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Review Article

A Case of Expanded Dengue Syndrome Manifested as Rare Fulminant Hepatic Failure

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Abstract

Dengue is a prevalent arthropod-borne viral disease in tropical and subtropical areas of the globe. Dengue clinical manifestations include asymptomatic infections; undifferentiated fever; dengue fever, which is characterized by fever, headache, retroorbital pain, myalgia, and arthralgia; and a severe form of the disease denominated dengue hemorrhagic fever/dengue shock syndrome, characterized by hemoconcentration, thrombocytopenia, and bleeding tendency. However, atypical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reportedcalled expanded dengue syndrome. We report a 45 years old gentleman with atypical and rare presentation of dengue disease marked by a dramatic and fatal acute(fulminant) liver failure. Condition improved after five days of conservative treatment. Hepatic complications in dengue are now increasingly observed with the most common case is hepatitis.While dengue virus infection leads to a mild to moderate elevation of liver transaminases in almost all cases, dengue hepatitis is self-limiting in almost all cases.Hepatic failure rarely dominates the clinical picture in adults. The main mechanism of dengue hepatitis is still unknown though both directviral infection and immune mediated damage have been suggested to be the cause of hepatocellular damage. To avoid otherwise preventable morbidity and mortality, physicians should have a highindex of suspicion for hepatic complications in patients with dengue illness and should manage thisaccordingly.

Keywords : acute liver failure; hepatitis; thrombocytopenia; expanded dengue syndrome; dengue fever

Introduction

Dengue, an arthropod-borne viral infection of humans, is endemic to tropical and subtropical regions of the world and represents an important public health problem. Dengue viruses are transmitted by the bite of the *Aedesaegypti* mosquito infected by the one of the four dengue virus serotypes: dengue-1, -2, -3, and -4. More recently, dengue disease has spread geographically to many previously unaffected areas and, as travelling around the world has become more accessible, physicians in temperate areas are more likely to see returning travelers with dengue infection. [1,2]

World Health Organization (WHO) classification of symptomatic dengue infection, continuously evolved, first in 1997 it divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 it improved into dengue with or without warning signs and severedengue. [3]

However, in 2011, WHO Regional Office for South East Asia (SEARO) revised and further improving the classification, divided into DF, DHF without shock or with shock (DSS) characterized by increased vascular permeability, thrombocytopenia (platelets <100,000), bleeding tendency, and, in a small percentage of patients, circulatory shock.[4,5,6,7]and expanded dengue syndrome. [8]

Expanded dengue syndrome is a new entity added to the classification system to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems that had been reported including gastrointestinal, hepatic, neurological, cardiac, pulmonary and renal systems. [8]

Liver involvement in dengue can be quite varied, with mild to moderate elevation of serum transaminases seen in up to 97% of cases. Other manifestations such as hypoproteinaemia, hypoalbuminaemia and hyperbilirubinaemia, and deranged coagulation parameters, have also been reported in varying rates depending on the population studied and disease severity. [9,10] Occasionally, severe dengue leads to acute hepatic failure [11,12]; however, the majority of these cases reported are among children. We present a 45 year old gentleman with fatal hepatitisleading to acute hepatic failure caused by dengue.

Case Report: A 45-year-old gentleman was admitted to Ad-din Women's Medical College Hospital, Dhaka, Bangladesh with a history of yellow coloration of skin, sclera and mucous membrane for two days and disorientation for one day. Six days prior the admission, he complained of fever, headache, retro-orbital pain, generalized body ache and weakness for three days followed by afebrile for last three days. There are spontaneous bleeding complaints in the form of nosebleeds, hematemesis and melana for several episodes one day prior admission to hospital. But he denies any abdominal pain or vomiting. His past medical history was positive only for a diagnosis of diabetes mellitus for last 2 two years for which he was taking tablet gliclazide daily regularly with good glycemic control. He had no previous history of jaundice, bronchial asthma, hypertension and heart disease. Patients do not smoke and do not consume alcohol.

