



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

Youssef Boutros¹
Mansour Rami¹
Fenianos Fady²
El Murr Tony^{3*}

¹Department of Internal Medicine, Diseases, Faculty of Medical Sciences-LU, Beirut, Lebanon

²Department of Infectious Diseases, Medical Director of SZUMC affiliated with the Faculty of Medical Sciences -LU, Zgharta, Lebanon

³Division of Internal Medicine Diseases, Head of Medicine Department at MEIH-UH affiliated with the Faculty of Medical Sciences-LU, Bsalim, Lebanon

Abstract

Although acute influenza is generally a self-limited, uncomplicated viral disease, it may be associated in some cases with severe rhabdomyolysis and Staphylococcus Aureus superinfection with considerable morbidity and mortality. Here we report a 17-year-old previously healthy male who presented for acute influenza A virus pneumonia complicated by rhabdomyolysis and staphylococcus aureus (*S. aureus*) septicemia. Laboratory studies were significant for elevated creatinine kinase up to 3270 IU/L and leucopenia first, followed by hyperneutrophilic leukocytosis and high C-Reactive Protein (CRP). Reversible acute kidney injury followed this episode. Rapid influenza antigen testing was positive for influenza A virus and bacterial cultures revealed the presence of methicillin-sensitive *S. aureus* in the bloodstream. This case highlights the importance of considering rhabdomyolysis as a manifestation of an influenza infection and secondary bacterial coinfection a frequent complication necessitating an early treatment with convenient antibiotic therapy.

Keywords

Creatinine Kinase; Influenza A; Rhabdomyolysis; Staphylococcus Aureus; Sepsis

Introduction

Influenza A is a negative-sense RNA virus that occurs in distinct outbreaks every year, mainly during the winter months. Changes in its surface proteins (hemagglutinin and neuraminidase) reflects its epidemiologic pattern. It is associated with a spectrum of respiratory illnesses, ranging from mild upper respiratory infection to acute respiratory distress syndrome, which depends on its type or subtype [1-3]. Although influenza virus can cause pulmonary infiltration or hypoxemia by direct damage to respiratory epithelial cells, it is known that secondary pneumonia or bacterial superinfection is major factor affecting mortality or prognosis [4]. Moreover, influenza A can rarely cause encephalitis, myocarditis, myositis, and rhabdomyolysis. The latter has been reported more frequently in the past few years, particularly in association with the novel H1N1 influenza A virus [1-3]. like in our reported clinical case.

Clinical Case Presentation

A previously healthy 17-year-old male presented first time to Saydet Zgharta-University Medical Center in Lebanon for seven days history of fever, chills, worsening dry cough, generalized myalgia and dark-colored urine. He had no known allergy or familial history of liver or kidney disease. The only medication he received prior to his presentation was acetaminophen 3 grs a day for five days. He denied alcohol or drug abuse. His physical examination revealed a well-nourished, normally-colored, conscious but diaphoretic male in moderate distress. He was febrile (102 F) and tachycardic. Blood pressure and respiratory rate were normal. Oxygen saturation was 98% on room air. He had bilateral crackles on the lung bases that did not clear after coughing, generalized weakness and diffuse muscle tenderness with decreased range of motion of his bilateral lower limbs. A remarkable erythematous papular lesions with pus discharge on the left flexion area of the elbow and on the right inguinal area were also noted.

His initial laboratory evaluation revealed positive influenza A and B rapid test, relative leucopenia (WBC = 2.5 G/liter; 40% neutrophils and 50% lymphocytes), hemoglobin of 13.6 g/dL, platelet count of 162000/μL, serum creatinine of 1.89 mg/dL and potassium of 4.6 mmol/L. Creatinine Kinase (CK) was elevated at 3270 IU/L, LDH of 517 IU/L, Erythrocyte Sedimentation Rate (ESR) of 72 mm/hr, D-Dimer of 2 μg/ml, and CRP of 29 mg/L. Lumbar puncture did not reveal any positive criteria for cerebrospinal fluid infection.

Article Information

DOI: 10.31021/ijcmc.20203140
Article Type: Case Report
Journal Type: Open Access
Volume: 3 Issue: 4
Manuscript ID: IJCMC-3-140
Publisher: Boffin Access Limited

Received Date: 10 February 2020

Accepted Date: 17 February 2020

Published Date: 19 February 2020

*Corresponding author:

Tony El Murr

Division of Internal Medicine Diseases
Head of Medicine Department at MEIH-UH
affiliated with the Faculty of Medical Sciences-
LU, Bsalim, Lebanon
Tel: (961) 3347473
Email: drtonimurr@hotmail.com

Citation: Boutros Y, Rami M, Fady F, Tony EM. Rhabdomyolysis and Staphylococcus Aureus Sepsis Secondary to Influenza A Infection: A Case Report and Review of the Literature. Int J Clin Med Cases. 2020 Feb;3(4):140

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Thoraco abdominopelvic CT (without i.v. contrast) showed subtle right lower lobe infiltrates with small pleural effusions, mild hepatosplenomegaly and retroperitoneal lymphadenopathies.

