Acute Hemolytic Anemia Following Semaglutide Injection: A Case Report

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Abstract

Background: Drug-induced immune hemolytic anemia is a serious adverse reaction that may result from drug administration, especially in cases of glucose-6-phospate dehydrogenase (G6PD) deficiency.

Objective: To report a case of acute hemolytic anemia in a 30-year-old Saudi male after receiving Semaglutide injection.

Case Report: A 30-year-old Saudi male with G6PD deficiency presented to the Emergency Department of Aseer Central Hospital, Abha City, Saudi Arabia with acute onset of yellow discoloration of the eyes, palpitation, mild backache, fatigue, and dark urine. The symptoms started one day after receiving the second dose of Semaglutide injection. He looked pale and the sclera were slightly icteric. Laboratory investigations showed high serum levels of liver enzymes and the total bilirubin. The RBCs count as well as the hemoglobin and the hematocrit were low, while reticulocyte count was high. The diagnosis was acute hemolytic anemia, most probably triggered by a recent Semaglutide injection. Following the discontinuation of Semaglutide, his clinical condition improved.

Conclusions: G6PD deficiency should be considered in all clinical settings, and the hemolytic conditions that can possibly be precipitated by drugs not well known to cause hemolysis. Screening of newborn infants to early detect G6PD deficiency early is highly recommended, especially in those with positive family history of G6PD.

Key Words: Semaglutide, Hemolytic anemia, G6PD deficiency, Case report.

Introduction

Drug-induced immune hemolytic anemia is a serious adverse reaction that may result from drug administration and immunization against the drug and/or red blood cells. The reactions are characterized by an abruptly or gradually increased red blood cells destruction through antibody-mediated complement activation (complement-mediated intravascular hemolysis) and antibody-mediated phagocytosis (Fc-mediated extravascular hemolysis), respectively. A large number of drugs have successively been described to cause immune hemolytic anemia (1).

Glucose-6-phospate dehydrogenase (G6PD) deficiency is an X-linked genetic deficiency estimated to affect more than 400 million people world-wide. It puts stress on red blood cells (RBCs), which may be further augmented under certain pathophysiological conditions and drug treatments. Individuals with G6PD deficiency are mostly asymptomatic under normal circumstances. Under normal circumstances, G6PD deficiency does not cause immediate harm to patients. However, when they become exposed to certain hemolytic drugs the results can range from mild hemolytic anemia to multi-organ failure and mortality (2).

The gold standard for the diagnosis of G6PD deficiency is quantitative spectrophotometry. However, the most widely used G6PD diagnostic in the field is the qualitative fluorescent spot test, presumably due to its low price. Several qualitative G6PD lateral flow assays have been introduced to the market over the last years that are suitable for diagnosis at the point of care and show better operational characteristics than the fluorescent spot test (3).

Smits and Van Raalte (4) noted that one of the newer anti-hyperglycemic drug classes receiving such scrutiny on safety are the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs). The glucagon-like peptide-1 receptor agonist (GLP-1RA). Semaglutide is the most recently approved agent of this drug class, and the only GLP-1RA currently available as both subcutaneous and oral formulation. These agents are based on the gut-derived incretin hormone GLP-1, which is a potent stimulator of insulin, while suppressing glucagon secretion (5).

Here, we report a 30-year-old Saudi male who experienced acute hemolytic anemia after receiving Semaglutide injection.

Case Report

On February 23rd, 2022, a 30-year-old Saudi male presented to the Emergency Department of Aseer Central Hospital, Abha City, Saudi Arabia with acute onset of yellow discoloration of the eyes, palpitation, mild backache, fatigue, and dark urine. The symptoms started one day after receiving the second dose of Semaglutide injection (0.25 mg SC). The first dose was received one week earlier. He received Semaglutide for body weight reduction.

