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Case Report

Aggressive diffuse large B-cell lymphoma with hemophagocytic lymphohistiocytosis: report of one case

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Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a rare fatal hyperinflammatory syndrome resulting in cytokine storm and secondary multi-organ impairment. The natural killer (NK)/T-cell lymphoma is the predominant subtype in patients with lymphoma-associated hemophagocytic syndrome (LAHS) in Asia. Yet the non-Hodgkin's B-cell lymphoma is a relatively uncommon trigger of HLH. We report a case of a 64-year-old woman who had a bone marrow-spleen type of diffuse large B-cell lymphoma (DLBCL) associated with HLH. The patient presented with EBV-positive infection, significantly increased inflammatory cytokines (IL-6, IL-8, IL-10), and dramatically increased aspartate aminotransferase (AST) and total bilirubin (TB), resulting the patient's aggressive clinical course and early death. This case may not only illustrate the nonspecific manifestation and rapidly progressive characteristics of HLH but also highlight the necessity of anti-inflammatory therapy for the treatment of lymphoma-associated HLH.

Keywords: Hemophagocytic lymphohistiocytosis, lymphoma, inflammatory cytokines

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare fatal hyperinflammatory syndrome with an incidence of 1/50,000 to 1/150,000 in the general population, resulting in cytokine storm and secondary multi-organ impairment [1]. Primary HLH is most common in children while secondary HLH is more frequent in adults. It has a variety of causes, including infections, autoimmune diseases, and malignancies [2]. However, it is important to note that secondary HLH often has more than only one etiology contributing to the systematic dysregulation. Several studies have demonstrated that natural killer (NK)/T-cell lymphoma is the predominant subtype in patients with lymphoma-associated hemophagocytic syndrome (LAHS) in Asia [3]. Yet the non-Hodgkin's B-cell lymphoma is a relatively uncommon trigger of HLH. Secondary HLH in adults usually manifests as an aggressive disease with high mortality rates. Here, we report a case of HLH secondary to bone marrow-spleen type of DLBCL, which manifested an aggressive clinical course.

Case presentation

A 64-year-old woman presented with approximately a 20-day history of upper abdominal pain and continuous high-grade fever. Initial workup showed a red blood cell count of 3.34×10^{12}/L, white blood cell count of 5.53×10^{9}/L, hemoglobin (Hb) concentration of 95 g/L, platelet count of 265×10^{9}/L, C-reactive protein level of 90.80 mg/L, and procalcitonin level of 2.48 ng/mL. The blood chemical values included AST, 54.90 IU/l; TB, 19.78 μmol/L; albumin, 31.97 g/L; potassium, 3.22 mmol/L. TORCH testing showed the positive findings for rubella IgG, cytomegalovirus IgG, and herpes simplex virus IgG. Positive serum anti-EBV VCA IgA and IgG antibody levels were detected. The computed tomography (CT) scan (**Figure 1**) revealed a hypodense lesion in the spleen, and multiple abdominal and retroperitoneal lymph nodes were observed. Subsequent lymph node ultrasound showed lymphadenopathy in the left neck region and left supraclavicular region. Then the patient underwent an ultrasound-guided needle biopsy of the left supraclavicular lymph node. Immunohistochemical results

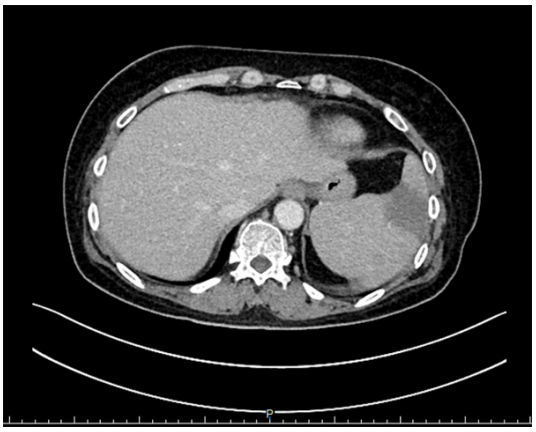

Figure 1. Abdominal CT scan shows splenomegaly with hypodense lesion.

