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Hemophagocytic Lymphohistiocytosis: an Under-recognized and Life-threatening Condition

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ABSTRACT

Diagnosis of hemophagocytic lymphohistiocytosis is a challenge in Nepal because of limited resources and the high prevalence of tropical febrile illness mimicking hemophagocytic lymphohistiocytosis. We retrospectively reviewed medical records of 21 patients who were diagnosed with hemophagocytic lymphohistiocytosis from 2010 to 2015 at a single center in Nepal. Two patients had a mutation in their perforin gene and underwent successful haploidentical stem cell transplantation. Marrow hemophagocytosis was found only in 57% of the patients. Five patients had hematological malignancy and were treated with disease-specific chemotherapy. Seven patients developed hemophagocytic lymphohistiocytosis secondary to an infection, including visceral leishmaniasis, scrub typhus, and Epstein Barr virus. EBV-associated hemophagocytic lymphohistiocytosis was refractory to hemophagocytic lymphohistiocytosis 94 protocol, including the addition of rituximab. Malignancy and infection-associated hemophagocytic lymphohistiocytosis was more common. The most common clinical presentations included fever, splenomegaly, hyponatremia, liver function derangement, hyperfibrinogenemia, hyperferritinemia, and cytopenia. With a mortality of 29% in our study cohort, hemophagocytic lymphohistiocytosis should be considered a lethal disease, and clinicians should maintain a high index of suspicion to diagnose this disease.

Keywords: Hemophagocytic lymphohistiocytosis; infection; malignancy.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterized by aberrantly activated macrophages and cytotoxic T cells.[1] Although HLH has broadly been classified into Familial (primary) HLH (FHLH) and secondary (acquired) HLH (SHLH), the trend has recently shifted towards categorizing HLH subgroups based on specific etiologies to address increasing recognition of clinical diversity and choice of initial therapy.[2] The prevalence, etiology, and outcome of HLH have never been studied in the Nepali population. Our report presents a collaborative analysis of HLH management over 5 years in a diagnostically challenging setting.

METHODS

We retrospectively reviewed medical records of 21 patients who were diagnosed with HLH from 2010 to 2015 at a single center in Nepal, and here, we describe the clinical/laboratory presentation and treatment outcome in this cohort of patients. The study was approved by the ethical board committee of Civil Service Hospital.

RESULTS

All patients were diagnosed with HLH based on histiocytic society HLH diagnostic criteria.[3] The median age of the study population was 30 years (range: 6-46 years), and 16 were male patients. Median time to

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diagnosis after presenting to our center was 9 days (5-13 days) , median ferritin was 2000 (range: 600-36000 ng/ml), median triglycerides was 265 (range: 178-560 mg/dl), median fibrinogen level was 128 mg/dl (range: 40-166 mg/dl), median hemoglobin level was 9 g/dl (range: 5-12 g/dl), and median platelet count was 56000/ mm^3 (range: 10000-120000/mm^3). Fever was the most common presenting complaint. Hepatomegaly was observed in 14% of the study population (3/21), while all the patients presented with splenomegaly (21/21). Some form of liver dysfunction was seen in all the patients, with the median bilirubin level at 3 mg/dl (range: 1.2-16 mg/dl) and median aspartate aminotransferase (AST) level at 178 units/liter (range: 56-1078 units/liter). Ten percent of the patients (2/21) were diagnosed with FHLH, 33% had HLH secondary to infection (7/21), 24% had malignancy-associated HLH (5/21), and etiology could not be identified in 29% of the patients (6/21). Central nervous system involvement in the form of seizure was observed in 10% of the patients (2/21), and 19% presented with disseminated intravascular coagulation (4/21).

Patients with FHLH were offered stem cell transplant after completing initial therapy of HLH 94 treatment protocol. Patients with secondary HLH were treated with disease-specific therapy, and patients with unknown etiology were treated with HLH 94 protocol. Twenty-nine percent of the patients (6/21) succumbed secondary to infection.

DISCUSSION

Diagnosis of HLH is challenging in South Asia because of a high prevalence of tropical febrile illness which can mimic the clinical presentation of HLH. Lack of availability of laboratory investigation, failure to maintain a high index of suspicion, and lack of data on genetic mutations lead to a delay in clinical recognition.[4] In our cohort, the median time from admission to diagnosis was nine days, which was much lower than reported in an Egyptian study (median duration= 34 days).[5] Despite poor economic status and lack of advanced health care, we presume that the diagnosis was possible within a short period because a majority of the patients presented to us after being evaluated extensively in other centers.

The presence or absence of hemophagocytosis does not confirm or exclude the diagnosis of HLH and is considered one of the less essential diagnostic criteria.[3] In our series, marrow hemophagocytosis was found only in 57% (12/21) of the patients. Contrary to this, cardinal features like hyperferritinemia, anemia, thrombocytopenia, hypofibrinogenemia, and hypertriglyceridemia were evident in 100% (21/21), 48% (10/21), 90% (19/21), 90% (19/21), and 52% (11/21) of the patients, respectively. Although not included in the diagnostic criteria, abnormal liver function tests and hyponatremia are common manifestations of HLH.[6,7] In our study, the entire cohort presented with some evidence of liver dysfunction (20/21 with elevated bilirubin and 21/21 with elevated AST), whereas hyponatremia was found in 52% (11/21) of the patients.

Five specific genetic defects have been identified in HLH, with a mutation in the perforin gene being the most common one.[8] Allogenic stem cell transplant is indicated in patients with genetic defects and certain immunodeficiency syndromes provided availability of suitable donor.[1] FHLH is usually fatal, with survival approximating two months unless an allogeneic transplant is performed.[8] Two of our pediatric patients were diagnosed with HLH based on the perforin gene mutation, and both underwent successful haploidentical stem cell transplant following disease control with etoposide and dexamethasone (HLH 94 protocol).

HLH has been described in the context of malignancies, primarily lymphoma.[1] In our cohort, five patients presented with HLH on the background of hematological malignancies (T-cell lymphoma, diffuse large B-cell lymphoma, acute myeloid leukemia/AML, and natural killer/NK cell lymphoma). These patients have high mortality, and require immediate control of HLH symptoms with treatment for underlying malignancy.[9] In our cohort, one patient received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) regimen, and 4 patients received either cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP) or dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide (SMILE) regimen for the treatment of HLH secondary to B and T-cell lymphoma, respectively. One patient was diagnosed with HLH secondary to chemotherapy while being actively treated for AML. Fifty percent (3/6) of patients with hematological malignancies died of infection, demonstrating high mortality.

Visceral leishmaniasis (VL) is a public health concern in Nepal, and this may have resulted in more patients with VL-associated HLH in our study. A patient of scrub typhus-associated HLH in our study responded well to treatment with doxycycline and rifampicin. EBV-associated HLH causes two-thirds of all infection-related HLH in Asian Countries.[10] In our cohort, both patients

were refractory to the HLH 94 protocol. Despite the addition of rituximab as a part of the salvage regimen, both patients eventually died. VL-associated HLH was treated with liposomal amphotericin B, and all patients responded well. Out of six patients with unknown etiology, five responded to HLH 94, and one succumbed to disseminated fungal infection.

CONCLUSIONS

To the best of our knowledge, our study is the first of its kind conducted on patients with HLH in Nepal. With a mortality of 29% in our study cohort, HLH should be considered a lethal disease, and clinicians should maintain a high index of suspicion to diagnose this disease. Early detection and timely referral to the experienced center with stem cell transplant facility would be a pivotal step to improve outcome of this lethal disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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