Open Access
Publish Free

http://jept.ir
doi 10.34172/jept.2022.24

Journal of Emergency Practice and Trauma
Volume 9, Issue 1, 2023, p. 66-71

Case Report

The importance of considering rhabdomyolysis as the underlying cause of myalgia in patients with COVID-19: A case report

Zahra Rezaie[1], Shima Heidari[1], Ahmad Salimzadeh[2], Fatemeh Sadat Pirooz[3], Farhad Najmeddin[1*]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Rheumatology Research Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Internal Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: August 3, 2022
Accepted: November 27, 2022
Published online: December 9, 2022

***Corresponding author:**
Farhad Najmeddin,
Email: f-najmeddin@sina.tums.ac.ir

Citation: Rezaie Z, Heidari S, Salimzadeh A, Pirooz FS, Najmeddin F. The importance of considering rhabdomyolysis as the underlying cause of myalgia in patients with Covid-19: a case report. Journal of Emergency Practice and Trauma 2023; 9(1): 66-71. doi: 10.34172/jept. 2022.24.

Abstract

Objective: Since the identification and spread of the novel coronavirus disease 2019 (COVID-19) in December 2019, respiratory presentations have been introduced as the main symptoms of this new type of viral disease; however, the extra-pulmonary features are raising awareness for researchers due to the vast diversity of vital organs affected by the virus. Among the wide range of clinical manifestations, limited data are available regarding rhabdomyolysis (RML) in COVID-19.

Case Presentation: In this report, we present a 58-year-old woman with COVID-19 presenting with RML, with extremely elevated creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels (3283 and 1280 U/L, respectively) as the second sign of disease. Since the onset of the COVID-19 pandemic, several COVID-19 induced RML cases have been reported, and timely diagnosis and proper management are of paramount importance.

Conclusion: Due to the findings that rhabdomyolysis can be a critical and missed cause of myalgia in COVID-19 patients, the importance of checking the serum level of CPK in patients with myalgia and fatigue in the era of COVID-19 upon their arrival will be highlighted.

Keywords: COVID-19, SARS-CoV-2, Muscle injury, Rhabdomyolysis, Acute renal failure

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a global pandemic (1).

While COVID-19, a member of the Coronaviridae family, was initially considered a respiratory disease with fever, cough, and dyspnea as the most prevalent manifestations (2), extra-pulmonary presentations, both organ-specific (e.g., cardiac, gastrointestinal, hepatic, renal, ocular, dermatologic, and rarely severe rhabdomyolysis) or non-organ-specific (e.g., myalgia, fatigue) rapidly presented to clinics worldwide as the virus increasingly disseminated and other symptoms were considered to be associated with SARS-CoV-2 (3,4).

Of the various reported organ-specific manifestations of COVID-19, rhabdomyolysis (RML) is important due to its critical outcomes. Despite the rare incidence of RML subsequent to COVID-19 (0.2% according to a study on 1099 patients in China) (5), the number of cases involving RML is increasing among reports (6,7). RML primarily presents with symptoms of myalgia, weakness, and fatigue; however, since COVID-19 shares these general presentations, RML can be missed in COVID-19 patients. (8)

Herein, we report the case of a patient with the confirmed SARS-CoV-2 infection who presented to the clinic with cardinal manifestations progressing to RML during hospitalization.

Case Presentation

A 58-year-old woman with a medical history of uncontrolled hypertension and probable diabetes mellitus was referred to the emergency department (ED) on November 7, 2020, complaining of respiratory problems (i.e., cough, fever and chills, dyspnea, anosmia, and myalgia), which had started six days earlier.

