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An unusual case of primary hepatic lymphoma with dramatic but unsustained response to bendamustine plus rituximab and literature review

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Abstract

Objectives: Primary hepatic lymphoma is an uncommon cause of hepatic space-occupying lesions.

Methods: We describe the case of a 73-year-old man with primary hepatic lymphoma, who presented with a low-grade fever and lower limb weakness which had progressed in the past 2 months.

Results: Abdominal ultrasound and computed tomography showed multiple small hepatic tumors. Echo-guided biopsy of the hepatic tumor demonstrated primary hepatic diffuse large B cell lymphoma. Moreover, bone marrow was uninvolved, but the bone marrow smear disclosed hemophagocytosis, which is uncommon in diffuse large B cell lymphoma. Chemotherapy with bendamustine and rituximab treatment was initiated with a dramatic response: hepatic tumors markedly shrank in size shown by follow-up computed tomography and the patient returned to his normal life. Nevertheless, the response was sustained for only 8 months. Finally, the disease resisted further chemotherapy and this patient died of a severe *Klebsiella pneumoniae* infection.

Conclusion: Chemotherapy with bendamustine and rituximab has shown a dramatic, but not durable, response in the present case with old age and multiple comorbidities.

Keywords

Hemophagocytosis, primary hepatic lymphoma

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Introduction

Primary hepatic lymphoma (PHL) is confined to the liver without evidence of lymphomatous involvement in any other lymphoid structures, such as lymph nodes, the spleen, or bone marrow.[1] PHL is an extremely rare and poorly characterized malignancy, accounting for only 0.016% of all extranodal lymphoma.[2] PHL predominantly affects middle-aged males.[3–5] PHL is usually either diagnosed late or mis-diagnosed due to its lack of specific symptoms or characteristic imaging features. Currently, PHL is considered to be associated with persistent inflammatory processes, such as chronic hepatitis C virus infection, rheumatoid arthritis, Sjögren syndrome, primary biliary cirrhosis, and autoimmune hepatitis.[6] Even though the appropriate line of chemotherapy has not been yet established, most authors agree that chemotherapy is the best therapy choice. Here, we report a case of PHL confirmed by liver biopsy with initial presentation of low-grade fever and progressive bilateral lower limb weakness. Rituximab combined with bendamustine was then given with an excellent, but not durable, response.

Case report

A 73-year-old man visited an outpatient clinic because of poor appetite, progressive bilateral lower leg weakness, and low-grade fever, especially in afternoons, for 2 months. No significant travel or cluster or contact history was reported. His medications were for control of hypertension, type 2 diabetes mellitus, dyslipidemia, peripheral artery occlusive disease, and an old cerebrovascular accident.

On physical examination, his temperature was 38.2°C, blood pressure was 98/51 mmHg, and pulse was 108 beats per minute. He had decreased muscle power (score 4 out of

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Table 1. Laboratory data.

Laboratory data	Unit	Reference range	Baseline	After the first cycle of chemotherapy
Hematocrit	%	40.4–51.1	25.8	28.9
Hemoglobin	g/dL	13.2–17.2	8.6	9.6
White cell count	k/μL	3.54–9.06	9.03	3.63
Differential count	%			
Neutrophils		41.2–74.7	75	76.8
Band forms			2	0
Lymphocytes		21.2–51	9	19.3
Monocytes		3.1–8.0	12	0.8
Eosinophils		0.2–8.4	2	2.5
Platelet count	k/μL	148–339	48	174
Mean corpuscular volume	fL	80–100	79.4	84
Total bilirubin	mg/dL	0.3–1	1.32	0.86
AST	U/L	8–31	25	54
ALT	U/L	0–41	20	49
ALP	U/L	34–104	113	106
Albumin	g/dL	3.5–5.7	1.9	3.7
Lactate dehydrogenase	U/L	140–271	560	358
Ferritin	ng/mL	28–365	3178	2995
Triglyceride	mg/dL	0–150	519	210
Fibrinogen	mg/dL	205.3–372.8	462.9	402.3
FDP	μg/mL	0–4.6	12.3	38.9
D-Dimer	μg/mL	0–0.56	4.09	17.39

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; FDP: fibrin degradation product.

5) over his bilateral lower legs and a palpable liver (5 cm below the right subcostal border). No heart murmur, palpable spleen, or lymphadenopathy was noted.

