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Dengue fever complicated with acute liver failure: A case report of expanded dengue syndrome and literature review

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Abstract

Dengue is the most common arboviral disease, the presentation of which ranges from asymptomatic illness to dengue shock syndrome. Liver is the most common organ affected in dengue, and liver involvement is asymptomatic in majority. Dengue fever is a rare, but a leading cause for acute liver failure in endemic regions. Here, we report a case of a 34-year-old male ethanol user (16 units per week), presented with typical features of dengue infection, which was confirmed serologically, complicated with acute liver failure without clinical, radiological or laboratory evidence of plasma leakage. He was managed with intravenous fresh frozen plasma and N-acetyl cysteine along with other recommended supportive therapies for acute hepatic failure. He made an uneventful recovery.

Keywords

Dengue hemorrhagic fever, dengue fever, acute liver failure, N-acetyl cysteine, fresh frozen plasma, ethanol

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Introduction

Dengue fever is the most common arboviral infection worldwide and is transmitted by *Aedes aegypti* and *Aedes albopictus*. Around 50 million dengue infections occur annually in around 100 tropical and subtropical countries. Dengue is endemic in Southeast Asia including Sri Lanka. Dengue virus is a single-stranded, enveloped RNA virus and has four serotypes identified up to now, numbered 1–4. The illness caused by dengue virus has been divided into four clinical spectrums. They are asymptomatic infection, acute febrile illness, classic dengue fever and dengue hemorrhagic fever including dengue shock syndrome. In the severe form of the disease, high level of viremia is associated with involvement of different organs including in particular liver, brain and kidney. Liver is the most common organ affected and shows spectrum of involvement ranging from asymptomatic elevation of hepatic transaminases to occurrence of acute liver failure. The exact mechanism of liver damage is still not completely understood. However, there are several mechanisms postulated including direct viral damage, immunological injury and hypoxic injury due to reduced hepatic perfusion during shock. Evidence-based guidelines are sparse to manage acute liver failure in dengue. However, the use of N-acetyl cysteine (NAC) for non-acetaminophen-related liver injury in particularly dengue-related liver injury has gained importance in the recent past.[1,2]

Case presentation

A 34-year-old Sri Lankan Tamil male, was presented to a tertiary care hospital in Northern Province of Sri Lanka with a history of high-grade fever of 3-days duration which was associated with myalgia, arthralgia and retro-orbital pain. He also had vomiting and loss of appetite for preceding 3 days. He never experienced an abdominal pain or distention. He had no mucocutaneous bleeding manifestations on presentation. He had no symptoms suggestive of either respiratory or urinary tract infection. There was no past medical history of note. He is an ethanol user, consuming 16 units per week for last 10 years. He did admit a history of binge drinking during the initial course of the illness to relieve his pain.

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On arrival, he was conscious and rational. He was febrile with a temperature of 38.6°C. He was not pale or icteric. His capillary refilling time was less than 2 s. There were no peripheral lymphadenopathy, petechial rashes, ecchymotic patches or stigmata of chronic liver disease.

His pulse rate was 84 beats/min and blood pressure 120/80 mmHg without a significant postural drop. There was no clinical evidence of pleural effusion or free fluid in the abdomen. Abdomen was soft, non-tender, and there was no hepatosplenomegaly. There were no features of neurological deficit or meningeal irritation. Rest of the clinical examination was unremarkable including the optic fundus.

Initial full blood count showed white blood cells (WBCs) of 3.91×10^9cells/L with neutrophil 3.22×10^9/L and lymphocytes 0.37×10^9/L. Hemoglobin, hematocrit and platelet were 16.1 g/dL, 46.1% and 142×10^9/L, respectively. Initial liver biochemistry showed alanine aminotransferase (ALT) 3760 U/L and aspartate aminotransferase (AST) 9352 U/L. Prothrombin time was 16.3 s (standard: 10–13 s). Renal function and urine full report were normal. The dengue non-structural protein 1 (NS1) antigen in serum became positive on day 3 of illness (day of admission).

He was managed in the ward during the initial 48 h with usual supportive care in addition to the standard fluid therapy according to the national dengue management protocol. During this 48 h, the clinical parameters remained within the normal limits.

