Received: 3 August 2023 | Revised: 19 September 2023 | Accepted: 29 September 2023

DOI: 10.1002/ccr3.8044

Clinical Case Reports Open Access WILEY

CASE REPORT

A case of hemophagocytic syndrome secondary to B-cell lymphoma

Hao Xing | **Luyao Ma** | **Longfei Wang** | **Qian Zhang** | **Zhenjing Jin**

Department of Hepatopancreatobiliary Medicine, The Second Hospital of Jilin University, Changchun, China

Correspondence
Zhenjing Jin, Department of Hepatopancreatobiliary Medicine, The Second Hospital of Jilin University, Changchun, China.
Email:jinzj@jlu.edu.cn

Funding information
Study on application of the diagnostic value and immune effect of IL#x2010;35 negative regulating Th9/IL#x2010;9 in HBV#x2010;associated hepatocellular carcinoma, Grant/Award Number: 20220203130SF; Study on immune mechanism and therapeutic target of Th22 cells regulated by IL#x2010;35 in primary biliary cholangitis, Grant/Award Number: YDZJ202301ZYTS043

Key Clinical Message

In this report we highlight a case of HPS secondary to B-cell lymphoma, aiming to facilitate the early recognition and treatment of HPS in its classic presentation by clinicians.

KEYWORDS

diagnosis, EB virus, hemophagocytic syndrome, lymphoma, therapy

1 | INTRODUCTION

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a group of syndromes in which multiple pathogenic factors lead to the proliferation of activated lymphocytes and histiocytes, which secrete large amounts of inflammatory cytokines.[1] HLH is a multi-organ hyperinflammatory syndrome caused by the secretion of large amounts of inflammatory cytokines from activated lymphocytes and histiocytes owing to multiple pathogenic factors. The mechanism of the disease is probably the activation of T lymphocytes and NK cells by pathogenic factors, which cause uncontrolled and continuous activation of these cells.[2] After the activation of T lymphocytes and NK cells, a storm of inflammatory factors and macrophage activation is triggered by an uncontrolled immune response. HLH usually has a rapid onset and progression, with a very high mortality rate and poor prognosis. In this case report, we report a case of a patient with secondary HPS, aiming to improve the diagnostic ideas for clinicians and, consequently, improve HPS diagnosis and treatment.

2 | CASE INFORMATION

A 60-year-old female with a history of cervical cancer was admitted to the hospital, with chief complaints of fatigue and darkening of urine for 10 days. Chest and lung CT scans showed an occupational lesion in the right lung

measuring 21 mm × 17 mm. The patient reported that she had been taking oral healthcare products for more than 3 months. Notably, laboratory findings on admission were significant for anemia, granulocytopenia, thrombocytopenia, hypertriglyceridemia, hyperbilirubinemia, and hepatocyte damage. The additional abdominal CT scan showed no significant evidence of liver fibrosis and occupying lesion. Hepatocyte damage and hyperbilirubinemia were treated with aggressive glycyrrhizin treatment, and the pancytopenia was treated with recombinant human granulocyte colony-stimulating factor and recombinant human thrombopoietin. The patient received transfusions to increase hemoglobin and thrombocyte levels. The summary of the laboratory findings during the hospital course is summarized in Table 1.

1. As the treatment continued, the patient had a high-grade fever for a week, and her bilirubin level increased. The bone scan showed uneven bone density in the lumbar spine and bilateral iliac crest and inert bone metabolism, highly suggesting hematological system diseases and myelinogenesis (Figures 1 and 2).

Symptoms and laboratory findings strongly suggest the possibility of malignancy and HPS. To clarify the diagnosis, we performed a pathological examination of the patient's sternal bone marrow, and pathological sections showed hemophagocytosis in the bone marrow (Figures 3 and 4), and the bone marrow histochemistry and immunology showed evidence of B-cell lymphoma. The patient had persistent fever, anemia, granulopenia, thrombocytopenia, hypertriglyceridemia, hypofibrinogenemia, elevated serum ferritin levels, low NK-cell activity, elevated Soluble CD25 levels, and hemophagocytosis in the bone marrow; thus, the patient was diagnosed with HPS based on the revised 2004 Histocyte Society diagnostic criteria.

