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Case report

Rhabdomyolysis associated with dengue fever in a lupic patient

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ABSTRACT

This report describes the case of a woman with systemic lupus erythematosus (SLE) that developed rhabdomyolysis after being infected by dengue virus. There are only a few cases of SLE accompanied by rhabdomyolysis, none of them associated with dengue fever.

Initially, the woman presented high fever, myalgia, muscular weakness, mild headache, polyarthralgia and thrombocytopenia reminding a lupus flare, but since the number of people infected by dengue at that time was high and the symptoms from both conditions are similar, a dengue serology was requested. After a few days, the patient developed rhabdomyolysis. She was then submitted to immunosuppressive drugs, urinary alkalization and vigorous hydration, which improved her muscle damage and inflammatory condition. The positive dengue serology was only available after the therapy above had been established. She was discharged in an asymptomatic state.

This case demonstrates how alike dengue fever and a lupus flare are, warning clinicians that, especially during an epidemic, both diseases should be carefully differentiated in order to establish a correct and efficient therapy.

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A rabdomiólise está associada à febre dengue em um paciente lúpico

RESUMO

Esse relato descreve o caso de uma mulher com lúpus eritematoso sistêmico (LES) que sofreu rabdomiólise em seguida à sua infecção pelo vírus da dengue. Foram relatados apenas alguns casos de LES com manifestação de rabdomiólise, nenhum deles associados à febre dengue.

A princípio, a paciente apresentava-se com febre alta, mialgia, astenia muscular, leve cefaleia, poliartralgia e trombocitopenia, lembrando uma exacerbação lúpica, mas considerando que o número de pessoas infectadas pela dengue na época era alto e tendo em vista que os sintomas das duas condições são parecidos, foi solicitada sorologia para dengue. Transcorridos alguns dias, a paciente apresentou rabdomiólise, tendo então sido tratada com

Palavras-chave:

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medicamentos imunossupressivos, alcalinização urinária e hidratação vigorosa, medidas que melhoraram seus danos musculares e a condição inflamatória. A sorologia positiva para dengue nos foi disponibilizada apenas depois da instauração do tratamento descrito acima. A paciente recebeu alta em estado assintomático.

Esse caso demonstra a grande semelhança entre a febre dengue e uma exacerbação lúpica; isso deve alertar o clínico para que, especialmente durante uma epidemia, faça uma cuidadosa diferenciação entre essas doenças, de forma a estabelecer uma terapia correta e eficiente.

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Introduction

From the first semester of 2011 to the first week of October 2011, there were 721,546 reported cases of dengue in Brazil.¹ Dengue fever is an arbovirus that typically manifests high fever, severe myalgia, arthralgia, headache, retro-orbital pain, and rash. Rare clinical manifestations include hepatitis, rhabdomyolysis and neurological presentations, such as encephalopathy, peripheral neuropathy, and Guillain-Barré syndrome.² Rhabdomyolysis is a disorder characterized by skeletal muscle injury, associated with the extravasation of intracellular constituents into the plasma, resulting in electrolyte disorders and even acute kidney injury.³

Symptoms such as fever, thrombocytopenia, or arthralgia are found in many diseases, including SLE, which is an inflammatory autoimmune disorder characterized by periods of remissions and relapses. Epidemiological studies of incidence and prevalence of SLE are scarce in Brazil, where high racial miscegenation and different weather conditions can influence the disease's complications. In Brazil, lupus is more common in the black population than any other. Within the entire Brazilian population, lupus affects women of reproductive age more than men, with a ratio of 9-10:1.⁴

A new infection by dengue virus in patients with previous diagnosis of lupus may mimic its reactivation.⁵ There have been a few reports illustrated in the literature of rhabdomyolysis in lupic patients and in other patients infected by dengue fever,^{2,6} but there are no cases combining all of these conditions: lupus, dengue and rhabdomyolysis together. Our objective is to describe the case of a patient previously diagnosed with lupus that manifested rhabdomyolysis secondary to dengue fever.

