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CASE REPORT

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A severe case of rhabdomyolysis after Moderna mRNA anti-COVID-19 vaccine with a literature review

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Abstract

The identification of rhabdomyolysis as a potential fatal adverse reaction to recent COVID-19 vaccines is essential. As the symptoms of rhabdomyolysis are not specific, the threshold to actively search for this complication should be low.

KEYWORDS

2019-nCoV vaccine mRNA-1273, COVID-19, COVID-19 vaccines, drug-related side effects and adverse reactions, molecular mechanisms of pharmacological action, rhabdomyolysis

1 | INTRODUCTION

We describe the case of a young man who reported muscle weakness 2 days after the first dose of a Moderna mRNA anti-COVID-19 vaccine. The blood and urine examinations confirmed acute rhabdomyolysis. We discuss the imputability of the vaccine and the potential pathophysiological mechanisms of this event.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the COVID-19 pandemic, which heavily and globally affected the healthcare systems. Vaccination against COVID-19 is essential to control the pandemic. Pivotal studies have shown a favorable tolerability profile of the marketed vaccines, including mRNA vaccines.

However, post-marketing surveillance has revealed several rare and/or unexpected potential adverse drug reactions (ADR), such as nervous system disorders, musculoskeletal and connective tissue disorders, and cardiac disorders. More specifically m-RNA vaccines have also been involved in such reactions. Mechanisms are unclear, but hypotheses include inadequate immune response and molecular mimicry.

Rhabdomyolysis is a pathological condition of skeletal muscle damage that leads to the release of toxic

intracellular material into the blood. Vaccines are one of the causes of rhabdomyolysis, including SARS-CoV-2 vaccine, but the role of the mRNA vaccines is not yet known. So is the role of infections, including infection with SARS-CoV-2. There have been a few published case reports describing rhabdomyolysis in individuals after receiving the COVID-19 vaccine. The mechanisms are discussed.

Rhabdomyolysis is a serious medical condition that can be fatal if severe and not managed early. The classic clinical triad of rhabdomyolysis is myalgia, weakness, and dark urine.[1] However, myalgia and weakness are unspecific symptoms and are also common side effects of a vaccine, which makes the detection of rhabdomyolysis difficult. Therefore, clinicians should be aware of this potential ADR and search for it actively when suspected.

2 | CASE PRESENTATION

The patient was a 20-year-old male, athletic and with no medical history, beginning his military service 2 weeks before the medical event. The patient received his first Moderna mRNA anti-COVID-19 vaccine dose on July 12, 2021. He was exempted from military activity for the next 2 days. On Day 2, he experienced muscle pain predominantly in the proximal muscles of his arms and impression of swelling of his forearms. On Day 3, he performed 1 h of personal training (pull-ups and push-ups). Subsequently, he had a persistent weakness with an inability to carry loads and fully extend his forearms. He took nonsteroidal anti-inflammatory drugs (ibuprofen and diclofenac), with minimal effect on the symptoms. Because of the persistent functional impact, he went to the emergency department of our hospital on Day 5.

The patient reported no ingestion of toxic substances, recreational drugs, or anabolic steroids. He was occasionally taking omega-3 and magnesium supplements. He presented no systemic, cutaneous, articular, or pulmonary manifestations. He had no personal or family history of auto-immune or autoinflammatory disease or metabolic myopathy.

On the physical examination, his vital signs were stable. His strength was M4+ at the proximal level of both arms, and his sensory function was intact. His skin was intact. No cutaneous or arthritic signs were noted. Only mild swelling of the elbows and forearms was present.

3 | INVESTIGATIONS, DIFFERENTIAL DIAGNOSIS, AND TREATMENT

Pertinent laboratory results are summarized in Table 1. CK elevation was over 145'000 U/L. An extensive blood test showed no auto-immune, endocrinological, metabolic, or dermatomyositis diseases (Table 1). We excluded infection with hepatitis viruses, HIV, CMV, EBV, and tuberculosis. The SARS-CoV-2 antibodies were negative as well as the nasal swab PCR test for COVID-19. The anti-HMGCR for immune-mediated necrotizing myopathy was negative. The workup for the metabolic myopathy of carnitine deficiency excluded this disease (dosage of free and total carnitine, Acyl-Carnitine, and the ratio Acyl-Carnitine/free carnitine were normal). Other causes of rhabdomyolysis such as glycogen storage disorders, disorders of lipid metabolism, and mitochondrial respiratory chain disorders have not been investigated as their clinical likelihood was low (first episode of rhabdomyolysis and acute presentation).