After admission, laboratory data revealed normocytic anemia, thrombocytopenia, mild cholestasis, and elevated lactate dehydrogenase (LDH; the results were shown in Table 1 in detail). Furthermore, extensive septic workup for fever of an unknown origin was completed, including chest X-ray, sputum acid-fast stain, serum tuberculosis polymerase chain reaction, blood culture, serum anti-HIV test, and echocardiography. All above tests were negative. Due to the anemia and reverse albumin/globulin ratio, serum immunofixation electrophoresis was checked and revealed a thin band of IgM/kappa monoclonal gammopathy. Furthermore, serum beta-2 microglobulin levels were elevated to 7.75 mg/L. As a result, a hematologist was consulted and a bone marrow study was performed. Bone marrow smear showed severe hemophagocytosis (Figure 1) and no abnormal population or light chain restriction indicated by flow cytometry. Serum tests revealed hypertriglyceridemia and hyperferritinemia. Abdominal ultrasonography also showed marked splenomegaly (splenic index: 6.9 cm × 5.1 cm). Hemophagocytic syndrome (HPS) was confirmed, but the etiology was still unclear.

Moreover, abdominal ultrasonography disclosed multiple hypoechoic lesions up to 2 cm on both lobes (Figure 2(a)). However, the viral hepatitis profile was negative for hepatitis B or C infection. Tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9, squamous cell carcinoma antigen, and prostatic specific antigen, were all within normal range. Abdominal computed tomography (CT) showed multiple ill-defined poor enhancing nodular lesions on both hepatic lobes

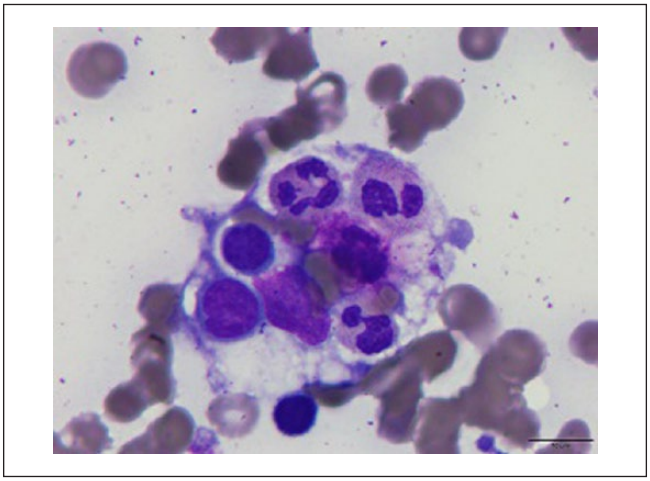

Figure 1. Bone marrow aspirate showing abnormal histiocytes and prominent phagocytosis of red cells, neutrophils, and platelets, compatible with hemophagocytosis under Liu's stain with 100× power field.

