Case Report

Hemophagocytic Lymphohistiocytosis Possibly Triggered by Craniotomy Surgery: A Rare Association with Uplifting Ending

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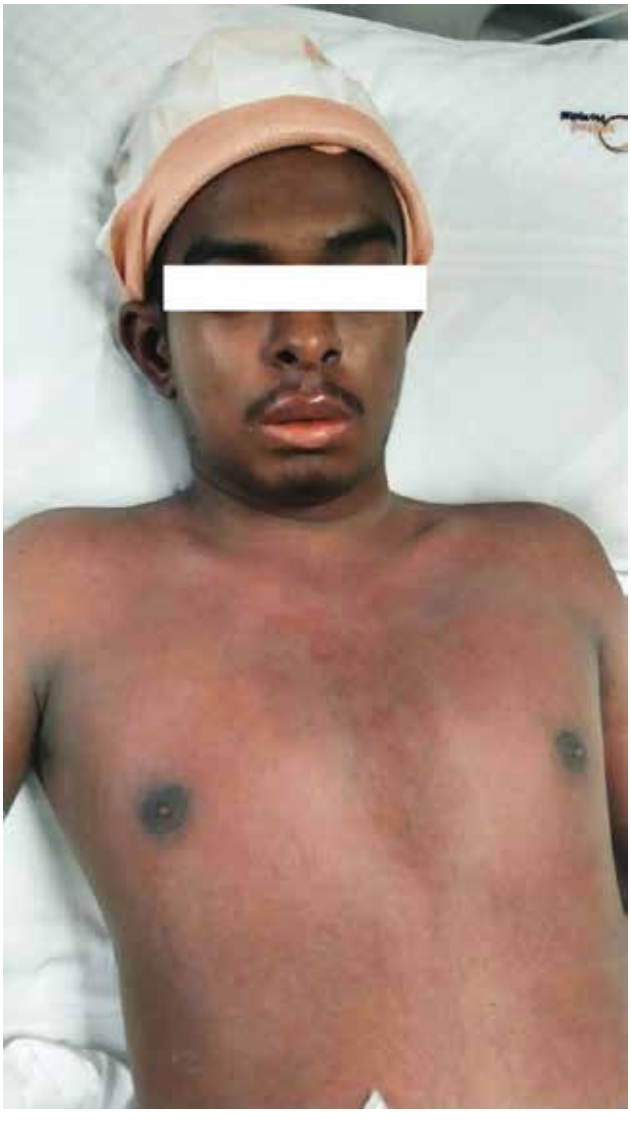
Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive inflammation and tissue destruction due to abnormal immune activation. HLH can occur as a familial or sporadic disorder, as well as can be triggered by a variety of events that disrupt immune homeostasis. In HLH, natural killer cells and cytotoxic lymphocytes fail to eliminate activated macrophages resulting in excessive CD8+ T cell and activation of more macrophages with highly elevated levels of interferon-gamma and other cytokines, which drive the pathology of HLH. Here, we present a case of 15 years old boy with HLH, which possibly was triggered after surgical intervention for arachnoid cyst in the right parietal lobe. It was a daunting challenge for us to evaluate and diagnose the patient promptly since he was critically ill and developed pancytopenia, along with grossly altered liver function test and markedly raised ferritin in a short period of time. But it was even more crucial to start treatment in the form of chemotherapy in such a patient who had very severe neutropenia as well as thrombocytopenia.

Introduction

A 15-year-old boy presented with high-grade fever, deep jaundice, generalized erythematous rash, neck rigidity, several episodes of seizure and lost motor power of the left hand, 11 days after craniotomy and fenestration of arachnoid cyst and fenestration of falx, communicating with opposite subarachnoid space surgery, for arachnoid cyst in the right parietal lobe. He started developing pancytopenia dramatically. His Hb fell from 11.5 gm/dl to 8.2 gm/dl, WBC from 8.0 x 10^3 µL to 0.5 x 10^3 µL, neutrophil from 75.2% to 8.2%, lymphocytes from 17.3% to 90.8%, platelet count from95 x 10^3 µL to 23 x 10^3 µL. His liver function was grossly altered (S. bilirubin 11.08 mg/dl, ALT 1574 U/L, AST 1050 U/L, 448U/L). Serum ferritin was markedly increased (2630 mg/dL), around 10 times than normal level. LDH level was also high (929 U/L). Blood and urine culture revealed no growth and CSF study was normal. ANA, anti dsDNA, as well as cANCA, and pANCA were negative. USG of the whole abdomen revealed normal-sized liver and spleen, with bilateral minimal pleural effusion and minimal ascites. Inj. Dexamethasone 10mg, IV once daily was started in meantime, keeping adult-onset still's disease in provisional diagnosis (as the patient had a high-grade fever, generalized rash, grossly altered LFT with markedly raised S. ferritin). But the patient did not respond to dexamethasone.



