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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO CEREBRAL MALARIA DUE TO DUAL INFECTION WITH PLASMODIUM FALCIPARUM AND VIVAX: PRECISE DIAGNOSIS FORESTALLED DEATH.

NEUROLOGY

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a systemic disorder of immune dysregulation which can occur as a primary syndrome (genetic) or arise secondary to infectious, rheumatologic, malignant or metabolic disorders. Primary HLH is mostly recognized in childhood whereas the secondary form has no age bar.

Literature on malaria-associated HLH is meager. We report a rare and unusual case of HLH which presented to us with cerebral malaria due to co-infection by Plasmodium falciparum and Plasmodium vivax. The bone marrow aspiration and biopsy showed proliferation of histiocytes with engulfed haematopoietic cells, however patient survived with aggressive treatment with antimalarials and Intravenous immunoglobulin (IVIG). Thus, this case report emphasizes the need for consideration of diagnosis of HLH in adult patients so as to provide timely diagnosis and prompt treatment to improve the clinical outcome.

KEYWORDS

haemophagocytic lymphohistiocytosis, secondary, Plasmodium, cerebral malaria

INTRODUCTION:

Haemophagocytic lymphohistiocytosis (HLH) is a potentially lethal hyper-inflammatory condition characterised by engulfment of haematopoietic cells by activated macrophages resulting in severe cytopenias [1-12]. Acquired HLH is known to develop secondary to infectious, autoimmune, neoplastic or metabolic disorders. HLH secondary to infectious disease is an important entity especially in tropics where infectious diseases are rampant and still pose a major threat. A timely diagnosis and prompt treatment can improve the clinical outcome as this disorder is usually associated with high morbidity and mortality owing to its under-recognition. Immunosuppression, immune modulation, chemotherapy and haematopoietic stem cell transplant are the currently considered treatment regimens for HLH.

Cerebral malaria is the most common complication and cause of death in severe *P. falciparum* infection. A strict definition of cerebral malaria has been recommended for sake of clarity and this requires the presence of unarousable coma, exclusion of other encephalopathies and confirmation of *P. falciparum* infection.

Here, we report a rare and unusual case of HLH secondary to dual infection by Plasmodium falciparum and vivax.

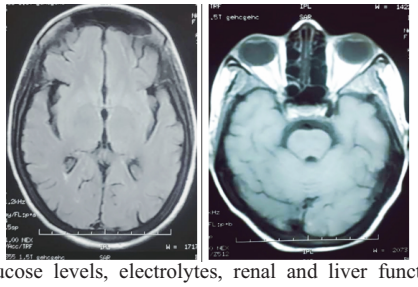
CASE REPORT:

A 40 year old male was brought to the emergency department with high grade fever, intractable generalized convulsions and loss of consciousness. During initial resuscitation he again had two attacks of focal seizures involving left side of his body. Family members complained of intermittent, high grade rise of temperature, associated with chills, headache, neck stiffness and generalized fatigue for last 10 days but no prior convulsion. Care givers also informed about a single self-limiting episode of non-traumatic epistaxis and passage tea colored urine 2 days back. This was not associated with any rash, joint pain, bone pain and cough with expectoration. Family, drugs and addiction history were non-contributory.

General examination revealed that the patient was pale, unarousable, had a GCS score of 7/15, not responding to painful stimuli and was febrile (104'F), dehydrated, pale and recorded blood pressure was 80/46 mm Hg. Deep tendon reflexes were diminished with bilateral extensor plantar responses. There was no lymphadenopathy, oedema, jaundice. However, splenomegaly up to 6cm was noted. Fundoscopy revealed no papilloedema. Rest of the physical examination was normal.

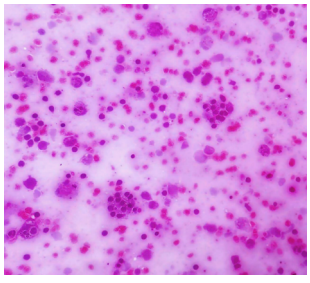
From the history and clinical findings a list of differential diagnoses was made: acute infective meningoencephalitis, cerebral malaria, metabolic encephalopathy, cerebrovascular accident due to presence of blood dyscrasia.

Complete hemogram on day 1 of admission revealed bicytopenia (Haemoglobin: 4.8 g/dl; WBC counts: 5620/cumm; Platelet counts: 19000/cumm) with reticulocyte index of 0.5 and Rapid Diagnostic Test (RDT) for malaria was positive for both falciparum and vivax. Microscopic slides of thick and thin Giemsa-stained blood smears showed the presence of trophozoites and schizonts of both *P. falciparum and vivax* with parasitaemia and thereby confirmed the result of RDT. An MRI of brain revealed no abnormality (see below).



