Favism induced methemoglobinemia in a G6PD deficient male with a subsequent hemolytic cascade, a therapeutic challenge: case report and review of literature

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October 8, 2020

Abstract

We report a 56-year-old male with methemoglobinemia and hemolytic anemia, secondary to fava bean ingestion. Methylene blue administration worsened the hemolysis as he was G6PD deficient but not diagnosed before. We have discussed the mechanism of hemolysis in such patients and the management of such cases.

Key Clinical Message:

The co-occurrence of acute hemolysis and methemoglobinemia secondary to favism in G6PD deficient individuals is rare. Identifying it promptly is of high clinical significance as treating methemoglobinemia, i.e., methylene blue can worsen hemolysis.

Introduction:

Hemolytic anemia, a form of anemia that causes premature rupture of erythrocytes, accounts for five percent of anemias[1]. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a well-known cause of hemolysis and currently affects around 400,000000 individuals globally. It has a notable prevalence in African, Asian, and Mediterranean countries [2]. Favism is a common trigger of oxidative stress in G6PD deficient people, which can lead to hemolysis. Additionally, fava bean ingestion can cause methemoglobinemia [3]. Methemoglobin is an abnormal variation in the hemoglobin in which the ferrous ($Fe2^{+}$) iron in heme is oxidized to the ferric ($Fe3^{+}$) state. The condition is usually acquired, secondary to oxidative stress in the body such as favism or infections, but can rarely be congenital[4]. The first-line treatment for methemoglobinemia is methylene blue. However, in G6PD deficient patients, methylene blue can potentiate hemolysis because of its oxidative effects [3]. It is vital to take a detailed history of patients presenting with hemolysis to identify the potential causes and avoid any additional oxidative stress.

Case presentation:

A 56-years old Qatari male, a known case of type-II diabetes mellitus and hypertension, presented with a five-day history of progressive dyspnea and dizziness. He also had a three-day history of mild hematuria and one episode of minimal non-bloody vomiting. The patient had no recent infection and no exposure to new medications. He is married (non-consanguineous), a smoker (5 cigarettes per day) but non-alcoholic with no history of illicit drug use.

Upon examination, he was vitally stable (afebrile, Blood pressure 136/76 mmHg, heart rate 93 beats per minute) other than an oxygen saturation (SPO^{2}) of 70% on room air. On examination, he had pallor and

jaundice. The rest of the physical exam was unremarkable. Arterial blood gas (ABG) analysis revealed SPO^2 of 101 %, and a methemoglobin (MetHB) level of 5.6 % [Table 1]. The patient was initiated on supplemental oxygen, but his SPO^2 remained low. Because of a high MetHgb level, a provisional diagnosis of methemoglobinemia was made, and he received methylene blue intravenously (IV) 80mg while in the emergency department. A complete blood analysis revealed low hemoglobin (Hgb) of 9.9 gm/dL, secondary to hemolysis [Table 1, Figure 2]. Chest x-ray and electrocardiogram were unremarkable. A urine dipstick analysis did not reveal significant blood or protein.

A repeated Hgb level after 24 hours showed a further drop to 7gm/dL. As he was symptomatic, two units of packed red blood cells (RBC) were transfused. Unexpectedly, his Hgb continued to drop further [Figure 2]. Continued hemolysis was evident, and a detailed history was retaken to identify the cause of hemolysis. The patient revealed an intake of large amounts of fava beans on the day of the starting of his symptoms. He had a history of eating fava beans in small amounts before without experiencing any symptoms. However, this time, the intake was considerably larger (six fava beans containing sandwiches). Because of suspicion of favism induced hemolysis, a G6PD level was sent, which came low [Table 1]. At this point, he was diagnosed with G6PD deficiency, aggravated by the ingestion of a large number of fava beans. His hemolysis was worsened by methylene blue, which was evident by a progressive drop in Hgb.

The patient was kept in the medical ward under close observation. He received a total of 3000 mg of IV Vitamin C in two divided doses. After two days, his SPO2 improved to 100 % on room air, and Hgb improved gradually to 11 gm/dL on the fifth day [Figure 2]. He was discharged as he became asymptomatic on day five with a follow-up in the acute medical assessment clinic.

Follow-up:

Follow-up lab work showed near-normal Hgb (12 gm/dL), normal bilirubin, and liver enzymes. The patient did not have any residual dyspnea. There was no jaundice, and his hematuria had resolved. He was discharged from the clinic with clear instructions about his diagnosis and to avoid fava beans in the future. He was taking aspirin for primary prevention of cardiovascular disease and was advised to discontinue it to avoid any oxidative stress.

Discussion:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent blood cell disorder in humans [5]. It is an X-linked genetic disorder caused by a defect in chromosome X (band X q28) [6]. It is usually diagnosed when patients present with signs and symptoms of hemolytic anemia, secondary to oxidative stress. It is usually triggered by infections, fava beans, and certain medications [7]. Various screening tests are available to detect G6PD deficiency, and the diagnosis is usually confirmed by quantitative measurement of nicotinamide adenine dinucleotide phosphate (NADPH) [8]. Treatment of acute episodes of hemolysis is by transfusion and, more importantly, elimination of the cause of oxidative stress[9].

