



Drug-induced Hemolysis in G6PD Deficiency: an Unusual Presentation of a Common Clinical Condition

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency can present a diagnostic dilemma owing to the varying degrees of disease severity and the wide range of precipitating factors. Here, we report a case of a 56-year-old man who presented with signs and symptoms of heart failure and, during the course of treatment, developed intravascular hemolysis. On investigation, he was found to be G6PD deficient. Following discontinuation of the fixed-dose combination of isosorbide dinitrate and hydralazine, the clinical condition of the patient improved, and there were no further episodes of hemolysis. The case highlights the need for a high degree of suspicion of G6PD deficiency in patients with unexplained signs and symptoms of intravascular hemolysis.

KEYWORDS

G6PD deficiency; isosorbide dinitrate; hydralazine; intravascular hemolysis

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INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited and sex-linked enzymopathies (1). The identification of G6PD deficiency was the result of several converging events, one being the observation that some, but not all, individuals developed hemolysis on administration of 8-aminoquinoline antimalarials (2). The characteristic history and the availability of rapid diagnostic kits for detection of the enzyme deficiency have made the disease detection and management easy in the clinical setting, especially in malaria endemic areas, where the patients typically present with acute symptoms of intravascular hemolysis following culprit drug administration. Owing to the varying degrees of disease severity and the wide range of precipitating factors, the disease sometimes poses a diagnostic dilemma (3–5). Here, we report an unusual presentation of a case of drug-induced hemolysis due to G6PD deficiency in a 56-year-old patient presenting with symptoms of heart failure.

CASE REPORT

A 56-year-old male patient of Asian race presented to the General Medicine outpatient department of Kasturba Medical College Hospital, Mangalore, India, with complaints of swelling of both feet and breathlessness on exertion since four days. He was a known case of type 2 diabetes mellitus on oral medications, glimepiride and metformin. There was no significant past history or family history of any medical illness; no history of hospitalization or prolonged medication intake. On examination, his pulse rate was 120 beats per min and blood pressure was 128/80 mmHg. Jugular venous pulse was elevated, and there was bilateral pitting edema up to the ankle. On systemic examination, there were bilateral basal crepitations, hepatomegaly, and third heart sound was heard in the mitral area. Considering the presenting complaints and the physical examination findings, cardiologist opinion was sought, and two-dimensional echocardiography was done. The echocardiography was suggestive of con-

gestive cardiac failure with ischemic heart disease and severe left ventricular dysfunction with an ejection fraction of 30%. A thin rim of pleural and pericardial effusion was also seen. Ultrasound abdomen showed a normal-sized spleen with minimal ascites and mild pleural effusion. Liver was 14 cm in size with normal echotexture. He was started on tablet digoxin 0.25 mg half-tablet on alternate days, a fixed-dose combination of isosorbide dinitrate 20 mg plus hydralazine 37.5 mg thrice daily, injection furosemide 20 mg intravenously thrice daily, low dose aspirin 75 mg once daily, atorvastatin 10 mg once daily, and ramipril 5 mg once daily. On day 1, the haemoglobin level was 118 g/L; the rest of the blood parameters were normal. On day 2 of the in-hospital stay, he complained of 4–5 episodes of vomiting, which was treated symptomatically. On day 3, the vomiting persisted, and on day 4, physical examination revealed icterus; however, the urine appeared clear. The patient was scheduled to undergo coronary angiography, but the procedure was withheld, and blood investigations ordered, which showed a haemoglobin level of 94 g/L with a total bilirubin of 64.12 micromol/L. The patient was evaluated to ascertain the cause for the drop in hemoglobin level. Stool occult blood was found to be negative. Peripheral smear showed normocytic normochromic anemia with features suggestive of hemolytic anemia. Also, elevated total bilirubin was seen, predominantly unconjugated. The possibility of drug-induced intravascular hemolysis was considered, and a workup for G6PD deficiency was done. Using the dye decolorization test, the patient was found to be positive for G6PD deficiency. Among the prescribed medications, the fixed-dose combination of isosorbide dinitrate plus hydralazine was suspected to be the culprit drug based on the limited evidence available. The drug was withheld, and the rest of the medications were continued. On days 7 and 8, there was a further drop in hemoglobin level to 62 g/L. The opinion of a hematologist was sought, and two units of packed cell transfusion were given. Then, the patient was started on antioxidants and vitamin supplements. No further drop in the hemoglobin level was observed on days 7 and 8, and he was discharged from the hospital with the following medications: ramipril, trimetazidine, furosem-

Tab. 1 Laboratory investigations performed during the hospital stay.

