VOLUME - 10, ISSUE - 12, DECEMBER - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Hematology

ADULT SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – A CASE SERIES

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ABSTRACT Hemophagocytic lymphohistiocytosis is a hyper-inflammatory condition that is either Familial (Primary) or Secondary to autoimmune diseases , infection, malignancy or other triggers.It is a cytokine storm syndrome where there inefficient antigen removal that leads to sustained cytokine release.It is a rare phenomenon occuring in adults that has got a specific trigger which is less documented and have a good response to steroids where as Familial form is a childhood disease due to genetic defects, both of which are life threatening and may need Allogenic bone marrow transplant. Macrophage activation syndrome is also a subtype of this entity that occurs in the treatment phase of SLE and Still's disease.We describe here 8 cases of secondary HLH, their primary triggers and treatment response.

KEYWORDS : hemophagocytic lymphohistiocytosis,macrophage activation syndrome

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome of uncontrolled immune activation caused by dysregulation of macrophages and lymphocytes resulting in increased levels of cytokines and significant tissue damage. HLH can present in two forms - Primary and Secondary. Primary HLH is the inherited form whereas Secondary HLH is triggered by infections, malignancy, rheumatological conditions or autoimmune diseases. Primary HLH , also called Familial HLH is an autosomal recessive disorder and 5 genes have been found to be associated with this condition. Proteins encoded by these genes facilitates the delivery of perforin to the cells which are to be killed. 70% cases develop symptoms before the age of 1 year. Secondary HLH is associated with viral infections such as EBV, CMV or herpes virus, vaccinations or autoimmune disorders. It is usually diagnosed in older patients and there is no family history.

The diagnosis of HLH is based on clinical, laboratory, morphological and genetic criteria. The diagnostic guidelines for HLH was revised by the Histiocyte society in 2004.

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 (5 out of the 8 criteria below)

- Initial diagnostic criteria (to be evaluated in all patients with HLH)
- Clinical criteria

Fever
Splenomegaly

- Laboratory criteria

Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)
Hypertriglyceridemia and/or hypofibrinogenemia

- Histopathologic criteria

Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy

- New diagnostic criteria
- Low or absent NK-cell activity (according to local laboratory reference)
- Ferritin ≥500 microgram/L
- Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml

Hemoglobin <9g/dL), Platelets <100 x 10^9/L, Neutrophils <1.0 x 10^9/L

In infants <4 weeks: Hemoglobin <10 g/dL

Fasting triglycerides ≥265 mg/dL, fibrinogen ≤1.5 g/L

HLH is a diagnostic challenge. We present a case series of 8 patients of secondary HLH with distinct aetiology. We highlight in this study the importance of prompt recognition, determination of etiology and early initiation of treatment in the management of secondary HLH.

MATERIALS AND METHODS

The study was performed in a tertiary care centre in Salem, Tamil Nadu, between January 2019 and August 2021. Adult patients suspected as HLH based on clinical criteria were evaluated. Patients who fulfilled the diagnostic guidelines laid down by the Histiocyte Society in 2004 were included in the study. The patients were treated with steroids and the underlying infection were concurrently managed. Patient characteristics, underlying etiology of secondary HLH and treatment outcome were compared.

OBSERVATIONS AND RESULTS

All 8 patients included in this study met the criteria for HLH. The median age of diagnosis was 58 years. Of the 8 patients 3 were females and 5 were males. Three patients had underlying comorbidities. Infection was the secondary cause in all the. Summary of cases given in Table 1.

CASE	1	2	3	4	5	6	7	8
AGE	57	60	59	56	76	22	38	62
SEX	Female	Male	Male	Female	Male	Female	Male	Male
COMORBIDITIES	Nil	HTN	T2DM	T2DM, HTN	Nil	Nil	Nil	RA, CKD
FEVER	YES	YES	YES	YES	YES	YES	YES	YES
SPLENOMEGALY	YES	YES	NO	NO	YES	YES	YES	YES
HEMOGLOBIN (g/dl)	5.4	12.5	11.7	11.1	7.1	10.8	5.2	7.9
PLATELE COUNT	130000	121000	50000	40000	117000	55000	4000	7000
NEUTROPHIL COUNT	2300	4709	3949	1015	3480	1500	182	240

TRIGLYCERIDES	628	225	397	293	212	239	108	218
HEMOPHAGOCYTOIS IN BM OR SPLEEN OR LYMPH NODES	-	-	-	-		-	PHAGOCYTOSIS	-
FERRITIN	>2000	3217.95	>2000	>2000	>2000	16710.82	485.21/8	3589.73

All patients presented with fever lasting more than 7 days and 6/8 patients had splenomegaly.

The 8 patients included in this study met the HLH Diagnostic criteria 2009. All patients presented with persistent fever, pancytopenia and/or splenomegaly. Etiological evaluation revealed 2 cases of dengue fever , 2 malaria and 1 typhoid fever. Cause could not be determined in 3 patients. 5 patients were initiated on steroids and the response was followed up using blood cell counts and serum ferritin values. 6 patients responded to treatment within an average duration of 2 weeks. The steroids were gradually tapered off over 6 weeks.

