HLH Masquerading Lymphoma: Diagnostic Dilemma and Treatment Outcomes

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Abstract A case series to illustrate difficulties faced in diagnosis, management and subsequent therapeutic approach patients presenting with HLH secondary to lymphoma. A retrospective review of patients treated for HLH and lymphoma in Clinical Hematology department of a tertiary care hospital in North India, was performed from Jan 2017 to April 2019. Follow up was included till September 2019. Diagnosis of HLH was made using HLH 2004 criteria along with H score. Only patients who fulfilled HLH 2004 criteria were included. Nine patients were treated during above period, three patients with Hodgkins lymphoma, two patients had DLBCL and four patients had T-cell lymphoma. All patients presented with features of HLH and underlying lymphoma was detected on further evaluation. All patients had H score above the cut off value for diagnosis of HLH. Out of 9 patients, 6 received lymphoma directed chemotherapy and 1 was given only steroids, 1 received IVIG with steroids. 1 died early, before institution of therapy. Out of the 6 patients who received chemotherapy, all attained remission status but two patients had early relapse. In the remaining 3 patients who could not be started on chemotherapy, all died within 3 weeks of presentation. Underlying lymphoreticular malignancy should be actively searched in adult patients presenting with HLH. Early diagnosis and initiation of disease specific therapy with or without specific HLH directed treatment can improve the historical poor prognosis.

Keywords HLH · Lymphoma · LAHS · Hemophagocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an immune regulatory disorder characterized by clinical signs and symptoms of extreme inflammation and development of cytopenias [1]. Initially described as a disease of pediatric population with familial inheritance, through time, syndrome of HLH has been recognised in adults as well [1].

HLH is caused by a defect in inflammatory signals that results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway. Even with currently recommended therapy, HLH is frequently fatal. Early institution of therapy is critical to control the hypercytokinemia that otherwise will lead to end-organ failure and death. HLH has been traditionally divided into primary and secondary [1]. Primary HLH typically manifests in children with documented genetic abnormalities of the cytotoxic function of NK cells and T cells. Secondary HLH tends to occur at older ages in the setting of an associated condition such as infection, malignancy, rheumatological conditions and immunosuppressive states without an identifiable genetic abnormality [1].

In adults, ~ 50% of all HLH has malignancies as an antecedent cause [2]. Amongst malignancies, lymphomas are most commonly associated with HLH; this disease entity is called lymphoma-associated hemophagocytic syndrome (LAHS) [3]. LAHS is relatively well-described and carries a poor prognosis [4]. HLH in the context of malignancy is considered as a big challenge to clinicians due to variable overlap of symptoms with other types of

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HLH, sepsis and multiorgan failure, thus resulting in higher incidence of misdiagnosis and mortality. Here we present a case series of patients with lymphoma related HLH.

Methods and Materials

Between Jan 2017 to April 2019, 9 adult patients with diagnosis of LAHS were treated in Clinical Hematology department at a tertiary care centre in North India. Diagnosis of HLH was made using HLH 2004 criteria when patients met at least 5 of 6 criteria. NK-cell activity and soluble IL2 receptor were excluded, as these could not be done due to financial and logistic constraints [5]. Data was collected from hospital information system regarding age, sex, underlying disease, treatment protocol, stage of chemotherapy, any underlying infection, treatment given for HLH, and outcome. Follow up was included till September 2019. H score were calculated for all patients [6].

Results

Nine adults (two females, seven males), aged 20–79 years (median age 48.8 years), were diagnosed as LAHS.

The clinical features and laboratory parameters are mentioned in Table 1. Patient characteristics are presented in Table 2.

There were 8 cases with de novo lymphoma and 1 had relapse of lymphoma. Total duration of illness ranged from 1 to 12 months, prior to presentation. Mean duration of illness (TDI) prior to diagnosis was 109.9 days (range 30–365 days).