Upon initial evaluation at the ED, the patient had tachycardia at 116 bpm, afebrile, hypertensive (164/64 mm Hg), and had an oxygen saturation of 76% on ambient air and 95% with reserve mask. The patient was found to be conscious, alert, and oriented after a mental status evaluation, cranial nerve examination revealed no abnormalities except hemifacial paresis. The force was 3/5 on both right and left sides. Since the patient had experienced falling and subsequently dysarthria, a brain CT was requested, which indicated no significant abnormality. Her laboratory data on the admission day are presented in Table 1. Laboratory tests, especially electrolytes, were also in a normal range. Furthermore, the liver and renal function test results showed an elevation in aspartate transaminase (AST), alanine aminotransferase (ALT), and creatinine. Considering the state of the pandemic, the patient's clinical features, physical examination, and chest radiography pointed at a possible viral infection, probably COVID-19. Chest CT revealed extensive bilateral ground-glass opacities, indicating viral pneumonia scattered across the two lungs with air bronchograms in the right upper lobe (Figure 1). Consequently, a nasopharyngeal swab was submitted to be tested for SARS-CoV-2 RNA, which came back as positive on November 9, 2020. The patient started receiving treatment for COVID-19. The initial treatment consisted of dexamethasone 8 mg IV, *interferon beta-1a* (ReciGen®) 44 every other day subcutaneous, famotidine 40 mg twice daily orally, atorvastatin 40 mg daily and heparin 5000 U three times per day subcutaneous. The patient underwent oxygen through a reservoir mask as the initial treatment for her acute respiratory distress syndrome (ARDS). Additionally, the patient was prescribed losartan 12.5 mg twice daily and amlodipine 5 mg daily to control her hypertension, and fluid restriction was advised to correct hyponatremia.

Table 1. Laboratory data on the admission date

	Variable	Value	Reference Range
Hematology	White cell count (*10^3/µl)	5.2	4-10
	Neutrophils	76.5	-
	Lymphocytes	19.6	-
	Hemoglobin (g/dl)	11-16	14.5
	Platelet count (*10^3/µl)	165	150-450
	Red cell count (*10^3/µl)	4.55	3.5-5.5
	Mean corpuscular volume (fL)	92.1	80-100
	Mean corpuscular hemoglobin (pg)	31.9	27-31
	Mean corpuscular hemoglobin concentration (g/dl)	34.6	32-36
	Hematocrit (%)	41.9	37-50
Biochemistry	Creatinine (mg/dl)	2.63	0.4-1.1
	Sodium (meq/L)	123.7	135-145
	Potassium (meq/L)	4.2	3.5-5
	Calcium (mg/dl)	8	8.6-10.3
	Phosphor (mg/dl)	3.3	3.9-7.7
	Blood sugar (mg/dl)	246	70-105
	Amylase (U/L)	36	<100
	Urea	77	-
Coagulation	Partial thromboplastin time (sec)	44	30-45
	INR	1.31	<1.3
	Prothrombin time (sec)	17.3	9.5-13.5
Liver	Aspartate aminotransferase (U/L)	157	10-40
	Alanine aminotransferase (U/L)	68	10-40
	Alkaline phosphatase (U/L)	136	180-1200
	Albumin (g/dl)	3.8	3.5-5.2
Inflammatory	ESR (mm/h)	85	0-10
	CRP (mg/l)	154.2	<6
Heart	Troponin I (ng/ml)	32.2	0-0.3
	CK-MB (lu/L)	97	0-24

On the second day of her hospitalization, the patient's potassium and phosphorous levels gradually increased (from normal levels on the admission day to 6.1 mEq/L and 9.8 mg/dL, respectively), while her calcium decreased, and her kidney function deteriorated as well (Figure 2). Considering the patient's electrolyte disturbance, tumor lysis syndrome and RML were taken into account. Due to the absence of common causes of RML (trauma, strenuous exercise, history of seizure or neuromuscular disorders, statin drug class use, alcohol intake, or smoking) her clinical and paraclinical features of RML were attributed to COVID-19. The patient started metoprolol 25 mg BD PO, alongside amiodarone drip and digoxin to manage atrial fibrillation. Heparin dosage was switched to the therapeutic drip of 1000 U/h. Furthermore, since the patient had an acute kidney injury (AKI), fluid therapy was added using balanced crystalloids (serum N/S 500 cc + 50 cc glucose 50%) QID and losartan was discontinued. Famotidine was also switched to pantoprazole 40 mg daily. To correct the patient's hyperkalemia, she was dialyzed via hemodialysis on the second day.

Creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) were requested on day 3, which were recorded 3283 U/L (normal: 195-700 U/L) and 1280 U/L (normal: 5-615 U/L), respectively (Figure 3) and due to a drop in O_2 saturation, endotracheal intubation was performed after the administration of fentanyl.

On the fifth day of hospitalization, suspected sepsis (hypotension, loss of consciousness, and severe lung involvement in chest CT) was found as the cause of empiric broad spectrum antimicrobial therapy with vancomycin as well as meropenem. Despite the efforts of the health care team, serum creatinine and potassium (K) continued to increase and the second session of hemodialysis was done on the fifth day of the patient's hospitalization.

Eventually, the case was expired early in the morning on 13 November, 2020.

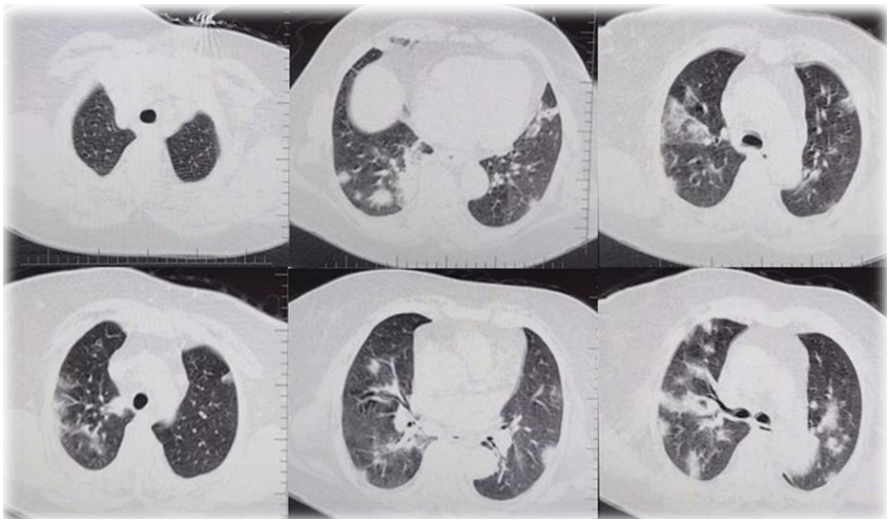

Figure 1. Chest CT imaging presentation in patient: extensive bilateral ground-glass opacities, indicating viral pneumonia scattered across the two lungs with air bronchograms in the right upper lobe

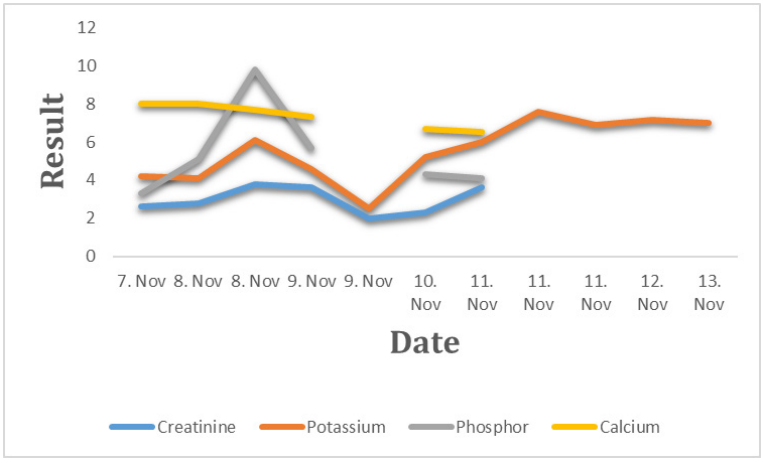

Figure 2. Variation of Creatinine, potassium, phosphor and calcium during hospitalization

