Review Article

Indian Journal of Cancer Education and Research
Volume 3 Number 2, July - December 2015
DOI: https://dx.doi.org/10.21088/ijcer.2321.9815.3215.4

HLH, Lymphoma, CMV and HLH : Heterogeneous Presentation of HLH in Lymphoma

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Abstract

Hemophagocytic Lymphohistiocytosis is a condition in which often there is a diagnostic delay due to non-specific clinical manifestations. We recently had two cases of Lymphoma associated hemophagocytic syndrome(LAHS)- while one presented with hemophagocytic lymphohistiocytosis (HLH) the other case developed HLH after achieving a complete remission secondary to a complication of chemotherapy. The description of the cases is followed by relevant discussion of pertinent points. In this article, we want to highlight the importance of evaluating for a lymphoproliferative disorder in a case of HLH as well as considering HLH in patients with lymphoma who have unexplained constitutional symptoms and cytopenias.

Keywords: Hemophagocytic Lymphohistiocytosis; Diffuse Large B Cell Lymphoma; T / Nk Cell Lymphoma; Hodgkins Lymphoma; Cytomegalovirus.

Hemophagocytic lymphohistiocytosis(HLH) is a rare potentially fatal condition with non specific clinical manifestations, where a prompt diagnosis is crucial [1]. As there are no specific manifestations, diagnosis is often delayed. HLH in adults is usually acquired. The common causes are infections(mostly viral), malignancies and autoimmune / immuno-deficiency conditions [2]. We describe here two cases of lymphoma who developed HLH at different time points in the course of the disease, while one was lymphoma driven HLH and the other occurred in a patient who was in remission, as a complication of chemotherapy.

An obese 26 year old male was referred for evaluation of high grade fever of 3 weeks duration associated with fatigue, myalgia and headache. Lymphadenopathy nor organomegaly could be made out on physical examination. Labs at presentation revealed Hb 110 g / L, total WBC count 1.23 x 10^9 / L with neutrophils 32 %, lymphocytes 54 %, monocytes 12%, eosinophils 2% and platelet count of 57.6 x 10^9 / L . LDH was 470 IU / L. Bone marrow aspirate was cellular with few atypical large cells and a diagnosis of acute leukemia was suspected, but could not be confirmed on flow cytometry. Meanwhile the patient continued to have high spikes of fever. An extensive work up work up for bacterial, fungal, mycobacterial, Cytomegalovirus(CMV), Epstein-Barr virus(EBV) infections was negative.

Meanwhile his serum ferritin levels progressively increased from 6570 pmol / L to 9689 pmol / L to 15044 pmol / L to 25623 pmol / L over a period of 3 weeks. Bone marrow was repeated which revealed hemophagocytosis with macrophages ingesting neutrophils and lymphocytes. There were 6% atypical lymphoid cells as well. His fasting triglyceride level was elevated – 4.17 mmol / L(normal range is 0.57 – 1.7). He was diagnosed to have Hemophagocytic Lymphohistiocytosis (HLH) in view of persistent fevers, cytopenias, hemophagocytosis, elevated ferritin, triglycerides and LDH. A whole body PET-CT scan was done, which revealed FDG avid extensive supra and infra diaphragmatic lymph nodes – largest measuring 5.5 x 2.2 cm. There were also extranodal deposits – subcutaneous nodule in the right anterior axillary fold, nodular deposits in anterior perihepatic regions, splenic lesions and extensive skeletal deposits. Axillary lymph node biopsy was suggestive of Diffuse Large B Cell Lymphoma (DLBCL) Immunohistochemical analysis showed neoplastic cells were positive for CD20, BCL2. Admixed large cells were positive for CD30;

negative for CD3, CD10, CD5, CD15 and ALK-1. Ki 67 index-55%. There were background CD3 positive lymphocytes. A diagnosis of Non Hodgkins lymphoma-Diffuse large B cell lymphoma-anaplastic variant Stage IV B presenting with HLH was made. He was initiated on steroids, soon after which his fever subsided. Subsequently he was started on R-CHOP(rituximab, cyclophosphamide, doxorubicin, vincristine, predinsolone) chemotherapy. His inflammatory markers progressively improved. He completed 6 cycles of chemotherapy and achieved complete remission(CR) and is now 6 months post chemo, maintaining a CR.

