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Original Article

COVID-19 vaccine induced rhabdomyolysis: Case report with literature review

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A R T I C L E   I N F O

1. Introduction

Coronavirus Disease 2019 (COVID-19) caused a significant impact on the health, economic and political systems in 2020, and by the end of the year, hope was born with the introduction of COVID-19 vaccines aiming at ending the pandemic. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is an enveloped, positive-sense, single-stranded RNA virus with viral spike glycoproteins, and the studied mechanism has contributed significantly to vaccination efforts and public health initiatives [1]. The coronavirus spike protein has been shown to mediate membrane fusion via the binding of cellular receptors

[2]. Herein we present the first case of COVID-19 vaccine-induced rhabdomyolysis to help clinicians easily identify such a problem in newly vaccinated patients.

1.1. Case presentation

We present a 21-year-old male patient with a past medical history of asthma who presented to the emergency department for progressively worsening pain and swelling in the lower back for one day after his first Pfizer/BioNTech COVID-19 vaccine injection. He described it as a 5 to 10 out of 10 sharp pain located at his mid to lower back with radiation to his left lateral thigh. The pain worsened with body movement. The patient tried over-the-counter pain medication with limited relief. He also noticed a darkened urine color before he came to the hospital.

The patient did not use any medication regularly. He denied excessive exercise, heavy weightlifting or body trauma after vaccination. He had no family history of autoimmune or musculoskeletal diseases, and surgical history was only significant for an uncomplicated appendectomy. Patient endorsed social marijuana use but denied other drug, alcohol, or tobacco use.

Transient elevated blood pressure was noticed at the beginning

of the hospitalization, but other vital signs were unremarkable. Physical examination was positive for tenderness to the paraspinal lumbar area upon palpation. The straight leg test was negative.

Pertinent lab results included Creatinine Phosphokinase (CPK) level more than 22,000 U/L (normal range 20−190 U/L), Aldolase 97.8 U/L (normal range 3.3−10.3 U/L), alanine aminotransferase 165 U/L (normal range 0−41 U/L), aspartate aminotransferase 675 U/L (normal range 5−40 U/L), high sensitive C-reactive protein 6.4 mg/L (normal range < 5.0 mg/L) and Lactate dehydrogenase 1525 U/L (normal range 135−225U/L). Urinalysis revealed clear yellow urine with positivity for blood and protein but negativity for Red Blood Cells (RBCs). Basic Metabolic Panel (BMP) showed normal potassium, bicarbonate, Blood Urea Nitrogen, and creatinine levels. Hepatitis B and C panels were negative except for hepatitis B surface antigen. Total and free carnitine levels were within the normal range. SARS-CoV-2 PCR was negative.

Anti-aminoacyl-tRNA synthetase antibodies (ab) (includes anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ), anti-SRP ab, anti-MI-2 ab, anti-TIF1-gamma ab, anti-MDA5 ab, anti-NXP2 ab, anti-PM/Scl-100 ab, anti-U3 RNP ab, U2 snRNP Ab, ANTI-U1-RNP AB, anti-Ku antibodies, anti−SS−A 52 KD ab IgG, ANA, and HIV antibodies were all negative. ESR, haptoglobin, TSH, and cortisol were in the normal range.

No musculoskeletal abnormalities were found on CT scan of the thoracic and lumbar spine. The right upper quadrant sonogram showed no abnormality in the liver, biliary tracts, gallbladder, or pancreas.

The patient had been hydrated with high volume IV normal saline for rhabdomyolysis. Morphine was given as needed for muscle pain. Follow-up lab results showed down-trending CPK and AST levels. Electrolyte level and renal functions have been within normal limits throughout the hospitalization. No change of urine color or urine output volume was noticed. The patient felt pain improved after treatments and was discharged after five days of hospital stay.

1.2. Impact of COVID vaccine on public health policy

Several studies have established that the most common symptoms that have resulted from SARS-CoV-2 are cough, fever, and myalgias [3]. The initial coronavirus case documented in humans was in 1960 and described as a cold. The United States currently has surpassed 32 million cases, 577 k deaths, and has successfully administered 257 million doses of the Covid-19 vaccine at the time of this paper [3,4].

