Case Report

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Expanded dengue syndrome in secondary dengue infection: A case of biopsy proven rhabdomyolysis induced acute kidney injury with intracranial and intraorbital bleeds

Ghazal Tansir, Chhavi Gupta, Shubham Mehta, Prabhat Kumar*, Manish Soneja, Ashutosh Biswas

Department of Medicine, All India Institute of Medical Science, New Delhi, India.

Summary **Dengue fever is endemic in the Indian subcontinent and can have myriad presentations. The term expanded dengue syndrome (EDS) is used for atypical manifestations in dengue fever. We present a rare case of EDS in a patient with secondary dengue infection who developed rhabdomyolysis induced acute kidney injury (RAKI) along with intracranial and intraorbital bleeds. Patient was successfully managed in our institute and was discharged in stable condition. To the best of our knowledge, this is the only reported case of simultaneous occurrence of these complications in a dengue patient. This case is being presented to make clinicians aware of the spectrum of dengue infection.**

Keywords: Acute tubular necrosis, acute febrile illness, choroidal hematoma

1. Introduction

Dengue is one of the most important arthropod-borne viral diseases. More than 50 million people residing in tropical areas are infected with dengue every year and its incidence has increased 30 times in the last 50 years (*1*). The dengue virus is an RNA virus from the genus Flavivirus transmitted *via* the bite of female *Aedes aegypti* mosquitoes. There are four virus serotypes, designated as DENV-1, DENV-2, DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that virus serotype and only partial cross immunity to other serotypes. However, secondary infection with another serotype or multiple infections with different serotypes can lead to a severe form of disease (*2*).

The clinical presentation of dengue has varied patterns ranging from asymptomatic infection, to severe bleeding, hemodynamic instability and even death. While fever, headache, malaise, bleeding manifestations, shock and hemoconcentration are known manifestations of the disease, certain atypical conditions have also been reported, which are now known as expanded dengue syndrome (*3*). Rhabdomyolysis induced acute kidney injury (RAKI) is one such atypical manifestation of dengue infection which is rarely seen and a single biopsy proven case has been reported so far (*4*). Similarly intracranial and intraorbital bleeds in dengue infection are very unusual (*5,6*). Expanded dengue syndrome (EDS) cases are underreported and pose a serious challenge for the treating physician.

2. Case Report

A 35 year old male patient with no prior comorbidities presented in emergency department in September 2017 with complaints of shortness of breath and reduced urine output for 6 days which was associated with hematuria, myalgia and rash over extremities. He also had swelling of right eye for the last 2 days that was associated with diminution of vision. These symptoms were preceded by fever of 6 days duration that subsided after taking antipyretics. He also gave history of dengue fever two years back for which he was admitted to a hospital for two days and had recovered completely. On examination, he was afebrile, blood pressure was 160/90 mm Hg, pulse rate- 110/min, respiratory rate-

**Address correspondence to:*
Dr. Prabhat Kumar, Department of Medicine, 3rd floor, Teaching Block, All India Institute of Medical Science, New Delhi 110029, India.
E-mail: drkumar.prabhat@gmail.com

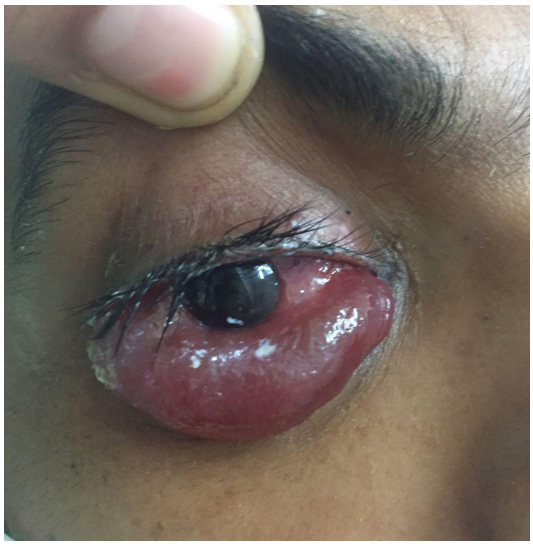

Figure 1. Conjunctival suffusion with eyelid edema of the right eye.

