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Case Report

A case report on HLH in a rural area- A missed diagnosis, challenges and recommendations

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Abstract

"Hemophagocytic lymphohistiocytosis (HLH) is a histiocytic disorder characterized by a highly stimulated, but ineffective, immune response to antigens, which results in a fatal cytokine storm with an inflammatory reaction". It is often underdiagnosed due to its vague presentation and similarities it shares with a spectrum of other diseases. To add to the obstacles, ruling out each causative mechanisms include underlying genetic defects as well as "trigger" factors, such as infections, malignancies, and autoimmune disorders consumes time and hence delays the diagnosis and treatment. Inspite of various advances in genetic testing and analysis diagnosis becomes a challenging event when it occurs in rural areas where very little is known about it. Here we present a case of a 2 month old female presenting with fever, decreased appetite and excessive irritability. The various parts of the Case report highlights the aspects of every barrier that came across to reach the diagnosis. Moreover, it also adds on how the perplexity of the social concerns limit the ability to obtain essential health care and thus paving way for some amendments that can be made to improve the healthcare status in rural areas.

Keywords: FHLH, Health care, HLH, Hemophagocytic lymphohistiocytosis, Rural areas, Recommendations, Reforms, SHLH.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome which is characterised by an bizarre hyperinflammatory response with heterogeneous aetiology.[2,3] Germline mutations in gene coding for proteins implicated in cytotoxic pathways have been described in patients with primary or FHLH immune deficiency syndromes, various viral infections, including Epstein–Barr virus (EBV), malignancies, and immunosuppression associated with SHLH.[4] Clinically, it is most often characterized by prolonged and persistent fevers, hepatomegaly, splenomegaly, hemophagocytosis, bilineage or trilineage cytopenias, hypertriglyceridemia, and/or hypofibrinogenemia. Neurological symptoms and multiorgan failures may be predominant in the beginning of the disease, or they may develop during the clinical course.[5,6] Rapid diagnosis and prompt initiation of treatment are paramount for survival in HLH. However, the rarity of this syndrome and the complex clinical picture often prove to be a barrier for it to be diagnosed.[7] Moreover, inefficient technology, lack of sufficient knowledge about the disease and many more challenges in rural areas impose threats to the patient's life.

Case Report

A 2 month old baby presented at the outpatient care with excessive irritability, decreased feeding and low grade fever since 6 days. History was negative for runny nose, cough, breathing abnormalities, and rash, swelling, gastrointestinal, genitourinary symptoms. She was discharged with symptomatic treatment. Two days later she was brought to the emergency room after an episode of febrile convulsions. There was no history of neck stiffness, vomiting, photophobia, bleeding or bleeding disorders that run in families. Milestones were achieved till date.

On Examination she had moderate pallor, icterus, and bilateral mild pitting edema. There was no lymphadenopathy or signs of Liver disease. Her temperature was 38.2C, Pulse rate: 148/min, Respiratory rate 38/min, Blood Pressure: 130/82mm Hg. There was a firm and non tender hepatosplenomegaly (liver span: 6.5cm; Spleen: 6cm)(Fig. 1). Chest auscultation revealed a grade 2 soft holosystolic murmur on the left lower sternal border (probably a Ventricular Septal Defect). Respiratory and Neurological examination was normal. Infections like Dengue, Malaria, Blood dyscrasias like Aplastic Anaemia, Hemolytic Anaemias, Lymphoma, and leukaemia were considered as the differential diagnoses.

Blood counts revealed Hemoglobin 5.4g/dL, Total leukocyte counts were 6800/cmm, Platelets 30,000/cmm which dropped to 10,000/cmm in 3 days, Hematocrit 16.2%. NS1 Antigen test was negative. Peripheral Smear examination did not reveal any parasites but highlighted presence of target cells and tear drop cells (Fig. 2). Bone Marrow examination revealed micronormoblastic hyperplasia of the erythroid series, Mild Dysplasia of the Myeloid series, Hyperplasia of the Lymphoid series, Dysmegakryocytosis, Hemophagocytes and Histiocytosis (Fig. 3,4),. The presence of Histocytosis paved a path for considering Autoimmune Lymphoproliferative syndromes. Liver Function tests revealed elevated SGPT: 344IU/L and Bilirubin: 2.2g/dL. Iron studies revealed elevated Serum

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Iron: 435mg/dL, serum Ferritin >1200mg/dL. Other investigations were in normal limits. (Table 1,2). Ultrasonography did not show any focal lesions or free fluid in abdomen.