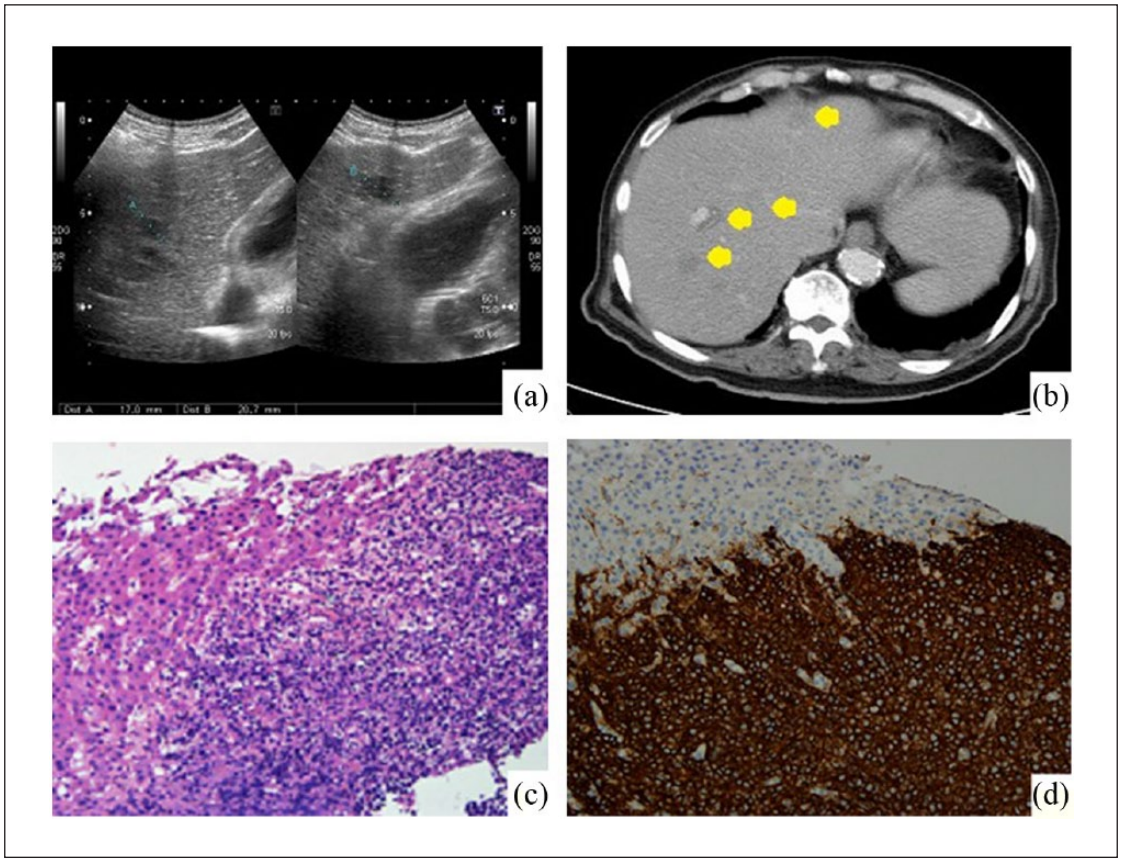

Figure 2. (a) Abdominal ultrasonography showing multiple hypoechoic lesions up to 2.07 cm on both lobes, (b) abdominal computed tomography showing ill-defined poor enhancing nodular lesions (yellow arrow) on both hepatic lobes, (c) the pathology of liver tumor specimen under H&E stain with 200× power field, and (d) these atypical cells were positive for CD20.

(Figure 2(b)). However, esophagogastroduodenoscopy and colonoscopy showed no evidence of gastrointestinal malignancy. Because the nature of multiple liver tumors was inconclusive, we performed a liver biopsy. Microscopic examination of the liver biopsy showed diffuse large B cell lymphoma (Figure 2(c)), identifying lymphoma cells CD20+/CD10−/BCL-6+/BCL-2+/cyclin D1−/EBER− (Figure 2(d)). Because of old age, multiple comorbidities, and the fragile clinical status of the present case, we initiated chemotherapy with rituximab and bendamustine (rituximab 375 mg/m^2 for 1 day; bendamustine 90 mg/m^2 for 2 days). After the first cycle of chemotherapy, follow-up laboratory data showed dramatic improvement of anemia, thrombocytopenia, hyperbilirubinemia, and hemophagocytosis indices, including triglyceride and ferritin levels (Table 1). After the second cycle of chemotherapy, abdominal CT revealed excellent treatment response with much smaller hypovascular lesions at both hepatic lobes compared with the prior study (Figure 3). However, a persistent fever occurred 1 month after finishing the total six cycles of chemotherapy with rituximab and bendamustine. Lymphoma relapse was highly suspected. However, whole body

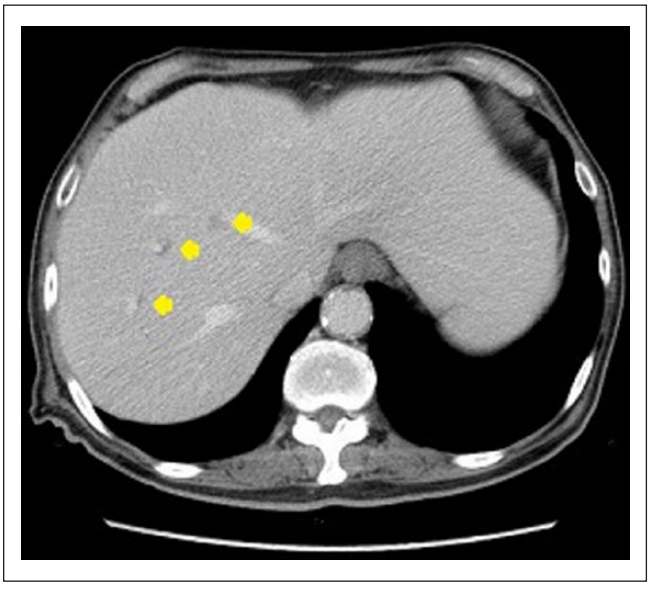

Figure 3. Small hypovascular hepatic lesions (yellow arrow) decreased in size compared with a prior study (Figure 2(b)) after the second cycle of chemotherapy.