The patient was diagnosed with G6PD deficiency at the age of two years. Since then, he has been strictly avoiding eating any beans or any other legumes. The patient denied receiving any medications other than Semaglutide, or recent consumption of any beans. He did not have abdominal pain, itching, fever, change in color of stools, bleeding from any site, or exposure to a recent trauma. He had no history of blood transfusion, allergy, or surgery. There is no history of alcohol intake or drug abuse. There is no history of traveling abroad or contact with a sick patient. He has a positive family history of G6PD deficiency (his brother).

On examination, the patient was pale and the sclera were slightly icteric. Results of chest, and heart examinations were unremarkable. The liver and spleen were not palpable. Body mass index was 32 kg/m2, temperature was 36.9°C, heart rate was 103/min, respiratory rate was 18/min, and SpO2 was 97%.

Abdominal ultrasound showed no abnormal findings. The details of laboratory findings are in Table (1).
The diagnosis for our G6PD case was acute hemolytic anemia, most probably triggered by a recent Semaglutide injection. Therefore, he was advised to avoid any possible triggers that may exacerbate hemolysis, and to stop receiving any further dose of Semaglutide. The patient was started on antioxidants and vitamin supplements. Blood transfusion was not necessary.

Following the discontinuation of Semaglutide, his clinical condition improved, and there were no further episodes of hemolysis. During the follow-up visit two weeks later, his hemoglobin level was 11.9 g/dL, and his serum levels of ALT, AST and LDH were within the normal ranges (48 U/L, 35 U/L, and 298 U/L, respectively). After a month, his hemoglobin increased to 13.2 g/dL and the total bilirubin became 1.6 mg/dL.

Table 1: Results of laboratory investigations at presentation

Investigations	Value
Liver function tests	
• Alanine transaminase (ALT)	66 U/L†
• Aspartate aminotransferase (AST)	40 U/L†
• Lactate dehydrogenase (LDH)	336 U/L†
• Alkaline phosphatase (ALP)	71 U/L
• Serum albumin	4.2 mg/dL
• Total proteins	7.4 mg/dL
• Total bilirubin	8.6 mg/dL†
• Direct bilirubin	0.7 mg/dL†
Hematological findings	
• WBCs	5.1 x 10^3/μL
• RBCs	3.79 x 10^6/μL‡
• Reticulocytes	2.8%†
• Platelet count	314 x 10^3/μL
• Hemoglobin	10.7 g/dL‡
• Hematocrit	40.5%‡
• Mean corpuscular volume (MCV)	88.9 fL
• Mean corpuscular hemoglobin (MCH)	32 pg
• Mean corpuscular hemoglobin concentration (MCHC)	35.9 g/dL
• Prothrombin time (PT)	12.3 sec
• Activated partial thromboplastin time (APTT)	28.6 sec
• International Normalized Ratio (INR)	0.85
Pancreatic function tests	
• Lipase	151 U/L
• Amylase	68 U/L
• Fasting blood glucose	95 mg/dL
• HbA1c	4.9%
Kidney function tests	
• Creatinine	0.9 mg/dL
• Urea	22 mg/dL
• Blood urea nitrogen (BUN)	9 mg/dL
Serum electrolytes	
• Chloride	104 mEq/L
• Sodium	140 mmol/L
• Potassium	3.61 mEq/L
• Calcium	9.7 mg/dL
• Magnesium	2.03 mg/dL

‡ Low levels † High level

Discussion

After receiving the second dose of Semaglutide for body weight reduction, our G6PD-deficiency patient developed symptoms suggestive of acute hemolytic anemia, with jaundice, palpitation, mild fatigue, and dark urine. Serum levels of ALT, AST and LDH as well as the total bilirubin level were all high. The RBCs count as well as the hemoglobin and the hematocrit were low, while reticulocyte count was high

Our patient was fully aware of being a case of G6PD deficiency, with a strongly positive family history of the same condition affecting his brother. Therefore, he has been strictly avoiding eating beans or any other legumes. He denied any history of blood transfusion, allergy, surgery, or drug abuse.

