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Case Report Open Access

Post-Vaccination Myositis and Myocarditis in a Previously Healthy Male

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Abstract

Rhabdomyolysis is the breakdown of muscle cells leading to the release of cellular constituents such as electrolytes, enzymes and myoglobin. There is a broad differential diagnosis for this condition. In this report we describe a 65 year old male who presented with weakness, rhabdomyolysis, and acute kidney injury five days after receiving the seasonal flu vaccine. Laboratory investigations showed elevated creatine kinase and troponin-I, and extensive cardiac investigations yielded a diagnosis of myocarditis. The cause of his clinical picture is explored in this case report.

Case Presentation

A 65 year old previously healthy male presented to hospital with profound weakness. Five days before admission he had received the seasonal influenza vaccine, comprised of one influenza A H1/N1 virus, one influenza A H3/N2 virus and one influenza B virus. Two days later, he developed bilateral crampy leg pain, muscle tenderness and weakness that progressed until the day of admission. He became unable to weight-bear and was brought to the emergency department by his wife. He denied symptoms of headaches, paresthesias, arthralgias or any new rash. An infectious review of systems was unremarkable and he did not have any constitutional symptoms. He was not taking any medications or herbal preparations prior to admission, and did not use recreational drugs.

On physical exam his vitals were: P 92, BP 124/84, RR 20, T 36.7°C and his O_2 saturation was 100% on room air. His neurological exam was significant for 4/5 strength in the hip flexors, hip extensors, hip abductors and hip adductors. He could not stand from the sitting position without the aid of his arms. The muscles of his arms and legs were also tender. His cardiac examination revealed a jugular venous pressure (JVP) two cm above the sternal angle. His apical beat was normal. Auscultation revealed a normal S1 and S2 without any extra sounds, murmurs or rubs. His respiratory exam revealed mild crackles in the left lower lung zone. The rest of the examination was unremarkable.

His blood counts were WBC 11 × 99/L, hemoglobin 123 g/L (MCV 83 fL) and platelets 134 × 109/L. Electrolytes included sodium 126 mmol/L, potassium 3.2 mmol/L, chloride 101 mmol/L, bicarbonate 17 mmol/L, phosphate 0.75 mmol/L and magnesium 0.97 mmol/L. Other investigations showed urea 11.6 mM/L, creatinine 157 mM/L, creatine kinase (CK) 7,736 U/L (normal <150 U/L) and troponin 9.44 g/L (normal <0.2 g/L). His ethanol level was negative. His EKG was normal sinus rhythm with a right bundle branch block, without ischemic features. A chest X-ray and contrast enhanced computed tomography scan of the chest revealed a hiatus hernia, a left lower lobe consolidation, and no evidence of pulmonary embolism (Figure 1).

Acute rhabdomyolysis was diagnosed and the patient received four liters of fluid over the ensuing 24 hours. During volume resuscitation he developed pulmonary crackles, his JVP increased to 5 cm above the sternal angle and his O_2 saturation decreased to 90% on room air. He was placed on supplemental oxygen and received a single dose of furosemide 40 mg IV, to which he responded well. He also received pipercillin-tazobactam for a possible left lower lobe pneumonia. No steroids were given. His creatinine, CK and troponin levels began to trend downwards after 12 hours, and almost completely normalized within five days (Table 1).

Category	Example
Autoimmune diseases	Dermatomyositis and polymyositis
Drugs and toxins	Numerous: including alcohol, cocaine, heroin, fibrates and statins.
Electrolyte disorders	Hypokalemia, hypernatremia, hyponatremia, hypophosphatemia, hypocalcemia, hyperosmolarity, ketoacidosis
Endocrine disorders	Hypothyroidism, hyperaldosteronism

Excessive muscle activity	Alcohol withdrawal, Exercise, Seizures.
Genetic disorders	Numerous: including disorders of glycolysis, glycogenolysis, lipid metabolism, mitochondrial pathways and nucleotide metabolism. Prolonged immobilization, artery occlusion.
Hypoxia Idiopathic Infections	Viral (coxsackievirus, Epstein-Barr virus, herpes viruses, HIV, influenza A and B). Bacterial (Clostridium, *F. tularensis*, Legionella, *Salmonella*, *S. pyogenes*, *S. aureus*). Parasitic (falciparum malaria).
Temperature	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Trauma and compression	Crush injury syndrome, Electrical injury.

