

Unexpected outcome (positive or negative) including adverse drug reactions

Rhabdomyolysis with acute renal failure triggered by the seasonal flu vaccination in a patient taking simvastatin

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Summary

A man in his 70s presented with bilateral, painful legs and feeling generally unwell following the seasonal flu vaccination. The patient had a background of B cell lymphoma in partial remission. His current medications included simvastatin. Initial investigations revealed rhabdomyolysis and acute renal failure. He was admitted to critical care for renal replacement treatment. Other causes of rhabdomyolysis were excluded and expert opinion agreed that the most likely cause was the influenza vaccination with the concurrent use of simvastatin. The patient's renal function gradually normalised and after several months the patient has regained full power in his legs.

BACKGROUND

This case represents an extremely rare but significant adverse reaction to the seasonal flu vaccination in patients concurrently taking simvastatin. This is especially pertinent at present with the introduction of additional influenza vaccinations, in particular to 'high risk patients' who will often also be taking a statin.

CASE PRESENTATION

A man in his 70s presented with a 3-day history of bilateral, painful legs and feeling generally unwell. The onset of these symptoms was within 24 h of receiving the seasonal flu vaccination (inactivated influenza virus; Imuvac 2009/2010). The patient required admission to intensive care unit for renal replacement treatment. He subsequently developed a hospital-acquired pneumonia and multi-organ failure.

His past medical history included B cell lymphoma in partial remission (with residual retroperitoneal disease, chemotherapy ended December 2008 and radiotherapy ended April 2009), ischaemic heart disease and atrial fibrillation.

His concurrent medications were cetirizine 10 mg once daily, digoxin 125 µg once daily, furosemide 40 mg once daily, warfarin and simvastatin 40 mg once at night. He had been taking simvastatin for 7 years without experiencing any side-effects.

There was no significant family history and, other than the vaccination, there had not been any changes to the patient's lifestyle or medications and there was no recent history of trauma.

Initial examination findings were unremarkable except for bilateral, tense, tender, oedematous lower limbs and a haemorrhagic rash on his abdomen and flanks. There was no evidence of local necrosis/pus at the site of vaccination (the patient's left arm). Power in the lower limbs was markedly reduced bilaterally (3/5) with intact reflexes. Tone and sensation were found to be normal.

The patient was hypotensive on admission and required inotropic support (norepinephrine) for the first day of his admission to the critical care unit.

INVESTIGATIONS

Initial investigations revealed rhabdomyolysis and renal failure with a serum creatine kinase 19 108 U/l, serum creatinine 212 µmol/l and serum urea 15.6 mmol/l. Other significant laboratory investigations included platelets $85 \times 10^9/l$, prothrombin time 35.4, partial thromboplastin time 52.6, fibrinogen 6900 g/l, C reactive protein 438 mg/l, myoglobinuria as well as evidence of myositis on ultrasound and MRI of both legs. Cerebrospinal fluid (CSF) biochemistry was normal with a protein count of 333 mg/l. A muscle biopsy was not carried out. Investigations, including an auto-immune screen, complement and immunoglobulin levels, thyroid function tests, kidney ultrasound and microbiology investigations, did not reveal any other causes for the rhabdomyolysis or renal failure. There were no positive blood cultures.

DIFFERENTIAL DIAGNOSIS

We felt that the patient had a severe myositis affecting both legs with subsequent multi-organ failure.

Gullain-Barré syndrome (GBS) and macrophagic myositis (MMF) are two other possible differential diagnoses that involve muscle disorders arising post-vaccination.¹ Both of these diagnoses have been excluded in view of the patient's clinical picture.

Rhabdomyolysis in GBS has been reported² and is thought to occur as a result of hyperexcitability in regional muscles due to severe axonal degeneration of motor nerve terminals. We felt that GBS was an unlikely explanation for his condition. This was further supported by normal cerebrospinal fluid protein content.

MMF is a rare inflammatory disorder of muscle that is thought to be caused by the persistence of vaccine-derived aluminium hydroxide at the site of injection.^{3 4} However, the vaccine the patient received did not contain an aluminium-based adjuvant.

Further differential diagnoses include infectious myositis caused by various bacterial, viral, fungal and parasitic agents. Infectious myositis is overall uncommon given the

relative resistance of the musculature to infection.⁵ The patient did not report any symptoms suggestive of an infectious illness prior to his vaccination and we felt that infectious causes were unlikely to be the cause of the patient's condition.

