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Severe Malaria With Secondary Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation, with marked hemophagocytosis in bone marrow. Secondary HLH, triggered by infections, malignancy, and autoimmune diseases, can manifest at any age, whereas primary HLH is predominantly recognized in childhood. Here we report a 10 year old child with Falciparum malaria with lab investigations revealing bicytopenia and an elevated C-reactive protein who despite on treatment with antimalarials and parasite clearance did not show clinical improvement. He was subsequently diagnosed with HLH. Within a week, child showed dramatic improvement without HLH specific therapy. Hence, malaria and HLH has common clinical presentation making it difficult to differentiate between therapy resistant malaria from HLH. A high degree of suspicion is required.

Keywords: Severe malaria, Falciparum malaria, Hemophagocytic lymphohistiocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation, with marked hemophagocytosis in bone marrow.1 Secondary HLH, triggered by infections, malignancy, and autoimmune diseases, can manifest at any age, whereas primary HLH is predominantly recognized in childhood.2,3 Viral infections, among other infectious agents, are common triggers for secondary HLH, with malaria being an exception, particularly associated with Plasmodium falciparum and vivax.2,4 Plasmodium falciparum, in particular, is frequently implicated in cases of secondary HLH. The precise pathogenesis of HLH in the context of malaria remains elusive, but it is believed to involve a complex interplay between the patient's genetic predisposition and an aberrant immune response induced by the persistent presence of the parasite.6 Although the treatment of familial or primary HLH has been extensively studied and documented, the optimal approach for treating secondary HLH remains speculative.5 This discussion is underscored by a case report detailing Severe Falciparum malaria with secondary HLH, wherein noteworthy improvement was observed solely with the administration of antimalarials. A case of Severe Falciparum malaria with secondary HLH is described here, and improvement was observed with Antimalarials alone. Within a week, child showed dramatic improvement without HLH specific therapy.

Clinical Presentation

We present a 10 year old male child born of non-consanguineous marriage admitted to DY Patil Hospital with an already diagnosed case of

Plasmodium Falciparum malaria of 2 day origin with complaints of fever and cough since 4 days, loose stools and red coloured urine since 3 days. He had already been administered with 3 doses of Inj. Artesunate along with antibiotics, Piperacillin-Tazobactam and Ofloxacin. On presentation, he had high grade fever spikes, tachypnea, hepatosplenomegaly, altered sensorium and breathlessness for which oxygen support via face mask was administered and relevant investigations were sent. Complete Blood Count [Hemoglobin-9.8g/dL(11.5-13.5), Total Leucocyte Count-7.69x103microL(4.5-13.5), Platelets-93x103microL(150-350)] suggested Microcytic hypochromic anemia and thrombocytopenia. Liver Function Test suggested raised SGOT[197U/L(15-40)] and SGPT[66U/L(10-35)]. Renal function test [Creatinine-0.38mg/dL(0.3-0.7), BUN-4.8mg/dL(5-18), Uric acid- 2.0mg/dL(2.2-6.6)] suggested normal study. Child was continued on Inj. Artesunate and Inj. Piperacillin-Tazobactam. Repeat malarial smear did not show malarial parasite. On Day 2 of admission, he had 1 episode of generalized tonic clonic convulsion, relieved on Inj.Midazolam and was loaded on Inj.Levetiracetam at 20mg/kg. MRI Brain plain suggested normal study. Child was grunting on the same evening, for which he was intubated and put on mechanical ventilator on pressure control mode. Lumbar puncture was done, findings suggested Aseptic picture with lymphocytic predominance (70%). Urine routine was done in view of red coloured urine, however there was no hematuria and Acute glomerulonephritis was ruled out. Ultrasonography of the abdomen suggested mild hepatomegaly, splenomegaly, mild ascites and bilateral minimal pleural effusion. 2D echo suggested thin rim pericardial effusion, serositis and bilateral small pleural effusion. Repeat Complete blood count [Hemoglobin-9.4g/dL(11.5-13.5), Total leucocyte count-6.92x103microL(4.5-13.5), Platelets-80x103microL(150-350)] reports suggested drop in haemoglobin and platelets and in spite of treatment with antimalarials and antibiotics, child had persistent high grade fever on Day 2 and 3 of admission, hence secondary hemophagocytic lymphohistiocytosis(HLH) was suspected and relevant investigations were sent. Investigations revealed Triglycerides- 247mg/dL(24-145), LDH-397U/L(110-295), Ferritin- 2132ng/mL(7-140), D Dimer- 744ng/mL(<500). 5 criteria's out of 8 of HLH (Dueling criteria) were fulfilled [Fever>38.5C, Splenomegaly, Cytopenia affecting 2 cell lines (Hemoglobin <9g/L, Platelets <100x103microL), Hypertriglyceridemia, Hyperferritinemia]. Bone marrow aspiration was dry. However, child became afebrile even before the decision of steroids was taken. Hence diagnosis of HLH was made and patient was not started on steroids. Child was weaned off ventilator, extubated and put on face mask and tapered to room air.

