Case Report

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G6PD deficiency resulting in massive hemolysis and acute renal failure

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ABSTRACT

Objectives: Glucose 6 phosphate dehydrogenase (G6PD) is an intracellular enzyme that protects cells from oxidative stress by catalyzing the first step of the pentose phosphate pathway. Since erythrocytes do not have mitochondria, the pentose phosphate pathway is the only resource for NADPH production. Decreased NADPH production in G6PD deficient erythrocytes, results in susceptibility to oxidative damage and hemolysis eventually. G6PD deficiency is an X-linked hereditary disorder and the most common enzyme deficiency in the world.1 Since the patients who have G6PD deficiency may be asymptomatic the actual incidence cannot be estimated. Usually, hemolytic episodes resolve themselves, however, in some cases, it may end up with severe complications such as acute renal failure.

A 43-year-old male patient was admitted to our emergency department with jaundice. His complete blood count and biochemical test results were consistent with acute hemolysis; further diagnostic tests evaluating hemolytic anemia, low G6PD levels indicated that G6PD deficiency is the most probable etiology. When a more detailed anamnesis was obtained, it is learned that the patient had eaten fava beans for the first time in his life. Since the patient was anuric and his renal function tests were worsening, we planned hemodialysis, several transfusions, and therapeutic plasma exchange (TPE). Our case is a rare one in which severe hemolysis and acute renal failure developed following fava ingestion due to G6PD deficiency and TPE and hemolysis were successful.

Keywords: G6PD, plasmapheresis, therapeutic plasma exchange (TPE) severe hemolysis, acute renal failure

Glucose 6 phosphate dehydrogenase (G6PD) is an intracellular enzyme that protects cells from oxidative stress by catalyzing the first step of the pentose phosphate pathway. Since erythrocytes do not have mitochondria, the pentose phosphate pathway is the only resource for NADPH production. Decreased NADPH production in G6PD deficient erythrocytes, results in susceptibility to oxidative damage and hemolysis.[1] Various medications, infections, and food may trigger hemolytic episodes by generating an oxidative environment.[2] Peripheral blood smear obtained at an acute hemolytic episode reveal microspherocytes, eccentrocytes, or "bite" cells, and "blister cells" with hemoglobin puddled to one side. Special stains can document the production of Heinz bodies, which are collections of denatured globin chains often attached to the RBC membrane.[3] Quantitative tests should be performed in suspected cases. G6PD deficiency is an X-linked hereditary disorder and the most common enzyme deficiency in the world.[1] The National Organization for Rare Disorders estimates that 400 million people worldwide are living with G6PD deficiency. The prevalence of the disorder is highest in Africa, Asia, the Middle East, Latin America, and the Mediterranean.[4] Due to its X-linked inheritance, it is more common in males

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however heterozygous females can also be affected.

Since the patients who have G6PD deficiency may be asymptomatic the actual incidence can not be estimated. Usually, hemolytic episodes resolve themselves, however, in some cases it may end up with severe complications such as acute renal failure.[5, 6] Here, we report our case of a G6PD deficient patient presenting with severe hemolysis and acute renal failure, treated successfully with therapeutic plasma exchange (TPE) and hemodialysis.

CASE REPORT

A 43-year-old male patient was admitted to our emergency department with yellow discoloration of his eyes and skin that became evident three days ago. He also mentioned dark urine discoloration. Nausea, vomiting, loss of appetite, and fever were accompanying his complaints. His medical history was unremarkable. His vital signs were a temperature of 36.5°C, heart rate 105 bpm, blood pressure 117/63 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 79%. He was tachypneic, also his skin was icteric and he had tenderness on the right upper quadrant on abdominal examination. His laboratory values on admission are included in Table 1. There was no pathology observed in abdominal ultrasonography. Both kidneys were normal in size and echotexture. The patient was admitted to our intensive care unit for further evaluation and treatment since he was tachypneic and hypoxic. As the patient was evaluated for severe hemolysis, his reticulocyte index was 5% (N:1- 3.5%), peripheral blood smear revealed, normocytic normochromic red blood cells (RBCs) with anisopoikilocytosis, several blister cells, and bite cells, no schistocytes were observed. Indirect and direct Coombs tests were negative and CD55, CD58 and CD59 levels were all in normal ranges. Also, several tests were performed to exclude Weil's disease and ceftriaxone treatment was initiated. A more detailed history showed that he had eaten fava beans for the first time in his life before the onset of his symptoms. As result hemolysis secondary to G6PD deficiency was considered. Keeping in mind that test results may come out normal in acute episodes because during the acute hemolytic episodes RBCs with the lowest G6PD activity undergo hemolysis and circulating RBCs may have relatively higher enzyme activity, G6PD enzyme activity test was performed before RBC transfusion. Enzyme level was 3.023 U/g Hb (N: 6.97-20.5 U/g Hb). Despite aggressive fluid resuscitation, the patient was anuric and his renal function tests were deteriorating progressively. As renal biopsy is done, it was consistent with acute tubulointerstitial nephritis, hemodialysis was planned by that time. Also, therapeutic plasma exchange (TPE) was done for three days considering severe hemolysis with Haemonetics MCS+ cell separator. Fresh frozen plasma is used as a replacement fluid. One plasma volume is replaced in each procedure. Blood volumes processed were 5799 mL, 6123 mL, 5881 mL, and