Treatment was started with presumptive diagnosis of Autoimmune Lymphoproliferative syndrome. Patient was placed on adequate hydration and Prednisolone was being given. Mild Clinical Improvement in the patient's condition was seen. Patient had high grade fever (38.8C) on the 4th day. Blood counts dropped hence Blood transfusions with packed cell and Platelet concentrates were administered. Patient's condition was stabilized by intravenous Monobact, Amikacin and Dexamethasone. A high order of suspicion of HLH was made and she was discharged and referred to a tertiary care hospital in a bigger city for further course. The Tertiary hospital investigations revealed: Deficient Perforin activity (77%) and elevated CD107a (21%) levels. Refer (Table 3,4)

The patient fulfilled 7/8 diagnostic criteria as set by the Histiocyte Society in order to be diagnosed with HLH. But confirmatory test could not be done by genetic analysis of Syntaxin 11 or Munc13-4 because of financial constraints as expressed by the patient's family.

The patient continues to be treated with High dose Dexamethasone, Etoposide and Antithymocyte Immunoglobulins. The idea of Hematopoietic stem transplantation was not advocated due to financial concerns.

Diagnostic criteria

Hemophagocytic lymphohistiocytosis can be diagnosed if there is a mutation in a known causative gene or if at least 5 of 8 diagnostic criteria are met:[8]

1. Fever (peak temperature of > 38.5° C for > 7 days)
2. Splenomegaly (spleen palpable > 3 cm below costal margin)
3. Cytopenia involving > 2 cell lines (Hb < 9 g/dL, absolute neutrophil count < 100/μL, platelets < 100,000/μL)
4. Hypertriglyceridemia (fasting triglycerides > 2.0 mmol/L or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 1.5 g/L or > 3 SD less than normal value for age)
5. Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)
6. Low or absent natural killer cell activity
7. Serum ferritin > 500 μg/L
8. Elevated soluble interleukin-2 (CD25) levels (>2400 U/mL or very high for age)

Our patient fulfilled: all criteria except the Elevated soluble interleukin-2 (CD25) levels. Because some of these tests may not be widely available the patient was referred to specialized centers for evaluation.

Table: Clinical challenges

S. No	Fallacy	Probable cause	Effect
1	Inefficient Outpatient care	• Human power crisis in rural areas • Physician burnout	Under diagnosis as Minor illness
2	Delayed Arrival for patient care	• Lack of awareness of fatality of simple presenting illnesses • Social inequality to immediate health care facilities	Progression of Disease
3	Wrong differential diagnosis	Lack of knowledge	• Delayed diagnosis • Complication of course of disease
4	Confirmatory tests not done	Expensive prices of healthcare	• Treatment given based on Preliminary tests • Probable Inheritance in other family members missed
5	Delayed diagnostic assays	Lack of effective healthcare tools and machinery in rural areas	Complication of course of disease

Table 1: Laboratory information

Date	Hb	TLC	PLT	HCT	RBC	RDW	S.IRON	SGPT	S.TG	S.FERRITIN
11/6/15	5.4	6800	30000	16.2	1.94	20	-	-	-	-
13/6/15	-	-	-	-	-	-	435	344	-	-
15/6/15	5.4	7800	10000	16.2	1.94	20	-	-	-	-
17/6/15	-	-	-	-	-	-	-	-	671	>1200
19/6/15	9.5	7500	94000	28.5	3.43	18.6	-	-	-	-

Table 2: Bone Marrow Examination

Site	Right tibial tuberosity
Material	Bone marrow aspiration
Cellularity	Hypercellular
Myeloid series	Mild myelodysplasia

