


# Rhabdomyolysis in Patients Hospitalized With COVID-19 Infection: Five Case Series

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## Abstract

The novel SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) is now known to cause acute respiratory distress, cytokine storm, and coagulopathy. Multiple other manifestations have been published in recent literature. Rhabdomyolysis is a syndrome of muscle damage, with release of intracellular contents into circulation. It is characterized by marked elevations of creatinine kinase levels and myoglobinuria. In this article, we describe a series of 5 cases who were admitted with COVID-19 pneumonia and had severe muscle injury, as demonstrated by significant elevation (>5 times upper limit of normal) of creatinine kinase levels likely secondary to SARS-CoV-2 virus. The median age for these patients was 65 years, and most of them suffered from diabetes and hyperlipidemia. All patients were hypertensive males. Four out of 5 patients had preserved kidney function at baseline and were chronic kidney disease (CKD) stage 2 or better. However, most of them suffered significant kidney injury and at the time of discharge one patient was CKD stage 2 or better, 2 were CKD stage 3 or worse, and 2 patients had renal failure and died due to complications of SARS-CoV-2 infection.

## Keywords

SARS-CoV-2, COVID-19, rhabdomyolysis, muscle injury

## Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic has spread worldwide with more than 20 million cases, and more than 800 000 deaths reported so far.<sup>1</sup> In the United States of America, by the third week of August 2020, more than 5½ million patients have been confirmed with the infection, with more than 175 000 deaths.<sup>1</sup> Since then the number of cases has continued to climb nationally and globally. Infected individuals can be asymptomatic carriers or have mild, moderate, or severe illness. Various manifestations of the disease process arising from this novel coronavirus are being reported in the literature. These include, but are not limited to, pulmonary, cardiovascular, hematologic, renal, and neurologic disorders.<sup>2–5</sup> Rhabdomyolysis is a syndrome of muscle damage, with release of intracellular contents into circulation. It is characterized by marked elevations of creatinine kinase (CK) levels and myoglobinuria.<sup>6</sup> We report a series of 5 cases with skeletal muscle injury related to SARS-CoV-2 infection.

## Cases

### Case 1

A 65-year-old African American male with past medical history (PMH) of hypertension (HTN), hyperlipidemia (HLP);

on pravastatin 40 mg), obstructive sleep apnea presented with 2 days of shortness of breath, cough, and diarrhea. The patient (Pt) became hypoxemic and hemodynamically unstable requiring intubation and pressor support. He had transaminitis on admission and developed oliguric acute kidney injury and rhabdomyolysis with a maximum CK of 7854 U/L (normal = 20–300 U/L). Patient expired on day 5 of hospitalization. Treatment included anticoagulation, azithromycin, and tocilizumab.

### Case 2

A 78-year-old Caucasian male with PMH of type 2 diabetes mellitus (T2DM), HTN, HLP (on atorvastatin 40 mg) was admitted to the hospital with severe mitral valve regurgitation and heart failure secondary to chordal rupture. Pt underwent mitral valve replacement and 3 vessel coronary artery

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bypass graft surgery. Fourteen days after surgery, patient became somnolent and hypoxic, requiring intubation. Pt tested positive for SARS-CoV-2. On postoperative day 25, he had worsening sepsis/septic shock requiring pressor support. His CK and creatinine started to rise even with aggressive intravenous hydration. On day 28 postoperatively, after tracheostomy procedure, Pt developed worsening metabolic/lactic acidosis, hyperkalemia, and hypotension. His CK climbed to >22 000 U/L, patient became anuric despite fluid boluses. Hemodialysis was initiated. Patient expired despite aggressive resuscitative efforts. Medications included hydroxychloroquine, methylprednisolone, and vitamin C.

### Case 3

A 67-year-old African American male with PMH of T2DM, HTN, HLP (on atorvastatin 40 mg), chronic kidney disease (CKD) stage 4 (baseline creatinine of 3.3 mg/dL, estimated glomerular filtration rate [eGFR] of 22.7), hemicolectomy secondary to pseudo-obstruction, was admitted with altered mentation, hypotension (blood pressure of 79/63 mm Hg), and hypoxia. He was hyperkalemic (6.6 mmol/L) and in acute renal failure (serum creatinine 14.8 mg/dL). On day 3 of hospitalization, CK rose to 6164 U/L, and creatinine worsened to 17.7 mg/dL (eGFR 3.3). Hemodialysis was initiated and while CK levels improved, renal function did not recover. Patient has continued to require hemodialysis post discharge. Medications included hydroxychloroquine, azithromycin, and steroids.

