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Case Report

Internal Medicine Section

Treatment Dilemma in an Unusual Case of Dengue Fever with Cardiomyopathy and Nephropathy: A Case Report

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ABSTRACT

Dengue is a viral illness in humans caused by the bite of infected *Aedes* mosquitoes, mostly *Aedes aegypti* and also *Aedes albopictus*. There are four serotypes of the Dengue virus that cause infection in humans and may lead to a variety of complications. Myocarditis and cardiomyopathy can occur in several viral and non viral infections, increasing morbidity and mortality. Nephropathy may also arise in dengue fever, causing complications. The case presented here involved both complications, nephropathy and cardiomyopathy, posing treatment challenges in terms of altering fluid and electrolyte status, which hindered fluid therapy as fluid overload would be detrimental. However, the complications were reversible with the normalisation of echocardiography and urea and creatinine levels. Long-term follow-up is necessary to monitor cardiac and renal function, as some patients may progress to Chronic Kidney Disease (CKD). The patient presented with fever, headache, vomiting, and haematuria, along with signs of fluid overload. There was a past history of fever, and since both Immunoglobulin G (IgG) and IgM Dengue antibodies were positive, this may be a case of a second episode of dengue fever causing complications. This case report emphasises the diagnostic and treatment challenges in a dengue patient with cardiomyopathy and nephropathy, where excessive fluid replacement may increase morbidity and mortality. Additionally, long-term follow-up of these patients is necessary.

Keywords: Expanded dengue syndrome, Multiorgan failure, Severe dengue

CASE REPORT

A 31-year-old non diabetic, non hypertensive female with no known addiction and last menstrual period 15 days before presented with fever and headache for the past 15 days, along with vomiting and haematuria for the past 13 days, as well as facial puffiness and pedal oedema for the past 12 days. The fever was high-grade, intermittent, accompanied by chills and rigors, without any complaints of bladder or bowel issues, abdominal pain, or rash. The patient experienced body aches without any history of arthralgia or arthritis. Facial puffiness followed by pedal oedema developed, with the puffiness worsening in the early morning. There was no history of photosensitivity, paroxysmal nocturnal dyspnoea, yellowish discoloration of eyes or urine. The patient did not take any Non Steroidal Anti-Inflammatory Drugs (NSAIDs) or other medications prior to this episode, and there was no history of allergies or immunisations. Although there was a history of indoor air pollution, there was no history of travel or visits to agricultural lands. The significant past history included an undocumented febrile illness three years ago, which resolved within five days with over-the-counter medication.

The patient visited her family physician on the 3rd day of the current febrile episode, who ordered a battery of investigations including routine blood and urine tests, malaria antigen test, dengue NS1, and IgM and IgM typhoid antibody tests. Remarkable findings included mild anaemia (haemoglobin 10.6 g/dL), thrombocytopenia (manual platelet count 110 * 10^3/cumm), and positive Dengue viral antigen (NS1).

During examination, the patient was conscious, alert, and cooperative. Facial puffiness was present with orthopnoea. There was mild pallor without any icterus, cyanosis, or clubbing. Lymph nodes were not palpable, and the jugular venous pulse was engorged and pulsatile. Bilateral pitting pedal oedema was observed. The pulse rate was 110/min, low volume, with a blood pressure of 90/60 mmHg. The respiratory rate was 29/min, thoracoabdominal. The temperature was 101°F with no skin rash. There were no signs of micronutrient deficiency.

Systemic examination revealed no hepatosplenomegaly, ascites, or abdominal tenderness. The apex was down and out with a hypokinetic nature. Fine end inspiratory crepitations were heard bilaterally at the lung bases. The neck was supple without any signs of meningeal irritation, and no abnormalities were detected in the examination of the neurological and rheumatology systems.

