Fulminant dengue hepatitis in sickle cell disease: Recovery against the odds

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ABSTRACT

Fulminant hepatitis is a potentially life-threatening disease that is evident through the findings of organ dysfunction, jaundice, and hepatomegaly, which is painful. Dysfunction of the endothelial cells and thus the damage of the endothelium is the probable mechanism, which is responsible for causing complications of hepatobiliary system in patients with sickle cell disease. Various acute as well as chronic manifestations of the hepatobiliary system, having varied severity and pathophysiology are associated with sickle cell disease. Dengue fever may also affect the liver starting from asymptomatic liver enzyme derangement to fulminant hepatic failure. This case series describes the first-ever association of fulminant hepatic failure resulting from the synergistic effect of dengue fever with sickle cell disease and thus highlights the importance of prevention of dengue fever in sickle cell patients, thereby preventing potentially lethal fulminant hepatic failure.

Keywords: Dengue, fulminant hepatitis, sickle cell disease, tropical diseases

Introduction

Dengue fever is a common cause of fever in developing countries. Dengue is considered to be one of the most important viral infections transmitted by arthropods which infect humans and affect the quality of life as well as mortality. The World Health Organization states that dengue fever affects about 50 to 100 million patients around the globe annually thus adding to the health care burden substantially. As a result, dengue fever has become one of the most serious public health issues. The presenting picture of dengue fever ranges from high-grade fever with chills, headache, intense myalgia to prostration, nausea, and vomiting. There is multisystem involvement in dengue fever, which has resulted in multi-organ failure with an increased rate of mortality even at a young age. With the increase in DENV infection, there is an increased rate of viremia, which is associated with organ involvement such as liver. Hepatic manifestations witnessed in dengue fever are either a result of direct virus-induced toxicity or dysregulated immune-mediated injury to the liver. Hepatoocytes and Kupffer cells are the prime targets of the dengue virus thus leading to profound liver injury. If dengue fever is suspected to be the cause of hepatitis, the differentials should consist of leptospirosis, malaria, and hepatitis A, B, and C as dengue is an unusual cause of hepatitis and the physician should beware of missing out on another cause of hepatitis in a dengue fever patient.

Sickle cell disease is a genetic illness caused by a mutation in the beta-globin gene, which results in the production of a defective hemoglobin protein S leading to a change in the shape of red blood cells. Sickle cell illness and the recurrent
blood transfusions used to treat it can cause serious liver damage. After injury to the liver, this illness can cause the liver to regenerate improperly. In this case series, we report two cases of young males with sickle cell disease who presented with fulminant hepatic failure as a result of dengue fever and thus emphasizing the importance of the synergistic effect of dengue and sickle cell in causing profound liver cell damage.

Because primary care physicians are often the first line of defense against dengue and sickle cell disease, they should be well aware of this concomitant complication arising out of these twin diseases in the rural areas of the world.

Case Series

Case 1

Patient information
A 30-year-old male patient presented with a 4-day history of diffuse myalgia, headache in the retro orbital region, abdomen pain, and intermittent fever associated with chills. There was no history of petechial spots on the body, bleeding from oral mucosa, and black colored stools. The patient was a known case of sickle cell disease since 16 years with sickle cell SS pattern, and there was no history of any hepatotoxic drug intake in the past.

Physical examination
On physical examination, pulse was 126 beats/min, regular in rhythm, normal in volume, pallor and icterus were present, blood pressure was 100/70 mmHg in right arm supine position, liver was palpable 1.5 cm below the right costal margin, and spleen was palpable as well as tender with Hackett’s grade 2. The patient was maintaining oxygen saturation of 98% on room air.

Diagnostic assessment
The laboratory investigations are shown in Table 1. As the patient complained about pain in abdomen and considering USG findings, CECT abdomen was done, which revealed hepatosplenoemegaly, minimal ascites, and bilateral pleural effusion without detection of gallstones or dilatation of the intrahepatic and extrahepatic bile ducts as shown in Figure 1.

Interventions
The differential diagnosis of dengue fever associated fulminant was considered weighing on the clinical data, laboratory investigations, and local epidemiology for dengue fever as our hospital was based in rural central India. As the patient had sickle cell disease, a final diagnosis was made as fulminant hepatitis as a result of dengue fever and sickle cell disease. The patient was managed with hydration through intravenous fluids and blood transfusion cells to obtain target hemoglobin of 10 mg/dL, intravenous antibiotics (ceftriaxone 2 g/day intravenously), and intravenous analgesics.

