

Possible association between rhabdomyolysis and mRNA SARS-CoV-2 vaccination in a patient with *RYR1* gene mutation

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A 30-year-old woman presented to hospital 8 days after vaccination against SARS-CoV-2 with the second dose of the Moderna mRNA vaccine. One day postvaccination, she noted flu-like symptoms, including chills and nausea. Three days postvaccination, she developed neuromuscular symptoms, including progressive bilateral upper and lower limb myalgia and weakness. At 7 days, she noticed cola-coloured urine. She had been vaccinated with the first dose of Moderna mRNA SARS-CoV-2 vaccine 6 months earlier, and had not displayed these symptoms or any complications.

The patient had no known history of SARS-CoV-2 infection. Her medical history included 5 previous episodes of rhabdomyolysis since age 10, usually triggered by viral infections. She had a previously identified mutation in the ryanodine receptor 1 (*RYR1*) gene at the canonical splice site (c.12624+1_124+2insT), which increased her risk for development of malignant hyperthermia and rhabdomyolysis. She had not had rhabdomyolysis following previous vaccinations. Additional medical history included schizoaffective disorder, latent tuberculosis 5 years ago, polycystic ovarian syndrome, iron deficiency anemia and obstructive sleep apnea. Her medications were atorvastatin, clozapine, lithium, flupentixol, ferrous gluconate and vitamin D. Her anti-psychotic medications had been prescribed since 2015. She had not had any recent dose adjustments or additions to her medication regimen. She reported not taking any herbal or over-the-counter substances.

The patient had no focal neurologic deficits, rashes or arthralgias. She had not had recent strenuous exercise, trauma or prolonged heat exposure, and she reported no alcohol or recreational drug consumption. At presentation, her blood pressure was 143/88 mm Hg, her heart rate was 118 beat/min, her respiratory rate was 16 breaths/min, her oxygen saturation was 98% on room air, and she had a temperature of 36.3°C. Cardiovascular, respiratory, abdominal and dermatologic examinations were unremarkable. Neurological findings included symmetric muscle power in the proximal and distal upper and lower limbs (4/5 using the Medical Research Council's scale for muscle strength), with an otherwise normal musculoskeletal examination. No altered mental status, diaphoresis, rigidity or hyperreflexia were evident.

Key points

- We report a case of severe rhabdomyolysis in a patient with a ryanodine receptor 1 (*RYR1*) gene mutation who presented 8 days after receiving a second dose of Moderna mRNA vaccine against SARS-CoV-2.
- Onset of rhabdomyolysis after SARS-CoV-2 vaccination is variable, ranging from less than 24 hours to 7 days after the administration of the vaccine, with symptoms that include limb myalgia, weakness and difficulty ambulating.
- In severe cases of rhabdomyolysis, clinicians should consider neuroleptic malignant syndrome, malignant hyperthermia and serotonin syndrome in their differential diagnosis.
- The mainstay of treatment for rhabdomyolysis is intravenous fluid resuscitation.
- For patients with an underlying medical condition that may make them more susceptible to rhabdomyolysis (e.g., muscle dystrophy, metabolic or mitochondrial myopathy, *RYR1*-related disease), clinicians should counsel on signs of rhabdomyolysis and should check the patient's creatinine kinase level within 1 week of vaccination.

Our differential diagnosis included rhabdomyolysis, malignant hyperthermia, serotonin syndrome and neuroleptic malignant syndrome, as well as viral infection. Although our patient was taking antipsychotic medication, neuroleptic malignant syndrome and serotonin syndrome were unlikely given that she had no autonomic instability, clonus, rigidity, hyporeflexia, hyperthermia or altered mental status.

The results of investigations are in Table 1. Initial blood tests at 8 days postvaccination showed a creatine kinase (CK) of 203088 (normal 30–150) U/L, with no evidence of renal impairment, and normal electrolyte levels. Urinalysis revealed blood (3+), with no red blood cells. A magnetic resonance imaging scan of her thighs showed diffusely heterogeneous, symmetric, intramuscular and intermuscular high T_2 and short tau inversion recovery signals involving the thigh musculature (Figure 1). We diagnosed rhabdomyolysis, possibly in association with vaccination, but we could not definitively rule out viral-induced rhabdomyolysis; we did not perform nasopharyngeal polymerase chain reaction testing for SARS-CoV-2.