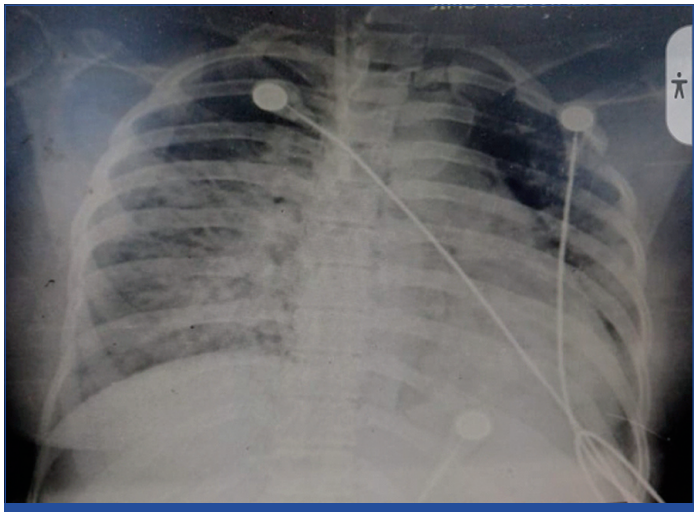
A provisional diagnosis of dengue viral fever with secondary bacterial infection, sepsis, and nephropathy was made. The patient was placed in a propped-up bed and provided moist oxygen delivery at 5 L/min. Noradrenaline was administered via intravenous infusion at a rate of 0.1 µg/kg/min due to persistently low mean arterial pressure below 60 mmHg. No intravenous fluids were given as there was volume overload detected on echocardiography, indicated by Inferior Vena Cava (IVC) collapsibility criteria. Global hypokinesia and an Left Ventricular Ejection Fraction (LVEF) of 35% without pericardial effusion were also observed. Arterial blood gas analysis revealed metabolic acidosis with low bicarbonate levels. The relevant investigation findings are mentioned below [Table/Fig-1].

Test parameters	Results (normal range)	Test parameters	Results
Haemoglobin (g/dL)	9.5 (13.5-16.5)	Sodium (mmol/L)	125 (135-145 257)
Total leucocyte count (/mm^3)	11,500 (4000-11000)	Potassium (mmol/L)	3.0 (3.5-5.5)
Platelet count	1,60,000/mm^3	Albumin (g/dL)	2.3 (3.4-5.4)
Peripheral smear	Normocytic normochromic anaemia, neutrophilia	Bilirubin/Liver enzymes	Within normal limit
Urea (mg/dL)	105 (6-24)	Procalcitonin (ng/mL)	1.7 (<0.5)
Creatinine (mg/dL)	6.1 (0.7-1.3)	International Normalised Ratio (INR)	1.1 (<1.3)

[Table/Fig-1]: Relevant laboratory findings.

Blood culture and sensitivity tests were performed, along with urine routine examination and culture sensitivity. Chest X-ray revealed pulmonary oedema [Table/Fig-2] with bilateral mild pleural effusion. Calcium, magnesium, and phosphate levels were normal, as were

the levels of Troponin I, Creatine Phosphokinase (CPK) , and CPK-MB. The Electrocardiography (ECG) showed sinus tachycardia. Blood samples were sent for Malaria parasite slide and dual antigen testing, IgG and IgM Dengue antibodies, Typhi Dot M, *Leptospira* IgM antibodies, and Scrub Typhus IgM antibodies.



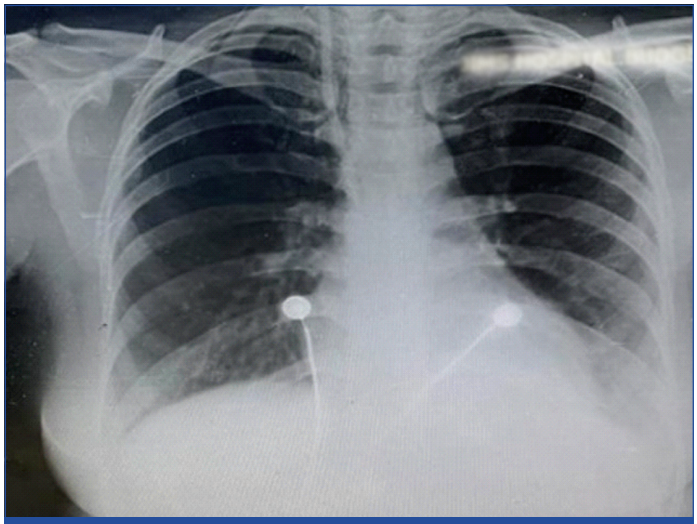
[Table/Fig-2]: Chest X-ray showing congestive cardiac failure.

