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Scrub Typhus Infection Precipitating Hemolysis in a Patient With G6PD Deficiency: A Case Report

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a well-known red blood cell enzymopathy and a cause of intravascular hemolysis. This case report presents a child with underlying G6PD deficiency who experienced an acute episode of extensive intravascular hemolysis induced by a scrub typhus infection. The key takeaway from this report is that scrub typhus infection can trigger extensive hemolysis in patients with even "mild" G6PD deficiency, and normal G6PD levels found during the acute phase of hemolysis do not rule out the possibility of underlying G6PD deficiency.

1 | Introduction

Glucose-6-phosphate dehydrogenase is a housekeeping enzyme that plays a vital role in the prevention of cellular damage from reactive oxygen species [1]. G6PD deficiency, most common enzyme deficiency in humans, is an X-linked disorder, and its estimated global prevalence is 4.9% [2]. Usually the enzyme deficient is asymptomatic until presenting with an acute episode of intravascular hemolysis after being triggered by an oxidant stress. An oxidant stress could be due to an infection, consumption of certain groups of drugs, or fava beans [3]. Scrub typhus is a tropical disease caused by *Orientia tsutsugamushi*, a gram-negative bacillus and an obligate intracellular parasite belonging to the family Rickettsiaceae. It is transmitted due to bites of infected chiggers (larval form of trombiculid mites). Mostly scrub typhus infection presents with flu-like symptoms (fever, headache, myalgia, etc.), and sometimes severe infection can lead to pneumonia, acute respiratory failure, shock, meningoencephalitis, and DIC [4]. Scrub typhus can rarely cause intravascular hemolysis on its own or trigger severe hemolysis in patients with G6PD deficiency [5, 6]. Here, we report a case of scrub typhus infection presenting with extensive intravascular hemolytic anemia, later diagnosed as being associated with mild G6PD deficiency.

2 | Case History/Examination

A 5-year-old male resident of Kathmandu, Nepal, presented to our center with a history of fever and dark-colored urine (Day 0). According to his mother, the child had been apparently well and actively playful until the previous day, when he developed a sudden fever. The fever was intermittent, with a maximum recorded temperature of 101°F. The child also had a headache, body aches, and passed dark-colored urine three times in the last 12 h (Figure 1). The child denied having any abdominal or back pain or any urinary or gastrointestinal symptoms. There was no history suggestive of upper respiratory tract infection, mechanical trauma, porphyria, or bleeding diathesis. The mother denied any recent consumption of beetroot, colored candies by her child, or the introduction of new foods into his diet. There was no significant travel or drug history. The child had no previous similar episodes, and there was no significant family history.

At presentation, the child appeared lethargic with tachycardia (pulse 114 bpm, normal volume). He was afebrile, with a normal respiratory rate, blood pressure of 90/50 mmHg (normal for his age, height, and gender), and oxygen saturation of 95% in room air. His Glasgow Coma Scale (GCS) score was 15/15.

FIGURE 1 | Note the color of collected urine (day of presentation).

Pallor and icterus were present, but there was no limb or facial edema, signs of dehydration, or lymphadenopathy. A thorough head-to-toe examination, including assessments of the central nervous system, chest, and abdomen, showed no significant abnormalities.

3 | Methods

3.1 | Investigation

Blood and urine investigations revealed anemia (Hb: 6.1 g/dL), leukocytosis (WBC count: 25.4×10^9 cells/L) with a differential count of [N65, L32, M2, E1], and elevated C-reactive protein (64.8 mg/L). Serum bilirubin was elevated (total: 5.28 mg/dL, indirect: 4.53 mg/dL), while renal function tests and electrolyte parameters were within normal limits. Peripheral blood smear showed anisopoikilocytosis and a reticulocyte count of 1.1% (corrected for anemia). Reports showed a negative direct Coombs test, significantly elevated lactate dehydrogenase (LDH: 1784 U/L), and low haptoglobin levels (13 mg/dL). Serum vitamin B12 level was in normal limit while iron profile revealed slightly high serum iron (164 mcg/dL) and serum ferritin (309 ng/mL). Urinalysis revealed a dipstick positive for heme protein, with no RBCs or pus cells. The urine test for myoglobin was negative.