### Case 4

A 58-year-old African American male with PMH of T2DM, HTN, HLP (on atorvastatin 20 mg) presented with complaints of headaches, worsening shortness of breath, and dry cough. On admission, patient was hypoxic, had transaminitis and acute renal insufficiency, with a creatinine of 2 mg/dL (baseline of 1.3 mg/dL). CK was elevated at 4625 U/L with concurrent transaminitis. During his hospital stay CK improved but creatinine remained elevated. Patient was discharged home on day 35 with home oxygen and has continued to require home oxygen 1 month after discharge. Treatment included anticoagulation, steroids, remdesivir, and convalescent plasma.

### Case 5

A 64-year-old African American male with PMH of T2DM, HTN, HIV (undetectable viral load on Odefsey) was admitted with shortness of breath, nausea, and vomiting. Patient was febrile and hypoxic but responded well to 2 L oxygen by nasal cannula. Laboratory data revealed a sodium of 123 mmol/L, potassium of 3.3 mmol/L, and transaminitis. On day 1 of hospitalization, his CK was 3135 U/L with a normal

serum creatinine of 1.0 mg/dL. CK, liver enzymes normalized during 1 week of hospital stay. Renal function remained normal. Treatment included azithromycin, vitamin C, and vitamin D.

## Discussion

Five patients with SARS-CoV-2 pneumonia developed rhabdomyolysis in a 2-month period between March and May during their hospitalization. Patients tested positive for COVID-19 on in-house testing done on nasopharyngeal swab using Abbott RealTime SARS-CoV-2 EUA Assay. The turnaround time for test result was within 48 hours in all cases and within 24 hours in most cases. The median age for these patients was 65 years, 4 patients had diabetes and 4 had hyperlipidemia. All patients were hypertensive. Four out of 5 patients had preserved kidney function at baseline and were CKD stage 2 or better. Presentation of these patients was myriad, and the onset of rhabdomyolysis occurred at different times during their illness. In 2 patients significant muscle injury was noted at time of admission, while the rest developed rhabdomyolysis during their hospital course. Most patients in this series suffered significant kidney injury and at the time of discharge only one patient was CKD stage 2 or better while 2 had CKD stage 3 or worse. Two patients who died due to complications of COVID-19 complications had complete renal failure.

Table 1 shows the demographic profile of each patient, their comorbid conditions and medications. It also reports the organ systems involved in symptomatology. It illustrates that various inflammatory markers peaked at varied times during the illness, and recovered at variable rates. Peaks of other inflammatory markers did not coincide with the peak CK levels. Also, the estimated length of stay, as predicted by various severity of illness measures, at the time of admission, was unreliable in these cases. Case 1 expired on day 5 of hospitalization, case 2 died 17 days after his COVID-19 diagnosis, case 3, 4 had a >30 day hospital stay and case 5 had a 7 day hospitalization. Figure 1 summarizes the trends in CK during the inpatient stay of each case. It shows that CK peaked. Figure 2 summarizes the creatinine levels corresponding to CK trends in these patients. Peak creatinine level occurred with or soon after the rise in CK but did not fall at the same rate consistently.

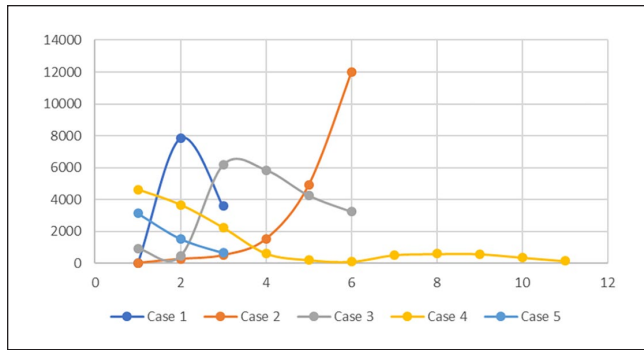
Case 2 was unique in our series as he acquired SARS-CoV-2 infection during hospitalization. His CK level remained stable during the early course of COVID-19 pneumonia, acute respiratory distress syndrome, and septic shock. However, he rapidly deteriorated after the tracheostomy and G-tube procedure. The clinical diagnosis was that of COVID-19 related cytokine storm precipitated by the intraoperative procedures, as no other causes were identified. Patient did not have malignant hyperthermia, or any other procedure-related complication.

