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Successful treatment of diffuse large B-cell lymphoma with secondary hemophagocytic lymphohistiocytosis by R-CHOP-E regimen: a case report

Ran Wu, Xiaohui Deng, Siguo Hao and Liyuan Ma

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare fatal clinical syndrome characterized by a hyperinflammatory condition caused by aberrantly activated macrophages and cytotoxic T cells, resulting in a cytokine storm and organ impairment. Lymphoma, especially B-cell lymphoma in Japan, is a common trigger of secondary HLH. In China, however, most cases of HLH secondary to lymphoma occur in patients with T-cell/natural killer-cell lymphoma or Hodgkiǹs lymphoma; HLH is relatively uncommon in patients with B-cell non-Hodgkin's lymphoma. We herein describe a man with diffuse large B-cell lymphoma (DLBCL) and secondary HLH who was successfully treated by R-CHOP-E chemotherapy. All symptoms resolved and laboratory indications of HLH normalized, and complete remission of the lymphoma was achieved. This rare case highlights not only the possibility of HLH secondary to DLBCL but also the importance of early initiation of R-CHOP-E chemotherapy.

Keywords

Diffuse large B-cell lymphoma, hemophagocytic lymphohistiocytosis, R-CHOP-E, chemotherapy, excisional biopsy, case report

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Department of Hematology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

Corresponding author:
Liyuan Ma, Department of Hematology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200090, China.
Email: maliyuan@xinhuamed.com.cn

Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a severe clinical syndrome associated with high morbidity and mortality rates. The disease is characterized by functional defects of natural killer (NK) cells and cytotoxic lymphocytes that result in the activation of T cells and macrophages.[1] The activated T cells and macrophages can produce a large amount of cytokines, leading to hyperthermia, pancytopenia, hyperlipidemia, abnormal coagulation, multiple organ failure, and rapid death.[2] Primary or familial HLH is associated with 16 types of genetic defects and is most common in children. In contrast, secondary HLH most frequently occurs in adults and can be caused by infections, malignancies, and immune system disorders.[3] Among all hematologic neoplasms, HLH is often observed in association with NK/T-cell lymphomas. However, it is uncommonly accompanied by non-Hodgkin's B-cell lymphomas.[4,5] In China, several single-center reports have indicated that NK/T-cell lymphoma was the predominant HLH subtype in patients with lymphoma-associated HLH.[6] In contrast, in the Caucasian population or in Japan, diffuse large B-cell lymphoma (DLBCL) is a predominant trigger of secondary HLH.[7]

The HLH-2004 protocol proposed by the Histiocyte Society has been widely adopted as the diagnostic criteria for HLH. Patients who were born with an HLH-associated molecular genetic abnormality or who meet at least five of the eight diagnostic criteria can be diagnosed with HLH.[8] We herein report a rare case of HLH secondary to DLBCL that was successfully treated by R-CHOP-E chemotherapy.

Case report

On 29 December 2018, a 66-year-old man presented with a continuous high-grade fever with no obvious cause; the fever had begun on 20 December 2018. A full blood cell count in the emergency department showed a white blood cell count of 4.99×10^9/L, hemoglobin concentration of 140 g/L, platelet count of 115.00×10^9/L, and C-reactive protein level of 87 mg/L. Subsequent lymph node ultrasound revealed lymphadenopathy in the left neck region (level IV lymph nodes). No obvious lymphadenopathy was found in the posterior peritoneum, right neck, bilateral supraclavicular region, bilateral axillary region, or bilateral groin region under ultrasound. However, positron emission tomography–computed tomography (PET-CT) on 28 December 2018 showed two sites of lymphadenopathy with increased fluorodeoxyglucose uptake: the left supraclavicular lymph node [14×6 mm, standardized uptake value (SUV) of 25.2] and the lymph node proximal to the abdominal aorta and iliac vessel (45×27 mm, SUV of 34.2). The seventh thoracic vertebra was also involved (SUV of 17.7), and splenomegaly was observed (no increase in SUV) (Figure 1(a)). The patient was diagnosed with DLBCL based on CT-guided biopsy of the lymph node proximal to the right iliac vessel on 4 January 2019. The immunohistochemistry results obtained on 11 January 2019 revealed the following: CD20 (+), CD79a (+), PAX5 (+), Ki-67 (70%), MUMI (95%), BCL2 (50%), BCL6 (20%), C-MYC (30%), CD10 (−), CD21 (−), CD23 (−), cyclin D1 (−), CD2 (rare+), CD3 (rare+), CD30 (rare+), CD4 (rare+), CD5 (−), CD7 (−), CD8 (rare+), CD56 (−), TIA1 (−), PER (−), P53 (−), GraB (−), AE1/AE3 (−), EBER (−), EMA (−), and ALK (−). These results indicated the presence of a non-germinal center B-cell subtype of DLBCL. Based on above examination results, the patient was eventually diagnosed and staged with DLBCL (IIIb) according to the pathological examination findings and the Ann Arbor staging

