CASE REPORT

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A Rare Case Report of Primary Hepatic Lymphoma Complicated by Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Primary hepatic lymphoma (PHL) is a rare disease characterized by non-specific clinical manifestations, laboratory findings, and imaging features, which may lead to misdiagnosis as hepatocellular carcinoma or hepatic infectious lesions. However, whether PHL can secondarily develop hemophagocytic lymphohistiocytosis (HLH) like other hematological lymphomas has not been reported. We present a diagnostically challenging case initially mimicking a pyogenic liver abscess. A 74-year-old woman with no history of past illness was admitted with persistent high fever accompanied by fatigue and loss of appetite for three weeks. Her vital signs were normal on physical examination. Computed tomography (CT), magnetic resonance imaging, and fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT showed a liver infectious lesion as a hepatic abscess. A subsequent laparoscopic exploration and liver biopsy confirmed the diagnosis of germinal center B-cell-like diffuse large B-cell lymphoma. Concurrently, with the progressive thrombocytopenia and hemoglobin reduction alongside persistent fever, the life-threatening complication of HLH secondary to PHL was reported by the further workup per the HLH-2004 criteria. The modified R-ECHOP chemotherapy regimen was initiated to address both conditions. During follow-up evaluations, significant myelosuppression was identified. The second-cycle chemotherapy regimen was modified to the R-miniCHOP protocol. After four cycles of chemotherapy, the follow-up 18F-FDG PET/CT scan indicated complete response of the liver tumor lesions.
In conclusion, PHL is rare and frequently clinically mistaken for a liver abscess. Histopathological examination remains the gold standard for definitive diagnosis. Similar to other hematological lymphomas, PHL may also secondarily develop HLH. Early recognition, diagnosis, and intervention are critical to improving prognosis.

Key words: hepatic abscess – diffuse large B – cell lymphoma – primary hepatic lymphoma – hemophagocytic lymphohistiocytosis – case report.

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Abbreviations: CMV: cytomegalovirus; CT: computed tomography; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; HIV: human immunodeficiency virus; HLH: hemophagocytic lymphohistiocytosis; MRI: magnetic resonance imaging; NHL: non-Hodgkin's lymphoma; NSE: neuron-specific enolase; PHL: primary hepatic lymphoma; R-ECHOP: rituximab, etoposide, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone; 18F-FDG PET: fluorine-18 fluorodeoxyglucose positron emission tomography.

INTRODUCTION

Primary hepatic lymphoma (PHL) originates directly in the liver without systemic involvement, which is an exceptionally rare subtype of non-Hodgkin's lymphoma (NHL), accounting for only 0.016% of newly diagnosed NHL cases [1]. PHL is most frequently classified as diffuse large B-cell lymphoma (DLBCL). Diagnostic criteria for PHL as defined by Lei in 1998 [2]. Due to the non-specific clinical manifestations and examination results associated with this disease, PHL poses diagnostic dilemmas, particularly when imaging findings overlap with hepatocellular carcinoma or infectious lesions. A combination of clinical suspicion, targeted imaging, and histopathological analysis is crucial for accurate differentiation.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome with the median survival time of less than 2 months for untreated HLH [3], which is caused by dysregulated immune activation, characterized by systemic cytokine storm and multiorgan

dysfunction [4]. Malignant tumors of the blood system, such as leukemia and lymphoma, are closely related with HLH. Tumor cells may trigger immune dysregulation and macrophage hemophagocytic activity through cytokine secretion or direct immune stimulation [4]. To date, no cases of HLH secondary to PHL have been reported in the existing literature. Here, we report the first documented case of PHL complicated by HLH.

CASE PRESENTATION

A 74-year-old woman with no history of past illness was admitted with persistent high fever accompanied by fatigue and loss of appetite for three weeks. Her vital signs were normal on physical examination.

The laboratory tests showed normal white blood cell counts, decreased hemoglobin (92 g/L), elevated C-reactive protein levels (138.2 mg/L) and lactate dehydrogenase (396 U/L). The comprehensive tumor marker panel in the female patient revealed a slightly elevated neuron-specific enolase (NSE), (20.02 ng/ml), while all other markers remained within normal ranges. The patient was tested negative for hepatitis A/B/C/E, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and mycobacterium tuberculosis. The blood culture was negative. Contrast-enhanced computed tomography (CT) revealed multiple ill-defined, clump-like lesions with slightly heterogeneous enhancement (Fig. 1). Magnetic resonance imaging (MRI) showed these lesions as hypointense on T1-weighted images (Fig. 2A) and hyperintense on T2-weighted images (Fig. 2B), with indistinct margins and uneven internal enhancement after contrast administration (Fig. 2C). Additionally, fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT demonstrated intense metabolic activity within the hepatic lesions (Fig. 3).