Erythroid series	Micronormoblastic hyperplasia
M:e ratio	5:1
Megakaryocytes	Dysmegakaryocytosis
Parasites	Not seen
Plasma cells	Within normal limits
Histiocytes	Increased
Tumor cells	Not seen
Impression	Micronormoblastic proliferation with dysmegakaryocytosis with increased histiocytes

Table 3: Flow cytometry perforin analysis

Lymphocyte sub population	Perforin	Normal range
Cd56+NK cells	77%	86+/-5%

Table 4: Flow cytometry granule release assay

Lymphocyte sub population	Expression of cd 107a in patient	Expression of cd 107a in normal
CD56+NK CELLS	21%	19%

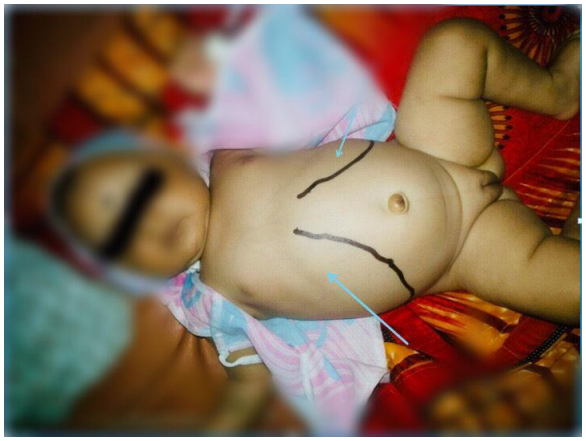

Fig 1: Liver and Spleen Span on Palpation

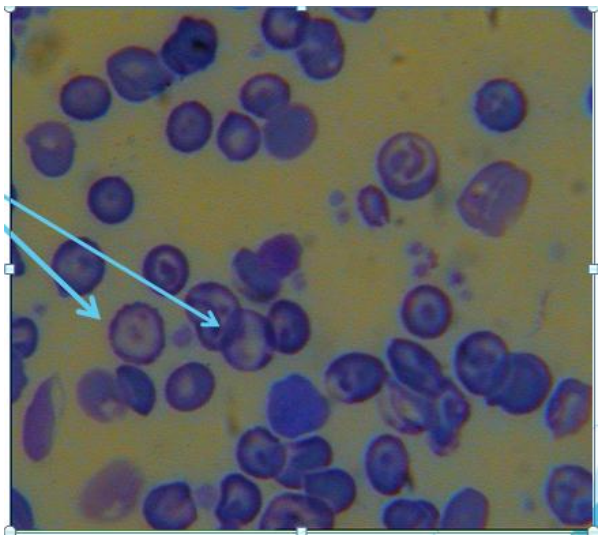

Fig. 2: Peripheral Smear showing Target cells

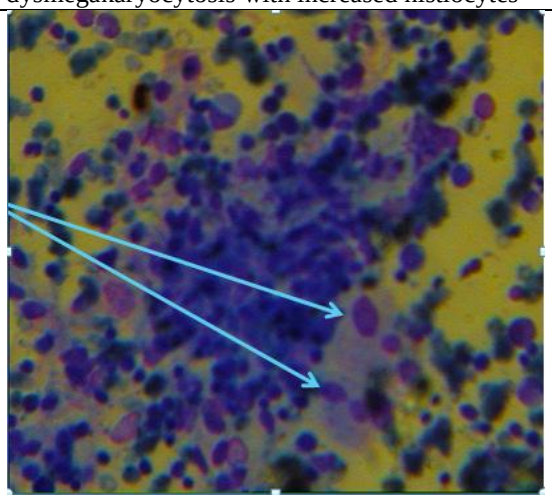

Fig 3: Bone marrow examination showing histiocytosis

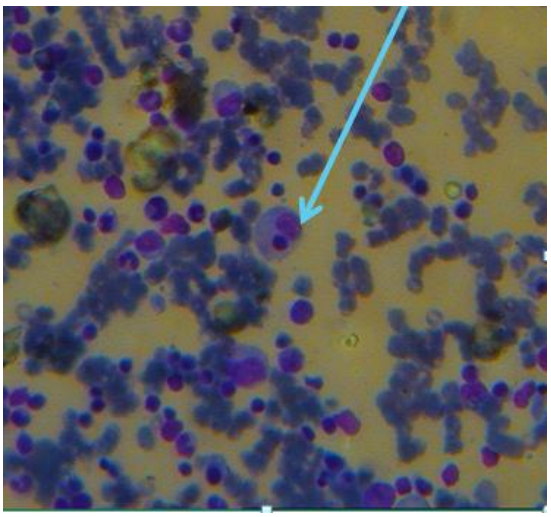

Fig. 4: Bone Marrow Examination showing Hemophagocyte

Discussion

HLH is a rare condition that is often difficult to recognize early enough to provide effective treatment. It presents with non-specific findings of systemic inflammatory response.[9] "Fundamentally, HLH is driven by out of control immune activation and subsequent tissue damage, in what is classified as a cytokine storm disorder".[10] Therefore HLH is often confused for sepsis, macrophage-activation syndrome (MAS) and other multi-organ system failures.[11] Primary or familial HLH is diagnosed when the patient has one of the mutations (STX11, PRF1, UNC13D, etc.) in the correct clinical setting. For secondary HLH, 8 criteria are proposed

(fever, hemophagocytosis in biopsy, splenomegaly, high ferritin, elevated soluble CD25, cytopenia, low natural killer cell activity, and hypertryglyceridemia or hypofibrinogenemia) and the presence of 5/8 of these criteria confirms the diagnosis in the correct scenario.[12] Our patient fulfills 8/9 of the diagnostic criteria of HLH. Prompt start of therapy is critical and lifesaving; however, therapy is often delayed due to delays in establishing the diagnosis. A high degree of suspicion and awareness is essential to save the lives of these patients. Clinical Care could have been better established in our patient if quicker referral to the tertiary center would have been advocated. Hence making a full proof diagnosis took almost a month which could have otherwise been fatal.

