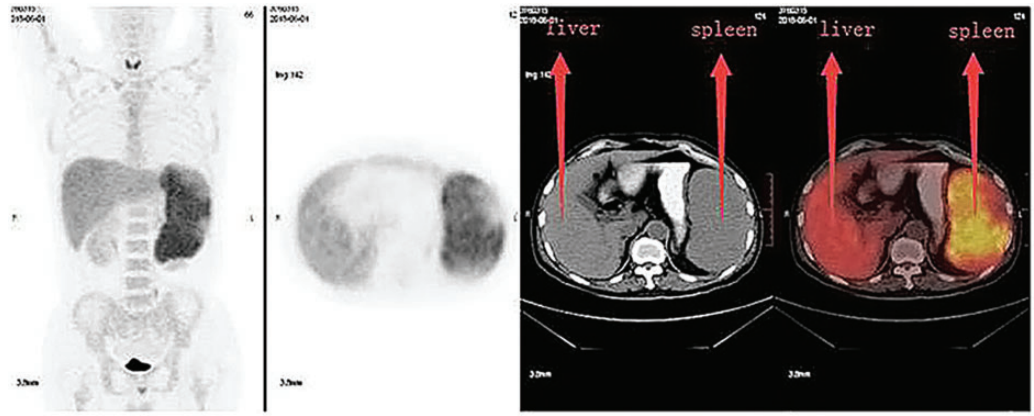

Figure 1. Results of positron emission tomography-computed tomography before rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. The liver and spleen displayed diffuse hypermetabolism.

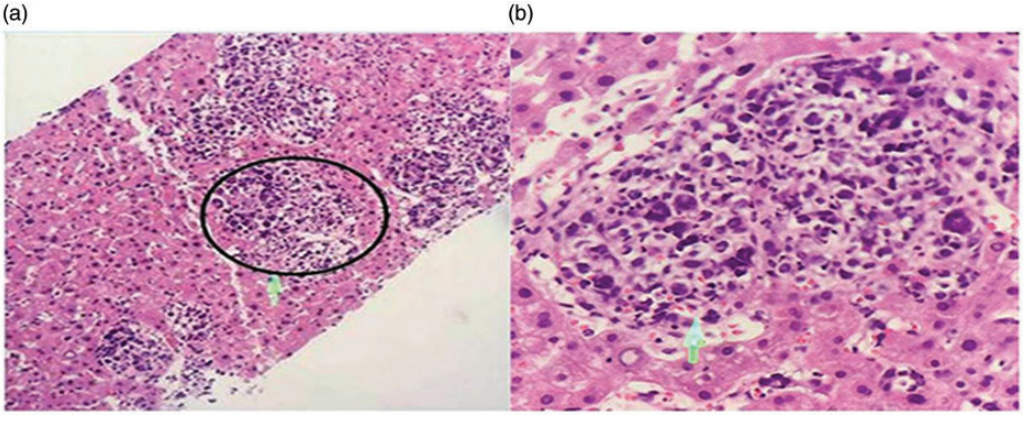

Figure 2. Results of hematoxylin and eosin staining of a liver specimen. (a) Low magnification (×20) of the liver specimen. (b) High magnification (×40) of the encircled portion in Figure 2(a). The hepatic lobule and hepatic cord were disordered with diffuse infiltration of large atypical lymphocytes.

Subsequently, liver biopsy guided by PET-CT was performed. Microscopic examination uncovered that the liver was diffusely invaded by large atypical lymphocytes, primarily within the portal triads (Figure 2). Immunohistochemical staining revealed that the tumor cells were positive for CD20, Bcl-2, Bcl-6, MUM1, and c-Myc but negative for CD3, CD4, CD8, and CD10 (Figure 3). Bone marrow aspiration and biopsy were performed during hospitalization, but no lymphoma cells were detected. Eventually, the diagnosis of PHS-DLBCL was made according to the aforementioned findings.

