

Case Report

Hemophagocytic Lymphohistiocytosis Secondary to Malignancy and Chemotherapy in Pediatric Patients: A Single-Institution Experience

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon yet potentially devastating systemic disease, arising from uncontrolled activation of the immune system. While the primary form of this disease can be caused by genetic mutation(s), the secondary form may be triggered by infection and hematologic, malignant, and metabolic conditions. The diagnosis of HLH remains a clinical challenge due to nonspecific symptoms. Proper diagnosis is significantly more difficult among patients with acute leukemia who have received chemotherapy. The objective of this study is to describe three unique cases of secondary HLH, describe the specific treatment, and improve the awareness of this condition. Two patients with acute myeloid leukemia (AML) and one with acute lymphoblastic leukemia were diagnosed with HLH, having fulfilled the criteria as outlined in the HLH-2004 protocol. They then received HLH-specific treatment. Two patients passed – one from refractory HLH and one from primary disease (i.e., AML) – and one patient remains alive 22 months after her allogeneic bone marrow transplant. The diagnosis of HLH requires the presence of any five of the eight criteria. Due to its heterogeneous presentation, it remains imperative that treating clinicians remain cognizant about HLH so that prompt diagnosis may allow appropriate treatment.

Keywords: Acute leukemia, ferritin, hemophagocytic lymphohistiocytosis

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that, if left untreated, may result in multiorgan failure, central nervous system dysfunction, opportunistic infection, and even death within 2 months.^[1] Hyperinflammation, resulting from immune dysregulation, is the driving pathogenesis for this syndromic disease. Primary HLH, mostly seen in infants and younger children, is characterized by familial inheritance or a mutation in genes associated with cytotoxic cell granules.^[1] In contrast, secondary HLH, often triggered by infection and/or malignancy, is seen primarily in older children or even adults with no family history or genetic cause.^[1,2] In such patients, symptoms of HLH can overlap with those resulting from malignancy (primarily leukemia or lymphoma) and/or therapy administered to treat the malignancy. These concurrent symptoms can challenge timely diagnosis and treatment of HLH. The goal of this study is to help raise awareness about HLH secondary to acute leukemias

(myeloid or lymphoid) and chemotherapy among children; in this study, we describe three patients who developed HLH following administration of chemotherapy for malignancy.

Case Reports

Case 1

A 9-year-old boy presented initially with fever, fatigue, bone pain, and abnormal labs including hyperleukocytosis with white blood cell of 288,000; he was diagnosed with acute myeloid leukemia [AML; Table 1]. On day-22 bone marrow evaluation, the patient was noted to have significant hemophagocytosis in an otherwise aplastic marrow. In addition, he was profoundly pancytopenic and febrile. On further investigation, we found elevated soluble interleukin-2 receptor (sIL-2R), hyperferritinemia, and hypertriglyceridemia, prompting the diagnosis of secondary HLH [Table 2 for symptoms]; he was treated with dexamethasone and etoposide, resulting in clinical and immunologic improvement. He then received a second block of chemotherapy for AML complicated by successive infectious episodes including

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candidemia, *Enterobacter*, and *Pseudomonas sepsis*; at the same time, he suffered from recurrence of HLH which had become unresponsive to treatment with dexamethasone/etoposide. He then received Campath as salvage regimen without any benefit and ultimately passed from HLH-related complication.

Case 2

A 14-year-old male was diagnosed with monocytic (M5) AML for which he completed four courses of chemotherapy without any infectious complication. At the end of therapy evaluation, he was positive for minimal residual disease (MRD) prompting treatment with a first course of salvage chemotherapy; however, his disease persisted, and he received a second course of salvage chemotherapy. His disease persisted twice more, and he was enrolled on two successive clinical trials. Finally, he was in remission after a fourth course of salvage chemotherapy. He then developed *Enterococcus bacteremia*, fever, pancytopenia, hyperferritinemia, persistent fever, and elevated sIL-2R. He was diagnosed with secondary HLH and treated with etoposide and dexamethasone, but he persisted with significant hemophagocytosis, fever, and elevated inflammatory markers at the end of 8 weeks, leading to further treatment with Campath that provided remission with regard to HLH. This was followed by matched sibling bone marrow transplant and an unsustained remission, and he ultimately died from leukemia.

Table 1: Patient characteristics

Number	Age (years)	Sex	Primary diagnosis	HLH criteria	Outcome of HLH	Overall outcome
1	9	Male	AML	6/8	Passed	Passed
2	14	Male	AML	5/8	Remission	Passed
3	11	Female	B-ALL	6/8	Remission	Alive

HLH – Hemophagocytic lymphohistiocytosis; AML – Acute myeloid leukemia; ALL – Acute lymphoblastic leukemia

Table 2: Diagnostic criteria set forth by hemophagocytic lymphohistiocytosis-2004 and criteria met by three cases in our study

