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Original Research Article

Analysis of patients of hemophagocytic lymphohistiocytosis secondary to infections

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis is characterized by an unremitting activation of CD8+ T lymphocytes and macrophages that leads to organ damage.
Methods: 40 patients diagnosed of having HLH secondary to infections admitted in the last 5 years in a tertiary hospital in Western Maharashtra, were studied retrospectively. The data was collected from the indoor patient records and files, detailed clinical profile and all relevant investigations were noted.
Results: 40 cases of diagnosed HLH were studied. Age group of 30-40 years was involved more (25%), followed by age group of 61-70 years. The condition was more common in males (64%). Dengue was more common having more chance of secondary HLH. Early diagnosis and treatment was effective in 90% cases.
Conclusions: HLH was seen to occur more in tropical fevers. The mortality rate was more in haematological malignancies. Early diagnosis and rapidly initiated treatment had a positive effect in decreasing the mortality rate of the condition.

Keywords: Hemophagocytic lymphohistiocytosis, Macrophages, Tropical fever, Haematological malignancies

INTRODUCTION

Hemophagocytic lymphohistiocytosis is characterized by an unremitting activation of CD8+ T lymphocytes and macrophages that leads to organ damage. This involves mainly the bone marrow, liver and the central nervous system. It is a potentially fatal hyper inflammatory condition as a result of a broad set of inherited diseases. It results as an impairment of T and NK lymphocytes cytotoxicity. It is associated usually with an underlying infection, malignancy or an autoimmune disease which can lead to a hyperactive immune response.[1-3] Evidence that suggests that patients with secondary HLH may also have a genetic predisposition.[4] HLH may occur without a known underlying condition, referred to as idiopathic HLH. It is vital however to differentiate between primary and secondary HLH because in the latter treatment of an underlying condition may prove to be beneficial.

HLH is classified into three subsets: familial HLH with autosomal recessive inheritance, HLH with partial albinism and X linked proliferative syndrome. There are two basic types primary and secondary. Secondary is the most common and occur secondary to infection. Early diagnosis and early immunosuppression can be lifesaving in these conditions. A diagnosis of HLH, as determined by the histiocyte society in 2004, is based on the following criteria.[5]

Molecular diagnosis confirming HLH, and/or five of the following parameters is essential for the diagnosis; fever peak temperature of >38.5°C for more than 7 days, palpable spleen >3 cm below costal margin, cytopenias involving at least 2 lines; Hb <9 g/dl, ANC <100/ul,

platelets <1,00,000/ul, hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis on bone marrow or spleen or lymph node, low or absent natural killer cell activity, serum ferritin >500 ug/l and elevated soluble interleukin levels CD 25 >2400 U/ml or positive genetic mutation. In the present article an attempt is being made to present a study of 40 cases in last 5 years in our setup of HLH secondary to infections.

A major obstacle in diagnosing a patient with HLH is the overlap of symptoms with a variety of other illness such as sepsis, primary liver failure, multiple organ dysfunction syndrome, and TTP. Secondly, patients with HLH tend to have a rising trend in serum ferritin levels, while patients with sepsis usually have an elevated, but static value for serum ferritin.

Multi-organ dysfunction syndrome (MODS), like HLH, can involve multiple organs; however, an elevated serum ferritin level is more indicative of HLH than MODS.[6]

METHODS

Forty patients diagnosed of having HLH secondary to infections admitted in the last 5 years in tertiary hospital in Western Maharashtra hospital and research centre, were studied retrospectively. The data was collected from the indoor patient records and files, detailed clinical profile and all relevant investigations were noted.

Inclusion criteria were patients of age more than 18 years diagnosed as HLH using the before mentioned criterion and patients diagnosed within 1week and treated for the same. Exclusion criteria were; patients below age 18 years and patients clinically diagnosed as HLH but not fitting the criterion before mentioned.

All the patients were treated with intravenous steroids especially dexamethasone 10 mg/m^2 for 1st 2 weeks and then 5 mg/m^2 for next 5 weeks. The treatment was initiated in all the cases within a period of 1week.

RESULTS

All the data was collected and the master chart was plotted accordingly. The results were drawn by comparison between the cases and final conclusion was drawn. Retrospective observational study of relation between the causes of secondary HLH was studied in 40 cases. Relation of occurrence of secondary HLH with the gender and age were correlated.

The age groups between 31-40 years had the most number of cases (25.6%) followed by 51-60 years (20.5%) 15.4% cases were in the age groups 61-70 years and ages below 30 years with 12.8 % cases. Male patients were affected in 71% cases and female in 29% cases (Table 1 and 2).

Table 1: Distribution of study subjects based on age.

Age group (years)	N (%)
≤20	5 (12.8)
21-30	5 (12.8)
31-40	10 (25.6)
41-50	4 (10.3)
51-60	8 (20.5)
61-70	6 (15.4)
>70	2 (5.1)
Total	40 (100)

Table 2: Distribution of study subjects based on gender.