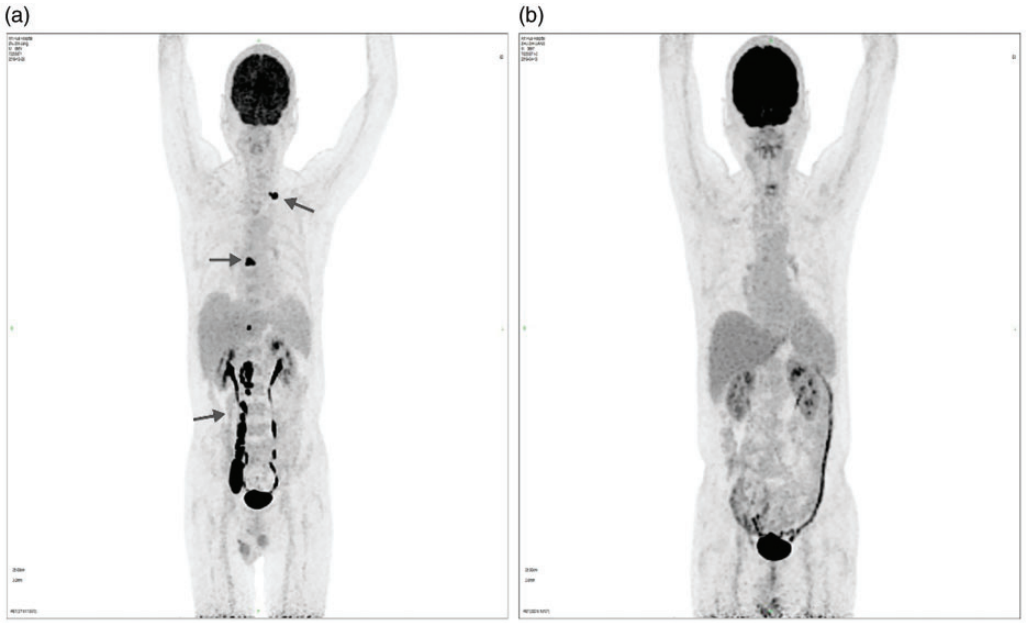

Figure 1. Positron emission tomography–computed tomography results. (a) Examination before chemotherapy revealed multiple sites of lymphadenopathy with increased fluorodeoxyglucose uptake. The left supraclavicular lymph node, lymph node proximal to the abdominal aorta and iliac vessel, and seventh thoracic vertebra were involved. (b) Interim response evaluation after four cycles of chemotherapy showed diminishment of the previous lymphadenopathy with decreased fluorodeoxyglucose uptake.

system. The international prognostic index (IPI) score was 4, indicating high-risk DLBCL. Additionally, typical hemophagocytic macrophages were observed in a bone barrow smear (Figure 2). This finding in combination with a fever (>38°C), bicytopenia (hemoglobin, 76 g/L; platelets, 82×10^9/L), splenomegaly, and increased levels of ferritin (18600 μg/L), soluble interleukin-2 receptor (IL-2R) (13540 U/mL), and triglycerides (2.52 mmol/L) tested on 11 January 2019 met diagnostic criteria for HLH according to the HLH-2004 protocol. Therefore, the patient was definitively diagnosed with HLH secondary to DLBCL.