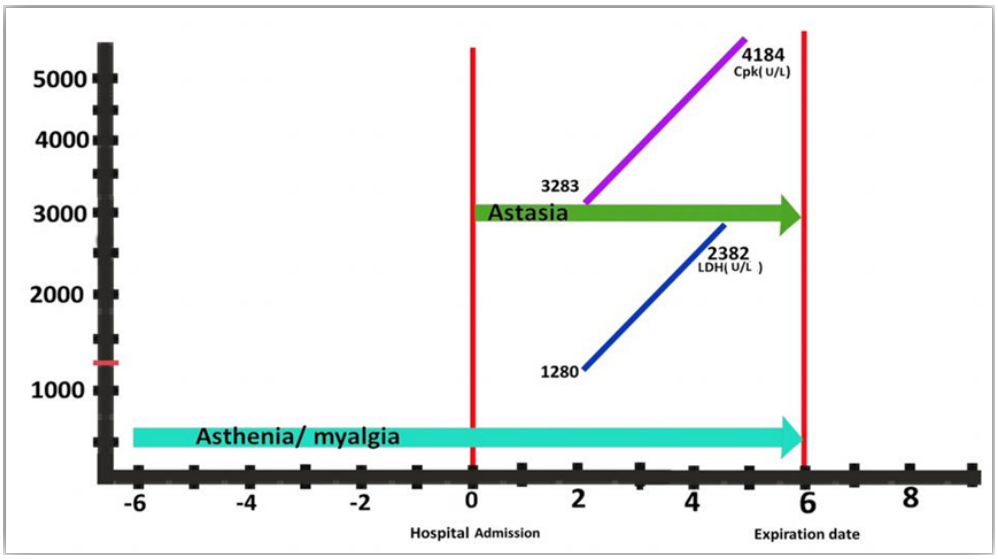

Figure 3. Clinical presentations and CPK/LDH variation during hospitalization

Discussion

RML, which is a complex medical condition due to the disruption of skeletal muscle integrity followed by the release of cell components (myoglobin, CPK, LDH, and potassium) into circulation, mostly ranges from asymptomatic illness with an elevation in the CK level to a life-threatening condition such as extreme electrolyte imbalances, elevations in CPK, AKI, and disseminated intravascular coagulation (9,10).

RML, which is known by triad of myalgia, weakness, and myoglobinuria (manifested by dark urine), may mostly occur as a result of direct traumatic injury (11).

Furthermore, hereditary enzyme disorders, drugs and toxins, many pathological situations such as endocrinopathies (diabetic ketoacidosis and non-ketotic hyperosmolar coma, and severe hyper- or hypothyroidism), temperature-induced states (neuroleptic malignant syndrome, malignant hyperthermia, hypothermia and heatstroke), electrolyte alterations, exertion or prolonged bed rest, and bacterial or viral infections can all be regarded as subsequent culprits of RML (7).

In the explanation of viral-induced RML mechanisms, three different theories have been considered as follows:

1. Direct invasion of myocytes
2. Immune cross-reactivity between myocytes and viral antigens, leading to "cytokine storm" and the occurrence of RML
3. Cytotoxic T-cell-mediated attack.

However, there still are many uncertainties regarding the mechanism of SARS-CoV-2 virus (12)

To the best of our knowledge, based on a search in google scholar and PubMed up to October 2020, 33 cases of RML following COVID-19 infection have been reported in 24 articles, which are shown in Table 2.

Suwanwongse and Shabarek (6) reported the first case of RML in an 88-year-old man who was later diagnosed with COVID-19 in April 2020.

Later in May and June 2020, seven cases of COVID-19-induced RML were reported. All patients had elevated CPK and LDH. Renal condition of all patients normalized after receiving aggressive isotonic intravenous fluid and all patients were subsequently discharged.

Buckholz et al, in July 2020, reported a case series of six patients including five males and one female with a mean age of 58 years. All patients had urinalysis consistent with RML; four developed acute renal injury, and two required dialysis (19). Jin and Tong (20) described a case of RML in a 60-year-old man who did not develop AKI and was improved with hydration and supportive care. Six other patients reported in July were candidates for aggressive fluid therapy due to high CPK and LDH and diagnosis of RML based on the clinical presentation and laboratory results. Three of these patients required hemodialysis (21,22,24).

