Hemophagocytic lymphohistiocytosis as the presenting symptom of aggressive Lymphoma: a case series and review of the literature

Karyn Revital Geiger^{1,4}, Oren Pasvolsky^{1,4}, Uri Abadi^{2,4}, , Lucille Hayman^{3,4}, Martin Ellis^{2,4}, Pia Raanani^{1,4}, Avi Leader^{1,4}

¹ Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel. ² Hematology Institute and Blood Bank, Meir Medical Center, Kfar-Saba, Israel.

³ Department of Pathology, Rabin Medical Center, Petah Tikva, Israel; ⁴ Sackler School of Medicine ,Tel Aviv University, Tel Aviv, Israel.

Background

- Lymphoma associated hemophagocytic syndrome (LAHS) is a major cause of hemophagocytic lymphohistiocytosis (HLH) in adults
- The dismal prognosis of LAHS is partially attributed to diagnostic and therapeutic challenges
- It is not known whether a more aggressive diagnostic and management strategy should be implemented in suspected LAHS

Objective

To depict the clinical course and outcome of patients presenting with HLH as the presenting symptom of an aggressive lymphoma

Table 1: Patient characteristics

Patient number	1	2	3
Age (Years)	68	66	64
Sex	Male	Female	Male
HLH Criteria			
Fever	YES	YES	YES
Splenomegaly	NO	NO	YES
Peripheral blood cytopenia> 1 lines	YES	YES	YES
Hypertriglyceridemia and/or hypofibrinogenemia	YES	YES	NO
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	YES	YES	YES
Low or absent NK cell activity ξ	NA	YES	NA
Elevated Ferritin	YES	YES	YES
Elevated soluble CD25 (soluble IL-2 receptor alpha) μ	YES	YES	NA
Number of criteria met	6	7	5

Cytopenias, hemoglobin <9 g/dL; platelets <100,000/microL; absolute neutrophil count <1000/microL

Hypertriglyceridemia-fasting triglycerides >265 mg/dL, hypofibrinogenemia-fibrinogen <150 mg/dL

Ferritin >500 ng/mL

NA, not available

Patient 1

Diagnostic criteria as shown in **Table 1**

- HLH manifested by fever and pancytopenia for 2 month prior to Admission to the hospital
- Treated according to the HLH-94 protocol
- Despite HLH directed therapy the patient showed rapid clinical deterioration and died within 10 days
- Diagnosis of anaplastic large cell lymphoma (ALCL) was done post mortem

Patient 2

- HLH manifested with 2 weeks of fever and anemia.
- Initial response to HLH-94 protocol
- During steroid tapering, HLH relapsed
- Thorough workup, including multiple PET-CTs and bone marrow biopsies (BMB), did not reveal histological evidence of lymphoma
- Patient died 8 months after presentation
- Figure 1** depicts a timeline of ferritin and sILR2 as markers of disease activity in this patient, with regard to the diagnostic workup and treatment the patient underwent
- Autopsy revealed diffuse large B cell lymphoma (DLBCL) involving the spleen and bone marrow and HLH in liver (**Figure 2**)

Patient 3

- HLH manifested with 3 month of fever, thrombocytopenia and lymphadenopathy
- Metastatic lung carcinoma 2.5 years earlier
- BMB and inguinal lymph node biopsies were unremarkable
- Repeat BMB compatible with ALCL
- Complete remission following R-CHOP treatment

Figure 1: Diagnostic work-up, treatment and response for patient 2

This figure shows HLH activity represented by sIL2R and ferritin in patient 2 on a timeline from hospital admission until death. The treatment and diagnostic work-up for causes of HLH are shown on this timeline.

* Tapering of steroids down to 2mg twice a week

** Ferritin units: ng/ml; sIL2R units: U/ml

***CSA, cyclosporin A; CT, Computed tomography; PET CT, Positron emission tomography CT; Rx, treatment; sIL2R, soluble interleukin 2 receptor

Fig 2 : Post mortem of patient 2 – hematoxylin eosin stain x 40 ,liver biopsy, few histiocytes with 3-4 intraplasmatic stacked red blood cells

Discussion

- These cases underscore difficulties in managing adult patients with LAHS, especially due to **delays in diagnosis and treatment**.
- Adults with HLH should undergo a **rigorous search** for malignancy, especially **occult lymphoma**
- In cases highly **suspicious** for LAHS, especially if the patient is **deteriorating, empirical chemotherapy** for B and T cell lymphoma should be contemplated, even prior to histological confirmation.