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A Case of Parvo-virus related Hemophagocytic Lymphohistiocytosis in a Patient of Delta-Beta Thalassemia

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Abstract
Hemophagocytic lymphohistiocytosis (HLH) is a clinico-pathologic entity characterized by excessive proliferation and activation of lymphocytes and histiocytes causing hemophagocytosis and other clinical manifestations. HLH can be primary or secondary. Secondary HLH is caused by infections, autoimmune diseases, or malignancies. Infection associated HLH is commonly associated with Epstein-Barr virus (EBV) and cytomegalovirus (CMV). But Parvovirus B19 (B19) infection is rare. HLH is likely under-recognized, which contributes to its high morbidity and mortality. Early diagnosis is crucial for appropriate therapy and good prognosis. Here we are presenting a case of 57 year old female with HLH associated with Parvovirus B19 infection in a background of Delta-Beta thalassemia.
Keywords: *Hemophagocytic lymphohistiocytosis, Parvovirus B19, cytokines, Serum Ferritin, hemolyticanemia.*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life threatening emergency. Parvo virus infection is rarely associated with HLH. We report here a case of Parvovirus related HLH in a patient with Delta-Beta thalassemia.

Case Report

57-year-old female, who is a known case of delta beta thalassemia presented with complaints of high-grade fever on and off, Weakness, fatigue, pain in left side of abdomen since one month. On examination severe pallor was observed and spleen was palpable. Laboratory investigations revealed following findings.

Parameters	Value	Reference range
Hemoglobin	5gm/dL	12.5-15g/dL
Total WBC count	1000/mm^3	4000-10000/mm^3
Platelet count	27000/mm^3	150000-400000/mm^3
ESR	140 mm/hr.	<20mm/hr.
CRP	76.8 mg/L	<5 mg/L
Sr.Bilirubin	4.5mg/dL	0-1.0 mg/dL
Sr.LDH	2592U/L	81-234U/L
Sr.Ferritin	11909 ng/dL	13-150 ng/mL
Fibrinogen	119g/dL	200-400g/dL
Sr.Triglyceride	213mg/dL	30-200 mg/dL

Tests for malaria and dengue were negative. Ultrasonography showed mild hepatomegaly (18.1cm) with moderate splenomegaly (20cm in size) In view of Pancytopenia bone marrow examination was performed. In a case of Delta-Beta Thalassemia alone, the bone marrow would be hyper cellular with erythroid hyperplasia. However, in this case, aspirate smears revealed M: E20:1, erythroid series was severely depleted with giant pronormoblasts (figure 1), hemophagocytosis (figure 2), and markedly increased marrow iron. Thus adiagnosis of hemophagocytosis associated withpure red cell aplasia due to Parvo – virus was suggested.

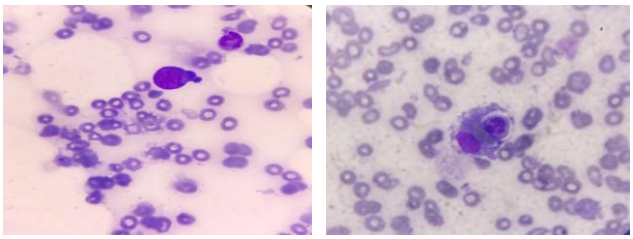

Figure 1: Giant Pronormoblast with cytoplasmic blebs in 100x

Figure 2: Hemophagocytosis – macrophage with engulfed neutrophil and RBC in bone marrow aspiration smear in 100x

Bone marrow biopsy also revealed hemopahgocytosis and eosinophilic parvovirus b19 viral inclusions (figure 3). This was later confirmed by positive serological test (IgM antibody) for Parvovirus b19

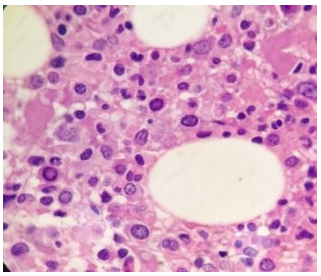

Figure 3: Inclusions of Parvovirus B19 infection in bone marrow biopsy in 100x

Thus the Final diagnosis, "Hemophagocytic syndrome associated with Parvovirus B19 infection in the background of delta beta thalassemia" was made based on the fact that she fulfilled six out of eight diagnostic criteria of HLH 2004 guidelines [fever, splenomegaly, Pancytopenia, hypofibrinogenemia, hemophagocytosis in bone marrow and hyperferritinaemia]