The diagnosis of liver abscess was established based on the aforementioned ancillary investigations. The patient received meropenem for five days. During this period, the patient maintained persistent high-grade fever. Inflammatory markers remained stable. Bone marrow puncture did not detect specific findings, and bone marrow culture was negative. Blood metagenomic NGS was also used to identify the source of infection, while no clinically relevant microorganisms were detected. Meanwhile, parasitic serology demonstrated positive Toxoplasma gondii antibodies. In accordance with clinical pharmacy consultation recommendations, sulfamethoxazole was added to the antimicrobial regimen as combination therapy. The patient developed recurrent high-grade fever accompanied by nausea and vomiting after a 2-day afebrile interval. The gastrointestinal symptoms (nausea and vomiting) were considered secondary to sulfamethoxazole therapy.

Given the evolving clinical complexity characterized by diagnostic uncertainty and therapeutic challenges, the microbiological evaluation via percutaneous hepatic biopsy and drainage fluid analysis constituted the cornerstone of evidence-based therapeutic decision-making. Despite repeated ultrasonographic assessments under real-time guidance, no safe percutaneous access route could be established due to the lesion's localization in the hepatic dome region.

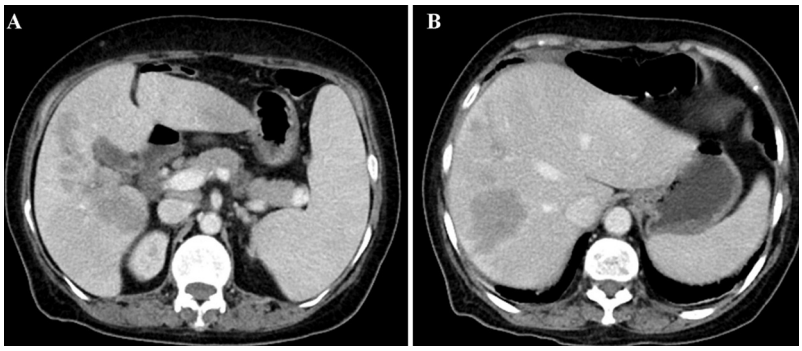

Fig. 1. Contrast-enhanced computed tomography (CT) revealed multiple ill-defined, clump-like lesions with slightly heterogeneous enhancement (A, B).

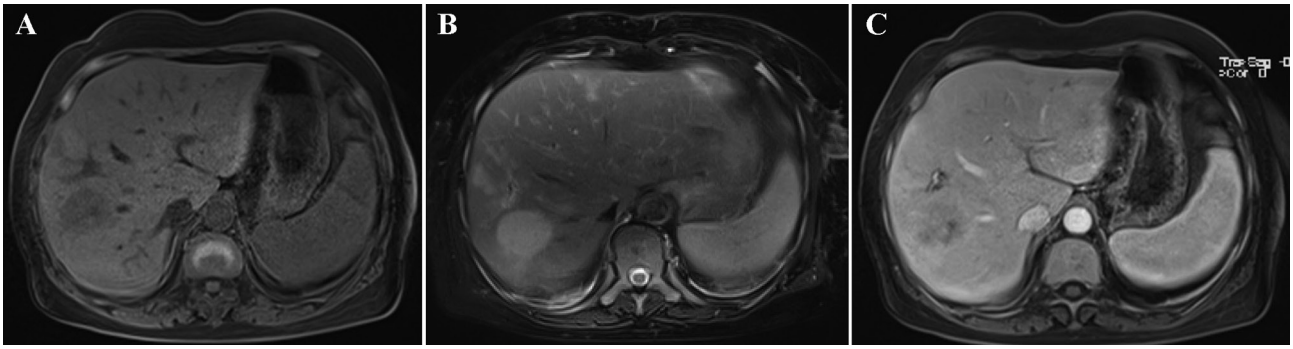

Fig. 2. Magnetic resonance imaging (MRI) showed these lesions as hypointense on T1-weighted images (A) and hyperintense on T2-weighted images (B), with indistinct margins and uneven internal enhancement after contrast administration (C).