Table 1: Laboratory investigations during hospital admission*

Investigation	8 days postvaccine	11 days postvaccine	20 days postvaccine	Reference range
Creatinine, µmol/L	69	67	66	58–110
Urea, mmol/L	1.8	–	–	2.7–6.7
Sodium, mmol/L	143	142	140	135–145
Potassium, mmol/L	3.3	5.3	3.7	3.5–5
Chloride, mmol/L	108	110	105	95–110
Magnesium, mmol/L	0.89	0.89	0.81	0.70–1.10
Phosphate, mmol/L	1.72	1.78	1.85	0.90–1.52
Calcium, mmol/L	2.12	2.33	2.30	2.10–2.60
Albumin, g/L	36	37	36	35–50
Creatine kinase, U/L	203 088	586 647	5772	30–150
Hemoglobin, g/L	129	126	99	115–165
Mean corpuscular volume, fL	86.1	90.1	94.1	82–99
Platelets, x 10 ⁹ /L	236	282	266	150–400
Leukocytes, x 10 ⁹ /L	9.6	10.8	6.7	4–11
Lymphocytes, x 10 ⁹ /L	1.9	2.5	2.3	1.5–4
Neutrophils, x 10 ⁹ /L	7.3	8.0	4.0	2–7.5
Venous blood gas				
pH	7.37	7.42	7.42	7.32–7.42
pCO ₂ , mm Hg	44	47	46	38–50
Bicarbonate, mmol/L	25	31	30	24–30
Liver enzymes				
Aspartate aminotransferase, U/L	673	1376	109	18–34
Alanine aminotransferase, U/L	68	191	94	0–34
γ-Glutamyl transferase, U/L	27	42	–	< 37
Alkaline phosphatase, U/L	96	96	–	38–126
Total bilirubin, µmol/L	8	11	–	< 21
Urinalysis				
Blood	3+	–	–	Negative
Protein	Negative	–	–	Negative
Ketones	Negative	–	–	Negative
Glucose	Negative	–	–	Negative

Note: ANA = antinuclear antibody, anti = antibody, ANCA = antineutrophil cytoplasmic antibody, AU = arbitrary units, HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A, MDA5 = melanoma differentiation-associated gene 5, pCO₂ = partial pressure of carbon dioxide, SRP = signal recognition particle, TIF1 = transcription intermediary factor 1. *Investigations for autoimmune markers (ANA screen, anti-Mi-2-α, anti-Mi-2-β, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-Ku, anti-PM/Scl-100, anti-PM/Scl-75, anti-Jo1, anti-SRP, anti-PL-7, anti-PL-12, anti-OJ, anti-Ro-52, anti-HMG-CoA reductase) were all negative, aside from P-ANCA and C-ANCA (both < 0.2 AU/mL at day 11 and < 1.0 AU/mL at day 20).

We treated the patient's rhabdomyolysis with intravenous fluid resuscitation. Given her *RYR1* mutation and the potential for malignant hyperthermia, despite absence of neurologic sequelae at 9 days postvaccination, we also started oral dantrolene (25 mg, 3 times a day). Her myalgia and weakness continued to worsen, with a peak CK of 586 647 U/L at 11 days postvaccination. Given the patient's 2-year history of statin exposure, we consulted a rheumatologist to exclude inflammatory myopathy. We had stopped atorvastatin at presentation. Testing for 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase antibody and a myositis panel were negative. After 7 days of treatment without

immunosuppression, she improved clinically, providing evidence against immune-mediated myopathy, and her CK normalized by day 10 of admission (18 days postvaccination).