Case report

In 2010, a thirty-nine year-old black woman developed malar rash, photosensitivity, oral ulcers and polyarthritis; she was diagnosed with SLE. At that time, her antinuclear antibody was 1/160 with a fibrillar cytoplasmic pattern, and she was treated with prednisone, azathioprine and hydroxicloroquine. Her symptoms resolved. However, in the first semester of 2011, she was admitted to the emergency room of a university hospital with high fever (39 degrees Celsius), chills, myalgia, muscular weakness, mild headache and polyarthralgia (shoulders, elbow, wrists, hips and knees). Her admission exams (Table 1) showed thrombocytopenia (60,000 per mm³), high C reactive protein (CRP), leukocytosis without neutrophilia,

Table 1 – Laboratory results

	Admission	Day 5	Day 9	Day 19	Discharge
Hemoglobine (g/dL)	13.7	10.3	10.1	8.9	10.3
Hematocrit (%)	42.4	30.3	31.5	27.4	32.2
Platelets (per mm ³)	60,000	36,000	101,000	244,000	254,000
Leukocytes (per mm ³)	29,500	10,000	11,000	8,400	9,500
Glucose (mg/dL)	85	95	90	65	N.M.
Urea (mg/dL)	27	24	34	25	34
Creatinine (mg/dL)	0.91	0.73	0.55	0.81	0.61
Albumine (g/dL)	3.0	2.6	2.2	3.1	N.M.
Globuline (g/dL)	3.6	3.7	3.0	3.4	N.M.
AST (U/L)	140	6,601	4,679	352	121
ALT (U/L)	62	1,115	1,325	422	136
Calcium (mg/dL)	7.1	7.1	7.0	8.5	8.9
Sodium (mEq/L)	134	136	138	138	138
Potassium (mEq/L)	3.3	4.2	4.4	3.3	4.0
CRP (mg/dL)	1.06	1.32	4.84	1.51	N.M.
ESR (mm/h)	25	53	51	38	N.M.
CK (U/L)	N.M.	A.U.L	45,265	9,117	2,681

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CK, creatine kinase; N.M., not measured; A.U.L., above upper limit.

hypoalbuminemia, erythrocyte sedimentation rate (ESR) discretely elevated, high liver enzymes [aspartate transaminase (AST) higher than alanine transaminase (ALT)]. Complement levels were in the inferior normal range. Antibodies to Deoxyribonucleic Acid (anti-DNA), anti-SSB/La, anti-Smith and antibodies to nuclear ribonucleoproteins (anti-RNP) were in the normal range. Urine analysis revealed proteinuria (30mg/dL). Dengue serology was requested upon admission, due to an epidemiologic suspicion: it was summer time in Rio de Janeiro, and there were a lot of patients affected by this arbovirus. She was medicated with symptomatic medications.

Five days after admission her symptoms worsened, and she manifested muscular weakness, red urine (Urine analysis: pH 8,5, density 1,015, false positive for hemoglobinuria (+++)) without erythrocytes, no evidence of erythrocyte dimorphism; 24-hour urine collection revealed 4,681.46mg of proteinuria) and increased edema, more pronounced in the arms. Creatine kinase (CK) was much higher than the upper limit detection rate of our test (dimension RXLMAX clinical chemistry system from Siemens, USA). The muscle injury was so elevated that four days passed before this enzyme could be detected, at which time it had reached a level of 45,265 (U/L). She also presented high AST (6,601U/L) and ALT (1,115U/L), hypocalcemia (7.1mg/dL), and metabolic acidosis, but electrolytes and renal function were still normal. Rhabdomyolysis was diagnosed and urinary alkalization plus vigorous hydration were started.

After 48 hours, the patient evolved with clinical and laboratory deterioration. She manifested generalized edema, now much worse on her lower limbs, making it difficult to palpate the leg's arterial pulses. Compartmental syndrome was suspected, and it was decided to submit her to pulse therapy with methylprednisolone (1g per day for three days). At this point, lupus flare was the main hypothesis for rhabdomyolysis. Only after administration of the pulse therapy was the dengue serology result available. IgM antibody was 20.38 Panbio (ELISA). Levels above 11 Panbio suggest recent dengue infection. Hepatitis virus and HIV serology were all negative. Urinary alkalization and vigorous hydration were maintained and symptoms improved. After 34 days in hospital, the patient was discharged and sent home with a supply of chloroquine, prednisone and azathioprine. At this moment, her laboratory exams showed improvement: liver enzymes were dropping (AST: 121U/L, ALT 136U/L), and her CK levels (2,681U/L) decreased 94.07% from the highest measurable value. She had no clinical symptoms.

