Case Report: A Case of Acute Intravascular Hemolysis in Dengue Fever

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Abstract. Acute intravascular hemolysis (AIH) with hemoglobinuria is a rare complication of dengue viral infection. Review of the literature revealed only one report of AIH as a complication of dengue fever (DF). We report a case of AIH with massive hemoglobinuria in a 17-year-old Sri Lankan male, in the febrile phase of DF. This unusual and rare complication warranted forced diuresis, to prevent acute kidney injury. This was a departure from the recommended fluid therapy for DF.

INTRODUCTION

Dengue is the most common arboviral infection and is endemic in Southeast Asia.^{1,2} Dengue viral infection (DVI) has diverse clinical presentations ranging from the more common and usually benign dengue fever (DF) to the less prevalent, but more serious severe dengue (SD), which encompasses dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).^{1–3}

Complications of DVI are not uncommon. Cardiac,⁴ neurological,^{5,6} ophthalmological,^{7,8} hepatic,⁹ pulmonary,¹⁰ and renal complications^{11,12} have been regularly reported in medical literature. Hematological disturbances are common to both DF and DHF.^{13,14} However, thrombocytopenia and clinical bleeding such as petechiae, ecchymosis, and gum bleeding are often mild. In DHF, severe mucosal bleeding manifesting as hematemesis, melena, menorrhagia, and concealed internal bleeding may occur and is a reflection of a severe disease. Two cases of hemolytic anemia complicating DHF have been reported.^{15,16} We found only one report of three cases of acute intravascular hemolysis (AIH) in a study of DVI from China.¹⁷ Here, we report on a 17-year-old Sri Lankan male with DF, complicated by AIH with massive hemoglobinuria in the febrile phase of the illness. This case is unique because this complication necessitated forced diuresis with boluses of isotonic saline and furosemide to prevent acute kidney injury (AKI), in addition to the maintenance fluid therapy used in the management of DF.

CASE REPORT

A 17-year-old adolescent male, was in good health, until 3 days before admission when he developed fever. Fever was accompanied by chills, backache, generalized malaise, anorexia, and an episode of vomiting. On the first day of fever, he was seen by a primary care physician and was treated with loratadine, paracetamol, and ciprofloxacin. He denied any headache, retro orbital pain, myalgia, abdominal pain, or skin rashes. He did not complain of any change in color of urine, dysuria, frequency, flank, or supra pubic pain. He had no past history of DF.

On day 3 of fever, he presented to the hospital and was admitted to the medical unit. On admission, the patient was a fairly nourished young man, who was febrile and ill looking, but did not appear to be dehydrated or in any acute

distress. Vital signs were as follows: temperature, 101°F; pulse, 96/minutes; respiratory rate, 22/minutes; BP, 110/70; and weight, 51 kg.

There was no pallor, icterus, skin rashes, lymphadenopathy, or peripheral edema. His cardiac, respiratory, abdominal, and neurological examinations were normal. On admission, dengue non-structural protein 1 (NS1) antigen was positive by the biosynex dengue test. The rest of the laboratory findings are shown in Tables 1 and 2. On the evening of admission, his urine was found to be black in color (Figure 1). The black urine was due to hemoglobinuria resulting from AIH. All urine samples since then were examined at the bedside and were consistently black in color.

On further inquiry, the patient denied any episodes of black or red urine in the past. There was no past history or family history suggestive of hemolytic anemia. There was no history of recent travel or bathing in rivers. Review of systems was unremarkable, and specifically there was no history of recurrent abdominal pain, jaundice, or anemia. He had not taken any medications, except the ones prescribed by the primary care doctor as noted previously. The patient had not ingested any dyes, toxins, or foods that may have caused the urine to turn dark red or black. The patient has not had any surgeries and the patient denied any allergies to medications or recent blood transfusions. The patient is a student who lives in a suburb of Colombo and admitted to being bitten by mosquitoes.

The patient continued to have fever with the passage of black-colored urine. Despite the unusual color of the urine, he was clinically stable and the renal functions remained within normal limits. Ultrasound scan of the abdomen and chest did not reveal any abnormalities or fluid leakage into the peritoneal or pleural cavities. He was managed with paracetamol, monitoring of vital signs, and close observation for evidence of plasma leakage. Maintenance quantum of fluid was administered both intravenously and orally in accordance with the Sri Lankan national guidelines for the febrile phase of DF.¹⁸

To prevent AKI secondary to hemoglobinuria, the patient was administered repeated boluses of isotonic saline (10 mL/kg) with 40 mg of IV furosemide from the inception of hemoglobinuria on day 1 of hospitalization (i.e., day 3 of illness) until day 6 (i.e., day 9 of illness). On administering the fluid boluses, the patient's urine became less dark (Figure 2); however, the color reverted to black when the fluid intake was reduced to the maintenance fluid regimen. All the samples of urine voided after forced diuresis were inspected at the bedside, and fluid boluses were repeated on an ad hoc basis