Recommendations

1. Inaccessibility to health care can be overcome by effective planning and allocating more funds to areas with scarce health services.
2. Provision of healthcare for rural areas hinge on the affordability of treatment and diagnostic costs. Hence research has to be done to provide efficient health care at lower costs.
3. Improving health literacy by educating the clinicians and rural population about such rare diseases.
4. Allocating more doctors and specialists to rural areas to reduce physician burn out and work load. Providing incentives will decrease stress and boost the will power to work with passion for effective health care.
5. Working on policies for BPL families so as to include health care costs within their budget.
6. Organizing Annual Training programs for rural Clinicians thus updating knowledge on diagnostic medicine.

Conclusion

Many minor and major ailments can have overlapping clinical Scenarios similar to our case and hence can be misdiagnosed and more often under diagnosed. It is essential for healthcare providers to be updated on the recent trends in HLH for considering it in their differential diagnosis of presentation similar to our case. A quicker identification and prompt referral to tertiary care will minimize the percentage of morbidity and mortality of treatable cases. Despite the recent advances on science and technology, the facilities remain limited to urban areas. Our case highlights the timely importance of diagnosing HLH and various clinical challenges encountered during the course. Our case presents an actual clinical picture of the quality of health care in the rural areas. Hence it can only be hoped that further educative and cost effective directives will be taken by health organizations in order to diagnose HLH earlier than it was being diagnosed in the rural areas.

Abbreviations

HLH: Hemophagocytic lymphohistiocytosis, FHLH: Familial Hemophagocytic lymphohistiocytosis, SHLH: Secondary Hemophagocytic lymphohistiocytosis, Hb: Hemoglobin, TLC: Total leukocyte count, PLT: platelet count, HCT: Hematocrit, RBC: red Blood cell count, S.IRON: serum Iron, SGPT: Serum glutamic pyruvic transaminase, S.TG: Serum Triglycerides, S. Ferritin: Serum ferritin

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None.

Conflict of Interest

None.

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