Discussion

Rhabdomyolysis is a syndrome characterized by muscle necrosis and release of intracellular muscle constituents into peripheral circulation. About 25 000 cases are reported each year in the United States.¹ The severity of illness ranges from asymptomatic elevation in muscle enzymes to life-threatening complications

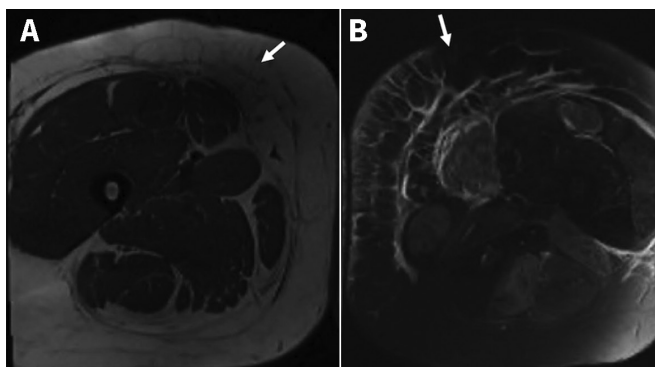


Figure 1: Magnetic resonance imaging (MRI) scans of the left thigh of a 30-year-old woman with rhabdomyolysis. (A) A T_1 -weighted MRI scan showed extensive fatty replacement (arrow) and edema in thigh musculature. (B) A T_2 -weighted MRI scan showed heterogeneous, diffuse hyperintense areas (arrow), with extensive edema affecting the tensor fascia latae, biceps femoris and vastus lateralis muscles.

involving acute kidney injury, disseminated intravascular coagulation, compartment syndrome and electrolyte abnormalities. Acute kidney injury is one of the most serious and common complications of rhabdomyolysis, with a mortality rate of about 10%.¹

Diagnosis

A thorough history and examination, in combination with CK measurements, are integral to diagnosing rhabdomyolysis. The characteristic triad of rhabdomyolysis symptoms is myalgia, weakness and dark urine; however, this occurs in only 10% of patients.¹ Rhabdomyolysis has numerous triggers, including exercise, medications (e.g., lithium) and infection (Box 1). Differentiating between syndromes that include rhabdomyolysis as a complication — including neuroleptic malignant syndrome, malignant hyperthermia and serotonin syndrome — can help direct onward management (Table 2).^{2,3}

With rhabdomyolysis, serum CK levels at presentation tend to be at least 5 times the upper limit of normal, often more than 5000 IU/L, although there is no absolute cut-off.¹ An MRI scan can be helpful for identifying the underlying cause, as symmetric muscle edema implies inflammatory and drug-related myopathies, and asymmetric edema suggests trauma.¹ A muscle biopsy can confirm the diagnosis, but is not usually necessary.

SARS-CoV-2 vaccination and rhabdomyolysis

Rhabdomyolysis has been described as a complication of viral infection, including SARS-CoV-2.⁴ One retrospective cohort study of 140 patients admitted to hospital with COVID-19 showed a 16.9% incidence of rhabdomyolysis; patients who developed rhabdomyolysis were significantly more likely to die than those who did not (47.1% v. 26.4%).⁴

As with other vaccinations, rhabdomyolysis may be associated with vaccination against SARS-CoV-2. As of Jan. 14, 2022, according to the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System, 214 cases of rhabdomyolysis have been reported after SARS-CoV-2 vaccination.⁵ Six case reports have been published. In the first report, an 80-year-old

Box 1: Common triggers associated with rhabdomyolysis¹

Traumatic triggers

- Multiple trauma
- Crush injury
- Coma
- Third-degree burn
- Electrical or lightning injury
- Surgery Immobilization

Exertional triggers

- Strenuous exercise
- Sickle cell trait
- Hyperkinetic states
- Malignant hyperthermia
- Metabolic myopathies
- Heat
- Seizures
- Neuroleptic malignant syndrome
- Mitochondrial myopathies