Patient was started on Oseltamivir 75 mg twice daily and broad-spectrum antibiotics (i.v. cefipime 6grs per day) for suspected pneumonia with aggressive intravenous hydration and sodium bicarbonate.

On the third day at hospital, the patient was still complaining from fever, severe bilateral calf pain and generalized fatigue. His blood pressure was normal as well as the arterial blood gas. His labs showed neutrophilic leukocytosis (WBC = 20.3 G/liter; 91% neutrophils and 7% lymphocytes), normal hemoglobin level of 12.8 g/dl but a severe thrombocytosis of $1009 \times 10^3 / \mu\text{L}$. The CRP increased to 297 mg/L but the CK and serum creatinine levels slightly decreased (CK = 3164 IU/L, sCr = 1.46 mg/dL). Aldolase level was elevated at 15.2 U/ml with a mild increase in the liver function tests. Urine analysis showed 40 WBCs per field. Bacterial cultures (blood, urine and limb lesions) yielded all a pure growth of methicillin-sensitive *S.aureus* strains. IV clindamycin (2400mg/day in 4 equally divided doses) was added to the treatment. Wright and Widal tests were negative and there was no detected schizocytes in the bloodstream. The work up for autoimmune diseases (ANA profile, anti-dsDNA, C3, C4, c-ANCA, p-ANCA, anti-CCP, serum and urine protein electrophoresis) came normal as well as the uroscan, transthoracic echocardiography, and the lower limbs venous ultrasound. Add that the patient underwent a biopsy of his elbow skin lesion [4-15].

On the sixth day at hospital, the patient became afebrile with net improvement of his respiratory and muscular signs and symptoms as well as his skin lesions. His WBC and CRP levels decreased to 10.3 G/liter and 96 mg/L respectively. Rhabdomyolysis improved also and CK level went down to 1223 IU/L. Control urine and blood cultures came negative. The same i.v. treatment was maintained for additional five days at hospital before the patient was discharged home on oral anti-staphylococcal agent linezolid 1200mg/day in 2 equally divided doses for ten days.

Before being discharged home, the patient was asymptomatic and his complete general and neurologic examination was quite normal. His labs showed a WBCs of 7.5 G/liter, Hgb of 11.6 g/dL, platelets count of $613 \times 10^3 / \mu\text{L}$, and CK level of 186 IU/L. Serum creatinine level, c-reactive protein and liver function tests was within normal range. Skin lesion biopsy revealed only acute pyomyositis and the transoesophageal echocardiography was normal with no signs of acute endocarditis. Repeated thoraco abdominopelvic CTscan showed significant decrease in the pleural effusions, the lower lobe infiltrates and the retroperitoneal lymphadenopathies.

Discussion

Rhabdomyolysis is a serious syndrome due to a direct or indirect muscle injury. It results from the death of muscle fibers and release of their contents into the bloodstream. Its severity ranges from asymptomatic elevations in serum muscle enzymes to life-threatening condition associated with extreme enzyme elevations, metabolic disturbance, and acute kidney failure. There are many traumatic and nontraumatic causes of rhabdomyolysis where the latter being more common. Nontraumatic causes include the use of certain medications (e.g: lipid lowering agents such statins or some antipsychotics), the use of illicit drugs or alcohol, extreme muscle strain, heat stroke, seizures, metabolic myopathies, sepsis and bacterial infections (e.g. mycoplasma pneumonia, falciparum malariae), and some viral infections (e.g. Influenza, HIV, Cocksackievirus, Cytomegalovirus, HSV) [16-18]. Upon his detailed medical history and physical examination, the normal lumbar puncture and electromyographic study as well as normal work up for auto-immune and connective tissue diseases, our patient appeared to have influenza related rhabdomyolysis with staphylococcal septicemia. This was confirmed by rapid influenza test, positive blood cultures and clear clinical and biologic improvement after corresponding antiviral and antibiotic treatment.

Although virus-induced myopathy is a well-recognized phenomenon dating back to the early 1900s, only few cases of H1N1-associated rhabdomyolysis have been reported in the literature which pathogenesis has been a matter of debate. To our knowledge, three hypotheses has been proposed :

1. Direct viral invasion
2. Immunologic mechanisms mediated by cytokines and
3. Direct muscle injury caused by circulating toxins.

