CASE IN POINT

Primary Hepatic Lymphoma: A Rare Form of Diffuse Large B-Cell Lymphoma of the Liver

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Background: Primary hepatic lymphoma is a rare, malignant lymphoma of the liver unlike the predominant lymph nodal or splenic involvement associated with other types of lymphoma. It is commonly associated with nonspecific symptoms and usually detected incidentally on imaging examination.
Case Presentation: An 84-year-old man was evaluated for upper back pain. Chest computed tomography showed multiple large lesions in the liver, leading to the diagnosis of primary diffuse large B-cell lymphoma of the liver. Within 2 weeks of detecting his liver mass, the patient developed hypercalcemia and hyperuricemia that led to rapid deterioration and admission for treatment. Further diagnostic testing was performed, and he was initiated on appropriate chemotherapy.
Conclusions: Primary hepatic lymphoma, a form of diffuse large B-cell lymphoma of the liver is a rare disease without specific clinical manifestations, biochemical indicators, or radiologic features except for space-occupying liver lesions. However, patients' conditions can deteriorate rapidly at an advanced stage as demonstrated in this case, which highlights the importance of a high level of suspicion for early diagnosis and treatment.

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Fed Pract. 2023;40(suppl 1). Published online February 23. doi:10.12788/fp.0365

Primary hepatic lymphoma (PHL) is a rare, malignant lymphoma of the liver. It differs from the predominantly lymph nodal or splenic involvement associated with other types of lymphoma. It is usually detected incidentally on imaging examination, commonly computed tomography (CT), for nonspecific clinical presentation. However, it has important clinical implications for early diagnosis and treatment as indicated in our case.

CASE PRESENTATION

An 84-year-old man presented to the emergency department for evaluation of upper back pain. The patient had a history of hypertension, diabetes mellitus, and was a former smoker. He had normal vital signs, an unremarkable physical examination, and a body mass index of 25. His laboratory studies showed a normal blood cell count and serum chemistry, including serum calcium level and α-fetoprotein, but mildly elevated liver function tests.

The patient's chest CT angiography showed no evidence of thoracic aortic dissection, penetrating atherosclerotic ulceration, or pulmonary artery embolism. Besides emphysematous changes in the lung, the chest CT was within normal limits. Liver CT demonstrated several subtle, relatively low-density, space-occupying lesions in both lobes of his liver, the largest in the right lobe, measuring nearly 8 cm with a prominent, contrast-enhanced vessel at the periphery (Figure 1).

Abdominal magnetic resonance imaging (MRI) showed hepatomegaly (the liver measured up to 19.3 cm in craniocaudal length) and multiple, large intrahepatic space-occupying lesions, the largest measuring 9.9 cm × 9.5 cm in the right lobe, as well as multiple lesions in the inferior right and left lobe with enhancing capsules surrounding the hepatic lesions (Figure 2). The kidneys, pancreas, spleen, and biliary ducts showed no abnormalities.

An ultrasound-guided core needle biopsy of the liver was performed. Flow cytometry showed a monoclonal B-cell population that was mostly intermediate to large based on forward scattered light characteristics. Immunohistochemical staining was positive for *CD20, BCL2, BCL6*, and *CD45* in the neoplastic cells. Anaplastic lymphoma kinase (ALK), *CD15*, *CD30*, and *CD10* were negative, as were cytokeratin AE1/AE3 and pan-melanoma. *CD3* highlighted background T cells. Ki-67 highlighted a proliferative index of approximately 75%, and the MYC stain demonstrated 50% positivity. This was consistent with diffuse large B-cell lymphoma (DLBCL). However, there was insufficient tissue on the MUM1-stained slide; therefore, it was inconclusive to distinguish a

