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

Sih-Han Liao1, Yin-Kai Chen2, Shan-Chi Yu3, Ming-Shiang Wu2, Hsiu-Po Wang2 and Ping-Huei Tseng2

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

Date received: 19 October 2016; accepted: 17 April 2017

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 7) 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.

1National Taiwan University Cancer Center, Taipei, Taiwan
2Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
3Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan

Corresponding Author:
Ping-Huei Tseng, Department of Internal Medicine, National Taiwan University Hospital, 10002, No. 7, Chung-Shan South Road, Taipei, Taiwan. Email: pinghuei@ntu.edu.tw
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 alphafetoprotein, 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.

| 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 | %      | 41.2–74.7       | 75       | 76.8                                |
| Neutrophils     | %    | 41.2–74.7       | 75       | 76.8                                |
| Band forms      |      | 2               | 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.
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
**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. Extralymph nodes account for 10%–25% of non-Hodgkin’s lymphomas, in which PHL is responsible for less than 1%.[2,7] 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, abdominal pain and general malaise. Other clinical complaints are also non-specific, including nausea with vomiting, abdominal pain and general malaise.

Our case had an unusual presentation with bilateral lower limb weakness and low-grade fever. Physical examination disclosed hepatomegaly, palpatable liver, and leg edema.[13,14,16] Fulminant liver failure has been reported, but is rare.[18,19] Laboratory data may reveal elevated LDH and normal tumor marker levels.[13,15] Furthermore, imaging findings in PHL are also non-specific. Solitary or multiple lesions and diffuse liver infiltration lesions mimicking metastatic carcinoma have been reported.[10] 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.[2,21,22] PHL is considered to be associated with persistent inflammatory processes, such as autoimmune disease or chronic viral infection of HCV, HBV, and HIV.[6,23] 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 β₂-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,
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 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 |

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 |
|------|-----|-----|----------------|-------------------|-------------------------------|--------------------------|------------|
| 139  | 56  | F   | Malaise, weight loss, and fever for 2 months | DLBCL – | –/–/NA | R-CHOP |
| 240  | 58  | M   | Right upper abdominal pain | DLBCL – | NA/NA/NA | Surgery followed by R-CHOP |
| 341  | 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 |
| 413  | 66  | F   | RUQ abdominal pain | DLBCL – | –/–/– | R-CHOP |
| 514  | 35  | M   | Fatigue, anorexia, weight loss, RUQ abdominal pain | DLBCL – | +/+– | R-CHOP |
| 624  | 45  | M   | Epigastric and RUQ pain, pruritus, itching, nonbilious vomiting, fatigue, weight loss | DLBCL – | –/+– | R-CHOP |
| 742  | 82  | F   | High-grade fever | DLBCL – | NA/NA/NA | Nil (poor condition) |
| 84   | 70  | M   | Right hypochondrium dull ache, myalgias, mildly elevated total bilirubin levels | DLBCL – | –/–/NA | R-CHOP |
| 915  | 65  | F   | Abdominal pain, fever, weight loss | DLBCL – | NA/+NA | CHOP |
| 1043 | 76  | F   | Chronic right-side chest and abdominal pain | DLBCL – | –/–/– | Surgery |
| 1144 | 57  | F   | Generalized edema | DLBCL NA | –/–/NA | Refuse |
| 1216 | 69  | M   | Weight loss, mental confusion, nocturnal fever, difficulty in ambulation, limb weakness, general fatigue | DLBCL – | –/–/– | R-CHOP |
| 1345 | 47  | M   | Fever, jaundice | DLBCL NA | NA/NA/NA | Nil (poor condition) |
| 1446 | 55  | F   | Intermittent low-grade fever, weight loss | DLBCL NA | –/–/– | Surgery |
| 1547 | 50  | M   | Hypochondrium pain | DLBCL NA | NA/NA/NA | R-CHOP |
| 1648 | 68  | F   | Right hypochondriac pain, anorexia | DLBCL – | –/–/– | R-CHOP |
| 1749 | 59  | F   | Fatigue, weight loss | DLBCL – | –/–/– | R-CHOP |
| 1840 | 58  | M   | General fatigue, abdominal discomfort | DLBCL – | –/+NA | R-CHOP |
| 1947 | 67  | M   | Fatigue, anorexia, jaundice, RUQ abdominal pain | DLBCL – | –/–/– | R-CHOP |
| 2049 | 71  | M   | RUQ abdominal pain | DLBCL – | NA/NA/NA | R-CHOP |

(Continued)
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.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by research grants funded by the Ministry of Science and Technology (MOST 105-2325-B-002-041-).