Despite the rise in vaccination status among the United States population, limited access and distribution to impoverished countries have stunted the global impact of the vaccine. Inequity and insufficient funding have led low and middle-income countries to suffer. Health policy efforts have drastically changed to accommodate the global shortage of vaccines and the vital need for increased mass production. Michaud and Kates (2021) emphasize that the Biden administration has implemented policy changes in four main areas: distribution of surplus Covid-19 vaccinations to regions in need, providing additional funding for global vaccination efforts (Gavi/COVAX), assisting in the expansion of vaccine manufacturing, and working in conjunction with pharmaceutical companies to waive patents on COVID-19 vaccines [5]. In addition to these efforts, several emergency supplemental bills have been enacted to address the COVID-19 pandemic, many of which detail procedural measures for the manufacturing and distribution of vaccines [6].

Additionally, future vaccination policy efforts must include targeting the hesitancy surrounding vaccinations. Studies have shown a high prevalence of COVID-19 vaccine reluctance and misinformation through mass media, and therefore policy efforts must

acknowledge this discrepancy [7]. This increase in uncertainty is coupled with the need for accurate information on the short-term and long-term side effects of the COVID-19 vaccines, as there is a definitive gap in the literature for this topic area [8].

1.3. Incidence of side effects

Analysis of adverse effects in recipients of the Pfizer BioNTech vaccine revealed that more than 70% of vaccine recipients report local injection pain after receiving either dose. The most common systemic adverse effects were fatigue and headache. Younger patients reported more local or systemic adverse effects compared to the older population. The 2nd dose produced a similar profile of systemic adverse effects seen after the first dose but occurred to a greater extent. Sixty-four vaccine recipients (0.3%) and six placebo recipients (0.1%) reported lymphadenopathy. 4 serious adverse events were reported among vaccine recipients to include shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia [9].

Similar investigation of adverse effects in recipients of the Moderna MRNA1273 vaccine demonstrated that more than 80% of vaccine recipients reported local injection pain after receiving either dose. The most common systemic adverse effects were headache, fatigue, and myalgia, respectively. Moderate to severe systemic effects were reported in 50% of participants after their second dose. Furthermore, mRNA-1273 was associated with a greater incidence of lymphadenopathy than the Pfizer vaccine [10].

The Johnson and Johnson (Ad26) data indicates the most frequent local adverse effects among the low dose (LD) and high-dose (HD) groups was injection site pain. Younger participants experienced systemic adverse effects more frequently than older groups regardless of whether they received LD or HD vaccines. Severe systemic effects occurred more frequently in Cohort 1. Five serious adverse events, including hypotension, nephrolithiasis, legionella pneumonia, multiple sclerosis exacerbation, and fever were reported, but were determined to be unrelated to the vaccine [11].

In general, most local and systemic adverse effects of all 3 SARS-COV-2 COVID-19 vaccines, including Pfizer, Moderna, and J&J, were characterized by adverse effects of mild-to-moderate severity and typically self-resolved within 2−3 days, as shown in Table 1. The Moderna vaccine was associated with more severe systemic adverse effects when compared to Pfizer. Severe systemic events were rare and only reported in less than 2% and 1.5% of the participants receiving the 2nd dose of Pfizer or Moderna vaccines, respectively. Limited data on the safety and efficacy of J&J after the first or second dose warrant further investigation.

Systemic symptoms including nausea, vomiting, and diarrhea were excluded from the data because they occurred at similar rates between the vaccine and placebo group for all three of the vaccines. During J&J clinical trial, injection site erythema and swelling were not reported as local adverse effects; arthralgias and chills were not reported as a systemic adverse effect. Reported averages of several systemic adverse effects for the Johnson & Johnson Ad26 vaccine were estimated from the clinical trial data, as it only provides qualitative values in their published report and a supplemental appendix [9−11].