After the definitive diagnosis, the patient received six cycles of R-CHOP chemotherapy. Encouragingly, the severity of skin

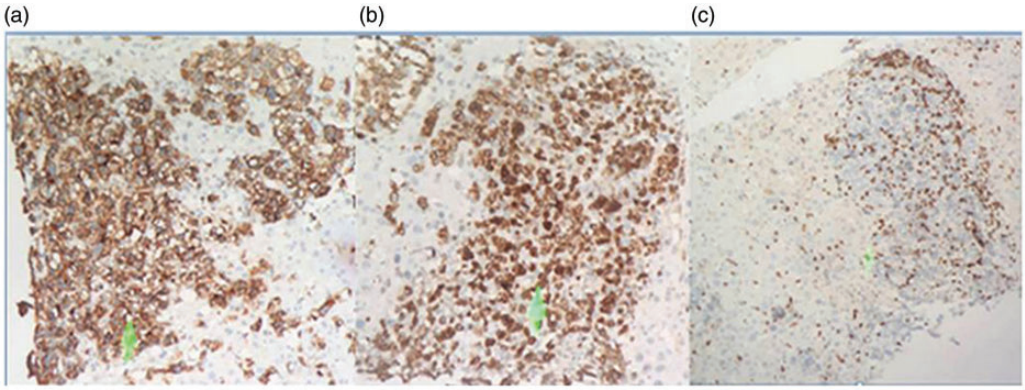

Figure 3. Results of immunohistochemical staining. The lymphoma cells were positive for CD20 and Bcl-2 but negative for CD3. (a) CD20 was diffusely and strongly positive. (b) Bcl-2 was diffusely and strongly positive. (c) CD3 was negative.

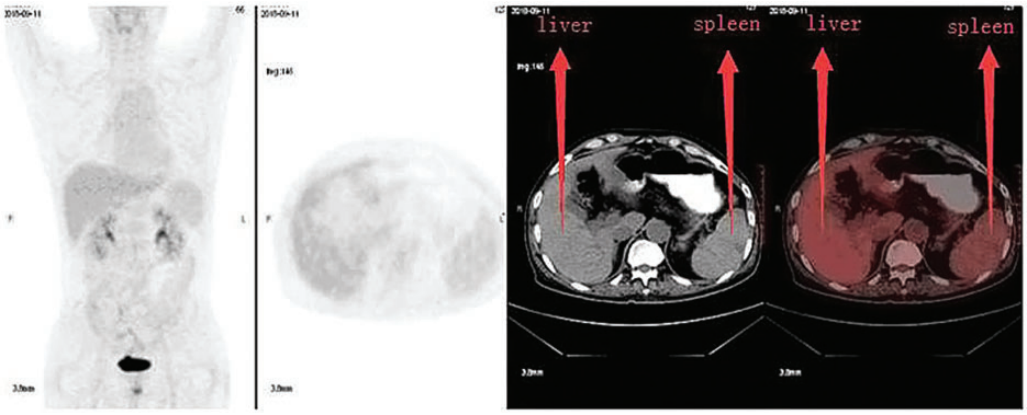

Figure 4. Results of positron emission tomography-computed tomography examination 1 month after the last cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. The diffuse hypermetabolism of the liver and spleen had disappeared.

jaundice in this patient greatly improved. PET-CT was repeated 1 month after the last cycle of R-CHOP chemotherapy, revealing that PHS-DLBCL was in complete remission (Figure 4). The patient was alive as of September 2019.

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Written informed consent was obtained from this patient prior to submission of this article for consideration as a case-based review.

Discussion

PHSL is a malignancy originating from lymphoid tissue or lymphocytes of the liver and spleen with or without lymphadenopathy.[2,4,5] It represents a rare entity, and the majority of cases are of T-cell origin, especially the γ/δ subtype.[2,5–7] PHS-DLBCL is remarkably rare. It is typically characterized by an old age at presentation, female predominance, a high frequency of bone marrow involvement, advanced stage, and higher IPIs.[4] The symptoms are

nonspecific, varying from loss of appetite, fatigue, low-grade fever, and night sweats to liver function abnormalities, hepatomegaly, and abdominal pain.[8] The typical radiologic characteristics of the disease are space-occupying lesions in the liver or spleen.[3] Some patients exhibit diffuse lesions, displaying hepatosplenomegaly.[9,10] Conversely, the current patient only had jaundice without other accompanying symptoms such as fever and lymphadenopathy, and no space-occupying findings were identified by a series of radiologic examinations. This extremely rare disease entity could represent a diagnostic challenge.