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TABLE 1
Relevant hematology and biochemistry investigations, by the day of illness

Laboratory investigations	Day 3	Day 5	Day 8	Day 10	Normal range
Hemoglobin	14	12.9	10.4	7.6	12–17 g/dL
MCV	89.2	89.4	97.3	98.9	76–96 fL
MCHC	35.3	34.5	32.4	31.9	31–35 g/dL
Red blood cell count	4.45	4.13	3.30	2.46	$3.8\text{--}5.5 \times 10^6/\mu\text{L}$
Hematocrit	39.7	36.8	32.1	23.7	36–50%
White blood cell count	5.23	4.79	6.72	7.7	$4.0\text{--}10 \times 10^3/\mu\text{L}$
Platelet count	113	63	74	150	$150\text{--}410 \times 10^3/\mu\text{L}$
Reticulocyte count	–	0.5%	–	–	0.5–1.5%
Indirect Coomb's test	–	negative	–	–	–
Direct Coomb's test	–	negative	–	–	–
Total bilirubin	–	1.33	3.14	–	0.3–1.2 mg/dL
Serum enzymes					
Alanine aminotransferase	78.8	209.9	–	–	< 50 U/L
Aspartate aminotransferase	198.6	542.5	–	–	< 50 U/L
Creatine kinase	–	1,007	–	–	< 171 U/L
Lactate dehydrogenase	–	2,617	3,199	–	208–378 U/L
Na	136	135	143	–	136–146 mmol/L
K	3.27	3.89	3.74	–	3.5–5.1 mmol/L
Urea	–	25.6	–	–	17–43 mg/dL
Serum creatinine	1.05	0.93	0.89	–	0.84–1.25 mg/dL

MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration.

whenever the urine was black in color. The fluid therapy was aggressive and dynamic to match the dynamics of ongoing AIH and hemoglobinuria. This required a total of three boluses of 0.9% saline per day. The total fluid intake of both oral and intravenous with the maintenance quantity was 4 L per day.

On day 8 of illness, he became afebrile and entered the convalescent phase of DF. The urine persisted to be dark in color until day 9 of the illness. On day 10 of illness, the urine color started to normalize and became light pink (Figure 3). He remained clinically stable throughout his hospital stay and recovered uneventfully and was discharged home on the 11th day of illness.

DISCUSSION

The patient was a 17-year-old adolescent male who presented to hospital with an acute febrile illness of 3 days duration in a region of the world with a high prevalence of DVI. The diagnosis of DVI was established on admission by a positive dengue NS1 antigen test. The patient's vital signs were stable, and he had no clinical evidence of SD such as DHF or DSS. However, on the evening of admission, the patient developed black/cola-colored urine. The

differential diagnosis of black/cola-colored urine is hematuria, hemoglobinuria, myoglobinuria, bilirubinuria, and pseudohematuria due to ingestion of toxins, certain medications, and foods.

In our patient, the black urine was due to hemoglobinuria because his urine spectrophotometry was positive for hemoglobin and he had only 2–5 red blood cells per high power field (HPF) on urine microscopy. His hemoglobinuria was secondary to AIH which was established by the presence of anemia, bilirubinemia, and elevated lactate dehydrogenase.¹⁹ Free hemoglobin in the serum, which is not cleared by tubular reabsorption in the kidney, manifests as hemoglobinuria, which imparts a black color to urine. Common causes for AIH with hemoglobinuria such as autoimmune hemolytic anemia, falciparum malaria, microangiopathic hemolytic anemia, venomous snake bites endemic in Sri Lanka, incompatible blood transfusions, G6PD deficiency, and ingestion of aniline dyes and other poisons were excluded by a combination of history, examination and laboratory investigations. Ciprofloxacin which the patient took on the first day of fever can rarely cause immune-mediated intravascular hemolysis.²⁰ This possibility is very unlikely in our patient as the Coomb's test was negative. In our clinical practice, AIH

TABLE 2
Other investigations, by day of illness

Investigation	Day 3	Day 5
Dengue NS1 antigen	Positive	–
Ultrasound Chest and abdomen	–	No evidence of plasma leakage to pleural or peritoneal cavities
Urine for bilirubin	–	Negative
Urine for myoglobin	–	Negative
Urine for free hemoglobin	–	Positive
<i>Plasmodium falciparum</i> antigen	–	Negative
Blood picture	–	Occasional spherocytes, bite cells, and blister cells. Lymphocytic predominance with viral forms.
Urinalysis	Urinalysis: black colored; slightly turbid; protein, 1+; blood, 1+; pus cells, 2–3/HPF; red cells, 2–3/HPF; no casts seen.