**Informed consent**

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

**References**

1. Caccamo D, Pervez NK and Marchevsky A. Primary lymphoma of the liver in the acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1986; 110: 553–555.
2. Lei KI. Primary non-Hodgkin’s lymphoma of the liver. *Leuk Lymphoma* 1998; 29: 293–299.
3. Yang XW, Tan WF, Yu WL, et al. Diagnosis and surgical treatment of primary hepatic lymphoma. *World J Gastroenterol* 2010; 16: 6016–6019.
4. Myoteri D, Dellaportas D, Arkoumani E, et al. Primary hepatic lymphoma: a challenging diagnosis. *Case Rep Oncol Med* 2014; 2014; 212598.
5. Elsayes KM, Menias CO, Willatt JM, et al. Primary hepatic lymphoma: imaging findings. *J Med Imaging Radiat Oncol* 2009; 53: 373–379.
6. Kikuma K, Watanabe J, Oshiro Y, et al. Etiological factors in primary hepatic B-cell lymphoma. *Virchows Arch* 2012; 460: 379–387.
7. Freeman C, Berg JW and Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972; 29: 252–260.
8. Rudders RA, Ross ME and DeLellis RA. Primary extranodal lymphoma: response to treatment and factors influencing prognosis. *Cancer* 1978; 42: 406–416.
9. Steller EJ, van Leeuwen MS, van Hillegersberg R, et al. Primary lymphoma of the liver: a complex diagnosis. *World J Radiol* 2012; 4: 53–57.
10. Kaneko K, Nishie A, Arima F, et al. A case of diffuse-type primary hepatic lymphoma mimicking diffuse hepatocellular carcinoma. *Ann Nucl Med* 2011; 25: 303–307.

**Table 3. (Continued)**

| Case | Age | Sex | Symptoms/signs | Histology subtype | Bone marrow hemophagocytosis | HBSAg/anti-HCV/anti-HIV | Treatment |
|------|-----|-----|----------------|-------------------|-----------------------------|-------------------------|-----------|
| 21   | 72  | F   | Early satiety, abdominal discomfort, rapid weight loss | DLBCL | − | NA/NA/NA | Cyclophosphamide and methylprednisolone |
| 22   | 25  | M   | Early satiety, fever, weight loss | DLBCL | NA | −/−/− | NA |
| 23   | 68  | F   | RUQ abdominal pain, weakness, anorexia, weight loss | DLBCL | − | −/−/− | R-CHOP |
| 24   | 53  | F   | Fever, chills, weight loss, myalgia, arthralgia, epigastic discomfort with nausea and vomiting | DLBCL | − | −/−/− | R-C × 2 + R-DHAP × 2 + R-CHOP |
| 25   | 64  | M   | Cough, chills, fever | DLBCL | NA | +/−/− | R-CHOP |
| 26   | 67  | M   | Fever, appetite loss, jaundice | DLBCL | NA | NA+/−/NA | Systemic chemotherapy |
| 27   | 69  | M   | Jaundice | DLBCL | NA | NA/NA/NA | NA |
| 28   | 73  | M   | Right flank pain | DLBCL | NA | −/−/− | R-CHOP |
| 29   | 55  | M   | No symptoms | DLBCL | NA | 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.
11. Ghose A, Sethi N, Li G, et al. Chemotherapy versus surgery in primary B-cell lymphoma masquerading as Klatskin tumor—a diagnostic and therapeutic dilemma. *Am J Ther* 2011; 18: e255–e257.

12. Agmon-Levin N, Berger I, Shatalrid M, et al. Primary hepatic lymphoma: a case report and review of the literature. *Age Ageing* 2004; 33: 637–640.

13. Aitelhaj M, Akaaboun S, Lkhouyaali S, et al. Primary hepatic lymphoma: a case report. *J Gastrointest Cancer* December 2014; 45(Suppl 1): 212–215.

14. Somaglino C, Pramaggiore P and Polastri R. Primary hepatic lymphoma in a patient with chronic hepatitis B and C infection: diagnostic pitfalls and therapeutic challenge. *Updates Surg* 2014; 66: 89–90.

