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CASE REPORT

Dengue Shock Syndrome in Sickle Sell Disease Precipitating Sickle Cell Hepatopathy: a Case Report

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Abstract: Sickle cell disease (SCD) is a known risk factor for the development of severe dengue, however, literature documenting dengue in SCD is scarce. Dengue fever further triggers the sickling process in a patient with SCD by augmenting endothelial dysfunction, the main identifiable cause behind organ dysfunction. Hepatic involvement in SCD due to enhanced sickling can be in the form of acute viral hepatitis, cholecystitis, acute sickle hepatic crisis, and more severe sickle cell intrahepatic cholestasis (SCIC). Initially starting as an acute sickle hepatic crisis, SCIC progresses to striking jaundice, enhanced bleeding tendency coupled with mostly renal failure. We report a rare case of a female, native of Chhattisgarh with SCD and dengue shock syndrome who had fatal hepatic complications resulting from accelerated severe endothelial dysfunction due to concurrent illnesses.

Keywords: Sickle cell disease; Dengue infection; Dengue shock syndrome; Acute hepatic failure; Sickle cell hepatopathy

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1. Introduction

India is home to a large number of people born with SCD alongside Brazil, and Iran. Replacement of glutamine by valine at the 6th position of the beta chain of haemoglobin leads to abnormally sickle-shaped adhesive red blood cells (RBCs) that interact with endothelium, causing functional nitric oxide (NO) deficiency and a persistent oxidative state (1–3). Around 300000 children are added to the existing SCD population annually.

Dengue is a mosquito-transmitted viral infection common in tropical regions. It infects 390 million people in a year worldwide. In most cases, it manifests as benign myalgia or arthralgia while in its severe form, it can cause multi-organ dysfunction and ultimately death. Chronic comorbid states like SCD are well-recognized risk factors for the progression of dengue from simple self-limiting viral infection to severe dengue (2). Damage to endothelial cells and resultant increased vascular permeability are pivotal to the development of severe dengue (3,4). Dengue fever triggers the sickling process in a patient with SCD by augmenting endothelial dysfunction, the main identifiable cause behind organ dysfunction.

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Combined targeting of endothelium by direct viral attack alongside haemoglobin S (HBs) polymerization and vasocclusion accelerates hepatorenal failure (5,6). Hepatic involvement in SCD due to enhanced sickling can be in the form of acute viral hepatitis, cholecystitis, choledocholithiasis, acute sickle hepatic crisis, and more severe SCIC. Initially starting as an acute sickle hepatic crisis SCIC progresses to striking jaundice, enhanced bleeding tendency coupled with mostly renal failure. Dengue by itself usually causes mild-moderate elevations in liver enzymes (6–8).

We report a rare case of an SCD female, a native of Chhattisgarh who was referred to our center with dengue fever in dengue shock syndrome and died due to fatal hepatic complications arising from accelerated severe endothelial dysfunction, due to existent comorbidity and dengue infection.

2. Case presentation

A 28-year-old female native of Chhattisgarh was referred to our emergency department with high-grade fever, abdominal pain, yellow discolouration of the skin and sclera for four days associated with altered sensorium and intermittent intermenstrual scanty bleeding per vagina for 24 hours. She was a known case of homozygous sickle cell disease. There was no history to suggest paracetamol toxicity or herbal drug ingestion.

On examination, the patient was unconscious with a GCS of

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Table 1: Laboratory parameters of the index case

