

Female with Glucose-6-Phosphate Dehydrogenase Deficiency Combined with Hereditary Spherocytosis

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ABSTRACT

G6PD deficiency is an x-linked recessive disease with abnormally low levels of glucose-6-phosphate dehydrogenase. As it is an X-linked disorder, the clinical manifestations of the disease are most commonly seen in males. However, heterozygous females can be affected in the presence of unfavorable lyonization. Hereditary spherocytosis is an inherited hemolytic anemia that results from a cytoskeletal defect in the red blood cell membrane. It is more commonly observed in North Americans and among people of northern European ancestry and is less commonly seen in African Americans or people of Southeast Asian ancestry. This case demonstrates an African American female patient with G6PD deficiency with a coexisting hereditary spherocytosis. To our knowledge, this is the first reported case of combined G6PD deficiency with hereditary spherocytosis in an African American female patient. Following basic ethical tenets, permission was obtained from the patient to write up and discuss this case and it was written in accordance with the Cleveland Clinic's HIPAA De-Identification Policy.

Keywords: Glucose-6-Phosphate Dehydrogenase, Hereditary Spherocytosis

INTRODUCTION

G6PD deficiency is an x-linked recessive disease with abnormally low levels of glucose-6-phosphate dehydrogenase, an enzyme involved in the production of NADPH, which helps prevent oxidative damage of red blood cells. Oxidative stress can lead to damage of the erythrocyte membrane, which can lead to intravascular and extravascular hemolysis. Since it is an X-linked disorder, it is most commonly seen in males. However, heterozygous females can be affected in the presence of unfavorable lyonization. G6PD deficiency is prevalent in 400 million worldwide. However, it is mostly asymptomatic, depending on residual enzyme activity. Hereditary spherocytosis is an inherited hemolytic anemia that results from a cytoskeletal defect in the red blood cell membrane. Frequently affected proteins of the cytoskeleton include spectrin and ankyrin. It is autosomal dominant inheritance in 75% of cases, and the incidence is 1/5000 in the United States. It is observed in North Americans

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and among people of northern European ancestry, and it is less commonly seen in African Americans or Southeast Asian populations. The following case demonstrates a female patient with G6PD deficiency with a coexisting hereditary spherocytosis. To our knowledge, this is the first reported case of combined G6PD deficiency with hereditary spherocytosis in an African American female patient.

CASE

A 46-year-old African American female with a past medical history significant for stage 1 pulmonary sarcoidosis, COPD and G6PD deficiency which was diagnosed at age 21 and was followed regularly in the outpatient hematology clinic. The patient typically reports tea colored urine, scleral icterus, and mild fatigue. She reports a family history significant for hemolysis of unknown etiology in her father and known G6PD carrier status in her daughter. She denied following G6PD dietary restrictions.

Physical exam showed splenomegaly, mild icterus and conjunctival pallor. Complete blood count revealed mild anemia with a hemoglobin of 8.7g/dL and MCV 90.7fL. Labs also revealed a high absolute reticulocyte count of 0.463M/uL, % reticulocyte of 13.2%, elevated LDH (275 U/L),

elevated total bilirubin (2.9 mg/dL), elevated unconjugated bilirubin (1.9 mg/dL) and low haptoglobin (<10 mg/dL). A peripheral blood smear demonstrated spherocytes and nucleated red blood cells (RBC) (Figure 1). Classically, G6PD deficiency has aggregates of precipitated hemoglobin called Heinz Bodies. However, they are not typically seen on the standard Wright's stain as they blend in with the rest of the hemoglobin present on the slide. CT scan of abdomen and pelvis demonstrated splenomegaly with 16cm in craniocaudal diameter. Otherwise, the scan was normal. G6PD deficiency screen test was positive, and G6PD quantitative was low at 4.6 U/g Hb, normal 9.9-16.6 U/g Hb. Peripheral blood with no alpha globin gene detected. Hemoglobin electrophoresis with no abnormal hemoglobin detected. Bone marrow biopsy demonstrated hypercellular bone marrow (greater than 90%) due to erythroid hyperplasia. The karyotype was 46XX, and flow cytometry was normal. Iron stain was present with no ringed sideroblasts. Normocytic anemia with anisocytosis, spherocytes, and rare blister cells were noted. RBC Band 3 Protein Reduction in Hereditary Spherocytosis was ordered for evaluation of spherocytosis. A reduction in red blood cell surface band 3 fluorescence was detected.