However, the patient had a genetic sequencing that excluded the genetic myopathy of a deficit of carnitine palmitoyl transferase II (CPT II).

TABLE 1 Laboratory tests.

Tests	Value	Reference range
Metabolic panel		
Potassium mmol/l	4	3.6–4.8
Sodium mmol/l	141	134–144
Calcium mmol/l	2.5	2.2–2.52
Phosphate mmol/l	0.91	0.8–1.45
Creatinine umol/l	72	62–106
CO_2 mmol/l	25	21–28
BUN mmol/l	2	1.49–3.5
C-reactive protein (CRP) mg/L	7	0–10
CK U/l	>100'000	47–222
Aldolase U/L	2.7	1.4–11
Alanine aminotransferase (ALT) U/L	687	12–50
Aspartate aminotransferase (AST) U/L	1930	14–50
Lactate dehydrogenase (LDH) U/L	1850	87–210
Thyroid-stimulating hormone (TSH) mUl/l	1.87	0.27–4.2
Glycated Hemoglobin (HbA1c) %	5.2	3–6
Lipid profile	Normal	Normal
Immunology		
Dermatomyositis antibodies (Jo1, PL-7, PL-12, EJ, OJ, SRP, Mi-2 a/b, MDA-5, TIF1 gamma, anti-SAE1, anti-SAE2, anti-NXP2)	Normal	

The urine dipstick was suggestive of myoglobinuria. Indeed, it was positive for hemoglobin but without red blood cells in the urinary sediment. As the dipstick does not make the difference between myoglobin and hemoglobin, a dipstick without red blood cells suggests the presence of myoglobin in the urine in favor of rhabdomyolysis.

The ultrasound of the arm muscles showed hyperechogenic patches within the biceps brachii and wrist flexor muscles on both sides, compatible with muscle overstress injury, but without any effusion. The electroneuromyography was normal. The patient did not have any chest pain and the electrocardiogram was normal.

Before the complete workout of the case, the etiological differential diagnosis was broad, including strenuous physical exercise, vaccine and other medication, autoimmune myopathies, or other diseases. After workout, the vaccine origin appeared the most plausible. The patient was admitted for hyper-hydration with intravenous normal saline and close clinical and paraclinical monitoring.

4 | OUTCOME AND FOLLOW-UP

Rhabdomyolysis was diagnosed based on acute muscular pain and elevated CK. The patient did not develop acute kidney injury or electrolyte abnormalities. His CK level decreased progressively to 10′060 U/L at discharge on Day 11 (Figure 1). At follow-up consultation on Day 14, the CK level decreased to 1′282 U/L and the patient was asymptomatic despite resuming progressive physical activity with good tolerance and normal strength. On Day 50, after a complete resumption of physical activity, his CK level was normal at 181 U/L.

Given the temporal link of the events and the suspected correlation between the COVID-19 vaccine and rhabdomyolysis, the mRNA vaccine was considered a potential cause. The causality assessment performed by our regional pharmacovigilance center concluded a possible association between the vaccine and the event despite the presence of aggravating causes like physical exercise and dehydration. The case was ultimately reported to the Swiss pharmacovigilance Center, Swissmedic. After a multidisciplinary discussion, we decided to forgo the second Moderna anti-COVID-19 vaccine dose for safety reasons.

5 | DISCUSSION

We have described a case of rhabdomyolysis following the administration of the Moderna mRNA anti-COVID-19 vaccine. We assessed the causal relationship between the vaccine and rhabdomyolysis to be possible. The patient also performed muscular exercises 3 days after vaccination. This exercise was much less intensive than usually performed and the muscular pain began on Day 2, before this exercise. The role of the vaccine remains highly possible even if exercise may have increased the severity of the rhabdomyolysis. Additionally extensive work-up of different causes of rhabdomyolysis did not allow us to identify any other specific causes.

The summary of product characteristics does not list rhabdomyolysis as an adverse reaction to the Spikevax® vaccine. Post-marketing surveillance has allowed the identification of new or rare ADRs associated with recently launched COVID-19 vaccines. We found 26 published case reports of rhabdomyolysis after receiving the COVID-19 vaccine (Table 2).

