


CASE REPORT

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A vegetable-induced hemolytic crisis in a G6PD deficient person: a case report

N. D. B. Ehelepola^{*} , A. N. Abayagunawardana and T. N. Sudusinghe

Abstract

Background: Hemolysis can occur in people with G6PD deficiency under oxidative stress. *Acalypha indica* is a tropical plant used as a medicinal plant as well as a vegetable. There are a few reported cases of *Acalypha indica* ingestion induced hemolysis in G6PD deficient people. All except one of them are from Sri Lanka. The information available at present (2017) about G6PD deficiency prevalence and variants of the G6PD gene among Sri Lankans is very sparse. There are no past reports on hemolytic crisis in a G6PD deficient person presenting mimicking leptospirosis.

Case presentation: A middle-aged Sri Lankan man presented on the third day of illness complaining of fever, head ache, arthralgia, myalgia, abdominal pain, vomiting, passing dark urine and reduced of urine volume. He gave a history of possible exposure to leptospirosis. He was pale, icteric and his liver was palpable 1 cm below costal margin and there were no other remarkable findings upon physical examination. He had neutrophilic leucocytosis. Leptospirosis was diagnosed. During the second assessment we noticed he was very pale and his urine sample pointed towards hemoglobinuria. Further questioning revealed he had consumed leaves of *Acalypha indica* as a vegetable. Acute hemolysis in a G6PD deficient patient following *Acalypha indica* ingestion was diagnosed. Blood transfusions were given to correct his anemia. Later, Brewer's test and quantitative assay of G6PD levels confirmed the diagnosis of G6PD deficiency.

Conclusions: A hemolytic crisis following oxidative stresses in G6PD deficient patients can present mimicking leptospirosis. Further investigations may reveal why the great majority of cases of acute hemolysis in G6PD deficient person following *Acalypha indica* ingestion are from Sri Lanka.

Keywords: G6PD deficiency, Hemolytic anemia, Glucose-6-phosphate dehydrogenase deficiencies, *Acalypha indica*, Leptospirosis, Case report, Sri Lanka

Background

Glucose-6-Phosphate Dehydrogenase (G6PD) is the enzyme that protects red blood cells against oxidative stresses [1–3]. G6PD deficiency is caused by point mutations in the coding region of the G6PD gene in the X chromosome [2–4]. The disease has a broad spectrum of biochemical and clinical phenotypes [1, 3]. G6PD deficient people are usually asymptomatic until exposure to an oxidative stress in the form of a drug such as primaquine, a food such as fava bean, a cosmetic such as henna (hena), a household chemical such as naphthalene or an infection that can result in acute hemolytic

anemia [1–4]. The foundation of the management of G6PD deficiency is avoiding oxidative stresses [2]. Blood transfusions and iron and folic acid supplements are administered after an episode of acute hemolysis [2]. It is the commonest enzyme deficiency worldwide affecting 400 million people [2, 3]. It is more prevalent in regions where malaria was endemic in Sri Lanka as well as in malaria endemic regions of tropical Africa, the Middle East, Mediterranean and South East Asia and provides some protection against malaria [1–4].

The information available at present (2017) about G6PD deficiency prevalence and variants of G6PD gene among Sri Lankans are very sparse [3, 4]. The overall prevalence of G6PD deficiency in Sri Lanka is less than three percent of the population [3]. Nevertheless, in some ancient villages where malaria has been endemic

*Correspondence: drehelepola@gmail.com
Teaching (General) Hospital–Kandy, Kandy, Sri Lanka

for centuries the frequency of occurrence is as high as 20.9% [3]. A recent Sri Lankan study demonstrates that males and females are equally affected by G6PD deficiency [3]. The only detailed report on G6PD gene variants among Sri Lankans is a study done in the Kataragama area [4]. Common G6PD gene variants reported among other Asian populations were rare or absent and 17 genetic variants were polymorphic in that population and the mutant allele was the major allele in 9 SNPs (single-nucleotide polymorphisms). [4]. Nine out of the 17 SNPs detected had a minor allele frequency greater than 10% and those seemed to be providing some protection against *Plasmodium falciparum* in males [4].

Acalypha indica, locally known as Kuppameniya (Fig. 1) is a tropical plant used in South and South East Asia, Africa and the Americas as a medicinal plant in local alternative medical practices as well as a vegetable [5].

There are few reported cases of the consumption of it as an alternative medicine, causing hemolysis in G6PD deficient patients and all but one of them are from Sri Lanka [6–9]. An acute hemolytic crisis in a G6PD

deficient patient can give rise to symptoms and signs [10] that mimic a leptospirosis infection [11] as we describe below, making initial clinical diagnosis more challenging and we did not find any similar cases reported before.

