

CASE REPORT

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Dengue haemorrhagic fever presenting with cholestatic hepatitis: two case reports and a review of literature

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Abstract

Background: Dengue fever is a common mosquito borne viral fever in South Asia, which causes significant morbidity and mortality. Dengue fever is well known to involve the liver, especially in dengue hemorrhagic fever. The hepatic involvement is usually that of a mild hepatitis with transaminase derangement without jaundice. In cases of dengue hemorrhagic fever where shock has ensued, a severe hepatitis with gross derangements of transaminases and bilirubin may occur. These are two rare cases of adult patients with dengue hemorrhagic fever presenting with a cholestatic type of jaundice.

Case presentation: This case report describes two female patients aged 30 and 46 years who presented with fever, icterus and biochemical analysis revealed cholestatic jaundice. Evolution of the clinical picture and dropping platelets prompted serological investigations in the form of dengue non-structural protein 1 antigen and dengue immunoglobulin M which confirmed acute dengue infection.

Conclusion: These cases highlight the importance of considering dengue fever as a differential diagnosis even in the presence of a cholestatic jaundice, especially in countries where dengue fever is endemic, and in travelers returning from dengue endemic countries. The early diagnosis of dengue fever and timely institution of supportive fluid management is essential to prevent morbidity and mortality.

Keywords: Dengue fever, Hepatitis, Cholestasis, Cholestatic jaundice

Background

Dengue fever is the commonest mosquito born viral illness known to man, with cases exceeding 2.2 million in 2010 [1]. Dengue viruses (DENV) are classified into four serotypes (DENV-1, 2, 3 and 4). Infection may be clinically asymptomatic or give rise to an undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) [2]. One third of the world population is at risk and with outbreaks occurring in cyclical epidemics in Asia, Sri Lanka is at a greater risk as it is a country naturally endemic to dengue [2-4]. An increasing number of patients whom present with the clinical picture of fever, myalgia and arthralgia, can evolve into dengue hemorrhagic fever with plasma leakage, which if not properly managed could very well progress to

worsening organ involvement with dengue shock. Liver involvement in dengue fever is typically that of a hepatitis which ranges from mild derangement of liver enzymes to fulminant hepatitis, with manifestations ranging from hypochondrial-pain, hepatomegaly and rarely even jaundice [5]. We describe two patients who had in addition to fever had cholestatic jaundice as an initial presenting symptom which was due to dengue infection.

Case presentation

1st case vignette

A 30 year old South-Asian female presented with 5 day history of high fever associated with severe myalgia, headache and yellowish discoloration of the skin. There was no history of contact with muddy water, alcohol consumption, or use of any drugs including antibiotics, anti-pyretics (acetaminophen) or antiemetics. Further history of blood transfusion, sexual promiscuity or any other high risk behavior could not be elicited. She

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denied any pale stools or pruritus. At the time of admission, general examination revealed she was febrile and icteric but had no conjunctival hemorrhage, pallor, lymphadenopathy, rashes or scratch marks. The respiratory system was unremarkable and the abdominal examination did not elicit right hypochondrial tenderness, palpable gall bladder or abdominal guarding. The cardiovascular examination was normal and she had an initial blood pressure of 90 mmHg systole and 60 mmHg diastole, without a postural drop. She was conscious, alert, well oriented and nervous system examination was otherwise unremarkable.

The initial complete blood count revealed thrombocytopenia with a platelet count of $69 \times 10^9/L$ (150–450), a normal white blood cell count (WBC) of $10.4 \times 10^9/L$ (4–11) with a predominance of lymphocytes (55%) and a hemoglobin of 11.0 g/dL (11–17). The blood picture mirrored the whole blood analysis and showed only thrombocytopenia, there was no neutrophil left shift or toxic granules and the red cell indices were normal. Liver functions showed a mildly elevated aspartate transaminase (AST) and alanine transaminase (ALT) which were 80 U/L (0–40) and 38 U/L (0–35) respectively with an elevated alkaline phosphatase (ALP) value of 450 U/L (100–360). Serum direct and total bilirubin levels were elevated at 6 mg/dL (0–0.3) and 9.1 mg/dL (0.3–1.9) respectively. Serum albumin was found to be reduced with a value of 2.3 g/dL (3.5–5.5), with a normal international normalized ratio (INR). The renal functions were within normal reference range. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also within normal parameters. The following day the platelet count continued to drop and her jaundice deepened. A positive dengue non-structural protein 1 antigen test (NS1) and a positive dengue IgM antibody ELISA test on day 6 confirmed the clinical suspicion and diagnosis of dengue fever. Hepatitis B surface antigen, hepatitis C antibody, hepatitis A and E antibodies, Epstein Barr Virus antibody and a retroviral screening were all negative. Leptospira microscopic agglutination test (LeptoMAT) titres were insignificant at 1:200 on day 6 and the titre value remained unchanged when the repeat test was performed on day 12 of the illness (a four-fold rise in titre or a high titre >1:800 is the gold standard for diagnosis). Blood cultures remained repeatedly negative.

