CASE REPORT

COVID-19 infection unmasking glucose-6-phosphate dehydrogenase deficiency

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Learning points for clinicians
Glucose-6-phosphate dehydrogenase (G6PD) enzyme plays a vital role in hexose monophosphate shunt pathway, essential for energy metabolism of red blood cells (RBCs). G6PD deficiency predisposes the destruction of RBCs from oxidative stress involving illnesses, drugs and chemicals. Coronavirus disease 2019 posed new challenges in diagnosing G6PD deficiency, given its association with hemolysis.

Case presentation
A 39-year-old African American male was admitted for coronavirus disease 2019 (COVID-19) infection and diabetic ketoacidosis. His vital signs were stable, except for hypoxia requiring 4–5 l on nasal cannula. He was started on insulin drip and transitioned to subcutaneous insulin. Remdesivir was started for COVID-19 infection. Hemoglobin was 13.6 g/dl on admission, but started dropping, with a nadir hemoglobin of 6.4 g/dl in 7 days. Haptoglobin <8 mg/dl, Lactate Dehydrogenase (LDH) >2000 U/l and reticulocytosis, suggestive of hemolytic anemia. No other cytopenias were seen. A direct antiglobulin test was negative and there was no prior history of blood transfusion or hematological disorders. Peripheral smear showed blister and bite cells (Figure 1) concerning for glucose-6-phosphate dehydrogenase (G6PD) deficiency. His G6PD level was found to be low at 3.9 U/g Hb (39% of mean normal). He received one unit of red blood cell (RBC) transfusion and was started on oral folic acid daily. Hemoglobin improved with COVID-19 infection recovery. The patient was discharged with stable hemoglobin. Repeat G6PD levels done in 4 weeks showed low activity at 2.3 U/g Hb (23% of mean normal). Gene sequencing showed hemizygosity for Variant A-(202), Ferrara I, confirming WHO class III variant of G6PD deficiency. The patient was counseled extensively on drugs to avoid and the possibility of hemolysis from stressful situations and infections.

Figure 1. Blister cells (arrows) and bite cells (arrow).
Discussion

G6PD deficiency is an X-linked recessive disorder and its gene is located on the X chromosome (band Xq28); the deficiency primarily affects African American males. Heterozygous female carriers can experience symptoms based on the degree of lyonization. The G6PD enzyme protects RBCs from oxidative stress (acute microbial illnesses), drugs (primaquine, hydroxychloroquine), chemicals (amyl nitrite, mothballs) and foods (fava beans) in Hexose Monophosphate Shunt Pathway and its deficiency leads to hemolysis. Clinical presentation varies from asymptomatic state to episodic anemia to chronic hemolysis.

G6PD deficiency has been classified into variants based on the magnitude of the enzyme deficiency and the severity of the hemolysis (see Table 1).

G6PD status is important in regulating reactive oxygen species (ROS) by maintaining redox homeostasis and keeping ROS at normal levels, as ROS at higher levels are cytotoxic. G6PD is required for the maintenance of the innate immune response, inflammasome activation and pathogen clearance through redox homeostasis; its deficiency may enhance viral infections.

COVID-19 is also influenced by genetic variants of G6PD deficiency, which, in turn, are related to an impaired immune response. Multiple factors (age, comorbidities, ethnicity) influence the morbidity and mortality of COVID-19 infections. Age-associated accumulation of oxidative stress from COVID-19 and impaired redox reactions from G6PD can worsen the severity of viral infections. It is unclear if hydroxychloroquine causes hemolysis in G6PD-deficient people with COVID-19; its use should be avoided if in doubt. The use of antioxidants and some anti-aging drugs, along with COVID-19 vaccinations, is promising for COVID-19 infection.

In our patient with this class III G6PD variant, hemolysis resolved and Hb normalized with supportive care and recovery from the infection, and no other triggers were identified.

Conclusion

G6PD is essential for an adequate immune response. It is important to check G6PD status in COVID-19-infected patients with hemolytic anemia. This is particularly important with ethnic groups predisposed to having deficiency, as it causes impaired cellular responses, viral proliferation and worsening oxidative damage.

Conflict of interest: None declared.

References

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| Table 1. Classification of G6PD deficiencies following WHO recommendations |
|------------------|------------------|------------------|
| G6PD variant*   | Enzymatic activity | Clinical symptoms       |
| Class I         | <1% or not detectable | Severe hemolytic anemia |
| Class II        | <10% (severe enzyme deficiency) | Intermittent hemolysis with infection, drugs or chemicals |
| Class III       | 10–60% (moderate enzyme deficiency) | Intermittent hemolysis with infection, drugs or chemicals |
| Class IV        | 60–90% of normal activity | No hemolysis |
| Class V         | >110%, increased enzymatic activity | No hemolysis |

*Other variants that are identified are G6PD A, variant similar to class III and G6PD Mediterranean variant, similar to class II deficiency.