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Remedy or tragedy: *Acalypha indica*-induced acute oxidative hemolysis associated with acute kidney injury and infective endocarditis: An initial presentation of G6PD Deficiency: A case report

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Abstract

Acalypha indica is used as an herbal broth in Sri Lanka for medicinal purposes. It can induce acute oxidative hemolysis and severe methemoglobinemia in G6PD deficiency patients. Leptospirosis is an endemic infection in Sri Lanka, resembling the clinical presentation of acute oxidative hemolysis in G6PD deficiency. As the presentation can mimic leptospirosis, a high index of suspicion is maintained when an infective focus is not identified in patients with fever, jaundice, and hematuria. Here, we present a case of a 33-year-old male patient with hemolysis following *Acalypha* herbal broth ingestion. He has recovered from acute oxidative hemolysis with supportive management, but he acquired infective endocarditis during inward stay through the central intravenous line, necessitating valve replacement.

Keywords

G6PD deficiency, oxidative hemolysis, *Acalypha indica*, kuppaimeniya

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Introduction

Red cells are protected from oxidative stress by the G6PD enzyme, which helps to produce nicotinamide adenine dinucleotide phosphate (NADPH).[1] G6PDD is a x-linked recessive illness.[1] Patients with G6PDD are often vulnerable to oxidative hemolysis. The prevalence of G6PDD in Sri Lanka ranges from 7.97% to 13.95% in Sri Lanka.[2] Its occurrence is equal in both males and females.[2] It has a wide range of clinical and biochemical manifestations, including asymptomatic nature to fatal oxidative hemolysis with or without methemoglobinemia.[3] Most drugs, foods, infections, household chemicals, toxins, and cosmetic products can induce acute oxidative hemolysis in individuals with G6PDD.[4] *Acalypha* is a tropical plant widely used as an herbal broth in Sri Lanka.[5] Previously healthy individuals experience the first episode of severe intravascular hemolysis once they consume *Acalypha* for the first time.[6] Leptospirosis is a zoonotic illness, more prevalent in tropical and subtropical countries.[7] Leptospirosis is an endemic infection in Sri Lanka. As the clinical presentation of G6PDD can mimic leptospirosis, it is tough to diagnose in the initial period when patients are not disclosing the history of consumption of herbal broth. In the Sri Lankan context, leptospiral exposure is often given in history.

Case report

A 33-year-old male patient was transferred from a local hospital (LH) to a tertiary care hospital for further management of suspected G6PD deficiency. He initially presented to a LH with a 1-day history of generalized weakness, dizziness, dark urine, and yellow discoloration of the skin after consuming *Acalypha* herbal remedy for common cold symptoms. He denied leptospiral exposure as no contact history of rodent or muddy water. He didn't use any other medication or any illicit

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drug. As the initial hemoglobin was 3.9 and increased bilirubin and reticulocyte count from LH with the blood picture, evidence of active oxidative hemolysis raised the suspicion of G6PDD. The patient also developed anuric acute kidney injury (AKI) with pulmonary edema, which needed hemodialysis (HD). On admission to the National Hospital of Sri Lanka, he was febrile, not cyanosed, and ill-looking, with Glasgow coma scale (GCS) 15/15, a saturation of oxygen 84 in room air, tachypneic with a respiratory rate of 28/min, a blood pressure of 110/70 mm Hg and pulse rate was 120/min. His respiratory examination revealed bilateral fine-end inspiratory crepitation in all three zones bilaterally. He was kept on 5l of oxygen. There was no saturation gap (measured saturation and arterial blood gas saturation) to suggest the presence of methemoglobinemia. His peripheral blood smear has revealed the presence of bite cells, blister cells, fragmented red blood cells (RBCs), Heinz bodies, and polychromasia which was suggestive for hemolysis. He was given his first slow low-efficiency dialysis (SLED). He developed reduced GCS due to dialysis disequilibrium syndrome. Noncontrast CT had evidence of acute cerebral edema. He was deteriorated and electively intubated and transferred to intensive care unit. He had an ICU stay of 28 days in total. The patient opted for plasmapheresis involving a multidisciplinary team, which included a physician hematologist, intensivist, nephrologist, and transfusion physician.

