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ACUTE FULMINANT HEPATIC FAILURE IN DENGUE INFECTION: A RARE COMPLICATION

Medicine

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ABSTRACT

Dengue fever is a mosquito borne illness caused by Dengue virus. Liver involvement in Dengue is very common and can cause a mild to moderate rise in transaminases but can rarely cause acute fulminant heaptic failure. We present one such case of a 30 year old Hypothyroid, Diabetic and morbidly obese female from Western India who presented with typical manifestations of Dengue fever. Basic laboratory parameters were normal on admission. Initially she responded to treatment but following that she developed acute fulminant hepatic failure and renal failure to which she finally succumbed. This case reveals one of the very rare and fatal complication of Dengue infection in the form of acute fulminant hepatic failure. Other factors including race, diabetes, haemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs may also play a role [188].

KEYWORDS

Dengue, Fulminant Hepatic Failure

1.INTRODUCTION

One recent (2013) estimate indicates that 390 million dengue infections occur every year, of which 96 million manifest clinically (with any severity of disease)[1].Dengue viruses, single-stranded positive polarity ribonucleic acid (RNA) viruses of the family *Flaviviridae*, are the most common cause of arboviral disease in the world. Dengue viruses have four serotypes, designated dengue types 1-4; and are transmitted mainly by bite of *Aedes aegypti* mosquito and also by *Aedes albopictus*.The infection is now endemic in more than 100 countries, particularly the South East Asia region, western Pacific region, and the Americas[2]. Recently an increasing trend of outbreaks of DF and its complicated forms has been reported in India [3]. Severe manifestations such as dengue haemorrhagic fever and dengue shock syndrome, as well as other unusual manifestations, are increasingly being reported in previously unaffected regions. Hepatic dysfunction is a well-reported feature both in dengue fever and in dengue hemorrhagic fever (DHF). Liver involvement in dengue infection can be quite varied, ranging from mild to moderate elevation of serum transaminases to fulminant liver failure. The mechanism may be prolonged shock, metabolic acidosis and DIC in complicated dengue causing ischemia resulting in severe hepatic dysfunction [4].Kuo et al., have reported that 82.2% of cases of dengue infection had elevated ALT levels. Similar study done by Kuo et al., reported similar results with elevation of AST and ALT in 93.3% and 82.2% patients respectively [5].Elevation of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) is common in acute dengue illness, occurring in 65–97% of dengue patients, peaking during the convalescent period of illness (days 7–10) [6,7,8,9]. Liver failure has been recognized as a complication and unusual manifestation of dengue [10,11] but occurred infrequently in 3 of 270 patients in Taiwan [12] and 5 of 644 patients in Vietnam [13]. In Malaysia, 8 of 20 pediatric DHF patients developed liver failure, 1 died, and the rest recovered completely [14]. In 2009, the World Health Organization (WHO) revised its dengue guidelines and proposed severe organ impairment as one category of severe dengue in addition to severe plasma leakage and severe bleeding. Severe liver involvement was defined as AST or ALT 1000 units/liter (U/L). [15]

2.Case presentation

We report a 30 year old Indian female from Gujarat, presented to SSG hospital Baroda. She was a non smoker and non alcoholic and a known case of hypothyroidism for 12 years on treatment. She was recently diagnosed with Type 2 DM for which she was not taking any treatment. She was morbidly obese with a BMI of 34kg/m2.

On admission she had high grade intermittent fever with chills and rigors for last 4 days, generalised bodyache, nausea and vomiting with watery diarrhoea for 1 day. There was no complaint of bleeding from any sites, dizziness, breathlessness, myalgia, decreased urine output, abdominal pain and rashes.

