Meloxicam-Induced Rhabdomyolysis in the Context of an Acute Ross River Viral Infection

Mahmood Al Kindi,1* Vidya Limaye,2 Pravin Hissaria1

1Department of Human Immunology, SA Pathology, Adelaide, Australia
2Department of Rheumatology, Royal Adelaide Hospital, Adelaide, Australia

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Acute rhabdomyolysis is a clinical and laboratory syndrome resulting from the breakdown of skeletal muscle, with the release of intracellular contents into the circulatory system, which can cause potentially lethal complications. Here we present the case of a patient who developed acute rhabdomyolysis after consumption of meloxicam for jaw pain and experienced generalized myalgias in the context of an acute febrile illness with generalized urticaria. Further investigation indicated elevated muscle enzymes and acute renal failure. Serological analysis revealed that the patient was positive for Ross River virus (RRV) IgM. Genetic studies to detect CYP2C9 polymorphisms were negative. Meloxicam was discontinued. He responded to conservative measures within 2 weeks. Oral aspirin challenge was negative, suggesting a drug-specific effect of meloxicam rather than a class effect. Our case indicates a causative role for meloxicam and/or acute RRV in rhabdomyolysis.

Key Words: RRV infection; meloxicam; rhabdomyolysis

CASE REPORT

A 74-year-old, previously healthy male presented to the emergency department with an acute febrile illness, rash, generalized myalgias, and jaw pain for 3 days. Examination showed generalized urticarial rash with no evidence of lymphadenopathy, mucosal lesions, proximal muscle weakness, or arthropathy.

The patient had taken meloxicam for the jaw pain for 3 days prior to presentation. Three days later, he developed proximal muscle weakness of the lower limbs. Laboratory tests revealed mild impairment of renal function, eosinophilia, and lymphopenia (Table). Muscle enzymes were markedly elevated, and serum myoglobin was detected. Viral serology revealed a positive response for IgM antibody against Ross River virus (RRV), suggestive of an acute infection, with negative IgM for hepatitis viruses A, B, and C, Epstein-Barr Virus, and Cytomegalovirus. Autoimmune serologies were also negative, including antinuclear antibody, extractable nuclear antigens, and antineutrophil cytoplasmic antibody (Table). Needle muscle biopsy of the left vastus lateralis performed at the time of proximal muscle weakness showed acute muscle necrosis with features of mitochondrial damage. Skin biopsy revealed features consistent with urticaria along with mild eosinophilic and neutrophilic infiltration without any evidence of vasculitis. Chest X-ray, electrocardiogram, and renal ultrasound were normal. The patient was treated with intensive fluid resuscitation, and normalization of his muscle enzymes and renal function occurred over the course of 1 week. Oral aspirin challenge (1-day protocol with...
incremental doses of ≤ 600 mg aspirin and a cumulative dose of 985 mg) was undertaken to seek a safe alternative, non-steroidal anti-inflammatory drug (NSAID). This was well tolerated, and no changes in clinical or laboratory parameters, including renal function or muscle enzymes, were detected after the procedure. Genetic tests to detect CYP2C9 polymorphisms were negative.

The chronology of events suggested a diagnosis of meloxicam-induced rhabdomyolysis in the context of acute RRV infection. Accordingly, the patient was advised to avoid meloxicam in the future.

**DISCUSSION**

Necrosis of muscle (rhabdomyolysis) is accompanied by the release of muscle contents, including myoglobin, creatine phosphokinase (CK), potassium, aldolase, lactate dehydrogenase, and glutamic-oxaloacetic transaminase, into the serum. Serum CK is the most sensitive enzyme marker of muscle injury.

There are a number of possible factors that may lead to acute rhabdomyolysis, and many patients present with multiple causes. The most common causes are exertion, crush injury, seizures, alcohol, viral infections, muscle enzyme deficiencies, electrolyte abnormalities, endocrinopathies, drug abuse, and statins.

Rhabdomyolysis is commonly associated with myoglobinuria, which can lead to acute renal failure. Weakness, myalgias, and tea-colored urine are the cardinal clinical manifestations of rhabdomyolysis.

Drugs are frequently implicated in rhabdomyolysis and may directly or indirectly impair muscle metabolism by altering the balance between energy production and expenditure. Sarcolemmal injury and increased permeability through the activation of phospholipase A, leading to the efflux of intracellular contents and the influx of sodium and calcium, are also proposed mechanisms of drug-induced muscle damage. The most common causative drugs include antipsychotics and antidepressants, sedative hypnotics, statins, drugs of addiction, and antihistamines.

