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Hemophagocytic Lymphohistiocytosis as a Rare Complication of *Plasmodium vivax* Malaria: A Case Report

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Abstract: ***Introduction: Hemophagocytic lymphohistiocytosis (HLH) is an uncommon, life-threatening hyperinflammatory condition induced by infections, cancers, or autoimmune disorders. Malaria, particularly Plasmodium falciparum, has been associated with secondary HLH, while studies involving Plasmodium vivax are scarce. Growing data indicates that P. vivax can induce severe illness, challenging its conventional classification as "benign malaria." Case Presentation: We present a young patient exhibiting chronic fever, cytopenias, hepatosplenomegaly, and biochemical indicators of systemic inflammation. The peripheral smear verified P. vivax infection, whereas the bone marrow investigation revealed hemophagocytosis. The laboratory assessment met the HLH-2004 diagnostic criteria, demonstrating hyperferritinemia and hypertriglyceridemia. The patient received intravenous antimalarials, supportive care, and immunomodulation, resulting in gradual clinical improvement. This instance underscores the growing acknowledgment of P. vivax as a possible catalyst for HLH. The clinical manifestations frequently coincide with those of acute malaria, complicating early identification. Prolonged recognition may lead to elevated morbidity and mortality rates. Reports from endemic countries indicate that increased awareness and prompt commencement of suitable antimalarial therapy, along with HLH-directed treatment where necessary, are essential for positive outcomes. Our case underscores the necessity of evaluating HLH in malaria patients presenting with enduring cytopenias and systemic hyperinflammatory indicators despite treatment. Conclusion: Plasmodium vivax may serve as an atypical yet significant etiological factor in hemophagocytic lymphohistiocytosis (HLH). Heightened clinical attention, prompt diagnosis, and suitable therapy are essential in averting negative outcomes.***

Keywords: Plasmodium vivax, malaria, hemophagocytic lymphohistiocytosis, cytopenia, case report

1. Introduction

Malaria remains a significant global public health issue, with approximately 263 million cases and 597,000 fatalities reported worldwide in 2023 [1]. Of the five Plasmodium species that infect humans, Plasmodium falciparum and Plasmodium vivax hold the highest clinical importance. Historically, P. falciparum has been deemed the primary cause of severe and deadly malaria, while P. vivax was traditionally viewed as "benign." This concept is currently being contested, as P. vivax is widely acknowledged to cause considerable morbidity and mortality, including severe consequences that were formerly virtually exclusively associated with P. falciparum [2].

P. vivax is the most geographically prevalent malaria parasite, endangering around 2.5 billion individuals across Asia, South America, the Middle East, and certain regions of Africa [3]. In contrast to P. falciparum, which is predominant in sub-Saharan Africa, P. vivax is extensively prevalent in South and Southeast Asia, particularly in India, where it constitutes a significant proportion of malaria-related hospitalizations [4].

Numerous studies and meta-analyses now indicate that P. vivax can induce life-threatening consequences, including severe anemia, acute respiratory distress syndrome (ARDS), cerebral malaria, shock, hepatic dysfunction, and multi-organ failure [5]. A meta-analysis conducted in India suggested that approximately 29% of patients with P. vivax exhibit severe symptoms, with fatality rates potentially reaching 12.9% among hospitalized cohorts [4]. The findings indicate that P. vivax malaria should not be regarded as clinically mild.

The pathogenicity of P. vivax is influenced by its distinctive biological characteristics. The parasite exhibits a pronounced affinity for infecting reticulocytes, resulting in comparatively low peripheral parasitemia. Nonetheless, patients frequently exhibit substantial systemic symptoms, indicating that immune-mediated inflammatory responses are pivotal [6]. Moreover, P. vivax produces hypnozoites, dormant hepatic stages that can reactivate weeks to months post-initial infection, leading to recurrent episodes and cumulative morbidity [6].