Nonexertional triggers

- Drugs and toxins
 - Antipsychotics, barbiturates, benzodiazepines, colchicine, corticosteroids, isoniazid, lithium, narcotics, neuroleptic agents, salicylates, phenothiazines, selective serotonin reuptake inhibitors, statins, theophylline, tricyclic antidepressants, zidovudine, antibiotics, monoamine oxidase inhibitors, caffeine, lysergic acid diethylamide (LSD), phencyclidine (PCP), cocaine, opiates, amphetamines, alcohol.
- Vaccination
- Electrolyte abnormalities
 - Hyponatremia, hypernatremia, hypokalemia, hypophosphatemia, hypocalcemia
- Endocrinopathies
 - Thyrotoxicosis, diabetic ketoacidosis, nonketotic hyperosmolar syndrome
- Inflammatory myopathies
- Infections (bacterial, viral)
- Delirium tremens

man with diabetes developed myalgia and weakness 2 days post-vaccination for SARS-CoV-2 with his second dose of Moderna.⁶ His CK peaked at 6546 U/L and was responsive to intravenous fluids. Similarly, a 21-year-old man with asthma presented with lower back pain and swelling for 1 day, with a CK of 22000 U/L, after his first Pfizer/BioNTech vaccine.⁷ Another report described a 28-year-old woman with no medical history who presented with myalgia and weakness and a CK of 17969 U/L, 5 days after her first Moderna vaccine.⁸ A 19-year-old man received the Johnson & Johnson vaccine and was noted to have myalgia and immobility 1 day after vaccination. He had a CK of 15 628 U/L and a negative myositis antibody panel.⁹ An 85-year-old woman with a recent history of cerebrovascular accident presented with

Table 2: Differentiating between syndromes that present with rhabdomyolysis^{2,3}

Characteristic	Neuroleptic malignant syndrome	Serotonin syndrome	Malignant hyperthermia
Inciting agent	Dopamine antagonist	Serotonin agonist	Inhaled or halogenated anesthetics
Onset	Days to weeks	< 24 hours	< 24 hours
Course	Resolves within 7–9 days of onset with treatment	Resolves within 24 hours of onset with treatment	Resolves within 24–48 hours of onset with treatment
Body temperature	Hyperthermia	Hyperthermia	Hyperthermia
Neuromuscular findings	Lead-pipe rigidity Bradyreflexia	Hyperreflexia Rigidity Tremor Myoclonus	Hyperreflexia Rigidity
Clinical features	Diaphoresis Catatonia or mutism	Diaphoresis Altered level of consciousness Increased bowel sounds	Diaphoresis Agitation Mottled skin

weakness, muscle cramps, hematuria, acute kidney injury and a CK of more than 14 000 U/L 2 days after her second dose of Moderna vaccine. Despite fluid resuscitation, she deteriorated and ultimately died of cardiac arrest, complicated in part by acute heart failure, infection and renal failure.¹⁰ Lastly, a 34-year-old man with carnitine palmitoyltransferase II deficiency (a disorder of long-chain fatty acid oxidation resulting in myopathy) developed rhabdomyolysis (CK 250 000 U/L) within 24 hours of receiving the AstraZeneca vaccine.¹¹

***RYR1* gene and rhabdomyolysis**

Our patient had a pathogenic mutation of the *RYR1* gene. This gene encodes the ryanodine receptor located in the sarcoplasmic reticulum membrane of skeletal muscle cells.¹² Dysfunction in *RYR1* can lead to impairment in muscle contraction, leading to weakness, and patients may have a lower threshold for rhabdomyolysis. As our patient had previously documented events of rhabdomyolysis secondary to viral illness, we believe she may have been sensitive to systemic inflammatory responses. Vaccines can induce the release of myotoxic cytokines, including tumour necrosis factor, resulting in skeletal muscle breakdown and subsequent rhabdomyolysis.⁹ In our patient, we speculate that the second dose of SARS-CoV-2 vaccine may have generated a more robust immune response, with myotoxic cytokine release leading to rhabdomyolysis, compared with the first dose. Although causality cannot be proven, the temporal relation between mRNA SARS-CoV-2 vaccination and development of myalgia, severe CK elevation and diffuse muscle edema on imaging supports a possible association, with a score of 2 on the Naranjo Adverse Drug Reaction Probability Scale (<https://www.evidencio.com/models/show/661>).