Second case is a 25 year old male, presented with progressively enlarging swelling in the right supraclavicular region of 7 month duration with fever for the past 1 month. Physical examination revealed bilateral cervical, axillary lymphadenopathy and splenomegaly. A whole body PET CT scan revealed extensive supra and infradiaphragmatic lymph node enlargement- largest being 4 x 2.5 cm. There was also FDG avid extranodal liver, spleen, distal ileal involvement as well as extensive skeletal involvement. A lymph node biopsy revealed nodular lymphocyte predominant Hodgkins lymphoma (NLPHL). Cells were positive for CD20, LCA, OCT2 and negative for CD3, CD30, CD15 and BCL6.There was a background of CD3 positive lymphocytes with CD4 more than CD8. Bone marrow was not involved. Clinical stage was Stage IV B. He was started on R-CHOP chemotherapy. A PET scan after 4 cycles of chemo documented complete remission. On day 7 of his 5th chemo he developed febrile neutropenia unresponsive to broad spectrum antibacterial and antifungal therapy. Ferritin level progressively went up to 29,798 pmol/L and LDH to 566 IU/L. CMV DNA copies were elevated at 54,995/ ml. He was started on ganciclovir induction therapy. He continued to be febrile on day 5 of ganciclovir therapy. PCR for Mycobacterium tuberculosis from peripheral blood was done and was negative. In view of persistent high fever spikes, cytopenias and very high ferritin levels, he was diagnosed to have hemophagocytic lymphohistiocytosis(HLH) and was given a dose of IVIG 400 mg/kg and started on dexamethasone IV therapy. His fever subsided the next day of starting steroids, again confirming the diagnosis of HLH which was secondary to CMV infection. At the time of this report he is much improved and ferritin has come down to 4368 pmol/L and CMV copies have come down to 865/ml.

HLH is a hyperinflammatory condition related to unregulated hyperactive macrophages and histiocytes due to defective NK/ cytotoxic T cell function [3]. It can be either familial or acquired. Familial cases present in early childhood due to mutations in PRF1, UNC13D, STX11, and STXBP2 [4]. Most common acquired causes are infections(49 %), malignancies (27 %), connective tissue disorders(7 %) and immunodeficiency syndromes(6 %) [1].Of the infections, viral infections, Epstein-Barr virus(EBV) is the commonest. Other viruses like CMV, hepatitis A, B and C, parvovirus, human herpes viruses 6 and 8, HIV, mumps, measles and rubella viruses are also associated with HLH. Mycobacterium tuberculosis and visceral leishmaniasis should be considered in endemic areas [4].

The proportion of each tumor type in adult patients with HLH in the context of a neoplasm is 35% for T-cell or natural-killer (NK) lymphomas, 32% for B-cell lymphomas, 6% for leukemias, 6% for Hodgkins lymphomas, 14% for other and non-specified hematologic neoplasms and 3% for solid tumors [5]. In children, acute leukemias are predominant cause for malignancy related HLH [6]. Solid tumors are usually not associated with HLH, exception being mediastinal germ cell tumors [5].

Both our cases were related to lymphoma. In the first patient, the diagnosis was DLBCL- anaplastic variant, whereas the second patient had Hodgkins Lymphoma- nodular lymphocyte predominant variant(NLPHL). While DLBCL is the most common malignancy related to HLH in the West and Japan [7,8], T/NK cell lymphomas are the predominant trigger in the Chinese and Korean population [9,10]. There is scarcity of data among Indian population regarding Lymphoma associated hemophagocytic syndrome(LAHS). In Far East Asia, intravascular B cell lymphoma is a unique subtype with special propensity to cause HLH [11]. Among Hodgkins lymphoma, there is equal propensity for all variants to cause HLH. In 90% of Hodgkins lymphoma cases, EBV can be a cotrigger for HLH [12]. In our patient with NLPHL, EBV serology was negative.

Cytomegaloviral reactivation usually occurs in the post trasplant setting. Non transplant lymphoma patients receiving immuno-suppressive chemotherapy are also at risk, albeit lesser, for CMV reactivation [13]. Our second case was diagnosed NLPHL and had excellent response to chemotherapy as evidenced by a CR by PET scan after 4 cycles. He developed CMV reactivation after 5th cycle which was probably the trigger for HLH. It is known that aggressive therapies for malignant hematological neoplasms can trigger HLH not only during induction and consolidation, but also during maintenance chemotherapy [14]. In such cases, where the malignancy itself is in remission, the prevalence of an infectious trigger ranges from 75% - 100% [6].

We can only speculate whether the lymphoma had any causative role in HLH in this case. A point worth note is that among chemo related HLH cases, invasive fungal and bacterial infections may also play a role.

The diagnosis of HLH is often delayed due to lack of specific clinical manifestations [1]. Janka et al have proposed a set of 8 criteria for diagnosis of HLH [3]. Five of these should be met to make a diagnosis of HLH. Clinicians should always consider a possibility of HLH while dealing with critically ill patients, as early diagnosis and institution of HLH specific therapy impacts the ultimate outcome significantly. In our first case, the diagnosis was delayed as we were strongly considering acute leukemia. When we were not able to establish that diagnosis, a repeat marrow showed hemophagocytosis and with rising ferritin levels, we were able to establish the diagnosis of HLH. An extensive work up for viral etiology was negative. In such a situation, lymphoma has to be strongly considered and a PET scan did reveal a lymphoma. Fortunately he responded well to dexamethaosne and chemotherapy and is now in CR, 6 months post chemotherapy.

