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BIOPSY PROVEN ACUTE TUBULAR NECROSIS DUE TO RHABDOMYOLYSIS IN A DENGUE FEVER PATIENT: A CASE REPORT AND REVIEW OF LITERATURE

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SUMMARY

Renal histology results are very scarce in dengue-associated rhabdomyolysis patients developing acute kidney injury (AKI). We report a case of dengue fever-induced AKI associated to rhabdomyolysis with a renal biopsy showing acute tubular necrosis (ATN) and renal deposition of myoglobin. A 28-year-old patient who presented dengue fever (DF) complicated by severe AKI and rhabdomyolysis is described. The patient required hemodialysis for three weeks. A renal biopsy revealed ATN with positive staining for myoglobin in the renal tubuli. The patient was discharged with recovered renal function. In conclusion, this case report described a biopsy proven ATN associated to DF-induced rhabdomyolysis, in which renal deposition of myoglobin was demonstrated. We suggest that serum creatine phosphokinase should be monitored in DF patients to allow for an early diagnosis of rhabdomyolysis and the institution of renal protective measures.

KEYWORDS: Dengue fever; Acute kidney injury; Acute tubular necrosis; Renal histology; Myoglobin; Rhabdomyolysis; Creatine phosphokinase.

INTRODUCTION

Dengue is currently the most important infectious viral mosquito-borne disease in the world. In recent years, there has been an explosive outbreak of this infectious disease, mainly affecting tropical countries, but also the warmer areas of developed countries, such as the southern United States. 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 present⁴¹.

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)⁴¹.

Different renal injuries have been described in dengue patients, such as an increase in serum creatinine, proteinuria, glomerulonephritis, hemolytic-uremic syndrome and acute kidney injury (AKI)^{4,10,16,37,39}. Most cases of AKI have been associated with DHF or DSS^{6,7,20-23,25,27,34,40}, but AKI has also been described in DF^{13-15,30,31}, albeit less commonly. Similarly, rhabdomyolysis with^{1,5,7,19} and without AKI^{9,24,28} has been described in dengue patients. Renal histology results from patients with dengue-associated AKI are scarce and to the best of our knowledge, there were no previous cases of biopsy proven ATN with renal myoglobin deposition due to rhabdomyolysis associated with DF^{31,37,39}.

We report a case of a young patient who developed AKI and

rhabdomyolysis associated with DF. A renal biopsy revealed acute tubular necrosis and positive staining for myoglobin in the renal tubuli. The literature on dengue-associated renal injury and rhabdomyolysis is reviewed and discussed.

CASE REPORT

A 28-year-old married male painter, from Sao Paulo, SP, Brazil, previously healthy, presented a 20-day history of fever, myalgia, muscle weakness, cough, nausea and vomiting, diarrhea, epigastric pain and lower limb edema. The patient history did not disclose any epidemiological clue for a specific infectious disease nor had he receive any nephrotoxic drug.

Laboratory blood analysis at the time of the first hospital admission revealed the following: creatinine (SCr) 11.6 mg/dL, urea 277 mg/dL, sodium 124 mEq/L, potassium 6.6 mEq/L, bicarbonate 15.6 mEq/L, SGOT 1,206 IU/L, SGPT 853 IU/L, amylase 121 IU/L, total bilirubin 0.38 mg/dL, alkaline phosphatase 68 IU/L, gamma-glutamyltransferase 104 IU/L, hemoglobin 14.2 g/dL, leukocytes 10,200/mm³, platelets 292,000/mm³ and C-reactive protein (CRP) 1.95 mg/dL. The urinalysis disclosed a specific gravity of 1,027, pH 5.0, protein 3+, glucose traces, red blood cells > 1 million/mL, leukocytes > 1 million/mL and no casts. Renal replacement therapy (RRT) was initiated.