FIGURE 1. Black urine on day 1 of admission (day 3 of illness). This figure appears in color at www.ajtmh.org.

with associated hemoglobinuria is usually encountered in patients with G6PD deficiency. But in our patient, no incriminating factors such as the ingestion of *Acalypha indica*, fava beans, sulphonamides, antimalarials, or consanguinity in the family could be elicited in the history.^{21–26} Thus, by a

FIGURE 2. Amber-colored urine following forced diuresis on day 2 of hospitalization (day 4 of illness). This figure appears in color at www.ajtmh.org.

FIGURE 3. Light pink urine color on the day of discharge (day 11 of illness). This figure appears in color at www.ajtmh.org.

process of exclusion we attributed the AIH and massive hemoglobinuria to DF.

During AIH, red cell lysis releases hemoglobin (Hb) into the circulation where it binds to the carrier protein haptoglobin. Once the haptoglobin binding capacity of plasma is exceeded, free Hb can be detected in the plasma. Free Hb is filtered through the glomerular membrane in the kidney and in the proximal convoluted tubule (PCT) Hb is reabsorbed. Once the reabsorptive capacity of the PCT is exceeded, Hb is excreted in the urine and imparts the characteristic black color.

Hemoglobinuria related AKI is driven by intrarenal oxidative reactions triggering a heme toxicity response due to the tubular deposit of hemosiderin.^{27,28} AKI can be prevented by ensuring a rapid tubular urine flow by forced diuresis. We achieved this objective by liberal use of intravenous 0.9% saline and IV furosemide. For a favorable outcome, it is essential to initiate diuresis very early at the inception of hemoglobinuria and must be sustained until hemolysis ceases and urine is no longer black.

Fluid management in a patient with dengue infection is critical to ensure a favorable outcome. Guideline recommendation of fluid for the febrile phase of both DF and DHF is only the maintenance quantity which should not exceed a maximum of 2,500 mL/day of both oral and intravenous fluid. Judicious fluid therapy was adjusted hourly based on physiological parameters of pulse pressure, heart rate, urine output, and hematocrit enables accurate fluid adjustments to prevent both fluid overload and shock. In this patient, we had to exceed the guideline-recommended fluid quota to achieve the primary goal of preventing AKI by ensuring a rapid tubular urine flow in the setting of ongoing AIH and hemoglobinuria. Despite the liberal use of IV saline and furosemide, there was no fluid overloading as evidenced by the absence of tachycardia, tachypnea, dyspnea, peripheral edema, elevated JVP, clear lung bases, and an $\text{spO}_2 > 95\%$ while breathing atmospheric air.

Clinicians should consider DVI as a possible cause for AIH and hemoglobinuria. Accurate identification of the clinical type as DF or DHF, and the phase of the illness as febrile, critical, or convalescent during which the AIH sets in will be of crucial importance in fluid management. For a patient with DHF in the critical phase, aggressive fluid therapy exceeding the calculated fluid quota in an attempt to prevent AKI by inducing diuresis in the setting of ongoing hemoglobinuria could aggravate the tendency for fluid overloading and leak of fluid into third spaces with attended respiratory compromise. Intravenous furosemide at this stage could lead to shock. Similarly, too much of fluid in the 24 hours of equilibration at the end of the critical phase and advent of convalescence could also lead to fluid overloading due to reabsorption of leaked fluid into the vascular compartment. The use of blood transfusions, IV saline, and IV furosemide during the critical and equilibration phases of DHF complicated with AIH would, thus, be a fine balancing act in preventing AKI on one hand by inducing forced diuresis, and preventing both fluid overload and shock on the other hand by the same intervention. This was not a concern for our patient as he had DF and not DHF and, hence, no critical phase and plasma leakage. In either case, a favorable outcome is yet feasible by a sound understanding of the clinical types of DVI as DF or DHF, correct identification of the phase of illness, close monitoring, and proper interpretation of physiological parameters reflecting cardiovascular compensation to fluid leakage, and the dynamics of AIH and hemoglobinuria with a propensity to develop AKI.

CONCLUSION

Acute intravascular hemolysis with hemoglobinuria is a rare complication of DF. To prevent AKI, forced diuresis is indicated. This is a departure from the national guidelines on fluid therapy in DF, which recommends a maximum of 2,500 mL/24 hours of both oral and intravenous fluids. Despite these recommendations, forced diuresis is a useful intervention to prevent AKI when DF is complicated with AIH and hemoglobinuria. However, in this clinical setting, it must be carried out with close clinical and laboratory monitoring to prevent cardiac and respiratory complications due to fluid overload.

Received October 7, 2019. Accepted for publication December 2, 2019.

Published online January 6, 2020.

Acknowledgments: We are grateful to S. Sivakumaran and A. A. Riyaaz for giving us access to the patient and useful comments on management and Jasmine Cisneros, RN, for proof reading and formatting the document. The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

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