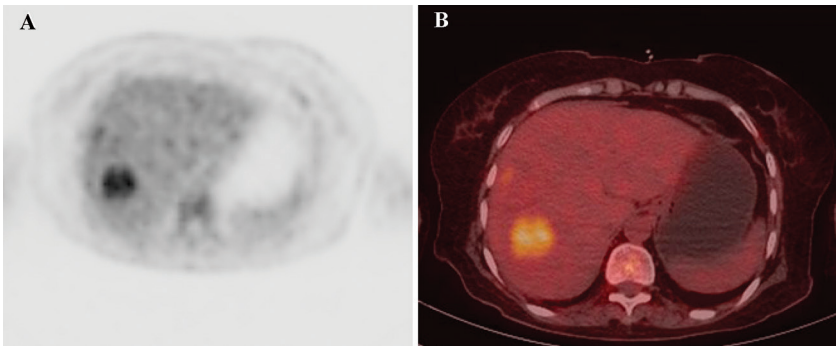

Fig. 3. ^{18}F-FDG PET/CT demonstrated intense metabolic activity within the hepatic lesions (A, B).

Following comprehensive multidisciplinary team review, surgical exploratory was determined to be the definitive diagnostic and therapeutic intervention for this patient. Laparoscopic-assisted partial hepatectomy was performed. And the postoperative biopsy revealed aggressive B-cell lymphoma, with a primary consideration of DLBCL of germinal center origin. Immunohistochemical staining indicated positive reactions for CD20, CD79α, and Ki-67 in the tumor cells, and the positive rate of Ki-67 was about 80% (Fig. 4). Fluorescence in situ hybridization (FISH) analysis demonstrated no evidence of BCL-2, BCL-6, or MYC gene rearrangements, and Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization was negative.

Following the operation, the patient exhibited decreased peak fever temperatures compared to prior readings. However, serial laboratory monitoring revealed progressive declines in hemoglobin (50 g/L) and platelets (33×10^9/L), raising suspicion for HLH. Further workup demonstrated: reduced NK cell activity 12.63% (reference range: >15.11%), elevated soluble CD25 (sCD25) 11,712.53 pg/mL (reference: <6,400 pg/mL), hyperferritinemia ≥500 μg/L (reference: 20-300 μg/L), and cytokine storm profile: IL-6 and γ-Interferon significantly elevated. The diagnosis of HLH was confirmed per the HLH-2004 diagnostic criteria [5].

The patient was diagnosed with PHL complicated by HLH. Following hematology recommendations, the modified rituximab, etoposide, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-ECHOP) chemotherapy regimen was initiated to address both conditions. After undergoing chemotherapy, the patient's mental state significantly improved, with no recurrence of fever. While during subsequent follow-up evaluations, significant myelosuppression was identified in the patient. The second-cycle chemotherapy regimen was modified to the R-miniCHOP protocol, which resulted in marked improvement in myelosuppression. The patient maintained

