Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 associated rhabdomyolysis leading to major amputation in the absence of macrovascular thrombosis

Rahul Kar, Allen G. Murga, Theodore H. Teruya, Sheela T. Patel*
Loma Linda University, Division of Vascular Surgery, United States

A R T I C L E   I N F O

Keywords:
Rhabdomyolysis
Coronavirus
Coronavirus disease 2019
Creatine kinase
Acute renal injury
Amputation

A B S T R A C T

A 50 year old patient presented with bilateral lower extremity weakness, lethargy, and dyspnea. Nasopharyngeal swab was positive for SARS-CoV-2. She progressed to acute hypoxemic respiratory failure and hemodynamic instability requiring intubation, pressor support, and hemodialysis. Maculopapular rashes developed on bilateral lower extremities with progressively worsening rhabdomyolysis. Bilateral lower extremity fascirotomies were performed with subsequent serial operative debridements to remove necrotic muscle. One month later, she required a right above knee amputation. There was no evidence of macrovascular thrombosis. A high clinical suspicion of rhabdomyolysis in COVID-19 patients is necessary to avoid major limb loss.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in Wuhan, China in December 2019. It has spread rapidly worldwide and was declared a pandemic in March 2020. COVID-19 patients most commonly present with fever, fatigue, myalgias, dyspnea, sore throat, dry cough, headache, anosmia, and ageusia. Rhabdomyolysis has been described as an initial presentation of COVID-19.1,2 Because of overlapping symptoms of generalized weakness, myalgias, and fatigue, the diagnosis of rhabdomyolysis in COVID-19 may be elusive and a high index of suspicion is necessary. The classic clinical triad of rhabdomyolysis is myalgia, muscle weakness, and brown-reddish urine and is present in less than 10% of cases. The hallmark of acute rhabdomyolysis is elevated creatinine kinase (CK) levels five to ten times normal (typically greater than 1000 U/L). Rhabdomyolysis is characterized by rapid destruction of muscle fibers and release of toxic intracellular muscle constituents (potassium, phosphates, CK, lactate dehydrogenase (LDH), aspartate transaminase (AST), myoglobin) into the systemic circulation. When myoglobin release into the bloodstream exceeds the protein-binding capacity, the excess pigment precipitates in the renal tubules leading to renal injury. The management of rhabdomyolysis is primarily supportive with prompt removal of causative factors, volume expansion, diuretics, urine alkalinization, and hemodialysis. Aggressive fluid resuscitation in a COVID-19 patient must be performed judiciously in order to avoid respiratory decompensation, particularly in patients with acute respiratory distress syndrome and heart failure. Skeletal muscle injury drives the process of rhabdomyolysis but the predominant morbidity is related to renal failure and limb loss is uncommon.

The pathogenesis of COVID-19 associated rhabdomyolysis has not been elucidated. Causes of rhabdomyolysis typically include: direct trauma (crush injury, burns, electrical injury, snake bites), exertion (marathon runners, weight lifters), ischemia or hypoxia (thrombus, embolus), dysregulated temperature states (malignant hyperthermia, heat stroke, extreme hypothermia, frostbite, neuroleptic malignant syndrome), drugs (statins, fibrates, alcohol, cocaine, amphetamines, lithium, antipsychotics, antidepressants, propofol, intravenous and intramuscular illicit drug use), inflammatory myopathies (polymyositis, dermatomyositis), seizures, sickle cell disease, electrolyte abnormalities (hypokalemia, hypophosphatemia, hyperosmolar conditions, hypo- and hypercalcemia, severe dehydration), endocrine disorders (severe diabetic acidosis with coma, myxedema), myopathies (metabolic disorders), autoimmune myositis (polymyositis, dermatomyositis). Infection with influenza A and B, parainfluenza, cytomegalovirus, adenovirus, coxsackievirus, enterovirus, respiratory syncytial virus, Epstein-Barr virus, human immunodeficiency virus, herpes simplex virus, hepatitis B and C have been known to cause rhabdomyolysis. Influenza virus is the most common cause of viral-induced rhabdomyolysis, accounting for approximately 33% of known cases.3 The first incidence of coronavirus-related rhabdomyolysis was reported in a case series of three SARS-CoV patients where they all developed acute kidney injury with peak CK levels ranging from 7000 to 330,000 IU/L.4 Prolonged immobility, medically induced paralysis, and prone positioning have been noted to trigger rhabdomyolysis in COVID-19 patients admitted with respiratory decompensation, subsumed under the term critical illness myopathy.5 Major limb loss with COVID-19 associated rhabdomyoly-
sis is rare and has only occurred in the setting of thrombotic acute arterial ischemia. The incidence of thrombotic disease in patients with COVID-19 has been reported as high as 31%. There are several reports of COVID-19 associated acute limb ischemia secondary to thromboembolic events presenting in patients without atherosclerotic risk factors resulting in high mortality and amputation.

