Hemophagocytic Lymphohistiocytosis in Malignant Hematology: Uncommon but Should Not Be Forgotten?

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Abstract

We describe Hemophagocytic lymphohistiocytosis (HLH) in the setting of hematologic malignancies. Seventeen cases of HLH were included in which the most common underlying diagnosis was aggressive lymphoma. We summarize clinical characteristics. The median overall survival (OS) from the time of HLH diagnosis was 8.4 months. Response to treatment was associated with better OS.

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome of excessive immune activation and an inflammatory cytokine storm leading to multiple organ failure. We report our experience in a large tertiary referral center on HLH in the setting of hematologic malignancies and describe responses to therapy and outcomes. Seventeen cases of HLH were included in which the most common underlying diagnosis was aggressive lymphoma (n = 7). The median time from diagnosis of primary hematologic condition to HLH was 3.1 months. The most common presenting features were fever (n = 15), splenomegaly (n = 13), and transaminitis (n = 14). The mean serum ferritin level was 21,000 ng/mL. Fourteen patients demonstrated evidence of hemophagocytosis in bone marrow or other organs. Among all patients, 12 received etoposide, 14 received dexamethasone, and 3 received cyclosporine. Intrathecal chemotherapy was administered to 3 patients. Overall, 7 patients (41%) responded to treatment with clinical and laboratory improvement. The median overall survival (OS) from the time of HLH diagnosis and the primary hematologic diagnosis was 8.4 months and 29.5 months, respectively. The OS was better among patients with HLH with aggressive lymphomas (12 months). Response to treatment was associated with better OS. Recognition of manifestations and prompt diagnosis of HLH are crucial to initiate prompt therapy and improve outcome.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome of excessive immune activation and an inflammatory cytokine storm leading to multiple organ failure.[1,2] HLH is predominantly a pediatric disease with familial genetic background, but sporadic cases particularly associated with infection and malignancies are described in the literature of adult patients.[3,4]

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Diagnosis and treatment of HLH are challenging in a setting of hematologic malignancies because manifestations are often attributed to the primary disease or its progression.[5-7] HLH is characterized clinicopathologically by fever, hepatosplenomegaly, cytopenias, liver dysfunction, and hemophagocytosis.[5,7]

We retrospectively report our experience in a large National Cancer Institute–designated tertiary referral center on HLH in the setting of hematologic malignancies and describe responses to therapy and outcomes based on administration of HLH-specific treatment protocols.[8]

Materials and Methods

We identified potential cases of HLH through a hematopathology database and pathology reports after institutional review board approval. Two authors reviewed all cases individually

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Table 1 Baseline Characteristics

Clinical Feature	N (%)
Age, median (range) (years)	59 (18-79)
Gender	
Male	10 (59%)
Female	7 (41%)
Ethnicity	
Caucasian	10 (59%)
Underlying Hematologic Disease	
T-cell NHL	5
CNS lymphoma	1
Hodgkin lymphoma	1
Myelodysplastic syndrome	3
Acute myeloid leukemia	1
T-cell LGL	1
EBV associated	3
Unknown	2
Time of HLH diagnosis from underlying disease (median) (mo)	3.1
Fever	15 (88%)
Splenomegaly	13 (77%)
Hepatomegaly	9 (53%)
Transaminitis	14 (82%)
Hyperbilirubinemia	12 (71%)
Serum triglycerides ≥265 mg/dL	11 (65%)
Serum fibrinogen ≤150 ng/dL	3 (18%)
Serum ferritin >3000 ng/mL	16 (94%)
Hemophagocytosis	14 (82%)
Hemoglobin (mean) (g/dL)	8.8
Platelets (mean) (μL)	62
Neutrophils (mean) ($\times 10^9$/L)	2.1

Abbreviations: CNS = central nervous system; EBV = Epstein–Barr virus; HLH = hemophagocytic lymphohistiocytosis; LGL = large granular leukemia; NHL = non-Hodgkin lymphoma.

