Case Report

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Uncommon Presentation of Dengue Fever in a G6PD-Deficient Adult: A Case Report

Internal Medicine Section

MEGHNA DUTTA[1], SANDIP KUMAR CHANDRA[2], SUSOBHAN MONDAL[3], SYAMASIS BANDYOPADHYAY[4], RAJESWAR SAMANTA[5]

ABSTRACT

Dengue fever presents a diverse clinical spectrum which can lead to many complications. The outcome of these presentations predominantly depends on early diagnosis and judicious management. While complications involving the haematological system, such as cytopenia and bleeding, are well-known in severe dengue infections due to various factors, the occurrence of haemolytic anaemia in dengue fever is rare. An alteration in the redox state of immune cells due to Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency may lead to atypical presentations of dengue infection, such as intravascular haemolysis. A 37-year-old male initially presented to the emergency department with a 6-day history of fever, red-colored urine and severe shortness of breath. Routine tropical fever work-up detected an infection with the dengue virus, while severe enzyme deficiency was attributed as the cause of haemolysis. The presence of splenomegaly, haematuria, hyperferritinaemia, transaminitis and raised triglycerides was suggestive of Macrophage Activation Syndrome (MAS), which was confirmed through a bone marrow biopsy. He was diagnosed with dengue fever, complicated by MAS and haemolytic anaemia due to G6PD deficiency.

Keywords: Haemolysis, Macrophage activation syndrome, Oxidative stress

CASE REPORT

A 37-year-old male, a businessman, presented to the emergency department with complaints of fever and reddish discoloration of urine for six days. He had also developed respiratory distress over the past two days. He denied any past history of urine discoloration, had no known co-morbidities, and no history of hospitalisation in the past. His only recent medication use was Tablet Paracetamol 650 mg every 12 hours for the last 48 hours. There was no significant travel history.

On initial assessment, he was haemodynamically unstable, with a body temperature of 100°F, a heart rate of 108 beats per minute, blood pressure of 110/70 mm Hg, a respiratory rate of 28 breaths per minute and oxygen saturation of 96% on room air. Auscultation of the respiratory system revealed bilateral basal crepitations. His abdomen was soft, with tenderness in all quadrants and a palpable spleen. Preliminary investigations revealed severe anaemia (haemoglobin - 4.5 g/dL), prompting the transfusion of one unit of Packed Red Blood Cells (PRBC).

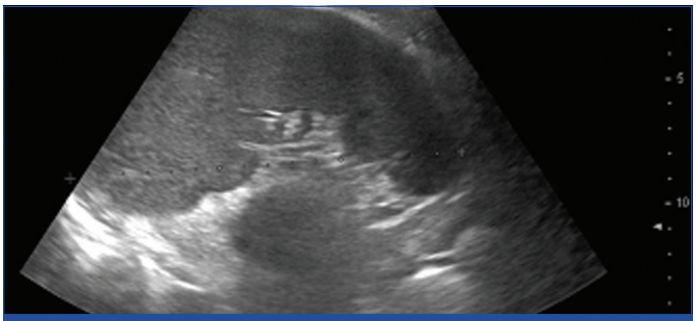
After basic resuscitation and the initiation of empirical treatment with intravenous normal saline at 60 mL/hr, Inj. Meropenem 2 g, Inj. Ondansetron 4 mg, Inj. Pantoprazole 40 mg, and Inj. Paracetamol 1000 mg, he was shifted to the Intensive Care Unit (ICU) and relevant investigations were conducted. Significant findings included normocytic normochromic anaemia with anisocytosis, raised reticulocyte counts, neutrophilic leukocytosis, worsening thrombocytopenia, elevated indirect bilirubin levels and increased serum creatinine levels, along with reactive Dengue IgM [Table/Fig-1]. He tested negative for malarial antigens and no malarial parasites were found on the peripheral smear. The extended Coombs test was negative. Further work-up for haemolysis revealed severe G6PD

Investigation (Normal range)	Day 6 of illness= IP Day 1	IP Day 3	IP Day 4	IP Day 5	IP Day 9 =Day of discharge
Hb (13.0-17.0 g/dL)	4.5	7.6	8.0	8.5	12.0
PCV (40-50%)	11.8	22.2	23.7	27.2	39.1
WBC (4000-10000/cumm)	21100	17800	8200	8300	6700
DC (N40-80%, L20-40%)	N64 L32	N87 L06	N88 L08	N86 L12	N67 L27
Platelet (1.5-4.0 lacs/cumm)	0.81	1.06	0.68	0.98	1.05
RBC	46NRBC/100WBC	20NRBC/100WBC	-	22NRBC/100WBC	
PT/INR (MNPT 13.3 sec)	16.3/1.21	-			15.8/1.18
C-reactive protein (<0.5 mg/dL)	3.1	7.7	-	6.2	-
Procalcitonin (<0.05 ng/mL)	-	15	-	8.8	-
Serum ferritin (20-250 ng/mL)	100000	26934	-	-	-
Plasma fibrinogen (200-400 mg/dL)	365	-		229	-