Unfortunately, the patient discontinued treatment after diagnosis, and follow-up visits showed that the patient died 7 days after discharge.

3 | DISCUSSION

HPS is classified into primary and secondary phagocytic syndromes based on the presence or absence of a clear HPS-related genetic abnormality.[3,4] Primary HPS is an autosomal recessive disorder involving 12 known associated genes in infants and children. Secondary HPS is classified as infection-associated HPS, malignancy-associated HPS, macrophage activation syndrome, and other types of HPS, depending on the underlying disease; rare HPS triggers include metabolic diseases.[5] Currently, infection-related HPS is the most common secondary HPS, with Epstein–Barr virus (EBV) being the leading cause, and it has been postulated that COVID-19 infection may lead to secondary HPS.[6] Malignancy-associated HPS often presents with hematological tumors as the primary disease, particularly lymphoma, acute leukemia, and multiple myeloma. The most common are T-cell and NK-cell lymphomas. Studies have shown that malignant lymphoma can act as an endogenous and persistent stimulus to activate $CD8^+$ T lymphocytes and NK cells, which, in turn, act as an initiating factor for this syndrome. In this case, the patient was clearly diagnosed with B-cell lymphoma, and there were no abnormal indicators of infection during the course of the disease. The ANA profile showed positive anti-mitochondrial M2 antibodies and positive 52 kDa protein antibodies; however, there was no evidence that PBC caused secondary HPS. Therefore, the patient's HPS was considered to be malignancy-associated HPS.

Currently, the most commonly used diagnostic criteria are the HLH-2004,[7] HScore,[8] and MH score,[9] of

TABLE 1 The laboratory findings during the hospital course (Ferritin level was not tested at the beginning of the hospital course).

Laboratory parameters	Reference range	Results on admission	Results after entering the hospital for 7 days	Results at HLH diagnosis
Hemoglobin g/dL	115–150	83	88	77
WBC counts 10^9/L	3.5–9.5	1.8	2.7	2.0
Platelets 10^9/L	125–350	19.0	16.0	37.0
Triglyceride mmol/L	0.56–1.71	2.80	3.23	5.11
Ferritin ng/mL	4.63–204	N/A	>1675.56	>1675.56
ALT u/L	7–40	389	501	188
AST u/L	13–35	474	337	99
Bilirubin μmol/L	2.00–20.10	275.89	553.44	378.42
ALP u/L	50–135	464	212	145
Γ-GT u/L	7–45	680	242	208
Fibrinogen g/L	2.00–4.00	2.92	2.33	6.70