We describe a patient with COVID-19 who presented with rhabdomyolysis and a CPK level of > 400,000 U/L who required a major lower extremity amputation in the absence of macrovascular thrombosis.

Case presentation

The patient is a 50 year old female who had been in her usual state of health when she presented with a two day history of generalized fatigue, nausea, vomiting, poor appetite, worsening dyspnea with exertion, and bilateral lower extremity tightness and cramping. On the morning of her admission, the patient developed such profound lower extremity weakness that she was unable to stand and was observed to be crawling on the floor. The next day, as she was dry heaving over the toilet, she lost consciousness for a few minutes. She did not have a recent history of strenuous exertional activity, injury, trauma, new medications, or temperature extremes. There was no recent travel history. Her husband had nasal congestion but had recently tested negative for SARS-CoV-2. She had not been vaccinated against COVID-19. The patient had never contracted COVID-19 prior to this admission. Her history was only significant for hypothyroidism. She had been compliant with levothyroxine, which was her only home medication. She did not smoke, drink alcohol, or use illicit substances or over-the-counter supplements. There was no known personal or family history of metabolic syndromes, autoimmune diseases, myopathies, neuromuscular disorders, seizures, or connective tissue disease.

Her initial vital signs in the emergency department included a temperature of 95 degrees F, blood pressure 126/73, heart rate 130 beats per minute, respiratory rate 26 breaths per minute, and oxygen saturation 92% on room air. Her weight was 60 kg with a body mass index (BMI) of 19 kg/m². Physical exam revealed a thin diaphoretic patient who was in obvious discomfort, complaining of diffuse generalized myalgias and weakness, predominantly in the legs. She was oriented and coherent but her speech was slow and pausing. There were coarse and diminished breath sounds. Cardiac and abdominal exams were normal. She had diffuse bilateral lower extremity muscle tenderness. There was no stigmata of traumatic injury with normal skin color and turgor. Her muscle compartments were soft. She was able to lift the lower extremities against gravity and she had palpable bilateral pedal pulses and no edema. Pertinent laboratory findings include positive COVID-19 reverse transcriptase-polymerase chain reaction test from a nasopharyngeal swab, white blood cell count 12 bil/L (normal 4.8-11.8 bil/L), hemoglobin of 19.6 g/dL (normal 10.5-15.0), platelet count 59 bil/L (normal 130-460 bil/L), D-dimer 600 ng/ml (normal 0-400 ng/ml), C-reactive protein 1.1 (0.0-0.8 mg/dL), creatinine 1.3 milligrams per deciliter (normal 0.7-1.3 mg/dL) and CK 1,518 U/L (normal 41-245 U/L). Thyroid stimulating hormone was elevated at 29.6 µU/mL (normal 0.7-3.8 µU/mL). Computed tomography of the chest indicated bilateral peripheral patchy ground-glass opacifications predominantly on the left side (Fig. 1).