TREATMENT

The patient required supportive treatment, which included haemofiltration for several days. The patient was also treated with empirical antibiotics because of his immunocompromised state as well as a persistent elevation in inflammatory markers.

OUTCOME AND FOLLOW-UP

The patient's renal function has gradually improved and is back to within normal limits. Despite the serum creatine kinase level returning to within normal limits on day 6, the patient's legs remained tender and weak for several months. The patient has now got normal power and function in his legs.

DISCUSSION

Rhabdomyolysis is the breakdown of striated muscle. The resultant leakage of the intracellular muscle constituents into the circulation may lead to acute renal failure. Trauma to the muscles is the most common cause of rhabdomyolysis. Other causes include exertion, muscle hypoxia, genetic defects, infections, body temperature changes, metabolic and electrolyte disorders, as well as drugs and toxins.⁶

The seasonal flu vaccination that is described in this case report, Imuvac 2009/2010 produced by Solvay Healthcare (Southampton, United Kingdom), contains haemagglutinin and neuraminidase antigens of three different inactivated influenza viruses propagated in fertilised hens' eggs. Muscular side-effects such as myalgia and arthralgia are described as occurring in more than 1/100 but less than 1/10 cases.⁷ Musso *et al*⁸ report a case in Argentina of a 73-year-old man who did not appear to have any other risk factors for developing rhabdomyolysis other than receiving an influenza vaccine (the report did not specify which particular vaccine).

Muscle syndromes ranging from myalgia to rhabdomyolysis have also been reported to complicate a number of acute viral infections, including those caused by the influenza A and B viruses.⁹ The incidence of rhabdomyolysis associated with viral infections is not clearly defined; however, a case series of 63 patients with influenza pneumonia reported an incidence of rhabdomyolysis as 9.5%.¹⁰

Statins are well-recognised to be associated with muscle syndromes such as myalgia, myositis and myopathy. In addition, rhabdomyolysis with acute renal impairment secondary to myoglobinuria has also been reported and the Committee on Safety on Medicines (CSM) estimate it to occur approximately once in every 100 000 treatment years. The CSM also advise that the use of concomitant treatment with drugs that increase plasma-statin concentration (eg, ciclosporin) increases the risk of muscle toxicity as does concurrent treatment with a fibrate and a statin.¹¹

There have been two reported cases of acute renal failure secondary to rhabdomyolysis triggered by an influenza vaccination on a background of cholesterol-lowering treatment. The first of these case reports describe a 68-year-old

man who was treated with both cerivastatin and bezafibrate and developed acute renal failure and rhabdomyolysis after receiving the influenza vaccine in Israel (again this case report does not specify which particular vaccine).¹² The second case report describes a 57-year-old man who developed rhabdomyolysis with acute renal failure following an inactivated influenza vaccine (inactivated split virion—Avantis Pasteur) in a renal transplant recipient who has been on simvastatin and ciclosporin A treatment.¹³

We believe this to be the first report of rhabdomyolysis with acute renal failure triggered by influenza vaccination in a patient whose only risk factor was concurrent simvastatin use.

A pilot study in Israel¹⁴ looked at 98 patients (52 receiving statins, 46 controls) who received an influenza vaccine (again this article does not specify which particular vaccine). They did not find any clinical or laboratory evidence to support influenza vaccination being associated with myopathy in patients taking statins. Given the small number of patients involved in this study, as well as the uncertainty regarding the specific vaccine that was administered, it is difficult to interpret the significance and applicability of these findings to this case report.

We believe given the time course of events and the absence of other causes, this case represents rhabdomyolysis with acute renal failure triggered by the influenza vaccine in a patient taking simvastatin. We conclude that while this clinical picture is extremely rare, it is an important complication that healthcare professionals need to be aware of, and maintain a high index of suspicion for, so that early recognition can enable the prompt use of appropriate treatment and, thus, diminish the renal dysfunction associated with this disorder. This is especially pertinent this coming influenza season with the increased awareness and uptake of influenza vaccinations.

Learning points

- ▶ Influenza vaccination may rarely trigger rhabdomyolysis in similar patients being treated with a statin.
- ▶ Myositis and the possibility of rhabdomyolysis should be considered in any individual presenting with severe myalgia or muscle weakness who has recently had the influenza vaccine and is also taking a statin or other myotoxic drugs.
- ▶ Patients using statins should be advised to seek medical advice if they develop muscle pains after an influenza vaccine.

Competing interests None.

Patient consent Obtained.

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