There are case reports of rhabdomyolysis induced by NSAIDs; however, rhabdomyolysis due to meloxicam has not been previously reported. Certain CYP2C9 polymorphisms change the metabolism of this class of drug, and thus have been shown to increase the risk for rhabdomyolysis. This phenomenon has most extensively been reported with celecoxib, a selective cyclooxygenase-2 inhibitor. In our case, meloxicam was the putative cause of our patient’s complications, based on the chronological sequence of events (i.e., development of symptoms within 3 days of consumption) and the absence of other myotoxic drugs. The initial presentation of rash and eosinophilia is suggestive of an allergic reaction to meloxicam. The most definitive test for allergy, re-challenge with meloxicam, was deemed inappropriate due to the severity of the initial reaction. Aspirin challenge confirmed that the reaction was a drug-specific effect, rather than a class effect of pharmacological inhibition of arachidonic acid metabolism.

Viral infections may also precipitate rhabdomyolysis. Clinical presentation can vary in severity from mild myalgias to overt muscle injury and acute renal failure in severe cases. Viruses implicated in such a reaction include influenza virus A/B, para-influenza virus, coxsackie virus, Epstein-Barr virus, herpes simplex virus, adenovirus, and cytomegalovirus. Viruses may damage muscles directly through the invasion of muscle fibers or indirectly through the activation of the immune response.

Mosquito-borne alphaviruses, such as RRV, have been reported to target bone, joint, and skeletal muscle tissue in a mouse model. Moreover, histological analyses have demonstrated that RRV infection results in severe inflammation of these tissues by infiltrating macrophages, NK cells, and CD4+ and CD8+ T lymphocytes.

Our patient had taken meloxicam in the context of an acute infection with RRV, and the subsequent rapid development of rhabdomyolysis suggested a causative role for meloxicam and/or RRV infection. As we did not perform a meloxicam challenge, it is unclear whether meloxicam was the primary cause or it exacerbated RRV-induced muscle injury.

**REFERENCES**

1. Ellinas PA, Rosner F. Rhabdomyolysis: report of eleven cases. J Natl Med Assoc 1992;84:617-24.
2. Grob D. Rhabdomyolysis and drug-related myopathies. Curr Opin Rheumatol 1990;2:908-15.
3. Kakulas B. Experimental myopathies. In: Walton JN, editor. Disorders of voluntary muscle. New York: Churchill Livingstone; 1981. p. 393-400.
4. Knochel JP. Mechanisms of rhabdomyolysis. Curr Opin Rheumatol 1993;5:725-31.
5. Rubin BB, Liauw S, Tittley J, Romaschin AD, Walker PM. Prolonged adenine nucleotide resynthesis and reperfusion injury in postischemic skeletal muscle. Am J Physiol 1992;262:H1538-47.
6. Armstrong RB, Warren GL, Warren JA. Mechanisms of exercise-induced muscle fibre injury. Sports Med 1991;12:184-207.
7. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis -- an overview for clinicians. Crit Care 2005;9:158-69.
8. Delrio FG, Park Y, Herzlich B, Grob D. Case report: diclofenac-induced rhabdomyolysis. Am J Med Sci 1996;312:95-7.
9. Knobloch K, Rossner D, Gössling T, Lichtenberg A, Richter M, Krettek C. Rhabdomyolysis after administration of diclofenac. Unfallchirurg 2005;108:415-7.
10. Tang C, Shou M, Rushmore TH, Mei Q, Sandhu P, Woolf EJ, Rose MJ, Gelmann A, Greenberg HE, De Lepeleire I, Van Hecken A, De Schepper PJ, Ebel DJ, Schwartz JI, Rodrigues AD. In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. Pharmacogenetics 2001;11:223-35.
11. Kirchheiner J, Störmer E, Meisel C, Steinbach N, Roots I, Brockmöller J. Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. Pharmacogenetics 2003;13:473-80.
12. Nauss MD, Schmidt EL, Panioli AM. Viral myositis leading to rhabdomyolysis: a case report and literature review. Am J Emerg Med 2009;27:372.e5-372.e6.
13. Tanaka T, Takada T, Takagi D, Takeyama N, Kitazawa Y. Acute renal failure due to rhabdomyolysis associated with echovirus 9 infection: a case report and review of literature. Jpn J Med 1989;28:237-42.
14. Naylor CD, Jevnikar AM, Witt NJ. Sporadic viral myositis in two adults. CMAJ 1987;137:819-21.
15. Konrad RJ, Goodman DB, Davis WL. Tumor necrosis factor and coxsackie B4 rhabdomyolysis. Ann Intern Med 1993;119:861.
16. Morrison TE, Whitmore AC, Shabman RS, Lidbury BA, Mahalangam S, Heise MT. Characterization of Ross River virus tropism and virus-induced inflammation in a mouse model of viral arthritis and myositis. J Virol 2006;80:737-49.
17. Seay AR, Griffin DE, Johnson RT. Experimental viral polymyositis: age dependency and immune responses to Ross River virus infection in mice. Neurology 1981;31:656-60.