revealed the following: CD21(+), CD23(+), CD20(++), PAX-5(++), Bcl-2(+80%), CD10(+), Bcl-6(+), MUM-1(+), c-myc(+40%), CD19(+), p53(+10%), CyclinD1(+), CD30(+), TdT(-), CD3(+), CD5(+), CK-pan(-), CK-L(35βH11)(-), p63(+), CD43(+), Ki-67(+80%), EBER(-), positive control(+). These results indicated a germinal center B-cell subtype of DLBCL.

Once the diagnosis was confirmed, the R-CHOP combination regimen was initially recommended to the patient while conducting further examinations including the bone marrow biopsy and PET-CT. Yet the patient became progressively dyspneic with PaO_2 55 mmHg and $PaCO_2$ 37 mmHg. Urgent investigations showed a red blood cell count of 2.67×10^{12}/L, hemoglobin concentration of 75 g/L, platelet count of 23×10^{9}/L, ferritin 13100.00 ng/ml, soluble interleukin-2 receptor (IL-2R) >7500.00 U/ml, interleukin-6 (IL-6) 311.00 pg/ml, interleukin-8 (IL-8) 35.40 pg/ml, and interleukin-10 (IL-10) 736.00 pg/ml. Based on the continuous fever (>38°C), splenomegaly, and the splenic lesions, the patient was definitively diagnosed with HLH secondary to DLBCL according to the HLH-2004 protocol.

After supportive treatments, the patient's breathing got better with improved PaO_2 and SaO_2. But the patient's blood cells especially the platelet count continued to decrease. Meanwhile, the bone marrow biopsy results (**Figure 2**) obtained afterward showed an infiltrate of tumor cells in the hematopoietic tissues. Immunohistochemistry results revealed the following: CD19(+), CD20(+), CD43(+), PAX5(+), CD3(+), Bcl-2(+), BCL-6(+), CD10(+), CD30(-), CD68(+), CD117(-), MPO(+), Ki-67(+60%), MUM-1(+). Salvage chemotherapy for the secondary HLH has been tried. However, only after one day of prednisone administration, the patient's clinical status worsened again with drooping eyelids, lethargy, increased heart rate (150 bp/min) and yellowing of the skin and sclera. A cerebral hemorrhage could not be excluded. After careful considerations and discussions with her family, her code status was changed to "do not resuscitate" (DNR). Despite the symptomatic supportive treatment for liver protection, infection control, blood product transfusion and dyspnea relief, the patient subsequently expired.

Discussion

HLH is a rare life-threatening disease resulting in a large amount of inflammatory cytokine hypersecretion. According to HLH-2004 protocol, the present case met the diagnostic criteria for both DLBCL and secondary HLH. This lymphoma is characterized by the involvement of the spleen and bone marrow.

Although extraordinary advances in understanding of HLH have been made, early death remains a major challenge in the treatment of HLH. As observed in our case, despite taking active preparation for further treatment once the diagnosis was confirmed, the patient's condition deteriorated day by day with significant impairment of organ function resulting in rapid death. The continuous decrease in platelet count, red blood cell count, and significant increase of AST and TB were detected (**Figure 3**). Besides, we tend to believe that the combination of the multiple risk factors including EBV infection, old age, hyperferritinemia, and thrombocytopenia might have contributed to the patient's poor survival, as consistent with other study results [4]. Moreover, despite the increased IL-2R, elevated serum levels of IL-6, IL-8, IL-10 were noted, which contribute to pathogenesis of HLH and the growth of tumor cells. This may indicate the active state of HLH, leading to aggressive clinical progression with poor prognosis [5].

