Classical Hodgkin's Lymphoma with Secondary Haemophagocytic Lymphohistiocytosis - A Rare Case Report

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Summary

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by immune activation and subsequent widespread organ damage. Patients affected by HLH commonly develop fever, cytopenias, liver damage, neurologic manifestations, and hypercytokinemia. In this case, we describe a 20 years oldfemale who presented with HLH and was subsequently diagnosed with Hodgkin lymphoma. This case highlights the importance of considering a cancer diagnosis in the differential diagnosis of patients presenting with HLH.

Keywords: Hemophagocytic lymphohistiocytosis, Hodgkin's lymphoma, malignancy

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a life threatening disorder causing multisystem organ failure. It is characterized by an excessive and uncontrolled immune response due to cytokine dysregulation and lymphohistiocytic proliferation.[1, 2] HLH is a secondary reaction to infection, medication, autoimmune or neoplastic diseases. Haematological malignancies are a well-known HLH aetiology, but the combination of Hodgkin's lymphoma and HLH is rarely reported at the time of diagnosis.[3] we report a case of Hodgkin's lymphoma revealed by HLH as an initial manifestation illustrating diagnostic difficulties and interest of rapid treatment.

It should be noted that the diagnostic criteria for HLH (Table 1) were devised for use in clinical trials and are therefore unlikely to capture every case of HLH. Because of the high mortality of HLH in the absence of appropriate treatment, we do not always require these diagnostic criteria to be met in order to initiate treatment. Specifically, treatment should not be delayed while awaiting the results of genetic or specialized immunologic testing.

Adults are more likely to have a secondary form of HLH than children, and adults with secondary HLH are more likely to have an underlying malignancy as the cause.

Table 1: Revised Diagnostic Guidelines for HLH4

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
1. A molecular diagnosis consistent with HLH *
2. Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
·Fever
·Splenomegaly
·Cytopenias (affecting >=2 of 3 lineages in the peripheral blood)
·Haemoglobin< 9 gm/dl (in infants <weeks: haemoglobin <10gm/dl)
·Platelets <100000 per cu mm
·Neutrophils<1000 per cu mm
·Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides >265 mg/dl;
·Fibrinogen <150 mg/dl
·Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy
·Low or absent NK-cell activity (according to local laboratory reference)
·S. Ferritin 500 microgm/L
·S. Soluble CD25 (i.e., soluble IL-2 receptor) >= 2,400 U/ml

*Homozygosity or compound heterozygosity for verified HLH-associated mutations (eg, PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, HPS) or gene defects of other immune regulatory genes (identified by whole exome sequencing [WES]).