In the case report of Ajmera et al. the authors reported a case of an 85-year-old patient who developed severe rhabdomyolysis with acute kidney injury that required renal replacement therapy after receiving the Moderna COVID-19 vaccine. He then developed multi-organ failure and cardiac arrest.[2] Three other fatal cases were reported. Kamura et al. described a 57-year-old patient who rapidly developed rapidly progressive rhabdomyolysis and infarctions of multiple organs. He died from multiple complications of thrombotic

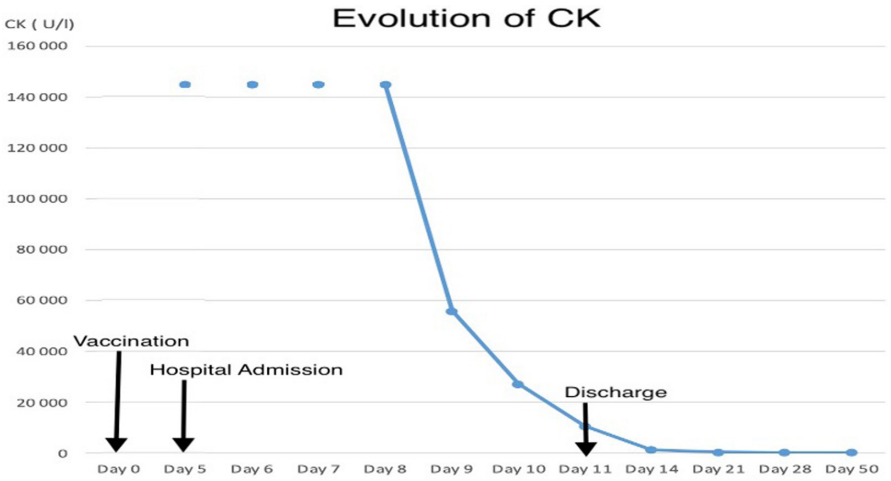

FIGURE 1 Graph evolution of CK with time (days).

TABLE 2 Published case reports of rhabdomyolysis following COVID-19 vaccination, as of December 30, 2022.

Study	Type of Vaccine and dose (D) number (1, 2 or 3)	Age (years), sex (M/F)	Time to symptoms (days)	CK peak (U/L)	Acute kidney injury Renal Replacement therapy (RRT)	Evolution (R = recovery, D = death)	Information
Sheka et al, 2023	mRNA-1273, Moderna, 1st D	20, M	2	>145'000	No	R	Moderate physical exercise
Ruijters et al. 11.2022,[6]	BNT161b2 mRNA Pfizer/BioNTech, 2nd D	80, M	1	280'600	Yes (RRT)	R	Treatment by statins
Pucchio et al. 10.2022,[7]	BNT161b2 mRNA Pfizer/BioNTech, 1st D	16, M	2	147'600	No	R	
Katz et al. 8.2022,[8]	BNT161b2 mRNA Pfizer/BioNTech, 2nd D	16 F	7	>200'000	No	R	Had heterozygous pathogenic variant in the DYSF gene (DYSF c.2643 + 1G > A) encoding dysferlin
Unger et al. 8.2022,[9]	BNT161b2 mRNA Pfizer/BioNTech, 3rd D	69, F	10	8'394	Yes	R	Treatment by statins, metformin
Imhof et al. 7.2022,[10]	BNT161b2 mRNA, Pfizer/BioNTech, 2nd D	65, M	7	90'373	Yes (RRT)	R	Treatment by statins, fibrates
Baba et al. 7.2022,[11]	mRNA-1273, Moderna, 3rd D	66, M	5	801	Yes	R	Presented papulovesicular–type vaccine-related eruption of papules and plaques. Takes fibrates
Sutcu et al. 6.2022,[12]	BNT161b2 mRNA, Pfizer/BioNTech, 2nd D	16, M	2	71'339	Yes	R	
Kimura et al. 5.2022,[13]	BNT161b2 mRNA Pfizer/BioNTech, 3rd D	76, M	2	9'800	No	R	Treatment by statins, suvorexant
Banamah et al. 5.2022,[14]	BNT161b2 mRNA, Pfizer/BioNTech, 3rd D	58, F	<1	9'200	Yes (RRT)	R	Polymyositis (adductors and gluteal bilaterally) Takes 3 antipsychotics
Durucan et al. 5.2022,[15]	BNT161b2 mRNA, Pfizer/BioNTech, 2nd D	24, M	14	>22'000	Yes	R	Lower extremity myositis and myocarditis
Cirillo et al. 3.2022,[4]	ChAd-Ox1 Adenovirus-based, AstraZeneca, 1st D	68, M	9	793'280	Yes	D	Multi-organ failure
Kim et al. 3.2022,[16]	BNT161b2 mRNA, Pfizer/BioNTech, 2nd D	30, M	6	4'778	No	R	Vaccine related myositis
Salter et al. 2.2022,[17]	mRNA-1273, Moderna, 2nd D	30, F	8	586'647	No	R	Patient with a ryanodine receptor 1 gene mutation. Takes an antipsychotic