The platelet count continued to drop rapidly in the following days reaching the lowest nadir value of $3 \times 10^9/L$ (150–450) with rising alkaline phosphatase and bilirubin levels (Table 1). On day 6 of the illness the patient became afebrile. As per the local guidelines and WHO dengue guidelines on management of critical phase of dengue hemorrhagic fever, she was maintained on a fluid regimen tailored to her body weight, with strict monitoring of the blood pressure, pulse pressure, heart rate and urine output.

On day 7 the patient became mildly tachypnoeic, and examination revealed reduced air entry in the right lung base which was stony dull to percussion and deep icterus, further abdominal examination elicited a small shifting dullness, signifying ascites. An ultrasound scan was done and confirmed a small right sided pleural effusion, an enlarged liver of 16 cm, without intra or extra hepatic bile duct dilatation, a thickened gall bladder wall of 7 mm in the absence of any gall stones and a sonographic Murphy's sign could not be elicited. Mild ascites was also noted. The blood pressure and urine output were maintained. A packed cell volume was done and showed only a mild rise. The fluid regimen was continued as per guidance, giving adequate fluids to maintain blood pressure and urine output.

On day 9 of the illness, the patient's clinical status and jaundice improved. Serial complete blood counts showed rising platelet counts. Similarly liver function tests revealed normalizing alkaline phosphatase and bilirubin levels. The patient was discharged on the 15th day of illness with normal cell counts and liver function parameters.

2nd case vignette

A 46 year old previously well South-Asian female, presented with six days of high fever, myalgia and jaundice. She too denied any history of contact with muddy water, recent drug usage, blood transfusion or any high risk behavior. On examination, she appeared ill, febrile to touch and deeply jaundiced. Abdominal examination revealed a mildly tender and firm hepatomegaly. The gallbladder was not palpable nor was there guarding or a positive Murphy's sign. The respiratory system examination revealed reduced air entry on auscultation and stony dullness to percussion in the base of the right lung. The cardiovascular examination was unremarkable, with a blood pressure of 100 mmHg systole and 70 mmHg without a postural drop. The nervous system examination was normal.

Whole blood analysis on presentation demonstrated thrombocytopenia with a platelet count of $10 \times 10^9/L$ (150–450) and a lymphocytic predominant (51%) white cell count of $7.8 \times 10^9/L$ (4–11) with a haemoglobin value of 11.6 g/dl with a packed cell volume of 34%. The liver enzymes were elevated with the AST more than the ALT which were 242 U/L (0–40) and 120 U/L (0–35) respectively. The alkaline phosphatase was mildly elevated with a value of 400 U/L (100–360), with a high direct bilirubin fraction of 12 $\mu\text{mol/L}$ (0–3.4) and total bilirubin of 23 $\mu\text{mol/L}$ (5–21). Albumin was found mildly reduced at 31 g/L (36–48). The INR was normal. The renal functions were normal. The ultrasound scan of the abdomen and chest confirmed an enlarged liver, with a cranio-caudal length of 16 cm. The gallbladder wall was thickened and measured 6 mm, a negative sonographic

Table 1 Chronology of platelet, PCV and liver biochemistry of both patients in case study 1 and 2

Day	AST U/L (<34)		ALT U/L (<40)		ALP U/L (100–360)		T.Bilirubin (0.1 -1.2 mg/dL)		D.Bilirubin (<0.3 mg/dL)		Platelet $\times 10^9/L$		PCV	
	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2
5	80		38		450		9.1		6		69		31.1%	
6	100	242	52	120	490	400	10.6	23	7.8	12	30	10	32%	34%
8	116	230	56	98	598	412	12.6	22	9.6	6	3	5	35%	34.2%
9	88	160	50	83	448	625	11.6	17.7	8.8	6.2	20	17	33%	30.1%
10		127		78		631		18		8		31		29.9%
11	70		44		368		4.8		3.0		55	62	32%	29.9%
12		88		45		378		16		3		128		30.8%
13	66		40		300		2		1.4		108		32%	
15	60		40		260		0.8		0.2		166		32%	

(Day- day of the illness, AST- aspartate transaminase, ALT- alanine transaminase, ALP-alkaline phosphatase, T.Bilirubin- total bilirubin, D.Bilirubin- direct bilirubin, PCV-packed cell volume, Pt 1- Patient discussed in case vignette 1, Pt 2- Patient discussed in case vignette 2).

Murphy's sign was noted and no gall stones were visualized. Leakage was confirmed as there was mild ascites and a pleural effusion in the right hemithorax. The ESR was 19 mm for the first hour and the CRP was mildly elevated with a value of 7 mg/L (0.0 – 5.0). The dengue IgM antibody was positive. A Lepto MAT was performed twice on day 7 and day 11 of the illness, and showed a titre of 1:400 (a four -fold rise in titre or a high titre >1:800 is the gold standard for diagnosis) without further rise. A hepatitis screen was performed and was found negative. EBV antibody was also negative. This patient was similarly managed with a fluid regimen tailored to her body weight as per guidance, with strict monitoring of hemodynamic parameters and urine output.