positron emission tomography-computed tomography (PET-CT) showed no evidence of lymphoma recurrence. Repeated bone marrow study disclosed residual hemophagocytosis. Steroid therapy with methylprednisolone was administered and the fever subsided. Furthermore, the patient's general condition gradually improved. Unfortunately, 3 months after the last cycle of chemotherapy with rituximab and bendamustine, a follow-up bone marrow study revealed aggregations of abnormal lymphoid cells, compatible with lymphoma with marrow involvement. As a result, treatment was switched to R-mini-CHOP (rituximab 375 mg/m^2 for 1 day, cyclophosphamide 400 mg/m^2 for 1 day, doxorubicin 25 mg/m^2 for 1 day, vincristine 1 mg/day for 1 day, and prednisolone 30 mg/day for 5 days), but a poor response was noted. The patient then received two cycles of R-EPOCH (rituximab 375 mg/m^2 for 1 day, etoposide 50 mg/m^2 for 4 days, cyclophosphamide 750 mg/m^2 for 1 day, doxorubicin 10 mg/m^2 for 4 days, vincristine 0.5 mg/day for 4 days, and prednisolone 30 mg/day for 5 days). A follow-up bone marrow study still showed residual lymphoma cells and hemophagocytosis. The disease was thereafter resistant to chemotherapy, after which the patient finally died of severe *Klebsiella pneumoniae* infection.

Discussion

The definition of extremely rare PHL confines the involvement to the liver without including any other lymphoid structures, such as the spleen, lymph nodes, or bone marrow.[1] Extranodal lymphomas account for 10%–25% of non-Hodgkin's lymphomas, in which PHL is responsible for less than 1%.[2,7,8] Due to its rarity, the absence of specific clinical manifestation, and imaging findings, cases with PHL are often late- or mis-diagnosed as cholangiocarcinoma, hepatocellular carcinoma, or liver metastases and thus have been inappropriately treated by chemotherapy or surgical resection.[9–11]

PHL affects men about twofold more than women and the usual age for presenting symptoms is the fifth decade.[12] The most common symptoms of PHL at initial presentation are abdominal pain and general malaise. Other clinical complaints are also non-specific, including nausea with vomiting, early satiety, weight loss, fatigue, difficulty in ambulation, limb weakness, and jaundice, often of short duration.[4,13–17] Our case had an unusual presentation with bilateral lower limb weakness and low-grade fever. Physical examination may disclose hepatomegaly, palpable liver, and leg edema.[13,14,16,17] Fulminant liver failure has been reported, but is rare.[18,19] Laboratory data may reveal elevated LDH and normal tumor marker levels.[4,13,15–17] Furthermore, imaging findings in PHL are also non-specific. Solitary or multiple lesions and diffuse liver infiltration lesions mimicking metastatic carcinoma have been reported.[20] The appearance of PHL is often hypoechoic on abdominal ultrasonography and low attenuated on contrast-enhanced CT. Rim enhancement, central necrosis, or target lesions have also been described.[5,21,22]

PHL is considered to be associated with persistent inflammatory processes, such as autoimmune disease or chronic viral infection of HCV, HBV, and HIV.[6,20] However, our case was negative for HCV, HBV, and HIV infection. Because laboratory data and image studies reveal no specific findings for PHL, liver core biopsy of the target lesions under ultrasound or CT guidance is necessary for accurate diagnosis. Bone marrow biopsy and other image studies must also be performed for staging to confirm that lymphoma is only confined to the liver.[4] The most common histologic subtype of PHL is diffuse large B cell lymphoma as shown in our present case. Additionally, mucosa-associated lymphoid tissue (MALT) lymphoma, Burkitt's lymphoma, follicular lymphoma, anaplastic large-cell lymphoma, mantle cell lymphoma, and hepatosplenic T cell lymphoma have also been reported.[4,6,20,23]