Table 1. Pfizer (n = 8183); Moderna (n = 30,420); J&J (n = 805). Estimated averages of local and systemic effects after either Pfizer or Moderna vaccine dose. In addition, the estimated average for the J&J dose represents a combination of adverse effects reported in both the low- and high-dose groups in the clinical trial. Placebo values can be found in the brackets above. The evaluation of systemic adverse effects, including arthralgia and chills, was excluded from the J&J trial and marked N/A = not available.

Table 1
COVID-19 side effects.

	SARS-CoV-2 COVID-19 Vaccines		
Vaccine	Pfizer BioNTech (BNT162B2) [9]	Moderna (MRNA-1273) [10]	J&J (JNJ78436735) [11]
Type	mRNA in lipid nanoparticles	mRNA in lipid nanoparticles	Non-replicating adenovirus vector
Efficacy	95%	94%	65%−75%
Administration	2 doses. 21 days apart	2 doses. 28 days apart	1 or 2 doses. 56 days apart
Local Symptoms- (%)			
Injection Site Pain	74.5 [27.25]	85.95 [17.25]	56.25 [11.5]
Systemic Symptoms- (%)			
Fever	8.0 [4.25]	8.15 [0.3]	16.75 [0]
Headache	39.5 [29.5]	45.65 [25]	42.5 [16]
Fatigue	47.75 [33]	51.25 [25.35]	46.5 [17.5]
Myalgia	25.25 [15.25]	40.35 [13.05]	37.5 [4]
Arthralgia	15.25 [8.75]	29.7 [11.3]	N/A
Chills	19.5 [11.75]	29.1 [5.8]	N/A

1.4. Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome characterized by skeletal muscle injury and necrosis with subsequent release of its intracellular components into the bloodstream. Etiology includes trauma (natural disasters, burns, electrical injury), exertion (marathon runners), ischemia or hypoxia (thrombus, emboli), dysregulated temperature states (malignant hyperthermia, heatstroke, extreme hypothermia, neuroleptic malignant syndrome), drugs (statins, fibrates, alcohol, cocaine, amphetamines, lithium, antipsychotics, antidepressants, propofol, amongst others), infection (influenza, Coxsackie, Epstein-Barr, HIV, Legionella, herpes simplex virus), inflammatory myopathies (polymyositis, dermatomyositis), seizures, sickle cell disease and rare genetic or metabolic disorders (glycogen storage diseases, carnitine palmitoyltransferase deficiency, thiolase deficiency, Duchenne and Becker muscular dystrophies, glucose-6-phosphate dehydrogenase deficiency) [12].

The classic triad on presentation includes myalgia, weakness, and dark urine. Other constitutional signs such as fever, chills, malaise, nausea, vomiting, tachycardia, muscle swelling, and tenderness can occur but are non-specific. A thorough history and physical examination are paramount to diagnosing rhabdomyolysis, considering the classic triad is present in less than 10% of patients. Patients with known risk factors (trauma, exertion, drugs, muscular disease, infection) and suggestive physical and laboratory findings should be suspected for this syndrome, and plasma creatine kinase (CK) determination should be done. Creatine kinase has been widely accepted as the gold standard over myoglobin, due in part to its long half-life of 36 h (vs. 2−4 h of myoglobin), thus decreasing false-negative results. In addition, urine myoglobin can be high, and muscle biopsy can confirm the diagnosis, although it is rarely needed [13].