Shanbhag et al presented a 19-year-old African-American male with severe RML with normal renal function and CPK > 500 000 U/L (26). Case reports of Murillo et al (25), Alrubaye and Choudhury (8), and Meegada et al (27) were also published in August, describing patients with severe RML due to COVID-19.

Similarly, several other cases of RML in COVID-19 patients were reported in the following months.

Although self-limiting myalgia occurs in acute viral prodromes, the persistent muscle weakness raises concern for underlying RML.

A serum creatine kinase five times more than the normal value is a classic laboratory finding for RML. Meanwhile, because of its short half-life, plasma myoglobin is not as sensitive as creatine kinase. Moreover, myoglobin can be detected in urine when the urine dipstick test is positive for blood, but there are no red blood cells in the sediment. The elevated AST and ALT levels are known as the other paraclinical abnormalities, which can also be resulted

Table 2. Case reports of rhabdomyolysis secondary to COVID-19

Author/Publication Date	Age/Gender	Reference
Suwanwongse and Shabarek, April 2020	88/M	(6)
Gefen et al, May 2020	16/M	(13)
Zhang et al, May 2020	38/M	(14)
Chan et al, May 2020	75/F 71/M	(15)
Valente-Acosta et al, June 2020	71/M	(16)
Rivas-García et al, June 2020	78/M	(17)
Borku Uysal et al, June 2020	60/M	(18)
Buckholz et al, July 2020	43/M 37/M 75/M 59/M 66/M 70/F	(19)
Jin and Tong, July 2020	60/M	(20)
Chedid et al, July 2020	51/M	(21)
Mukherjee et al, July 2020	49/M	(12)
Chong and Saha, July 2020	37/M	(22)
Samies et al, July 2020	16/M	(23)
Solís et al, July 2020	46/M	(24)
Murillo et al, August 2020	48/M	(25)
Alrubaye and Choudhury, August 2020	35/F	(8)
Shanbhag et al, August 2020	19/M	(26)
Meegada et al, August 2020	19/M	(27)
Husain et al, September 2020	38/M	(28)
Taxbro et al, September 2020	38/M	(29)
Singh et al, September 2020	67/M 39/M 43/M 70/M	(7)
Cunha et al, September 2020	46/F	(30)
Foster et al, October 2020	40/M	(31)
Anklesaria et al, October 2020	57/M	(32)

from COVID19 (8).

In the case reported in the present study, the diagnosis of RML was made based on elevated CPK, the clinical symptoms (myalgia and fatigue) and electrolyte imbalance (hyperkalemia, hyperphosphatemia, and hypocalcemia) followed by the increased creatinine as well as the occurrence of AKI.

In general, in RML, aggressive fluid management is recommended to enhance renal perfusion, in order to prevent vasoconstriction and kidney damage caused by myoglobin. On the other hand, conservative fluid therapy should also be considered to prevent the worsening of the ARDS in critically ill patients.

In our case, due to oliguria and limitations in fluid therapy, this was not performed aggressively.

The present study also had some limitations, which are discussed below. The first one was lack of data on basal CPK and histopathological findings. Additionally, documents for ruling out other etiologies of RML like various viral infections were not available.

Conclusion

Based on our results, RML can be known as the early presentation of COVID-19. Although further studies are needed to investigate the prevalence of RML in COVID-19, the understatement is possible due to misdiagnosis.

In case of a pandemic, clinicians should consider RML as a differential for myalgia and fatigue in patients with COVID-19to prevent the occurrence of a life-threatening condition like AKI by early diagnosis and management of this crisis (Aggressive intravenous hydration to ensure urine output of 200-300 mL/h to correct dyselectrolytemia and to monitor laboratory markers).

The main finding of this study was checking serum level of CPK upon arrival in patients with COVID-19 who present symptoms of myalgia and fatigue.