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon yet potentially fatal hyperinflammatory condition marked by persistent fever, hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and the presence of hemophagocytosis in bone marrow or tissue biopsy [7]. HLH can be classified as primary (genetic) or secondary, with the latter induced by infections, autoimmune disorders, or malignancies. Although viral infections are the predominant infectious triggers, malaria has been infrequently documented as a causative factor [8].

Instances of P. vivax–associated HLH are exceedingly rare yet clinically pertinent. The etiology is believed to entail the unregulated activation of macrophages and T-lymphocytes, resulting in a "cytokine storm" that induces tissue destruction and multi-organ failure. Due to its non-specific appearance, HLH may be inadequately identified in places endemic to malaria. Delayed diagnosis or overlooked identification might be lethal, as HLH necessitates prompt anti-malarial treatment alongside immunomodulatory measures in some instances [8].

In malaria-endemic nations such as India, clinicians often confront P. vivax malaria. Nonetheless, HLH as a complication is infrequently documented, and awareness continues to be minimal. Articulating such cases is essential to underscore diagnostic difficulties, emphasize the necessity for awareness when malaria presents with cytopenias and hepatosplenomegaly, and direct doctors towards timely identification and intervention.

2. Case Report

A 23-year-old previously healthy female presented to the emergency department with a three-day history of high-grade intermittent fever, accompanied by generalized fatigue, malaise, anorexia, and myalgia. No history of cough, rash, bleeding tendencies, burning micturition, shortness of breath, altered mental status, recent travel, or prior medical illnesses was noted. She stated that she does not take any regular medications or herbal supplements.

Upon admission, the patient exhibited alertness, accompanied by fever (102.4°F), tachycardia (112 bpm), and hypotension (BP 96/60 mmHg). The physical examination indicated moderate pallor, icterus, and splenomegaly, measuring 4 cm below the left costal margin. No evidence of lymphadenopathy, hepatomegaly, or focal neurological deficits was observed. The respiratory and cardiovascular examination yielded no significant findings.

Initial laboratory results revealed haemoglobin: 7.6 gm/dL, total leukocyte count: 3200 /µL, platelet Count: 58,000 /µL, total bilirubin: 2.1 mg/dL, aspartate aminotransferase(AST): 92 IU/L, alanine aminotransferase ALT: 84 IU/L, ferritin levels measured at 12,780 ng/mL, triglycerides: 388 mg/dL, Lactate dehydrogenase(LDH) : 645 U/L, fibrinogen: 140 mg/dL and C-reactive protein(CRP): 227 mg/L (summarized in table 1).

The examination of the peripheral smear identified trophozoites and schizonts of Plasmodium vivax. The diagnosis was validated through a rapid diagnostic test (RDT) that identifies P.vivax-specific lactate dehydrogenase (Pv-LDH). Tests for Plasmodium falciparum yielded negative results. Both blood and urine cultures yielded no growth. Serologic tests for HIV, hepatitis B and C, dengue, leptospira, and Epstein-Barr virus yielded negative results.

The patient was initiated on intravenous artesunate in accordance with the national malaria guidelines, accompanied by supportive care such as fluid administration, antipyretics, and monitoring. Over the subsequent 72 hours, she continued to exhibit fever and her clinical condition deteriorated. Subsequent laboratory tests indicated ongoing pancytopenia, deteriorating liver enzyme levels, and increased serum ferritin and triglyceride concentrations. Based on these findings, secondary hemophagocytic lymphohistiocytosis (HLH) was considered likely.

