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CASE REPORT

Uncovering an undisclosed diagnosis: a glucose-6-phosphate dehydrogenase deficiency diagnosis in a critically ill adult

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency affects over 400 million people worldwide. The most common variant of G6PD deficiency in the United States is the A-variant, which is present amongst African-Americans. Most people with this variant, however, do not experience severe hemolysis unless under extreme circumstances. Here, we present the case of a 44-year-old African-American male who under circumstances of multiple admissions for critical illness eventually presented with a masked diagnosis of G6PD deficiency.

KEYWORDS
G6PD, hemoglobinopathies, hemolysis

1 | INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked inherited disorder that affects over 400 million people worldwide of primarily Mediterranean, African, and Asian ancestry. In certain conditions, including acute infections, administration of oxidizing medications, or consumption of fava beans, G6PD deficiency may precipitate a hemolytic crisis [1]. G6PD deficiency is currently divided into five WHO grade classifications: WHO grade I has < 10% of normal enzyme activity and chronic hemolytic anemia, WHO grade II has < 10% of normal enzyme activity with a severe enzyme deficiency, WHO grade III exhibits 10%–60% of enzyme activity which is mild to moderate with intermittent hemolysis, WHO grade IV has 60%–100% enzyme function, and WHO grade V has twice normal increased enzyme function. This classification, however, is currently under review and the proposition of combining grades II and III has been discussed [2]. The most common variant of G6PD deficiency in the United States is the A- variant, which is present among African-Americans, and is considered WHO class III [2]. Most people with this variant, however, do not experience severe hemolysis unless under extreme circumstances.

2 | CASE REPORT AND DISCUSSION

Here, we present the case of a 44-year-old African-American male with atrial flutter on apixaban, hypertension, stage IV chronic kidney disease (CKD), and diastolic cardiomyopathy who was admitted to the neurological intensive care unit (NICU) with sudden-onset aphasia and right-sided weakness in the setting of hypertensive urgency (blood pressure 250/180). The patient had no personal or family history of jaundice, need for splenectomy, or known inherited hemolytic anemia. A non-contrasted computed tomography (CT) scan showed a left thalamic hemorrhagic stroke with intraventricular extension. Due to the development of increased intracranial pressure, he underwent extra ventricular drain (EVD) placement; within 10 h of presentation, he was intubated for airway protection in the setting of worsening respiratory and mental status.

On hospital day (HD) 5, the patient was noted to be hypoxic by his pulse oximeter to 80%–85% (SpO_2) on an FiO_2 of 70% via mechanical ventilation; however, an arterial blood gas (ABG) test showed a normal arterial oxygen level of 98 mmHg (PaO_2). The methemoglobin

