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A Case Report and Literature Review
An unusual presentation of Compartment syndrome, Rhabdomyolysis and Dengue Fever

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Introduction

We report a case of Dengue fever complicated with compartment syndrome and rhabdomyolysis. Both of these manifestations occurring in the same patient isextremely unusual.

Case Presentation

A 16-year-old man with no known chronic illnesses presented to the Teaching hospital of Jaffna, Sri Lanka, with a history of fever for two days, frontal headache, vomiting twice and loose stool twice for one day. Apart from flushing and being febrile and a capillary refill time of 3 seconds, examination was otherwise normal with no postural drop in blood pressure. Dengue antigen, nonstructural protein 1 (NS1 antigen) was positive on day two and was managed for dengue fever. He made a steady recovery until day 6 of his illness where he developed severe calf pain and tenderness with swelling of calves with poor peripheral circulation and muscle weakness. Urine output was normal throughout. There were no bleeding manifestations and duplex scan of the lower limbs indicated compartment syndrome.

Immediate fasciotomy was performed. Two Ultrasound scans showed no evidence of fluid leakage and 2 D echo was normal. Within the next two days, he went on to develop acute kidney injury, swelling of both upper limbs with poor peripheral circulation and compartment syndrome of both upper limbs were detected with duplex scan. He also went on to develop rhabdomyolysis with dark colored urine and rising creatinine phosphokinase (CPK) levels peaking at 24780 iU/L on day 9 of illness. ALT 228 and AST 513 iU and serum creatinine was 1.8mg dL on day 7 reaching a maximum of 2mg/dL on day 10. Dengue IgG and IgM were positive on day 7. Leptospira antibody was negative while plasma fibrinogen level and ESR were normal.

In-hospital management included optimal hydration with intravenous and oral fluids, strict input/output charting, daily urinalyses, and close monitoring of the blood urea, creatinine, electrolytes, CPK, and platelet count. Adequate urine output was achieved and alkalinization of the urine with sodium bicarbonate was also instituted. Despite aggressive treatment, he developed multi organ failure and died on day 11 of his illness.

Discussion

This is a case which illustrates an unusual presentation of dengue fever with compartment syndrome in all four limbs and rhabdomyolysis with acute kidney injury.

Dengue is currently the most important infectious viral mosquito-borne disease in the world. In fact, the number of cases worldwide that are annually reported to the World Health Organization (WHO) increased from approximately 900 in the 1950s to almost one million at present[1]. Dengue is a multifaceted disease that can manifest as an undifferentiated fever, classical dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [1].

This patient presented early in his illness during the peak of an epidemic in Jaffna with typical clinical features of dengue fever which was supported by his full blood count showing leucopenia with thrombocytopenia and a positive dengue virus antigen (NS1). He was managed according to the current national guidelines[2] and made a good recovery up to the sixth day of his illness. When this patient developed compartment syndrome followed by rhabdomyolysis, the ultrasound scans of the abdomen did not show evidence of fluid leakage to pleural or peritoneal cavity and 2D echocardiogram was also normal and did not show evidence of bleeding or fluid leakage to the pericardial space.

As documented in the literature, the cardinal feature of dengue hemorrhagic fever (DHF) results from a transient increase in vascular permeability that causes fluid leakage from the intravascular to the interstitial compartment, leading to haemo-concentration, and circulatory collapse, which contribute to mortality and significant morbidity[3].Our patient showed no evidence of any fluid leakage.

Capillary leak syndrome is seen in various situations, sepsis and dengue being the major infectious causes[4]. The mechanisms of capillary leak may involve increased hydrostatic pressure, decreased oncotic pressure, or increased

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permeability of the capillary endothelium[5]. Among the other infectious causes of capillary leak leading to compartment syndrome; Brucellosis, Hantavirus infection, and sepsis have been mentioned in the literature [6].

Idiopathic systemic capillary leak syndrome (SCLS) or Clarkson's disease is another important cause of capillary leakage, where there are recurrent episodes of hypovolemic shock, edema, hemo-concentration, and hypoalbuminemia. Episodes of systemic capillary hyperpermeability due to various cytokines have been implicated in the pathogenesis of this disorder[7,8].

The most common bleeding manifestations of dengue include petechiae, gum bleeding, GI bleeding and hemoptysis although rarer sites are often involved[9]. This patient did not have bleeding from any of these sites although he bled in to his muscles in the limbs. A case report from South India has shown that bleeding in dengue might lead to abdominal compartment syndrome in rare cases[10] and another case report from India has shown the occurrence of right forearm compartment syndrome due to dengue viral infection [11].

Although prompt fasciotomy was performed and adequate hydration was given with antibiotic cover, he developed Rhabdomyolysis characterized by the typical triad of generalized weakness, myalgia, and dark urine/myoglobinuria associated with a CPK that was more than five times the upper limit of normal[12] leading to acute kidney injury as indicated by worsening renal functions and rising CPK levels. There are only five previously reported cases of dengue induced rhabdomyolysis and AKI (table 1). All of them presented elevated CK levels, four studies reported myalgia, three reported muscle weaknesses and four studies presented dark urine, positive urinary myoglobin and oliguria. Renal replacement therapy was performed in three cases and renal biopsy was done only in one.