Prompt start of therapy is crucial and lifesaving. However, treatment is often delayed owing to the nonspecific clinical and laboratory findings. Tamamyan et al. retrospectively reviewed

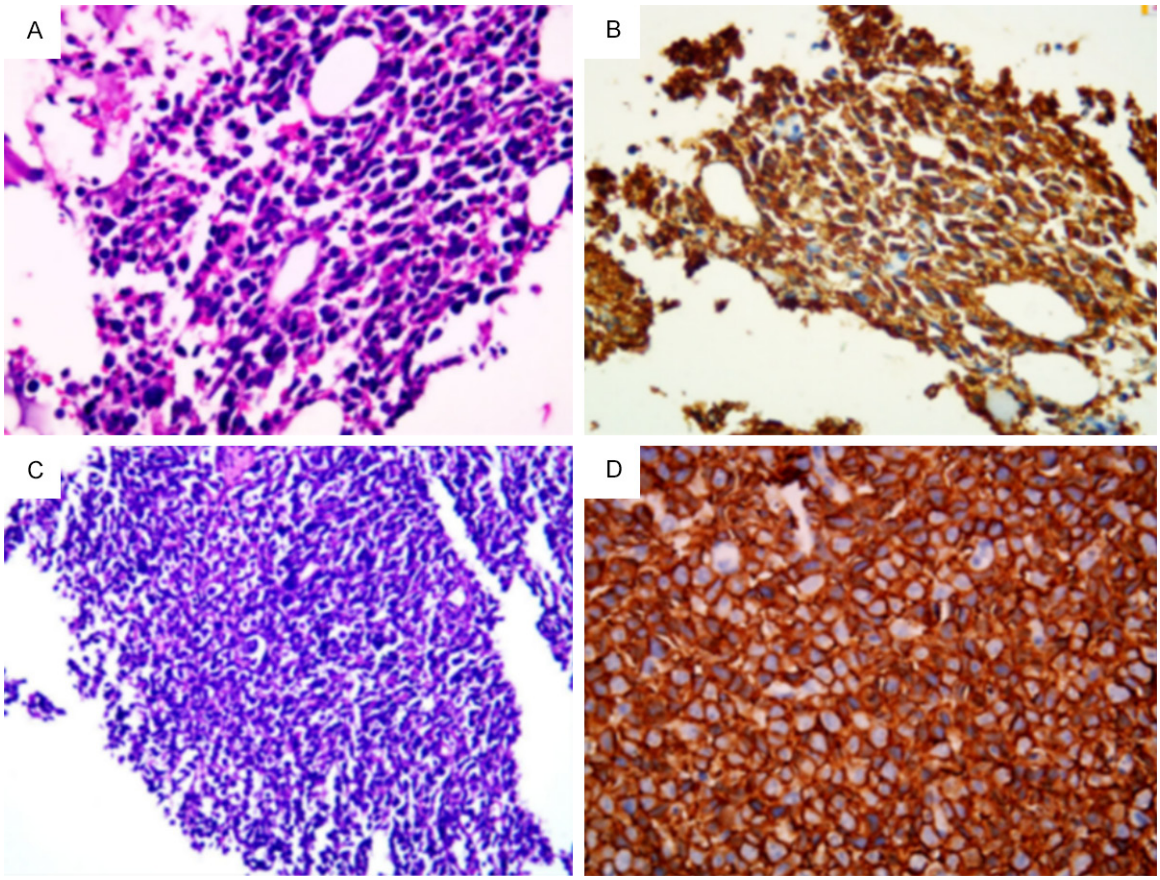

Figure 2. Morphologic and immunohistologic findings in the biopsy of the left supraclavicular lymph node and bone marrow. A. Appearance of the left supraclavicular lymph node (H&E×200). B. Immunohistochemical stain for CD20 showing the positive reactivity in the left supraclavicular lymph node (×200). C. Bone marrow smear (H&E×100). D. Strong expression of CD20 in bone marrow (IHC×400).

