Hemophagocytic lymphohistiocytosis in a patient of paroxysmal cold hemoglobinuria triggered by malaria: A Case Report

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Hemophagocytic lymphohistiocytosis in a patient of paroxysmal cold hemoglobinuria triggered by malaria: A case reportKEY CLINICAL MESSAGE With Plasmodium falciparum and HLH, malaria is an uncommon but potentially deadly disease. Although HLH can be lethal if left untreated. It also offers a proposed method for identifying and treating malaria-related HLH.

ABSTRACT

Introduction and importance: Hemophagocytic lymphohistiocytosis (HLH) is a fatal disease caused by the overactivation of tissue macrophages in response to environmental factors. Because HLH has many clinical symptoms with malaria, which is the underlying cause, identifying the condition can be difficult.*Case presentation:* We present a rare case of HLH triggered by malaria in a 15-year-old male patient of paroxysmal cold hemoglobinuria (PCH), which developed as a response to latent syphilis. The patient presented with fever and hematuria, diagnosed with malaria by Plasmodium Falciparum; he was started on Artesunate with anemia correction and cold avoidance. After antimalarial therapy, the patient's clinical condition worsened, and he met the criteria for HLH. Treated with IV dexamethasone and injection epokine under strict surveillance the patient showed complete recovery.*Clinical Discussion:* Pakistan has reported an only case of malaria with Plasmodium vivax and HLH. Nonetheless, several instances of Plasmodium falciparum and vivax infections have been documented in China and India. Patients in each of these situations have a decent prognosis. The fatality rate from HLH is not widely known, however secondary HLH is fatal without treatment.*Conclusion:* This report aims to alert physicians, about the complication of HLH in malaria and to present a model approach to diagnose and treat it when linked to PCH.**Keywords:** Paroxysmal cold hemoglobinuria, hemophagocytic lymphohistiocytosis, malaria, case report

1 INTRODUCTION Hemophagocytic lymphohistiocytosis (HLH) is a sporadic syndrome of pathologic immune activation caused by a variety of environmental triggers such as infection, cancer, and rheumatologic disorders. Because of the HLH syndrome's rarity, diversity, and complexity, diagnosis is difficult [1]. Malaria, a vector-borne disease caused by Plasmodium species is a rare cause of HLH, hence it is difficult to diagnose due to significant overlap in clinical features and laboratory findings between these two entities, which can be complicated by pre-existing paroxysmal cold hemoglobinuria (PCH) rarely found in the literature [2]. PCH is a type of autoimmune hemolytic anemia (AIHA) caused by atypical IgG autoantibodies that bind to their target RBC antigen and fix complement at 4 °C. After complement activation, cold-reactive antibodies primarily cause intravascular hemolysis producing symptoms including hemoglobinuria, pallor, jaundice after cold exposure [3]. We present the first reported case of HLH in a 15-year-old patient with PCH triggered by acute febrile illness secondary to malaria. This case underscores the importance of considering a broad differential diagnosis in patients presenting with fever and hemolysis, particularly in areas with a high

prevalence of malaria. Additionally, it highlights the need for prompt recognition and management of HLH, as it can have life-threatening complications if left untreated.

2 PRESENTATIONS OF CASE

This work has been reported in line with the CARE 2013 guidelines [4]. A 15-year male patient, with a known case of PCH secondary to latent syphilis now presented to a tertiary care hospital with the complaint of fever and hematuria for 2 weeks. According to the patient, he was in his usual state of health 2 weeks back when he developed high-grade intermittent fever, documented as 102-104F with chills without rigor. The patient denies coughing, sore throat, shortness of breath, headache, abdominal pain, and other gastrointestinal symptoms. Furthermore, he developed hematuria 2 weeks back without burning in micturition or passage of the stone. For these complaints, he visited the emergency department thrice where Artesunate was prescribed but the fever did not resolve. On examination, he was alert and oriented with intact Glasgow Coma Scale (GCS), blood pressure of 100/80 mm/Hg, heart rate of 90 beats/min, a temperature of 101 F and respiratory rate of 18 breaths/min. Pallor was positive, but there was no jaundice, clubbing, cyanosis, palpable lymph nodes, pedal edema, or raised jugular venous pressure. His abdominal examination revealed a soft, non-tender abdomen with spleen palpable 5 cm below the costal margin. The rest of the systemic examinations were unremarkable.

The patient's workup revealed anemia, 3+ blood in urine, high serum ferritin, hypertriglyceridemia, and raised lactate dehydrogenase levels**(Table 1).** Considering the lab workup, clinical impression, and the endemic risk of malaria in Pakistan, a malarial parasite was ordered, which was positive with a falciparum parasitic load of 0.3%. Diagnosed with malaria, he was started on IV Artesunate 2.4mg/kg given at 0, 12, and 24 hours. For the correction of anemia tablet of folic acid 5mg, a tablet of Vitamin B6, B1, and B12 BD, tablet of ferrous sulfate 200mg BD were ordered along with avoidance of cold exposure, proton pump inhibitor for gastrointestinal prophylaxis, and mobilization for deep venous thrombosis prophylaxis.