The pathogenesis of dengue-associated muscle injury is unclear. Different mechanisms have been hypothesized, such as direct viral invasion or immune-mediated injuries of the muscle fibers. Striated skeletal muscles from mice inoculated with dengue type2 viruses exhibited myofibril destruction, sarcoplasm involution, mitochondrial changes and aggregates of electron-dense material and cytoplasmic glycogen particles [17].

Dengue viral infection has also been associated with increased production of inflammatory cytokines which may cause muscle injury particularly tumor necrosis factor alfa (TNF alpha) [18,19].

Acute kidney injury associated with myoglobinuria is the most serious complication of both traumatic and nontraumatic rhabdomyolysis and may be life-threatening. As seen in the cases reviewed, acute renal failure is a frequent complication in patients with dengue and rhabdomyolysis. The exact mechanisms by which rhabdomyolysis impairs renal function are unclear, but experimental evidence suggests that intrarenal vasoconstriction, direct and ischaemic tubular injury, and tubular obstruction all play a role [20].

Myoglobin becomes concentrated along the renal

Author, year and country	Gunasekera et al, 2000, Ceylon[13]	Davis & Bourke, 2004, East Timor[14]	Karakus et al, 2007, Surina-me[15]	Acharya et al, 2010, India[16]	Bandyopadhyay et al, 2013, Brazil [11].	Current case
Gender and age	Female 28y	Male 33y	Male 66y	Male 40y	Male 28y	Male 16y
Type of Dengue	NR	DHF	DSS	NR	DF	DF
Mayalgia	YES	NR	YES	YES	YES	YES
Muscle weakness	YES	NR	NR	YES	NR	YES
Dark Urine	YES	NR	YES	YES	YES	YES
Urine for myoglobin	+	NR	+	+	Not done	Not done
Oliguria	YES	NR	YES	YES	YES	No
CPK iu/L	>5000	17548	156900	29000	4063	24780
Creatinine	8.8	NR	3.6	2.6	14.8	2
Renal biopsy	NO	NO	NO	NO	ATN	NO
RRT	PD,HF	NR	NR	NR	HD	NO
Out come	recovery	death	death	NR	Recovery	death

Table1: Comparison of the current case with the cases of dengue with rhabdomyolysis and AKI previously described

NR not reported; DHF dengue hemorrhagic fever; DSS dengue shock syndrome; RRT renal replacement therapy; HD hemodialysis; HF; hemofiltration; ATN acute tubular necrosis

tubules, where it precipitates when it interacts with the Tamm-Horsfall protein, particularly in the presence of acidic urine. Myoglobin seems to have no marked nephrotoxic effect in the tubules unless the urine is acidic; hence, the common practice of urinary alkalinization as part of supportive treatment measures was done in our patient as well.

Acute kidney injury has been reported with CPK values as low as 5000 U/L, but this usually occurs with coexisting conditions such as sepsis, dehydration, and acidosis [20]. In our patient there was hardly any evidence of sepsis and dehydration was prevented with hydration to produce adequate amounts of urine. Acidosis was also prevented by infusion of bicarbonate to produce alkaline urine and blood PH was not acidotic until the last day as shown by the blood gas analysis (table 2).

Date	7/1/2015 6pm	8/1/2015 7am	9/1/2015 7am	9/1/2015 6pm	10/1/2015 7am	10/1/2015 2pm
PH	7.39	7.36	7.5	7.5	7.4	7.2
PCO_{2} mmHg	20	18	21.8	26.1	16	14
PO_{2} mmHg	150	185	122	103	138	101
HCO_{3}^{-} mmol/l	16.6	10.2	20.2	21.1	11.5	

Table 2: Values of arterial blood gases after developing compartment syndrome.

$PaCO_2$: partial pressure of arterial oxygen; PaO_2 partial pressure of arterial carbon dioxide; HCO_3^-

We were unable to perform muscle biopsy on this patient as we did not get the consent from his parents.

Conclusion

Compartment syndrome and rhabdomyolysis should be recognized as a possible complication of dengue fever and should be reflected as such in medical textbooks especially in light of the possibility of acute renal failure and high mortality. A diagnosis of dengue fever may always not have a smooth recovery as shown in this case.

Clinicians should note that the presentation of rhabdomyolysis can be subtle but its complications, in particular, acute kidney injury and multiorgan failure, can be devastating. These adverse effects are preventable with early recognition and institution of the appropriate management. We feel it is important that all patients with dengue fever should have a urinalysis done and that those who test positive for blood should have urine microscopy and a CPK test in order to determine if the patient may have rhabdomyolysis. This approach could be potentially life-saving.

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