Armstrong et al. [19] showed that human skeletal muscle cells in tissue culture were susceptible to influenza virus. Moreover, Desdouts et al. [20] studied the susceptibility of cultured primary human skeletal muscle cells to influenza A virus and noticed the presence of specific nuclear and cytoplasmic viral nucleoproteins using indirect immunofluorescence staining. They were also able to detect expression of $\alpha 2,3$ and $\alpha 2, 6$ -linked sialic acid receptors on the surface of myoblasts which are believed to be the same receptors used by this virus to bind to the human respiratory epithelium. This evidence strongly suggests that direct viral invasion may have a causative role in precipitating rhabdomyolysis. Despite these mechanisms and since the beginning of the 2009 H1N1 pandemic, viral detection by immunofluorescence and electronic microscopy has been difficult to prove in many cases so some authors have proposed an immune-mediated process. Otherwise, in some reported studies where the virus was well identified and cultured, the level of the inflammatory cytokines were not elevated raising suspicion around the theory of cytokines induced direct muscle injury and to date no specific toxins have been isolated in cases of Influenza A induced rhabdomyolysis.

A report by Tanaka et al. [21] identified influenza virus as the implicated agent in nearly 33% of known viral-induced rhabdomyolysis. The earliest recognition of the syndrome was called "benign acute childhood myositis" which is a benign self-limited illness, without significant complications, that occurs during epidemics of influenza A and B. The patient usually complains of diffuse muscle pain, tenderness, and sometimes swelling develop during the first week of influenza illness (typically on the calf muscles). A decrease range of motion is noted in the affected patient who may refuse to walk or walk on his or her toes, and refuse to dorsiflex the feet. On examination, the calves are very tender. This whole scenario reminds us of our patient who described typically a severe bilateral calf tenderness and fear from walking without assistance upon his admission.

After the declaration of pandemic "new strain" of influenza A by the World Health Organization in June 2009 that caused a high mortality worldwide, Padilla et al. [22] describes 18 cases of influenza A pneumonia, of which 62% had elevated CK and lactate dehydrogenase levels. Then, several studies and reports showed that an elevation in creatinine kinase level should be considered as an index of severity of illness in patient with influenza A infection. In a report of 505 patients from 148 intensive care units in Spain [23], an elevation of the creatinine kinase level, in patients with confirmed influenza A infection, was correlated with greater degree of kidney failure, longer stays in the ICU and deterioration of pulmonary function. Our case report describes rhabdomyolysis due to influenza infection which is considered the most frequently reported viral cause of rhabdomyolysis. There are 12 reported cases in the English literature since 2009 [5-14].

Back to those reported cases, we conclude that there was not a sex predilection among infected patients and the median age reported was 24 years. Out of twelve, eleven patients tested positive for 2009 H1N1 influenza A. Two patients were immunosuppressed due to chronic steroid therapy. The reported creatinine kinase levels ranged from 1,317 to 1,127,000 UI/L with a mean value of 206,908 UI/L. 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 presented an acute respiratory

failure and were mechanically ventilated, two of whom died of multi-organ dysfunction and the remaining patients had been discharged home after aggressive medical therapy. Add that, two cases of Influenza A infection were complicated with compartment syndrome and posterior encephalopathy syndrome well controlled after full recovery from the viral illness. The most commonly reported symptoms on presentation were diffuse myalgia and generalized non specific fatigue. Because it is uncommon that a patient with this viral illness complains of dyspnea and hypoxemia which severity is not proportional to the chest X-ray findings (as in our case), physicians should rule out acute tracheobronchitis that may cause an obstruction of the central airways and lead to an impairment of gas exchange [24].

Furthermore, in a 2016 systematic review of the frequency of influenza and bacterial coinfection, the rate of bacterial coinfection ranged from 2 percent in studies of children seen in mixed settings (emergency department, hospital) to 26 percent in hospitalized children to 50 percent in children hospitalized in the intensive care unit [25]. *Streptococcus pneumoniae* accounted for 35 percent of coinfections (which risk may be reduced due to specific immunization strategies), and *S.aureus* accounted for 28 percent (usually in previously healthy children as reported in our case, except of MRSA that is transmitted via skin or another infected individual). Numerous etiologies of these coinfections have been pointed toward the proapoptotic influenza A virus protein (PBI-F2) that enhances susceptibility to bacterial infection [26].

In light of the recently reported seasonal Influenza trends and because the percentage of respiratory specimens testing positive for influenza in clinical laboratories is increasing according to the CDC, we expect more cases of influenza A infection complications to be reported and we strongly recommend that fatal cases of coinfection with influenza and *S.aureus* should be reported to the Centers for Disease Control and Prevention (CDC) [27]. Moreover, early empirical antiviral treatment with oseltamivir and wide spectrum antibiotic (fluoroquinolone or combination of beta-lactam and macrolide) should be administered in all patients who suspect coinfection (as done in our case) then therapy should be adjusted according to the organism identified by cultures [26].

Conclusions

The proportion of outpatient visits and inpatient admissions to the hospital for Influenza A coinfections and complications such as rhabdomyolysis continues to increase worldwide. Considering the extent of morbidity and mortality associated, a careful consideration should be given to the condition, especially to the patient with prominent weakness or multiple comorbidities. So aggressive fluid therapy, urine alkalization, and convenient antiviral and antibiotic therapy may be lifesaving and could prevent harmful manipulation.

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