On clinical examination, he was conscious but disoriented with GCS 10/15. Heart rate was 110 bpm, blood pressures 90/70 mm of Hg, respiratory rate 14 breaths/min, axillary temperature 98.4ºF.SaO2 was 95% in room air. Bi pedal edema was absent. Hemorrhagic suffusions or other skin lesions were present in the form of left subconjuctival hemorrhage, positive rumple leed test and multiple petechial rash over both lower legs. On examination of the head and neck, he was anemic and icteric. No enlargement of lymph nodes nor increased jugular venous pressure. On precordial examination heart sounds were audible and normal in all auscultatory areas with no murmur. On abdominal examination, there was no ascites with normal bowel sound. There was marked right upper quadrant tenderness; liver and spleen were not palpable. On chest examination, breath sound was vesicular with reduced air entry over both bases. There were no added sounds. Flapping tremor was present.

Admission						Discharge	Follow up
Day of Illness	6	7	8	10	12	15	22
Haemoglobin (g/dL)	9.1	11.8	12.1	12.3	12.4	12.1	13.4
Hematocrit(%)	27	33.1	35.8	35.6	35.5	36.1	39.8
Total WBC (/c mm)	3600	3970	4650	5100	5230	5500	7600
Platelet count (/ cmm)	16000	35000	63000	96000	126000	273000	330000
Total bilirubin (mg/dL)	11.3	10.8	9.9	7.6	6.5	4.3	1.1
Direct bilirubin (mg/dL)	9.2	8.6	7.9	6.2	5.9	3.2	
Albumin (g/dL)	2.1	2.6	2.8	3.1	3.3	4.0	4.1
ALT(U/L) AST(U/L)	2456 3567	2623 3432	2240 2648	1846 1988	1145 1332	629 522	76 52
ALP(U/L)	196	154	106				97
Creatinine (mg/dL)	0.93						0.86
LDH(U/L)	786			548			214
Activated partial thromboplastin time (seconds)	48	40	38	36			36
Prothrombin time (seconds)(control)	35	26	22	18	14		13
Ammonia(μ/dL)	352			156			40
HBsAg	Negative						
IgM Anti HBc	Negative						
Anti HCV	Negative						
IgM Anti HAV	Negative						
IgM Anti HEV	Negative						
S. Electrolyte	Na-132 K-3.8 HCO3-26						
Anti Dengue Antibody IgM IgG	 Positive Positive						
USG of W/A	Thickened	Gall bladder	Mild	ascites			
Chest X ray		Bilateral	pleural	effusion			

Table 1: Laboratory investigations of the patient.

The patient's serology was positive for IgM and IgG antibodies, suggestive of secondary dengue infection. 13So diagnosis of dengue hemorrhagic fever with dengue hepatitis with acute hepatic failure was made as a part of expanded dengue syndrome.

The patient was managed conservatively with supportive care. Since he had features of grade II hepatic encephalopathy, he was managed in the ward with parenteral ceftriaxone, proton pump inhibitor, oral lactulose, oral N acetyl cysteine and other supportive care. He required transfusion of 3 units of whole blood, 8 units of FFP, as he had deranged coagulation parameters with an ongoing hemorrhage. Subsequently, he became hemodynamically stable, conscious, oriented and his blood parameters were closely monitored; no further transfusions were deemed necessary.

The patient made good clinical improvement and was discharged after nine days of hospital stay. He was in good health at a follow-up visit one week later.