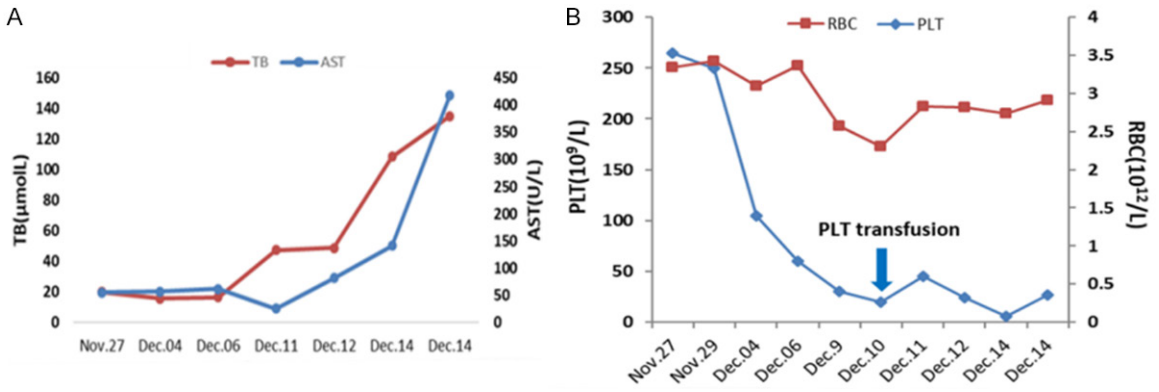

Figure 3. Laboratory values during the patient's clinical course. A. Increased levels of aspartate aminotransferase (AST) and total bilirubin. B. The counts of platelets (PLT) and red blood cells (RBC).

cases of malignancy-associated HLH and they reported that only 21% of the patients met the HLH-2004 criteria, while the majority of patients had an incomplete workup. This consequently resulted in only 27% of patients getting HLH-directed therapy [6]. Hence, it seems necessary to add additional diagnostic variables that are easily and quickly obtained to promote ear-

lier consideration, which includes elevated hepatic enzymes, renal failure, coagulopathy, coagulopathy, and elevated β_2 microglobulin [7].

Malignancy-directed workup has been emphasized. Studies show R-CHOP chemotherapy is effective for the treatment of DLBCL. Yet the clinical deterioration can be extremely rapid so that patients often die before effective treatment is provided for the primary cause. As noted in our case, R-CHOP therapy was initially recommended to the patient as soon as the diagnosis was confirmed. However, the patient's condition deteriorated rapidly since then; there was a high risk of death if the patient did not receive chemotherapy, but she was also at risk of death due to chemotherapy-induced toxicity. There was a report that a patient with HLH secondary to DLBCL died after chemotherapy [8]. Unfortunately, only after one day of prednisone administration, the patient's clinical status continued to deteriorate, and chemotherapy had to be stopped by her family's request. In such a situation, it seems that secondary and uncontrolled inflammation must be addressed. Inflammatory cytokines could lead to multiple organ failure which prevents the cancer-targeted therapies. Actually, the therapy should depend on the primary trigger, organ functions, and the performance status of the patient [9]. Some experts recently suggested a two-step approach to the treatment of malignancy-associated HLH should be considered [10]. HLH-directed therapy which targets the cytokine storm such as corticosteroids and polyvalent immunoglobulins could be used upfront, buying more time for the further specific malignancy-directed therapy. However, there is still no definite conclusion whether therapy for the malignancy or the uncontrolled inflammation should be addressed because of lack of clinical trials.

In conclusion, we report a case of EBV-positive, bone marrow-spleen type of DLBCL associated with HLH, resulting in an aggressive clinical course. This case will not only illustrate the nonspecific manifestations and rapidly progressive characteristics of HLH but also highlight the necessity of anti-inflammatory therapy for the treatment of lymphoma-associated HLH.

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Disclosure of conflict of interest

None.

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