HLH workup showed Soluble IL-2 receptor (sCD25): 6,500 U/mL (elevated), fibrinogen level: 140 mg/dL (decreased) and bone marrow aspiration demonstrated a significant presence of hemophagocytic histiocytes consuming erythroid and myeloid precursors (Figure 1). Subsequent laboratory findings revealed lactate dehydrogenase (LDH) was 645 U/L, uric acid 8.6 mg/dL, serum ferritin 529 ng/dL, erythrocyte sediment rate (ESR) 128 mm/1st hour, anti-nuclear antibody (ANA) was negative and rheumatoid factor was negative (summarised in table 1). The H-Score was determined to be 253, indicating a probability of HLH exceeding 99%. The diagnosis of HLH was established based on the HLH-2004 criteria, with the patient meeting six of the eight diagnostic criteria: fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, low fibrinogen, and hemophagocytosis in the bone marrow [1].

Table 1: Key laboratory findings of patient

Name of Test	Measured Values	Reference values
Haemoglobin	7.6 gm/dL	12-16 gm/dL
Total leucocyte count	3200	4000-11000
Platelet count	58000	1.5-4.5 lac
Peripheral Smear	Pancytopenia with normocytic normochromic anaemia with no schistocytes	
Total bilirubin	2.1 mg/dL	0.5-1.5 mg/dL
Aspartate aminotransferase (AST)	92 U/L	<35 U/L
Alanine aminotransferase (ALT)	84 U/L	<35 U/L
Alkaline phosphatase (ALP)	112 U/L	30 – 120 U/L
Blood urea	26 mg/dL	20-40 mg/dL
Creatinine	0.7mg/dL	0.7-1.2 mg/dL
C- Reactive Protein (CRP)	227 mg/dL	<5 mg/dL
Erythrocyte sediment rate (ESR)	128 mm/1st hour	20 mm/1st hour
Lactate dehydrogenase (LDH)	645 U/L	120 – 246 U/L
Uric acid	8.6 mg/dL	2.5 – 6.2 mg/dL
Serum Ferritin	2529 ng/dL	10-150 ng/dL
Serum Iron	193 mcg/dL	35-120 mcg/dL
Total iron binding capacity (TIBC)	231	162-261 mcg/dL
Serum folate levels	13.4 mg/dL	2.7-20 mg/dL
Serum B_{12} levels	890 mcg/dL	239-931 mcg/dL
Fibrinogen levels	140 mg/dL	200-400 mg/dL
Serum triglyceride levels	450 mg/dL	< 150 mg/dL
Rheumatoid factor	9.8 IU/mL	< 14 IU/mL
Serum Complement factor (C3/ C4)	Normal	
Antinuclear antibodies (ANA)	Not detected	

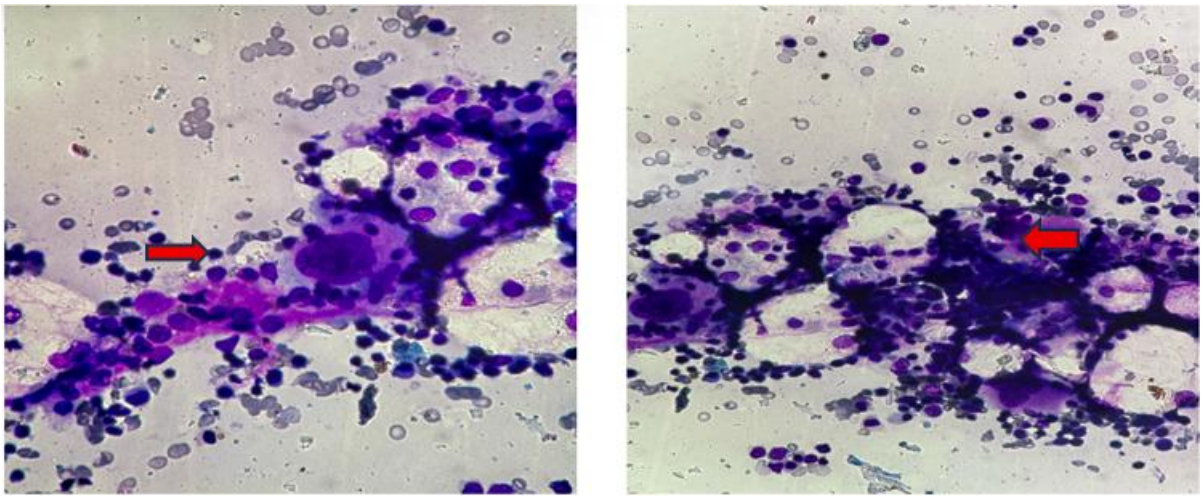

Figure 1: Bone marrow aspirate stained with Giemsa stain(100x) showing numerous histiocytes are seen actively engulfing erythrocytes, leukocytes, platelets and their precursors