Discussion: Dengue is a worldwide public health problem and causes innumerous deaths. More than 40% of the world's population lives in dengue endemic areas, and the World Health Organization estimates that about 2.5 billion people in 100 countries are at risk of infection and that as many as 100 million people are infected by dengue viruses every year. In the majority of infected people, dengue is an auto-limited disease that resolves in 5–7 days. However, approximately 500,000 people develop a severe form, leading to about 20,000 deaths annually. Consequently, approximately 0.5%

of dengue patients develops a severe form and requires a specialized treatment. [2,14]

Dengue virus infection is a disease that found in children and adults with the main symptoms of fever, muscle and joint pain that usually worsens after the first three days. This disease is an acute febrile illness accompanied by bleeding manifestations with potential shocking and can lead to death in children<15 years, but not likely to attack adults.15Signs of this disease are sudden high fever 2 to 7 days with no obvious cause, weakness, lethargy, anxiety, heartburn, accompanied by signs of bleeding in the skin (petechiae), bruising (ecchymosis) or rash (purpura).Sometimes there are other spontaneous bleeding manifestations such as nosebleeds, bleeding gums to dysentery. Severe symptoms can lead to decreased awareness or shock. [16]

Laboratory results in dengue fever are found in thrombocytopenia (20% of the baseline on dengue hemorrhagic fever is a sign of plasma. Serological tests results in dengue are influenced by the type of dengue infection, whether it is the primary/first, or secondary/reinfection. IgM antibodies are detectable by days 3–5 after the onset of illness, rise quickly in two weeks and decline to undetectable levels after 2–3 months, because this lateappearance, the first five days of clinical illness are usually negative of IgM. In dengue secondary infection, the rise of IgM are not as high as primary infection, and sometimes absent / undetectable completely. [17]

IgG antibodies in primary infection, evolves relatively slow, with low titres 8-10 days after fever onset, increase subsequently and remain for many years, whereas in secondary infection it evolves rapidly, with high titres soon after fever onset and persist to a lifelong period. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Ratio of IgM/IgG titre less than 1.2 is considered a secondary dengue infection. But to be noted, titre ratio only could be validly use as a data if the IgG/IgM serological test is using pure quantitative means, not by qualitative or semi-quantitative. [18]

NS1 antigen detection is widely used and cost-effective, NS1 could be detected from day 1-8 of fever onset, unaffected by a primary or secondary dengue infection. In conclusion, by combining the serological (IgG and IgM) and NS1 tests, clinicians could rapidly assess the dengue diagnosis with its types (primary or secondary infection) and applies the best treatment. [19]

In 2011, based on many reports of cases with dengue-related unusual manifestations and organ complications, WHO-SEARO further improved and revised 2009 WHO guidelines by adding a new entity, that is expanded dengue syndrome (unusual/atypical manifestation of dengue), these include neurological, hepatic, renal, cardiac and other isolated organ involvement, that could be explained as complications of severe, profound shock or associated with underlying host conditions/diseases or coinfections. [8]

Acute liver failure in associated with DHF/DSS was initially reported during the 1987 epidemics in Indonesia in the 1970s. Later it was reported during the 1987 epidemic in Thailand and 1990 epidemic in Malaysia [20]. The pathogenic mechanism of acute liver failure have not yet fully elucidated. The virus may have replication phase in hepatocytes causing hepatic injury and the development of Councilman-Rocha Lima bodies similar to yellow fever infection and other viral hemorrhagic diseases [21,22]. Cytokine-related damage and ischemic hepatitis may also play a part [23,24. Also a dengue virus-specific CD4+ and CD8+ T cells may cause cytolysis 25. The dengue virus targets both the hepatocyte as well as kupffer cell and following internalization induces tumor necrosis factor-related apoptotic damage 26. The virus enters the hepatocytes and kupffer cells by phagocytosisand receptor-mediated endocytosis, respectively [25]. Dengue characteristically causes zone 2 necrosis of the liver. Liver biopsy usually reveals massive infiltration by the virus,with minimal mononuclear cell infiltrate [27]. Other findings include Councilman bodies, kupffer cell hyperplasia, andmicrovesicular steatosis [25].

