ORIGINAL RESEARCH PAPER

Pathology

KEY WORDS:
Hemophagocytic Lymphohistiocytosis, Cytokine, Immunosuppression, Hyperferritinemia

UNMASKING HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN CHILDHOOD : A CASE REPORT

Dr. Pratikshya S Ray Post Graduate Student(2nd year), Department of Pathology, Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India.

Dr. Saswat Acharya Post Graduate Student(3rd year), Department of Pathology, Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India.

Dr. Deepika Sahu Assistant Professor, Department of Pathology, Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India.

Dr. Rashmi Patnayak Professor and Head of Department, Department of Pathology, Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India.

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare hematologic syndrome presenting either as an inherited life-threatening inflammatory disorder in children or as a secondary disease in adults. Inherited HLH involves inborn defects in lymphocytes and includes autosomal recessive and X-linked disorders characterized by uncontrolled activation of T cells and macrophages and overproduction of inflammatory cytokines. Secondary or acquired HLH occurs in the settings of infections, systemic connective tissue disease and lymphoid malignancies, possibly due to underlying genetic predisposition to develop HLH. The mechanisms leading to secondary HLH have yet to be fully determined and the disease remains frequently undiagnosed and thereby untreated. Herewith we report a case of an 8 year old male child presented with a history of on- and-off fever and vomiting, was referred to our Department of Pathology for bone marrow aspiration and biopsy, who was ultimately diagnosed with HLH. This case report illustrates the difficulties in the diagnostic workup of HLH, mainly related to early identification of the underlying disease and rapid instauration of appropriate therapy.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening state of immune hyperactivation that is characterized by dysregulated and uncontrolled activation of natural killer (NK) cells, CD8+ cytotoxic T-cells and macrophages, leading to a cytokine storm which forms the core pathogenic mechanism that results in multi-organ failure and death.

HLH presents as two distinct clinical entities: Primary and Secondary

- Primary HLH presents in early childhood as the result of genetic mutations that impair the interaction between NK cells, CD8+ cytotoxic T-cells and antigen-presenting cells. It is further subdivided by hereditability of the genetic mutations involved (X-linked disorders) or the clinical syndromes with which it can be associated (i.e. Chediak Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative disorder etc.). Forms without an associated genetic syndrome are typically referred to as familial HLH. The genetic defects in primary disease are associated with proteins perforin, PRF1, IJNC13D, MUNC18-2, Rab27a, STX 11, MUNC 13-4, SII3D1A or BIRC4 genes)
- Secondary HLH presents in adults (mean age of approximately 50 years) in response to an acute illness trigger rather than an underlying genetic mutation. The most common triggers involved in secondary HLH include infection, malignancy and autoimmune disorders. Classically, HLH, which occurs in the context of an autoimmune disorder, is referred to as macrophage activation syndrome (MAS).

HLH has characteristic clinical and laboratory signs such as prolonged fever, hepatosplenomegaly, pancytopenia, liver dysfunction, hypertriglyceridemia, hyperferritinemia and high cytokine levels.

HLH has high mortality rate when it is untreated, but even after extensive treatment focused on immunosuppression coupled with cytotoxic chemotherapy, the result might still be fatal.

Case Presentation

A 8 year old male child presented with a history of on-and-off fever since 1 month and vomiting since 15 days. On examination, blood pressure was 90/60 mmHg, pulse was 112 beats per minute and respiratory rate was 24 breaths per minute. Per abdomen examination revealed Grade I soft, non-tender hepatosplenomegaly with ascites. He was admitted and resuscitated with IV fluids resulting in successful resolution of hypotension.

Investigations revealed Hemoglobin : 9.8 gm/dL, Total leukocyte count : 2100 / mm^3, Differential leukocyte count : Neutrophil – 42.7%, Lymphocyte – 50.2%, Monocyte – 6.3%,Eosinophil – 0.8%, Basophil – 0% and Total platelet count of $70X10^3/\mu L$. Peripheral smear was negative for malarial parasite, Dengue NS1 antigen – Negative and IgM Scrub Typhus –Negative. CRP : 36.2 mg/dl, LDH : 795.5 IU/L, D-dimer : 2.8 µg/ml FEU and Serum Ferritin : >1500 ng/ml. Renal function test and liver function test revealed values within normal range. Serum triglyceride was markedly elevated (424mg/dl). Hemoglobin electrophoresis revealed no abnormal hemoglobin. Blood culture didn't show any bacterial growth. Ultrasonography of abdomen and pelvis revealed mild ascites and minimal bilateral pleural effusion. High resolution CT scan of lungs showed bilateral ground glass opacities. Clinician then advised for Bone marrow study.

DISCUSSION

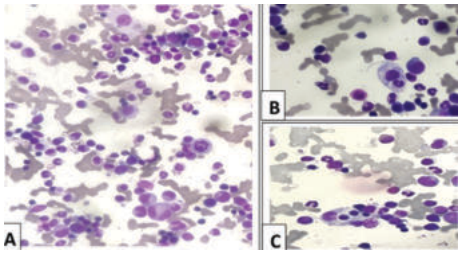

Figure A is representative of 40x (High power) focus of Bone marrow aspirate smear; **Figures B & C** are representative of 100x (Oil Immersion) foci of Bone marrow aspirate smears stained by Giemsa stain.

Bone Marrow Aspiration revealed normocellular to hypocellular smears with suppression of erythropoiesis and myelopoiesis. Megakaryocytes are normal or reduced. Marrow macrophages are markedly increased and many of them demonstrate phagocytosis of ingested leukocytes, platelets and mature erythrocytes. Histiocytes display rounded contour with cytoplasmic projections.

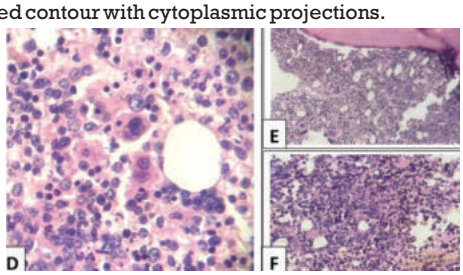

Figure D is representative of 100x (Oil Immersion) focus of Bone marrow biopsy section; **Figures E & F** are representative of 40x (High Power) foci of Bone marrow biopsy sections stained by Giemsa stain.

Bone Marrow Biopsy revealed macrophages engulfing erythrocytes, leukocytes and platelets.

Findings from Bone Marrow Aspiration and Biopsy favor diagnosis of Hemophagocytic lymphohistiocytosis.

CONCLUSION

HLH is a condition where a complete understanding of the pathogenesis, early diagnosis and proper management has an important role in determining patient outcome. Genetic mutations causing impairment in the function of cytotoxic T lymphocytes and natural killer cells have been identified as the root cause of familial HLH; however, the specific pathogenesis of acquired HLH is unclear.

Investigating the detailed mechanisms behind cytokine storms offers insights into targeted therapeutic approaches, potentially aiding in early intervention and improving the clinical outcome of HLH patients. Urgent immunosuppressive therapy is necessary to control hyperinflammation. Hematopoietic stem cell transplantation in familial forms and multi-targeted combination therapy may be essential for disease control, but further trials are required to determine the optimal treatment mode for HLH.

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