Symptomatic and supportive therapy including glutathione, magnesium isoglycyrrhizinate, ademetionine 1,4-butanedisulfonate, omeprazole, and human albumin was given after admission. Although formal R-CHOP-E chemotherapy was administered to the patient upon establishment of the DLBCL diagnosis on 12 January 2019, low-dosage (10 mg/day) dexamethasone was given immediately after CT-guided biopsy on 4 January 2019 to prevent further worsening of the patient's condition. The R-CHOP-E chemotherapy drug dosages were as follows: rituximab, 375 mg/m^2 on day 0; cyclophosphamide, 750 mg/m^2 on day 1; liposomal doxorubicin, 20 mg/m^2 on day 1; vincristine, 1.4 mg/m^2 on day 1; prednisolone, 60 mg/m^2 on days 1 to 5; and etoposide, 100 mg/m^2 on day 1. This treatment regimen was accompanied by symptomatic supportive treatment for liver protection, infection prevention, blood product or albumin transfusion, and dyspnea relief. Following the first cycle of chemotherapy, the patient's clinical manifestations were ameliorated; additionally, his HLH-related

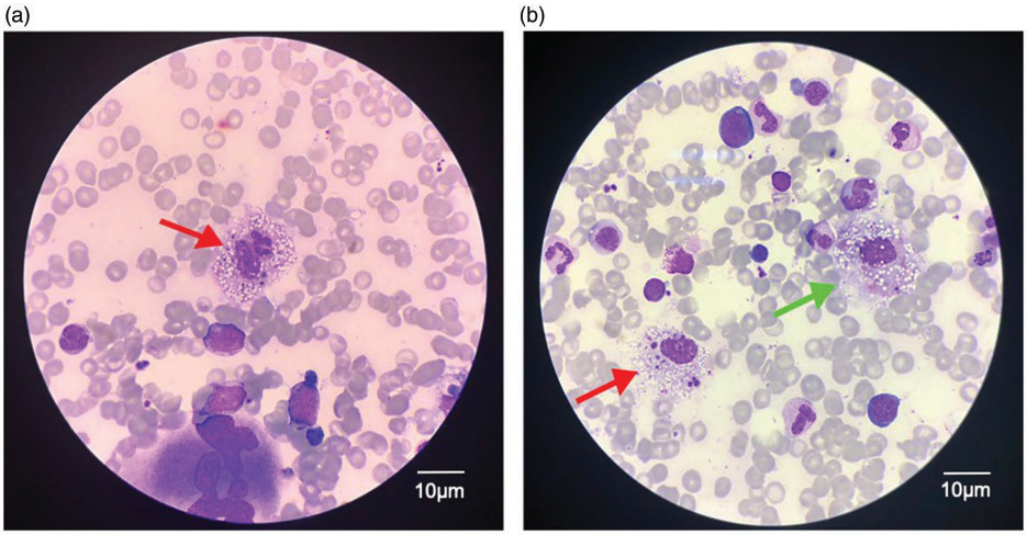

Figure 2. Bone marrow smear showed typical macrophage phagocytosis. (a, b) Red arrowhead indicates neutrophil and thrombocyte phagocytic macrophages. (b) Green arrowhead indicates thrombocyte phagocytic macrophages (Wright–Giemsa stain).

abnormalities such as the fever and abnormal levels of ferritin, hemoglobin, platelets, soluble IL-2R, triglycerides, and liver enzymes returned to normal levels (Figure 3(a)–(h)). The patient was then given intrathecal chemotherapy (methotrexate + cytarabine + dexamethasone) for prophylaxis against lymphoma CNS infiltration followed by a second cycle of R-CHOP-E chemotherapy and two cycles of R-CHOP chemotherapy. The patient finally achieved complete remission after four cycles chemotherapy according to the interim response evaluation by PET-CT (Figure 1(b)). Considering the patient's high-risk IPI score and secondary HLH, we planned to administer high-dose chemotherapy with autologous hematopoietic stem cell transplantation consolidation after another two cycles of R-CHOP chemotherapy.