Gender	Frequency (%)
Male	26 (71)
Female	14 (29)
Total	40 (100)

Tropical fevers like dengue, malaria (7.7%), leptospirosis (2.6%) were having more chance of secondary HLH. Dengue was most common in the tropical fevers in 12.8% cases. Second most common condition causing HLH was malignancy followed by PUO in 12.5% and 10.3% cases respectively (Figure 1).

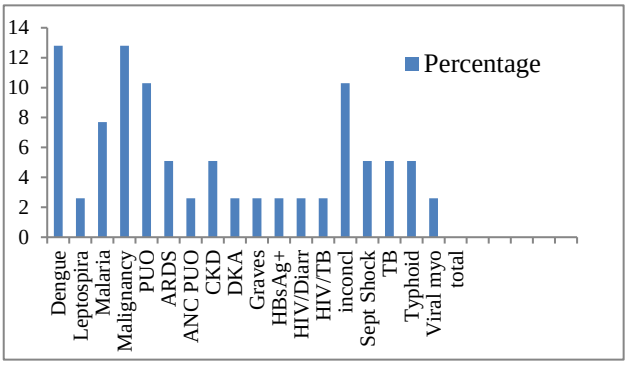

Figure 1: Distribution of study subjects based on secondary conditions.

45% patients had a haemoglobin (Hb) levels between 79.9 g/dl, 27.5% had more than 11 g/dl, 22.5% patients had less than 7g/dl and only 5% had Hb levels between 10-10.9g/dl. There were 60% patients who had total leucocyte count less than 4000/cumm, 30% cases had counts between 4000 to 11000/cumm and 10% had counts more than 11000/cumm. Less than 50000/cumm platelet counts were seen in 47.5% patients, counts between 50000-100000/cumm were seen in 10% cases, counts between 100000-1,50000/cumm were seen in 25% cases and more than 1,50000/cumm were seen in 17.5% cases. Less than 500 µg/dl serum ferritin was seen in 22% patients and 18% patients had serum levels more than 500 µg/dl. Serum triglyceride levels less than 150 mg/dl were noted in 35% patients, between 150-199 mg/dl in 20% cases and more than 200mg/dl in 45% cases.

All the patients were treated with intravenous steroids especially dexamethasone 10mg/m^2 for 1st two weeks and then 5 mg/m^2 for next 5 weeks. The treatment was initiated in all the cases within a period of 1week.

The haematological malignancy cases were the most common cause of death in 50% cases. Early diagnosis and treatment was effective with a good outcome in 90% cases (Figure 2).

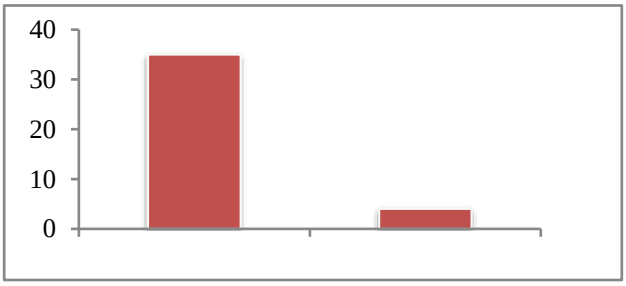

Figure 2: Outcome of the treated cases. X-axis is outcome 90% recovery 10% death and Y-axis is number of cases.

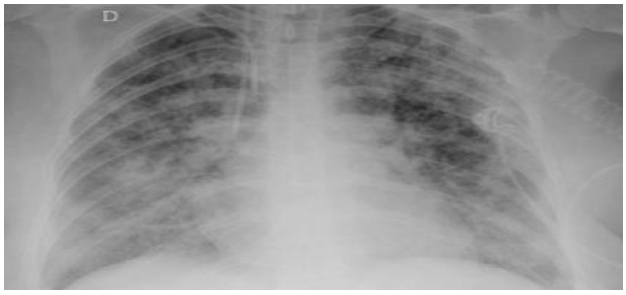

Figure 3: X ray of ARDS patient.

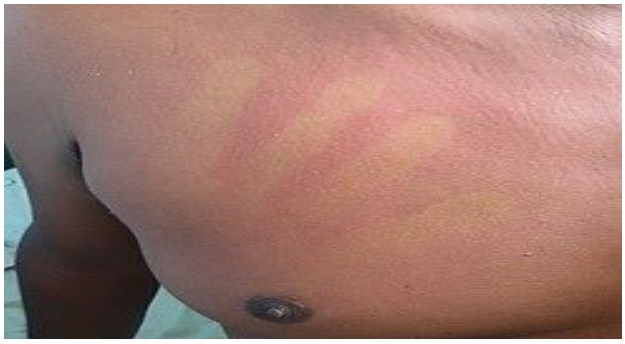

Figure 4: Blanching rash in dengue.