Follow-up and outcome
During the course of hospital stay, laboratory parameters improved along with clinical improvement. Further management was done through blood transfusion to maintain optimal hemoglobin levels, continuing proper hydration and other supportive measures including hydroxyurea. The patient was ultimately discharged in stable condition 15 days following admission and is presently doing well on follow-up with normal liver enzymes.

Case 2

Patient information
A 19-year-old male presented with the chief complaint of body ache, extreme pain in the joints, vomiting (2–3 episodes per day)

Table 1: Laboratory investigations of case 1

| Lab Parameter | Day 1                                      | Day 3                                      |
|---------------|--------------------------------------------|--------------------------------------------|
| CBC           | Hb-4.6 g/dL, MCV-69.2 fl, Platelet count-0.75/dL, WBC count-50400/dL | Hb-7.8 g/dL (after 2 unit of blood transfusion), MCV-72.4 fl, Platelet count-1.7/dL, WBC count-92700/dL |
| LFT           | Total protein-7.8 g/dL, Albumin-3.2 g/dL, Aspartate aminotransferase-3200 units/l, Alanine aminotransferase-1500 units/l, Alkaline phosphatase-57 IU/l, Total bilirubin-8.9 mg/dL | Total protein-7.3 g/dL, Albumin-3.5 g/dL, Aspartate aminotransferase-4062 units/l, Alanine aminotransferase-1624 units/l, Alkaline phosphatase-137 IU/l, Total bilirubin-7.9 mg/dL |
| KFT           | Creatinine-1.7 mg/dL, Urea-47 mg/dL, Sodium-132 mmol/L, Potassium-5.5 mmol/L | Creatinine-1.8 mg/dL, Urea-44 mg/dL, Sodium-144 mmol/L, Potassium-5.2 mmol/L |
| D-Dimer       | 2689                                       | -                                         |
| LDH           | 294                                        | -                                         |
| INR           | 1.6                                        | 1.03                                      |
| HBsAG, HCV, HIV | Negative                           | Positive                                   |

MCV - Mean corpuscular volume; LFT - Liver function test; KFT - Kidney function test; LDH - Lactate dehydrogenase; INR - International normalised ratio
and intermittent fever with rigors since 3 days. The patient had a family history of sickle cell disease and was diagnosed with sickle cell disease at the age of 14 years with SS genotype and he was on regular follow-up with the medicine outpatient department for the same. He was on tablet hydroxyurea since last 2 years. There was no history of any petechial spots or bleeding from oral mucosa.

Physical examination
On physical examination, pulse was 106 beats per minute, regular, pallor and icterus were present, and blood pressure was 110/70 mmHg in right arm taken in supine posture. The patient was maintaining an oxygen saturation of 97% on room air. Tenderness was present in the abdomen in the right hypochondrium region and liver was palpable 1 cm below the coastal margin in the midclavicular line.

Diagnostic assessment
The laboratory investigations are mentioned in Table 2 as comparing day 1 with day 5. The differential diagnosis of sickle cell crisis associated with dengue fever was considered and the patient was tested for nonstructural protein 1 (NS1) antigen, which was positive. A final diagnosis of fulminant hepatitis with dengue fever and sickle cell disease was made.

Intervention
The initial management was comprised of hydration with intravenous fluid resuscitation, analgesia, and use of prophylactic antibiotics. On Day 3 (two days after admission), there was clinical deterioration, which was noted as painful hepatomegaly (liver was now palpable 3 cm below the right costal margin), drowsiness, and respiratory failure. The patient was monitored regularly for platelet count, which showed a declining trend. Renal function tests were normal. As the patient had hepatitis, a complete viral hepatitis (A, B, and C) serology panel was done, which was negative. Abdominal ultrasonography (done on day 3) revealed hepatomegaly with no other significant findings.

Follow-up and outcome
The patient responded well to the treatment and showed clinical improvement subsequently with a rise in platelet count and a decrease in hematocrit. The patient was ultimately discharged in stable condition on day 13 following admission and is presently doing well on follow-up.

Discussion
Fulminant hepatitis is a dangerous and acute entity having significantly high mortality, especially in patients with sickle cell anemia and dengue; however, the pathophysiology for the same remains unclear. One possible mechanism of dengue fever