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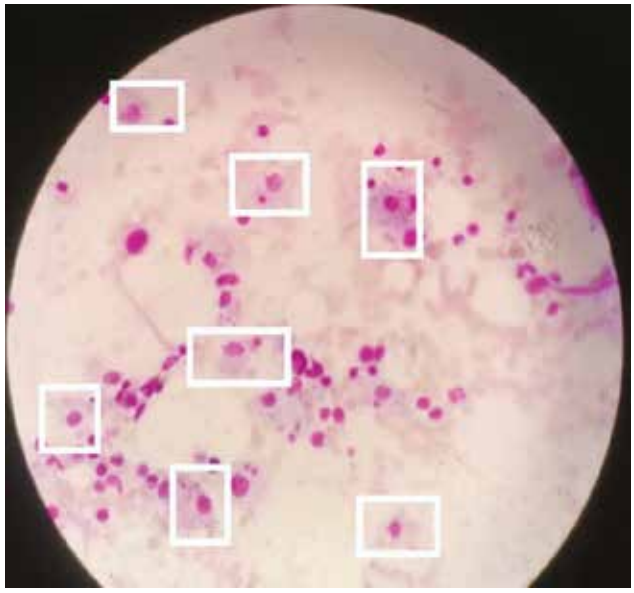
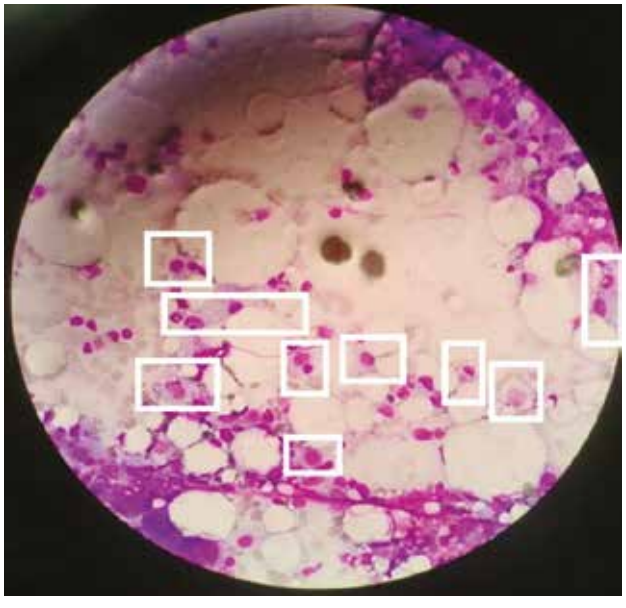
A bone marrow examination was done to evaluate the cause of pancytopenia and aspirated marrow particles showed hypoplastic marrow with marked hemophagocytosis (Figure 2A & 2B).

Bone marrow biopsy revealed hypocellular marrow with some histiocytes (Figutre 2C). Immunophenotyping of bone marrow revealed, 70% of T cells, mature with an altered CD4/CD8 ratio. B cells are 16% and polyclonal – both Lamda and kappa were moderately positive. No other cell cluster classifying other lymphoproliferative disease was seen.



2A



2B

Figure 2A & 2B: Bone marrow aspirate smear showed marked hemophagocytosis

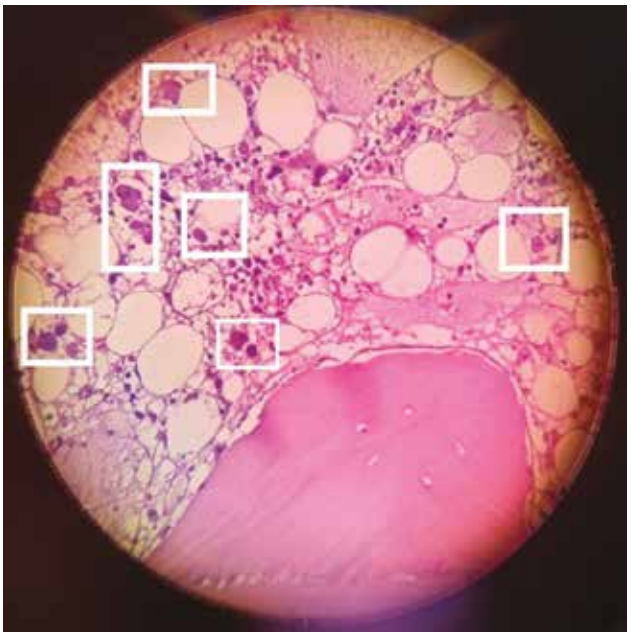


Figure 2C: Bone marrow biopsy demonstrating histiocytes, showing features of hemophagocytosis

After making the confirmed diagnosis, Inj Dexamethasone was increased to 10mg – twice daily. Inj. Etoposide was started (as per HLH treatment protocol 2004) along with dexamethasone. During the initiation of treatment patient's haemoglobin were 10.0 gm/dl, WLC 0.3 x 10^3 µL, neutrophil 12.5%, and platelet count 68k. Strict barrier nursing, prophylactic antibiotics, antifungal, and antiviral was provided. High-grade fever subsided after 1st dose of Inj Etoposide.