1 patient succumbed to the illness and one patient was lost to follow up.

DISCUSSION

HLH is first described in 1939, HLH : "Histiocytic medullary reticulosis" byScott and Robb-Smith as a sporadic disease caused by sporadic neoplastic proliferation of histiocytes. Later, in 1952, Farquhar published HLH as familial immune dysregulatory disorder in childhood : familial hemophagocytic reticulosis Secondary form has been first documented by Risdall and collegues in 1979.

Secondary HLH is a heterogenous disorder uncommon in adults. It is associated with infections, malignancy, metabolic disorders and autoimmune conditions. [1] Secondary HLH is arbitrarily divided into three groups depending on triggers and associated diseases.Infection associated (IAHS) contributes 34% where many infections including Ebstein barr viral infection and Dengue fever has been documented. Autoimmune disease-associated HLH is denoted A-HLH(8%) also called as MAS (Macrophage Activation Syndrome), whereas HLH triggered by malignancy predominantly Lymphomas (52%) denoted as MAHS /LAHS .The various triggers given in table .2

Infection	Epstein.Barr virus, herpes simplex virus, cytomegalovirus, influenza virus
Malignancy	NK/T.cell lymphoma nasal type, anaplastic large cell lymphoma
Autoimmune disease	Systemic idiopathic juvenile arthritis, systemic lupus erythematosus
Post.allo.HSCT	Immunologic reaction at engraftment
Drug hypersensitivity	Carbamazepine, phenobarbital, sulfamethoxazole

Pathogenesis of secondary HLH is unclear. It has been postulated that cytokine storm with increased levels of IL 2, IL 6, TNF, prostaglandins and interferon causes the overactivation of the antigen presenting cells (histiocytes and macrophages), and CD8+ T cells. This process results in the activation of the Cytotoxic T lymphocytes. There is also marked proliferation of histiocytes and macrophages.[2,3] These activated cells phagocytose other cells such as RBCs, platelets and WBCs causing pancytopenia and also there is infiltration of the phagocytic histiocytes in other hematopoeitic areas like liver ,spleen and lymph node. In liver,there is Kupffer cell hyperplasia & portal and sinusoidal cytotoxic T-cell infiltrate with variable hemophagocytic histiocytes,a pattern similar to chronic persistent hepatitis.

The phagocytosis may not be evident in all the times since this is a cyclical process where it is documented in about 25-100% and absence of bone marrow phagocytosis does not rule out HLH.

The relative frequency of association between infecting organisms (e.g., Mycobacterium tuberculosis, Salmonella Typhi, and Leishmania sp.) that trigger a TH1 immune response and reactive hemophagocytic syndromes might suggest that the syndromes result from a poorly regulated or inappropriate TH1 response to intracellular pathogens. However, Tsuda and colleagues found no evidence of a marked shift towards a TH1 cytokine profile in patients with HLH associated with nonviral infections [4] Even though the diagnosis is based on HISTIOCYTE SOCIETY 2004 criteria,this doesn't always apply for the secondary forms and the criteria needs to be revised.A recent study showed 3 out of 4 criteria that includes Fever, splenomegaly, cytopenias, hepatitis plus one of four immune markers (hemophagocytosis, increased ferritin, hyperTG, hypofibrinogenemia, absent or very decreased NK cell function)5. Many centres doesnot do NK cell activity, sCD25 and sCD163.

All of of our patients had hepatitis features and this is only an additional criteria in the primary form. For adults, H-score performances are better when determined at presentation. Fardet *et al* in their study reported that a cut off H score of 169 ensured rather high degrees of sensitivity & specificity and classification accuracy 6.Sepsis also has documented hemophagocytosis and this needs to be differentiated as secondary HLH needs immunosuppression and sepsis needs broad spectrum antibiotics7.

All of our patients were started on steroids and follow up was done with serum Ferritin and serum Triglycerides. Also one patient with salmonella typhi infection recovered without steroid therapy.[8]The distinction of primary from secondary HLH is important, as allogeneic bone marrow transplantation is the therapy of choice in patients with familial HLH who attain remission [9,10]In patients without a clear diagnosis of familial HLH, bone marrow transplantation should be considered if remission is not attained by 8 weeks of chemotherapy and immunotherapy that includes Corticosteroids(dexamethasone) as monotherapy ,in CS failure Cyclosporin A can be tried.Etoposide in EBV infection gives a very good outcome.

Immunotherapy is based on HLH-94 Guidelines that include an Induction therapy include Dexamethasone and Etoposide/Cyclosporin A for 8 weeks followed by maintanence therapy with as 2 weekly pulse.

In our case series , all were suspected to be due to infection and there was a very good response to early steroid therapy and the mean period of diagnosis ranges from 7-9 days.One patient died due to intracerebral bleed due to persistant cytopenia even after introducing cyclophosphamide and etoposide where the patient had EBV and dengue co- infection when he was in waiting for Allogenic Bone marrow transplant.

CONCLUSION :

A high index of clinical suspicion should be there to diagnose secondary HLH and this needs to be differentiated from sepsis as both are medical emergencies.Also the prognosis is better that the primary forms , there is need to reassess a criteria that has better specificity.

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