On examination she was oriented to time, place and person and appeared to be dehydrated with dry tongue and capillary filling time less than 2 seconds and warm extremities. Saturation by oximetry was 87% on room air which rose to 98% on nasal O2 at 2L/min. RBS was 441mg/dl with negative urine for ketone bodies. Patient was having hypotension and tachycardia. The touriniquet test was positive with the presence of more than 10-14 petichiae per square inch. She had regular menses with three live births. Family history was negative for any major medical illness. The CVS system was normal on examination. Air entry was reduced in bilateral lungs diffusely with no abnormal breath sounds. Abdominal obesity was present with Liver and Spleen not palpable and tenderness was present in right hypochondriac region.

The Complete blood count was within normal limits with a reduced platelet count. Peripheral smear was negative for malarial parasites. The transaminases on admission were ALT-100 IU/L, AST- 150 IU/L and ALP- 80 IU/L and serum bilirubin was within normal range. Renal function was normal with S.creatinine-0.5mg/dl and appropriate urine output against input. Electrolytes were within normal limits. The coagulation profile was also normal with INR of 1.3 . Urine analysis showed glycosuria with trace protein and 7-10 pus cells/hpf and presence of amorphous substance. Dengue NS1 antigen was found to be positive in serum with other viral markers(Hepatitis B, Hepatitis C and HIV) negative.

A working diagnosis of Dengue shock syndrome was made and fluid therapy was started as per standard guidelines. Insulin was started as per sliding scale. Thyroxine was continued. The electrolytes were continuously monitored. She stabilised initially with reduction in stool frequency and fever was resolved. She was closely monitored for vitals and hemodynamic status.

The next day patient became drowsy and irritable however pressure maintained but she developed tachypnea and tachycardia with oxygen normal saturation. Repeat hemogram showed a trend towards third space leak with rising haemoglobin with packed cell volume. Following this, the coagulation parameters started worsening with bleeding from Vein Flow sites. Sugars and electrolytes were within normal limits. There were no signs of focal neurological deficit or meningeal irritation. Patient developed severe breathlessness and altered sensorium for which endotracheal intubation was done and patient was put on ventilatory support. Transaminases showed an exponential rise with ALT- 5436 IU/L AST- 32540 IU/L Bil(T)-4.6 mg/dl, Bil(Direct)-2.2 mg/dl, Bil(Indirect)-2.4 mg/dl suggestive of acute fulminant hepatic failure. Renal failure ensued with rise in urea and creatinine.

The patient had malena and hematuria and worsening sensorium. Fluid therapy was instituted through central venous line along with infusion of Fresh Frozen Plasma and Platelet concentrate. Blood pressure was falling and vasopressor in the form of Nordrenaline and inotropes in form of dobutamine were started but the patient showed poor response to the therapy.

The coagulation parameters could not be corrected despite adequate transfusion and the course ended fatally for the patient.

DISCUSSION

Dengue infection is a very common tropical infection worldwide. It is estimated that 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses[16].Although mild to moderate elevations of transaminases are seen in 80–90% of cases of dengue fever [17], fulminant hepatic failure is an uncommon manifestation [18].Dengue related ALF has been well described in the literature, although the majority of reports are amongst children with few case reports in adults. The lack of acute liver failure in our study was not unusual, as the incidence of acute liver failure in dengue patients was 1.1% in studies by Trung and Kuo [19,20]. Liver damage has been found to be more common among females in the large study from Brazil[31] (74.6% of females compared to 52.2% of males) with 4.2% of them having acute hepatitis.

Our case is one such rare case of acute fulminant failure which was relatively anicteric as compared to the cases described till date which have high levels of bilirubin along with high rise in liver enzymes. Initially the illness followed classical course of dengue with a febrile phase, critical phase which then turned into liver involvement in the form of fulminant hepatic failure. Some authors have postulated that in adults, non-communicable comorbidities and other underlying medical conditions may have a role in predisposing individuals to the severe forms of dengue[21,22]. The severe course in our patient could have something to do with the comorbidities like diabetes mellitus and thyroid disease which can affect the liver independently. Several studies indicate poor prognosis of fulminant hepatic failure from DF [23-25].. In the present case the liver enzymes were only mildly raised on presentation with normal levels of serum bilirubin. But within 24 hours the patient developed severe liver involvement with tremendous rise in hepatic enzymes along with deranged coagulation parameters, which were suggestive of acute fulminant hepatic failure. In this case the AST was approximately 6 times as compared to ALT which is in accordance with literature which has shown that AST raises higher than ALT levels [26].