Case presentation

A 45 year old Sri Lankan man presented to us with a 2 day history of fever, head ache, arthralgia, myalgia especially affecting the lower limbs and lower abdominal pain. In addition he had vomiting and passing of dark colored urine for one day. He said that there was an apparent reduction of volume of urine he passed. The day before he had taken treatment from a general practitioner and has been on oral amoxicillin, paracetamol (acetaminophen) and vitamin B complex tablets since then. As his symptoms got aggravated he was admitted to our hospital.

He is used to standing bare footed at the mouth of a large urban drain (polluted with animal excreta) discharging into a stream after the rains and catching fish because he noticed the fish of the stream concentrating there to eat matter flushed along the drain. The last time he did this was 6 days before admission. That indicates his exposure to leptospirosis. His past medical history and the family history were unremarkable except that there was a history of an allergic reaction to an unidentified agent 2 decades ago that needed hospitalization.

Upon examination there was a mild pallor and icterus but no conjunctival suffusion, no fever. His pulse rate was 88/min, blood pressure was 120/80 mm mercury, his lungs were clear to auscultation and his liver was felt 1 cm below the right costal margin. The results of his central nervous system examination were normal. There was neutrophilic leucocytosis. Leptospirosis was diagnosed and intravenous ceftriaxone and supportive therapy was initiated.

Upon the second assessment the patient was very pale and a sample of urine from him indicated hemoglobinuria as shown in Fig. 2.

Further details were asked and he revealed that he had eaten cooked leaves of Kuppameniya (*Acalypha indica*) 1 day before the onset of fever, but denied any diagnosed hematological disease affecting his brother or relatives from the maternal side of his family. He did not know about any illness during his neonatal period.

Hence we started a workup for the possibility of hemolytic anemia as well. Table 1 summarizes his laboratory investigation results.

He denied ingestion of other drugs or food that may induce hemolysis. A hemolytic crisis triggered by *Acalypha indica* in a G6PD deficient person was diagnosed, antibiotic was stopped. Blood transfusions were given (700 ml packed cells during the day 3, 350 ml each on day 4 and day 6). A consultant hematologist's opinion



Fig. 1 An *Acalypha indica* plant (arrow head), a small one, locally known as Kuppameniya grown at the Royal botanical gardens, Peradeniya, Sri Lanka



Fig. 2 A urine sample from the patient on third day of the illness

obtained. After his symptoms subsided on the fifth day after admission, he was sent home on ferrous sulfate 400 mg and ascorbic acid 100 mg thrice daily, folic acid 1 mg daily supplements with a list of drugs to be avoided. Reticular cell count was repeated 6 weeks after discharge. It has returned to normal (0.5%). Patient was again referred to the hematologist, a positive Brewer's test confirmed the diagnosis. Brewer's test [12] is the only test available at Sri Lankan state hospitals like ours for confirmation of G6PD deficiency [3]. Later a G6PD qualitative reflex quantitative estimation was performed and level was 2.0 U/g Hb (reference range 4.60–13.5) and that further confirmed the diagnosis.

Discussion and conclusions

Diagnosis

He was presented to us with a history of likely exposure to leptospira organisms, and symptoms that are suggestive of leptospirosis [11] which is a common infection in his locality. In the same week he got admitted, we got several cases of leptospirosis including three patients with Weil's disease. His physical examination findings were also compatible with leptospirosis. Hence it was our

first differential diagnosis. A dengue epidemic was also going on in his locality. We do not usually see icterus in dengue, especially within 3 days after the onset of fever although dengue patients also can present with a similar signs and symptoms. The color of his urine sample during our second assessment in day 1 at hospital and his pallor and icterus prompted us to ask for more details and to do a workup for acute hemolysis. That helped us to come to the correct diagnosis and manage his problem. Many clinicians we know give less emphasis to inspection of urine in the present era (compared to two decades ago). However, that made a big impact in the diagnosis of this patient. His presenting symptoms can be attributed to hemolysis in a G6PD deficient patient [10]. Hemolysis induced by leptospirosis (or even by another infection) in this G6PD deficient patient was also a possibility. Acute hemolysis can occur due to leptospirosis per se even in normal people [13]. However, he had no fever after admission and despite of the stopping of ceftriaxone after the first dose, he recovered promptly. That excludes those possibilities. Nonetheless, had he had leptospirosis as well, the diagnosis and management of the patient would have been more difficult. The great majority of Sri Lankan hospitals do not have the facilities to perform serological or PCR tests for leptospirosis making confirmation of the diagnosis very difficult.