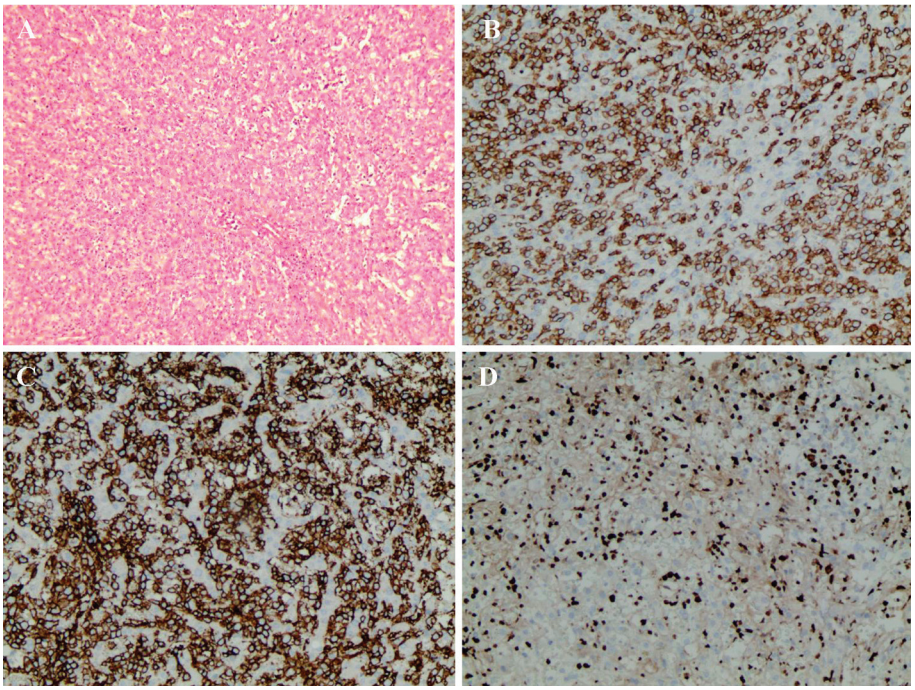

Fig. 4. Histopathological feature and immunohistochemical CD20 positive staining confirmed the diagnosis of germinal center B-cell-like diffuse large B-cell lymphoma. Microscopy showed the HE staining (A) (x100) and the immunohistochemical staining of the CD20(B), CD79α(C), and Ki67(D) (x200).

good general condition throughout the treatment course. After four cycles of chemotherapy, a follow-up ^{18}F-FDG PET/CT scan showed that the tumor lesions had significantly reduced in size and resolved (Fig. 5).

DISCUSSION

Primary hepatic lymphoma is a distinct clinicopathological entity characterized by its exclusive localization to the hepatic parenchyma, demonstrating an absence of both peripheral lymph node involvement and bone marrow infiltration, accounting for 0.4% of extranodal lymphoma [6, 7]. The etiology and pathogenesis of PHL remain poorly understood. Current evidence suggests that chronic liver inflammation may trigger immune activation, potentially leading to malignant lymphocyte proliferation and PHL development. Immune deficiency disorders and infectious agents, including hepatitis C, hepatitis B, hepatitis E, HIV, and CMV have been implicated as drivers of this condition [8-11]. While, our patient notably had no history of immune deficiency disorders and tested negative for HIV, CMV, EBV and hepatitis A/B/C/E.

Primary hepatic lymphoma commonly presents with non-specific clinical manifestations such as persistent high-grade fever, right upper quadrant pain, unintentional weight loss, fatigue, and hepatomegaly [12]. Tumor markers in PHL demonstrate limited diagnostic utility due to poor specificity and sensitivity. In our patient, tumor markers were within normal levels, except for NSE. Conventional imaging modalities also lack pathognomonic features for PHL, rendering it radiologically indistinguishable from other hepatic lesions [11]. PHL is particularly prone to misdiagnosis as liver abscess in patients with recurrent high fever, as demonstrated in this case. The patient presented with persistent high fever as the primary clinical manifestation. Imaging modalities including contrast-enhanced CT, MRI, and even ^{18}F-FDG PET/CT suggested infectious lesions, leading to an initial diagnosis of liver abscess. However, no specific pathogenic microorganisms were identified, and aggressive antimicrobial therapy proved ineffective. Consequently, PHL diagnosis requires a multimodal histopathological approach incorporating tissue examination, immunohistochemical analysis, and gene rearrangement detection. And diagnostic confirmation of primary hepatic DLBCL necessitates rigorous exclusion of secondary hepatic involvement by systemic lymphoma [11].

Notably, this patient exhibited progressive thrombocytopenia and hemoglobin reduction alongside persistent fever, prompting urgent evaluation for HLH, a life-threatening hyperinflammatory syndrome with the median survival time of less than 2 months for untreated HLH [3]. Hemophagocytic lymphohistiocytosis is caused by dysregulated immune activation, characterized by systemic cytokine storm and multiorgan dysfunction [13]. It is classified into primary (genetic) and secondary (acquired) forms. Infections, malignancies, and autoimmune disorders constitute the three predominant underlying pathological processes driving secondary HLH. Malignant tumors of the blood system, such as leukemia and lymphoma, are closely related with HLH. Tumor cells may trigger immune dysregulation and macrophage hemophagocytic activity through cytokine secretion or direct immune stimulation [4, 13]. Clinicians should maintain high suspicion for HLH in patients with persistent fever (>1 week) and cytopenia. Early diagnosis requires systematic evaluation per HLH-2004 criteria [5], including measurements of soluble IL-2 receptor (sCD25), NK cell activity, cytokine profiling, triglycerides, fibrinogen, ferritin levels, and bone marrow examination. Timely therapeutic intervention guided by these parameters is critical to reduce mortality.