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a clinico-pathologic entity caused by genetic or acquired defect in regulation of cytotoxic immune function leading to cytokine storm.[1] Primary HLH is caused by various mutations in the NK/T cell cytotoxic pathway and is seen in children. The secondary causes include viral infections, other infections, malignancies, rheumatologic disorders and immune deficiency syndromes.[2] In secondary HLH triggered by viral infections, the viral protein inappropriately activates the cytotoxic immune pathway. Normally, the activated NK cells and cytotoxic T lymphocytes kills the infected cells and reduces the antigen load. But in HLH, complex mechanisms down regulate these pathways resulting in prolonged activation of immune system. This results in excessive proliferation and activation of lymphocytes and histiocytes releasing plethora of cytokines which causes hemophagocytosis throughout the reticulo-endothelial system, tissue damage and various clinical manifestations.[1,3]

Among the viral infections Epstein-Bar virus followed by Cytomegalovirus are common whereas Parvo virus B-19 infection is unusual. Parvo virus B19 is a single strandard DNA virus belonging to Parvoviridae family. It is transmitted by respiratory droplets. The clinical syndrome of HPV B19 infection depends on the host. It causes erythema infectiosum in children and acute polyarthritis in adults.[1] In patients with hemolytic disorders such as sickle cell disease, hereditary spherocytosis (HS), autoimmune hemolysis, thalassemia, and paroxysmal nocturnal hemoglobinuria (PNH) it causes aplastic crisis. Of these hemolytic diseases, the most common disease is hereditary spherocytosis.[4]. Case reports are available in which HPV B19 infection induced aplastic crisis causes decompensation and unveils the underlying hereditary hemolytic diseases. The virus has a predilection for infecting the erythroid progenitor

cells and causes lysis resulting in reduced erythroid precursors but with normal myeloid series.[4]. Also it causes temporary arrest in hematopoiesis and hemophagocytosis resulting in Pancytopenia.

Diagnosis of HLH is challenging as the clinical features are non-specific and cause confusion with any inflammatory condition like sepsis and malignancy. The diagnostic criteria are based on 2004 HLH guidelines which includes fever, splenomegaly, Pancytopenia (at least two lineages must be affected), hypertriglyceridemia (>= 265 mg/100mL) and/or hypofibrinogenemia (<=150mg/100mL), hemophagocytosis in bone marrow, lymph node or spleen with three additional criteria added in 2004 namely low/absent NK-cell-activity, hyperferritinaemia (> 500 ng/mL) and high-soluble interleukin-2-receptor level (>2400U/mL)[5]. of these Eight criteria, at least five must be present for diagnosis. Our case had six out of eight criteria. Bone marrow is a common tool to diagnose hemophagocytosis with a sensitivity of 83% and specificity of 60%[5]. However it is not pathognomonic of HLH and its absence cannot rule out the disease. On the other hand ferritin levels >10,000 micro/mL has 90% sensitivity and 96% specificity for diagnosis.[6]. It is reliable and cost effective in 93% cases.[3]. Soluble IL-2 receptors reflects the activated T-cells and NK-cells activity and its rising levels have more specificity.[6]

Parvo virus B19 associated HLH is characterized by benign clinical course and carries better prognosis than other viral associated HLH[1]. Many patients recover spontaneously whereas some patients need immune – suppressive therapy. The aim of therapy is to target the activated immune cells to decreases the cytokine release and to remove the stimulus by killing the pathogen infected antigen presenting cells.[7] Agents like dexamethasone etoposide, immunoglobulins, anti CD-20 antibody Rituximab, cyclosporine and Tacrolimus are the commonly used drugs.

In spite of appropriate therapy and prolonged hospital stay, our patient succumbed to death due to septic shock.

Conclusion

HLH is a life threatening and complex clinical syndrome which has nonspecific clinical findings. High index of suspicion is needed for early diagnosis and is fatal if left untreated. Thus cases with prolonged fever, cytopenias should be screened for investigations like Sr. Ferritin levels which are helpful in early diagnosis.

As hemolytic anemias have increased risk for Parvovirus infection, presence of pure red cell aplasia with giant pronormoblast in bone marrow instead of erythroid hyperplasia is highly suggestive of Parvovirus B19 infection and Parvovirus B19 serology should be done for confirmation.

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