Overall, Hodgkin Lymphoma (HL) accounted for 3/9 (~ 33.3%) cases and Non Hodgkin Lymphoma (NHL) for 6/9 (~ 66.67%) cases. Amongst NHL, there were 4 (66.67%) cases of T cell lymphoma (2 cases of Anaplastic large cell lymphoma (ALCL), 2 cases of Hepatosplenic T cell lymphoma) and 2 cases of Diffuse large B cell lymphoma (DLBCL).

All patients had fever ($> 38.3^{\circ}\text{C}$) at time of diagnosis. Splenomegaly and hepatomegaly were present in all cases. Two patients had encephalopathy on presentation (one septic and one hypercalcemic). All patients had anemia, thrombocytopenia and hyperferritinemia. Mean values of

Table 1 Patient characteristics

Diagnostic features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Hb (g/dl)	7.2	7.2	8.4	— — 8	8.2	8.7	7.5	4.2	4.7
Platelet count (/ μl)	55,000	32,000	93,000	69,000	67,000	46,000	30,000	52,000	46,000
ANC (/ μl)	3300	3940	1285	4320	6980	12,125	3774	1450	95
Palpable liver (below costal margin)	1 cm	2 cm	1 cm	2 cm	1 cm	Just palpable	2 cm	2 cm	1 cm
Palpable spleen (below costal margin)	4 cm	3 cm	2 cm	3 cm	1 cm	2 cm	3 cm	2 cm	4 cm
Serum ferritin (ng/ml)	4373	23,007	12,072	54,882	1699	3432	4556	6196	3643
Fasting S. Triglycerides (mg/dl)	415	933	168	487	300	258	460	673	112
S. fibrinogen (g/l)	3.8	0.35	3.8	1.47	4.24	4.94	2.29	3.39	3.1
Hemophagocytosis in bone marrow	+	+	+	+	+	+	+	+	+
Lymphoma involvement (bone marrow)	+	—	—	+	+	+	+	—	+
Hepatic dysfunction (SGOT > 30)	53	66	47	200	246	30	161	41	60
CNS involvement	—	—	—	—	+	—	+	—	—
LDH (N < 185)	507	745	317	990	355	225	746	762	289
Lymphoma diagnosed on	Bone marrow study	Lymph node biopsy	Lymph node biopsy	Bone marrow study	Bone marrow study	Bone marrow study	Bone marrow study	Lymph node biopsy	Bone marrow study
H score (≥ 169)	229	309	271	337	170	228	221	273	210

Table 2 Treatment offered and outcomes

S. no.	Age/sex	Duration of illness	Infection (microbiological/radiological)	EBV PCR	Underlying malignancy	Treatment offered	Outcome (from the day of first presentation)
331	20 years/M	60 days	–	Not detected	HSTCL	CHEOP + HLH1994	Received 4 cycles CHEOP, Relapsed with HLH
2	38 years/M	60 days	–	Not detected	T-ALCL	CHEOP + HLH1994	Received 6 cycles CHEOP, had CNS Relapse of lymphoma
3	61/F	120 days	<i>E. coli</i> , EBV +	1160 copies	Relapsed Hodgkin	ICE + STEROIDS	Completed 3 cycles of ICE, in remission
4	23 years/M	30 days	Bilateral pneumonia	Not detected	T cell-ALCL	Steroids + IVIG	Expired day + 16
5	79 years/M	365 days	Bilateral pneumonia	Not detected	Hodgkin lymphoma	Steroids	Expired day + 15
6	62 years/M	120 days	–	Not detected	Hodgkin lymphoma	ABVD + Steroids	Completed 6 cycles ABVD, in CR at 26 months
7	66 years/M	60 days	<i>E. coli</i>	Not detected	DLBCL	HLH 2004 + R CHOP	Completed 6 cycles RCHOP, in CR at 16 months
8	63 years/F	45 days	–	Not detected	DLBCL	R-CHOP + Steroids	Completed 6 cycles R CHOP, in CR at 32 months
9	28 years/M	120 days	<i>E. coli</i>	Not done	HSTCL	Steroids	Expired on day + 2