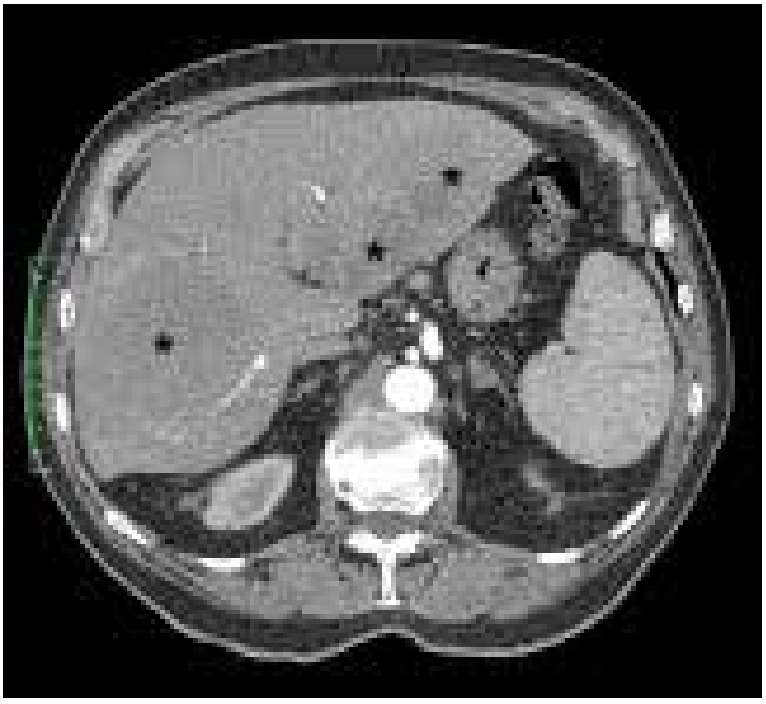
nongerminal center derived from germinal center–derived DLBCL.

Two weeks after the initial CT examination, the patient's condition quickly deteriorated, and he was admitted for severe weakness with evidence of severe hypercalcemia, hyperuricemia, and renal insufficiency (Table). His lactate dehydrogenase (LDH), a nonspecific marker of tissue turnover, was severely elevated at 1027 IU/L (reference range, 105-333 IU/L). The patient received calcitonin, zoledronic acid, IV fluid for hypercalcemia and acute renal insufficiency, and rasburicase for severe hyperuricemia.

To get additional tissue for further tumor characterization, a repeat liver biopsy was performed along with other diagnostic tests, including head MRI, bone marrow biopsy, and fluorodeoxyglucose (FDG) full-body positron emission tomography (PET). Repeat liver biopsy showed only necrotic debris with immunostaining positive for *CD20* and negative for *CD3*. B-cell lymphomas tend to retain *CD20* expression after necrosis, so the presence of *CD20* staining was consistent with a necrotic tumor. Again, there was insufficient tissue on the MUM1-stained slide. Head MRI showed no evidence of tumor involvement. Full-body PET showed abnormally elevated standardized uptake value (SUV) of radioactive tracers in several areas: multifocal, large area uptake within both right (SUV, 19) and left (SUV, 24) hepatic lobe (Figure 3A), retroperitoneal lymph node (SUV, 3.9), and a right lateral pleural-based nodule (SUV, 17.9) (Figure 3B). There was no uptake in the spleen, bone, mediastinum, or other parts of the lung. Attenuation CT obtained with PET again detected those lesions in the liver but also a new, right lateral subpleural-based mass (11 mm) that was not present on the initial CT obtained a month earlier. Bone marrow biopsy showed normocellular marrow without dysplasia nor morphologic or immunophenotypic evidence of lymphoma/leukemia.

The diagnosis was primary DLBCL of the liver with retroperitoneal lymph nodes and right lung metastasis. The patient was started on systemic chemotherapy of R-CHOP (rituximab with reduced cyclophosphamide, doxorubicin, vincristine, and prednisone).

FIGURE 1 Axial Liver Computed Tomography Angiography



Asterisks indicate multiple, large hypo-dense lesions in the liver and a contrast-enhanced vessel at the periphery around a large lesion in the right lobe.

DISCUSSION

Lymphoma is a tumor that originates from hematopoietic cells typically presented as a circumscribed solid tumor of lymphoid cells.[1] Lymphomas are usually seen in the lymph nodes, spleen, blood, bone marrow, brain, gastrointestinal tract, skin, or other normal structures where lymphoreticular cells exist but very rarely in the liver.[2] PHL is extremely rare due to the lack of abundant lymphoid tissue in the normal liver.[3] It accounts for 0.4% of extra-nodal lymphomas and 0.016% of non-Hodgkin lymphoma.[4-6] The etiology of PHL is unknown but usually it develops in patients with previous liver disease: viral infection (hepatitis B and C, Epstein-Barr, and HIV), autoimmune disease, immunosuppression, or liver cirrhosis.[5-7]