Further studies are also recommended to investigate the effect of the elevated muscle enzymes in the presence or absence of clinical symptoms on determining the prognosis of patients with COVID-19.

Authors' Contribution

Conceptualization: Farhad Najmeddin.
Data curation: Zahra Rezaie, Shima Heidari, Fatemeh Sadat Pirooz.
Investigation: Zahra Rezaie, Shima Heidari, Fatemeh Sadat Pirooz.
Methodology: Zahra Rezaie, Shima Heidari.
Project administration: Zahra Rezaie, Shima Heidari.
Supervision: Farhad Najmeddin, Ahmad Salimzadeh.
Validation: Farhad Najmeddin, Ahmad Salimzadeh.
Writing – original draft: Zahra Rezaie, Shima Heidari.
Writing – review & editing: Farhad Najmeddin, Ahmad Salimzadeh.

Competing Interests

None.

Ethical Approval

Informed consent was obtained from the patient companion for the publication of this report.

Funding

None.

References

1. WHO. The COVID-19 Pandemic. WHO; 2020. Available from: https://www.who.int/europe/emergencies/situations/covid-19
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623. doi: 10.1016/j.tmaid.2020.101623.
3. Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. Clin Imaging. 2020;66:35-41. doi: 10.1016/j.clinimag.2020.05.013.
4. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. Front Med (Lausanne). 2020;7:526. doi: 10.3389/fmed.2020.00526.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
6. Suwanwongse K, Shabarek N. Rhabdomyolysis as a presentation of 2019 novel coronavirus disease. Cureus. 2020;12(4):e7561. doi: 10.7759/cureus.7561.
7. Singh B, Kaur P, Mechineni A, Maroules M. Rhabdomyolysis in COVID-19: report of four cases. Cureus. 2020;12(9):e10686. doi: 10.7759/cureus.10686.
8. Alrubaye R, Choudhury H. Severe rhabdomyolysis in a 35-year-old woman with COVID-19 due to SARS-CoV-2 infection: a case report. Am J Case Rep. 2020;21:e926733. doi: 10.12659/ajcr.926733.
9. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020;267(4):877-82. doi: 10.1007/s00415-019-09185-4.
10. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis--an overview for clinicians. Crit Care. 2005;9(2):158-69. doi: 10.1186/cc2978.
11. Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J. 2015;15(1):58-69.
12. Mukherjee A, Ghosh R, Aftab G. Rhabdomyolysis in a patient with coronavirus disease 2019. Cureus. 2020;12(7):e8956. doi: 10.7759/cureus.8956.
13. Gefen AM, Palumbo N, Nathan SK, Singer PS, Castellanos-Reyes LJ, Sethna CB. Pediatric COVID-19-associated rhabdomyolysis: a case report. Pediatr Nephrol. 2020;35(8):1517-20. doi: 10.1007/s00467-020-04617-0.
14. Zhang Q, Shan KS, Minalyan A, O'Sullivan C, Nace T. A rare presentation of coronavirus disease 2019 (COVID-19) induced viral myositis with subsequent rhabdomyolysis. Cureus. 2020;12(5):e8074. doi: 10.7759/cureus.8074.
15. Chan KH, Farouji I, Abu Hanoud A, Slim J. Weakness and elevated creatinine kinase as the initial presentation of coronavirus disease 2019 (COVID-19). Am J Emerg Med. 2020;38(7):1548.e1-1548.e3. doi: 10.1016/j.ajem.2020.05.015.
16. Valente-Acosta B, Moreno-Sanchez F, Fueyo-Rodriguez O, Palomar-Lever A. Rhabdomyolysis as an initial presentation in a patient diagnosed with COVID-19. BMJ Case Rep. 2020;13(6):e236719. doi: 10.1136/bcr-2020-236719.
17. Rivas-García S, Bernal J, Bachiller-Corral J. Rhabdomyolysis as the main manifestation of coronavirus disease 2019.