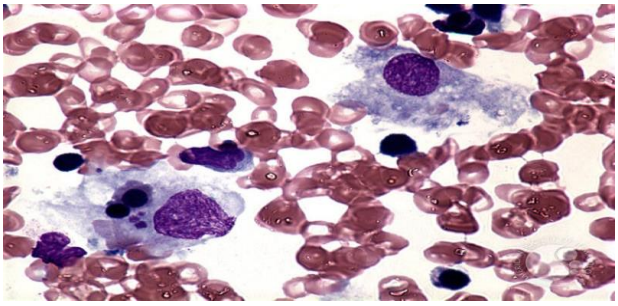

Figure 5: Bone marrow image of HLH.

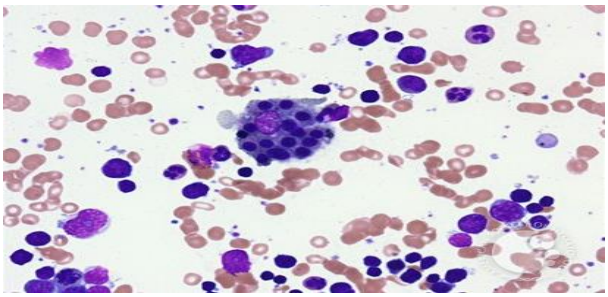

Figure 6: HLH in patient of CLL.

DISCUSSION

The age groups between 31-40 years had the most number of cases (25.6%) followed by 51-60 years (20.5%). Males were most commonly affected seen in 71% cases. The median age at diagnosis was 42 (range 22-68 years) with a male predominance of 6:1.

Tropical fevers like dengue, malaria (7.7%), leptospirosis (2.6%) were having more chance of secondary HLH. Dengue was more common in the tropical fevers in 12.8% cases. Second most common condition causing HLH was malignancy followed by PUO in 12.5% and 10.3% cases respectively. All 7 patients included in the study by Lizamarie et al met criteria for secondary HLH. Four patients (57%) had secondary HLH due to an infection and 3 (43%) had an underlying malignancy. The median time from presentation to initiation of treatment was 4 weeks (range 1-12 weeks).[7] A retrospective cohort study performed by Otrock and Eby on 73 adults with secondary HLH showed that infection was the most common underlying etiology (41.1%), followed by malignancy (28.8%), autoimmune diseases (6.8%), and post solid organ transplant (2.7%). However, no discernable cause could be elucidated in a large subset (17.8%) of the documented cases. EBV and human immunodeficiency virus (HIV) were the most frequent infections causing HLH, while lymphoma was the most commonly associated malignancy. While a number of cases of lymphoma associated HLH have been reported, there is limited literature on HLH secondary to hepatitis B infections. In the study performed by Otrock and Eby, only one patient had hepatitis B-associated HLH.[8]

Other viral etiologies implicated in HLH development include hepatitis B (HBsAg was positive in our patient), hepatitis C and CMV.[9] A case series submitted from China showed similar results, indicating malignancy and viral infections as the most common factors for secondary HLH . The clinical features of HLH can be non-specific, which adds to the difficulty of its diagnosis. This is evident from a Chinese study consisting of 103 adults which concluded that >96% of patients with HLH presented with a high-grade fever, while 79.6% had splenomegaly, and 53.4% had lymphadenopathy. Among the laboratory findings, 98.4% of the patients had a

significant elevation of serum ferritin (≥500 µg/l), cytopenia was found in 98% of the patients, bone marrow hemophagocytosis was seen in 87.4% of the patients and hypertriglyceridemia was noted in 85% of the patients.[10]

In our study all patients were treated with intravenous steroids, within one week, especially dexamethasone 10mg/m^2 for 1st two weeks and then 5 mg/m^2 for next 5 weeks. Without therapy, survival of patients with active familial HLH is approximately 2 months. The first international treatment protocol for HLH was organized by the histiocyte society in 1994 and led to reported survival of 55%, with a median follow-up of 3.1 years. The HLH-94 protocol included an 8 week induction therapy with dexamethasone, etoposide, and intrathecal methotrexate.[11]

In the adult HLH protocol at UTMDACC we have added alemtuzumab, a monoclonal antibody directed against CD52 (an antigen expressed on the surface of mature T, NK-cells and macrophages) to etoposide and dexamethasone. This was based on reports indicating that alemtuzumab as a single agent can be successful as a bridge to allogeneic stem cell transplant in pediatric HLH patients who had failed frontline etoposide, cyclosporine or etoposide with anti-thymocyte globulin (ATG) based standard regimes.[12]

CONCLUSION

Prompt initiation of immunochemotherapy is essential for survival, but timely diagnosis may be challenging because of its variable presentation, and the time needed for diagnostic testing. Therapy is complicated by dynamic clinical course, high risk of treatment-related morbidity, and disease recurrence. HLH was seen to occur commonly in tropical fevers in our study with the mortality rate being more in haematological malignancies. Early diagnosis and rapidly initiated treatment had a positive effect in decreasing the mortality rate of the condition. Fever with a varied presentation should not be taken lightly, possibility of HLH should be considered in appropriate situations and treatment should be initiated rapidly for the same.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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