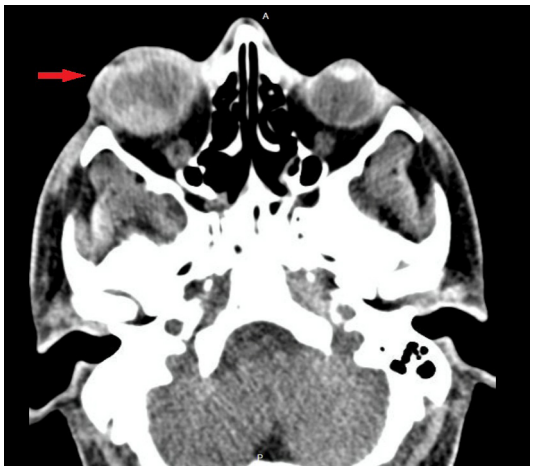

Figure 2. Axial NCCT of orbits showing expansion of the right posterior segment with hyperdense hematoma over the choroid (arrow).

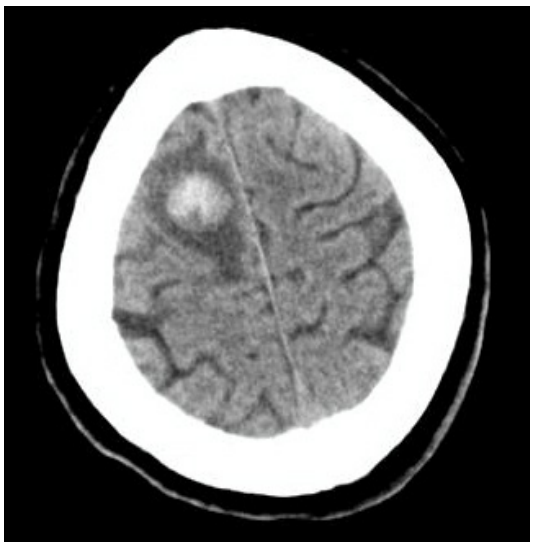

Figure 3. NCCT head showing right frontal hematoma (3.5 × 8.0 mm) with perilesional edema.

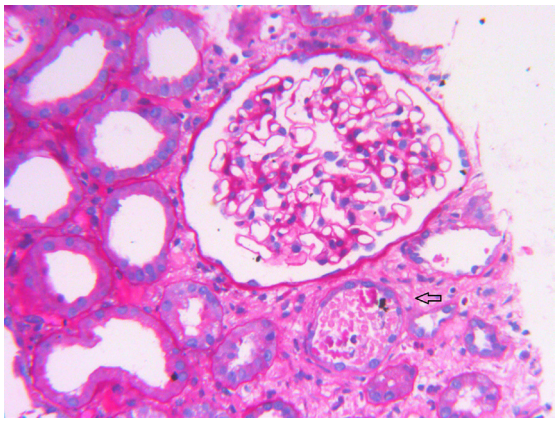

Figure 4. Renal biopsy showing normal glomerulus, dilated proximal tubules with tubular epithelial cell swelling and necrosis. Some of the tubules contain proteinaceous substances (arrow).

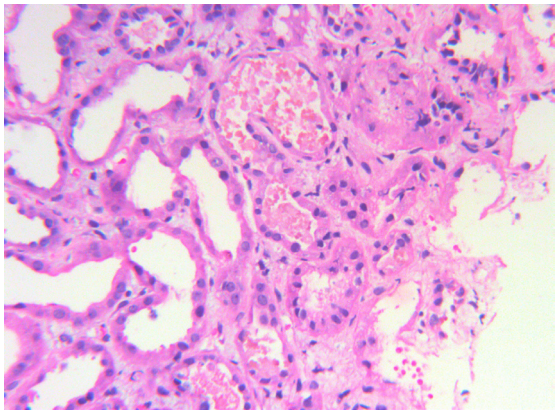

Figure 5. PAS stain highlights thinning and loss of PAS positive brush border.

30/min and had oxygen saturation of 90% on room air. There was conjunctival suffusion and eyelid edema with impaired vision in the right eye (Figure 1). There were fine basal crepitations over the chest and ascites was present. He had no focal neurological deficit at the time of admission. A suspicion of dengue was kept and following investigation were done immediately.