Methemoglobinemia, on the other hand, is a disorder of hemoglobin where ferrous ($Fe2^+$) iron in heme is oxidized to the ferric ($Fe3^+$) state. It is usually acquired, secondary to oxidative stress in the body, but can rarely be congenital [4]. Physiologically, various enzyme systems such as NADH methemoglobin reductase, NADPH methemoglobin reductase, ascorbic acid, and glutathione reductase systems keep a check on the accumulation of methemoglobin in the blood [10]. However, there are instances where these mechanisms are insufficient to counter the conversion of hemoglobin to methemoglobin, consequently promoting an oxidative state in the body. This can be either due to the overproduction of methemoglobin or under conversion to hemoglobin due to unavailable enzyme mechanisms. The former can be secondary to exposure to certain drugs, chemicals, or food items, but can sometimes be hereditary [11]. Inability of enzyme systems to counteract methemoglobin can be secondary to enzyme deficiencies, such as G6PD deficiency.

Usually, the patients typically have a low SPO^2 on pulse oximeters but a falsely high SPO^2 on arterial blood gasses (ABG) [12]. The treatment depends on the level of methemoglobin in the body and symptoms. The first step is to immediately remove any possible precipitator if present. The treatment of choice for

symptomatic or asymptomatic patients with a level of methemoglobin >30 percent is methylene blue (1-2mg/kg) [13]. Methylene blue is reduced to leuko-methylene blue via NADPH dependent methemoglobin reductase. This, in turn, reduces methemoglobin back to hemoglobin, hence correcting the abnormality [14] [Figure 1].

Rarely, patients can present with co-occurrence of methemoglobinemia and G6PD deficiency[3, 15-18] . In such cases, extreme caution is required while administering methylene blue as they do not have sufficient levels of NADPH to reduce it. Otherwise, a cascade of oxidative hemolysis ensues secondary to underlying G6PD deficiency, resulting in a vicious cycle of further methemoglobinemia [10].

The most frequent cause of this co-occurrence reported in the literature is the ingestion of fava beans, which can induce methemoglobinemia as well as potentiate G6PD deficiency simultaneously [3, 15-18]. All the reported cases in the literature are male, with median age of 6 years (range 1 – 56). All them were newly diagnosed with G6PD deficiency upon presentation with MethHgb. Median Hgb was 8gm/dL (4.6 – 9.9) and median MetHgb was 8 % (5.6 – 35). 1 patient (our patient) received methylene blue, and 3 received Vitamin C. All of them recovered and were discharged. Our patient was also male and had taken a full meal consisting of fava beans before presenting. Although his methemoglobin level was 5.6 percent, he was given methylene blue due to his symptoms, which worsened his hemolytic anemia [Table 2].

Interestingly, our patient had a history of favism in the past without developing any symptoms. Only this time, he ate a larger amount of fava beans which led to hemolysis and methemoglobinemia. Hence, while treating patients with methemoglobinemia one should be vigilant that a history of fava beans ingestion without any symptoms does not rule out G6PD deficiency. It in fact depends upon the number of beans ingested over a certain period of time [19].

Conclusion:

Favism is a rare cause of the co-occurrence of methemoglobinemia and hemolysis in G6PD deficient individuals. Severity of hemolysis in G6PD deficient individuals is dependent on the number of fava beans ingested. It is vital to identify the presence of G6PD deficiency in patients presenting with methemoglobinemia, as the initiation of methylene blue in such individuals can result in a cascade of oxidative hemolysis.

Tables and figures:

Table 1. Basic lab-work (WBC: white blood cell, RI: reticulocyte index, LDH: lactate dehydrogenase, PS: peripheral smear, Hgb: hemoglobin, HgbE: hemoglobin electrophoresis CRP: c-reactive protein, MetHgb: methemoglobin)

Table 2 . Reported cases of methemoglobinemia and G6PD deficiency secondary to favism (Hemoglobin: Hgb, Methemoglobin: MetHgb (normal 0 - 1.5%), Glucose-6-phosphate dehydrogenase: G6PD)

Figure 1 . Mechanism of reduction of methemoglobin to hemoglobin by methylene blue; concept taken from Percy MJ et al. [14].

Figure 2. Trend of hemoglobin of the patient throughout the hospital stay.

Acknowledgements:

Authors would like to thank Dr. Percy MJ for permitting reproduction of the Figure 1.

Author contributions:

Conceptualization: FA, BM

Patient consent: BM

Literature review: FA, AB, SJ, ID, MM, MU, MY

Manuscript writing: FA, BM, AB, SJ, ID

Data collection: FA, AB

Radiology part in writing and images: AB

Critical review and modifications: FA**,** MU, MY

Final review and approval: FA, AB, SJ, ID, MM, MU, MY

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