Serum creatinine (0.9-1.3 mg/dL)	1.7	-	1.3	1.1	-
Serum total bilirubin (upto 1.0 mg/dL)	3.9	-	5.8	3.4	-
Serum direct bilirubin (upto 0.2 mg/dL)	0.5	-	1.9	1.1	-
ALT (10-40 U/L)	280	-	139	68	-
AST (10-42 U/L)	1458	-	642	81	-
ALP (53-128 U/L)	156	-	128	73	-
GGT (7-64 U/L)	31	-			
Urine routine and microscopy	-			10-12 WBC/hpf, 6-8 RBC/hpf	2-4 WBC/hpf, 0-2 RBC/ hpf

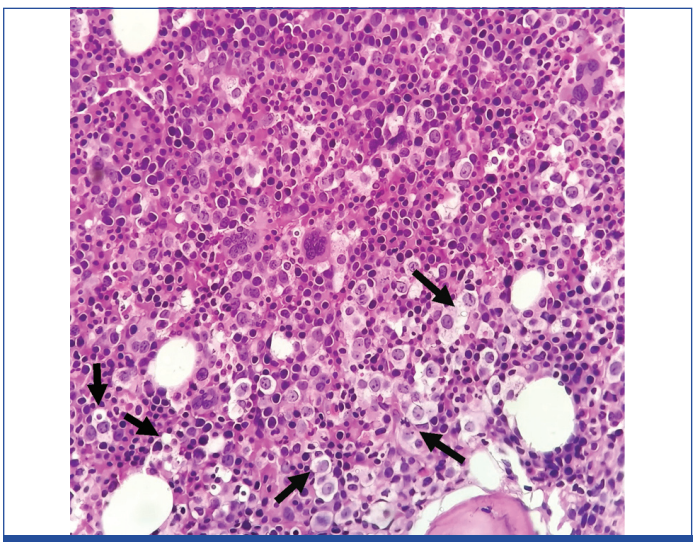
[Table/Fig-1]: Investigation profile.
IP: Inpatient; Hb: Haemoglobin; PCV: Packed cell volume; WBC: White blood cells; DC: Differential count; N: Neutrophils; L: Lymphocytes; RBC: Red blood cells; NRBC: Nucleated RBC; PT: Prothrombin time; MNPT: Mean normal prothrombin time; INR: International normalised ratio; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase

deficiency using manual spectrophotometry. Abdominal imaging suggested moderate splenomegaly [Table/Fig-2], bilateral renal parenchymal disease, gallbladder sludge, and mild right-sided pleural effusion.



[Table/Fig-2]: Moderate splenomegaly on ultrasound abdomen.

In view of splenomegaly, haematuria, hyperferritinemia, transaminitis, and elevated triglycerides, MAS was suspected. Bone marrow aspiration cytology indicated a reactive marrow with erythroid hyperplasia. Bone marrow biopsy confirmed a reactive marrow with haemophagocytes [Table/Fig-3]. He was managed by a multidisciplinary team of internists, intensivists, haematologists and urologists. Management included conservative treatment with intravenous fluids, supplemental oxygen via High Flow Nasal Oxygen (HFNO), which was later tapered off, bladder irrigation for haematuria, hepatoprotective measures and intravenous corticosteroids (Inj. Dexamethasone 8 mg) for the treatment of MAS. Multiple units of PRBC were transfused. Other supportive measures included Inj. Furosemide 20 mg and 20% Human Albumin. He gradually improved both clinically and symptomatically. His platelet count increased, ferritin levels approached normal, liver enzymes returned to normal, and haematuria resolved. After nine days of institutional treatment, he was discharged in a haemodynamically stable condition.



[Table/Fig-3]: Bone marrow biopsy showing reactive marrow with haemophagocytes (marked with arrow)- Haematoxylin and Eosin stain, 40x magnification.

He was followed-up in the outpatient department one week after discharge, where he was found to be clinically improved, with bilateral vesicular breath sounds, a heart rate of 70 beats per minute, blood pressure of 130/80 mm Hg, and maintaining oxygen saturation on room air. He also reported the resolution of all presenting symptoms. His laboratory parameters showed significant improvement, with haemoglobin at 11.8 g/dL, WBC count at 6000/cumm with 60% neutrophils, platelet count at 155,000/cumm, INR at 1.17, serum ferritin at 460 ng/mL, serum creatinine at 0.9 mg/dL, and normal urinalysis.