15. Zentar A, Tarchouli M, Elkaoui H, et al. Primary hepatic lymphoma. *J Gastrointest Cancer* 2014; 45: 380–382.

16. Aitelhaj M, Akaaboun S, Lkhouyaali S, et al. Primary hepatic lymphoma: a case report and review of the literature. *Age Ageing* 2014; 45(Suppl 1): 212–215.

17. Ma YJ, Chen EQ, Chen XB, et al. Primary hepatic diffuse large B cell lymphoma: a case report: primary hepatic diffuse large B cell lymphoma. *Hepat Mon* 2011; 11: 203–205.

18. Haider FS, Smith R and Khan S. Primary hepatic lymphoma presenting as fulminant hepatic failure with hyperferritinemia: a case report. *J Med Case Rep* 2008; 2: 279.

19. Thompson DR, Faust TW, Stone MJ, et al. Hepatic failure as the presenting manifestation of malignant lymphoma. *Clin Lymphoma* 2001; 2: 123–128.

20. Swadley MJ, Deliu M, Mosunjac MB, et al. Primary and secondary hepatic lymphomas diagnosed by image-guided fine-needle aspiration: a retrospective study of clinical and cytomorphologic findings. *Am J Clin Pathol* 2014; 141: 119–127.

21. Gatselis NK and Dalekos GN. Education and imaging. Hepatobiliary and pancreatic: primary hepatic lymphoma. *J Gastroenterol Hepatol* 2011; 26: 210.

22. Delshad SD, Ahdoot JJ and Portocarrero DJ. Primary hepatic lymphoma. *Clin Gastroenterol Hepatol* 2010; 8: e49–e50.

23. Masood A, Kairouz S, Hudhud KH, et al. Primary non-Hodgkin lymphoma of liver. *Curr Oncol* 2009; 16: 74–77.

24. Tammana VS, Begum R, Oneal P, et al. A novel use of early radiation therapy in the treatment of hyperbilirubinemia in a patient with primary hepatic lymphoma and chronic hepatitis C. *Case Rep Gastrointest Med* 2014; 742456.

25. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007; 109: 1857–1861.

26. Serrano-Navarro I, Rodriguez-Lopez JF, Navas-Espejo R, et al. Primary hepatic lymphoma: favorable outcome with chemotherapy plus rituximab. *Rev Esp Enferm Dig* 2008; 100: 724–728.

27. Noronha V, Shafi NQ, Obando JA, et al. Primary non-Hodgkin’s lymphoma of the liver. *Crit Rev Oncol Hematol* 2005; 53: 199–207.

28. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235–242.

29. Walter E, Schmitt T, Dietrich S, et al. Rituximab and bendamustine in patients with CD20+ diffuse large B-cell lymphoma not eligible for cyclophosphamide, doxorubicin, vincristine and prednisone-like chemotherapy. *Leuk Lymphoma* 2012; 53: 2290–2292.

30. Horn J, Kleber M, Hieke S, et al. Treatment option of bendamustine in combination with rituximab in elderly and frail patients with aggressive B-non-Hodgkin lymphoma: rational, efficacy, and tolerance. *Ann Hematol* 2012; 91: 1579–1586.

31. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2011; 12: 460–468.

32. Ackler S, Mitten MJ, Chen J, et al. Navitoclax (ABT-263) and bendamustine +/- rituximab induce enhanced killing of non-Hodgkin’s lymphoma tumours in vivo. *Br J Pharmacol* 2012; 167: 881–891.

33. Weidmann E, Neumann A, Fauth F, et al. Phase II study of bendamustine in combination with rituximab as first-line treatment in patients 80 years or older with aggressive B-cell lymphomas. *Ann Oncol* 2011; 22: 1839–1844.

34. Czuchlewski DR, Oupadla SL and Zhang QY. Diffuse large B-cell lymphoma with florid hemophagocytosis. *Int J Hematol* 2009; 89: 1–2.

35. Ohno T, Ueda Y, Nagai K, et al. The serum cytokine profiles of lymphoma-associated hemophagocytic syndrome: a comparative analysis of B-cell and T-cell/natural killer cell lymphomas. *Int J Hematol* 2003; 77: 286–294.

36. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131.

37. Miyahara M, Sano M, Shibata K, et al. B-cell lymphoma-associated hemophagocytic syndrome: clinicopathological characteristics. *Ann Hematol* 2000; 79: 378–388.

38. Devitt K, Cerny J, Switzer B, et al. Hemophagocytic lymphohistiocytosis secondary to T-cell/histiocyte-rich large B-cell lymphoma. *Leuk Res Rep* 2014; 3: 42–45.