Plasmapheresis was withheld for a while to proceed with supportive management. The patient originally received six points of blood transfusion. He was also given a total of 11 SLED cycles for AKI. Total bilirubin, reticulocyte count, and blood picture were monitored during the inward stay. G6PDD was diagnosed by the Brewer's test and the presence of Heinz bodies with the clinical picture. Leptospirosis was excluded through history and investigations. Leptospiral polymerase chain reaction (PCR) was negative and paired leptospiral microscopic agglutination test (MAT) did not demonstrate a fourfold rise and neither of the titers were significant. Enzyme levels were not done in a acute setting as with ongoing hemolysis, and the facilities are not available to do the enzyme levels in the state sector of Sri Lanka. The patient also could not afford to do enzyme levels outside. Through repeated red cell concentrate (RCC) transfusion and SLEDs, the patient was stabilized for acute oxidative hemolysis and AKI. The patient contracted ventilator associated pneumonia (VAP) and sepsis, evidenced by increased procalcitonin levels. Despite high-end antibiotics, the patient started to have high spike fever, and his blood and HD catheter cultures became positive for *Corynebacterium*. Infective endocarditis (IE) was diagnosed through 2D echo, and multiple vegetations were found in the aortic valve. As the patient had initial normal 2D echocardiography on admission and another normal 2D echocardiography during hospital stay, IE was acquired during hospital admission. The patient was transferred to the cardiothoracic unit for further management of IE as the acute oxidative hemolysis part was settled.

Discussion

There are limited case reports regarding the occurrence of acute oxidative hemolysis following *Acalypha indica* ingestion in G6PDD. G6PD is an enzyme responsible for the synthesis of NADPH in the hexose monophosphate pathway.[1] NADPH helps to counter the oxidative stress imparted in the RBCs by various chemicals.[1] Individuals with G6PDD have mutations in the X-linked gene of Xq28.[1] Patients with G6PDD are more vulnerable to most of the chemicals of daily use.[4] Most individuals remain asymptomatic for long unless the hemolytic episode is severe. *Acalypha* is widely used as an herbal remedy in Sri Lanka, with limited evidence in the literature.[5] People with G6PDD, when they consume the *Acalypha* for the first time, may get acute oxidative intravascular hemolysis. Although *Acalypha* can cause methemoglobinemia in the presence of G6PDD, evidenced by limited literature, there is no strong evidence to suggest methemoglobinemia is due to *Acalypha* in the absence of G6PDD.[3] Methemoglobinemia was not observed in our patient, as he has no cyanosis and normal oxygen partial pressure levels.

Leptospirosis also has a similar presentation to G6PDD, where people are deeply icterus and develop anuric AKI.[8] In tropical countries, diagnosing G6PDD is difficult when the patient is having a history of muddy water or rodent exposure. Leptospirosis was excluded through history and investigations in our patient. Acute kidney injury in leptospirosis is caused by aacute tubular necrosis or tubulointerstitial nephritis (ATN or TIN).[9] AKI in G6PDD is due to nephrotoxic effects of filtered hemoglobin from intravascular hemolysis.[10] A study done by Pradoo et al. found that most of the patients with poisoning with *A. indica* have developed methemoglobinemia.[3] It is the only study attributing methemoglobinemia to *A. inidica* poisoning.[3] But our patient didn't develop methemoglobinemia. They also recorded the onset of symptoms, and it was within 24 h since the ingestion of *Acalypha*.[3] Our patient had developed symptoms 8 h after consuming *Acalypha*. Also, their study's duration of hemolysis before remission was within 5 days.[3] Our patient went into remission after 1 month of supportive management, which is quite a long period compared to their study. Remission was confirmed by the blood picture with no oxidative hemolysis and no change in markers of intravascular hemolysis.

Diagnosis of G6PDD should be made with the measurement of G6PD enzyme levels,[1] But it is not widely available in the state sector of Sri Lanka. With a clear consumption history, occurrence of symptoms shortly after consumption, G6PDD can be diagnosed with Brewer's test (Methemoglobin reduction test) in the presence of Heinz bodies and other peripheral features of blood picture. Heinz bodies are not specific for G6PDD.[11] A negative Brewer test does not exclude G6PDD.[11] Once the acute oxidative hemolysis was diagnosed, disease severity and remission were monitored through serial measurement of total and indirect bilirubin, LDH, hemoglobin, and blood picture, which was done in our patient. If these values

are coming down in the absence of a trigger for hemolysis, the patient can be managed successfully without plasmapheresis.[12] We have done the supportive management without going for early plasmapheresis; we managed the patient with repeated RCC transfusions and HD. Patient has developed new fever spikes, he was found to have new vegetations in the aortic valve in two dimensional echocardiography despite having two negative initial echocardiography. He was diagnosed with hospital acquired culture positive IE.

Conclusion

Acalypha herbal broth can induce acute oxidative hemolysis with or without methemoglobinemia in people with G6PDD. It can be fatal, depending on the severity of the episode. Supportive management with multiple RCC transfusions with avoidance of triggers helps to achieve remission.

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Author's contribution

All authors participated in the management of patients. K.G.K.U.K., K.V.L., and J.C.C. conceived and prepared the manuscript. G.G.L., S.M., and R.D.S.G. edited and supervised the final manuscript.

Availability of data and materials

The manuscript includes all the information supporting our conclusions and relevant references. There are no data sheets related to this case report.

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Our institution does not require ethical approval for reporting individual cases or case series.

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Consent for publication

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