Discussion

HLH is an inflammatory syndrome that occurs in the setting of pathologic immune system activation and is manifested by a characteristic constellation of clinical features. A variable spectrum of disease and presentation is involved, with an interplay of genetic, environmental, and clinical factors. The pathogenesis of HLH is poorly understood. The basis of this syndrome is abnormal activation of the immune system, allowing for excessive inflammation and tissue destruction. Host blood cells, including white blood cells, red blood cells, and platelets, are phagocytized by inappropriately activated macrophages in a phenomenon termed hemophagocytosis. Furthermore, tissues are infiltrated, causing local inflammation and destruction.7 A cytokine storm is created by macrophages, NK cells, and CTLs, leading to excessive release of cytokines such as interferon-gamma, tumor necrosis factor-alpha, and interleukins. These factors further propagate inflammation and are responsible for the complications of the syndrome and multiorgan failure.8 This syndrome has been described in the setting of viral, bacterial, fungal, and parasitic infections, with the Epstein-Barr virus being the most implicated pathogen. HLH occurring in the context of malarial infection is very rare, and literature on this association is limited. There is a significant overlap between features of malaria and HLH, raising a diagnostic dilemma. Patients with malaria often present with fever, splenomegaly, anemia, thrombocytopenia, and elevated inflammatory markers. However, high ferritin, high triglyceride, and low fibrinogen levels are uncommon in malaria and may suggest superimposed HLH. A review of the literature revealed 28 cases of HLH associated with malaria worldwide. All reported cases confirmed the

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diagnosis of malaria through visualization of the parasite on peripheral blood smear or bone marrow biopsy. The temporal relationship between malarial infection and the development of HLH in these cases was sufficient to establish it as the likely trigger. Thus far, only Plasmodium falciparum and vivax are the two malaria species associated with HLH, with Plasmodium falciparum being implicated in most cases. Some patients with HLH improve with early identification and prompt treatment of the trigger. HLH-specific therapy typically consists of a combination of etoposide, glucocorticoids, methotrexate, and intravenous immunoglobulin. Among the 28 published cases of HLH associated with malaria, 18 patients (65%) experienced clinical improvement and resolution of abnormal laboratory findings after typical treatment courses with antimalarials alone.7 Patients who were unresponsive to initial therapy or had clinical decompensation were also treated with immunosuppression. Four patients (14%) were treated with glucocorticoids, and six patients (21%) received intravenous immunoglobulin.7 Most patients with malaria-associated HLH recovered after antimalarial therapy alone, as did our patient who did not require HLH-specific therapy. All reported patients with HLH-associated malaria were recovered, and no mortalities were observed.

Conclusion

Malaria-associated secondary HLH is rare. If fever, splenomegaly, and an elevated ferritin level are present in the patient, HLH should be highly suspected, and relevant examinations should be conducted. Most patients with malaria-associated HLH recover after antimalarial therapy alone. A satisfactory outcome can be achieved for patients through early diagnosis of the primary disease, along with timely intervention and a multidisciplinary approach.

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