Acalypha indica induced hemolysis in G6PD deficient person

All reported cases [6–9] and other cases we have seen of *Acalypha indica* induced hemolysis in a G6PD deficient person were subsequent to the use of it as an alternative medicine. Usually they add other medicines also to the herbal broths. But this patient had eaten it as a vegetable in the form of typical Sri Lankan dish “*mellum (mallung)*” (leaves shredded and cooked with grated coconut kernel). *Acalypha indica* grows in many regions of tropical Asia and Africa and America and is used as a medicinal plant as well as a vegetable [5]. Nonetheless all except one report of *Acalypha indica* induced hemolysis in G6PD deficient patients are from Sri Lanka. The only other report we found was from the neighboring Tamil Nadu state of India [9]. That may be mere coincidence or may be because some G6PD deficiency genotypes and G6PD enzyme phenotypes common among Sri Lankans are more susceptible to *Acalypha indica* induced hemolysis. The prevalence G6PD gene variants among Sri Lankans were demonstrated to be different from other Asian populations [4]. That supports the speculation stated before. However, at present tests for G6PD gene variants are unavailable at Sri Lankan hospitals, and even at the national Medical Research Institute-Colombo. Hence, we were unable to determine the G6PD deficiency

Table 1 Synthesis of his laboratory investigation results (important ones are in *italics fonts*)

Test	Reference range	The day of the illness				
		Day 3	Day 4	Day 5	Day 6	Day 7
White cell count ($\times 10^9/l$)	4.0–10.0	24.10 → 24.13	30.28	22.15		9.8
Neutrophils %	50–70	64.9 → 65.3		86.18		64
Lymphocytes %	20–40	28.8 → 28.3		11.3		35
Hemoglobin (g/dl)	11–16	7.7 → 7.3	5.9	6.2		8.0
Hematocrit (%)	37–54	22.7 → 22.5	18.6	17.62		24.3
Platelets count ($\times 10^9/l$)	150–450	280 → 287	315	309		386
Serum lactate dehydrogenase (LDH) in U/l	140–330	6840				
Reticulocyte count %	0.3–3.0	8.71				
Serum alanine transaminase (ALT) in U/l	7.0–45	21.1	29			
Serum aspartate transaminase (AST) in U/l	13.0–31.0	82.0	114			
Serum alkaline phosphatase (ALP) in U/l	53.0–128.0	98				
Serum bilirubin—total (micro mol/l)	3.0–21.0	115.1				
Serum bilirubin—direct (micro mol/l)	1.0–7.0	11.9				
Serum gamma-glutamyltransferase (GGT) in U/l	15.0–30.0	17				
Blood urea (mmol/l)	2.10–7.10	7.09				
Serum creatinine (mg/dl)	0.90–1.30	0.58	0.6			
Serum sodium (mmol/l)	133–148	142				
Serum potassium (mmol/l)	3.5–5.5	5.0				
Chest X ray		Normal				
12 lead electrocardiogram		Normal				
Blood picture (blood taken day 2 and report arrived day 4)		<i>Normocytic normochromic red cells with marked polychromacia, red cell fragments and blister and bite cells were seen. Absolute neutrophil leucocytosis with left shift. Platelets were normal. Summary: Evidence of hemolysis compatible with that due to oxidant stress on a G6PD deficient patient</i>				

genotypes of our patient. Further studies are necessary for a clarification.

Severe hemolysis

On day 2 his hemoglobin was 5.9 g/dl even after the transfusion of 700 ml packed cells. He had eaten a large portion of the dish to stress to his children the importance of eating vegetables. That may have contributed to severe hemolysis. There is a published study on predictors of severe hemolysis with G6PD deficiency following exposure to oxidants stress [14]. They reported those predictors as the male gender, negative family history, presence of fever and vomiting, a younger age and high Alkaline phosphatase levels. This study was done on a pediatric population [14]. Our patient was an adult but he also had those factors, except the last two.

Conclusions

Hemolytic crisis following oxidative stresses in G6PD deficient patients can present mimicking leptospirosis. The inspection of urine can give a useful clue towards the correct diagnosis. Consumption of *Acalypha indica* leaves as a vegetable can results in severe hemolytic

anemia in some G6PD deficient patients. Screening and awareness campaigns regarding G6PD deficiency in high prevalence areas can reduce the probability of such patients getting a life-threatening hemolytic crisis as in this case. Further studies may reveal whether certain G6PD deficiency genotypes and G6PD enzyme phenotypes common among Sri Lankans are more susceptible to *Acalypha indica* induced hemolysis.

