Unexpected Primaquine-Induced Hemolysis in a G6PD Normal Patient: A Case Report from Nepal

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KEY CLINICAL MESSAGE

Primaquine can induce hemolytic anemia even in patients with normal G6PD levels. Routine monitoring of hemoglobin and bilirubin is essential during treatment to detect early hemolysis, emphasizing the need for caution with primaquine use despite normal G6PD screening results.

Abstract

Primaquine, an antimalarial drug, is essential for preventing relapses of Plasmodium vivax. However, it poses a risk of hemolytic anemia, particularly in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. This case report details a 27-year-old male with normal G6PD levels who developed hemolytic anemia following primaquine therapy for P. vivax malaria. Despite a normal quantitative G6PD analysis, the patient experienced a significant drop in hemoglobin, necessitating early discontinuation of the drug. This case highlights the potential for hemolysis in G6PD-normal patients, underscoring the importance of close monitoring and the limitations of current G6PD screening methods.

K E Y W O R D S

Infectious Diseases, General Medicine, Hematology, Toxicology

Introduction

Primaquine (PQ) is an 8-aminoquinoline drug which is used for malaria treatment and prophylaxis(1). Primaquine is the key anti-malarial drug that eliminates *Plasmodium vivax* hypnozoites and thus prevents relapses(1,2). In order to prevent relapse, *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known no to be G6PD deficient, and people with G6PD deficiency) are treated with a 14-day course (0.25-0.5 mg/kg body weight daily) of primaquine in all transmission settings(3). Though it is widely recommended, it is commonly not given to malaria patients because of its hemolytic toxicity in glucose-6-phosphate dehydrogenase (G6PD) deficient patients(4,5). Following primaquine drug therapy, the degree of hemolysis depends on the dose administered and the severity of the enzyme deficiency(6). The exact definitions for severe or clinically significant primaquine associated hemolysis or hemolytic anemia are not established and the diagnosis is based on decrease in hemoglobin level and/or clinical manifestations(5). WHO recommends G6PD activity assessment before administration of primaquine for radical cure(3). No diagnostic method is applied in hospital settings in low resource settings to screen G6PD enzyme activity prior to antimalarial treatment, and is usually detected during the course of primaquine therapy (7), when patients present to healthcare units with classical signs of hemolytic anemia(8). Approach to safe primaquine therapy hooks upon the ability to test and confirm G6PD normal status but the expensive technique which demands good laboratory conditions and qualified technicians restrict the access to these tests(7,9). We present a case of hemolytic anemia following PQ treatment in an individual with quantitative G6PD analysis within normal range.

Case Presentation:

A 27-year-old male driver presented to the emergency department of College of Medical Sciences Teaching Hospital with the chief complaint of fever and fatigue for 7 days, accompanied by 3 episodes of vomiting over 4 days, along with pain over the epigastrium. The patient was asymptomatic until the onset of the fever, which was intermittent and associated with chills and rigor. According to the patient, the fever was higher in the evening around 5 pm and relieved in the morning. The maximum recorded temperature was 103°F.

Upon examination, the patient was alert and conscious. His blood pressure was 110/60 mm Hg, measured on the right hand; respiratory rate - 20 breaths/min; axillary body temperature - 99.8°F; pulse - 107 beats/min; and SpO2 - 96%.

Investigation & Treatment:

A provisional diagnosis of malaria was made. A rapid malaria antigen test revealed positive for *Plasmodium vivax* , and serological tests for typhoid, dengue, scrub typhus, brucella, Leptospira, hepatitis, and HIV were negative. A blood sample was sent for G6PD analysis to a nearby laboratory. Laboratory investigations on the day of admission (day 0) revealed normal hemoglobin levels (12.8mg/dl), leukopenia (3370/mm3), thrombocytopenia (45,000/mm3), and a USG of the abdomen and pelvis revealed a few calculi in the lumen of the gallbladder, with one measuring 7 mm. He was admitted to the hospital and given IV paracetamol 1 gm, IV pantoprazole. He was also started on Tab. Chloroquine 10 mg per kg (600 mg for 2 days and 300 mg on the third day) and Tab. Primaquine 0.25 mg per kg (15 mg for 14 days) as per the National Malaria Treatment Protocol 2019(10).