The platelet count continued to drop reaching a nadir of $5 \times 10^9/L$ (150–450) on day 8 of the illness, and subsequently began to rise. The alkaline phosphatase and bilirubin continued to rise till day 10 of the illness, after which the liver functions began to normalize (Table 1). The patient was discharged on day 12 of the illness, being afebrile for 4 days with a platelet count of $128 \times 10^9/L$ (150–450) and a near normal bilirubin level.

Discussion

Dengue infection is usually associated with liver involvement, and this is more frequently seen among women, patients with a primary infection and in those with DHF [5]. This claim is reinforced as hepatomegaly is frequent and commoner in patients with DHF than in those with DF [6,7] as are transaminase levels higher in DHF/DSS than in DF, though the rise is transient and tend to normalize on recovery [6,8]. In dengue infections, elevation in serum AST is greater than ALT levels, similar to the pattern seen with alcoholic hepatitis [9]. Though other indicators of liver function such as serum bilirubin and alkaline phosphatase can also be deranged their incidence is relatively less in comparison to the often seen

rise in transaminase levels (7.2%, 16.3% and 93.3% respectively) [10]. The causative dengue serotype is also a factor with a greater degree of hepatic involvement in infections with DENV-3 and DENV-4 [11]. Furthermore there is a suggested correlation between acetaminophen administration for fever, and the degree of liver damage [12].

The exact pathogenesis of liver injury in dengue is yet to be determined. The liver cells may be damaged through one or more of the following mechanisms: direct cytopathic effect of the virus, killing of virus-infected cells by the host immune response- the activated lymphocytes, antibodies against dengue proteins cross-reacting with host cell proteins and as a nonspecific effect of shock [13,14]. Another form of hepatic involvement which is known to occur in dengue fever is an acalculous cholecystitis. However these patients will have the characteristic right hypochondrial tenderness and a positive Murphy's sign with the ultrasound confirming the thickened gallbladder and elicitation of a sonographic Murphy's sign as well. Furthermore elevations in total bilirubin and alkaline phosphatase are not common in cholecystitis as the inflammation is restricted to the gall bladder [15,16]. Jaundice is seen in fulminant hepatitis secondary to dengue [17], but neither of our patients progressed to this stage of hepatic dysfunction. The development of bilirubinemia and cholestatic jaundice, without fulminant hepatitis is thought to occur due to ongoing inflammatory process of dengue infection, which can effectively reduce the diameter of the lumen of the biliary canaliculus, causing obstruction. This can be attributed directly or indirectly to the effects of the dengue virus [5].

Alternate causes of cholestatic jaundice should be considered. Ultra-sonographic imaging in our patients failed to demonstrate gall stones, and furthermore the normalizing bilirubin with the recession of jaundice made a sinister cause like carcinoma of the head of the pancreas unlikely.

Intestinal flukes such as *Fasciola Hepatica* may cause an obstructive pattern of jaundice, but the clinical picture seen in acute/liver phase of the infection is different from the characteristic symptoms and biochemical derangement to that of dengue, additionally it is the chronic/biliary phase that classically produces jaundice in *Fasciola Hepatica* infection [18]. Though exclusion would have been useful, jaundice was unlikely to be attributable to a liver fluke. Our patients had jaundice, but neither of them complained of preceding or associated pruritus. Though known to occur, the frequency and intensity of pruritus has poor correlation to the severity of jaundice, and is more commoner in chronic cholestatic jaundice than in obstructive variant, and even less so when the obstructive pathology is benign. Pruritus can also be absent [19]. Pale colored clay stools, another feature of obstructive jaundice was also absent, and this most likely due to that fact the obstruction was partial. Serological diagnosis of dengue was confirmed using dengue IgM and NS1 as they were positive. Though NS1 is commonly an early indicator it can be detectable even late in the disease and though not the ideal choice, it may be useful even in late presenters considering availability of investigational facilities [20,21]. Overall the clinical picture, serological diagnosis and rapid improvement of jaundice upon clinical recovery favored cholestatic jaundice being secondary to dengue infection in both our patients.

Cholestatic jaundice in otherwise uncomplicated DF/DHF has been reported only scarcely in medical literature, once in a neonate with dengue fever [22] and two other adults [5]. We report this rare phenomenon in two cases of adult patients with dengue haemorrhagic fever. Further studies are required into the incidence and exact mechanism of hepatic damage giving rise to the observed clinical picture of cholestasis in dengue haemorrhagic fever, which is probably a poorly appreciated hepatic manifestation.

Conclusion

These cases highlight that in addition to deranged liver enzymes, cholestatic pattern of jaundice may be an under recognized clinical manifestation of dengue fever. A high suspicion of dengue should be present when other supportive clinical and laboratory criteria are present in addition to that of jaundice. Countries that are endemic to dengue and regions that have epidemic outbreaks should be vary of the different presentations that may mask dengue fever.

Consent

Written informed consent was obtained from both patients for publication of this Case Report. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

JY carried out the literature search and drafted the manuscript; AR and RN did critical revision for important intellectual content in the manuscript and gave the final approval of the version to be published; SJ helped substantially in literature search and drafting the manuscript. All authors provided clinical care for the patient and have read and approved the final manuscript.

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