Since diffuse large B cell lymphoma is chemosensitive, chemotherapy is usually the first-line treatment modality for the majority of patients. Furthermore, multi-modality treatments with concurrent surgery or radiotherapy have previously been applied to patients.[3,11,24] The standard chemotherapy treatment for diffuse large B cell lymphoma is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The treatment response and survival significantly increase with the addition of rituximab, a chimeric monoclonal antibody.[25] However, the most appropriate treatment must be individualized depending on the patient's performance status and comorbidity. Poor prognostic factors for PHL treatment include advanced age, constitutional symptoms, cirrhosis, bulky disease, unfavorable histologic subtypes, high proliferation rate, and elevated LDH and β_2-microglobulin levels.[26,27] Although R-CHOP is the standard first-line chemotherapy treatment for patients with CD20+ diffuse large B cell lymphoma, most of the available data focus primarily on younger patients with limited comorbidities.[28] For frail elderly patients, as in our case, attenuated immunochemotherapy treatment (R-miniCHOP or bendamustine with rituximab (B-R)) has been proposed as an alternative therapeutic regimen with favorable efficacy and acceptable toxicity.[29–32] However, the number of cases utilizing B-R treatment is relatively small and further prospective studies with larger sample sizes are warranted. As a result, the German High-Grade Non-Hodgkin Lymphoma Study Group has introduced a phase II trial-"B-R-ENDA" with B-R in elderly patients with aggressive lymphoma for whom treatment with CHOP-like chemotherapy is not feasible.[29,33]

In our case, the bone marrow study revealed hemophagocytosis. HPS represents an immune response disorder, which may be caused by infections, autoimmune diseases, disseminated carcinomas, and hematologic malignancies, and especially non-Hodgkin's lymphoma; the so-called lymphoma-associated HPS.[34,35] The common clinical manifestations include persistent high-grade fever, hepatosplenomegaly, cytopenia, coagulopathy with hypofibrinogenemia, liver dysfunction, hypertriglyceridemia, hyperferritinemia,

Table 2. Revised diagnostic guidelines for hemophagocytic syndrome.

Molecular diagnosis
PRF1, UNC13D, STXBP2, RAB27A, STX11, SH2D1A, or XIAP
Or
⩾5 of the following 8 diagnostic criteria
Fever
Splenomegaly
Cytopenias (affecting ⩾2 of 3 lineages)
Hemoglobin < 9 g/dL
Platelets < 100,000/μL
Neutrophils < 1000/μL
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ⩾ 265 mg/dL
Fibrinogen ⩽ 150 mg/dL
Hemophagocytosis in bone marrow, spleen, or lymph nodes
Ferritin ⩾ 500 ng/mL
Decreased or absent NK-cell activity
Soluble CD25 ⩾ 2400 U/mL

and hemophagocytosis in bone marrow or other reticuloendothelial organs.[36] HPS is regarded as a poor prognostic factor with reduced survival in lymphoma.[37] The criteria for the diagnosis of lymphoma-associated HPS are listed in Table 2.[38] Our case completely fits the diagnostic criteria. Previous studies have shown a higher prevalence of hemophagocytosis in subjects with T- or NK-cell lymphoma than in B cell lymphoma.[39] We searched case reports of primary hepatic diffuse large B cell lymphoma on "PubMed" from 2006 to 2015 (Table 3).[4,9,10,13–18,22,24,26,40–56] Among a total of 29 case reports (20 with bone marrow information), no hemophagocytosis has ever been reported. The differences with regard to survival, clinical, and pathologic characteristics between T-/NK-cell- and B-cell-associated HPS remain unclear.[57] In the Japanese literature, a subtype of diffuse large B cell lymphoma, an Asian variant of intravascular lymphomatosis, was emphasized by its association with HPS.[58,59] The association between CD5-positive B cell lymphoma and HPS has been proposed.[37]

Table 3. Case reports of primary hepatic diffuse large B cell lymphoma found on PubMed from 2006 to 2015.