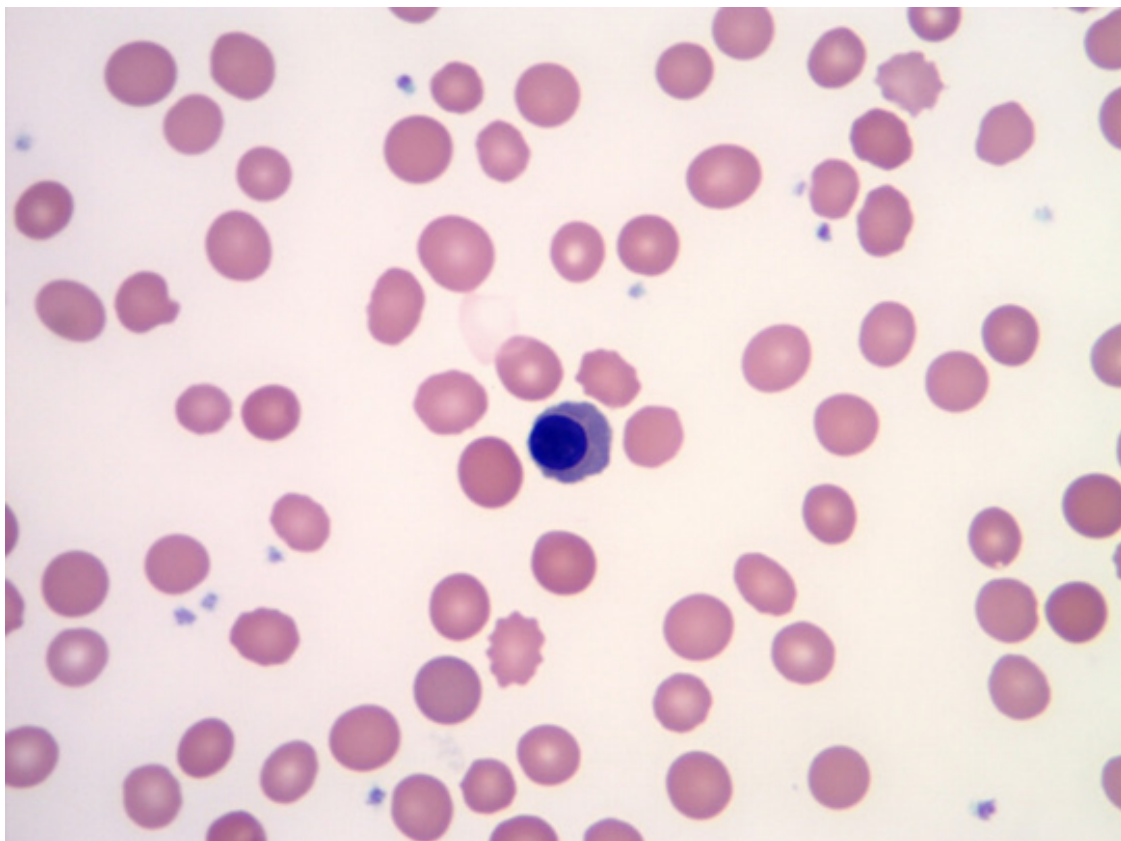


Figure 1. Peripheral blood smear with spherocytes and a nucleated red blood cell.