Most clinicians use an arbitrary CK value of five times the upper limit of normal to guide therapy. However, its use in predicting the risk of acute kidney injury has not been formally established. Other clinical factors should be used to assess disease severity, such as volume status, urine output, concurrent sepsis or organ failure, electrolyte homeostasis, or comorbid conditions. Regardless of the cause of injury, myoglobin and muscle enzymes (creatine kinase, aldolase, lactate dehydrogenase) and electrolytes leak into the extracellular space leading to the complications seen in this syndrome. Myoglobin is nephrotoxic and can precipitate in the renal tubules leading to acute kidney injury, the most serious complication which can occur in up to one-third of patients [14]. Hyperkalemia and hyperphosphatemia can occur through direct intracellular release, and rapid accumulation of potassium in the serum can lead to malignant ventricular arrhythmias and cardiac arrest. Calcium salts can deposit in the damaged muscle causing

severe hypocalcemia. Elevated liver enzymes can be seen, and isolated high aspartate aminotransferase (with a normal alanine aminotransferase) could be a clue that rhabdomyolysis is occurring. A global hypovolemic state can ensue as intravascular fluid is third spaced and remains sequestered into injured muscles, further increasing the risk of prerenal acute kidney injury, and in some instances, even causing a compartment syndrome. The release of prothrombotic substances from damaged muscles can activate the clotting cascade and lead to disseminated intravascular coagulation.

Treatment aims to prevent complications and mainly consists of aggressive fluid resuscitation to prevent prerenal azotemia and acute kidney injury. It has been reported that early intervention with intravenous hydration has decreased the incidence of acute kidney injury [15]. The rate of normal saline infusion can begin as vigorous as 1.5 L/h if hemodynamic stability is desired, to target a urinary output of 200−300 mL/h, provided no other limiting comorbidities are present (heart failure or chronic kidney disease). Intravenous hydration can be decreased to 300−500 mL/h once hemodynamic stability is achieved and should be continued until CK levels fall under 1000 [16]. Many experts have recommended urinary alkalinization with the addition of bicarbonate or mannitol to limit the toxic effects of myoglobin on the renal tubules and decrease the risk of hyperkalemia, although this is controversial [17,18]. The causative agent should be eliminated if identified and feasible. Electrolytes should be monitored frequently and corrected to prevent fatal ventricular arrhythmias and cardiovascular collapse. A persistently elevated creatine kinase or a second peak 48 h after therapy is initiated could suggest ongoing muscle damage and the development of a compartment syndrome, and emergent fasciotomy may be needed to protect muscle integrity. Although rare, if disseminated intravascular coagulation and hemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary. For patients with refractory hyperkalemia, persistent acidosis, or oliguric renal failure with fluid overload, renal replacement therapy becomes lifesaving. If the diagnosis is rapidly established, the overall prognosis of this syndrome remains favorable. Considering that most rhabdomyolysis causes are reversible, most patients recover kidney function [12].

1.5. COVID and rhabdomyolysis

Rhabdomyolysis causes muscle cell injury and breakdown. The mechanism behind SARS-CoV2 causing rhabdomyolysis is not clear. However, viral cell invasion and cytokine-mediated direct muscle cell damage have been implicated [19]. Notably, Type II pneumocyte cytoplasm in early stages and colonic mucosa in COVID-19

patients presented with diarrhea contained the viral particles [19]. In the related MERS-CoV (Middle East Respiratory Syndrome) cases from 2005, viral particles were found in the skeletal muscle-invading macrophages [20]. Since both SARS-CoV2 and the related MERS-CoV use the angiotensin-converting enzyme II receptors, this is a highly suggested route for SARS-CoV2 viral invasion [20]. ACE2 receptors are found in several organs, including oral and nasal mucosa, lungs, small intestine, colon, liver, and kidneys [21].

Several case reports have discussed incidences of rhabdomyolysis with COVID-19 and its implications as summarized in Table 2 [19,20,22–27]. Unfortunately, rhabdomyolysis with its symptoms such as fever, myalgia, and signs (elevated liver enzymes and lactate dehydrogenase) is similar to COVID-19 itself and may go unrecognized [22]. This is concerning as COVID-19 patients with concomitant rhabdomyolysis were found to have an increased risk of deterioration, increased risk of ICU admission (90.9% vs. 5.3%), increased mechanical ventilation (86.4% vs. 2.7%), and increased risk of in-hospital death [28]. Two independent risk factors for in-hospital deaths were creatine kinase (CK) levels greater than 1000 IU/L and serum myoglobin levels greater than 1000 ng/ml [28]. However, Bach et al. clarify that while both CK and myoglobin levels are monitored, Myoglobin levels are less useful in diagnosing rhabdomyolysis due to increased false-negative results, caused by

myoglobin's short half-life [23]. However, this suggests the need for CK monitoring in all SARS-CoV2 patients to screen for rhabdomyolysis.

