

## CLINICAL VIGNETTE

# Sulfonylurea-Induced Hemolysis in a Patient with G6PD Deficiency

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### Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a rare X-linked disorder commonly associated with hemolysis.<sup>1-6</sup> Common triggers for hemolysis include infection, stress, food, and medications.<sup>7</sup> The most commonly associated medications include sulfa drugs and anti-malarial agents, and this can also be seen with sulfonylureas.<sup>4,8,9</sup> We present a 66-year-old man with acute hyperproliferative anemia from presumed sulfonylurea-induced extravascular hemolysis in the setting of newly diagnosed G6PD deficiency.

### Case Presentation

A 66-year-old man from Abu Dhabi presents to establish primary care. His only symptoms were intermittent nausea and heartburn for 1-2 years without abdominal pain or blood in his stools. Past history includes DM2, hyperlipidemia, and benign prostatic hypertrophy. Initial labs revealed acute normocytic anemia with Hgb 8.2 g/dL (13.5-17.1). Three weeks prior when establishing care with endocrinology his Hgb was 10.5 g/dL. Repeat Hgb the following day was 7.9 g/dL with a reticulocyte index of 5.82% (0.5-2.5%). With concerns for possible gastrointestinal bleeding, he was directed to the emergency department for further evaluation.

Upon presentation to the emergency department his vital signs included a temperature of 36.8, heart rate 104, respiratory rate 16, blood pressure 142/69, and SpO2 99% on room air. Physical exam revealed a thin frail male in no distress. He had no conjunctival pallor or scleral icterus and his cardiopulmonary exam was unremarkable. His abdomen was soft, nontender, without organomegaly. His rectal exam was without masses, hemorrhoids, fissures, or blood in his stool. Repeat labs were notable for Hgb of 7.7 g/dL, and he was admitted. Intravenous access was established, he was started on IV pantoprazole and kept NPO. Additional labs including iron studies, coagulation panel, vitamin B12, folate, haptoglobin, lactate dehydrogenase, metabolic panel, thyroid stimulating hormone, and urinalysis were unremarkable. *H. pylori*, Parvovirus B19, and HIV also returned negative. Endoscopy and colonoscopy on hospital day two and three respectively were normal, and he remained asymptomatic. He refused transfusion and further inpatient evaluation and was discharged with close outpatient follow up. Hgb on discharge was 6.8 g/dl and was 8.5 g/dl at one week follow up. Additional ambulatory testing one week after discharge revealed a very low G6PD level of 0.6 U/g Hgb (9.9 to 16.6 U/g Hgb). When discussing this diagno-

sis, the patient recalled previously being diagnosed with G6PD deficiency after a similar episode of hemolysis after eating fava beans. He also started glipizide 5 mg one month prior to presentation. Glipizide was discontinued and three weeks after discharge his Hgb improved to 9.9. He was subsequently started on sitagliptin-metformin 50-1000 mg BID and canagliflozin 100 mg qday and his HbA1c improved from 11.7 one month prior to 5.0. His fasting glucose at that time was 143 mg/dL, yielding a glucose to HbA1c ratio of 28.6. Timeline of events displayed in Figure 1.

### Discussion

The patient presented with acute hyperproliferative normocytic anemia, most commonly caused by acute blood loss or hemolysis, prompting endoscopy despite no evidence of bleeding on exam. After normal endoscopy and colonoscopy, he was evaluated for extravascular hemolysis. Low G6PD levels and recent addition of glipizide were consistent with his course. Improvement after discontinuation of the offending agent further supported this explanation. It was possible that hemolysis occurred earlier and was not captured at the time of testing.

G6PD deficiency is a rare X-linked enzymatic disorder affecting red blood cells that affects approximately 400 million people worldwide.<sup>3-6</sup> It is most commonly seen in parts of Africa, Asia, the Mediterranean, and the Middle East.<sup>10</sup> This disorder is commonly associated with hemolysis, which results from a reduction in glutathione leading to the denaturation of Hgb in the setting of oxidative stress.<sup>11</sup> The associated hemolysis is often asymptomatic and predominantly extravascular resulting from rigid and non-deformable red blood cells that are susceptible to destruction by reticuloendothelial macrophages in the bone marrow, spleen, and liver.<sup>12</sup> Symptomatic patients often experience jaundice, pallor, abdominal pain, and dark urine. Hemolysis often occurs within 2-4 days of drug ingestion and is associated with an average drop in Hgb of 3-4 g/dL.<sup>12</sup> Most cases are self-limiting with hemolysis resolving within 7 days.<sup>13</sup> Common triggers include infection, stress, food such as fava beans, and, as seen in this case, medications.<sup>7</sup> The most commonly associated medications include sulfa drugs and anti-malarial agents, however, this is also seen with sulfonylureas.<sup>4,8,9</sup>

G6PD deficiency can also lead to a reduction in HbA1c due to increased red blood cell turnover during hemolysis. While the

patient was started on pharmacologic therapy for the management of his diabetes, it is likely that hemolysis contributed to the improvement seen in his HbA1c. Due to the impact of hemolysis on HbA1c, an elevated fasting glucose to HbA1c ratio (26.54 vs. 18.36) has been shown to be a good indicator for G6PD deficiency and can help support the diagnosis.<sup>14</sup> The ratio of 28.6 seen in this case further supports hemolysis from G6PD deficiency.

Hemolysis is a known side effect of sulfonylureas and is reported in approximately 1% of cases.<sup>15</sup> The most common etiology is extravascular hemolysis in the setting of G6PD deficiency.<sup>15</sup> However, there are also reports of immune-complex mediated hemolysis.<sup>7</sup> Limited information exists on rates of hemolysis or cross-reactivity with other sulfonylurea in patients with G6PD deficiency. Treatment involves discontinuation of the offending agent. G6PD testing should be considered in patients with anemia after starting sulfonylurea agents, or those with a family history of anemia. Sulfonylurea agents should be used cautiously in patients with known G6PD deficiency.

### Conclusion

Acute hemolytic anemia is a rare side effect of sulfonylureas seen in patients with G6PD deficiency. Prompt recognition is essential so the offending agent can be discontinued.

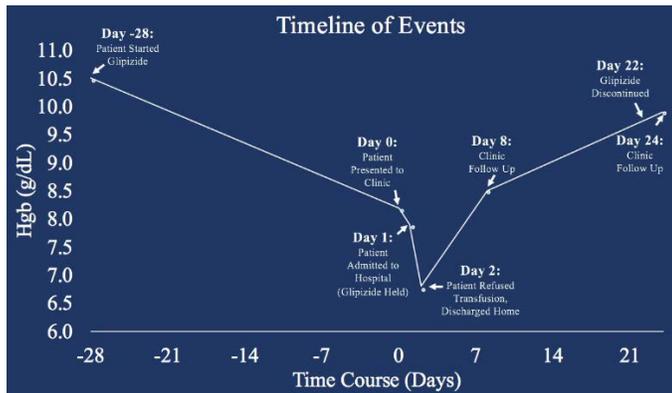


Figure 1: Graph depicting timeline of events.

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