The patient was initiated on intravenous dexamethasone (10 mg/m²/day) alongside ongoing antimalarial therapy. During the subsequent five days, she exhibited clinical improvement: resolution of fever, restoration of appetite, and stabilization of hemodynamic parameters. Blood counts showed gradual improvement, with hemoglobin at 10.4 g/dL, total leukocyte count at 4,600/µL, and platelets at 92,000/µL by Day 7. Ferritin levels decreased to 420 ng/mL, and triglyceride levels returned to normal. The tapering of corticosteroids occurred over a four-week period. The patient was discharged on Day 10 in stable condition with primaquine for 14 days and continues to be well during follow-up.

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH), traditionally associated with viral infections, is being increasingly documented in cases of malaria, particularly with Plasmodium vivax. P. vivax, previously regarded as "benign," can induce significant immune dysregulation resulting in HLH. Patients commonly exhibit fever, hepatosplenomegaly, and cytopenias, which can resemble severe malaria and result in delayed diagnosis. Early identification of HLH in malaria patients exhibiting persistent cytopenias and hyperinflammatory characteristics is essential for prompt management [8].

The earliest notable case was reported by Sung et al. (2011), detailing a patient in Korea diagnosed with hemophagocytic lymphohistiocytosis (HLH) secondary to Plasmodium vivax infection. The case highlighted the successful reversal achieved through antimalarial therapy alone, underscoring the significance of early diagnosis and treatment [9]. Since that time, numerous case reports from various regions, including India, Nepal, and the Middle East, have documented the occurrence of HLH in conjunction with P. vivax infection. This condition frequently presents with pancytopenia, hyperferritinemia, hypofibrinogenemia, organ dysfunction, and bone marrow hemophagocytosis [10].

P. vivax generally produces low parasite loads; however, it can elicit heightened immune responses. Persistent antigen exposure may lead to hyperactivation of macrophages and cytotoxic T lymphocytes, resulting in a cytokine storm, which is characteristic of HLH pathogenesis. In HLH, elevated levels of IFN-γ, TNF-α, IL-6, and IL-18 have been consistently observed, with potential amplification during P. vivax infection attributed to its biological behavior and immune activation patterns [10].

In malaria-endemic regions, the clinical manifestations of persistent fever, cytopenias, and organomegaly are frequently ascribed to severe malaria or sepsis. The overlap with HLH diagnostic criteria—fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, hemophagocytosis— results in frequent underrecognition or misdiagnosis of the condition. The delay may have serious consequences due to HLH's elevated morbidity and mortality unless immunomodulatory therapy is commenced without delay [9,10].

Case reports indicate favorable results when antimalarial treatment is administered alongside immunosuppression, such as corticosteroids, especially in instances of P. vivax–induced HLH. Sung et al. [9] reported a case that resolved with antimalarials alone, whereas other cases required steroids for resolution [11,12]. The findings highlight the significance of early diagnosis, bone marrow assessment, and dual-focused therapy aimed at both the pathogen and the hyperinflammatory condition.

This case, in conjunction with previous reports, emphasizes the developing recognition that P. vivax may not be inherently benign. In regions such as South Asia, where P. vivax is common, clinicians must evaluate the possibility of HLH in patients exhibiting persistent symptoms following the clearance of malaria parasites. Case reporting enhances awareness of this life-threatening complication and facilitates improved patient outcomes.

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