Discussion

HLH is a rare clinical syndrome characterized by a hyperinflammatory condition caused by aberrantly activated macrophages and cytotoxic T cells, resulting in a cytokine storm and organ impairment. The pathogenesis and molecular biological origin of primary or familial HLH are clear. Secondary HLH is usually caused by triggers such as viral infections, malignancy, or autoimmune processes. The clinical course of HLH is complicated, and the prognosis is extremely poor with a high risk of mortality.[9] Notably, the prognosis of malignancy-associated HLH is the worst among all types of HLH.[10] Lymphoma is a common trigger of malignancy-associated HLH, and HLH can occur during the onset or progression of lymphoma. T/NK-cell lymphoma or B-cell lymphoma is a common inducer of secondary HLH.[4–7]

In the present case, the patient concurrently met the diagnostic criteria for both DLBCL and secondary HLH. The patient's general condition deteriorated day by day, and he showed progression to acute liver failure and dyspnea due to pulmonary edema. We highly suspected lymphoma

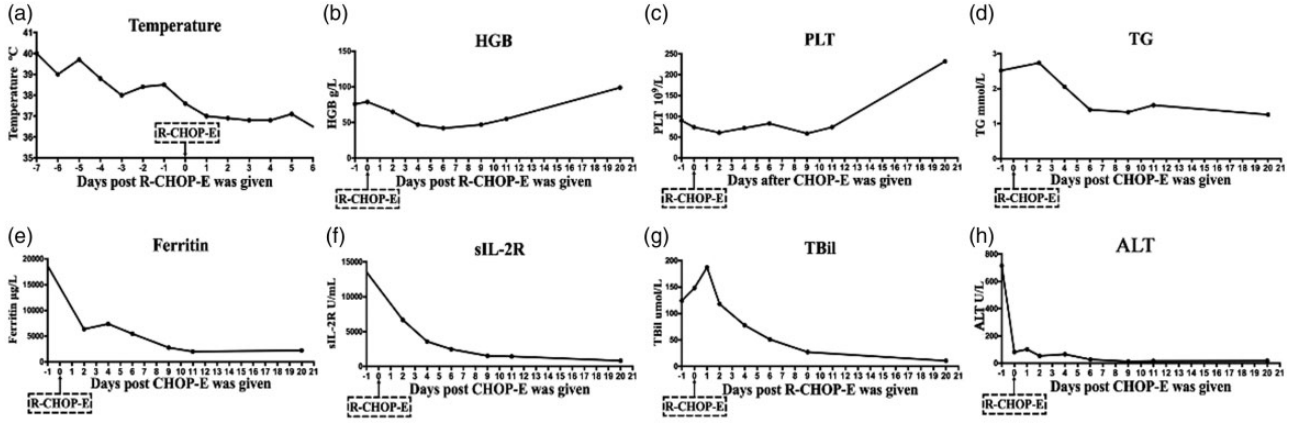

Figure 3. Responses of clinical and laboratory parameters to the first cycle of R-CHOP-E chemotherapy. (a) The persistent fever was relieved after the application of R-CHOP-E chemotherapy. (b, c) Bicytopenia (hemoglobin and platelets) was aggravated as an adverse effect during the initial period of chemotherapy and eventually recovered to normal levels before the second cycle of R-CHOP-E chemotherapy. (d–h) The significantly high levels of triglycerides, ferritin, sIL-2R, TBil, and ALT normalized after the first cycle of R-CHOP-E chemotherapy. HGB, hemoglobin; PLT, platelet count; TG, triglycerides; sIL2R, soluble interleukin-2 receptor; TBil, total bilirubin; ALT, alanine aminotransferase.