	Day 1	Day 2	Day 3	Day 4	Reference
Haemoglobin	5.4	3.1	7.9	6.4	12-18 g/dl
PCV	15.2	8.5	24.6	20.2	36-54 %
MCV	88.9	88.5	94.6	95.3	80-96 fL
MCHC	35.5	36.5	32.1	31.7	30-36 %
Platelets count	37	43	38	24	150k-450k/µL
Reticulocyte count	9.96	7.93		3.05	0.2-2 %
TLC	59.89	71.34	31.55	15.11	4k-11k/µL
DLC (N/L)	61.8/21.9	51.7/28.5	73.2/17.8	52.9/40.3	N- 40-75%, L- 20-45%
Sodium	131	135	138	-	135-145 mEq/L
Potassium	4.3	3.8	5.6	-	3.5-5.5 mEq/L
Chloride	98	99	96	-	98-107 mEq/L
Urea	67	72	64	-	15-45 mg/dL
Creatinine	2.1	2.2	2.9	-	0.80-1.80mg/dL
Uric acid	9.8	10	10.4	-	2.4-7 mg/dL
Calcium	8	8.6	9.2	-	8-10.4mg/dL
Phosphate	4.9	5.9	High	-	2.5-4.5 mg/dL
Bilirubin (T/C)	23/11.8	24.4/13.5	25.4/14.6	-	T-0.2-1.0 mg/dL, C-0-0.25mg/dL
ALP	181	180	165	-	40-130 IU/L
AST	23250	14060	7260	-	5-40 IU/L
ALT	7180	5290	4130	-	5-40 IU/L
Total Protein	5.3	5.7	4.9	-	6-8gm %
Albumin	2.9	3.1	2.9	-	3.8-5.5 gm/dL
CRP	108	94	96	-	0-5 mg/L
LDH	-	9670	-	-	
PH	7.233	-	7.235	-	
HCO3	8	-	14	-	
Lactate	11.4	-	5.1	-	
Anion Gap	22	-	10	-	
PCO2	19.6	-	34.2	-	
PO2	59.4	-	109	-	
Glucose	82	-	126	-	
PT	41.5	-	-	-	12-15 seconds
aPTT	46.4	-	-	-	28-32 seconds
PTI	29	-	-	-	80-100%
INR	3.42	-	-	-	1.00

TLC: Total leukocyte count; DLC: Differentiated leukocyte count; N/L: Neutrophils/lymphocyte;
T/C: Total/conjugated; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase;
CRP: C-reactive protein; LDH: Lactate Dehydrogenase; PT: Prothrombin time; aPTT: activated partial thromboplastin time.

E3VTM4, Blood pressure of 90/70 mm Hg on inotropic support, pulse rate of 140 beats per minute, and oxygen saturation (SpO2) of 98%. Severe pallor, conjunctival chemosis, and marked icterus were present. On abdominal examination, the liver was palpable 4 cm below the right costal margin, and the spleen was not palpable. Upon auscultation, she had bilateral basal crepitations. There were no documented focal neurological deficits or meningeal signs.

A review of her available past medical records revealed an HbS of 77.3% and HbA of 17.3% on haemoglobin electrophoresis (HPLC assay). There were no records available about her last blood transfusion, or any episodes of previous sickle cell crisis and admission. Considering the clinical possibility of acute onset febrile illness with hepatic involvement, tropical fever serologies were obtained. In the meantime, the patient was put on empirical doxycycline and hydroxyurea tablets. Initial laboratory parameters revealed severe anaemia with a haemoglobin of 5.4g/dl, thrombocytopenia with a platelet count of 37000/mm3, and leucocytosis (Table 1). Abdominal ultrasound revealed hepatomegaly and moderate ascites (Figure 1); Doppler revealed normal flow in hepatic veins and inferior vena cava. The spleen was not visualized due to possible auto-splenectomy. Her RT-PCR for SARS-CoV2 was negative. The biochemistry panel revealed severely deranged liver enzymes and coagulation profiles, suggesting fulminant hepatic failure. In addition, there

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Figure 1: Transabdominal ultrasound image showing liver enlargement.

was evidence of acute kidney injury. Echocardiography revealed normal ejection function and no regional wall motion abnormalities. Dengue NS1 antigen was negative but dengue IgM antibodies came back positive. Scrub typhus, Malaria, coombs test, hepatitis A, B, C, and E, HIV, and HSV serology were negative. The patient was diagnosed with dengue shock syndrome with dengue hepatitis and sickle hepatic crisis. N-acetyl cysteine (NAC) was added to the treatment given the liver failure to avail of transplant-free survival benefits. Blood, random donor platelet (RDP), and fresh frozen plasma (FFP) transfusions were initiated to lower HbS concentration in circulation and reverse coagulopathy. Her arterial blood gas (ABG) parameters did not improve, possibly due to capillary leak and additional volume overload from multiple blood transfusions, leading to increased ventilatory support requirement. On day two of admission, haemodialysis was done due to progressively decreasing urine output, and worsening chest X-ray (CXR) parameters indicating volume overload, refractory metabolic acidosis, and acute kidney injury. Her urine output didn't improve despite haemodialysis; anuria persisted and therefore, the inotropic support could not be reduced. She remained hemodynamically unstable. The patient did not improve and succumbed to her illness almost 90 hours into admission.