DISCUSSION

To our knowledge, this is the first reported case of G6PD deficiency in combination with hereditary spherocytosis in a female. G6PD deficiency is a X-linked recessive hereditary disease with low levels of glucose-6-phosphate dehydrogenase [1,2]. There are over 200 known G6PD mutations and epidemiologically, G6PD deficiency affects over 500 million people worldwide making it one of the most common enzyme deficiencies [3]. G6PD deficiency is observed in various rates throughout the world with the highest prevalence seen in Asian, African, Mediterranean and Middle Eastern populations [4]. G6PD is an enzyme in the pentose phosphate pathway involved in the production of NADPH that maintains glutathione in a reduced state during oxidant stress [1,2]. Lower levels of G6PD leave red blood cells susceptible to hemolysis during oxidant stress such as oxidant drugs, fava beans, or infection (1). Female patients that are heterozygous for G6PD deficiency can experience lyonization which can lead to red cell mosaicism with both normal and deficient phenotypes present simultaneously [5]. The cell population that is G6PD deficient has a propensity to lyse during exposure to an oxidant trigger [2]. Clinical manifestations of G6PD are usually seen in hemizygous males, however skewed lyonization can result in clinical manifestations in females. Individuals with G6PD deficiency are typically asymptomatic outside of experiencing acute hemolytic anemia in response to the previously mentioned triggers. Supportive care and avoidance/removal of triggers is the recommended treatment; however, transfusions may be required during episodes of acute hemolytic anemia [6].

Hereditary spherocytosis (HS) is an inherited hemolytic anemia that results from a cytoskeletal defect in the red blood cell membrane. In North America and among people of northern European ancestry, HS is seen in approximately 1 per 2000 individuals [7]. Hereditary spherocytosis is less commonly seen in African Americans or people of Southeast Asian ancestry [8]. Defects of RBC membrane proteins compromise the linkage between the inner membranes to the outer lipid bilayer [9]. These defects impair the plasticity of the erythrocyte and result in an osmotically fragile and spheroidal-shaped RBC called a spherocyte [9]. The most common affected membrane proteins affected are ankyrin, band 3 and spectrin [10]. Classically, patients present with varying degrees of anemia, splenomegaly, jaundice, reticulocytosis and family history of hemolytic anemia [10,11]. Guideline management for HS includes folate supplementation in patients with moderate to severe HS [12]. Surgical management with splenectomy is indicated based on symptoms as well as laboratory values. Splenomegaly alone is not an indication for splenectomy as most

patients with HS will have mild to moderate splenomegaly. Splenectomy is recommended when Hgb is 6.0-8.0g/dL, the reticulocyte count is greater than 10%, Bilirubin is >51 $\mu\text{mol/L}$, and spectrin molecules per erythrocytes (% of normal) between 40 and 60% [13]. While effective in reducing hemolysis, splenectomy does increase a patient's lifetime risk of infection from encapsulated organisms [14]. As such, a careful risk vs. benefit discussion should be had with the patient.

For this patient, a repeat ultrasound of the spleen was ordered and revealed stable splenomegaly. The treatment plan was to monitor hemolysis labs, monitor spleen size and symptoms from splenomegaly, encourage adherence to G6PD diet, give supplemental folic acid and to transfuse packed red blood cells if patient has symptomatic anemia or if hemoglobin is less than 7.0g/dL. Furthermore, genetic counseling was recommended.

CONCLUSION

In conclusion, a comprehensive review of the patient and their labs is necessary for quality patient care. This case demonstrates the importance of broadening the differential diagnosis and evaluating the peripheral blood smear, especially when the leading diagnosis does not fully explain the clinical picture. Though transient splenomegaly is common in G6PD deficiency, this patient's splenomegaly was initially attributed to her disease and additional history of stage 1 pulmonary sarcoidosis. The persistent reticulocytosis and anemia were attributed to the patient's lack of adherence to a G6PD diet. However, further workup did reveal the additional diagnosis of HS. This additional diagnosis clarified the clinical picture and ultimately changed this patient's treatment options with the consideration of splenectomy.

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