haemoglobin, absolute neutrophil count and platelet count were 7.12 g/dl (4.2–8.7 g/dl), 4141/ μ l (95–12,125/ μ l) and 54,444/ μ l (30,000–93,000/ μ l) respectively. Mean ferritin was 12,651 ng/ml (3643–54,882 ng/ml). Hypertriglyceridemia was seen in 6 out of 9 patients with mean triglyceride value of 422.2 mg/dl (range 112–963 mg/dl). Hypofibrinogenemia was seen in only 2/9 patients with a mean serum fibrinogen value of 3.04 g/l (range 0.35–4.94 g/l). FDG-PET scan was done in 7/9 patients. All 7 patients had FDG-avid lymph nodes above and below diaphragm with patchy bone marrow involvement and extramedullary liver involvement. CMV and EBV were tested in eight out of nine patients, EBV was positive in one patient with 1160 copies detected by PCR, while CMV was not detected in any of the tested patients.

All patients were heavily treated in peripheral centers with antimicrobials, and were later referred to hematology department for persisting fever, cytopenia involving at least two cell lineages. One patient, case number 7, was treated with HLH 2004 protocol at a peripheral center for 7 weeks duration, prior to presentation. He had transient improvement for 2–3 weeks duration but again had symptomatic worsening with increased fever spikes, progressive cytopenia, and was thereby referred to hematology department.

Initially all patients were diagnosed with HLH, and were given steroids with or without IVIG. Steroids with or without IVIG were unable to curb HLH in all patients. Out of nine patients, 6 were given chemotherapy, remaining three could not be started on chemotherapy due to infectious complications. 1 patient succumbed to his illness

prior to establishment of diagnosis. In patients who were started on lymphoma directed chemotherapy, HLH resolved within 2 weeks of first chemotherapy cycle. Amongst the cases who received chemotherapy, all had initial improvement, and attained remission status post 1st cycle of chemotherapy. Four of these six cases continue to be in remission status on follow up, while two cases had an early relapse. Relapse cases included, one case diagnosed with ALK-Anaplastic large cell lymphoma, completed 6 cycles of chemotherapy and had disease resolution in end of treatment PET-CT, but had an early CNS relapse, within 4 weeks of last chemotherapy cycle. Currently he is on salvage regimen. The other case, diagnosed hepatosplenic T cell had disease progression after 4 cycles of chemotherapy. Disease progression was accompanied with features of HLH with high grade fever, hyperferritinemia, splenomegaly, pancytopenia and presence of hemophagocytosis and residual disease in repeat bone marrow examination. He was given salvage therapy but had continued disease progression. He is currently on salvage regimen, being planned for Allogenic stem cell transplant.

In our case series, all patients had initial diagnosis of HLH. In patients in whom underlying lymphoma was picked early, institution of chemotherapy could be done earlier. Five patients were diagnosed on the basis of bone marrow involvement. In four of our patients, diagnosis of malignancy was made with involved lymph node biopsy, after disease assessment using PET-CT. In patients who only received HLH specific protocols, HLH could be controlled only for few days. Lymphoma directed chemotherapy led to complete resolution of HLH. In

patients who were given malignancy directed chemotherapy, outcomes were better, all of them survived at 1 month of follow up.

Out of four patients with T cell NHL, lymphoma chemotherapy could be given to only two. Though both of them had initial improvement, both relapsed within 6 months of therapy. Comparatively both patients of B cell NHL, were given chemotherapy, both completed 6 cycles of therapy and are in CR at 16 months and 32 months of follow up.

Median event free survival was 137 days. Median overall survival not reached. Individual median event survival was not calculated for lymphoma subsets, due to low sample size.