Day of in-hospital stay	Total bilirubin (micromol/L)	Direct bilirubin (micromol/L)	Indirect bilirubin (micromol/L)	Haemoglobin (g/L)	Other laboratory investigations
Day 1	–	–		118	–
Day 4	64.12	17.78	46.34	94	Coombs test – negative Mean corpuscular volume 75.1 fl (reference range, 83.0–101.0) LDH level 354 U/L (reference range, 0–250)
Day 5	86.18	23.42	3.67	84	Peripheral smear – microcytic hypochromic with neutrophilic leucocytosis and features of hemolysis. No Heinz bodies seen. G6PD – decolorization > 6 hours
Day 6	87.21	30.95	3.29	75	–
Day 7	108.58	56.60	3.04	74	Stool occult blood – negative
Day 8	51.64	26.16	1.49	62	Blood transfusion given
Day 9	44.28	24.96	1.1	82	–

G6PD, glucose-6-phosphate dehydrogenase

ide, glimepiride + metformin, ivabradine, pantoprazole, ferrous sulphate, folic acid, and vitamin C tablets. During the follow-up visit two weeks later, his hemoglobin level was 112 g/L, and he was hemodynamically stable. The haemoglobin increased to 130 g/L after a month, suggesting that the initial anemia was due to iron deficiency. Table 1 shows the important lab investigation values during the course of the hospital stay.

DISCUSSION

G6PD is not an uncommon condition in India. The frequency of occurrence in India is 8.5% (6). This is in agreement with the global estimated prevalence of 8% in malaria endemic countries (7). G6PD deficiency can be classified into five classes with class I representing severe deficiency, characterized by chronic nonspherocytic hemolytic anemia and normal erythrocyte function (8). Class IV corresponds to normal enzyme activity and, class V, increased activity. Class II G6PD deficiency, with less than 10% of normal enzyme activity, is more common in Asians and the Mediterranean population. The case reported here is unique in that this middle-aged patient had no previous history suggestive of hemolysis and, during the treatment of the presenting complaints, developed intravascular hemolysis to drug(s) not commonly implicated in causing hemolysis. Except for a report of hemolysis in two patients, there is no substantial evidence to avoid the use of isosorbide dinitrate (9). While some suggest avoiding the drug due to the possible risk of hemolysis, not all have included it in the list of drugs to be avoided (10, 11). There is, however, a recent report of late-life presentation of hemolysis due to G6PD deficiency following administration of intravenous nitroglycerin (12). There is limited evidence implicating hydralazine in G6PD hemolysis (13–15). In fact, we were unable to find any reports of hydralazine-induced hemolysis in G6PD deficiency. The drug has been implicated in hemolysis due to the formation of immune complexes. However, this mechanism is unlikely to be responsible for the acute intravascular hemolysis seen in this patient (13). Also, the Coombs test was negative. The drug monograph of hydralazine states the following hematological adverse reactions: Blood dyscrasias, consisting of a reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura (16). There is no recommendation regarding its use in patients with G6PD deficiency. The initial episode of vomiting was suspected to be due to the irritant effect of the drugs prescribed. However, the persistence of vomiting followed by the occurrence of jaundice raised the suspicion of intravascular hemolysis. We decided to evaluate the G6PD status of the patient as no other cause for intravascular hemolysis was apparent. Dechallenge confirmed the diagnosis as there was no further intravascular hemolysis, barring the immediate period following drug withdrawal, as determined via the hemoglobin levels, and there was an improvement in the hemoglobin status subsequently despite the continuation of all the other drugs. While furosemide is also known to cause hemolysis in G6PD deficient patients, the improvement in the patient's condition despite the con-

tinuation of furosemide rules it out as the precipitating drug (17). A rechallenge was not performed as there was no pharmacological compulsion for continuing with isosorbide dinitrate plus hydralazine and, hence, would be unethical. Based on the WHO-UMC causality assessment scale and the Naranjo scale, the causality was judged to be probable. We were unable to determine the class of G6PD enzyme variant and confirm which of the two drugs in the fixed-dose combination caused the adverse event.

This case highlights the importance of suspecting the presence of G6PD deficiency in an unrelated clinical setting precipitated by a drug not well known to cause oxidative hemolysis. In population with a G6PD deficiency of 3–5% or more in males, screening of new born infants is recommended (8). Fluorescent spot test, a qualitative assay, is a suitable test for the detection of G6PD deficiency, as compared to the more definitive quantitative tests, in heterozygous males and homozygous females in high-burden, resource-poor areas (18). Early recognition using simple laboratory tests will avoid unnecessary investigations and prolonged hospital stay.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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