The patient was treated with intravenous proton pump inhibitor, ondansetron, and a furosemide infusion at a rate of 60 mg/24 hours. Broad-spectrum antibiotics were initiated due to the initial diagnosis of secondary bacterial infection, sepsis, and high bacterial count with elevated procalcitonin levels in the presence of shock. Initial antibiotic regimen included intravenous meropenem 1 gm stat after a proper skin test, followed by intravenous meropenem 500 mg every eight hours, and intravenous doxycycline 100 mg twice daily after a proper skin test. However, the antibiotics were de-escalated within 48 hours as cultures turned up sterile. Sodium bicarbonate tablets, 500 mg every eight hours, were administered due to a pH of 7.24 and bicarbonate level of 12 mEq/L (22-29 mEq/L) in the presence of Acute Kidney Injury (AKI). Free Thyroxine (FT4), Thyroid Stimulating Hormone (TSH), and cortisol levels were normal. Catheterisation was performed, and the patient was on oral feed with potassium chloride supplementation.

Fever profile reports revealed positive IgM Dengue antibodies by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) with a titre of 12.08 (>11 positive), as well as positive IgG Dengue antibodies by GAC ELISA with a titre of 17.05 (>11 positive). These findings suggested a diagnosis of severe dengue infection according to World Health Organisation (WHO) criteria, with a possibility of past infection with the dengue virus. Other reports were unremarkable, and urine analysis revealed haematuria with 30 RBCs per high-power field and 2+ proteinuria without any casts or microorganisms.

Inotrope and Frusemide infusions were titrated by monitoring vital parameters and IVC collapsibility. Blood and urine cultures yielded negative results, but D-Dimer levels were elevated at 500 ng/mL (Normal <400 ng/mL), while NT-proBNP levels were significantly high at 7322 pg/mL (Normal up to 125 pg/mL). Ultrasound Whole Abdomen (USG WA) revealed gallbladder sludge with a thickened and oedematous gallbladder wall, along with mild ascites and bilateral pleural effusion. The urine albumin-to-creatinine ratio was elevated at 1200 mg/gm (Normal <30 mg/gm) of creatinine, while antineutrophil cytoplasmic antibody profile and antinuclear antibody Hep 2 tests yielded negative results. C3 and C4 levels were within the normal range.

The nephrologist recommended haemodialysis, which was initiated on the day of admission via central cannulation and performed on three successive days. There was gradual improvement in urea and creatinine levels, and urine output increased from anuria to 500 mL/day on the second day of haemodialysis. Gradually, facial puffiness and pedal oedema decreased, and noradrenaline was discontinued after two days. Lasix infusion was stopped after three days when urine output exceeded 2500 mL/24 hours and urea levels reached 45 mg/dL and creatinine levels dropped to 2.3 mg/dL. A repeat echocardiography performed four days after the initial one revealed normal wall motion with an EF of 60% and no wall motion abnormalities. The patient responded well to treatment, and urea and creatinine levels returned to normal 10 days after admission. However, the urine albumin-to-creatinine ratio remained elevated at 800 mg/gm of creatinine. A normal chest X-ray confirmed recovery from congestive cardiac failure [Table/Fig-3].



[Table/Fig-3]: Chest X-Ray showing recovery from congestive cardiac failure.