TABLE 2 (Continued)

Study	Type of Vaccine and dose (D) number (1, 2 or 3)	Age (years), sex (M/F)	Time to symptoms (days)	CK peak (U/L)	Acute kidney injury Renal Replacement therapy (RRT)	Evolution (R = recovery, D = death)	Information
Kamura et al. 2.2022,[3]	mRNA-1273, Moderna, vaccine, 1st D	57, M	14	74'800	Yes (RRT)	D	Multiple complication due to thrombotic microangiopathy
Kalekar et al. 2.2022,[18]	ChAd-Ox1 Adenovirus-based, AstraZeneca	31, F	10	15'000	No	R	
Huang et al. 2.2022,[5]	ChAd-Ox1 Adenovirus-based, AstraZeneca, 2nd D	44, M	14	151'058	Yes (RRT)	D	Acute compartment syndrome and myositis
Al-Rasbi et al. 2.2022,[19]	BNT161b2 mRNA, Pfizer/BioNTech, 1st D	37, M	12	93'046	Yes	R	Myocarditis, pulmonary hemorrhage and extensive myositis
Vutipongsatorn et al. 1.2022,[20]	BNT161b2 mRNA, Pfizer /BioNTech Patient A: 1st D Patient B: 2nd D	55 72, F	2 1	11'300 10'222	Yes Yes	R R	Dermatomyositis and inflammatory myositis.
Hakroush et al. 9.2021,[21]	BNT161b2 mRNA, Pfizer/BioNTech, 2nd D	85, F	14	14'243	Yes	R	ANCA-associated vasculitis with rhabdomyolysis and pauci-immune crescentic glomerulonephritis
Ajmera et al. 9.2021,[2]	mRNA-1273, Moderna, 2nd D	85, F	2	>14'000	Yes (RRT)	D	Treatment by statins, clopidogrel, trazodone
Gelbenegger et al. 8.2021,[22]	Ad26.COV2.S, Janssen, 1st D	19, M	2	44'180	No	R	
Elias et al. 8.2021,[23]	BNT161b2 mRNA, Pfizer/BioNTech, 1st D	81, M	3	>17'000	Yes	R	Quadriceps fasciitis; Treatment by statins, Nintedanib
Faissner et al. 8.2021,[24]	mRNA-1273, Moderna, 1st D	28, F	7	17'959	No	R	
Nassar et al. 6.2021,[25]	BNT161b2 mRNA, Pfizer/BioNTech, 1st D	21, M	1	>22'000	No	R	Smokes marijuana
Mack et al. 5.2021,[26]	mRNA-1273, Moderna, 2nd D	80, M	2	6'546	No	R	COVID-19 infection 3 months prior; Treatment by statins
Tan et al. 4.2021,[27]	ChAd-Ox1 Adenovirus-based, AstraZeneca, 1st D	34, M	<1	250'000	No	R	CPT II deficiency

microangiopathy 14 days after receiving his first dose of mRNA Moderna vaccine.[3] Finally, 2 fatal cases with the ChAd-Ox 1 Adenovirus-based vaccine were reported by Cirillo et al.[4] and Huang et al.[5]

In rhabdomyolysis cases, cardiac involvement must be considered, as many myocarditis and pericarditis have been reported. In the study of Bots et al.—a population-based descriptive cohort and a nested self-controlled risk interval study using 5 European databases that included over 35 million individuals—the authors concluded the myocarditis rates were elevated in individuals less than 30 years old after both doses of the Pfizer vaccine and the second dose of the Moderna vaccine.[28]

In our case report, myocarditis was unlikely, as the patient did not have chest pain, and the electrocardiogram was normal.