Although he had defervescence on day 5, he became restless. His conscious state, pulse rate blood pressure and capillary blood glucose were normal, and there was no postural drop or bleeding manifestations. Abdominal examination revealed mild tenderness in the right upper quadrant. Full blood count showed WBC 4.17×10^9cells/L (neutrophil 64%, lymphocytes 30%), hemoglobin 17.6 g/dL, hematocrit 46.8% and platelet count 27×10^9cells/L. Liver biochemistry was as follows: ALT of 8648 U/L, AST of 28,373 U/L, alkaline phosphatase 155 U/L (range: 46–116), albumin 37 g/L and total bilirubin 55.1 µmol/L with direct bilirubin 30 µmol/L. Prothrombin time was elevated to 21.3 s. His other routine biochemical investigations such as blood glucose, renal function tests, serum calcium and venous blood gas were within normal range. A bed side ultrasound scan did not reveal any evidence of plasma leakage.

On the same day night, ceiling of medical care was escalated and patient was transferred to High Dependency Unit. At this point of care, he was diagnosed with acute liver failure with grade III hepatic encephalopathy evidence by deranged liver biochemistry, coagulopathy and altered level of sensorium, and he was started on intravenous NAC infusion (150 mg/kg in 250 mL of 5% dextrose over 15 min, then 50 mg/kg in 500 mL 5% dextrose over 4 h followed by 100 mg/kg in 1000 mL of 5% dextrose over 16 h). Furthermore, he also received lactulose and metronidazole as a part of the treatment for hepatic encephalopathy. Throughout the course of illness, he had never experienced a shock and his vitals were stable except the altered level of consciousness. He was never given supra-therapeutic dose of paracetamol, any other medicines, herbals or traditional medicines that could cause liver injury. He had no clinical, laboratory or radiology evidence of plasma leakage throughout the course of illness. Furthermore, he also developed features of alcohol withdrawal and it was managed with intravenous thiamine and short acting benzodiazepines.

With the above treatment, his cognitive state started to improve. AST and ALT started to decline gradually from the day 6 of the illness as shown in Table 1. On day 7 of illness, the dengue serology (both immunoglobulin G (IgG) and immunoglobulin M (IgM)) was positive. Even though co-existence of alcoholic hepatitis was considered, however, it does not explain the degree of elevation of transaminases in this patient. Since the clinical scenario and the serological evidence confirmed a dengue infection, we did not explore for an alternate cause of hepatic injury other than the work up for co-infections with primary hepatitis virus A, B and C which all became negative. On day 15, patient was sent home after complete recovery.

On review a month later, he was asymptomatic and had successfully abstained from alcohol. His follow-up liver profile and ultrasound scan of the abdomen showed no abnormalities except mild fatty liver.

Discussion

Dengue is becoming the most rapidly spreading mosquito-borne viral disease worldwide. Around 50 million dengue infections occur annually in around 100 tropical and sub-tropical countries. More than 70% of the population at risk for dengue worldwide live in Southeast Asia and Western Pacific region. Dengue is endemic in Southeast Asia including Sri Lanka. Dengue virus is a member of the Flaviviridae family and the genus Flavivirus.[3] It is an RNA virus and has an envelope. There are structural and non-structural proteins encoded by the virus. Structural proteins are capsid, precursor membrane and envelope. There are seven non-structural proteins, and one of them is used as a diagnostic antigen in the initial phases of the illness (NS1). Dengue virus has four serotypes (DENV 1–4).[4] Initially, only in Southeast Asia all serotypes were found, but now all serotypes were found in all tropical and subtropical regions.[5,6] During lifetime, patients can be infected with more than one serotype of dengue virus. Based on the antibody-dependent enhancement theory, second infection with heterologous serotypes is more severe than primary infection.[7] In a meta-analysis by Soo et al.[8] showed that DENV-3 from the Southeast Asia region displayed the greatest percentage of severe cases in primary infection, whereas DENV-2, DENV-3 and DENV-4 from the Southeast Asia region, as well as DENV-2 and DENV-3 from non-Southeast regions displayed the greatest percentage of severe cases in secondary infection. Dengue virus is transmitted by the mosquitos *A. aegypti* and *A. albopictus*.[4]

As per the 2009 World Health Organization (WHO) guidelines,[9] dengue infection is classified according to the

Table 1. Results of laboratory tests of the patient.