DISCUSSION

The patient was a 37-year-old adult male who presented to the hospital with an acute febrile illness of six days' duration in a region with a high prevalence of dengue virus infection. He also reported reddish discoloration of urine and respiratory distress. The differential diagnoses for reddish discoloration of urine include haematuria, haemoglobinuria, myoglobinuria, bilirubinuria and pseudo-haematuria due to toxins, certain medications and foods [1]. The discoloration of urine in index patient was due to the presence of red blood cells. While complications involving the haematological system, such as cytopenia and bleeding, are well-known in severe dengue infections due to various factors, the occurrence of haemolytic anaemia in dengue fever is rare [2]. Index patient exhibited predominantly extravascular haemolysis, as evidenced by the presence of normocytic anaemia, a raised reticulocyte count, hyperbilirubinaemia, moderate splenomegaly and a reactive marrow with erythroid hyperplasia.

Index patient had no incriminating factors such as ingestion of sulfonamides, antimalarials, fava beans, or a history of consanguinity in the family. Thus, through a process of exclusion, we attributed the haemolytic anaemia in index patient to dengue fever and G6PD deficiency. G6PD is an enzyme present in the cytoplasm of human cells that participates in the pentose phosphate pathway, providing reducing energy by maintaining levels of the coenzyme Nicotinamide Adenine Dinucleotide Phosphate (NADPH). NADPH is crucial for both the oxidant and antioxidant systems of cells. In both scenarios, NADPH participates in the production of Reactive Oxygen Species (ROS). G6PD-deficient red blood cells undergo both intravascular and extravascular haemolysis due to their sensitivity to any additional oxidative stress, leading to cellular damage and premature destruction of erythrocytes. As part of the innate immune system, ROS are required for phagocytosis. When there is severe G6PD deficiency, the lack of oxidative metabolism may lead to a decrease in oxygen-dependent phagocytosis, as seen in chronic granulomatous disease, which can allow for viral replication [3,4].

G6PD-deficient individuals infected with the dengue virus may have higher viral titers, which could be significant for enhanced virus

transmission. Furthermore, granulocyte dysfunction and higher viral loads in this population may result in a more severe form of dengue infection [4]. Studies have shown that monocytes in G6PD-deficient patients demonstrate increased vulnerability to dengue virus infection, with superior replication capabilities compared to those from a control group [3]. Despite the apparent connection between G6PD deficiency and enhanced multiplication of the dengue virus, no documented trials have been conducted to elucidate the mechanism behind this observation [5].

A cross-sectional study was conducted among 196 patients positive for dengue infection to investigate the relationship between the severity of dengue infection and G6PD deficiency. However, no association was found, as severe dengue was not linked to G6PD enzyme deficiency or the presence of G6PD gene mutations [6]. There have been reported cases suggesting an increased occurrence of Dengue Haemorrhagic Fever in G6PD-deficient individuals compared to those without the deficiency [5]. The interplay between these conditions makes managing such cases challenging. Judicious fluid management under close observation and appropriate blood transfusions are cornerstones in managing complicated dengue infections [7].

CONCLUSION(S)

Though unusual, haemolytic anaemia is a potential clinical feature of dengue. Therefore, in addition to bleeding manifestations such as epistaxis, gum bleeds, gastrointestinal bleeding, hypermenorrhoea, and haematuria, physicians must consider haemolysis as a reason for anaemia in dengue. This also implies that dengue virus infection should be regarded as one of the infectious causes of haemolytic anaemia, alongside *Mycoplasma pneumoniae* and other pathogens. G6PD-deficient patients may experience more severe manifestations of haemolysis. As the incidence of DENV infection rises and the understanding of the pathophysiology of the disease increases, physicians must maintain a high index of suspicion for atypical manifestations of dengue. A heightened level of awareness is crucial for timely diagnosis and treatment, ultimately minimising morbidity and mortality.

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PARTICULARS OF CONTRIBUTORS:

1. Junior Consultant, Department of Internal Medicine and Rheumatology, Apollo Multispeciality Hospitals Limited, Kolkata, West Bengal, India.
2. Consultant, Department of Internal Medicine and Rheumatology, Apollo Multispeciality Hospitals Limited, Kolkata, West Bengal, India.
3. Consultant, Department of Internal Medicine and Rheumatology, Apollo Multispeciality Hospitals Limited, Kolkata, West Bengal, India.
4. Senior Consultant, Department of Internal Medicine and Rheumatology, Apollo Multispeciality Hospitals Limited, Kolkata, West Bengal, India.
5. Final Year Postgraduate Resident, Department of Internal Medicine and Rheumatology, Apollo Multispeciality Hospitals Limited, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Meghna Dutta,
Flat 5B, Nirvana Apartments, 462, Dum Dum Park, Kolkata-700055,
West Bengal, India.
E-mail: yourfriendmeghna@gmail.com

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