The diagnosis of PHL can be challenging due to its rarity, vague clinical features, and nonspecific radiologic findings. The common presenting symptoms are usually vague and include abdominal pain or discomfort, fatigue, jaundice, weight loss, and fever.[5] Liver biopsy is essential to its diagnosis. The disease course is usually indolent among most patients with PHL. In our case, the patient presented with upper back pain but his condition deteriorated rapidly, likely due to the

TABLE Laboratory Values

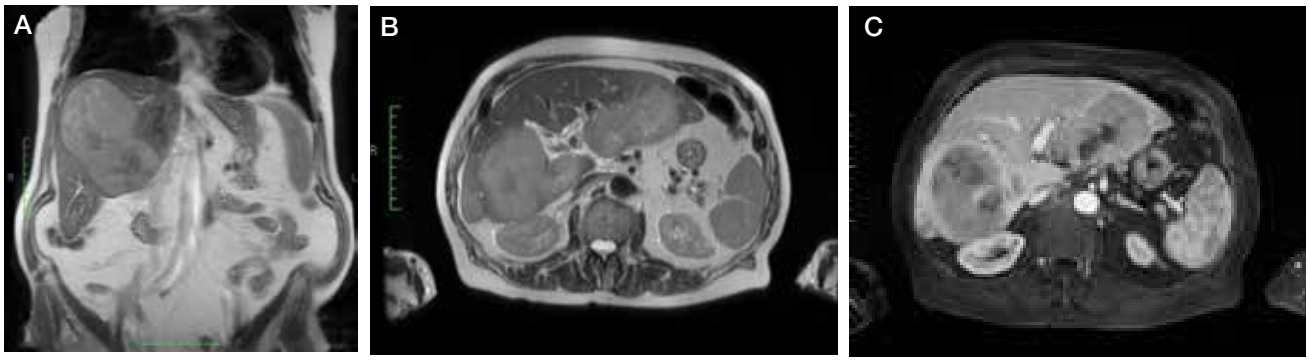
Laboratory studies	Results	Reference range
Sodium, mEq/L	138	136-145
Potassium, mEq/L	3.7	3.5-5.0
Chlorine, mEq/L	96[a]	98-107
Carbon dioxide, mEq/L	28	22-31
Blood urea nitrogen, mg/dL	28[a]	9-25
Creatinine, mg/dL	1.5[a]	0.7-1.3
Calcium, mg/dL	14.0[a]	8.4-10.4
Aspartate transaminase, U/L	58[a]	5-34
Alanine aminotransferase, U/L	26	8-40
Alkaline phosphate, U/L	211[a]	40-150
Total bilirubin, mg/dL	1	0.2-1.2
α-fetoprotein, ng/mL	1.6	1.0-8.8
D-dimer, ng/mL	429[a]	< 243
Parathyroid hormone, pg/mL	< 4[a]	8.7-77.7

[a]Value not in reference range.

advanced stage of the disease. Diagnosis of liver lymphoma depends on a liver biopsy that should be compatible with the lymphoma. The criteria for diagnosis of PHL defined by Lei include (1) symptoms caused mainly by liver involvement at presentation; (2) absence of distant lymphadenopathy, palpable clinically at presentation or detected during staging radiologic studies; and (3) absence of leukemic blood involvement in the peripheral blood smear.[7] Other authors define PHL as having major liver involvement without evidence of extrahepatic involvement for at least 6 months.[8] In our case, the multiple large lesions of the liver are consistent with advanced stage PHL with retroperitoneal lymph nodes and right lung metastasis. DLBCL is the most common histopathological type of lymphoma (65.9%). Other types have been described less commonly, including diffuse mixed large- and small-cell, lymphoblastic, diffuse histiocytic, mantle cell, and small noncleaved or Burkitt lymphoma.[5-7]