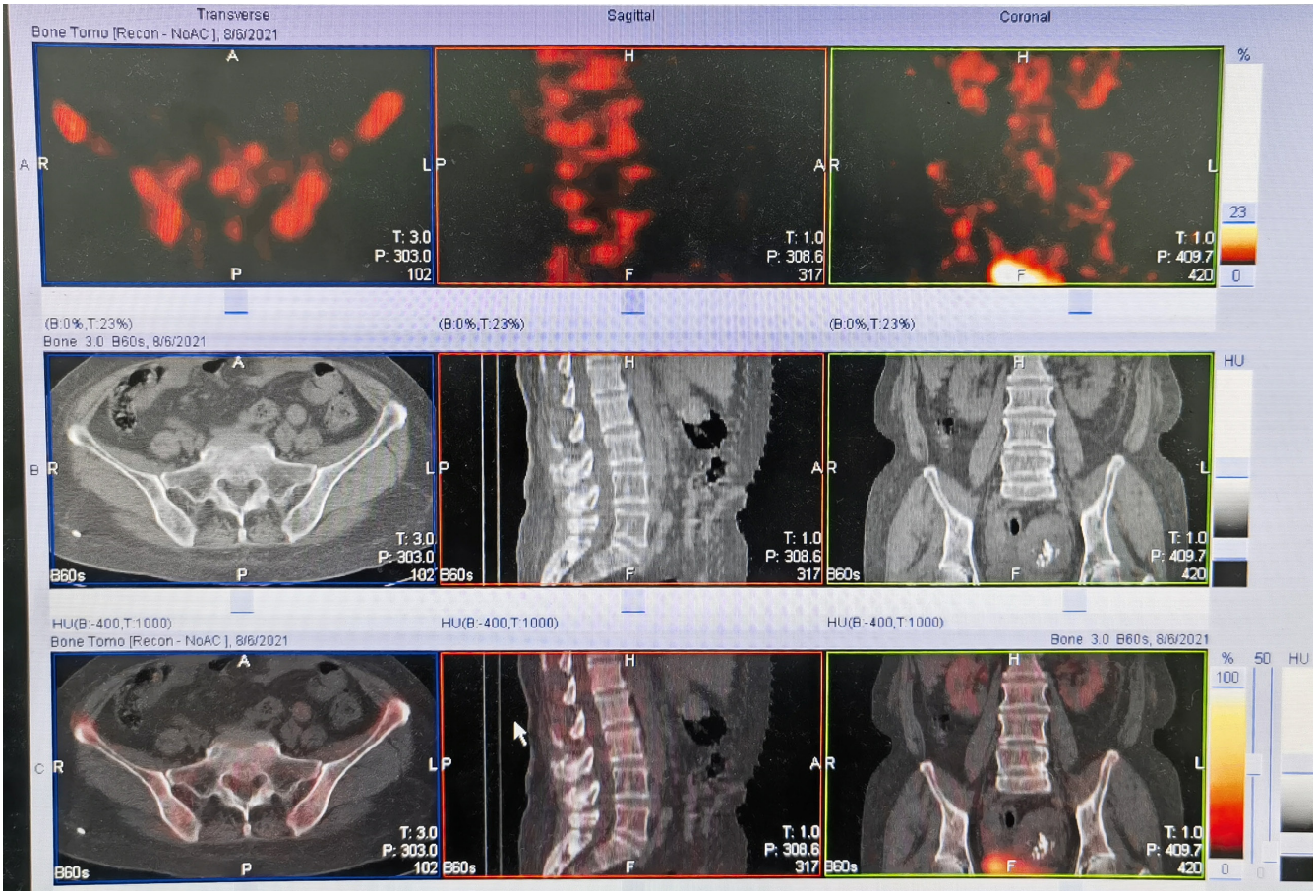
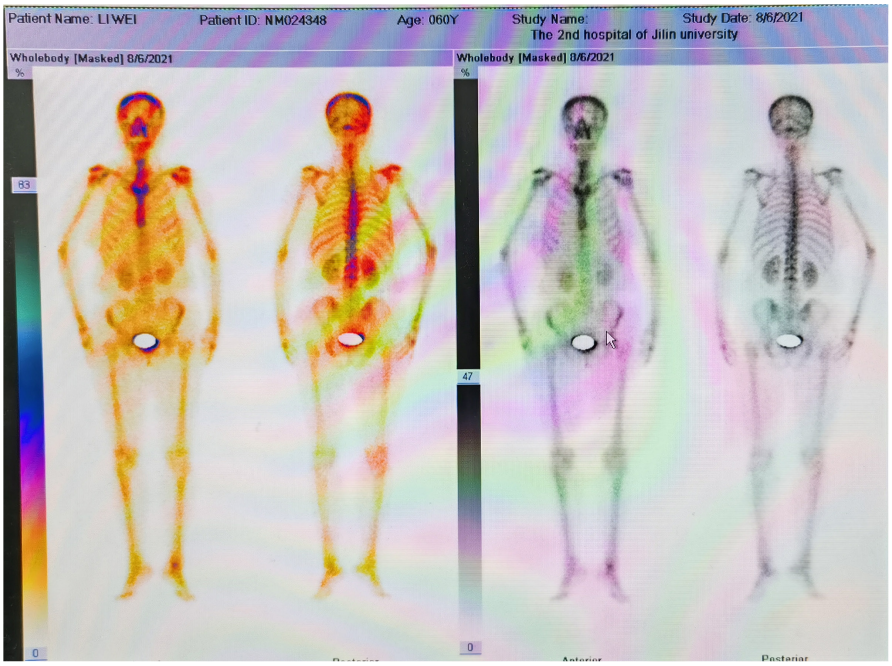