3. Discussion

The exact pathogenesis of liver injury in dengue is unclear but among the various hypotheses, the role of hypoxia and vascular leakage is well recognized. More recently, the role of viremia-linked interleukin storm has been highlighted as an immune mechanism causing hepatic involvement. Chronic conditions like SCD, hypertension, diabetes, ischemic heart disease, and alcohol use are known risk factors for the development of severe dengue, but literature documenting dengue in SCD is scarce (3,6,7). Severe dengue causes mild-moderate elevations in liver enzymes - mainly aspartate aminotransferase (AST) - whereas in uncomplicated SCD unconjugated hyperbilirubinemia is seen with elevations in AST due to the increased haemolysis or ineffective erythropoiesis (8).

Hepatic involvement in SCD can be in the form of acute viral hepatitis, cholecystitis, choledocholithiasis, acute sickle hepatic crisis, and more severe SCIC. Initially starting as an acute sickle hepatic crisis, SCIC progresses to striking jaundice, enhanced bleeding tendency coupled with mostly renal failure. Serum alanine aminotransferase (ALT) and AST levels have been documented to rise more than 3000 and 9000 respectively with bilirubin levels as high as 273 mg/dl. Alongside a deranged coagulation profile, elevations of blood urea, creatinine, and ammonia are also seen (6–8).

Our patient had a history of abdominal pain and rapidly pro-

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gressing jaundice. Her liver enzymes were markedly elevated with AST as high as 23000 and ALT of 7000. The enzymes dropped insignificantly with the initiation of therapy during her short stay but remained higher than the ranges documented so far in the literature for SCIC or dengue shock syndrome. Renal impairment is postulated to be reversible in SCIC but her kidney functions did not improve despite dialysis. Post-mortem liver biopsy in SCD patients with SCIC shows dilated canaliculi with bile plugs and bile-stained microinfarcts (8); however, we could not perform post-mortem biopsies due to the refusal of the patient's family.

We believe that the propensity of endothelial damage in SCD and dengue precipitated our patient's liver failure, causing SCIC - the most severe variant of sickle hepatopathy - which is ultimately proved to be fatal. Dengue replication directly damaged the endothelium causing inflammation and coagulopathy, leading to accentuated sickling, increased plasma leak, and a profound shock.

Early aggressive red cell exchange transfusion (aRCE) targeted at decreasing HbS level and improving viscosity with hydration has been postulated as the best treatment modality in patients with SCD and severe dengue (3,9). Although understudied, the reasonable strategy in hepatic crises management of SCD starts with simple blood transfusions followed by aRCE transfusion in severe cases with limited or no improvement in hepatic status. Almost 50% fatality within 24 hrs is documented in patients with SCD and dengue infection (2). Among 17 probable cases of SCIC documented so far only 9 have survived (8). Our patient survived only for 90 hours despite early ICU admission and treatment initiation, haemodialysis, and transfusions. Although plasmapheresis was planned early, it could not be done due to financial constraints.

4. Conclusion

Management of hepatic failure in dengue infection in patients with SCD is a physician's dilemma. A liver biopsy is not always possible and distinguishing sickle cell hepatopathy from dengue hepatitis purely based on clinical features and laboratory parameters is not feasible in the absence of histological confirmation. A scarcity of data regarding management, complications, outcome, and survival rates limits our scope further. Since our country is a major contributor to the global SCD population and dengue epidemics are an annual event, it becomes increasingly important to formulate guidelines for the management of dengue-associated complications in SCD.

5. Declarations

5.1. Acknowledgment

None.

5.2. Conflict of interest

The authors declare no conflict of Interest.

5.3. Funding and supports

The authors received no specific funding for this work.

5.4. Authors' contributions

All authors contributed to the study's conception and design. The idea for the article was conceived by ZM, MG, and NA. Material preparation and data acquisition were performed by ZM, SB, NA, and CS. Data analysis and the first draft of the manuscript were written by ZM, SB, and MG. All authors commented on versions of the manuscript. SB, CS, MG, and ZM performed the literature search. ZM and MG critically revised the work. All authors read and approved the final manuscript.

5.5. Ethical statement

The study was conducted in accordance with the Declaration of Helsinki.

5.6. Informed consent

The patient has provided written consent for publication and images. No identifying factors have been disclosed.

5.7. Availability of supporting data

To protect the privacy of the participant the data cannot be shared.

5.8. Using artificial intelligence chatbots statement

The authors did not use artificial intelligence chat bots to write the manuscript.

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