Hemogram showed hemoglobin: 9 gm/dL, total leucocyte count (TLC): 7,000/cu mm, platelet count: 29,000/cu mm. Renal and liver parameters were grossly deranged, urea/creatinine:130/9.5 mg/dL, total bilirubin: 3 mg/dL, aspartate transaminase/alanine transaminase (AST/ALT): 16,280 / 5,982 U/L. Urine examination showed gross proteinuria and > 100 RBCs/hpf without any casts or dysmorphic RBCs. Arterial blood gas analysis (ABG) showed severe metabolic acidosis. Serum electrolytes and coagulation profile were normal. Serum creatine phosphokinase (CPK) was 6,400 U/L (Normal: 20-200) and lactate dehydrogenase (LDH) was 10,240 IU/L (Normal: 100-400). Ultrasound abdomen showed gall bladder wall edema with moderate ascites and normal kidneys. Dengue serology was positive for both IgM and IgG in high

Table 1. Summary of patients with dengue associated rhabdomyolysis induced acute kidney injury

Ref.	Age, Sex	Diagnosis	Treatment	Duration of hospital stay	Outcome
Gunasekera *et al*. 2000 (*16*)	28 yr, F	Dengue with RAKI	Forced alkaline diuresis, hydration Antibiotics,	NA	Recovered
Karakus *et al*. 2007 (*17*)	66 yr, M	Dengue with RAKI, pneumonia, septic shock and respiratory failure	Mechanical ventilation, ionotropes	47 days	Death
Acharya *et al*. 2010 (*18*)	40 yr, M	Dengue myositis, RAKI with respiratory failure	Mechanical ventilation	NA	Recovered
Wijesinghe *et al*. 2013 (*19*)	42 yr, M	Dengue with RAKI	Hemodialysis, forced alkaline diuresis	9 days	Recovered
Sunderlingam *et al*. 2013 (*20*)	17 yr, M	Dengue, RAKI, MRSA infection with refractory shock	Antibiotics, ionotropes and hydration	NA	Death
Jha R *et al*. 2013 (*21*)	21 yr, M	Dengue with RAKI	Hemodialysis	9 days	Recovered
Repizo *et al*. 2014 (*4*)	28 yr, M	Dengue with biopsy proven RAKI	Hemodialysis	21 days	Recovered
Siriyakorn N *et al*. 2015 (*22*)	17 yr, M	Dengue, RAKI, severe hepatitis and coagulopathy	Hemodialysis, Mechanical ventilation	12 days	Death
Mishra A *et al*. 2015 (*23*)	21 yr, M	Dengue with RAKI	Hydration, forced alkaline diuresis	9 days	Recovered
Present case	35 yr, M	Dengue, biopsy proven RAKI, intracerebral and intraorbital bleed	Hemodialysis, antibiotics	30 days	Recovered

yr: years, M: Male, F: Female, RAKI: Rhabdomyolysis induced acute kidney injury.

titres, confirming our diagnosis of secondary dengue infection. Other relevant tests for malaria, leptospirosis and rickettsial infections were negative. Chest X ray and ECG was normal. A possibility of dengue associated RAKI was kept, however urinary myoglobin levels couldn't be done because of its unavailability in our institute.

He was given broad spectrum antibiotics and was transfused with multiple random donor platelet concentrates. He also received alternate-day dialysis for RAKI. Ophthalmologist's opinion was taken for right eye swelling and an ultrasound B-scan showed a choroidal hematoma measuring 15 × 10 mm. This was confirmed on non-contrast computed tomography (NCCT) of the orbit (Figure 2). He was also given topical antibiotics for orbital cellulitis. On the seventh day of admission he noticed weakness of left lower limb. NCCT head showed an intracranial bleed in the right frontal region with minimal perilesional edema (Figure 3). This was conservatively managed and his power gradually improved. Subsequent reports showed normalization of platelet count, liver enzymes, CPK and LDH levels in the next two weeks. However, there was minimal improvement in renal function rendering the patient oliguric and dialysis-dependent for a long time. The unusually slow renal recovery prompted us to carry out a renal biopsy. Biopsy showed normal glomeruli, dilated proximal tubules with tubular epithelial cell swelling and necrosis along with deposition of proteinaceous granular substances (Figure 4 and Figure 5). Hence, rhabdomyolysis induced acute tubular necrosis was proven histopathologically. He received a total of 12 cycles of hemodialysis, following which his urine output improved and renal function tests normalized. He was discharged after a month-long stay in October 2017.

3. Discussion

India has the largest number of dengue cases, with about 33 million apparent and another 100 million asymptomatic infections occurring annually. It is a well known fact that primary or first infection in nonimmune person usually causes inapparent or mild infection. However, subsequent dengue infection by a different serotype causes more severe illness. Although pathogenesis is not well-defined, the antibody dependent enhancement effect, cross-reactive T cells and shift from Th1 to Th2 pathway leads to a cytokine storm, which is possibly responsible for severe illness during secondary infection (*7,8*).

