Precursor B Cell Acute Lymphoblastic Leukemia Presenting with Repeated Episodes of Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by dysregulated activation of cytotoxic T-lymphocytes and macrophages, resulting in excessive cytokine release and tissue damage. Although hematological malignancies and the chemotherapies used to treat them are frequently identified as triggering factors for HLH, B lymphoid leukemias are rarely implicated. In this report, we present an interesting case of a patient who presented with symptoms of HLH and was subsequently diagnosed with B-cell acute lymphoblastic leukemia. The further course of chemotherapy was complicated by another episode of HLH. This case highlights the complexity and the diverse triggers of HLH in the context of B lymphoid leukemia. Recognizing this atypical presentation is important to institute timely management strategies.

Keywords

► acute lymphoblastic leukemia
► hemophagocytosis
► cytokine storm
► immune system
► infections

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon hematological disorder resulting from an uncontrolled activation of cytotoxic T-lymphocytes (CTL), natural killer (NK) cells, and macrophages leading to excessive cytokine production.1 The classical clinical manifestations of HLH stem from a cytokine storm are characterized by high-grade fever, hepatosplenomegaly, liver dysfunction, cytopenias, hyperferritinemia, and hemophagocytosis occurring within the bone marrow, liver, spleen, or lymph nodes. Neurological symptoms, such as cranial nerve palsies and seizures occur in about 10% of patients.2

Familial HLH (FHL), also termed primary HLH, predominantly presents during childhood and arises due to mutations in genes encoding granule-dependent lymphocyte toxicity.3 Conversely, the secondary form of HLH, more commonly observed in adults is frequently caused by infections, malignancies, and autoimmune disorders. Malignancy-triggered HLH (M-HLH) is predominantly linked with T-cell or NK cell malignancies. Its diagnosis often presents significant challenges owing to symptom similarity with more common conditions such as sepsis. Moreover, patients with sepsis may manifest disseminated intravascular coagulation (DIC), thereby exacerbating diagnostic complexities due to shared characteristics such as altered coagulation profiles and thrombocytopenia with HLH. M-HLH may manifest concomitantly with the underlying disease, postchemotherapy (Ch-HLH), or even during disease remission, the latter often triggered by infectious agents.4 While malignancies such as acute myeloid leukemia, diffuse large B-cell lymphoma, and Hodgkin lymphoma have been implicated in M-HLH cases, reports of precursor B-cell acute lymphoblastic leukemia (pre-B-ALL) remain sparse.5,6

In this report, we present the case of a 19-year-old man who initially exhibited symptoms of HLH and was subsequently diagnosed with pre-B-ALL.
diagnosed with pre-B-ALL. Another episode of HLH complicated subsequent chemotherapy, likely attributable to a fungal infection contracted during chemotherapy.

**Case**

A 19-year-old man was admitted with a persistent fever lasting 6 days (101–102°F), accompanied by a cough with minimal expectoration and petechiae on both lower limbs. Additionally, he reported experiencing yellowish discoloration of his eyes for 3 days prior to his presentation to the emergency unit. Upon physical examination, his temperature was 102°F, pulse rate 116 beats per minute, and blood pressure 106/60 mmHg. Pallor and scleral icterus were evident, along with bilateral infrascapular crepitations. The spleen and liver were palpably enlarged, 3 and 2 cm below the costal margin. Further, a petechial rash was observed on both lower limbs and the anterior chest wall.

Laboratory investigations revealed a hemoglobin level of 70 g/L (normal 120–150 g/L), white blood count 0.9 × 10^9/L (normal 4–10 × 10^9/L), platelet count 13 × 10^9/L (normal 150–300 × 10^9/L), lactate dehydrogenase 676 U/L (normal <250 U/L), total bilirubin 4.4 mg/dL (normal 0.6–1 mg/dL), and serum ferritin 2,980 µg/L (normal 30–300 µg/L). Coagulation parameters were deranged, with prothrombin time 44 seconds (normal 26–32 seconds), and fibrinogen 0.9 g/L (normal 1.5–3.5 g/L). Serum albumin, aspartate aminotransferase, and alanine aminotransferase were within normal limits. A bone marrow aspirate and biopsy were performed to determine the underlying cause of pancytopenia, revealing a marked increase in hemophagocytic activity (Fig. 1a, b). No granulomas or atypical cells were identified. Serological tests for various viruses and pathogens including cytomegalovirus, Epstein–Barr virus, parvovirus B19, hepatitis A, B, C, dengue virus, and human immunodeficiency virus, as well as blood and bone marrow cultures, and serum galactomannan returned negative results. High-resolution computed tomography demonstrated areas of ground-glass opacity in both lung fields, predominantly in the left lower lobe.

The patient was diagnosed with HLH secondary to atypical pneumonia and was administered intravenous immunoglobulin (IVlg) at a dose of 0.4 g/kg/d for 5 days. During the third day of IVlg therapy, the patient’s fever subsided, followed by a gradual improvement in blood counts over the subsequent days. Coagulopathy ameliorated, with bilirubin and ferritin levels returning to normal by day 10. The patient was discharged on the 13th day of admission with a confirmed diagnosis of secondary HLH (H score 225 points; 96–98% probability).