The etiology of the rhabdomyolysis in COVID patients remains unclear. In the Buckholtz et al. study of 6 patients with COVID and Rhabdomyolysis, 5 out of 6 were male, and 3 out of 6 had no significant past medical history or medication use. The mean age was 58, Acute kidney injury was developed in four patients, and two required dialysis, two of the patients (one male and one female) died [24].

In the Khosla et al. study of five patients with rhabdomyolysis, all five were male, median age 65. Four out of five patients had CKD stage 2 or better before COVID infection. On discharge, three out of those four had worsened kidney function and 2 had renal failure. Of note, Patient # 5, the only patient not on a statin or any other myotoxic drug, had the best overall outcomes, including improvement of renal function, liver enzymes, and duration of hospital course [26]. In the Finsterer et al. case series, of the 32 patients with SARS-CoV2 and rhabdomyolysis, 18 had prior exposure to myotoxic drugs. Of note, in 7 of these cases, they had rhabdomyolysis before being tested COVID-19 positive. Hereditary myopathies were not excluded [25]. Therefore, in these cases, it is possible that there was underlying muscle damage or that the SARS-CoV2 exacerbated the pre-existing muscle damage from myotoxic drugs.

Table 2
COVID-19 infection induces Rhabdomyolysis.

Study#	Age	Sex (M: Male. F: Female)	Past Medical. History	Clinical Presentation	Peak CK (U/L)	AST/ ALT (U/L)	Peak. Cr (mg/ dL)	LDH (U/L)	Myotoxic Drug Use	Outcome
Alrubaye [22]	35	F	None	Myalgia, Fever, Cough, Diarrhea	71,000	1900/ 450	.82	401	No	Survived, Discharged Day 4
Bach [23]	Adol-les-cent	M	Obesity	Myalgia, Anosmia,M Loss of Appetite, Recurrent Anaphylaxis	174,300	NR	.82	NR	No	Survived, Discharged Day 9
Buckholz [24] Patient1	43	M	None	Myalgia, Cough, Fever	75,240	1474/ NR	13.35	NR	NR	Survived
Buckholz [24] Patient2	37	M	None	Myalgia, SOB, fever	82,960	902/ NR	1.47	NR	NR	Survived
Buckholz [24] Patient3	75	M	Deep Vein Thromb-osis	Rhinorrhea Back pain, Weakness	3636	56/NR	1.78	NR	NR	Survived
Buckholz [24] Patient4	59	M	None	Fever, Cough, Diarrhea	8310	186/ NR	1.29	NR	NR	Died
Buckholz [24] Patient5	66	M	HTN	Fever, SOB, Cough	10,100	263/ NR	1.22	NR	NR	Survived
Buckholz [24]Patient 6	70	F	MM, CKD	Malaise, SOB, Cough	460,300	>6000/ NR	12.30	NR	NR	Died
Jin [26]	60	M	NR	Fever, Cough then Lower limb pain and weakness (after Day 9)	17,434	373/ 172	74.4	2347	NR	NR
Khosla [19]Patient1	65	M	HTN, HLD, OSA	SOB, Cough, Diarrhea	7854	NR	NR	NR	Yes	Died
Khosla [19]Patient2 cont,	78	M	HTN, DMII, HLD	SOB, New Mitral Regurgitation due to chordae rupture	22,000	NR	NR	NR	Yes	Died
Khosla [19]Patient3	67	M	HTN, HLD, DMII, CKD4	Hypotension, Hypoxia and Altered Mental Status	6164	NR	17.7	NR	Yes	Survived, ESRD requiring Hemodialysis
Khosla [19]Patient4	58	M	HTN, HLD, DMII	SOB, Cough, headache, hypoxia	4625	NR	2.0	NR	Yes	Survived, Discharged Day 35
Khosla [19]Patient5	64	M	HTN, DMII, HIV (undetec-ted viral load)	SOB, Fever, Nausea, Vomiting, hypoxia	3135	NR	1.0	NR	No	Survived
Rivas-García [20]	78	M	HTN, DMII	Intermittent fever, severe myalgia, muscle weakness, dark urine, 2 weeks of asthenia	22,511	NR	3.2	972	No	Survived
Suwanwongse [27]	88	M	HTN, CKD, HFrEF, etc …	Bilateral lower extremity weakness, Dry cough	13,581	NR	1.38	364	NR	NR
Finsterer [25] Mini-review of 32 patient reports	Rang-ed from 16 to 80	4 F, 25 M, 3NR	Varied, Majority had HTN	Varied	Range: 328 to >427,656	Varied	Varied	Varied	Varied	Varied