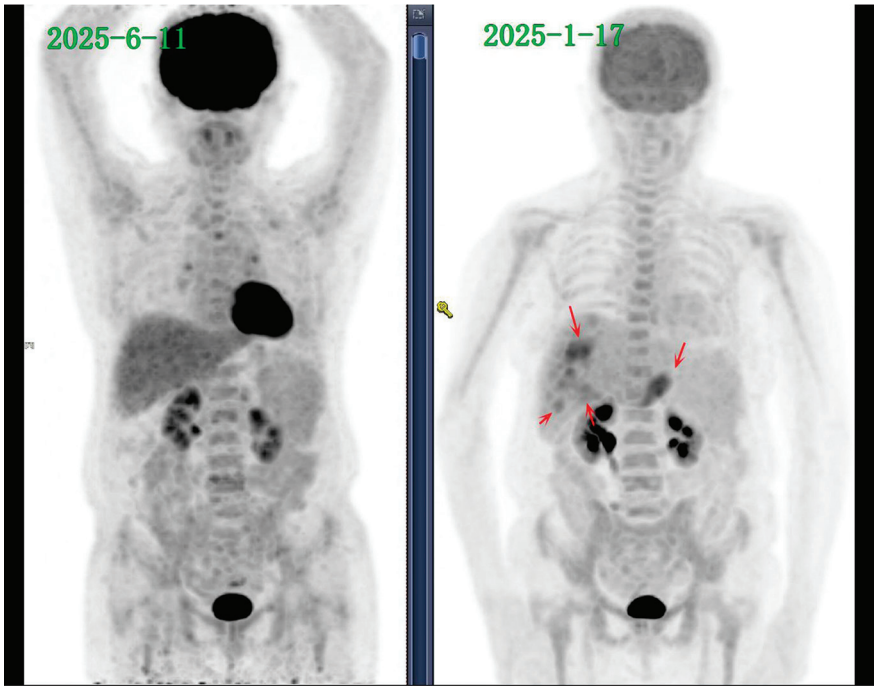

Fig. 5. Compared to the pre-chemotherapy PET-CT scan from January 17, 2025, the follow-up PET-CT scan performed on June 11, 2025, after four cycles of chemotherapy, revealed that the liver tumor lesions had significantly shrunk and resolved.

To date, no cases of PHL complicated by HLH have been reported in the existing medical literature. For our patient, the diagnosis of HLH secondary to PHL was first reported by the further workup showing reduced NK cell activity, elevated sCD25, hyperferritinemia, and increased IL-6 and γ-Interferon per the HLH-2004 diagnostic criteria.

No standardized treatment protocols currently exist for PHL given the rarity of the disease. Clinical management options include surgical resection, radiation therapy, systemic chemotherapy, or multimodal combinations thereof [14, 15]. Primary hepatic lymphoma typically demonstrates chemosensitivity as evidenced in a retrospective cohort review of 24 patients with a complete remission rate of 83.3% and a 5-year overall survival rate of 83.1% [14]. R-CHOP regimen represents the most widely utilized therapeutic protocol [16]. However, for patients with HLH secondary to lymphoma and adequate organ function, an etoposide-containing combination chemotherapy regimen targeting both HLH and lymphoma is recommended [17]. Therefore, for our patient diagnosed with PHL complicated by HLH, the modified R-ECHOP chemotherapy regimen was initiated to address both conditions. After undergoing chemotherapy, the patient's mental state significantly improved, with no recurrence of fever. While during subsequent follow-up evaluations, significant myelosuppression was identified in the patient. The second-cycle chemotherapy regimen was modified to the R-miniCHOP protocol, which resulted in marked improvement in myelosuppression. After four cycles of chemotherapy, a follow-up ^{18}F-FDG PET/CT scan indicated complete response of the liver tumor lesions.

CONCLUSIONS

Primary hepatic lymphoma is a rare disease characterized by non-specific clinical manifestations, laboratory findings, and imaging features, which may lead to misdiagnosis as hepatic infectious lesions. Histopathological examination remains the gold standard for definitive diagnosis. Similar to other hematological lymphomas, PHL may also secondarily develop HLH. Early recognition, diagnosis, and intervention are critical to improving prognosis. Currently, there is no standardized treatment protocol for PHL, though the R-CHOP regimen is widely recommended. For patients with PHL complicated by HLH, the selection of chemotherapy regimens must address both malignancies, simultaneously, with individualized adjustments tailored based on the patient's overall condition and disease severity.

Conflicts of interests: None to declare.

Authors' contributions: Y. Z. drafted the paper. L.X. and L.L. collected the case information. S.W. provided the figures. A.L. drafted and proofed the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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