Name of test	Day of illness									Follow-up visit Day 45
	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 15	
Hb (g/dl)	16.1	16.4	17.6	17.8	15.3	15.1	15.3	14.9	14.2	
Hct (%)	46.1	47.5	46.8	48.3	41.7	42.0	42.3	40.7	40.6	
WBC ($\times 10^9$/L)	3.91	3.24	4.17	5.16	7.89	3.66	4.61	5.03	5.81	
Platelet ($\times 10^9$/L)	142	92	27	40	50	69	73	103	294	
AST (U/L)	9352	12,358	28,373	20,586	7401	5781	2157	1503	84	26
ALT (U/L)	3760	5161	8648	5319	3314	2958	1867	1660	290	31
ALP (U/L)			155	187		159				
Albumin (g/L)			37	42	34	33				
Total bilirubin (μmol/L)			55.1	69.3		41.6		13.7		12.3
Direct bilirubin (μmol/L)			25.3	37.1						2.8
Creatinine (μmol/L)				85	80	70				
PT (s)		18.9	21.3		9.8					
CPK (U/L)					306					
NS1 antigen	Positive									
Dengue IgM					Positive					
Dengue IgG					Positive					

Hb: hemoglobin; Hct: hematocrit; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; CPK: creatine phospho kinase; NS1: non-structural protein 1; IgM: immunoglobulin M; IgG: immunoglobulin G.

level of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver involvement, increasing hematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding or organ failure). Classic dengue fever is characterized by fever with severe headache, retro-orbital pain, fatigue and severe myalgia and arthralgia ("break bone fever").[10]

Liver is a frequently involved organ in dengue infection.[11–13] If a dengue patient complains of abdominal pain, nausea, vomiting and anorexia, liver involvement should be suspected.[14] Mild to moderate elevation of transaminases is seen in both dengue fever and dengue hemorrhagic fever. Parkash et al.[15] described that patients with dengue infection had elevated AST and ALT of 86% and 95%, respectively. Even though liver involvement is mild in most of the cases, there are acute liver failure cases associated with high morbidity and mortality due to complications such as encephalopathy, severe bleeding, renal failure and metabolic acidosis. Our patient had only grade III hepatic encephalopathy without any other complications. The pathogenesis of liver damage in dengue is still not known, but there are several postulated mechanisms. Postulated hypothesis includes direct effect of the virus causing hepatocyte necrosis and apoptosis, host immune response on liver cells, circulatory compromise, metabolic acidosis and/or hypoxia caused by hypotension or localized vascular leakage inside the liver.[16–18] Frequency of liver involvement associated with dengue has been increasingly recognized, and isolated liver involvement in the absence of shock and other dengue-associated complications is also rising. Severe liver involvement can occur in the absence of fluid leakage, after peak of viremia and since it is associated with high interleukin (IL)-17 and IL-10 levels, possible immune mechanism leading to hepatic damage may play a major role.[12,19,20] In this case, severe hepatic injury is probably due to either immune-mediated or direct damage (necrosis) caused by virus as he had been hemodynamically stable throughout the course of the illness.

A study done by Ruth Priya and Smitha[21] concluded that individuals with diabetes, hypertension, renal failure, ischemic heart disease and alcohol consumption have more severe dengue and they might be benefited from more intensive care or close monitoring. As alcohol is a well-known cause of liver damage, it could be a contributing factor for severe liver involvement in dengue infection. Hepatocytes and Kupffer cells are important targets for dengue virus.[22] Acute and chronic alcohol intake induce mitochondrial toxicity in hepatocytes and affect their metabolizing capacity. There are studies shown that binge drinking of alcohol induces bacterial translocation from the gut, and this triggers activation of Kupffer cells.[23] Combined effect of bacterial translocation due to alcohol and dengue virus infection may cause a hyperactivation of Kupffer cells that can lead to significant worsening of the disease as occurred in our patient.

NAC is used for the treatment of acetaminophen toxicity. Use of NAC in acute liver failure due to other etiologies including viral hepatitis showed significantly higher transplant-free survival, and the benefits appeared to be confined to patients with early hepatic encephalopathy. It was also associated with reduce the mortality and use of NAC is safe.[24,25]

Conclusion

This case clearly demonstrates that dengue fever could cause acute hepatic failure without plasma leakage or overt bleeding and could be a cause for extremely high hepatic transaminases level. In addition, chronic ethanol usage or binge drinking could play a role to enhance the hepatic damage triggered by dengue virus. Detailed case-controlled studies to assess the effect of alcohol on severity of liver involvement in dengue infection are warranted.

Author contributions

All three authors were involved in the assessment and management of the patient. All authors collected and analyzed data. All authors read and approved the final manuscript.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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