3.2 | Treatment

The clinical findings and investigation results indicated ongoing intravascular hemolysis with a likely infectious etiology. Empirical treatment with intravenous cefotaxime was initiated. However, the patient's pallor worsened, and urine

FIGURE 2 | Note the gradual change in color of urine (left to right).

continued to be dark throughout the day, accompanied by several episodes of fever. The patient was transferred to the pediatric intensive care unit (PICU) for unstable vital signs (tachycardia and hypotension) on the evening of the day of admission (Day 0). In the PICU, additional blood investigations, including a tropical fever panel (dengue, malaria, scrub typhus, leptospirosis, typhoid fever, and brucella), were conducted, and 2 pints of packed red blood cells were transfused to address a hemoglobin level of 3.1 g/dL. The child was found to be positive for anti-scrub typhus IgM antibody. G6PD spectrophotometry revealed an enzyme level of 7.46 U/g Hb, which is within normal limits. Abiding to the seropositive status and clinical symptoms suggestive of scrub typhus, oral azithromycin was added to the treatment (Day 1).

4 | Outcome and Follow-Up

The patient's condition gradually improved. Following 48 h in the ICU and 3 pints of blood transfusion, the child was moved to the general pediatric ward with improved hemoglobin (6.5 g/dL), hematocrit (20%), corrected reticulocyte count of 4.4%, yellowish urine, and stable vital signs (Day 3). The following 6 days in general ward were uneventful, with no fever and urine returning to a clear and transparent state (Figure 2). The child was discharged from the hospital on the ninth day of admission with hemoglobin of 6.9 g/dL. He was called for follow-up after 12 weeks with iron profile and G6PD enzyme level test, which revealed a normal iron profile and G6PD enzyme level of 3.06 U/g Hb. The patient's guardians were counseled about their child's disease, future diet, precautions, and possible genetic transmissions.

5 | Discussion

The presence of clinical features such as pallor, icterus, and dark-colored urine, along with laboratory findings of rapidly increasing anemia (in the absence of bleeding), indirect hyperbilirubinemia, and transient high serum iron indicate hemolysis. A dipstick positive for heme protein, with no RBCs and negative myoglobin, suggests hemoglobinuria. The presence of anemia, indirect bilirubin-predominant hyperbilirubinemia, markedly elevated LDH, and hemoglobinuria are suggestive of intravascular hemolysis [7–9]. Additional features of hemolysis include decreased serum

haptoglobin and increased reticulocyte count. Haptoglobin binds free hemoglobin released from lysed red blood cells, and its decline is a significant indicator of hemolysis [10]. An elevated reticulocyte count reflects a bone marrow response to anemia, though in this case, the initial count was 1.1%, which is within the normal range. The peak reticulocyte response typically occurs 4–7 days after the insult [11–13], explaining the lag, initially normal count, and subsequent increase of reticulocyte count as in our case. Hemoglobin levels generally begin to recover 8–10 days after the offending agent is removed [11].

Common clinical features of scrub typhus include fever, headache, myalgia, and often an eschar at the site of chigger bite. An eschar, characterized by painless cutaneous necrosis with a black center (up to 1 cm in size), is observed in 50%–80% of cases and has high diagnostic value [4, 14]. Laboratory diagnosis of scrub typhus can be done using various methods, including molecular assays, indirect immunofluorescence assay (IFA), immunochromatographic tests (ICT), the Weil-Felix test, and enzyme-linked immunosorbent assay (ELISA). IFA is considered the gold standard [15, 16]. In our case, a rapid diagnostic serology kit was used, which employs rapid immunochromatography to qualitatively detect IgM and IgG antibodies. Although IFA is more accurate, reliable, and detailed than ICT, it requires more resources and expertise to perform and is not readily available in resource-poor settings like ours'. In our case, the child was diagnosed with scrub typhus on the basis of IgM seropositive status in ICT, a reliable tool in the absence of IFA [16]. After confirmation, for treating scrub typhus in young children, azithromycin is preferred over doxycycline due to its safety and better tolerability [17, 18].