She was started on intravenous fluid resuscitation, intravenous levophytoxine, empiric antibiotics, and hydrocortisone. She was not started on our institutional protocol of prophylactic-dose anticoagulation (enoxaparin 40 mg subcutaneously daily for hospitalized COVID-19 patients) because of her thrombocytopenia. Over the next 24 hours, her condition deteriorated with worsening lethargy and increasing oxygen requirements. Straight catheter retrieved scant dark urine. Urinalysis was positive for blood and no red blood cells were seen microscopically. Urine toxicology screen was negative. She underwent endotracheal intubation for hypoxia. She required pressor support and was started on hemodialysis. Echocardiogram indicated a normal ejection fraction. She was weaned off pressors and subsequently extubated 4 days after admission. Her fluid balance was positive four liters since admission. She complained of severe bilateral lower extremity pain. Vascular surgery consultation was requested at this time for possible compartment syndrome. On physical examination, large maculopapular rashes were noted along the right lateral, right medial, and left medial aspects of the lower leg with overlying skin blistering (Fig. 2). These areas were exquisitely tender with pain elicited upon passive stretching of the muscles. The muscle compartments were noted to be soft and thus compartment pressures were not measured. She had decreased motor function with inability to elevate the lower extremities and diminished movements of the ankles and toes. There was mild bilateral ankle edema. The feet were warm without skin changes. Bilateral pedal pulses were weakly palpable. Arterial duplex indicated triphasic pedal waveforms with no evidence of thrombus in the macrocirculation. The CK had increased to 447,800 U/L (normal 41-245 U/L). Serum and urine myoglobin were not tested. Aminotransferases were elevated [ALT 1,465 U/L (normal 7-37 U/L), AST 6,053 (normal 0-30 U/L)]. Her inflammatory markers were high: LDH 3,760 U/L (normal 120-260 U/L), ferritin 14,770 ng/ml (normal 12-300 ng/ml), C-reactive protein 7.4 (normal 0.0-0.8 mg/dL), D-dimer 7400 ng/ml (normal 0-400 ng/ml), procalcitonin 2.62 µg/l (normal 0.0-0.15 µg/l). WBC count was 38.6 bil/l (normal 4.8-11.8 bil/L). Her coagulation parameters were deranged with platelet count 13 bil/L (normal 130-460 bil/L), INR 3.8 (normal 0.8-1.1), and PT/PTT 60.4 seconds (normal 25.1-36.5 seconds).

Based on the significant tenderness in the calves, evolving maculopapular rash with blistering, and rising creatinine kinase levels, we performed bilateral two-incision four-compartment lower extremity fasciotomies to rule out muscle necrosis. There was no significant muscle bulging nor hematoma. There was dusky brown muscle in all compartments which had no response to electrocautery, most notably on the right lateral and bilateral medial aspects (Fig. 2). Over the next several days following the fasciotomies, CK levels plummeted to near normal values. She continued to have palpable pedal pulses. Her platelet counts normalized and she was started on a prophylactic anticoagulation regimen per our institutional protocol. She underwent serial operative debridements of both lower extremities with removal of substantial portions of nonviable muscle (Fig. 3). Muscle cultures were negative for bacteria or fungi. Muscle tissue samples did not show any evidence of direct COVID-19 viral invasion or presence of microthrombi on pathological examination. Because of persistent motor dysfunction, electromyography was conducted and no axonal injury was found. Further investigation indicated no immunologic causes with unremarkable anti-nuclear antibody (ANA), anti-Jo-1, anti-SSA/SSB, anti-RNP, anti-dsDNA, anti-SSc-70, anti-Smith, antineutrophil cytoplasmic antibody, and antineutrophil cytoplasmic antibodies. Active viral infections associated with rhabdomyolysis including influenza A and B, coxsackievirus, respiratory syncy-
Fig. 2. Maculopapular rashes with blistering observed on the right lateral, right medial, and left medial aspects of the lower extremities (a,b,c). Dusky dark muscle compartments following fasciotomies (d, e, f).

Fig. 3. Necrotic muscle following serial debridements (a). Healed right above knee amputation and granulating left lower extremity wounds (b).

tial virus, Epstein-Barr virus, herpes simplex, parainfluenza, adenovirus, echovirus, human immunodeficiency virus, and cytomegalovirus were negative. Hepatitis viral panel was negative. Thrombophilia work-up (lupus anticoagulant, factor V Leiden mutation, prothrombin mutation, anticardiolipin antibodies, protein C, protein S, antithrombin III) was negative. Peripheral smear was unremarkable.

One month after admission, she underwent right above knee amputation because of the paucity of viable muscle. At the time of this writing, the patient is 3 months from her initial admission and able to participate in a physical therapy program. Her renal function has normalized and she is off hemodialysis. The right above knee amputation has healed. The left lower extremity fasciotomy sites are nearly closed with healthy granulation tissue (Fig. 3). The patient gave consent for the publication of the details of her case.