(CR, JB). Patients were included if they met at least 5 of 8 standard diagnostic criteria: fever ≥38.5°C, splenomegaly, peripheral blood cytopenias (hemoglobin <9 g/dL, platelets <100,000/μL, absolute neutrophil count <1000/μL, hypertriglyceridemia [fasting triglycerides >265 mg/dL]), hypofibrinogenemia (fibrinogen <150 mg/dL), hemophagocytosis in bone marrow or other organs, ferritin >3000 ng/mL in the absence of evidence of iron overload or change from prior baseline, elevated soluble CD25 (soluble interleukin-2 receptor alpha), and natural killer cell function if tests were obtained.[1] Descriptive statistics were used for baseline characteristics, and Kaplan–Meier estimates were used for overall survival (OS).

Results

Seventeen patients with HLH were included. The median age was 59 years (18-79 years), 10 patients (59%) were male, and 10 patients (59%) were Caucasian. The underlying diagnosis was aggressive lymphoma in 7 patients (T-cell non-Hodgkin lymphoma in 5 patients, central nervous system lymphoma in 1 patient, and Hodgkin lymphoma in 1 patient), myelodysplastic syndrome in 3 patients, Epstein–Barr virus related in 3 patients, large granular lymphocyte leukemia in 1 patient, acute myeloid leukemia in 1 patient, and in 2 patients there was no known underlying cause. The median time from diagnosis of primary hematologic condition to HLH was 3.1 months. Among all patients, 15 (88%) had fever, 13 (77%) had splenomegaly, 9 (53%) had hepatomegaly, 14 (82%) had transaminitis, 12 patients (71%) had hyperbilirubinemia, and 11 (65%) had elevated triglycerides. Sixteen patients had a serum ferritin level >3000 ng/mL (mean serum ferritin was 21,000 ng/mL), and 3 patients (18%) had low fibrinogen of <150 mg/dL. Fourteen patients (82%) demonstrated evidence of hemophagocytosis or increased histiocytes in bone marrow or other organs. The mean hemoglobin was 8.8 g/dL, and the mean platelet count was 62/μL. Table 1 summarizes the baseline characteristics.

Ten patients (59%) had skin rash, and 10 patients (59%) had neurologic symptoms (lumbar puncture was performed in 6 patients). Renal failure was documented in 10 patients (59%), and 7 patients (41%) had respiratory failure (4 were intubated). Fifteen patients (88%) had evidence of infection, including 6 patients (34%) with sepsis. Eight patients (44%) had evidence of coagulopathies.

Among all patients, 12 (71%) received etoposide, 14 (82%) received dexamethasone, and 3 (18%) received cyclosporine. Intrathecal chemotherapy was administered to 3 patients (18%). Overall, 7 patients (41%) responded to treatment with clinical and laboratory improvement. One patient with refractory HLH and hepatosplenic T-cell lymphoma underwent successful matched related donor allogeneic stem cell transplantation with achievement of complete remission of both diseases. The median duration of hospitalization for all patients was 57 days. The median OS from the time of HLH diagnosis and primary hematologic diagnosis was 8.4 months and 29.5 months, respectively (Figure 1). The OS was better among patients with HLH with aggressive lymphomas (Table 2). Response to treatment was associated with better OS (Figure 2).

Discussion

HLH is a rare but life-threatening condition in the setting of hematologic malignancies.[1,7] Diagnosis is often missed or delayed given the overlap of HLH manifestations with a primary hematologic condition.[9] The systematic assessment of diagnostic criteria can help the clinician identify cases efficiently. Awareness between the hematologist and the oncologist of this disease and its diagnostic criteria can help to identify early-onset cases. Prompt initiation of therapy is warranted because it improves outcomes. Infection is a common denominator in HLH.

To our knowledge, this is one of the largest adult patient series treated with an HLH 94-like protocol in a single