Liver involvement in dengue infection could be suspected in patients with dengue fever complaining of abdominal pain, nausea, vomiting and anorexia [6]. Hepatomegaly is present in both dengue fever and DHF but is more common in dengue fever [7]. Clinical jaundice has been detected in 1.7%-17% in various series[27,29,30] and hyperbilirubinemia has been found to be as high as 48%[28].Our patient presented with similar complaints but abdominal pain was absent and there was no evidence of hepatomegaly on clinical examination. Our patient did not have clinical jaundice even with raised hepatic enzymes, which suggested an early anicteric course of liver damage. In a study from Mumbai, India, have found 5 cases of dengue associated ALF out of a total of 56 cases (8.9%) of ALF, while Tan et al from Malaysia showed 8 out of 155 adult ALF cases (5.2%) to have dengue[32,33]. Adult dengue patients developed ALF at a median of 7.5 d (5 to 13 d) after the inception of fever. Occasionally, ALF may in patients who seem to be recovering from dengue[34]. After a period of 3-7 d incubation, the natural course runs in form of fever lasting for 2-7 d, and subsequently a critical phase may occur during defervescence starting from 3-7 d of the illness when plasma leakage dominates the clinical picture[34].Our patient ran a similar course of illness and developed fulminant hepatic failure on 6th day after the first episode fever.Though we did not use N-acetyl cysteine, in the management of patients with dengue with ALF, besides supportive measures specific measures have also been tried with success. There have been reports of use of N-acetyl cysteine (NAC) in various case series[36].Use of molecular adsorbent recirculating system (MARS) has also been reported in dengue associated ALF[37]. Once acute fulminant hepatic failure develops due to any reason, the cahnces of survival are generally minimal with very few options of management , liver transplantation being one of them but liver transplantation becomes a difficult proposition in lieu of hemodynamic compromise, bleeding, and organ impairment seen during dengue infection. Acute hepatic failure due to dengue infection with subsequent complete recovery has been reported in two adult patients from India, one from Singapore, one from USA and one from Sri Lanka[38-41]. However in none of the reports, the liver enzymes were as high as that seen in our patient.

TABLE 1

Test	Result
Dengue NS1 by ELISA	Positive
Hepatitis E antibody	Negative
Hepatitis A antibody	Negative
Hepatitis C antibody	Negative
HIV antibody	Negative

TABLE 2

VARIABLE	LAB RANGE ADULT	ON ADMISSION	12hr	24hr
hematocrit				
Hemoglobin	12-16mg/dl	10.70	11.90	13.10
White blood cell	4000-11000/cumm	4500	2900	3500
Neutrophil	40-80%	70	70	58
Lymphocyte	20-40%	28	28	40
monocyte	1-6%	01	01	01
Platelet count	1,50,000-4,10,000/cumm	63000	46000	7000
RBC	3.8-4.8 million/cumm	4.71	4.99	5.44
Total bilirubin	0.1-1.2mg/dl	0.5	4.3	4.6
Direct bilirubin	0-0.4mg/dl	0.2	2.0	2.2
Indirect billirubin	0.1-0.8mg/dl	0.3	2.3	2.4
Urea	14-40mg/dl	29	61	49
CREATININE	0.6-1.2mg/dl	0.52	2.92	2.69
PROTHOMBINE TIME	10.8-13.3sec		58.7	22.8
PT (CONTROL)			11.2	9.2
INR	2.5-4.5		4.82	2.3
SGPT	14-63IU/L		5436	4865
SGOT	0-41IU/L		32540	30729
ALP	42-141IU/L			80
S.potassium	3.5-5.5mEq/L	3.8	7.8	6.4

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