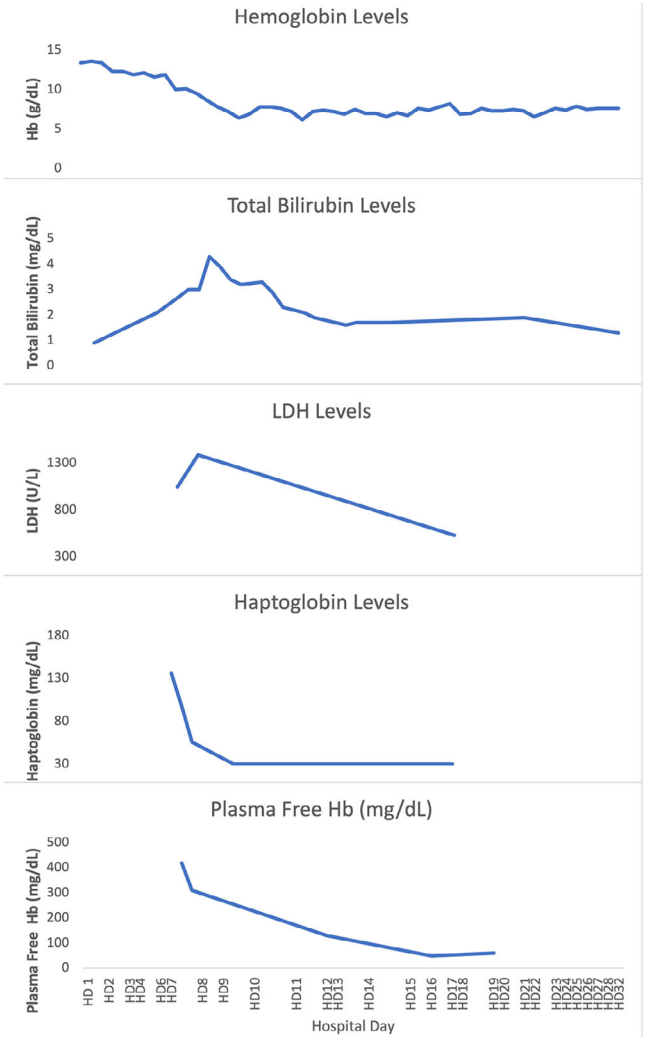

FIGURE 1 Trends in hemolytic parameters during the hospital stay for the patient with G6PD deficiency diagnosis. G6PD, glucose-6-phosphate dehydrogenase.

level peaked at 7%; a review of his medication list during and prior to admission was not suggestive of a culprit agent. At this point, a decision to not administer methylene blue was made. A complete blood count (CBC) was significant for hemoglobin (Hb) 10 gram/deciliter (g/dL), a drop of 1.5 g/dL in 13 h and down from 13.4 g/dL upon admission. An absolute reticulocyte count was mildly elevated at 106,000/mcL. Lactate dehydrogenase (LDH) and plasma-free Hb were markedly elevated at 1,050 units/liter (U/L) and 420 mg/dL, respectively, while an initial haptoglobin was normal at 136 mg/dL, but became undetectable 48 h later with total/indirect bilirubin following a similar trend (Figure 1). Due to concern for an intrinsic red cell disorder causing acute intravascular hemolysis, including either an inherited or autoimmune hemolytic anemia, hematology was consulted. Review of the peripheral smear, which was obtained prior to any blood transfusions, was significant for few spherocytes and frequent blister and bite cells (Figure 2), raising concern for G6PD deficiency. Direct antiglobulin test (DAT) was positive (1+) for IgG, and elution was negative. An

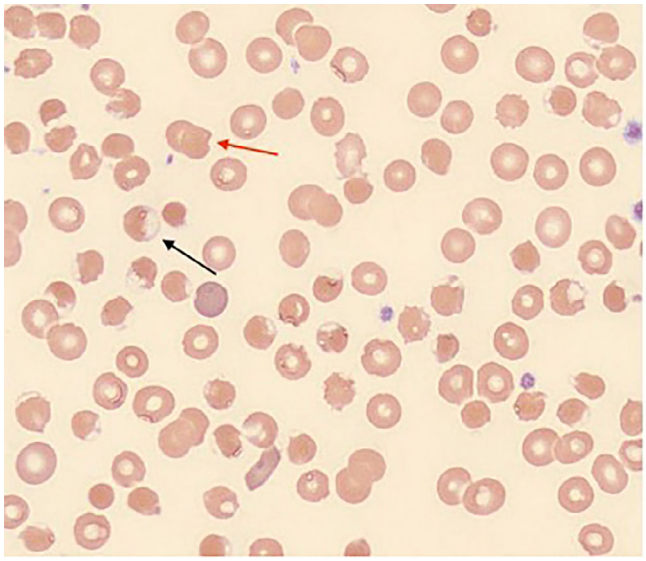

FIGURE 2 Peripheral blood morphology. This is an image of the peripheral smear that shows the presence of hemighost or blister cell (black arrow) and bite cells (red arrow). This can be seen in the acute phase of active hemolysis in G6PD deficiency. G6PD, glucose-6-phosphate dehydrogenase.

initial G6PD quantification using the kinetic method and measuring absorbance at a wavelength of 340 nm was at the low end of the normal range at 138 units/trillion RBC. A thorough workup of disorders causing intravascular hemolysis was negative, including flow cytometry for a paroxysmal nocturnal hemoglobinuria clone. Due to the high suspicion for G6PD deficiency and further decline in hemoglobin to a nadir of 6.4 g/dL, necessitating packed red cell transfusions, *G6PD* gene sequencing was sent and further use of oxidative drugs was avoided.