Painless jaundice is a common clinical manifestation of many diseases, such as viral hepatitis, ischemic hepatitis, alcohol- or drug-induced hepatitis, primary biliary cirrhosis, hemochromatosis, malignancies, Wilson's disease, and autoimmune hepatitis.[11–15] The differential diagnosis of painless jaundice is broad and complicate. Laboratory workups including a complete blood cell count; serum AST, ALT, ALP, total and direct bilirubin, and γ-glutamyl transpeptidase measurements; and urinalysis should be performed in the initial evaluation of painless jaundice, which can help clarify whether it is an obstructive process.[11] Once an obstructive process is strongly suspected, imaging should be considered, such as ultrasonography, contrast-enhanced CT, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography.[11] If the etiology is unclear after these tests, liver biopsy and autoantibody tests are recommended.[11] In this article, this patient was finally diagnosed on the basis of the results of liver biopsy.

The pathogenesis of the disease remains unclear. Findings from previous studies indicated that the disease occurred more frequently in patients with immunodeficiency or immunosuppression, thus leading to aggravated clinical symptoms, some of which are life-threatening.[2] The patient in this study had no underlying immunosuppression, viral infection, or chronic liver disease. Therefore, we speculate that he harbored a specific gene profile associated with PHS-DLBCL.

It is extremely difficult for physicians to accurately diagnose PHS-DLBCL, especially in patients who only have jaundice without significant space-occupying lesions on imaging. It is essential to perform PET-CT followed by PET-CT–guided liver biopsy to confirm the diagnosis. Early diagnosis and timely treatment can greatly improve patient prognosis.

PHS-DLBCL had a rapid and aggressive evolution prior to diagnosis, and the disease is quickly fatal.[16] The overall prognosis is poor, and the median overall survival for these patients has been estimated to be approximately 33 months.[17] Unfortunately, PHS-DLBCL is often diagnosed in an advanced stage in which therapeutic interventions offer little benefit.[3] The treatment of PHS-DLBCL includes surgery, radiotherapy, chemotherapy, and immunotherapy. Surgery combined with radiotherapy was previously considered to achieve favorable improvement. However, with the rapid development of chemotherapy, especially emerging targeted drugs, immunochemotherapy is considered the best treatment option for PHS-DLBCL, but the appropriate chemical protocol has not been established.[18] The R-CHOP regimen was speculated to be the first-line treatment for PHS-DLBCL.[19] Given the rarity of the disease, further studies on the optimal treatment for PHS-DLBCL should be performed. In our report, the patient quickly received R-CHOP chemotherapy after a diagnosis was reached, and a good response was achieved.

In conclusion, PHS-DLBLC is an extremely rare subtype of non-Hodgkin's lymphoma that progresses rapidly and possesses a high mortality rate. Jaundice may

be the only clinical manifestation of this rare entity. Most patients exhibit hepatosplenomegaly, and no patient with jaundice as the primary symptom was previously reported. Because of its atypical clinical manifestations, it is extremely difficult to quickly obtain a definitive diagnosis. Liver biopsy guided by PET-CT technology is essential for the diagnosis of PHS-DLBCL. R-CHOP chemotherapy is an effective treatment for this disease according to our results.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iDs

Tingting Zhang https://orcid.org/0000-0001-8598-6769
Zhihe Liu https://orcid.org/0000-0002-9264-094X