FIGURE 1 Bone scan imaging shows uneven bone density in the lumbar spine and bilateral iliac crest.

FIGURE 2 Bone scan imaging shows that the bone metabolism of the lumbar spine and bilateral iliac crest were inert.



which the HLH-2004 and HScore are the most common. The International Society for HPS revised the diagnostic criteria for Histiocytosis in 2004.[7] HLH can be diagnosed if any of the following criteria are met as follows: (1). Molecular diagnosis consistent with HLH: pathological mutations have been found in the current HLH-related pathogenic genes, such as PRF1, UNC13D, STX11, STXBP2, Rab27a, LYST, SH2D1A, BIRC4, ITK, AP3β1,

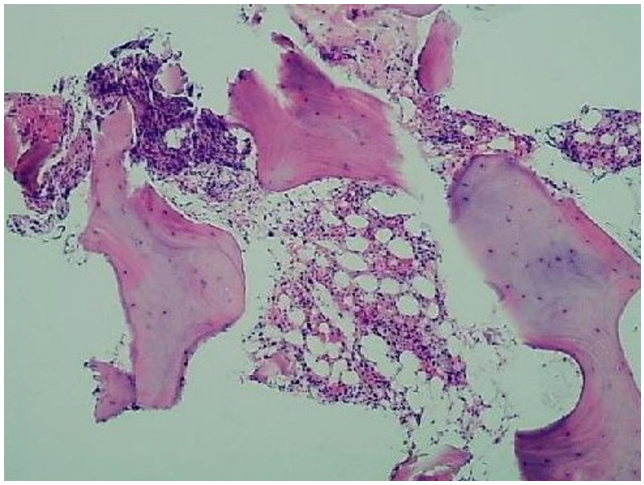


FIGURE 3 Sternal biopsy (HE staining, 4x) shows atypical lymphocytes suspected of lymphatic system malignancy.

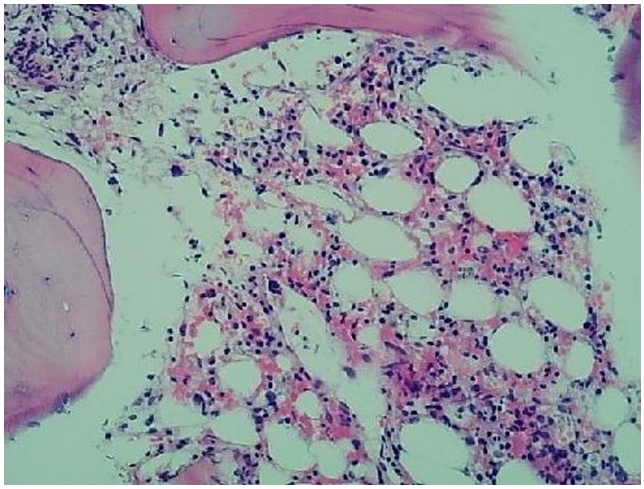


FIGURE 4 Sternal marrow biopsy (HE staining, 10x) shows hemophagocytosis in multiple cells.