After one week, he was transferred to Hospital das Clinicas, University

of Sao Paulo Medical School, Sao Paulo, Brazil. At admission, he was pale, had a blood pressure of 140/90 mmHg and oliguric (150 mL/24 h), with a dialysis catheter in his right internal jugular vein and had no evidence of systemic hemorrhagic phenomena. His physical exam was otherwise unremarkable. Laboratory tests performed at admission revealed: SCr 14.8 mg/dL, serum urea 323 mg/dL, hemoglobin 11.8 g/dL, leukocytes 9,400/mm³, platelets 469,000/mm³, albumin 3.6 g/L and CRP 2.5 mg/dL. The patient presented serum creatine phosphokinase (CK) 4,063 IU/L, serum lactic dehydrogenase 657 IU/L, uric acid 13.4 mg/dL and phosphorus 9.2 mg/dL, suggesting rhabdomyolysis. The urinalysis showed protein > 1 g/L, red blood cells > 100/field, and leukocytes 20/field. A subsequent 24 h proteinuria showed 0.83 g of protein/24 h. Anti-nuclear factor, antineutrophil cytoplasmic antibodies, C3 and C4 complement fractions, rheumatoid factor and anticardiolipin antibody levels were normal. A renal ultrasound disclosed normal kidneys. Serology for HIV, leptospirosis, hepatitis C, hepatitis B and syphilis were negative. Patient tested positive for hepatitis A and cytomegalovirus immunoglobulin G. Five days after admission, a positive test for dengue was obtained (IgM, ELISA assay). As the patient had a clinical picture and serology consistent with dengue infection without hemorrhagic phenomena, low platelet count or evidence of plasma leakage, he was diagnosed with a case of dengue fever complicated by rhabdomyolysis and AKI.

After two weeks on RRT, due to non-recovery of renal function, a percutaneous renal biopsy was performed. The biopsy included 11 glomeruli with normal volume and cellularity, dilated tubules with foci of epithelial cellular necrosis, interstitial area with focal fibrosis (approximately 10%) and normal arterioles. Immunofluorescence assays for IgA, IgG, IgM, C1q, C3 and fibrinogen were negative. The pathological diagnosis was acute tubular necrosis. Myoglobin immunohistochemistry staining was positive in the renal tubuli (Fig. 1 A and B).

Three weeks after admission, RRT was interrupted and patient was discharged with SCr 2.4 mg/dL, normal urine output and urinalysis with pH 5.5, specific gravity 1015, blood +, protein 0.3 g/dL, 12 WBCs and

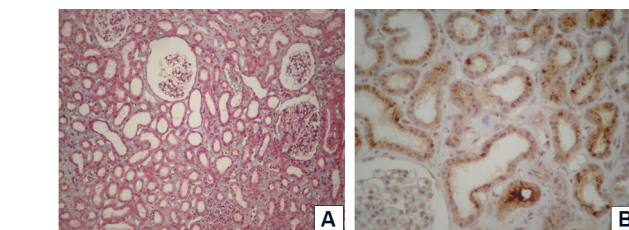


Fig. 1 - A. Light microscopy of renal tissue stained with Masson's trichrome (20X). Note the presence of diffuse acute tubular necrosis and preserved glomeruli. In the interstitial area, thin fibrosis lines and edema are evident. **B.** Immunostaining of renal tissue. Note the positive immunostaining for myoglobin in the cytoplasm of the tubular cells.

3 RBCs. After three weeks, he returned to the outpatient facility with no complains and an unremarkable physical examination. Laboratory tests performed at that time revealed a SCr of 0.98 mg/dL.

DISCUSSION

To the best of our knowledge, the current case is the first biopsy proven description of rhabdomyolysis and AKI associated with DF in which ATN and myoglobin staining in the renal tubuli was demonstrated.

There are only four previously reported cases of dengue-induced rhabdomyolysis and AKI (Table 1), but renal biopsy was not performed on those patients^{1,7,15,19}. All of them presented elevated CK levels, three studies reported myalgia, two reported muscle weaknesses and three studies presented dark urine, positive urinary myoglobin and oliguria. Renal replacement therapy was performed in two cases.

There are also case descriptions of dengue-associated rhabdomyolysis with myalgia, dark urine and highly elevated CK levels without AKI development^{3,7,9,24}. In addition, AKI was not reported in series of patients with dengue-induced quadriparesis or myositis and high CK levels^{28,33}. Although rhabdomyolysis is a well-known risk factor for AKI, the presence of other simultaneous injury factors, such as hypovolemia or

Table 1
Comparison of the current case with the cases of dengue with rhabdomyolysis and AKI previously described

Author, year, country	Gender, age	Type of dengue	Myalgia	Muscle weakness	Dark urine	UMyo	Oliguria	CK (IU/L)	Cr (mg/dL)	Renal biopsy	RRT	Outcome
Gunasekera <i>et al</i> , 2000, Ceylon (ref 14)	Female, 28 y	NR	yes	yes	+	+	yes	>5,000	8.8	no	PD, HF	recovery
Davis & Bourke, 2004, East Timor (ref 7)	Male, 33 y	DHF	NR	NR	NR	NR	NR	17,548	NR	no	NR	death
Karakus <i>et al</i> , 2007, Suriname (ref 19)	Male, 66 y	DSS	yes	NR	+	+	yes	156,900	3.6	no	NR	death
Acharya <i>et al</i> , 2010, India (ref 1)	Male, 40 y	NR	yes	yes	+	+	yes	29,000	2.6	no	NR	NR
Current case, 2013, Brazil	Male, 28 y	DF	yes			ND	yes	4,063	14.8	ATN	HD	recovery

UMyo: urinary myoglobin; CK: serum creatine phosphokinase; Cr: serum creatinine; RRT: renal replacement therapy; NR: not reported; PD: peritoneal dialysis; HF: hemofiltration; DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome; DF: dengue fever; ND: not done; ATN: acute tubular necrosis; HD: hemodialysis.

dehydration, acidosis and aciduria, must be present to cause clinically relevant myoglobinuria-induced renal injury.