Case	Age	Sex	Symptoms/signs	Histology subtype	Bone marrow hemophagocytosis	HBsAg/anti-HCV/anti-HIV	Treatment
1[39]	56	F	Malaise, weight loss, and fever for 2 months	DLBCL	–	−/−/NA	R-CHOP
2[40]	58	M	Right upper abdominal pain	DLBCL	–	NA/NA/NA	Surgery followed by R-CHOP
3[41]	63	M	A 20-kg weight loss in 6 months, hyporexia, asthenia, occasional fever, night sweats, abdominal pain, jaundice	DLBCL	–	−/−/−	Surgery followed by R-CHOP
4[13]	66	F	RUQ abdominal pain	DLBCL	–	−/−/−	R-CHOP
5[14]	35	M	Fatigue, anorexia, weight loss, RUQ abdominal pain	DLBCL	–	+/+/−	R-CHOP
6[24]	45	M	Epigastric and RUQ pain, pruritus, itching, nonbilious vomiting, fatigue, weight loss	DLBCL	–	−/+/−	R-CHOP
7[42]	82	F	High-grade fever	DLBCL	–	NA/NA/NA	Nil (poor condition)
8[4]	70	M	Right hypochondrium dull ache, myalgias, mildly elevated total bilirubin levels	DLBCL	–	−/−/NA	R-CHOP
9[15]	65	F	Abdominal pain, fever, weight loss	DLBCL	–	NA/+/NA	CHOP
10[43]	76	F	Chronic right-side chest and abdominal pain	DLBCL	–	−/−/−	Surgery
11[44]	57	F	Generalized edema	DLBCL	NA	−/−/NA	Refuse
12[16]	69	M	Weight loss, mental confusion, nocturnal fever, difficulty in ambulation, limb weakness, general fatigue	DLBCL	–	−/−/−	R-CHOP
13[45]	47	M	Fever, jaundice	DLBCL	NA	NA/NA/NA	Nil (poor condition)
14[46]	55	F	Intermittent low-grade fever, weight loss	DLBCL	NA	−/−/−	Surgery
15[47]	50	M	Hypochondrium pain	DLBCL	NA	NA/NA/NA	R-CHOP
16[48]	68	F	Right hypochondriac pain, anorexia	DLBCL	–	−/−/NA	R-CHOP
17[9]	59	F	Fatigue, weight loss	DLBCL	–	−/−/−	R-CHOP
18[10]	58	M	General fatigue, abdominal discomfort	DLBCL	–	−/+/NA	R-CHOP
19[17]	67	M	Fatigue, anorexia, jaundice, RUQ abdominal pain	DLBCL	–	−/−/NA	R-CHOP
20[49]	71	M	RUQ abdominal pain	DLBCL	–	NA/NA/NA	R-CHOP

(Continued)

Table 3. (Continued)

Case	Age	Sex	Symptoms/signs	Histology subtype	Bone marrow hemophagocytosis	HBsAg/anti-HCV/anti-HIV	Treatment
21[50]	72	F	Early satiety, abdominal discomfort, rapid weight loss	DLBCL	–	NA/NA/NA	Cyclophosphamide and methylprednisolone
22[22]	25	M	Early satiety, fever, weight loss	DLBCL	NA	−/−/−	NA
23[26]	68	F	RUQ abdominal pain, weakness, anorexia, weight loss	DLBCL	–	−/−/−	R-CHOP
24[18]	53	F	Fever, chills, weight loss, myalgia, arthralgia, epigastric discomfort with nausea and vomiting	DLBCL	–	−/−/−	R-C × 2 + R-DHAP × 2 + R-CHOP × 2
25[51]	64	M	Cough, chills, fever	DLBCL	NA	+/−/−	R-CHOP
26[52]	67	M	Fever, appetite loss, jaundice	DLBCL	NA	NA/+/NA	Systemic chemotherapy
27[53]	69	M	Jaundice	DLBCL	NA	NA/NA/NA	NA
28[54]	73	M	Right flank pain	DLBCL	NA	−/−/NA	R-CHOP
29[55]	55	M	No symptoms	DLBCL	–	NA/+/NA	Surgery followed by CEOP

HBsAg: hepatitis B surface antigen; anti-HCV: anti-hepatitis C virus antibody; anti-HIV: anti-human immunodeficiency virus antibody; DLBCL: diffuse large B cell lymphoma; NA: not available; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RUQ: right upper quadrant; R-C: rituximab and cyclophosphamide; R-DHAP: rituximab, cytarabine, and cisplatin; CEOP: cyclophosphamide, epirubicin, vincristine, and oral prednisolone.

Lymphoma-associated HPS is caused by the hyperactivation of T-cells and macrophages, resulting in the overproduction of Th1 cytokines, such as interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-α. The cytokine storm is directly or indirectly induced by Epstein–Barr virus–infected neoplastic cells. In contrast to T-/NK-cell lymphoma, the cytokine storm in B cell lymphoma is caused by reactive T-cells and neoplastic cells themselves with elevated serum levels of TNF-α, IL-6, IL-10, and IL-12.[35,60]

Conclusion

In conclusion, PHL, despite its rarity, should be considered in the differential diagnosis of hepatic space-occupying lesions. Furthermore, the presence of HPS should be documented as it may serve as a prognostic factor for treatment outcomes. Chemotherapy with bendamustine and rituximab has shown a dramatic, but not durable, response in the present case with old age and multiple comorbidities. Further studies to determine appropriate chemotherapy treatment for PHL are warranted.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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