Key: CK: Creatinine Kinase, LDH: Lactate Dehydrogenase, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, NR: Not reported, HTN: Hypertension, DMII: Diabetes Mellitus type 2, CKD: Chronic Kidney Disease, HFrEF: Heart Failure with reduced Ejection Fraction, MM: Multiple Myeloma, SOB: Shortness of Breath.

1.6. Influenza vaccine and rhabdomyolysis

Despite its rarity, vaccine-related rhabdomyolysis is previously described in various literature in relation to the influenza vaccine. Callado et al. reported a patient who developed rhabdomyolysis five days after receiving the H1N1 vaccine [29]. He was admitted with lower back myalgia and developed ascending weakness. Laboratory studies showed CK of 7600 IU/L, and the LDH was 2828 IU/L. Later in his hospital course, he had AKI, persistent oliguria, and pulmonary edema that required renal replacement therapy. Raman et al., who described a case of rhabdomyolysis after one week of receiving the influenza vaccine, augmented their hypothesis. They reported a 57-year-old Caucasian man with a history of a cadaveric kidney transplant who developed generalized malaise, dark urine with CK of 17,000 U/l about one week after receiving an inactivated influenza vaccine. They did a muscle biopsy that showed scattered regenerating and degenerating fibers with no significant inflammatory infiltrate [30]. The same conclusion was reached by Plotkin et al. [31].

Muscle syndromes including myalgia, myositis, and rhabdomyolysis are well-known complications of influenza virus infection [32]. However, limited data is available about the role of the influenza vaccine in the development of muscle syndromes, including rhabdomyolysis. Various hypotheses were developed to explain the mechanism of vaccine-induced rhabdomyolysis. The aforementioned studies suggested that statin/fibrate therapy background in their cases resulted in the development of rhabdomyolysis while the vaccine acted as a trigger [29—31]. On the other hand, Chazan et al. found no clinical or laboratory correlation between the influenza vaccine and the development of myopathy in patients taking statins [33]. More studies are needed to explain the mechanism of vaccine-induced rhabdomyolysis and the possible ways to avoid it.

In our patient, rhabdomyolysis was evident by clinical picture with muscular pain and laboratory confirmation showing markedly elevated CPK levels. He was treated adequately with fluids and discharged safely. All possible etiologies for rhabdomyolysis were searched for and were negative. Intake of Marijuana might have shared this problem [34], although patients have been using it daily and temporal correlation in favor of the vaccine. Also, Hepatitis B was reported in one case report to cause rhabdomyolysis [35], but the timing of the vaccine just one day before disease onset favors vaccine side effects as the cause of such a problem.

2. Conclusion

Although COVID-19 vaccines are generally safe and encouraged for everyone, side effects can happen. Rhabdomyolysis has been documented with COVID-19, but clinicians should be vigilant about the possibility of rhabdomyolysis following COVID-19 vaccination as early diagnosis and treatment carry an excellent prognosis.

Declaration of competing interest

The authors of these paper certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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