based on the PET-CT scan results. To prevent further worsening of the patient's condition, we administered dexamethasone as a pre-phase treatment for lymphoma and sequentially began lymphoma-specific treatment after performing the biopsy but prior to receiving the pathology report. This was a difficult decision in the present case. The patient was at high risk of death if he did not receive chemotherapy, but he was also at risk of liver failure or death due to chemotherapy-induced toxicity. One report described a patient with HLH secondary to DLBCL who died after chemotherapy.[11] Finally, we promptly administered chemotherapy after repeated communication with the patient and his relatives because disease-specific treatment should be initiated immediately if a malignancy is identified. In patients with lymphoma-associated HLH, treatment with an etoposide-containing chemotherapy regimen should be strongly considered.[12] Hence, we chose the R-CHOP-E regimen for both DLBCL and HLH. Surprisingly, all indications of HLH were alleviated after only one cycle of chemotherapy, and complete remission of DLBCL was achieved during the interim response evaluation after four cycles of chemotherapy.

In summary, this case highlights the following important points regarding the management of HLH in adults. (1) Whenever possible, an excisional biopsy should be performed because of the overwhelming reactive T-cell infiltrates in lymphoma-associated HLH. (2) An interdisciplinary team should aggressively pursue invasive diagnostics because the typical manifestations of lymphomas require the use of PET-CT and sometimes repetitive tissue harvesting. (3) To prevent organ failure, treatment should not be delayed when the diagnosis of HLH has been established. (4) Dexamethasone/etoposide can be used as lymphoma pre-phase treatment with sequential administration of lymphoma-specific treatment. (5) In contrast to HLH triggered by NK/T-cell lymphoma, newly diagnosed DLBCL with secondary HLH is very rare in China, and the prognosis is relatively better. R-CHOP-E chemotherapy is an effective treatment for this condition. (6) Autologous stem cell transplantation consolidation might be beneficial in patients who have DLBCL with secondary HLH and a high IPI score.[13,14]

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Author contributions

LM made substantial contributions to the design of the present study. RW performed the data collection and data analysis. RW and LM wrote the manuscript. XD and SH provided help in conceiving and designing the study. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Liyuan Ma https://orcid.org/0000-0003-1589-7300

Statement of ethics

The patient described in this report gave his informed consent for the use of his anonymized data. Ethical approval for the present study was given by the ethics committee of Xinhua Hospital.

References

1. Janka GE and Lehmberg K. Hemophagocytic syndromes–an update. *Blood Rev* 2014; 28: 135–142.
2. Brisse E, Wouters CH and Matthys P. Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders. *Cytokine Growth Factor Rev* 2015; 26: 263–280.
3. Machowicz R, Janka G and Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH and sepsis. *Crit Rev Oncol Hematol* 2017; 114: 1–12.
4. Rosado FG and Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013; 139: 713–727.
5. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Annu Rev Med* 2012; 63: 233–246.
6. Li F, Yang Y, Jin F, et al. Clinical characteristics and prognostic factors of adult hemophagocytic syndrome patients: a retrospective study of increasing awareness of a disease from a single-center in China. *Orphanet J Rare Dis* 2015; 10: 20.
7. Sano H, Kobayashi R, Tanaka J, et al. Risk factor analysis of non-Hodgkin lymphoma-associated haemophagocytic syndromes: a multicentre study. *Br J Haematol* 2014; 165: 786–792.
8. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131.
9. Risma KA and Marsh RA. Hemophagocytic lymphohistiocytosis: clinical presentations and diagnosis. *J Allergy Clin Immunol Pract* 2019; 7: 824–832.
10. Parikh SA, Kapoor P, Letendre L, et al. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clin Proc* 2014; 89: 484–492.
11. Patel R, Patel H, Mulvoy W, et al. Diffuse large B-cell lymphoma with secondary hemophagocytic lymphohistiocytosis presenting as acute liver failure. *ACG Case Rep J* 2017; 4: e68.
12. Schram AM and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015; 125: 2908–2914.
13. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 2013; 369: 1681–1690.
14. Shimazaki C, Inaba T and Nakagawa M. B-cell lymphoma-associated hemophagocytic syndrome. *Leuk Lymphoma* 2000; 38: 121–130.