39. Hirai H, Shimazaki C, Hatsuse M, et al. Autologous peripheral blood stem cell transplantation for adult patients with B-cell lymphoma-associated hemophagocytic syndrome. *Leukemia* 2001; 15: 311–312.

40. Miyagawa K, Shibata M, Noguchi H, et al. Methotrexate-related primary hepatic lymphoma in a patient with rheumatoid arthritis. *Intern Med* 2015; 54: 401–405.

41. Peng JX, Wang LZ, Tan ZJ, et al. Concomitant non-Hodgkin’s lymphoma in colon and liver: report of a rare case and review of literature. *Int J Clin Exp Pathol* 2015; 8: 3257–3261.

42. Chahdi Beltrame M, De Santibanes M, Ardiles V, et al. Primary related primary hepatic lymphoma in colon and liver: report of a rare case and review of literature. *Int J Clin Exp Pathol* 2015; 8: 3257–3261.

43. Takeuchi N and Naba K. Primary hepatic lymphoma is difficult to discriminate from a liver abscess. *Case Rep Gastrointest Med* 2014; 742456.

44. Valladolid G, Adams LL, Weisenberg E, et al. Primary hepatic lymphoma of liver. *J Hepatobiliary and pancreatic: primary hepatic lymphoma.*

45. Lee JA, Jeong WK, Min JH, et al. Primary hepatic lymphoma mimicking acute hepatitis. *Clin Mol Hepatol* 2013; 19: 320–323.
46. 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.

47. Pan B, Wang CS, Han JK, et al. 18F-fluorodeoxyglucose PET/CT findings of a solitary primary hepatic lymphoma: a case report. World J Gastroenterol 2012; 18: 7409–7412.

48. Okada T, Nishimura T, Nagashima Y, et al. A case of primary hepatic malignant lymphoma accompanied by cholecystitis. Gan To Kagaku Ryoho 2012; 39: 2018–2020.

49. Zafar MS, Aggarwal S and Bhalla S. Complete response to chemotherapy in primary hepatic lymphoma. J Cancer Res Ther 2012; 8: 114–116.

50. Li Y, Du Y and Yang HF. Primary hepatic lymphoma: a large mass surrounding multiple intrahepatic vessels. Clin Gastroenterol Hepatol 2011; 9: e41–e42.

51. Balduzzi C, Yantorno M, Mosca I, et al. Primary hepatic lymphoma: an infrequent cause of focal hepatic lesion. Acta Gastroenterol Latinoam 2010; 40: 361–366.

52. Chan WK, Tse EW, Fan YS, et al. Positron emission tomography/computed tomography in the diagnosis of multifocal primary hepatic lymphoma. J Clin Oncol 2008; 26: 5479–5480.

53. Kaneko F, Yokomori H, Sato A, et al. A case of primary hepatic non-Hodgkin’s lymphoma with chronic hepatitis C. Med Mol Morphol 2008; 41: 171–174.

54. Kim H, Kim KW, Park MS, et al. Lymphoma presenting as an echogenic periportal mass: sonographic findings. J Clin Ultrasound 2008; 36: 437–439.

55. Nonami A, Takenaka K, Harada N, et al. Primary hepatic lymphoma 1 year after resection of hepatocellular carcinoma. J Clin Oncol 2006; 24: 5784–5786.

56. Chen HW, Sheu JC, Lin WC, et al. Primary liver lymphoma in a patient with chronic hepatitis C. J Formos Med Assoc 2006; 105: 242–246.

57. Yu JT, Wang CY, Yang Y, et al. Lymphoma-associated hemophagocytic lymphohistiocytosis: experience in adults from a single institution. Ann Hematol 2013; 92: 1529–1536.

58. Shimazaki C, Inaba T and Nakagawa M. B-cell lymphoma-associated hemophagocytic syndrome. Leuk Lymphoma 2000; 38: 121–130.

59. Murase T, Nakamura S, Tashiro K, et al. Malignant histiocytosis-like B-cell lymphoma, a distinct pathologic variant of intravascular lymphomatosis: a report of five cases and review of the literature. Br J Haematol 1997; 99: 656–664.

60. Sano T, Sakai H, Takimoto K, et al. Rituximab alone was effective for the treatment of a diffuse large B-cell lymphoma associated with hemophagocytic syndrome. Int J Clin Oncol 2007; 12: 59–62.