AKI has also been reported in DHF, DSS and DF without rhabdomyolysis. Hemodynamic instability, hemolysis, glomerular injury and direct action of viral particles on renal tissue have been considered as possible injury mechanisms^{6,10,25,30,32,34,37}. In fact, the current patient presented proteinuria but the renal biopsy did not disclose glomerular injury.

Myositis and rhabdomyolysis have been considered as rare complications of dengue infection but few authors have systematically assessed their occurrences. MALHEIROS *et al.*²⁶ performed muscle biopsies in 15 patients with DF and myalgia during an epidemic outbreak in Brazil. Only three patients presented mild increased CK levels. They found mononuclear infiltrates in 12 biopsies, lipid accumulations in 11 and rare foci of myonecrosis in three (one case had an elevated CK level). Seven out of 16 patients with serologically proven dengue infections in India presented muscle weakness and increased CK levels¹⁸. A muscle biopsy was performed in one patient, revealing myositis¹⁸. SAID *et al.* prospectively assessed CK levels and the incidence of myositis in 101 patients with serologically proven dengue in Saudi Arabia³⁵. In that study, 91% of the patients had elevated CK, 63.4% complained of myalgia and 2.9% had muscle weakness. MISRA *et al.* evaluated 39 patients with positive dengue serology during a dengue outbreak in Northern India²⁹. Transient muscle dysfunction with CK levels of approximately 1,000 U/L was observed in 11 (73.3%) patients with DF, in 18 (81.8%) with DHF and in the two patients with DSS. This collection of data suggests that muscle injury is not uncommon in dengue and has probably been underreported.

The pathogenesis of dengue-associated muscle injury is unclear. Different mechanisms have been hypothesized, such as direct viral invasion of and immune-mediated injury to the muscle fibers. Striated skeletal muscles from mice inoculated with dengue type 2 viruses exhibited myofibril destruction, sarcoplasm involution, mitochondrial changes and aggregates of electron-dense material and cytoplasmic glycogen particles³². The dengue virus has demonstrated high efficiency in infecting and replicating in human primary muscle satellite cells³⁸ and muscle cells were demonstrated to be highly susceptible to *in vitro* infection by the dengue 2 virus. The infected cells exhibited increased expression of inflammatory genes and the IP-10 protein and elevated intracellular calcium³⁶. Dengue virus infection has also been associated with increased production of inflammatory cytokines which may cause muscle injury^{11,12}.

In conclusion, DF may cause rhabdomyolysis-associated ATN. Dengue virus-associated muscle injury is probably under-recognized and underreported. CK levels should be monitored in dengue patients to allow for an early diagnosis of rhabdomyolysis and the institution of renal protective measures.

SUPPORT AND FINANCIAL DISCLOSURE

The authors declare that they have no relevant financial interests.

CONSENT

Written informed consent was obtained from the patient for the publication of this Case report and any accompanying images. A copy

of the written consent is available for review by the Series Editor of this journal.

RESUMO

Necrose tubular aguda comprovada por biópsia em paciente com dengue e rabdomiólise

Resultados de histologia renal são muito escassos em pacientes com rabdomiólise e injúria renal aguda (IRA) associada a dengue. Descrevemos caso de dengue complicado por rabdomiólise e IRA no qual a biópsia renal mostrou necrose tubular aguda (NTA) e deposição renal de mioglobina. Paciente de 28 anos que apresentou dengue complicado por IRA grave e rabdomiólise é descrito. Ele necessitou de diálise por três semanas. A biópsia renal mostrou NTA, com imunohistoquímica fortemente positiva para mioglobina nos túbulos renais. O paciente recebeu alta com recuperação da função renal. Em conclusão, descrevemos caso de dengue complicado por IRA e rabdomiólise, em que a biópsia renal mostrou NTA e deposição de mioglobina. Sugerimos que creatinofosfoquinase deve ser monitorizada em pacientes com dengue para permitir o diagnóstico precoce de rabdomiólise e a instituição de medidas protetoras para o rim.

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