Fathy et al. (6) stated that symptoms of hemolytic anemia can be fatigue, confusion, light headedness, dizziness, weakness, pale skin, or even in some cases heart failure. An important clue in defining that hemolysis is the cause of the anemia, is an increased reticulocyte count that is not preceded by any bleeding or recent correction of iron or other nutrient deficiency. Indicators of RBCs destruction may occur, such as elevated lactate dehydrogenase enzyme and bilirubin levels. Common markers of hemolysis include bilirubin, lactate dehydrogenase, and reticulocytes are increased (2).

Hassan et al. (7) noted that G6PD deficiency is an inherited, sex-linked, metabolic disorder characterized by an enzyme defect that leads to premature destruction of RBCs when exposed to certain medications or chemicals, or consumption of beans. The severity of associated symptoms varies greatly, depending upon the form of the disorder that is present. Some people may have no symptoms at all, but when symptoms are present, they may include fatigue, pale color, shortness of breath, rapid heartbeat, jaundice or yellow skin, dark urine and enlarged spleen. Other rare manifestations may include hemoglobinuria, shock and renal failure.

The responsible gene in G6PD deficiency has been mapped to Xq28. In females, the disease traits on the X chromosome can be masked by the normal gene on the other X chromosome. Since males only have one X chromosome, if they inherit a gene for a disease present on the X, it will be expressed. Men with X-linked disorders transmit the gene to all their daughters, who are carriers, but never to their sons. Women who are carriers of an X-linked disorder have a 50% percent risk of transmitting the carrier condition to their daughters, and a 50 percent risk of transmitting the disease to their sons (8).

The observed high levels of serum ALT, AST and LDH in our patient are most probably due to the acute hemolytic anemia, not due to Semaglutide-related hepatotoxicity. It has been reported that in large clinical trials, serum enzyme elevations were not more common with Semaglutide therapy than with placebo or comparator agents, and no instances of clinically apparent liver injury were reported. Treatment with Semaglutide is often associated with improvements in serum aminotransferase levels (and hepatic steatosis) making them possible treatments for nonalcoholic fatty liver. There have been no published case reports of hepatotoxicity due to Semaglutide and the product label does not list liver injury as an adverse event (7).

Our patient was not diabetic. His HbA1c was 4.9%. However, he received the weekly subcutaneous injections of Semaglutide for weight reduction since he was obese, with body mass index 32 kg/m2. Pancreatitis did not occur after receiving Semaglutide, since he had normal levels of serum lipase and amylase, as well as fasting blood glucose. Moreover, his kidney function was not affected, as indicated by the normal levels of serum creatinine, urea and BUN.

It has been reported that the Semaglutide is somewhat special among GLP-1RAs given that it is the only drug available as both subcutaneous injection and as an oral formulation (9). It provides a beneficial effect on body weight, blood pressure and lipid profile (10). However, partly due to the widespread presence of GLP-1 receptors, several adverse effects have been observed, of which pancreatitis was initially flagged as a safety alert (11).

There are many published lists of known and suspected hemolytic drugs which proved to be unsafe for G6PD deficient patients, such as some anti-malarial drugs (12), and the fixed-dose combination of isosorbide dinitrate plus hydralazine (13).

However, the definitive determination of drug-induced hemolytic anemia is difficult (14). Therefore, the susceptibility of G6PD-deficient populations to certain drug treatments and the subsequent potential risks of hemolysis remain important public health issues to be investigated. Assessing the hemolytic potential of newly developed compounds prior to human testing is crucial for creating safe alternatives for G6PD deficient populations (2).

Conclusions

This case highlights the importance of considering the presence of G6PD deficiency in all clinical settings, and the conditions that can possibly be precipitated by drugs not well known to cause hemolysis. Screening of newborn infants to early detect G6PD deficiency is highly recommended, especially in those with positive family history of G6PD. Further studies are needed to confirm the pathophysiology of hemolytic anemia associated with Semaglutide administration.

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