References

1. Karpate A, Barcena C, Hohl D, et al. Cutaneous presentation of hepatosplenic T-cell lymphoma-a potential mimicker of primary cutaneous gamma-delta T-cell lymphoma. *Virchows Arch* 2016; 469: 591–596. DOI: 10.1007/s00428-016-2006-x.
2. Shi Y and Wang E. Hepatosplenic T-Cell Lymphoma: a Clinicopathologic Review With an Emphasis on Diagnostic Differentiation From Other T-Cell/Natural Killer-Cell Neoplasms. *Arch Pathol Lab Med* 2015; 139: 1173–1180. DOI: 10.5858/arpa.2014-0079-RS.
3. Dhingra R, Winter MW, Yilmaz OH, et al. An Unusual Presentation of Primary Hepatic Diffuse Large B-cell Lymphoma of the Liver. *Cureus* 2018; 10: e2242. DOI: 10.7759/cureus.2242.
4. Farag F, Morcus R, Ramachandran P, et al. Fever of Unknown Origin due to Primary Hepatic Diffuse Large B-cell Lymphoma: a Case Report. *Cureus* 2019; 11: e4220. DOI: 10.7759/cureus.4220.
5. Lewis KL, Spagnolo D, Radeski D, et al. Refractory alpha/beta-Hepatosplenic T-cell Lymphoma With Secondary CNS Dissemination and Severe Morbidity Related to Intrathecal Chemotherapy: a Case Report and Literature Review. *Clin Lymphoma Myeloma Leuk* 2019; 19: e564–e567. DOI: 10.1016/j.clml.2019.05.014.
6. Morales-Polanco MR, Drijansky-Morgenstern R, Murillo-Meza E, et al. Primary hepatosplenic large B-cell lymphoma: a rare aggressive tumor. *Case Rep Gastroenterol* 2008; 2: 109–115. DOI: 10.1159/000120757.
7. Madabhavi I, Modi G, Panchal H, et al. Hepatosplenic Gamma Delta T-Cell Lymphoma (HSGDTCL): two Rare Case Reports from Western India. *Int J Hematol Oncol Stem Cell Res* 2017; 11: 296–300.
8. Liu Y, Jiang J, Wu Q, et al. A Case of Primary Hepatic Lymphoma and Related Literature Review. *Case Reports Hepatol* 2016; 2016: 6764121. DOI: 10.1155/2016/6764121.
9. Zhang X, Sun M, Zhang L, et al. Primary hepatosplenic CD5-positive diffuse large B-cell lymphoma: a case report with literature review. *Int J Clin Exp Pathol* 2013; 6: 985–989.
10. Kashimura M, Murayama K and Kojima M. Primary hepatic and hepatosplenic diffuse large B-cell lymphomas with intrasinusoidal and interstitial lymphomatous infiltration. *Int J Surg Pathol* 2013; 21: 531–534. DOI: 10.1177/1066896913483897.
11. Roche SP and Kobos R. Jaundice in the adult patient. *Am Fam Physician* 2004; 69: 299–304.
12. Gentile NM and Greenlund AC. 66-year-old woman with painless jaundice. *Mayo Clin Proc* 2012; 87: 1021–1024. DOI:10.1016/j.mayocp.2012.03.018
13. Radovanovic M, Dushenkovska T, Cvorovic I, et al. Idiosyncratic Drug-Induced Liver Injury Due to Ciprofloxacin: a Report of Two Cases and Review of the

Literature. *Am J Case Rep* 2018; 19: 1152–1161. DOI:10.12659/AJCR.911393.
14. Abu-Wasel B, Eltawil KM and Molinari M. Benign inflammatory pseudotumour mimicking extrahepatic bile duct cholangiocarcinoma in an adult man presenting with painless obstructive jaundice. *BMJ Case Rep* 2012; 2012: 006514. DOI: 10.1136/bcr-2012-006514.
15. Zeidner JF and Sydnor E. Painless jaundice. *Am J Med* 2010; 123: 601–603. DOI: 10.1016/j.amjmed.2010.03.007.
16. Kheyri Z, Ali Asgari A, Zare Mehrjerdi A, et al. Fulminant Hepatic Failure due to Primary Hepatic Lymphoma: a Case Report. *Middle East J Dig Dis* 2013; 5: 168–170.
17. El-Fattah MA. Non-Hodgkin Lymphoma of the Liver: a US Population-based Analysis. *J Clin Transl Hepatol* 2017; 5: 83–91. DOI: 10.14218/jcth.2017.00015.
18. Liao SH, Chen YK, Yu SC, et al. An unusual case of primary hepatic lymphoma with dramatic but unsustained response to bendamustine plus rituximab and literature review. *SAGE Open Med Case Rep* 2017; 5: 2050313x17709190. DOI: 10.1177/2050313x17709190.
19. Sato M, Kuroda H, Yoshida M, et al. [Successful treatment with combination of plasma exchange and chemotherapy for CD5-positive primary hepatosplenic diffuse large B-cell lymphoma complicated with acute liver injury]. *Rinsho Ketsueki* 2014; 55: 958–964.