Abbreviations

G6PD: glucose-6-phosphate dehydrogenase; PCR: polymerase chain reaction; SNP: single-nucleotide polymorphisms.

Authors' contributions

NDBE, ANA and TNS contributed to management of this patient. NDBE did the literature survey and wrote the manuscript. ANA and TNS approved the manuscript after perusal. NDBE, ANA and TNS approved final the version to be published and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All the information supporting our conclusions and relevant references are included in the manuscript. There are no data sheets related to this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

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References

- Monteiro WM, Franca GP, Melo GC, Queiroz AL, Brito M, Peixoto HM, Oliveira MR, Romero GA, Bassat Q, Lacerda MV. Clinical complications of G6PD deficiency in Latin American and Caribbean populations: systematic review and implications for malaria elimination programmes. *Malar J.* 2014;13:1. <https://www.ncbi.nlm.nih.gov/pubmed/24568147>. Accessed 28 Mar 2017.
- Frank JE. Diagnosis and management of G6PD deficiency. *American family physician.* 2005;72:1277. <https://www.ncbi.nlm.nih.gov/pubmed/16225031>. Accessed 30 Mar 2017.
- Gunawardena S, Kapilnanda GM, Samarakoon D, Maddevithana S, Wijesundera S, Goonaratne LV, Karunaweera ND. Prevalence of G6PD deficiency in selected populations from two previously high malaria endemic areas of Sri Lanka. *PLoS ONE.* 2017;12(2). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5289554/>. Accessed 30 Nov 2017.
- Dewasurendra RL, Rockett KA, Fernando SD, Carter R, Kwiatkowski DP, Karunaweera ND, MalariaGEN Consortium. G6PD gene variants and its association with malaria in a Sri Lankan population. *Malar J.* 2015;14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4343272/>. Accessed 30 Nov 2017.
- Encyclopedia of Life. *Acalypha indica.* <http://160.111.248.29/pages/1145503/details>. Accessed 29 Apr 2017.
- Lamabadusuriya SP, Jayantha UK. *Acalypha indica* induced haemolysis in G6PD deficiency. *Ceylon Med J.* 1994;39:46. <https://www.ncbi.nlm.nih.gov/pubmed/8194149>. Accessed 30 Mar 2017.
- Sellahewa K. *Acalypha indica* induced haemolysis in G6PD deficiency. *Ceylon Med J.* 1994;39:145. <https://www.ncbi.nlm.nih.gov/pubmed/7820896>. Accessed 30 November 2017.
- Senanayake N, Sanmuganathan PS. Acute intravascular haemolysis in glucose-6-phosphate dehydrogenase deficient patients following ingestion of herbal broth containing *Acalypha indica*. *Trop Doct.* 1996;26:32. <https://www.ncbi.nlm.nih.gov/pubmed/8693563>. Accessed 30 Nov 2017.
- Narasimhan D, Kumar S, Murali A, Satish M, Mambatta A. Acute intravascular hemolysis triggered by herbal remedy. *J Forensic Toxicol Pharmacol.* 2014;3:1. https://scholar.google.com/scholar?hl=en&as_sdt=0,5&cluster=344831849905870647. Accessed 20 Jan 2018.
- Goldman L, Scharfer A. *Goldman's Cecil medicine, vol. 1.* 24th ed. Philadelphia: Saunders Elsevier; 2012. p. 1059.
- World Health Organization. *Human leptospirosis: guidance for diagnosis, surveillance and control.* Geneva: WHO; 2003. http://apps.who.int/iris/bitstream/10665/42667/1/WHO_CDS_CSR_EPH_2002.23.pdf. Accessed 29 Apr 2017.
- Brewer G, Tarlov A, Alving A. The methemoglobin reduction test for primaquine-type sensitivity of erythrocytes. A simplified procedure for detecting a specific hypersusceptibility to drug hemolysis. *JAMA.* 1962;180:386. <https://www.ncbi.nlm.nih.gov/pubmed/13872968>. Accessed 9 Dec 2017.
- Greer JP, Arber DA, Glader B, List AF, Means RT, Paraskevas F, Rodgers GM. *Wintrobe's Clinical Hematology.* 13th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 813.
- Al-Sweedan SA, Jdaitawi H, Khriesat WM, Khader YY, Al-Rimawi HS. Predictors of severe hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency following exposure to oxidant stresses. *Hematol Oncol Stem Cell Ther.* 2009;2:354. <https://www.ncbi.nlm.nih.gov/pubmed/20118060>. Accessed 28 April 2017.

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