Table 1. Patients laboratory results on admission, before and after TPE

	Reference Range	On Admission	Before first TPE*	After first TPE*
Hemoglobin	13.6-17.2 g/dl	8.1	7.6	8.3
Platelet count	156 - 373 10^3/mm^3	297	225	174
Leukocyte count	4.5 - 10.3 10^3/mm^3	24.6	23.5	19.7
Total bilirubin	0.3-1.2 mg/dl	7.49	8.3	3.5
Indirect bilirubin	0.1-1 mg/dl	6.4	4.07	1.82
LDH*	0-248 U/L	1403	2979	912
AST*	0-50 U/L	77	210	86
ALT*	0-50 U/L	47	154	119
CK*	< 172 U/L	989	1578	211
Creatinine	0.66-1.09 mg/dl	1.6	6.11	4.28
Coombs Tests (direct/indirect)		negative		
INR*	0.8-1.2	1.14	1.2	1.1

*TPE: Therapeutic plasma exchange, LDH: Lactate dehydrogenase, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, CK: Creatinine kinase, INR: International Normalized Ratio

plasma volumes processed were 3636 mL, 4014 mL, 3954 ml for each day respectively. Each session lasted approximately two hours. The color of filtered plasma following TPE was black. (Figure 1) Following these interventions, patients' clinical condition and laboratory findings improved. (Table 1) The patient underwent hemodialysis ten times and TPE for three days during his stay for twenty-three days. Eventually, as the renal functions improved, diuresis began. The patient was discharged with a scheduled follow-up plan from the outpatient clinic.

RESULTS

G6PD deficiency is one of the most common hereditary disorders. G6PD is responsible for producing reduced glutathione by catalyzing the first step of the pentose phosphate pathway which is the only antioxidant defense mechanism in RBCs.[7] RBCs lacking G6PD, consumes available reduced glutathione rapidly and becomes more vulnerable to oxidative damage as they expose to oxidative substances. Consequently, ongoing oxidative stress ends up with hemolysis.[8] RBCs that are most severely damaged undergo hemolysis intravascularly, nevertheless, hemolysis is mostly extravascular.[9]

G6PD deficient subjects generally don't have any symptoms unless they expose to certain medications, infections, and/or food. Rarely severe hemolysis may occur. As seen in our patient, detailed anamnesis revealing ingestion of fava beans was the cause of hemolysis; emphasizing the importance of careful medical history taking in daily practice.

"Vicine, convincing, ascorbate, and L-dopa" are substances that are present in high amounts in fava beans are thought to be toxic. These substances oxidate reduced glutathione by generating free oxygen radicals and cause hemolysis in G6PD deficient people.[10]

Favism is defined as acute hemolysis that occurs 24-48 hours after ingestion of fava beans. All subjects with favism show G6PD deficiency to the contrary, all subjects with G6PD deficiency may not experience acute hemolytic episodes following ingestion of fava beans. Despite its low incidence, few cases of severe hemolysis accompanied by renal failure are present in the current literature.[11]

Acute renal failure secondary to acute tubular necrosis and tubulointerstitial nephritis due to hemoglobinuria is a complication of severe hemolysis that is observed following severe hemolytic episodes in patients with G6PD deficiency.[12, 13]

The underlying mechanism that results in kidney injury secondary to hemoglobinuria is not fully understood. Studies are pointing that various factors may take part in renal injuries, like exposure to ferrihemate which is nephrotoxic (which is converted from hemoglobin in pH < 6.5), obstruction of renal tubules by hemolyzed red cells which is nephrotoxic. intravascular coagulation