The spectrum of dengue hepatitis usually ranges from asymptomatic stage to its severe form as acute fulminant hepatic failure. Clinical manifestations of disease include abdominal pain, nausea, anorexia and vomiting, hepatomegaly and abdominal tenderness. [28- 30] These clinical manifestations are more often seen in dengue fever (DF)than in dengue hemorrhagic fever (DHF). Clinical deep jaundice has rarely been reported.31 Dengue hepatitis usually occurs during first or second week of illness but has rarely been reported during the recovery phase of infection.[32]

Although elevation of serum transaminases is invariably seen in patients with dengue, incidence of acute liver failure in adult dengue patients is less than 1%, as indicated by various large studies [33,34]. In the present case, features of hepatic failure, coinciding with the peak of serum transaminases and prothrombin time, developed on day 6 of the illness, which is consistent with the findings in other cases reported in the literature [32,33,35].Transaminases can be elevated five to ten times the normal in DHF23. Acute hepatitis is more commonin dengue fever, while fulminant hepatic failure is more common in DHF [23,27]. Acute hepatitis is seen in lessthan four percent of patients with dengue [36]. Aspartatetransaminase [AST] elevation is more commoner and higherthan ALT elevations, and this is similar to that of alcohol ichepat it is [25,26]. Transaminase elevations peak on the 7thto 8th day [23]. The higher AST values are presumably due to release from injured myocytes. [33]

Jaundice and raised alkaline phosphatase have also been observed in DHF as was seen in our patient 24. Fact orswhich worsen liver disease in dengue include presence of shock, acidosis, and preexisting alcoholic liver disease, diabetes, hepatotoxic drug use, sickle cell disease, and race [23,24]. Coexisting Hepatitis B infection does not seem to worsen the prognosis although acetaminophen and antiemetic usage may predilect to further liver damage [25]. Shock, acidosis, severe thrombocytopenia, bleeding diathesis, and encephalopathy were associated with mortality in dengue [23,36]. Dengue encephalopathy is associated with very high levels of transaminases 26. Serotypes 1 and 3 are more hepatotropic than the others although all four serotypes can be associated with hepatic dysfunction [23]. Also some serotypes may have more epidemic potential than the others, and therefore they replicate faster leading to higher levels of viremia [25]. We did not have facility for serotype identification in our hospital.

Management of acute liver failure in severe dengue is similar to hepatic failure from any other cause. Patients require nursing in a quiet environment with head-end elevated and serial monitoring of serum aminotransferases, coagulation parameters, plasma glucose and electrolytes. Periodic surveillance for infection and prompt initiation of antibiotics at any sign of systemic inflammatory response syndrome are crucial. Attention should be paid to maintain adequate hydration and haemodynamic stability. Fresh frozen plasma (FFP) and platelet transfusion is reserved only for active bleeding and invasive procedures. [37] N-acetyl cysteine (NAC) therapy, though not routinely indicated in non-acetaminophen related acute liver failure, may benefit patients with other aetiologies. [38] A retrospective analysis in dengue-associated liver failure showed survival advantage if NAC therapy was instituted in early (grade I or II coma) liver failure stage. [39] In patients with worsening parameters, a prognostic model such as King's College criteria or Model for End-Stage Liver Disease (MELD) score may be used to determine the likelihood of spontaneous recovery and identify patients who will require orthotopic liver transplantation. However, to the best of our knowledge, there are no cases in the current literature of dengue-related acute liver failure managed with liver transplantation.

In contrast to other aetiologies of acute liver failure in adults, case fatality in dengue-related hepatic failure is considerably lower. For instance, eight patients managed with standard medical therapy alone in one series had 100% survival [10]. On the contrary, dengue infection in the paediatric population results in a relatively higher rate of acute liver failure 40 and up to 50% mortality. [40,25,36]

Conclusion: In conclusion, primary dengue can rarely cause fulminant hepatic failure and death, which may be prevented by early and aggressive supportive measures that include volume resuscitation, treatment of coagulopathy, acidosis, and encephalopathy. Most of the patients with dengue related fulminant hepatic failure recover with supportive therapy.

Conflict of interest: None declared

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