EDS is a terminology introduced by the WHO in 2012 to encompass the unusual manifestations of dengue involving severe damage to the liver, heart,

kidneys or brain. They may be related to underlying co-morbidities, associated co-infections or prolonged shock. Certain high-risk groups such as pregnant, infants, geriatric group, patients with coronary artery disease, hemoglobinopathies and immunocompromised individuals are particularly susceptible to developing EDS. As clinicians, we must be aware of these atypical features so that we can suspect dengue early, especially during ongoing epidemics.

Dengue has been associated with multiple patterns of renal involvement. These include proteinuria, glomerulonephritis, IgA nephropathy, hemolytic uremic syndrome and acute tubular necrosis (*9*). Despite the multitude of patterns of involvement, acute kidney injury (AKI) remains a poorly studied area in dengue infection. Various studies have found the prevalence of AKI in dengue to be between 1-13% (*10-12*). The mechanisms proposed for this affliction of the kidneys include direct viral action on renal tissue, hypoperfusion secondary to shock, and rhabdomyolysis.

Rhabdomyolysis is characterized by muscle necrosis leading to release of muscle enzymes like creatine phosphokinase, lactate dehydogenase, aldolase and myoglobin in the systemic circulation. It has been described in a few case reports among dengue patients (*13*). These patients present with severe myalgias and have high levels of muscle enzymes, most often in thousands. It is caused by either a direct viral or toxin-mediated effect on myocytes and is associated with renal failure in 57% of cases. Deposition of myoglobin in the tubules leading to direct or ischemic tubular injury, tubular obstruction or intrarenal vasoconstriction, are responsible for the renal failure. Although not traditionally believed to be associated with myositis, dengue virus is being recognized now as a cause. Studies have found histopathological changes of myositis even in dengue patients devoid of muscular symptoms (*14,15*). Renal tubular injury caused by rhabdomyolysis has been scarcely reported among dengue patients. To the best of our knowledge nine such cases have been reported, with only a single biopsy-proven case (Table 1) (*4,16-23*). Three out of the nine patients died, proves the seriousness of this condition (*17,20,22*). Treatment includes hydration with normal saline and forced alkaline diuresis with sodium bicarbonate to maintain adequate urine output. However, in oliguric AKI intravenous fluids should be judiciously used and hemodialysis should be commenced as soon as possible. Four out of these nine patients required dialysis for deteriorating AKI. Apart from AKI, other complications of rhabdomyolysis include compartment syndrome, arrhythmias, disseminated intravascular coagulation (DIC), hepatic dysfunction and metabolic acidosis (*24*). Any delay in diagnosis and treatment of these complications can be detrimental. In the present case too, the patient developed oliguric renal failure along with hepatitis as a complication of rhabdomyolysis for which he received several sessions of hemodialysis.

Along with renal involvement, our patient also had intracranial and ophthalmic complications. Neurological manifestations have been described in dengue fever, with encephalitis being the most common. The pathogenesis has been postulated to be due to direct viral invasion, increased capillary permeability, capillary hemorrhage, DIC, dyselectrolytemias and fulminant hepatic failure. Intracranial hemorrhage in dengue patients is an unusual entity with a study finding only 3% of cases of dengue encephalopathy attributable to it (*5*).

Ophthalmic complications in dengue has recently been recognized and reported more often. Studies have found 60% dengue patients to have ocular complications with subconjunctival hemorrhage being most common. Posterior segment involvement is reported too, with macular edema, vascular occlusion, vitreous hemorrhage, optic neuropathy, chorioretinitis, retinal hemorrhages and cotton wool spots (*6*). Our patient had both orbital cellulitis and choroidal hematoma with loss of vision that was opined to be irreversible by the ophthalmologists. This patient is an example of the complicated turn of events that dengue fever can have.

In conclusion, in a dengue patient with AKI, CPK and LDH levels should be always screened to look for rhabdomyolysis, as early diagnosis and treatment can have a favorable outcome. A thorough neurological examination should be carried out in such critical patients and even subtle signs should be evaluated appropriately. Managing dengue infection can be challenging for treating physician if patient develops EDS, which carries an unfavorable prognosis.

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