MAGT1, CD27, etc. (2). Five of the following eight criteria are met as follows: (1) fever: temperature > 38.5°C for more than 7 days; (2) splenomegaly; (3) hematocrit; (4) hypertriglyceridemia and/or hypofibrinogenemia; (5) phagocytosis found in bone marrow, spleen, liver, or lymph nodes; (6) elevated serum ferritin, with ferritin quantification >500 μg/mL; (7) NK-cell activity is reduced or absent; (8) sCD25 is elevated. Combined with the patient's auxiliary examination results, the current patient met all the above eight criteria, and the diagnosis of phagocytic syndrome was clear. Because the patient's main clinical manifestation is liver damage, we must consider the possibility of secondary HPS when the cause of liver damage is unclear, accompanied by complete hematocrit and persistent hyperthermia. Early bone marrow aspiration biopsy, quantitative determination of ferritin, NK-cell activity, sCD25, and other tests should be performed to clarify the diagnosis as soon as possible.

The patient's main clinical manifestations were jaundice, predominantly elevated bilirubin and transaminases in the liver, and a significantly decreased triple system on routine blood tests. No liver cirrhosis was found on abdominal enhanced CT. To further clarify the cause of the impaired triplet system, the patient underwent bone marrow aspiration and quantification of NK cell activity, sCD25, serum ferritin, and EB-DNA. Based on the patient's clinical manifestations and diagnostic criteria for HPS, the patient was finally diagnosed with HPS.

Studies have shown that the pathogenesis of HPS is the inability of the abnormally activated immune system to clear inflammatory factors, which leads to the inability of the body to release the abnormal state of the immune system; therefore, the current treatment principle of HPS is to control the primary disease based on the suppression of inflammatory factors.[10–12] Dexamethasone combined with etoposide is often used internationally as the main induction therapy for 8 weeks, and its efficacy is evaluated after 2–3 weeks of induction therapy. Salvage therapy should be performed early if the response is poor. There is no unified recommendation for salvage therapy; however, doxorubicin combined with etoposide and dexamethasone chemotherapy regimen, pegaspargase combined with doxorubicin, etoposide, and dexamethasone chemotherapy regimen, or a mixed immunotherapy regimen with anti-thymocyte globulin can be used as the main treatment.[4,13] The patient in this study had HPS secondary to B-cell lymphoma and was recommended to be transferred to the hematology department for dexamethasone combined with etoposide and to undergo bone marrow transplantation as soon as possible after remission. HPS is a rapidly progressive and highly lethal disease with a median survival time of no more than 2 months in patients with untreated HPS.[14,15] Shuo et al. showed that the survival rates of 147 patients with phagocytic syndrome at 1, 3, 6, and 12 months after treatment were 69%, 52%, 45%, and 39%, respectively, with the highest mortality rate in EBV infection-associated phagocytic syndrome, with patients mostly dying within 3 months.[5] The patient was followed up for 10 days after discharge, and we learned that the patient had died. Therefore, if a patient presents with unexplained liver damage, decreased trilineage, and persistent hyperthermia, phagocytic syndrome must be considered. Tests such as bone marrow aspiration biopsy, quantitative ferritin assay, NK-cell activity, and sCD25 can help clarify the diagnosis early and improve the patient's prognosis.

AUTHOR CONTRIBUTIONS

Hao Xing: Conceptualization; data curation; investigation; resources; writing – original draft. **Luyao Ma:** Formal analysis; visualization; writing – review and editing. **Longfei Wang:** Investigation; writing – review and editing. **Qian Zhang:** Investigation; writing – review and editing. **Zhenjing Jin:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; supervision; writing – review and editing.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.cn) for English language editing.