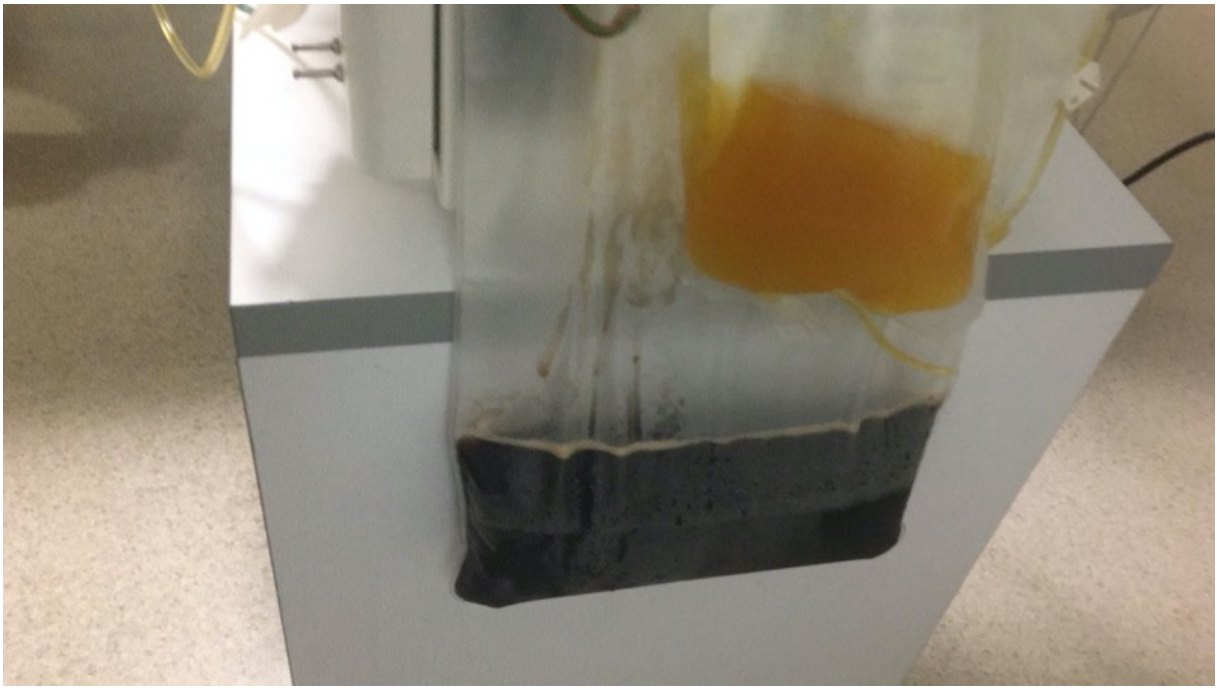

Figure 1. Image of filtered plasma following plasmapheresis

causing a release of thromboplastin factors, altered renal blood flow, and decreased glomerular filtration rate, or by a combination of the above.[1, 14, 15] Renal biopsies obtained reveal acute tubular necrosis and tubulointerstitial nephritis histopathologically. Rare cases of acute cortical necrosis due to hemolysis have also been reported.[16] Acute kidney failure secondary to hemoglobinuria cannot be predicted. Patients with accompanying volume defect, sepsis, acidosis, and/or taking nephrotoxic medications are at higher risk for developing renal failure.[11] Since our patient was not taking any nephrotoxic medication, we thought hemoglobinuria resulting in acute tubular necrosis and tubulointerstitial nephritis was the reason for his condition. Another possible cause of acute renal failure may be tissue hypoxia due to severe anemia in the patient with metabolic acidosis as well. Nevertheless lacking additional findings of other organ dysfunction made this explanation less possible.

The most effective management strategy in hemolysis is to prevent it by avoiding triggers.

Cases that result in severe anemia may require transfusions. Splenectomy is indicated in patients who need transfusions repeatedly.[17] In massive intravascular hemolysis, Hemoglobin clearance mechanisms become saturated and excess plasma free-hemoglobin easily moves into the renal parenchyma causing damage to the kidneys. Acute renal failure secondary to hemolysis can be prevented and treated as well with efficacious hydration and forced alkaline diuresis (keeping pH of urine > 6.5).[18] Furosemide or mannitol may be beneficial in patients with oliguria, renal replacement therapies may be needed in more severe cases.[9]

TPE is the procedure that macromolecules are eliminated from plasma for therapeutic purposes. The clinical benefits are based on removal of pathologic substances or on the replacement of abnormal components of plasma if necessary.

Even though TPE is not mentioned in management strategies of severe hemolysis in patients with G6PD deficiency; TPE can accelerate resolution in cases of acute tubular necrosis and tubulointerstitial nephritis by preventing continuous hemolysis and hemoglobinuria as in our case.[20]

CONCLUSION

Favism is a more common condition than estimated and rarely may result in severe hemolysis associated with renal failure. Currently, there is no approved treatment algorithm in the literature for such cases. Plasmapheresis may be an important treatment option in these patients by breaking the vicious cycle of hemolysis and reversing renal failure.

Authors' Contribution

Study Conception: MED, YŞ,; Study Design: MED, YŞ,; Supervision: MED, YŞ,; Materials: İŞY; Data Collection and/or Processing: İŞY,; Statistical Analysis and/or Data Interpretation: MED, YŞ,; Literature Review: MED,; Manuscript Preparation: MED and Critical Review: YŞ.

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None.

Conflict Of Interest

None.

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