Eleven days following discharge, the patient presented again with a recurrence of initial symptoms. Splenomegaly had worsened, with the spleen now palpable 5 cm below the costal margin. Laboratory investigations revealed a recurrence of pancytopenia and worsening coagulopathy, including a markedly reduced serum fibrinogen level (0.7 g/L [normal 1.5–3.5 g/L]). The ferritin level was also significantly elevated (7,620 µg/L). A repeat bone marrow examination (Fig. 1c, d) revealed marked hemophagocytosis, alongside the presence of large atypical cells this time (H score 284 points; >99% probability). Immunophenotyping demonstrated positivity for CD45 (dim), CD10 (bright), CD19 (bright), and CD34 (partial), while CD20 was negative, indicative of a diagnosis of pre-B-ALL. The patient commenced induction therapy for leukemia, consisting of prednisolone, vincristine, daunorubicin, pegylated-asparaginase, cytarabine, and intrathecal methotrexate. After induction chemotherapy, the patient achieved a measurable residual disease (MRD)-negative remission. There was also a reduction in spleen size and resolution of coagulopathy by day 11 of induction.

The patient commenced consolidation therapy and remained asymptomatic for 3 months when he was readmitted with high-grade fever and respiratory distress. Laboratory findings were notable for pancytopenia, hypofibrinogenemia, elevated bilirubin, and ferritin. The serum galactomannan level was elevated (1.6 IU). The patient received antifungal therapy (liposomal amphotericin B) and broad-spectrum antibiotics while awaiting blood culture results. Although a bone marrow examination was performed again to investigate suspected disease relapse, no leukemic cells were identified on morphology, and the MRD was negative by flow cytometry. However, there was marked hemophagocytosis in the bone marrow. The patient’s clinical condition deteriorated, necessitating mechanical ventilation, and unfortunately, he succumbed to his symptoms 3 days following their onset.

**Discussion**

HLH represents a hyperinflammatory syndrome characterized by immune dysregulation, leading to cytokine overproduction and consequent tissue damage.1 Although HLH is frequently associated with infections, autoimmune diseases, and malignancies, its occurrence in the context of B lymphoid leukemia is exceedingly rare. Our case reports on this uncommon entity...
emphasize the importance of maintaining a high clinical suspicion. The diagnostic challenge of M-HLH is underscored by its clinical and laboratory features, often overlapping with more common conditions such as sepsis and DIC. Moreover, conventional diagnostic criteria for HLH, such as the HLH-2004 criteria, may prove inadequate for diagnosing M-HLH, given that manifestations such as cytopenias, elevated ferritin levels, and organomegaly may arise from the underlying malignancy itself. It is also important to note that the HLH-2004 criteria were developed using the pediatric population and has not been validated for use in adults. In addition, some of the tests included in the HLH-2004 criteria (soluble interleukin [IL]-2 receptor and NK cell activity) are difficult to obtain. Given the aggressive nature of M-HLH with a mortality rate exceeding 80%, the timeliness of diagnosis and urgent initiation of therapy are crucial.7 Tamamyan et al have proposed an 18-point extended diagnostic criteria utilizing readily available laboratory variables for the early detection of adults with M-HLH, with outcomes of patients meeting the extended criteria similar to those who met the HLH-2004 criteria.8

It is hypothesized that M-HLH is a consequence of the impaired immune function of CTL, leading to excessive macrophage activation and subsequent release of proinflammatory cytokines (tumor necrosis factor-alpha, IL-6).9 Additional factors include dysregulated cytokine production, ongoing antigen stimulation by malignant cells, and therapy-induced immunosuppression, predisposing to infective triggers.7,9 Hematological malignancies, particularly T/NK cell malignancies are frequently associated with HLH. Rare forms of B-cell lymphoma, such as intravascular B-cell lymphoma also frequently present with HLH.10 However, B-lymphoblastic leukemia-triggered HLH comprises only a minor proportion, accounting for merely 6.4% of cases. To date, less than 30 cases have been documented in the literature.5,7,10–12

Although M-HLH can manifest before or during leukemia diagnosis and treatment, distinct patterns are associated with B-cell ALL and T-cell ALL. Our case presents a unique scenario where one HLH episode preceded a B-ALL diagnosis, while another occurred during chemotherapy, a feature typically linked to T-ALL.8

There is no consensus regarding the optimal management of M-HLH. The treatment objectives are to suppress the overactive immune system and address the underlying etiology. Therapeutic strategies must be individualized, accounting for the precipitating malignancy, patient performance status, and concurrent treatments. Lehmburg et al13 treated four patients of ALL-associated HLH with the HLH-2004 protocol and reported dismal results (two deaths, two relapses).10 Similarly, Pan et al14 reported discouraging outcomes in a larger cohort of nine ALL patients treated with HLH-directed therapy (overall response rate: 68.2%).12 These studies highlight the importance of timely initiation of antileukemic chemotherapy over HLH-directed therapy. In our case, the patient had a favorable response to antileukemic therapy alone, obviating the need for additional HLH-specific interventions.

The first episode of HLH in our patient was managed on the lines of infection-triggered HLH with IVIg and broad-spectrum antibiotics. This approach effectively resolved the initial HLH episode. However, the diagnosis of leukemia may have been missed, likely due to obscured bone marrow features resulting from florid hemophagocytic activity. Subsequent implementation of leukemia-directed therapy successfully mitigated the second HLH episode. The occurrence of a third HLH episode was linked to probable fungal pneumonia, hypothesized to be a consequence of the immunosuppressive effects of chemotherapy (Ch-HLH). Given the recurrent nature of HLH episodes, PHL was strongly suspected. However, genetic analysis could not be performed due to cost constraints.

**Conclusion**

In conclusion, the report underscores the infrequent manifestations of B-ALL as HLH. It is important to have a high index of clinical suspicion, given that bone marrow examinations may not unveil blast cells at the onset of HLH, due to pronounced hemophagocytosis.

**Declaration of Patient Consent**

A written, informed consent was obtained.

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None.

**Conflict of Interest**

None declared.

**References**

hemophagocytosis, characteristics, and outcomes. Cancer 2016;122(18):2857–2866