Unfortunately, the patient's condition was complicated by the development of acute respiratory distress syndrome, rhabdomyolysis complicated by acute kidney injury necessitating continuous renal replacement therapy, acute liver injury and *Clostridium difficile* infection. Throughout his stay in the ICU, plasma free Hb levels were followed due to the concurrent presence of active liver injury which also elevated LDH and lowered haptoglobin levels. However, as conservative measures were enacted and infection treatment ensued, the patient's free Hb, LDH, methemoglobinemia, and blood transfusion needs also improved. He slowly stabilized and improved after these events and was ultimately transferred to a long-term acute care hospital on HD 28. His *G6PD* gene sequencing returned hemizygous for the A-deficiency (p.[Val68Met; Asn126Asp]) consistent with a diagnosis of G6PD deficiency [3].

Based on the genetic analysis, lab abnormalities, and particularly the peripheral smear, it was determined that the patient did in fact have G6PD deficiency. His initial G6PD level were within normal limits, however this is well-known phenomenon can occur with active hemolysis due to the presence of significant reticulocytosis, which increases the catalytic activity of G6PD as reticulocytes, unlike mature red blood

cells, can still produce G6PD [4]. Typically, patients with a G6PD variant A-deficiency do not experience severe hemolysis unless under the circumstances of extreme critical illness, which was the case for this patient [3]. Although he had known cardiac disease and CKD, neither had been particularly decompensated in his past which masked his diagnosis, in addition to the lack of any offending medications. The combination of these with his intracranial hemorrhage and severe sepsis likely precipitated his hemolytic crisis. There is evidence that also suggest that those with stroke and G6PD deficiency have poorer outcomes, however this was only studied with respect to acute ischemic strokes and not hemorrhagic strokes [5].

This case demonstrates how a diagnosis of G6PD can be unmasked in an ICU setting. We have alluded to the fact that our patient likely is a WHO grade III, though we realize that newer classifications are being discussed that support a merger of the grade II and grade III variants. Our case study adds to this discussion. In general, there should be a high index of suspicion to investigate further when there is a discrepancy between the SpO_2 and PaO_2, even without a history of hemolysis, as was the case with this patient. G6PD deficiency can cause this inconsistency as well as methemoglobinemia in patients [6, 7]. G6PD is responsible for catalyzing the NADPH, which has several functions, one of which is preventing oxidative damage by keeping hemoglobin in the ferrous state. When patients undergo hemolysis in the setting of G6PD deficiency, it is due to oxidative damage that occurs to the hemoglobin molecule itself. The mechanism by which G6PD causes methemoglobinemia is via inhibition of NADPH-flavine reductase which precludes the reduction of methemoglobin and in that state is unable to bind to oxygen which causes hypoxia to organs [6]. On further co-oximetry testing, there were no other causes that could have led to this SpO_2 and PaO_2 discrepancy. Our patient's level of methemoglobinemia, while elevated, did not reach the level of greater than 20%–30% in which treatment would be indicated [8]. The mainstay of the treatment of methemoglobinemia is typically methylene blue, which would have exacerbated his G6PD hemolysis given that it requires the enzyme G6PD to function properly [9].

3 | CONCLUSION

Our case highlights the importance of a thorough investigation for seemingly disconnected abnormal laboratory values in a critically ill patient. G6PD deficiency is often asymptomatic in heterozygous females, but in hemizygous males, can present as a hemolytic crisis later in life during a severe illness or stressor, depending on the genetic mutation/degree of enzyme impairment. Since we were able to diagnose our patient early on, we were able to better tailor his medical management to the point where he was able to leave the ICU and continue to recover.

AUTHOR CONTRIBUTIONS

Brittany M. Kasturiarachi participated in the patient's care and wrote manuscript and provided manuscript edits. David Robinson participated in the patient's care and provided manuscript edits. Kristine Karkoska participated in the patient's care and provided manuscript edits. Jahnavi Gollamundi participated in the patient's care and provided manuscript edits and obtained images of the patient's peripheral smear.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The appropriate consent forms were obtained from our patient's next of kin and have been uploaded with this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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