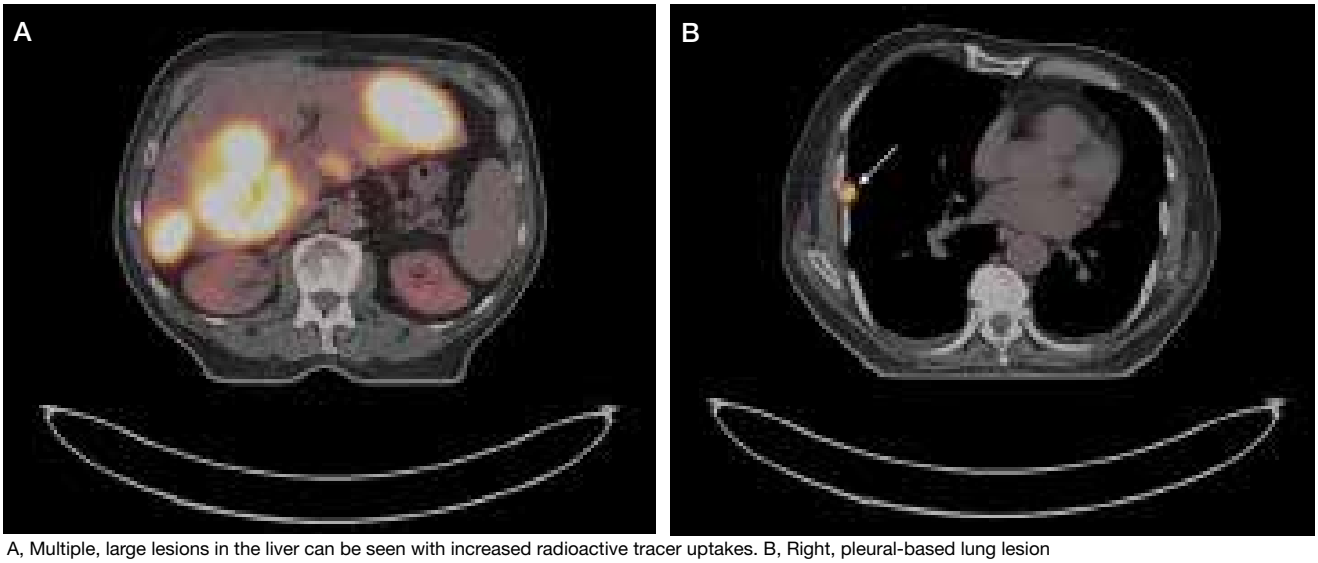
Currently, there is no consensus on PHL treatment. The therapeutic options include surgery, chemotherapy, radiation therapy, or a combination of therapies.[7] Most evidence regarding treatment and tumor response comes from case series, as PHLs are rare. Surgical resection in a series of 8 patients showed a cumulative 1- and 2-year survival rate of 66.7% and 55.6%, respectively.[9] Chemotherapy is the recommended treatment option for extra-nodal DLBCL, making it a choice also for the treatment of PHL.[10] Page and colleagues demonstrated that combination chemotherapy regimens helped achieve remission for 83.3% of patients.[11] Since PHL is chemo-sensitive, most patients are treated with chemotherapy alone or in combination with surgery and radiotherapy. The most common chemotherapy regimen is R-CHOP for

FIGURE 2 Magnetic Resonance Images of the Abdomen



A, T2-weighted coronal image of liver lesions that indicate a relatively high T2 signal compared with the remainder of the hepatic parenchyma. B, T2-weighted axial image shows iso- to hyper-intense hepatic lesions. C, Contrast-enhanced, fat-saturated T1-weighted image shows minimal lesion enhancement.

FIGURE 3 Fused Computed and Positron Emission Tomography



A, Multiple, large lesions in the liver can be seen with increased radioactive tracer uptakes. B, Right, pleural-based lung lesion can be seen with increased radioactive tracer uptake.

CD20-positive B-cell lymphoma. The use of the R-CHOP regimen has been reported to achieve complete remission in primary DLBCL of the liver.[12]

CONCLUSIONS

Primary DLBCL of the liver is a very rare disease without specific clinical manifestations, biochemical indicators, or radiologic features except for space-occupying liver lesions. However, patients' conditions can deteriorate rapidly at an advanced stage, as demonstrated in our case. DLBCL requires a high level of suspicion for its early diagnosis and treatment and should be considered in the differential diagnosis for any hepatic space-occupying lesions.

Acknowledgments

We appreciate Lynne Dryer, ARNP, for her clinical assistance with this patient and in the preparation of the manuscript.

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Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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Ethics and consent

Patient consent for the publication was obtained from the patient in this case report.

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