All three cases who did not receive chemotherapy had a very aggressive and rapid progression of disease along with presence of microbiologically/ radiologically evident infections and succumbed within 4 weeks of presentation.

In addition, H-score was calculated for all patients. H-score values ranged from 170 to 337. All patients met HLH criteria by H score, taking the cut off ≥ 169 . Mean H-score value was 249.7, way above the cut off kept for diagnosis.

Discussion

Lymphoma with HLH is reported to be associated with poor prognosis but studies on LAHS are limited, especially in adults. This is first such case series from India.

In series of studies from 2197 adult HLH patients, malignancy associated HLH (M-HLH) was shown to account for approximately 50% of adult HLH. The most common tumour types responsible were hematological neoplasms (93.7%) amongst which T- or NK cell lymphoma/ leukemia accounted for 35.2%, followed by B-cell lymphoma (31.8%), other non-specified hematologic neoplasms (14.4%), leukemia (6.4%) and Hodgkin lymphoma (5.8%) [2]. In our case series T cell lymphomas accounted for maximum number of cases (44.4%), Hodgkin lymphoma (33.33%) and B cell NHL (22.2%).

In a study by Li et al., out of 69 patients with HLH, 16 (23%) cases were identified as LAHS [7]. Their results showed most common clinical feature as fever, seen in all patients. All patients had hyperferritinemia, cytopenias involving at least two cell lineage. Hypofibrinogenemia and splenomegaly were seen in 93.8% and 81.3% patients respectively. Median overall survival was only 37 days [7]. In our case series also fever was the most common clinical feature seen in all patients. Hyperferritinemia, cytopenias involving at least 2 cell lineages, hepatomegaly and splenomegaly was seen in all patients. Hypofibrinogenemia was seen in only 33.33% patients. Median event free

survival in our case series was 137 days, median overall survival is yet to be reached.

In a study done by Takashi et al., analysis of 52 adult patients with HLH, LAHS was reported in 26 patients. Twenty four out of these twenty six patients (96%) received chemotherapy. Twenty one of twenty six patients (81%) had uncontrollable HLH and died. Median survival of LAHS patients was 83 days [8]. In our case series, only 6 patients (66.6%) received chemotherapy. In patients who received chemotherapy all were alive but two have relapsed. Median event free survival was 137 days.

In our case series chemotherapy was given in only 66.67% patients which was much less compared to other studies [7, 8] in which $> 90\%$ patients received chemotherapy. Most common reason was delay in diagnosis and concomitant infectious complications. All these patients who could not be given chemotherapy had succumbed to their illness. In our case series all patients who had early initiation of chemotherapy, had better outcomes, emphasizing the role of quick diagnosis and initiation of disease specific therapy with or without specific HLH directed treatment.

Though sample size of the present study is small and higher survival rates were noted as compared to previous case studies which may be due to prompt institution of lymphoma specific therapy. Also, many adults with aggressive HLH may be misdiagnosed as sepsis, do not receive proper treatment and die before reaching a tertiary care hospital. This leads to a bias in patients referred and getting managed at a tertiary care centre.

Conclusion

HLH in adults can be a manifestation of underlying lymphoreticular malignancy which may be missed if appropriate investigation is not carried out. All adult patients with HLH without any evident primary cause should be thoroughly worked up for lymphoma. Investigations like PET CT scan, lymph node biopsy or bone marrow examination aid in picking up malignancies in such cases. Lymphoma associated HLH is an aggressive form of HLH and early initiation of treatment can improve otherwise historical poor prognosis in these patients. Treatment includes diseases directed chemotherapy with or without HLH specific therapies.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Statement This study was a retrospective study; data of patients was collected from the hospital database, including demographics as well as patient and disease related characteristics (laboratory data, treatment, and outcome). All data analyzed were a part of routine diagnosis and treatment. Diagnosis and treatment of patients were according to national guidelines and practices. Complete anonymity of patients has been maintained. The paper does not involve primary research.

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