Tropical diseases, disseminated intravascular coagulation (DIC) (via ISTH scoring), hemolytic uremic syndrome, and immune hemolysis as the possible cause of acute extensive intravascular hemolysis were excluded based on laboratory findings. Heeding to medical literature and our clinical experience, only scrub typhus positive status was not fully convincing as the cause of this presentation, because scrub typhus-associated extensive hemolysis has been rarely reported. Furthermore, a normal G6PD level during an acute crisis does not rule out G6PD deficiency, as G6PD tests may be negative during or immediately after a hemolytic episode due to the destruction of old, G6PD-deficient red blood cells and the higher G6PD content in newly formed cells, which may yield falsely normal results [19]. Suspecting this, the patient was advised for G6PD spectrometry, the gold standard for measuring G6PD activity [20], 3 months after hospital discharge. The follow-up report showed a G6PD level of 3.06 U/g Hb, while the normal laboratory reference range is 4.6–13.5 U/g Hb, and mild deficiency is defined as 2.76–4.5 U/g Hb. In cases where the cause of hemolysis remains unclear despite extensive investigation, including normal G6PD activity during the acute phase, we suggest repeating quantitative G6PD testing once the hemolysis resolves. This is particularly important if there is a relevant family history of G6PD deficiency, a history of oxidative stress triggers (such as infection, certain drugs, or fava beans), or if the patient resides in an endemic region of G6PD deficiency. In the absence of pyruvate kinase level determination, second most common red blood cell enzymopathy, we presumed that pyruvate kinase deficiency was less likely due to the lack of common clinical features suggestive of this condition, including chronic hemolysis, neonatal jaundice, or a history of hemolytic diseases in his siblings [21]. However, we recognize that the absence of these features does not definitively exclude the diagnosis.

Infections such as viral hepatitis, typhoid fever, pneumonia, and upper respiratory and gastrointestinal infections are known triggers for hemolytic episodes in individuals with G6PD deficiency [22]. However, in this case, aside from the scrub typhus infection, no other potential triggers for hemolysis could be identified. The common hematological features associated with scrub typhus are mild anemia, thrombocytopenia, and leucocytosis/leucopenia [23]. Infrequent hematological complications of scrub typhus infections are coagulation abnormalities, DIC, hemophagocytic syndrome (HPS), and hemolytic anemia. The scrub typhus may rarely cause an intravascular hemolysis by itself or sometimes may precipitate a severe hemolysis in G6PD-deficient patients [5, 6]. Oxidative stress, RBC membrane damage, antibody cross-reaction and endothelial damage are proposed mechanisms of scrub typhus-induced hemolysis [6]. In G6PD-deficient patients, the interaction of these factors may result in an extensive hemolysis event even in mild deficiency states as in our case. Scrub typhus infection in human hosts with G6PD deficiency has a worse prognosis than in healthy individuals [24, 25]. To the best of our knowledge, no studies have been published yet regarding the prevalence of scrub typhus-associated hemolysis. We are not sure if the incidence of scrub typhus presenting with hemolytic anemia is rare because of underdiagnosis or its rare occurrence. We hope that this report will enhance awareness of the coexistence of these conditions in a single case.

Reference Laboratory Values

WBC: white blood cells: reference range: 4×10^9 cells/L to 8×10^9 cells/L.

CRP: C-reactive protein: < 10 mg/L.

Hb: hemoglobin: 13–18 g/dL.

Total bilirubin 0.2–1 mg/dL.

Indirect bilirubin: < 0.3 mg/dL.

LDH: lactate dehydrogenase: < 248 U/L.

Serum iron: 50–150 mg/dL.

Serum ferritin: 15–300 ng/mL.

Author Contributions

Ravi Shukla: conceptualization, investigation, methodology, writing – original draft. **Mandira Shrestha:** formal analysis, supervision. **Chaitanya Darshan Bhattarai:** methodology, resources. **Kiran Lamichhane:** investigation, visualization. **Paras Yadav:** methodology, resources. **Debendra Tamatta:** writing – review and editing.

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Ethics Statement

Approval was provided by the Department of Pediatrics and Institutional Review Committee (IRC) of Nepal Medical College and Teaching Hospital, Kathmandu, Nepal. Written informed consent was obtained from the patient's guardian for the publication of any potentially identifiable images or data included in this article. The patient's information was anonymized before the study, and confidentiality was strictly maintained by the researchers.

Consent

Written informed consent for publication of this report and accompanying images was obtained from the patient's father, in accordance with the journal's patient consent policy. As the patient is a minor, the patient's consent was waived.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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