| Lab Parameter | Day 1 | Day 5 |
|---------------|-------|-------|
| CBC           |       |       |
| Hemoglobin    | 7 g/dL | Hb-9 g/dL (after 2 unit of blood transfusion), |
| MCV           | 70.2 fL | MCV: 72.4 fL, |
| Platelet count | 0.21/dL | Platelet count: 0.60/dL (after platelet transfusion), |
| White blood cell count | 6000/dL | WBC count: 10200/dL |
| LFT           |       |       |
| Total protein | 6.9 g/dL | Total protein: 7.3 g/dL, |
| Albumin       | 3.6 g/dL | Albumin: 3.5 g/dL, |
| Aspartate aminotransferase | 2880 units/l | Aspartate aminotransferase: 2133 units/l, |
| Alanine aminotransferase | 1740 units/l | Alanine aminotransferase: 1740 units/l, |
| Alkaline phosphatase | 50 IU/l | Alkaline phosphatase: 137 IU/l, |
| Total bilirubin | 7.2 mg/dL | Total bilirubin: 7.9 mg/dL |
| KFT           |       |       |
| Creatinine    | 0.7 mg/dL | Creatinine: 0.8 mg/dL, |
| 0.9 mg/dL,    |       | Urea: 46 mg/dL, |
| Urea-52 mg/dL,|       | Sodium: 144 mmol/L, |
| Sodium-132 mmol/l,| | Potassium: 4.8 mmol/L, |
| Potassium     | 5.1 mmol/l | |
| D-Dimer       | 2770 | - |
| LDH           | 328 | - |
| INR           | 1.32 | 1.2 |
| HBsAG, HCV, HIV | Negative | Positive |
| NS1 antigen for dengue | | |

MCV - Mean corpuscular volume; LFT - Liver function test; KFT - Kidney function test; LDH - Lactate dehydrogenase; INR - International normalised ratio
leading to hepatitis is the response of the host to the invading virus, which causes alteration in the perfusion in various tissues of the body as an attempt to preserve perfusion to be provided to vital organs in order to sustain life. Thus, the liver receives less oxygen and the hepatocytes liberate transaminases, which are later detected through blood investigations. Transaminases might represent the degree of injury to the hepatocytes; however, there is no correlation with prognosis.[4]

In sickle cell disease, there is polymerization of hemoglobin S leading to vaso‑occlusion as well as hemolytic anemia. This is responsible for the acute and chronic symptoms arising out of sickle cell disease. There is a continuous state of dysfunction in the endothelial cells and a nitric oxide deficiency, continuous oxidative state, sterile systemic inflammation, hypercoagulability, increased neutrophil adhesion, and platelet activation.[5]

The treatment protocol has not been defined through various studies. Hydration, oxygen supplementation, antimicrobial treatment, analgesia, and blood component transfusion are among the therapeutic measures for sickle cell disease and dengue fever. Despite the lack of research establishing ideal hemoglobin S values, exchange transfusion in order to reduce the fraction of hemoglobin S decreased the process of sickling and is the most commonly used management strategy. If there is coagulopathy, the patient can be transfused fresh frozen plasma.

Dengue infection in patients with sickle cell disease is a problematic phenomenon with an increased risk of systemic complications, which are caused as a result of sickling process. Given the projected incidence of Sickle Cell Disease and the occurrence of frequent outbreaks of dengue fever in India, it is an underreported and unrecognized association, which is of importance for the primary care workers.[6] Dysfunction of the endothelium is the major pathophysiology for the emergence of clinical symptoms in both dengue virus patients and sickle cell disease patients. The activation of endothelial cells during dengue infection causes an increase in vascular permeability, and the likely mechanisms include direct infection through virus or the release of various cytokines by immune cells that are infected.[7]

The interplay of all of these variables with the complicated process of pathology associated with infection of dengue virus, including damage to endothelium and activation of platelet, may cause dysfunction of organs as shown in Figure 2.

In both cases, the likely cause of hepatitis is the synergistic effect of dengue virus with sickle cell disease as leptospirosis, malaria, and hepatitis A, B, and C were ruled out and the patients tested positive for dengue NS1 antigen. They also responded well to hydration and blood transfusion further supporting our postulate.

This is the first case series that associate the synergism of sickle cell disease and dengue in producing fulminant hepatitis to the best of our knowledge.

As the primary care physicians work on the frontline treating patients with dengue fever, they should be vigilant for the development of fulminant hepatic failure in sickle cell patients, which can prove to be fatal if not diagnosed on time.

**Conclusion**

In conclusion, dengue virus infection can cause severe and acute consequences of sickle cell disease, such as hepatitis. It is critical to underline that physicians understand how to spot early unexpected and possibly deadly complications in sickle cell disease patients, as well as problems caused by dengue infection, in order to deal with the dual problem they may face during dengue outbreaks.

**Key points**

- Sickle cell patients contracting dengue infection should be monitored for the development of hepatitis.
- Clinicians combatting dengue fever on the frontline should be vigilant to detect early signs of hepatitis and liver failure in patients who have sickle cell disease in order to prevent mortality.

**Informed consent**

Informed consent was taken from both the cases described in this case series.

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**Conflicts of interest**

There are no conflicts of interest.

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