After 1st week of chemotherapy, his ferritin dramatically improved from 1230 mg/dL then to 150 mg/dl. Liver function tests started improving from 2nd week of chemotherapy and onwards (S. bilirubin from 11.08 mg/dl to 2.5 mg/dl, ALT from 1574 U/L to 476 U/L, AST from 1050 U/L to 116, ALP from 448U/L to 245 U/L). From 3rd week of chemotherapy, his blood counts started to improve gradually. After 11th weeks of chemotherapy, his Hb was 10.4gm/dl, TLC 8.0 x 10^3µL, neutrophil 60%, lymphocyte 36%, platelet count 320k. Triglycerides became 110 mg/dl, which previously was 220mg/dl. Jaundice, skin rash, and neurological features, as well as a general condition, were improved gradually and the patient is doing well now. However, due to financial constraints, genetic testing could not be done. Hence, the primary or secondary cause could not be determined.

Discussion:

The incidence of HLH is not well reported worldwide. It is a potentially fatal condition that results from the uncontrolled activation of macrophages by cytokines released by cytotoxic T cells, causing end-organ damage. The persistent activation of macrophages, NK cells, and cytotoxic T cells in patients with HLH leads to excessive cytokine production resulting in a cytokine storm, which is thought to be responsible for the multiorgan failure and the high mortality of this syndrome[1].

Hence, HLH is considered a great diagnostic challenge for clinicians, as it mimics numerous common clinical conditions, and on the other hand, delayed diagnosis can cost the lives of patients.

HLH can be familial (primary) or secondary to a variety of conditions such as infections (often associated with viral infections, eg EBV, CMV, parvovirus, HSV, varicella-zoster virus, human herpes virus 8, H1N1 influenza virus, HIV, alone or in combination)[2], autoimmune diseases (SLE, RA, dermatomyositis, systemic sclerosis, mixed connective tissue disease, antiphospholipid syndrome, Sjögren's syndrome, ankylosing spondylitis, vasculitis, and sarcoidosis)[3], malignancies (most commonly lymphoid cancers including B[4], T[5], NK cell and leukemias[6]and solid tumours), and even alteration of immune homeostasis, such as surgical procedure.

Several mutations that cause congenital immunodeficiency syndromes are also associated with an increased incidence of HLH. For example, XMEN disease[7], chronic granulomatous disease, X-linked lymphoproliferative disease[8], Gricelli syndrome[9], CD27 (TNFRSF7) deficiency, Hermansky-Pudlaksyndrome[10] and Chediak-Higashi syndrome[11].

It is noteworthy, genetic predisposition plays a crucial role in the occurrence of HLH. Several HLH gene mutations map to loci that code for elements of the cytotoxic granule formation and release pathway, and have been labelled familial hemophagocytic lymphohistiocytosis (FHL) loci. [12-13]

Although HLH primarily affects infants, it can be diagnosed in all ages, and the male-to-female ratio is close to 1:1. However, in our case, though the surgical procedure is thought to trigger HLH, infection and genetic predisposition could have played a role.

According to HLH diagnostic criteria 2004 of the American society of haematology, HLH can be diagnosed, if the molecular diagnosis is consistent with HLH, or 5 out of 8 diagnostic criteria are fulfilled[14]. The diagnostic criteria are:

1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood: Hemoglobin <90 g/L, platelets <100 × 109/L, Neutrophils <1.0 × 109/L),
4. Hypertriglyceridemia (fasting triglycerides ≥265 mg/dL) and or hypofibrinogenemia (Fibrinogen ≤1.5 g/L),
5. Hemophagocytosis in bone marrow or spleen or lymph nodes with no evidence of malignancy.
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥500 μg/L,
8. sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL.

Since HLH presents with multiple organ involvement (eg, respiratory system, cardiovascular system, skin, kidneys, nervous system), it is a diagnostic challenge to identify HLH from its several differential diagnoses, eg, septicaemia, macrophage activation syndrome (MAS), multiple organ dysfunction system, liver disease/ liver failure, autoimmune lymphoproliferative syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or drug-induced thrombotic microangiopathy (DITMA).

The mortality rate of adult patients diagnosed with HLH exceeds 50%[15]. Early recognition and treatment with chemotherapeutic agents or bone marrow transplant may reduce mortality. As per HLH treatment protocol, 2004,[15] chemo-immunotherapy includes etoposide phosphate, dexamethasone, and cyclosporine. In patients with CNS involvement, intrathecal therapy with methotrexate and corticosteroids is indicated. Hematopoietic stem cell transplantation (HSCT) is recommended for patients with familial disease or molecular diagnosis, and patients with severe and persistent or reactivated disease.

In our patient, it was difficult to diagnose the case as HLH as there was no usual triggering factor other than surgery. And it was also very challenging to start chemotherapy in our patient because of continued high-grade fever with very severe neutropenia, deranged liver function and neurological conditions. But patient responded gradually to treatment and recovered from cytopenias and other complications. So prompt diagnosis and initiation of treatment can reduce mortality in such types of life-threatening conditions.

Conclusion

Since HLH is a life-threatening syndrome, it should be suspected and investigated in patients with conditions involving multiple organs. It was a great challenge not only to diagnose this critically ill 15-year-old boy in a short period but also to treat him optimally with chemotherapy. Eventually, the patient responded well to chemotherapy and is doing well now.

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