Blood glucose levels, electrolytes, renal and liver function tests, cerebrospinal fluid (CSF) study and coagulation panel were normal.

Subsequently, 3 units of packed red blood cells were transfused after drawing blood samples for several other investigations and patient was put on intravenous artesunate, antibiotics, anti epileptics, and other supportive measures. Despite initiation of anti-malarial treatment, patient continued to have fever, weakness and also developed petechiae, gum bleeding, epistaxis, hematuria and melena. Hematological parameters also continued to worsen. Meanwhile, other laboratory investigations revealed hypertriglyceridemia (542mg/dl), hypofibrinogenemia (1.0g/l) increased serum ferritin (10620ng/ml), and increased LDH levels (860U/L). Hence, bone marrow aspiration was ordered on 4th day of admission which revealed erythroid hyperplasia and a markedly increased number of benign looking histiocytes with small round nuclei and abundant cytoplasm, exhibiting striking phagocytosis of erythrocytes and platelets.



Many histiocytes also revealed the presence of engulfed pigment.

However, malarial parasite was not detected on bone marrow examination. This case satisfied the diagnostic criteria for HLH and diagnosis of HLH secondary to bi-positive malaria was made on 6th day of admission. To rule out other causes of secondary HLH, EBV capsid antigen, CMV DNA, PCR for HHV6, HSV (1, 2), HIV (1, 2), HBsAg, anti-HCV, rk39, Leptospira-IgM, Dengue profile, Toxoplasma IgM, ANA profile were sent. And all of the tests answered negative.

IVIG was administered over five days and following this therapy, the clinical as well as laboratory parameters shown improvement.

DISCUSSION

The term hemophagocytosis describes the pathologic finding of activated monocytes, macrophages and histiocytes which engulf erythrocytes, leukocytes and platelets in bone marrow and other tissues and was first reported in 1939 [2] by Farquhar & Claireaux [7] in 1952. Familial forms of HLH occur due to mutations either in the perforin gene or in genes important for the exocytosis of cytotoxic granules containing perforin and granzymes. This leads to inability to induce apoptosis of target (infected) cells and ineffective down regulation of the immune response. Acquired forms of HLH are usually associated with viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (7%) and immune deficiency states (6%) [2, 3, 6]. However, HLH is often under-recognized, especially in adults, and specific therapy is not considered early in the disease course [5]. Role of infections in causing HLH was first described in 1979 in a case series of viral associated HLH among renal transplant patients [9]. Few years later, possible bacterial etiology was discovered as well [10]. Since then, many viral (particularly EBV), bacterial, fungal and parasitic infections have commonly been implicated in causation of HLH [3,4]. Amongst the protozoan family, Leishmania, Plasmodium primarily vivax species and Toxoplasma gondii have been encountered in cases of HLH [3,6].
HLH secondary to Plasmodium falciparum infection was first reported by Anwar M, et al. [11] in 1995 in a young male. Literature review revealed that since then, only 20 cases of HLH secondary to malaria have been reported until 2017, highlighting the rarity of this condition [12]. Till now only 12 cases of HLH secondary to Plasmodium falciparum have been documented [11-24]. **Of the 20 cases previously reported, only 3 patients had dual infection with P. vivax and P. falciparum. This adds to the specialty of our case.**

Our patient presented with loss of consciousness, seizures, high grade fever, splenomegaly, bicytopenia along with presence of ring forms of Plasmodium falciparum and vivax on smear. Later on, high serum ferritin and triglyceride levels, low fibrinogen level were also found and the bone marrow examination revealed hemophagocytosis, thus fulfilling diagnostic criteria for diagnosis of HLH. Malarial parasite was not observed in bone marrow in our case. Even, in the previous reported 12 cases of falciparum induced HLH, only 1 case had the demonstrable parasite in bone marrow [11-24] but still malaria was considered to be the most likely cause of HLH due to temporal relationship to the illness.

While allogenic stem cell transplant is the only curative treatment for familial HLH, management of secondary HLH includes treatment of underlying condition along with immunosuppressive therapy in the form of corticosteroids, etoposide, IVIG and cyclosporine to target the hyperactivated T cells and histiocytes as per the HLH 2004 protocol [13]. It is recommended that treatment for HLH should be started when there is a high clinical suspicion, even when results of some diagnostic studies are pending as HLH can be rapidly fatal without specific intervention [8]. In majority of the reported cases of HLH secondary to malaria, complete recovery has been observed even when the patient received the antimalarial treatment alone, while, few required additional immunosuppression [11-24].

To conclude, HLH secondary to malaria, although exquisitely rare, can be a potentially fatal condition, if not diagnosed early and treated aggressively. Poor response to antimalarials, rapid downhill course, and supportive blood investigations can easily clench the diagnosis and lives can be salvaged.

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