Discussion

Several conditions may lead to rhabdomyolysis, such as trauma, drugs, genetic disorders, endocrine, metabolic and infectious diseases.³ This condition is rarely described in rheumatologic diseases. Six cases of rhabdomyolysis in lupic patients have been reported in the literature: two of them had discoid lupus, and four had SLE. The precipitating factors responsible for the induction of rhabdomyolysis in three of these patients were: the use of myotoxic drugs in one case and bacterial infection in two cases. In the remaining cases, no precipitating factors were identified.⁶

When the patient arrived at the hospital, the first hypothesis was lupus reactivation, since her main complaint was arthralgia and her laboratory exams showed thrombocytopenia, with high CRP. After the positive serology for dengue was received, it was clearer the infection was the precipitating factor for the rhabdomyolysis. The clinical manifestations of dengue and lupus flare may be similar, and this may confound physicians. However, in a review of Medline's database, only a few reports of dengue mimicking a lupus flare were found.⁵

It is important that, in countries where dengue is a common disease, clinicians carefully distinguish a lupus flare from a dengue infection. In this case, the epidemiology of dengue (summer time and the high number of infection cases at the time) was the leading clue to request the serology.

Evidence suggests that bacterial and viral infection could become a trigger for a new or relapsing lupus flare in genetically predetermined individuals. This has been proven, for example, in Cytomegalovirus infection. Studies show that Epstein-Barr virus infection presents immunologic aberrations of B cells and apoptosis and molecular mimicry that perpetuate autoimmunity in SLE.⁷ There are no studies proving a relationship between dengue and SLE, but recently there has been a report which considers the possibility of dengue virus triggering a dysfunctional immune response resulting in the development of autoimmunity and SLE with lupus nephritis.⁸ In the literature, there are no reports of rhabdomyolysis associated with dengue fever in a lupic patient.

Viruses that commonly cause rhabdomyolysis are influenza A and B, HIV, Coxsackie and Epstein-Barr.³ Dengue shares several features with these viruses, and there have been few cases of dengue with rhabdomyolysis.⁹ There is no proved cause for this association, but some hypotheses have been proposed. Direct viral invasion of the muscle had not been demonstrated, but some muscle biopsies showed marked inflammation, varying from mild lymphocytic infiltrate to foci of severe myonecrosis. Myotoxic cytokines, especially TNF released in response to virus infection, may have been the cause of the muscle injury.¹⁰⁻¹²

In the case reports describing rhabdomyolysis due to dengue, patients were treated with urinary alkalization and vigorous hydration, with favorable outcome in one case and death in the other.⁹ The patient described in our case was infected with a viral disease, but initially she was treated with pulse therapy with methylprednisolone because her clinical deterioration was attributed to lupus exacerbation. The dengue serology was only released after this treatment was established. Her clinical outcome was favorable.

No specific treatment for dengue exists, apart from analgesia and medications to reduce fever.² In this case, methylprednisolone was used because of the suspicion that the patient was clinically deteriorating due to a lupus flare. Some authors argue there is no evidence *in vivo* to support the use of antiviral agents, drugs that reduce vascular permeability, nor corticosteroid, and that high-dose methylprednisolone fails to reduce mortality in severe dengue shock syndrome (DSS).¹³ Others suggest that a single dose of intravenous methyl prednisolone, 1g intravenous over 20 min as rescue medication to highly selected patients who develop hypotensive DSS, reduces mortality ($p=0.01$).¹⁴ Nevertheless, the author of this article emphasizes the importance of randomized clinical trials to

confirm this fact. Regarding the rhabdomyolysis treatment, there is only one case reporting that steroid therapy should be considered for the treatment of rhabdomyolysis or myopathy associated with Cytomegalovirus infection in order to prevent renal failure or fatal progression of the disease.¹⁵ Therefore it is impossible to know if the steroids used in the patient had any influence in her outcome, since there are no clinical trials available addressing this specific case.

Conclusion

There are few cases of SLE manifesting rhabdomyolysis, none of them previously associated with dengue fever as described in our case report. Although rhabdomyolysis is an uncommon presentation of this viral infection, dengue fever clinical manifestations may mimic lupus flare. Rheumatologists, clinicians and infectologists should be aware of common manifestations of these diseases in order to identify more severe cases.

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Conflicts of interest

The authors declare no conflict of interest.

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