Table 1: Common causes of rhabdomyolysis.

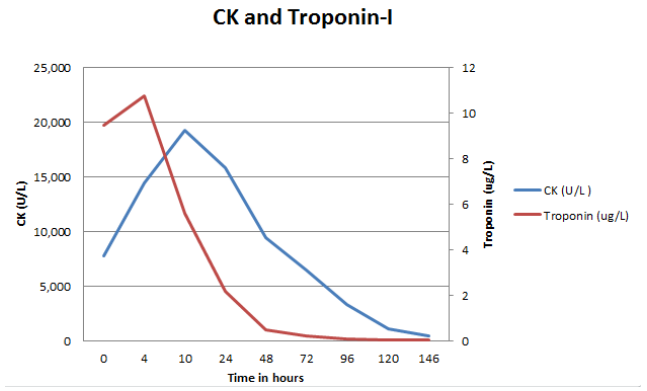

Figure 1: CK (U/L) vs. time in hours.

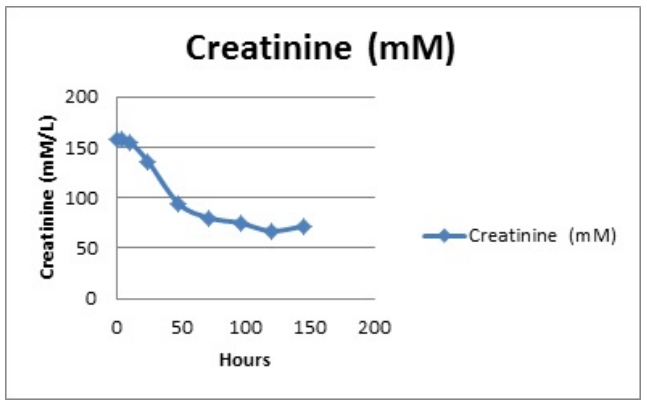

Figure 2: ANA was 1:160, (non-specific) homogeneous pattern

ANA was 1:160, homogeneous pattern (non-specific), anti-dsDNA, ENA panel, C3, C4, rheumatoid factor and ANCA tests were negative. Serum protein electrophoresis was consistent with an acute phase reaction and urine protein electrophoresis was negative. Dipstick urinalysis revealed 1+ protein and 1+ blood and his urine was positive for myoglobin. Microscopy revealed granular casts, urate crystals and no evidence of red cells. HIV, hepatitis B and C tests were negative. Blood and urine cultures yielded no growth. Computed tomography scans of the head and lumbar spine were negative and no other cause was found to explain the patient's weakness. An echocardiogram performed on day three revealed normal biventricular systolic function without any regional wall motion abnormalities. Cardiac MRI on day four confirmed the diagnosis of myocarditis. The patient recovered fully, and was safely discharged home on day six (Figure 2).

Discussion

This patient presented with a gradual onset of weakness and muscular pain. He had received the influenza vaccine five days prior to the onset of symptoms. Laboratory investigations indicated rhabdomyolysis, myocarditis, and acute kidney injury, which all resolved by day six of admission.

In rhabdomyolysis there is a breakdown of muscle cells leading to release of cellular constituents such as electrolytes, myoglobin and many cellular enzymes including creatine kinase. This can lead to life threatening consequences such as electrolyte imbalances, acute renal failure and disseminated intravascular coagulation. There are numerous known causes of rhabdomyolysis [1,2] which are summarized in Table 1.

Aggressive fluid management is key in avoiding myoglobin-induced oxidative damage to the kidney [2] This patient was treated with modest fluid resuscitation, including a total of four liters of normal saline over the first 24 hours, because of the concern of volume overload in the context of suspected cardiac myositis. During his admission he did develop signs of volume overload (increased JVP and respiratory crackles) and the infusion rate was titrated accordingly. He also received a small amount of furosemide.

As there was no evidence on history, physical, or lab of another cause for rhabdomyolysis, we felt that his presentation was most in keeping with an autoimmune/inflammatory syndrome induced by external adjuvants. Connective tissue causes of myositis were ruled out by the relatively normal Antinuclear Antibody titer and ANCA tests, and negative ENA, C3 and C4 and RA; as well as the fact that the illness resolved without any specific treatment for connective tissue diseases. Serum and urine protein electrophoresis and physical exam were not suggestive of Guillain-Barré. Similarly, his infective work-up was negative. His cardiac work-up suggested myocarditis and not myocardial infarction as a cause for his elevated troponins.