On day 1, the definitive diagnosis of *Plasmodium vivax* malaria was confirmed from a peripheral blood smear. Spectrophotometry showed a total G6PD activity of 8.4 U/g Hb, which is well within the normal range. Hemoglobin had dropped to 11.7 g/dl, but within the normal range for the treatment of malaria. Investigations revealed hyperbilirubinemia (4.2 mg/dl). The cytology report revealed normocytic normochromic anemia with thrombocytopenia. There were no signs of icterus. Primaquine continued. On day 2, the lab results showed decrease in hemoglobin (9.8 g/dl), and hyperbilirubinemia (4.2 mg/dl). The drop in hemoglobin was still within the normal limit and since there were no clinical symptoms, PQ was continued. On day 3, hemoglobin dropped further to 9.5 g/dl. PQ was withheld and the patient was kept under close observation of his vital signs and further laboratory workup. The laboratory parameters improved from day 4.

Outcome and Follow-Up:

The patient was discharged on day 6 with Cefixime 400 mg BD and Doxycycline 100 mg BD for 7 days. On day of discharge, he had a hemoglobin level of 10.7g/dl. Genomic DNA sequencing of the G6PD gene couldn't be performed due to lack of necessary infrastructure.

Case Discussion:

Primaquine is a well-established treatment for Plasmodium vivax but is known to carry a risk of hemolytic anemia, particularly in patients with G6PD deficiency. The World Health Organization (WHO) recommends screening for G6PD deficiency before starting primaquine therapy(3). Previous studies have reported a small risk of hemolysis in patients with normal G6PD levels, with one study documenting a 0.3% (1/389) incidence of clinically significant hemolysis(11). While there have been reports of hemolytic anemia in patients who tested negative for G6PD deficiency using rapid diagnostic tests (RDTs), this case is unique in that the patient's G6PD levels were quantitatively within the normal range(12). This finding challenges the reliability of current laboratory screening methods and suggests that clinicians should exercise caution even when G6PD test results suggest a lower risk(11).

This case represents the first known instance of significant hemolytic anemia induced by primaquine in a patient with a normal quantitative G6PD analysis. Detailed monitoring was possible due to the patient being admitted to a tertiary care center. Daily hemoglobin levels were measured, allowing for the early identification of hemolysis and the timely discontinuation of primaquine after three doses. The occurrence of hemolytic anemia in this patient, despite a normal quantitative G6PD analysis, suggests that current screening methods may not be foolproof. It cannot be assumed that any G6PD field test has perfect sensitivity even in optimal laboratory settings(13). Possible causes could include operator error during sample preparation and processing, cold chain issues that compromised the integrity of the sample or screening kit, or a lack of adequate climate control to ensure that tests were conducted under appropriate conditions.

The delay in recognizing hemolysis in this case, due to the hemoglobin levels initially being within the expected range for anti-malaria treatment, further emphasizes the need for better early markers of hemolytic anemia(11). Identifying such markers could enable clinicians to make more informed decisions regarding the continuation of primaquine treatment quickly, thereby reducing the risk of severe hemolytic crises. The patient didn't show any physical signs and symptoms, and his urine color was normal even when his Hb dipped by almost 25% on day 4. Such absence of clinical sign and symptoms despite the significant decrease in hemoglobin suggests that there would be substantial risk of delayed presentation to the hospital if this case was managed on an outpatient basis without proper follow-up.

The National Malaria Treatment Protocol 2019 of Nepal encourages G6PD screening prior to 14-day PQ regimen but they aren't done routinely because of lack of necessary infrastructure, fears of additional costs, and very low incidence of PQ-induced severe hemolysis for a low-dose PQ regimen provided over an extended period(10,14). This case shows that exposing patients to PQ treatment even after quantitative G6PD testing exposes patients to an increased risk of hemolysis. It underscores the need for clinicians to remain vigilant when prescribing primaquine at all levels of G6PD. It highlights the limitations of current G6PD testing and the importance of close monitoring for signs of hemolytic anemia. In settings where daily monitoring is not feasible, such as outpatient care in low-resource environments, the risk of late presentation and severe anemia increases.

Conclusion:

Hemolytic anemia is a significant complication associated with the use of primaquine. Therefore, screening for G6PD deficiency is essential before initiating primaquine therapy, and heightened vigilance is necessary even when G6PD levels are within the normal range on screening. There is a need for clearer instructions on how to detect signs of hemolysis.

AUTHOR CONTRIBUTIONS

AK and SS wrote the case report and UK identified case and presented idea to publish this particular case report. AK, NL, IB and CB revised and edited it critically. UK and NR provide constant supervision. The

authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST

None

DATA AVAILABILITY STATEMENT

All the required data are available in the manuscript itself.

ETHICAL APPROVAL

None

CONSENT

Written informed consent was taken from patient for publication of the report.

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