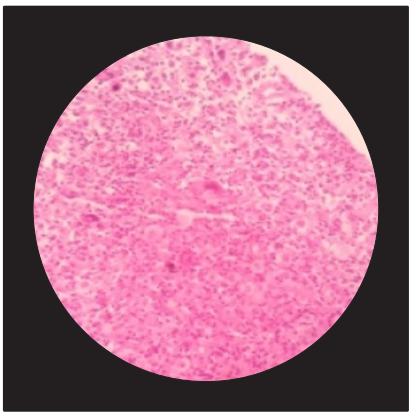

Figure 1: lymph node biopsy showing Reed Sternberg cells

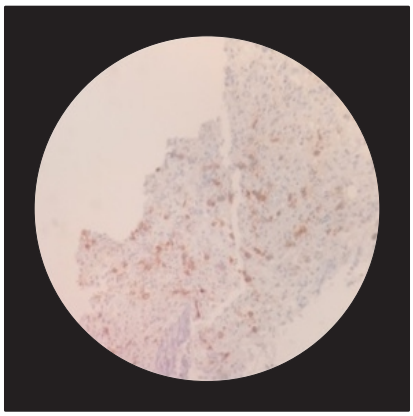

Figure 2: CD 15 positivity on immunohistochemistry

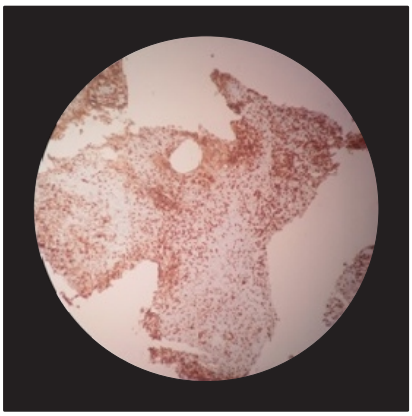

Figure 3: CD 30 positivity on histochemistry

Case Report

A 20 years old female presented to GCRI with 3 months history of persistent fever, generalized weakness, abdominal pain. On clinical examination hepatosplenomegaly with neck, axillary and inguinal nodes were palpable. Complete blood picture showed anaemia and thrombocytopenia with haemoglobin of 6.6 mg/dl, total leukocyte count of 4700 mg/dl and platelet count of 8000 per cu mm. Kidney function tests were normal. Total bilirubin was 2mg/dl, Serum glutamic oxaloacetic transaminase was 140 Units/L and serum glutamic pyruvate transaminase was 35 Units/L.S. Ferritin was 16000ng/ml and Fibrinogen was 139mg/dl. Urine routine microscopy was suggestive of +1 proteinuria. CECT of neck, thorax and abdomen suggested cervical, mediastinal, abdominal lymphadenopathy with splenic infiltration.

After confirming 5 out of 8 criteria for clinical diagnosis of HLH, and lymph node and bone marrow biopsy report being awaited, patient was started on iv dexamethasone, following which patient improved, that anasarca subsided, jaundice decreased

Bone marrow aspirate examination revealed normocellular marrow.Trephine biopsy suggestive of normocellular marrow with grade 3 fibrosis and large Reed Sternberg cells immunoreactive for CD15 and CD30.Sections of lymphnode biopsy shows Reed Sternberg cells immune reactive for CD15, CD30 and PAX5 favouring classical Hodgkin's lymphoma (Figure 1,2,3).

After confirmation of classical Hodgkin lymphoma with Immunohistochemistry on lymphnode biopsy as well as bone marrow biopsy, patient was started with ABVD chemotherapy (Adriamycin 25mg/m^2, Bleomycin 10 IU/m^2, Vinblastin 6mg/m^2, Dacarbazine 375mg/m^2). After completion of 2 cycles of ABVD, there was complete recovery of cytopenia, and resolution of systemic symptoms.

Discussion

HLH is a hyper inflammatory syndrome mediated uncontrolled activation of immune cells(macrophages, lymphocytes and histiocytes) and elevated cytokines such as Tumour necrosis factor alpha,interleukin-6,interferon gamma and macrophage inflammatory protein one alpha. Familial form is autosomal recessive presenting during childhood and diagnosed by identification of mutations in HLH associated genes PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A or BIRC.[4,5] These mutations affect exocytosis of cytotoxic granules in natural killer cells leading to a hyper inflammatory state. Acquired HLH can present at any age. The association between HLH and hematologic malignancies including Hodgkin's lymphoma is well described, with 1% of these patients developing HLH.[6]

In a multicentre retrospective case series of 68 patients with HLH[7], Schramm et.al found most common underlying disorder was malignancy(49%) followed by infection, auto immune and idiopathic HLH. Among malignancies, B lymphoid were most common followed by myeloid, T lymphoid and solid. Among B lymphoid neoplasms Hodgkin's lymphoma (6%) was the most common. Amongst infections EBV (9%) and CMV (9%) have the highest incidence.

A study in Sweden by Machaczka et al[6] studied 8 patients with haematological malignancy HLH. Out of them only 1 patient survived. Two patients treated with immunosuppressive therapy (steroids, IVIG) died shortly after HLH diagnosis. Six patients were treated with modified HLH-94 protocol, out of which 2 did not respond. Four patients who initially responded died within an average of 2.4 months. They concluded that HLH associated with lymphoma had poor outcome.

Consistent with other studies.[8, 9] patients with lymphoma associated HLH had a worse prognosis than those without it (median survival 2.8 months versus 10.7 months).

Among patients who are acutely ill or deteriorating, and no secondary causes identified, HLH specific therapy based on the HLH-2004 protocol or enrollment in a clinical trial is suggested. More than half of patients treated with the HLH-2004 regimen achieve five-year survival.

Therapy based on the HLH-2004 protocol consists of eight weeks of induction therapy with etoposide (VP-16) and dexamethasone with cyclosporine with intrathecal therapy for those with CNS involvement. For the intrathecal therapy, hydrocortisone and intrathecal methotrexate are given. Induction therapy is followed by continuation therapy with same agents.[4]

Conclusion

There should be strong suspicion of HLH in patients presenting with cytopenias, splenomegaly and recurrent fever as systemic symptoms. Apart from infection, malignancy should be strongly suspected as secondary cause in any patient with HLH.

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