Although mRNA vaccination against SARS-CoV-2 is the most likely trigger of rhabdomyolysis in our patient, she was also taking lithium and atorvastatin, which may have been confounding or contributing factors. A negative HMG-CoA reductase antibody, and improvement without immunosuppression, argues against statin-associated, immune-mediated necrotizing

myopathy, but statin use has been associated with increased risk of rhabdomyolysis in individuals with *RYR1* mutations.¹³ Use of antipsychotics is also a known risk factor for rhabdomyolysis, particularly in patients taking multiple agents, as in our patient.¹⁴

Clinical course

Our patient’s neuromuscular symptoms began 3 days postvaccination, with a peak in CK 11 days postvaccination (Figure 2). The typical time course of CK is a rise within 12 hours of muscle injury, peaking within 1–3 days and declining 3–5 days after cessation of muscle injury.¹ Our patient’s CK peaked later than expected, and her CK level was higher than other published cases. Whether these differences are related to a vaccine-specific rhabdomyolysis response or her underlying risk factors is unclear.

Of note, the very high CK level did not result in renal impairment. However, our patient was young, with normal renal function before the rhabdomyolysis, and at this degree of CK

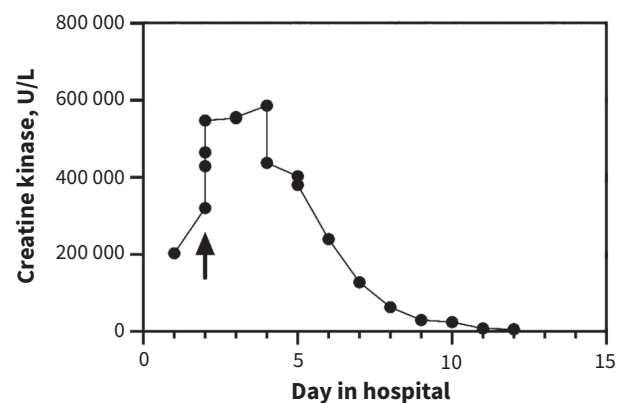


Figure 2: Change in creatine kinase levels from time of hospital admission to discharge. The peak level was at 586 647 U/L on day 4 of admission. Arrow points to the day that oral dantrolene was initiated.

elevation, an average 30-day risk of kidney injury is 74%, with only 11% of patients requiring renal replacement therapy.¹⁵ In addition, our patient also had markedly elevated liver enzymes. It is unclear if this was related to rhabdomyolysis or to treatment with dantrolene, which has been associated with hepatotoxicity.² It is difficult to differentiate between liver and muscle injury, and as such, the clinical context must determine whether further investigation of liver disease is warranted.

Lastly, it is unclear whether our patient's condition improved simply from administration of intravenous fluids, which is the standard of care for rhabdomyolysis, or whether dantrolene was efficacious. Dantrolene acts as an inhibitor of the ryanodine receptor, and is typically used for malignant hyperthermia to assist with reduction of hyperthermia, CK levels and rigidity.¹⁶ We used dantrolene because of the degree of the patient's CK elevation and her pre-existing *RYR1* mutation, but clinical guidelines are lacking. Dantrolene may have attenuated muscle necrosis in our patient, but may not help in cases of vaccine-related rhabdomyolysis with different risk factors.

Conclusion

We report a case of rhabdomyolysis, possibly associated with mRNA vaccination against SARS-CoV-2, in a patient with *RYR1* mutation whose other risk factors included use of a statin and multiple antipsychotic medications. To ensure prompt identification and treatment of rhabdomyolysis, clinicians should consider close monitoring after SARS-CoV-2 vaccination in patients who may have a susceptibility to rhabdomyolysis, such as those with neuromuscular conditions including muscle dystrophy, metabolic or mitochondrial myopathy, or *RYR1*-related disease. In these patients, we suggest clinicians obtain serum CK levels within 7 days of vaccination and advise patients to monitor for clinical features of rhabdomyolysis.

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