Rheumatology (Oxford). 2020;59(8):2174-6. doi: 10.1093/rheumatology/keaa351.
18. Borku Uysal B, Ikitimur H, Yavuzer S, Islamoglu MS, Cengiz M. Case report: a COVID-19 patient presenting with mild rhabdomyolysis. Am J Trop Med Hyg. 2020;103(2):847-50. doi: 10.4269/ajtmh.20-0583.
19. Buckholz AP, Kaplan A, Rosenblatt RE, Wan D. Clinical characteristics, diagnosis, and outcomes of 6 patients with COVID-19 infection and rhabdomyolysis. Mayo Clin Proc. 2020;95(11):2557-9. doi: 10.1016/j.mayocp.2020.09.005.
20. Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. Emerg Infect Dis. 2020;26(7):1618-20. doi: 10.3201/eid2607.200445.
21. Chedid NR, Udit S, Solhjou Z, Patanwala MY, Sheridan AM, Barkoudah E. COVID-19 and rhabdomyolysis. J Gen Intern Med. 2020;35(10):3087-90. doi: 10.1007/s11606-020-06039-y.
22. Chong WH, Saha B. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with rhabdomyolysis and acute kidney injury (AKI). Am J Med Sci. 2020;360(6):738-9. doi: 10.1016/j.amjms.2020.07.032.
23. Samies NL, Pinninti S, James SH. Rhabdomyolysis and acute renal failure in an adolescent with coronavirus disease 2019. J Pediatric Infect Dis Soc. 2020;9(4):507-9. doi: 10.1093/jpids/piaa083.
24. Solís JG, Esquivel Pineda A, Alberti Minutti P, Albarrán Sánchez A. Case report: rhabdomyolysis in a patient with COVID-19: a proposed diagnostic-therapeutic algorithm. Am J Trop Med Hyg 2020;103(3):1158-61. doi: 10.4269/ajtmh.20-0692.
25. Murillo F, Ramos G, Del Pozo JL, Valdez LM, Zagaceta J. SARS-CoV-2 infection with associated rhabdomyolysis and probable myocarditis. Eur J Case Rep Intern Med. 2020;7(9):001867. doi: 10.12890/2020_001867.
26. Shanbhag A, Manaktala PS, Rizvi H, Frey K, Narayanan R. COVID-19 presenting as severe rhabdomyolysis with normal renal function. Cureus. 2020;12(8):e9556. doi: 10.7759/cureus.9556.
27. Meegada S, Muppidi V, Wilkinson DC 3rd, Siddamreddy S, Katta SK. Coronavirus disease 2019-induced rhabdomyolysis. Cureus 2020;12(8):e10123. doi: 10.7759/cureus.10123.
28. Husain R, Corcuera-Solano I, Dayan E, Jacobi AH, Huang M. Rhabdomyolysis as a manifestation of a severe case of COVID-19: a case report. Radiol Case Rep. 2020;15(9):1633-7. doi: 10.1016/j.radcr.2020.07.003.
29. Taxbro K, Kahlow H, Wulcan H, Fornarve A. Rhabdomyolysis and acute kidney injury in severe COVID-19 infection. BMJ Case Rep. 2020;13(9):e237616. doi: 10.1136/bcr-2020-237616.
30. Cunha M, Pinho I, Lopes M, Trigueiros F, Braz S, Medeiros F. A case of corticosteroid-responsive SARS-CoV-2 related massive rhabdomyolysis. IDCases. 2020;22:e00946. doi: 10.1016/j.idcr.2020.e00946.
31. Foster A, Khan Z, Siddiqui A, Singh S, Atere M, Nfonoyim JM. It's complicated: a case report on a COVID-19-positive HIV patient presenting with rhabdomyolysis and acute kidney injury. SAGE Open Med Case Rep. 2020;8:2050313x20965423. doi: 10.1177/2050313x20965423.
32. Anklesaria Z, Frankman J, Gordin J, Zhan J, Liu AK. Fatal rhabdomyolysis in a COVID-19 patient on rosuvastatin. Cureus. 2020;12(10):e11186. doi: 10.7759/cureus.11186.