Case Report

Rhabdomyolysis Secondary to Influenza A Infection: A Case Report and Review of the Literature

Mario F. Fadila, Kenneth J. Wool

Department of Internal Medicine, University of Alabama at Birmingham, Health Center Montomery, USA

Abstract

Context: Rhabdomyolysis is a serious clinical syndrome that results from damage to skeletal muscles. Common causes include drugs, crush injuries, seizures, heat, exertion, and infection. Viral infections, particularly Influenza A, have been recognized as a cause of rhabdomyolysis. **Case Report:** Our report describes a 58-year-old male who presented with viral pneumonia secondary to Influenza A virus infection. His hospital course was complicated by acute renal failure secondary to rhabdomyolysis, which was attributed to an overwhelming viremia. We discuss the differential diagnosis of rhabdomyolysis and review the literature for cases of Influenza A-related rhabdomyolysis. We also discuss the proposed mechanisms for the condition. **Conclusion**: The scope of clinical manifestations of Influenza A infection extends beyond pulmonary syndromes. Rhabdomyolysis is being increasingly recognized as a complication of Influenza A infection with considerable morbidity and mortality.

Keywords: Creatinine kinase, H1N1, Influenza A, Myositis, Rhabdomyolysis

Address for correspondence: Dr. Mario F Fadila, Department of Internal Medicine, University of Alabama at Birmingham, Health Center Montomery 2055 East South Boulevard, Suite 200, Montgomery, Alabama-36116, USA. E-mail: mariofadila@yahoo.com

Introduction

Influenza A is a negative-sense RNA virus, a member of the *Orthomyxoviridae* family. It is known for its seasonal occurrence and historical pandemics. Influenza A is associated with a spectrum of respiratory illnesses, ranging from mild upper respiratory infection to acute respiratory distress syndrome. Infrequently, influenza can cause extra-pulmonary complications, including encephalitis, myocarditis, pericarditis and rhabdomyolysis. The latter has been reported more frequently in the past few years, particularly in association with the novel H1N1 influenza virus.[1-10] We report an unusual case of massive rhabdomyolysis secondary to influenza A virus infection and review the literature for similar case.

Access this article online	
Quick Response Code:	Website: www.najms.org
	DOI: 10.4103/1947-2714.153926

Case Presentation

A 58-year-old male presented with a complaint of 4 days of fever, chills, worsening dry cough, generalized body aches and dark-colored urine. He was initially evaluated at a local urgent care center where he tested positive for Flu-A using rapid antigen test. Patient was referred to our hospital for further management due to hypoxia. He had no known history of liver or kidney disease and was not on any medication. He denied alcohol or drug use. Physical examination revealed a well-nourished, diaphoretic male in moderate distress. He was febrile (102 F) and tachypneic. Blood pressure and pulse were normal. Oxygen saturation was 92% on 2L oxygen by nasal cannula. He had bibasilar crackles with scattered rhonchi. Generalized weakness and diffuse muscle tenderness were noted.

Initial laboratory evaluation revealed leukocyte count of 12900/μL, hemoglobin of 17.3 g/dL, platelet count of 203000/μL, creatinine of 3.6 mg/dL and potassium of 4.6 mmol/L, No urine analysis was obtainable since patient was anuric. Creatinine kinase was elevated >1,000,000 IU/L. Chest radiograph demonstrated increased interstitial markings. CT scan of the chest showed subtle right lower lobe consolidative changes.

Patient was started on Oseltamivir 75 mg twice daily and broad-spectrum antibiotics for suspected influenza pneumonia. His sputum and blood cultures were negative.

Work up for his renal failure included a negative renal ultrasound and serology for autoimmune etiologies. Despite aggressive hydration and intravenous sodium bicarbonate, his kidney function continued to deteriorate and creatinine rose to 8.7 mg/dL. On the third hospital day patient developed respiratory insufficiency requiring intubation and mechanical ventilation. His arterial blood gas revealed combined respiratory and metabolic acidosis. He was started on hemodialysis. Nevertheless, he had worsening hyperkalemia, hypocalcemia, and metabolic acidosis. On the fourth hospital day patient went into cardiac arrest and died despite aggressive resuscitation.