**Table 1.** Baseline Demographic Characteristics and Inflammatory Markers in Patients With Rhabdomyolysis<sup>a</sup>.

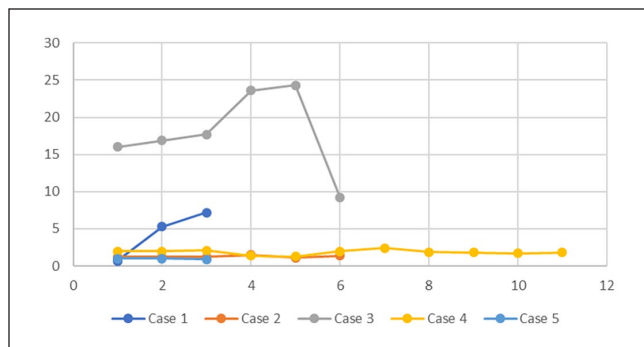
Data	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	65	78	67	58	64
Race	AA	C	AA	AA	AA
BMI (kg/m <sup>2</sup> )	30.14	27.25	31.31	32.96	34.90
Comorbidities	HTN, HLP	T2DM, HTN, HLP, CAD	T2DM, HTN, HLP, CKD-3	T2DM, HTN, HLP	T2DM, HTN, HIV
Outpatient medications included	Lisinopril pravastatin	Metformin atorvastatin	Atorvastatin	Metformin, atorvastatin	Metformin Odefsy
Outpatient baseline kidney function creatinine (reference range 0.7-1.5 mg/dL); eGFR (reference range >60)	0.9; >60	1.2; 62.2	3.3; 22.7	1.3; >60	1.2; >60
Type and duration of symptoms	Respiratory, 2 days	Respiratory, 5 days	Respiratory, 4 days	Respiratory and GI, 7 days	Respiratory and GI, 1 day
APACHE IV score	89	48	79	61	50
Estimated mortality	60%	11.5%	42%	25.3%	13.2%
Estimated length of stay (days)	9.2	2.7	6.2	6.9	3.9
Levels of CK and other inflammatory markers at time of diagnosis of SARS-CoV-2 infection					
CK (reference range 20-300 U/L)	Not checked	29	945	Not checked	3135
Creatinine level corresponding to CK (reference range 0.7-1.5 mg/dL)	0.7	1.2	14.1	2.0	1.0
D-dimer (reference range <0.5 µg/mL FEU)	2.66	7.36	1.7	<0.50	1.45
Ferritin (reference range 30-400 ng/mL)	38893	1612	1242	440	1297
CRP (reference range 0.0-0.7 mg/dL)	21	16.41	4.36	14.27	11.87
Procalcitonin (reference range 0-0.08 ng/mL)	Not checked	0.32	3.16	Not checked	Not checked
LDH (reference range 135-225 U/L)	Not checked	Not checked	286	204	371
Peak value for CK and other inflammatory markers					
CK (reference range 20-300 U/L)	7854, Day 3	>22000, Day 17	6164, Day 4	4625, Day 4	3135, Day 1
Creatinine (reference range 0.7-1.5 mg/dL)	5.3	1.4, Day 17	24.3, Day 6	2.4, Day 20	1.0, Day 1
D-dimer (reference range <0.5 µg/mL FEU)	>20, Day 3	11.14, Day 17	19.32, Day 21	3.5, Day 11	1.45, Day 1
Ferritin (reference range 30-400 ng/mL)	38893, Day 2	>100000, Day 17	3604, Day 25	3822, Day 9	1587, Day 3
CRP (reference range 0.0-0.7 mg/dL)	46.23, Day 3	16.41, Day 17	21.86, Day 6	28.03, Day 11	13.65, Day 3
Procalcitonin (reference range 0-0.08 ng/mL)	Not checked	0.54, Day 17	Not checked	0.89, Day 13	Not checked
LDH (reference range 135-225 U/L)	Not checked	>2500, Day 17	624, Day 5	845, Day 11	384, Day 5
Recovery CK and other inflammatory markers prior to discharge					
CK (reference range 20-300 U/L)	3579, Day 5	Pt expired on day 17	3242, Day 7	58, Day 30	654, Day 3
Creatinine level corresponding to CK (reference range 0.7-1.5 mg/dL)	8.0		11.3, Day 31	1.3, Day 35	0.9, Day 4
D-dimer (reference range <0.5 µg/mL FEU)	Not checked. Pt expired on day 5		Not checked	<0.50, Day 24	0.85, Day 3
Ferritin (reference range 30-400 ng/mL)	29447, Day 3		1479, Day 29	651, Day 34	1331, Day 3
CRP (reference range 0.0-0.7 mg/dL)	Not checked		13.54, Day 9	2.33, Day 34	13.38, Day 3
Procalcitonin (reference range 0-0.08 ng/mL)	Not checked		Not checked	0.09, Day 30	Not checked
LDH (reference range 135-225 U/L)	Not checked		531, Day 9	209, Day 34	384, Day 3

Abbreviations: AA, American African; C, Caucasian; BMI, body mass index; HTN, hypertension; HLP, hyperlipidemia; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; CKD-3, chronic kidney disease stage 3; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; CK, creatinine kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; LDH, lactate dehydrogenase; CRP, C-reactive protein.