Diagnostic criteria	Patient 1	Patient 2	Patient 3
1. Fever	✓	✓	✓
2. Splenomegaly	×	×	✓
3. Cytopenia affecting at least 2 of 3 lineages in peripheral blood	✓	✓	✓
4. Hypertriglyceridemia and/or hypofibrinogenemia	✓	✓	✓
5. Hemophagocytosis	✓	✓	×
6. Reduced natural killer cell activity	Unable to perform	Unable to perform	Unable to perform
7. Ferritin >500 ng/mL	✓ (4890)	✓ (15,754)	✓ (1000)
8. Soluble CD 25(sIL-2R)	✓ (10,654)	✓ (1604)	✓ (7728)

✓ – Patient met criterion; × – Patient did not meet criterion

Case 3

A 3-year-old female initially presented with B-cell precursor average-risk acute lymphoblastic leukemia (ALL) but sustained isolated bone marrow relapse 1 year after completion of the first treatment course. She then remained in remission for a year following completion of salvage chemotherapy regimen, but she sustained a second bone marrow relapse; this was treated with salvage chemotherapy, leading to MRD-negative remission at day 48 of induction therapy. Shortly afterward, her clinical course was complicated by the development of persistent fever, pancytopenia, hepatosplenomegaly, elevated sIL-2R, hypertriglyceridemia, and hyperferritinemia, prompting HLH-directed therapy for 2 months. She responded well, allowing her to proceed to bone marrow transplant. The posttransplant course was complicated by engraftment syndrome and a resurgence of HLH, which was managed with dexamethasone alone. Thereafter, multiple infectious problems including systemic adenovirus infection, gastrointestinal graft-versus-host disease, and candidemia were noted. Six-month posttransplant, she again developed prolonged fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, and elevated sIL-2R with no obvious focus of infection. It was felt that this represented a third resurgence of HLH; remission was attained by treatment with dexamethasone alone. After a prolonged hospital course, the patient was eventually discharged, and at 11 years of age, she is currently in remission for over 30 months with good quality of life.

Discussion

In 2004, the Histocyte Society published the criteria to diagnose primary and secondary HLH.^[3] According to their guidelines, a patient with HLH should present with five out of the following eight diagnostic criteria: fever, splenomegaly, cytopenia affecting two of the three peripheral lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent natural killer cell activity, hyperferritinemia, and elevated sIL-2R levels (sCD25). Secondary HLH can occur due to bacterial or viral infections or as a complication of treating malignancies; HLH can be the initial clinical diagnosis, masking an underlying malignancy, or it can develop during the treatment of a malignancy as seen in patients in this study.^[3] None of our patients had abnormal genetics or history suggesting familial HLH, and NK-cell functional assay could not be performed on any of the patients due to prolonged leukopenia.

The possible pathogenesis of secondary HLH during the treatment of malignancy is that neoplastic cells, such as malignant T cells, produce pro-inflammatory cytokines such as tumor necrosis factor alpha and IL-6 that could lead to overactivation of macrophages.^[4] It is also postulated that malignant neoplastic histiocytic cells secrete cytokines that induce hemophagocytosis.^[2]

Treatment of HLH involves suppressing the overactive immune system, specifically the macrophages, using immunosuppressive agents such as chemotherapeutic drugs and steroids. In this study, treatment was based on the HLH-2004 protocol which calls for the use of etoposide and dexamethasone.

Unlike previous reports involving patients with only HLH secondary to lymphoid malignancy,^[4-7] our study identifies two out of three patients with acute leukemia of myeloid lineage. The findings from our study are similar to other reports in the literature where secondary HLH has been reported among leukemia and lymphoma patients who have received systemic chemotherapy. We hypothesize that myelosuppression driven immune dysregulation may contribute to infection and subsequent development of HLH. A Japanese study identified other risk factors such as older age, female gender, and a polymorphism involving the IRF5 gene.^[7,8] The Japanese study by Moritake *et al.*^[7] also found that sIL-2R <10,000 and receiving chemotherapy during maintenance (rather than induction) therapy were associated with better patient outcomes.

Regardless, the reported incidence of secondary HLH remains extremely low;^[7] this could be due to the rare occurrence of HLH and the nonspecific findings of HLH, especially in the setting of chemotherapy or preparative regimen of bone marrow transplant-induced profound myelosuppression. To improve diagnosis, we suggest that patients with pancytopenia and prolonged unexplained fever be checked for markers of inflammation such as ferritin and sIL-2R. It has been suggested that therapeutic interventions, such as maintaining IgG level >400 mg/dL with periodic administration of intravenous immunoglobulin, may help prevent the development of secondary HLH among pediatric acute leukemia patients.^[7]

New experiments are being conducted to develop more targeted therapy for HLH. JAK1/2 inhibitors, such as ruxolitinib, are immunosuppressive agents and have been used experimentally to treat murine models of primary HLH.^[9]

Conclusion

Secondary HLH is a deadly yet underdiagnosed condition. The goal of this study is to help raise the awareness of HLH secondary to AML or ALL and chemotherapy in pediatric patients. Awareness among

practitioners should improve the prognosis for these patients by increasing diagnostic rates and by preventing cases whenever possible.

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Conflicts of interest

There are no conflicts of interest.

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