FUNDING INFORMATION

This study was funded by the" Study on application of the diagnostic value and immune effect of IL-35 negatively regulating Th9/IL-9 in HBV-associated hepatocellular carcinoma," issued to Zhenjing Jin by the Social Development Science and Technology Department of Jilin Province (20220203130SF), and the" Study on immune mechanism and therapeutic target of Th22 cells regulated by IL-35 in primary biliary cholangitis," issued to Zhenjing Jin by the Department of Basic Research in Jilin Province (YDZJ202301ZYTS043).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Hao Xing https://orcid.org/0000-0002-6510-5132
Luyao Ma https://orcid.org/0000-0001-5838-0673
Longfei Wang https://orcid.org/0000-0002-5980-8077
Qian Zhang https://orcid.org/0009-0005-5340-5727
Zhenjing Jin https://orcid.org/0009-0003-6210-4526

REFERENCES

1. Daver N, McClain K, Allen CE, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer*. 2017;123(17):3229-3240. doi:10.1002/cncr.30826
2. Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. *Annu Rev Pathol*. 2018;13:27-49. doi:10.1146/annurev-pathol-020117-043625
3. Chinese Society of Physicians, Hematology Group, Chinese Society of Medicine, Pediatrics Branch, Chinese Expert Alliance on Hemophagocytic Syndrome. Chinese Guidelines for the Diagnosis and Treatment of hemophagocytic syndrome. *Chin Med J*. 2022;2022(20):1492-1499.
4. Wang X-W. Progress in the study of phagocytic syndrome. *JGME*. 2000;13(3):181-184. doi:10.3969/j.issn.1008-8199.2000.03.015
5. Shuo L, Jingshi W, Yini W, et al. Etiology and prognostic analysis of 147 patients of phagocytic syndrome. *J clin Hematol*. 2014;27(4):559-563. doi:10.13201/j.issn.1004-2806.2014.07.005
6. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatol Int*. 2021;41(1):7-18. doi:10.1007/s00296-020-04636-y
7. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:10.1002/pbc.21039
8. Hejblum G, Lambotte O, Galicier L, et al. A web-based Delphi study to identify helpful criteria for the diagnosis of hemophagocytic syndrome in adult patients. *PLoS ONE*. 2014;9(4):e94024. doi:10.1371/journal.pone.0094024
9. Minoia F, Bovis F, Davì S, et al. Development and initial validation of the macrophage activation syndrome/primary Hemophagocytic Lymphohistiocytosis score, a diagnostic tool that differentiates primary Hemophagocytic Lymphohistiocytosis from macrophage activation syndrome. *J Pediatr*. 2017;189:72-78.e3. doi:10.1016/j.jpeds.2017.06.005
10. Li W-Y, Xue H-M. Pathogenesis, diagnosis, and treatment of EBV infection-associated phagocytic syndrome. *Chinese Journal of Maternal and Child Clinical Medicine*. 2011;7(2):92-96. doi:10.3877/cma.j.issn.1673-5250.2011.02.001
11. Wang JS, Wang Z, Wu L, Tian LP, Chen X. Clinical analysis of 14 cases of lymphoma-associated phagocytic syndrome. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2009;17(5):1352-1355.
12. Peng Y, Liu YY, Lei X, et al. Analysis of clinical diagnostic features of secondary phagocytic syndrome with liver failure as the main manifestation. *Chinese Electronic Journal of Diagnostics*. 2019;7(4):269-272. doi:10.3877/cma.j.issn.2095-655X.2019.04.011
13. Yoon JH, Park SS, Jeon YW, et al. Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy. *Haematologica*. 2019;104(2):269-276. doi:10.3324/haematol.2018.198655
14. Janka GE. Familial hemophagocytic lymphohistiocytosis. *Eur J Pediatr*. 1983;140(3):221-230. doi:10.1007/BF00443367
15. Henter JI, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. *Acta Paediatr Scand*. 1991;80(4):428-435. doi:10.1111/j.1651-2227.1991.tb11878.x

How to cite this article: Xing H, Ma L, Wang L, Zhang Q, Jin Z. A case of hemophagocytic syndrome secondary to B-cell lymphoma. *Clin Case Rep*. 2023;11:e8044. doi:10.1002/ccr3.8044