The patient was discharged 14 days after admission with instructions for follow-up in the Medicine, Cardiology, and Nephrology Outpatient Department (OPD). During the two-week follow-up visit, the patient was doing well, with normal results for complete blood count, urea, creatinine, sodium, and potassium. However, the urine albumin-to-creatinine ratio remained elevated at 475 mg/gm of creatinine, indicating the need for long-term follow-up.

DISCUSSION

Dengue fever is known to cause multisystem involvement and can lead to significant morbidity and mortality. A recent large review study reported a median mortality rate of 5.13% (range 0.5-38.6) in severe dengue [1]. In this case, the patient experienced reversible cardiomyopathy and nephropathy with a positive response to treatment.

According to the WHO classification from 2009, dengue fever is categorised into dengue (with or without warning signs) and severe dengue, which involves multiorgan involvement affecting the Central Nervous System (CNS), heart, liver, and other organs. Dengue can affect the cardiovascular system and lead to conditions such as myocarditis, pericardial effusions, cardiomyopathy, Atrioventricular (AV) block, atrial fibrillation, and ectopic ventricular beats [2]. The prevalence of myocarditis in hospitalised dengue patients is reported to be 11.28%. Moreover, the risk of myocarditis is higher in patients with non severe dengue with warning signs or severe dengue (46.6%) compared to non severe dengue patients (9.72%) [2]. The dengue virus directly invades cardiomyocytes, endothelial cells, and myocardial interstitial cells, leading to increased proinflammatory markers and abnormalities in calcium homeostasis [3]. While myocarditis is typically reversible, delayed diagnosis can sometimes result in fatalities [3]. Cardiac Magnetic Resonance Imaging (MRI) can be used to diagnose myocarditis by identifying myocardial oedema and late contrast enhancement. Dilated Cardiomyopathy (DCM) affects the heart muscles, causing weakening and contractile dysfunction that is not associated with ischaemic heart disease, valvular heart disease, or hypertension. Key diagnostic criteria for DCM include left ventricular systolic

dysfunction (EF <55%), dilatation with normal left ventricular wall thickness [4]. DCM is the most common reason for cardiac transplantation and the third most common cause of congestive heart failure [5]. Exertional breathlessness and exercise intolerance are common modes of presentation, but asymptomatic patients may also be incidentally found to have cardiomegaly [6]. Infections, toxins, metabolic derangements, and inflammation are common causes of DCM, although many cases remain idiopathic. Viral infections, particularly adenovirus, are the most common cause of viral myocarditis in adults. Although initially thought to be rare, myocarditis is actually the most common cardiac manifestation of dengue, leading to cardiomyopathy [7]. A cohort study conducted in Sri Lanka showed increased myocardial involvement in dengue patients without long-term complications [7]. Unusual dengue cases reported from Sri Lanka have highlighted cases of myocarditis, such as in a successfully treated 17-year-old female who received steroids and careful fluid therapy [8]. Another similar study focused on dengue patients with sinus node involvement and those with volume overload, where fluid therapy posed challenges [9].

Primary dengue infection provides lifelong immunity against the specific serotype involved, but infection with a different serotype can lead to severe and potentially life-threatening conditions such as Dengue Haemorrhagic Syndrome (DHS) and Dengue Shock Syndrome (DSS). Severe secondary infections are caused by antibody-dependent enhancement [10].

Dengue fever can also affect the renal system, leading to glomerulonephritis, proteinuria, and severe Acute Kidney Injury (AKI). The incidence of AKI in dengue ranges from 0.83-14.40%, with a mortality rate of 11.30-60% [11-13]. The mechanisms of Dengue-Associated Kidney Injury (DAKI) are described in [Table/Fig-4] [12-15].