While there are no specific manifestations in LAHS, a Japanese group has proposed certain conditions to be met in a lymphoma patient to make a diagnosis of LAHS in adults [15] (Table 1). While our first patient satisfied all the conditions, our second patient refused a repeat bone marrow, but we could establish a diagnosis of HLH with persistent high grade fever without bacterial, fungal etiology, CMV viremia (54,995 copies per ml), progressively increasing ferritin and LDH values. Also the excellent response to dexamethasone therapy substantiates the diagnosis.

Both our patients presented with clinical stage IV lymphoma and B symptoms. Large population based studies have shown that HLH is more common in T- Non Hodgkins Lymphoma(T-NHL) with advanced stage and B symptoms [16]. Whether this holds true in case of B-NHL or Hodgkins Lymphoma is not known.

Finally, with regards to treatment of LAHS, because of heterogeneity of cases and retrospective nature of data, there are no definite guidelines. The contentious issue is whether a HLH directed therapy or a

Table 1: Diagnostic Criteria for Adult LAHS [15]

1.	High fever for more than a week (peak > 38.5 °C)
2.	Anemia, hemoglobin < 9 g / dL or thrombocytopenia, platelets < 100,000 / μL
3.	i. Lactate dehydrogenase (LDH) > 2 × upper limit
	ii. Ferritin > 1,000 ng / ml
	iii. He patosplenomegaly on imaging
	iv. Fibrin degradation product (FDP) > 10 $\mu g/mL$
4.	Hemophagocytosis in bone marrow, liver or spleen
5.	No evidence of infection
6.	Histopathologically confirmed malignant lymphoma

A diagnosis of LAHS requires that all of the above items are fulfilled.
Of item 3, at least two of the four sub-items (i-iv) should be fulfilled.
When items 1 to 5 are present for 2 weeks and glucocorticoids and gamma globulin therapy is not effective, a diagnosis of probable LAHS can be made and chemot herapy against malignant lymphoma can be started.

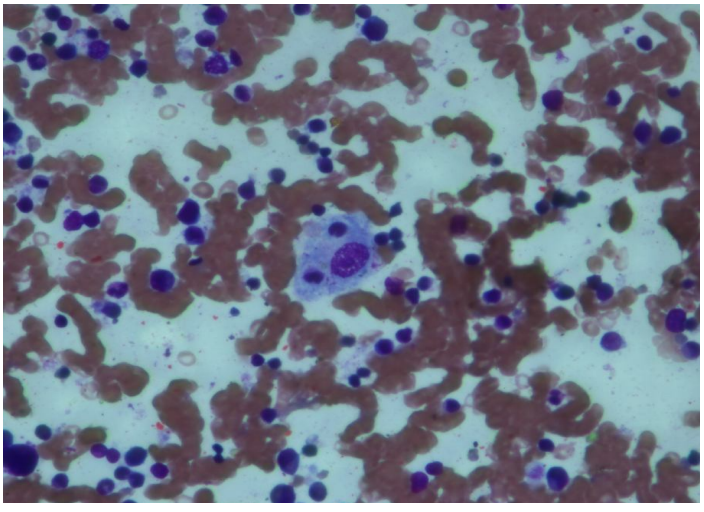

Fig. 1: (40X Geimsa stain) Bone marrow aspirate smear showing hemophagocytosis

Lymphoma directed therapy or a combination should be initiated. Agents used in HLH are glucocorticoids, IVIG, cyclosporine and etoposide. Logical reasoning will be that chemotherapy directed at the lymphoma should take care of hyperinflammation associated with HLH. If the inflammatory response does not simmer down with chemo, then HLH directed therapy should be started promptly. If HLH directed therapy is chosen at first instance, then this has to be followed by lymphoma directed chemotherapy. Antiinfective prophylaxis and regular surveillance for secondary infections or reactivation(fungi, CMV, EBV) should be a strong consideration.

In HLH during chemotherapy, as in the second patient in the above series, chemotherapy should be postponed. A rigorous search for a infectious trigger should ensue and if detected treated aggressively. Glucocorticoids and/or IVIG should be started to counter overactive macrophage and histiocytes. Though HLH 2004 protocol includes etoposide in acquired HLH, this has not been specifically studied in LAHS [3].

Lymphoma associated hemophagocytic syndrome is a well recognized, but heterogeneous condition, where more research is required to better understand the interplay between systemic immune hyperactivation, tumor-mediated immune suppression, and autoimmunity and to develop novel targeted therapeutic agents.

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