Discussion

Rhabdomyolysis is a potentially life-threatening clinical syndrome that results from damage to skeletal muscle resulting in the release of toxic intracellular contents.[11] Common causes include traumatic vs. non-traumatic, with the latter being far more common. The differential diagnosis for rhabdomyolysis includes drugs of abuse (cocaine, heroin, amphetamine) and alcohols (ethanol, methanol and ethylene glycol), which we ruled out with a negative toxicology screen. Our patient was not on any prescription or non-prescription drugs commonly associated with rhabdomyolysis, such as statins, fibrates, salicylates or steroids. A careful history and physical exam ruled out other common causes such as trauma, prolonged immobilization, excessive muscle activity, compartment syndrome, or heat exposure. Electrolyte abnormalities can lead to rhabdomyolysis; however, considering the timeline in our case, we believe they were a result rather than an etiology of muscle cell damage. A negative rheumatologic panel ruled out connective tissue disorders, such as polymyositis, dermatomyositis or Sjogren's syndrome. Considering the clinical presentation, an infectious etiology was thought responsible for rhabdomyolysis in our patient.

Numerous bacterial, viral and fungal infections can lead to rhabdomyolysis. Viral infections in particular have a recognized association with a wide spectrum of muscle disorders, ranging from acute non-specific myalgia to severe myositis and rhabdomyolysis. A report by Tanaka *et al*.[12] identified influenza virus as the implicated agent in nearly 33% of known viral-induced rhabdomyolysis. The earliest recognition of the syndrome was called "myalgia cruris epidemica"[13] or "benign acute childhood myositis." It describes an acute myopathy during the convalescent phase of viral respiratory infections in children characterized by bilateral calf pain and tenderness, with resultant difficulty in ambulation. It was usually benign and without significant complications.

On April 2009, a novel virulent Influenza A virus of swine origin was identified,[14] A/California/07/2009, also known as "swine flu". In June 2009, it was declared pandemic by the World Health Organization after its global spread and confirmed human-to-human infectivity. The new strain was more virulent and caused significant morbidity and mortality in a younger patient population. A report by Padilla *et al*.[15] describes 18 cases of 2009 influenza pneumonia, of which 62% had elevated creatinine kinase levels, one of the most consistent laboratory characteristics in addition to elevated lactate dehydrogenase. Even moderate degree of creatinine kinase elevation has proven to be a biomarker of severity of illness in patients with influenza A infection. In a report of 505 patients from 148 ICUs in Spain,[16] Creatinine Kinase correlated with greater degree of renal dysfunction, more pulmonary involvement and increased duration of mechanical ventilation in patients with influenza A infection.

The frequency of myositis and rhabdomyolysis in patients with influenza A is unclear. There are 12 reported cases in the English literature since 2009.[1-10] They describe rhabdomyolysis attributed to influenza A virus infection. The median age reported was 24 years and half were females. Two patients were immunosuppressed due to chronic steroid therapy. The most commonly reported symptoms on presentation were myalgia and weakness. Eleven patients had confirmed novel 2009 H1N1 influenza A infection. The reported creatinine kinase levels ranged from (1,317-1,127,000) with a mean value of 206,908. Eight patients suffered acute kidney injury, five of which required hemodialysis. Patients who did not require renal replacement therapy were treated with generous hydration and IV sodium bicarbonate. Five patients were mechanically ventilated for respiratory insufficiency, two of whom died of multi-organ dysfunction. The remaining patients had complete recovery after prolonged hospitalization. One case was complicated with posterior reversible encephalopathy syndrome and another with compartment syndrome.

The pathogenesis of rhabdomyolysis in patients with influenza has been a matter of debate. Postulated hypotheses include:

1. Direct muscle invasion by the influenza virus,
2. Immunologic reaction "cytokine storm" resulting in collateral muscle damage, and
3. Circulating viral toxins causing direct muscle injury.

Most recently, Desdouits *et al*.[17] studied the susceptibility of cultured primary human skeletal muscle cells to

influenza A virus. Viral isolates from 2009 pandemic and 2008 seasonal influenza A were introduced to *in vitro* cultures of differentiated muscle cells, "myotubes", and undifferentiated muscle cells, "myoblasts". They were able to detect nuclear and cytoplasmic viral nucleoproteins using indirect immunofluorescence staining.

They were also able to detect expression of α2,3 and α2, 6-linked sialic acid receptors on the surface of muscle cells. These are the same receptors located on the surface of respiratory epithelium to which influenza virus is believed to bind.[18] In addition, evidence of viral replication and budding, and subsequent muscle cell lysis were detected in their experiments. The pandemic virus was replicated at higher titers than the seasonal virus. The levels of inflammatory cytokines were not elevated in the supernatants of cultured cells, arguing against the previous theory of cytokine induced muscle injury. Their data showed evidence that Influenza A virus can infect primary human muscle cells *in vitro*.