1. Action of virus on renal tissue: a) viral antigen directly affects the cells of the kidney; b) antiviral antibodies causing immune mediated mechanisms; c) release of inflammatory mediators [12].
2. Haemodynamic instability inflammatory cytokines cause activation of the complement system and injury to the endothelium increases vascular permeability with intravascular volume depletion. Shock reduces renal perfusion and causes acute tubular injury. Hypotension and sepsis may occur which need inotropic support. Acute Kidney Injury (AKI) without haemodynamic instability also may occur [13].
3. Rhabdomyolysis: direct invasion by the virus with myotoxic cytokines may lead to myonecrosis. Intrarenal vasoconstriction, tubular vasoconstriction and injury may occur. Creatinine Kinase (CK) levels may rise with myoglobinuria in AKI patients, though CK levels may also rise without AKI [13].
4. Glomerulonephritis: direct viral effect on the cells. Reversible mesangial proliferation may occur [14].
5. Haemolytic Uremic Syndrome (HUS): triad of haemolytic anaemia, thrombocytopenia and AKI with thrombotic microangiopathy, but recovery of renal function may occur with survival in most patients [15].

[Table/Fig-4]: Proposed mechanisms of Dengue-Associated Kidney Injury (DAKI) [12-15].

In this patient, the second mechanism mentioned in the table above appears to be the most likely cause of acute renal failure, which may also explain the elevated inflammatory markers (ESR and CRP) and total counts mentioned in the report.

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, AKI is defined as a rise in serum creatinine of >0.3 mg/dL, a rise in serum creatinine of more than 1.5 times the baseline, or a decrease in urine volume to <0.5 mL/kg/hour for six hours [16]. A systematic review conducted by MallhiTH et al., showed that the Acute Kidney Injury Network (AKIN) criteria were more sensitive, as they diagnosed a higher incidence of dengue-induced AKI (3.3% to 13%) [17]. Another review of 5 studies by Mallhi TH et al., demonstrated that the AKIN criteria had higher sensitivity, defining AKI as a 1.5 times increase in serum creatinine within seven days from baseline (compared to serum creatinine >2 mg/dL) or a rise in serum creatinine >26.2 micromoles/liter from baseline within 48 hours. Basu G et al., and Kuo MC et al., reported a very high incidence of DAKI using the RIFLE criteria (Risk of renal dysfunction, Injury to kidney, Failure or Loss of kidney function, and End-stage kidney disease) (41.1% and 27.1%, respectively), but this was due to a smaller number of dengue patients (n=28) and the application of RIFLE (risk, injury, and failure) criteria in only half of the patients [13,14]. There are no guidelines regarding when to initiate haemodialysis in DAKI, nor the dosage or modality of Renal Replacement Therapy (RRT) for treating DAKI. DAKI can progress to Chronic Kidney Disease (CKD), and a gradual reduction in Glomerular Filtration Rate (GFR) with increased proteinuria is characteristic. AKI patients requiring dialysis have a worse outcome with a higher risk of progression to CKD [18]. Extended longitudinal follow-up is necessary for DAKI patients to monitor the GFR rise [19]. Hypotension and shock are associated with a higher incidence of DAKI [20]. A haematocrit level >46.5 is associated with a 4.7-fold higher incidence of DAKI [21]. Severe dengue with concurrent DAKI has a mortality rate of 64% [10]. The patient in this case report presented with severe dengue with cardiomyopathy and nephropathy, which responded to treatment with normalisation of echocardiography, urea, and creatinine. However, proteinuria persisted in the range of macroalbuminuria even after recovery, indicating the need for regular follow-up as the patient experienced hypotension and required haemodialysis, both of which are independently associated with an increased risk of progression to CKD.

CONCLUSION(S)

Severe dengue with multisystem involvement carries a high-risk of morbidity and mortality. Cardiomyopathy and AKI are well known reversible complications that require prompt diagnosis and treatment to prevent complications and mortality. Although guidelines regarding dialysis are not specific, dialysis should be utilised in the treatment of DAKI to prevent complications. Additionally, patients with DAKI who present with hypotension, haemoconcentration, or require dialysis should be closely monitored for an extended period to track GFR, proteinuria, and the progression to CKD.

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