In Table 2, we have mentioned 2 case reports of myocarditis cases following the COVID-19 vaccine. The first one published by Durucan et al. was about a 28-year-old patient who was diagnosed with rhabdomyolysis and myositis 2 weeks after receiving his 2nd dose of Pfizer vaccine. A week later, he presented with myocarditis.[15]

The second one by Al-Rasbi et al. described the case of a 37-year-old patient who developed myocarditis, pulmonary hemorrhage, and extensive myositis with rhabdomyolysis 12 days after the first dose of Pfizer mRNA COVID-19 vaccine. The authors discuss a possible link between the mRNA COVID-19 vaccine and immune-mediated myocarditis. However, the exact mechanism is not known yet.[19]

Post-marketing surveillance is based on spontaneous reports from healthcare professionals and patients to national pharmacovigilance centers. The continuous analysis of pharmacovigilance databases allows the rapid identification of potential new safety signals. However, those data should be carefully interpreted as they do not prove any causal link between a pharmaceutical product and an adverse event.[29]

One of the biggest pharmacovigilance databases, the one from the World Health Organization (WHO) (VigiAccess), reported (last updated on December 30, 2022) 1042 cases of rhabdomyolysis for all COVID-19 vaccines combined out of the 4'830'709 individual case safety reports recorded following vaccination (last updated on January 8, 2023).[30]

Based on a search of the Vaccine Adverse Events Reporting System (VAERS) database from the United States (last updated on December 30, 2022), there have been 358 reports of rhabdomyolysis following COVID-19 vaccines: 179 for Pfizer, 137 for Moderna, 41 for Janssen, and 1 for an unspecified COVID-19 vaccine.[31]

To the best of our knowledge, rhabdomyolysis has not yet been identified as a signal by any health authorities. However, the existence of several case reports should alert physicians to this potential adverse event.

In our case report, our patient benefited from genetic sequencing that excluded the genetic myopathy of a deficit of carnitine palmitoyl transferase II (CPT II). It is a rare neuromuscular disease that may present with the increase of CK; common triggers are infection, exercise, dehydration, and fasting. COVID-19 vaccination has also been reported as a trigger for rhabdomyolysis in the case of Tan and al.[27]

Rhabdomyolysis is described in various infections, for example, mycoplasma pneumonia, influenza A virus, and more recently SARS-CoV-2. Hypothetic mechanisms include tissue hypoxemia, direct myocyte invasion, low enzyme activity or activation of lysosomal enzymes or endotoxins, and molecular mimicry, inducing auto-immune response of the organism. For SARS-CoV-2 infection, direct myocyte damage by cytokines was privileged because rhabdomyolysis was identified with a peak of inflammatory markers.[4] Moreover, macrophages containing viral particles and infiltrating myocytes have been found in MERS-CoV patients.[32]

Vaccination-induced rhabdomyolysis has been described for influenza H1N1 and recombinant zoster vaccine[33,34] and more recently for the COVID-19 vaccine with many reported cases.[11] However, physiopathological mechanisms are unclear. Huang ST et al. proposed an abnormal immune response to previously circulating auto-antigens or muscle antigens released by myonecrosis. The antigenic similarity between SARS-CoV-2 spike protein and human protein (molecular mimicry) was also mentioned.[5] Fatal thrombotic microangiopathy with rhabdomyolysis in a Japanese patient after mRNA-1273 vaccine (Moderna) suggested vaccine-induced complement activation.[3] Some patients with dermatomyositis have T-cell receptors specific for SARS-CoV-2, suggesting that the virus or mRNA vaccine can contribute to myositis, by the activation of interferon type 1 response and pro-inflammatory cascade.[20]

This case was the opportunity for clinical lessons. First, before considering rhabdomyolysis as an adverse reaction to a vaccine, other causes should first be ruled out. The identification of rhabdomyolysis is essential as it can be fatal. Second, the classic clinical triad of rhabdomyolysis is not often present and the symptoms are not specific, since myalgia and weakness are common after any vaccination and/or a viral infection. Therefore, the threshold to actively search for rhabdomyolysis should be low.

6 | CONCLUSION

We have provided an example of severe rhabdomyolysis with one of the highest CK levels occurring after the administration of the first dose of the Moderna mRNA

anti-COVID-19 vaccine dose, in a patient without any genetic disease, as well as a literature review of other case reports. The pathophysiological mechanisms of COVID-19 vaccination-induced rhabdomyolysis are unclear. However, a few hypothetic mechanisms have been described suggesting mainly abnormal immune response. Such events represent an opportunity for clinical lessons.

AUTHOR CONTRIBUTIONS

Maria Sheka: Conceptualization; methodology; writing – original draft; writing – review and editing. **Yann Coattrenec:** Conceptualization; writing – review and editing. **Kuntheavy Ing Lorenzini:** Conceptualization; writing – review and editing. **Mathieu Nendaz:** Conceptualization; methodology; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing note applicable to this article as no datasets were generated or analysed in this study.

INFORMED CONSENT

Written and oral consent was obtained from the patient for the publication of his case.

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