Since its emergence in 2009, pH1N1 has continued to circulate every season. For the 2013-14 season it predominated, accounting for nearly 96% of the total subtyped Influenza A viruses.[19] More than 99% of the pH1N1 viruses tested by the CDC this season have been antigenically similar to A/California/7/2009 strain. According to our literature review, we are the first to report a case of Influenza associated rhabdomyolysis for the 2013-14 season. We expect more cases to occur in light of the recently reported seasonal Influenza trends.

Conclusions

Influenza A continues to be an annual global burden. The scope of clinical manifestations extends beyond the typical respiratory syndromes to involve various organs. Rhabdomyolysis in particular is being increasingly recognized. Considering the extent of morbidity and mortality associated, a careful consideration should be given to the condition, especially to the patient with prominent body aches and weakness. Aggressive fluid therapy, urine alkalization and early renal replacement therapy may be lifesaving if instituted early.

References

1. Parikh M, Dolson G, Ramanathan V, Sangsiraprapha W. Novel H1N1-associated rhabdomyolysis leading to acute renal failure. Clin Microbiol Infect 2010;16:330-2.
2. Ayala E, Kagawa FT, Wehner JH, Tam J, Upadhyay D. Rhabdomyolysis associated with 2009 influenza A (H1N1). JAMA 2009;302:1863-4.
3. Lai CC, Wang CY, Lin HI. Rhabdomyolysis and acute kidney injury associated with 2009 pandemic influenza A(H1N1). Am J Kidney Dis 2010;55:615.
4. Unverdi S, Akay H, Ceri M, Inal S, Altay M, Demiroz AP, *et al*. Acute kidney injury due to rhabdomyolysis in H1N1 influenza infection. Ren Fail 2011;33:450-1.
5. Fearnley RA, Lines SW, Lewington AJ, Bodenham AR. Influenza A-induced rhabdomyolysis and acute kidney injury complicated by posterior reversible encephalopathy syndrome. Anaesthesia 2011;66:738-42.
6. Gutierrez RL, Ellis MW, Decker CF. Rhabdomyolysis and pandemic (H1N1) 2009 pneumonia in adult. Emerg Infect Dis 2010;16:565.
7. D'Silva D, Hewagama S, Doherty R, Korman TM, Buttery J. Melting muscles: Novel H1N1 influenza A associated rhabdomyolysis. Pediatr Infect Dis J 2009;28:1138-9.
8. Tosun MS, Ertekin V, Orbak Z. Rhabdomyolysis-induced acute renal failure associated with 2009 influenza A (H1N1) virus infection in a child with Crigler-Najjar syndrome. J Emerg Med 2012;42:310-1.
9. Slobogean BL, Reilly CW, Alvarez CM. Recurrent viral-induced compartment syndrome. Pediatr Emerg Care 2011;27:660-2.
10. Chen SC, Liu KS, Chang HR, Lee YT, Chen CC, Lee MC. Rhabdomyolysis following pandemic influenza A (H1N1) infection. Neth J Med 2010;68:317-9.
11. Khan FY. Rhabdomyolysis: A review of the literature. Neth J Med 2009;67:272-83.
12. 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.
13. Lundberg, A. Myalgia cruris epidemica. Acta Paediatr 1957;46:18-31.
14. CDC, The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010. (Accessed January 14, 2014, at http://www.cdc.gov/h1n1flu/cdcresponse.htm).
15. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, *et al*. INER Working Group on Influenza. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;361:680-9.
16. Borgatta B, Pérez M, Rello J, Vidaur L, Lorente L, Socías L, *et al*. pH1N1 GTEI/SEMICYUC. Elevation of creatine kinase is associated with worse outcomes in 2009 pH1N1 influenza A infection. Intensive Care Med 2012;38:1152-61.
17. Desdouits M, Munier S, Prevost MC, Jeannin P, Butler-Browne G, Ozden S, *et al*. Productive infection of human skeletal muscle cells by pandemic and seasonal influenza A(H1N1) viruses. PLoS One 2013;8:e79628.
18. Sullivan SJ, Jacobson RM, Dowdle WR, Poland GA. 2009 H1N1 influenza. Mayo Clin Proc 2010;85:64-76.
19. Flannery B, Thaker SN, Clippard J, Monto AS, Ohmit SE, Zimmerman RK, *et al*. Centers for Disease Control and Prevention (CDC). Interim estimates of 2013-14 seasonal influenza vaccine effectiveness - United States, February 2014. MMWR Morb Mortal Wkly Rep 2014;63:137-42.

How to cite this article: Fadila MF, Wool KJ. Rhabdomyolysis secondary to influenza A infection: A case report and review of the literature. North Am J Med Sci 2015;7:122-4.

Source of Support: Nil. **Conflict of Interest:** None declared.