After 4 days, the patient switched to oral Artem 80/480mg BD for 3 days and malarial parasite and blood culture were repeated, both reported to be negative. Post transfusion, the patient then developed a high-grade fever of 102 F along with hypotensive episodes. Lab investigations showed static Hb but progressive neutropenia, deranged SGPT-active hemophagocytosis, lymphocytosis, hyperferritinemia, and hypertriglyceridemia **(Table 1).** The patient was taken over by hematology and started on IV dexamethasone 8mg IV BD for HLH and injection epokine (erythropoietin) 10000 IU on alternate days. As the fever was not settling, Infectious disease was taken on board and started empirically on IV meropenem 1 gm 8 hourlies. However, the patient was not responding to current steroids, and the dose of dexamethasone was increased to 16 mg IV BD with gastrointestinal and bone prophylaxis, keeping the patient in a warm environment. The fever started spacing out and the patient and laboratory investigations started showing signs of improvement.

Now that the patient was stable, he was discharged with prophylaxis primaquine tablet 0.25 mg/kg stat, injection erythropoietin SC 10000 IU thrice a week in daycare, dexamethasone PO 16 mg BD, omeprazole PO 40 mg a half hour before breakfast, tablet calcium carbonate and vitamin D3 PO OD, folic acid PO 5mg OD, tablet Vitamin B1+ B6+ B12 OD, tab ferrous sulfate PO 200mg OD. Moreover, the patient was counseled to maintain a warm temperature at home by wearing thick mittens and socks, avoiding cold beverages/food, cold bath or cold exposure, and wearing warm undergarments continuously. Follow-up was arranged in the hematology clinic after 2 weeks. No long-term side effect was noted from malaria.

3 CLINICAL DISCUSSIONS Malaria, an infectious disease caused by a parasitic protozoan of the genus Plasmodium, has a wide range of clinical symptoms and is transmitted by mosquitoes. [5] After medical history, peripheral blood smear and/or rapid diagnostic tests were used to make the diagnosis of malaria. Malaria is the primary condition for which artemisinin is used. [6] Our patient was given IV artesunate initially, then switched to oral artesunate, and subsequently given primaquine as prophylaxis. HLH is a potentially lethal illness characterized by excessive activation of tissue macrophages [7]. It can manifest itself in both primary/familial and secondary forms. Although HLH is most typically diagnosed in children, its secondary form can occur at any age. Cases of secondary HLH include those caused by autoimmune diseases,

malignancy, or infections. The most prevalent cause is viral infections. It can also be triggered by bacterial, fungal, or parasitic infections. It is still unclear how HLH develops. Normally, a negative feedback loop between cytotoxic lymphocytes and natural killer cells controls the inflammatory response of macrophages. But because this regulatory system is dysfunctional in HLH, macrophages are not cleared from the body and instead remain hyperactivated. Additionally, they invade tissues, inducing inflammation and tissue damage [8]. The diagnostic guideline for the condition has been set as the HLH-2004 clinical guidelines [1]. If either criteria A or B are satisfied, the condition of HLH can be diagnosed **(Table 2).** In our patient, criteria B was fulfilled as he had a fever, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia, hemophagocytosis, and hyperferritinemia. However, NK-cell activity and sCD25 antigen levels were not available in this case.

PCH is a self-limiting, uncommon type of AIHA that mostly affects children and young adults and is generally caused by a viral infection [9]. Even if the actual cause is frequently not known, earlier, latent or congenital syphilis had been associated with secondary PCH [10]. It was clear from this case that malaria infection was the likely cause of HLH development. The only two malaria species known to date to be linked to HLH are Plasmodium falciparum and Plasmodium vivax, with Plasmodium falciparum being responsible in the majority of instances. However, it is rare for PCH patients to experience HLH triggered by acute febrile illness secondary to malaria. To our knowledge, this is the first instance from Pakistan in which a patient with paroxysmal cold hemoglobinuria due to latent syphilis acquired HLH caused by P. falciparum. Pakistan being a malaria-endemic country has reported fewer cases of HLH-associated malaria [11]. However, various cases have been reported in India and China [12-15]. In all these cases, patients have a good prognosis and have been given supportive care, treatment of aggravating factors, and immunosuppressive medications, as they are all components of the secondary HLH treatment plan (steroids, IVIG, and other antianemia drugs). Although the death rate from HLH is not well documented, secondary HLH is lethal in the absence of therapy [16]. One of the side effects of HLH in malaria is prolonged hemophagocytosis, which causes extended anemia. The presence of hyperbilirubinemia, acute kidney failure, encephalopathy, convulsions, and coagulation disorders are further consequences [17].**4 CONCLUSION** PCH, a rare type of anemia with the combination of HLH triggered by malaria is unique in this case. Our patient's clinical deterioration after an early response to antimalarial medications aided in the diagnosis of this disease, which led to more stringent surveillance and supportive care, following which he had a complete clinical recovery. To reduce morbidity and mortality, early detection, prompt treatment, identifying at-risk patients and further conducting research studies are all crucial.

AUTHOR CONTRUBUTUION Saad Khalid, MBBS: conceptualization, data collection, project administration and supervision. Abdul Subhan Talpur, MBBS: conceptualization, data collection, project administration and supervision. Zobia Ansari, MBBS: writing the paper, visualization, review and editing. Fatima Mansoor, MBBS: writing the paper. Muhammad Jawad Farooq, MBBS: validation. Rabia Zaheer, MBBS: validation. Asadullah Memon, MBBS: validation.

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Ethical approval was not required for this case report as it did not involve any interventions or experimentation on human subjects and did not contain any identifiable information about the patient**PATIENT CONSENT STATEMENT**

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.**ORCID** Zobia Ansari https://orcid.org/0000-0003-0965-7757

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TABLE LEGENDS

Table 1: Lab investigations before and after treatment**Table 2:** HLH-2004 diagnostic guidelines [1]. The diagnosis of HLH can be established if criteria A or B is fulfilled.

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