<sup>a</sup>The timeline shows that inflammatory markers peaked at different times during the disease process and recovered at variable rates.



**Figure 1.** Creatinine kinase (CK) trend in patients with rhabdomyolysis.



**Figure 2.** Creatinine trend in patients with rhabdomyolysis.

Case 5 had the shortest course and best outcomes with rhabdomyolysis and was the only patient not on statin therapy at the time of admission.

As the SARS-CoV-2 pandemic continues to affect populations worldwide, recognizing risk factors and various manifestations of infection is essential to improving our ability to manage patients afflicted by this illness.

In our patient series, other causes of nontraumatic rhabdomyolysis were ruled out. None of the patients had seizures or connective tissue disease. Statin therapy was held in all patients with rise of CK. Muscle injury from a variety of viruses have been reported in the literature. Typical presentation is with myalgia or polymyositis. In contrast, several of our patients with significantly elevated CK levels did not complain of increased muscle pain. Virus-induced rhabdomyolysis is rare. In the United States, the most common cause of viral myositis, in children are influenza A and B viruses.<sup>7</sup> Myositis in children occurs predominantly with influenza B, with an incidence of 6% with influenza A and 34% with influenza B infection.<sup>8</sup> A review of 300 children with influenza-induced myositis found that incidence of rhabdomyolysis was 3%.<sup>9</sup>

In their study on the extrapulmonary complications of influenza in adults, Sellers and colleagues<sup>10</sup> compiled characteristics of 27 cases of rhabdomyolysis in the setting of influenza reported in the literature. Of these 27 patients with

influenza-associated rhabdomyolysis, 12 (44%) were more than the age of 60 years, and 15 (55%) were women. Most of these patients were infected with influenza A as 37% (10/27) were positive for A(H3N2), 14% (4/27) were positive for A(H1N1), and 40% (11/27) had an unspecified influenza A virus. Only 2 patients (7%) were infected with influenza B.<sup>10</sup>

Other viruses implicated in rhabdomyolysis include HIV, enterovirus including coxsackie virus groups A and B, parainfluenza, hepatitis B and C, adenovirus, and respiratory syncytial virus.<sup>7</sup> There are also 3 cases of rhabdomyolysis caused by the original SARS-associated coronavirus in Taiwan reported in the literature in 2005.<sup>11</sup> All 3 patients were on mechanical ventilation and developed acute renal failure.

The exact mechanism of pathogenesis of skeletal muscle injury with viral illnesses remains unclear. In 2005, Hsiao and colleagues<sup>12</sup> reported on the immunohistochemical characteristics of various tissues in 6 SARS-CoV patients suffering from the original SARS virus. They found that SARS-CoV was present in the cytoplasm of type II pneumocytes only during the early stage of the disease. In patient who had symptoms of diarrhea, SARS-CoV staining was also identified in the mucosal epithelium of the colon. They did not find any evidence of viral staining in other organs including kidney, liver, lymph node, and spleen. The skeletal muscle specimens of 2 patients who had rhabdomyolysis were also negative for SARS-CoV.

Several studies have reported myocardial injury from the ongoing novel SARS-CoV-2 coronavirus illness. Current data indicate potential mechanisms of cardiac injury include direct viral entry through the angiotensin-converting enzyme 2 receptor and toxicity in host cells, hypoxia-related myocyte injury, and immune-mediated cytokine release syndrome.<sup>13</sup>

Jin and colleagues<sup>14</sup> described a case of rhabdomyolysis as a late complication in 1 patient with COVID-19 in Wuhan, China.<sup>14</sup> To our knowledge this is the first case series of rhabdomyolysis with both early and late presentations in COVID-19 patients. All our patients had varied clinical course and outcomes. Clearly, the mechanism of skeletal muscle injury from SARS-CoV-2 infection needs further investigation.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Informed Consent

Verbal informed consent was obtained from the surviving patients for their anonymized information to be published in this article.

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