There is a paucity of reports linking the influenza vaccine as a cause for rhabdomyolysis and/or myocarditis. There are three case reports of rhabdomyolysis after flu vaccine. However, all three patients were

taking a statin drug and neither had features of myocarditis. Similar to our case, there are two reports of patients who were taking a statin drug that developed myalgias and progressive weakness 24 hours post influenza vaccination with subsequent rhabdomyolysis and acute kidney injury [3,4]. Additionally, another case of muscle aches and weakness leading to rhabdomyolysis one week post influenza vaccination has been described in a 57 year old renal transplant patient who was also taking simvastatin and cyclosporin A [5]. Our patient was not on similar confounding drugs, and in particular, no statin. Additional research yielded a case of a 60 year old gentleman who developed polyarthropathy, orbital myositis and posterior scleritis ten days after receiving the 1993 Fluvirin vaccine [6]. Given his ocular involvement, he was treated with oral prednisolone and acetazolamide and dramatically improved over the next four months.

Shoenfeld et al. suggests grouping different autoimmune manifestations that are seemingly triggered by an external adjuvant into a syndrome complex, referred to as autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [7]. By definition, an adjuvant is a substance which triggers an antigen-specific immune response, aimed at stimulating the innate and adaptive immune systems [8]. Numerous mechanisms have been proposed to explain this interaction, and there is some suggestion that individuals who develop autoimmune phenomena following vaccination have a genetic risk or an underlying disease that activates immune responses [9]. ASIA is characterized by a myriad of neurocognitive manifestations, including chronic fatigue, cognitive impairment and amnesia, as well as the development of inflammatory musculoskeletal findings including arthritis and myositis [10]. Our patient's presentation would be more in keeping with the latter end of the disease spectrum. He fulfills the original diagnostic requirements proposed by Shoenfeld et al. (Table 2) [7]. Although inflammatory myopathies have been well described following vaccination [8], including macrophagic myofaciitis (MMF) [11], the occurrence of myocarditis has not. Furthermore, our patient did not manifest a locally stereotyped or immunologically active lesion at the site of inoculation, which would argue against MMF. Despite the atypical nature of our patient's presentation, including cardiac involvement, we believe that his intense inflammatory response may be attributed to his recent vaccine in the absence of other causes, especially given the timing of adjuvant exposure.

Major Criteria:
- Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
- Myalgia, Myositis or muscle weakness
- Arthralgia and/or arthritis
- Chronic fatigue, un-refreshing sleep or sleep disturbances
- Neurological manifestations (especially associated with demyelination)
- Cognitive impairment, memory loss
- Pyrexia, dry mouth, Removal of inciting agent induces improvement
- Typical biopsy of involved organs
Minor Criteria:
- appearance of autoantibodies/antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syn.)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. MS, SSc)

Table 2: Criteria suggested ASIA diagnosis.

For the diagnosis of ASIA, the presence of at least 2 major or 1 major and 2 minor criteria must be apparent. Table reprinted from Journal of Autoimmunity, vol. 36 [1], Yehuda Shoenfelda and Nancy Agmon-Levin, 'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants, pages 4–8, Copyright 2011, with permission from Elsevier.

As described in a recent systematic literature review and meta-analysis, while local injection site pain and headache are known reactions, serious reactions are infrequently attributed to the influenza vaccine [12]. Though cases of myositis have been described in adults after hepatitis B or BCG vaccination [13,14], cases linking the influenza vaccine to myositis are rare without confounding factors. Although an argument can be made regarding the patient's pneumonia as a possible confounder, we found no evidence in the literature to suggest that respiratory infections can result in acute skeletal and cardiac myopathies. In addition, we are not convinced that the patient had an infectious process. Based on the patient's clinical and laboratory findings, a presumptive diagnosis of a post-vaccination inflammatory syndrome was made. The patient recovered promptly in hospital without the usage of immunomodulatory agents.

Conclusion

The incidence of rhabdomyolysis and myocarditis post vaccination is limited to case reports at this time. Given the benefits of the influenza vaccine, especially in the health care setting [15], and the rarity of this putative complication, we do not discourage its routine usage when clinically indicated. However, greater surveillance to establish the existence of this posited entity and to evaluate its risks should be pursued.

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