Discussion

Coronavirus disease 2019 has rapidly enveloped the world in a pandemic after emerging in Wuhan, China in December 2019. Although respiratory symptoms predominate, multiple systems are affected including cardiovascular, hematologic, renal, neural, and musculoskeletal. SARS-CoV-2 binds with the widely expressed angiotensin converting enzyme (ACE) 2 receptor complex via spike glycoproteins on its cell membrane to gain entry into human cells. The SARS-CoV-2 virus causes overac-
tivation of the immune system with cytokine release and elevation of inflammatory markers (white blood cell count, D-dimer, ferritin, lactate dehydrogenase, C-reactive protein). This results in diffuse endothelial inflammation with microvascular damage and an intensely prothrombotic state. The endotheliitis leads to an increased risk of arterial and venous thrombotic complications, including myocardial infarction, deep vein thrombosis, pulmonary embolus, arterial ischemic strokes, and acute limb ischemia.12,15 Active COVID-19 infection can manifest antithrophophilid antibodies which may contribute to hypercoagulability and thrombotic microangiopathy.16 It has been proposed that any patient who presents with thrombotic events during the pandemic should undergo COVID-19 testing. Anticoagulation treatment should be considered for all hospitalized patients with COVID-19 infection.17,18 The optimal anticoagulation management for these patients has been subject to debate. The largest randomized controlled trial of 1,098 hospitalized ICU patients with COVID-19 is a multiplatform adaptive-design trial (MPT) incorporating three studies (ATTACC, ACTIV-4a, REMAP-CAP) to evaluate therapeutic dose anticoagulation versus prophylactic dose anticoagulation. The authors report that in critically ill patients, therapeutic dose anticoagulation with heparin or low-molecular weight heparin did not lead to improved survival to hospital discharge nor did it reduce the days required organ support.19 Other randomized trials have also corroborated the lack of benefit of therapeutic anticoagulation over prophylactic anticoagulation in hospitalized patients with COVID-19.20,21 Since elevated D-dimer has been found to correlate with disease severity and prognosis, D-dimer has been used to guide anticoagulation strategy in COVID-19 patients. The ACTION trial randomized 615 hospitalized patients with COVID-19 with elevated D-dimer and compared therapeutic for 30 days to standard prophylactic anticoagulation. Treatment with therapeutic anticoagulation did not improve mortality, duration of hospitalization, or duration of oxygen use.22 Unfortunately, thrombosis rates are found to be high despite prophylactic or therapeutic anticoagulation.23 Most current guidelines recommend that critically ill patients with COVID-19 receive standard prophylactic doses of anticoagulation. Therapeutic anticoagulation is generally recommended only for diagnosed macrothrombi. Our institutional protocol for COVID anticoagulation includes enoxaparin 40 mg subcutaneous daily for all hospitalized COVID-19 patients. Contraindications to anticoagulation include active bleeding, platelet count < 60 bil/L, or INR > 1.8. An individualized approach to therapeutic dosing for high-risk COVID-19 patients is taken at our institution. We currently do not have a D-dimer threshold to guide anticoagulant dosage or escalation.

Our case was unique in that a relatively healthy patient presented with early rhabdomyolysis (admission CK > 1000) and decompensated rapidly to hypoxic respiratory failure requiring endotracheal intubation and the need for hemodialysis. The patient was resuscitated judiciously (positive 4 liters over 4 days) with concomitant hemodialysis. There was no excess fluid sequestration suggestive of capillary leak syndrome within the lower extremities which led to muscle compression or stran-
13. Wichmann D, Serhake J, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med.* 2020;173:268-277. doi:10.7326/M20-2003.

14. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi F, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020;191:9-14. doi:10.1016/j.thromres.2020.04.024.

15. Vulliamy P, Jacob S, Davenport RA. Acute aorto-iliac and mesenteric arterial thromboses as presenting features of COVID-19. *Br J Haematol.* 2020;189:1053–1054. doi:10.1111/bjh.17670.

16. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al. Lupus anticoagulant and abnormal coagulation tests in patients with COVID-19. *N Engl J Med.* 2020;383:288-290. doi:10.1056/NEJMoa2016566.

17. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18:1094–1099. doi:10.1111/jth.14817.

18. Bikdelli B, Madhavan MV, Jimenez D, Buchi T, Dreyfus I, Dröggèt E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:2950–2973. doi:10.1016/j.jacc.2020.04.031.

19. Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med.* 2021;385:777–789. doi:10.1056/NEJMoa2103417.

20. Sadeghipour P, Talanaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi T, Farrokhpoor M, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA.* 2021;325:1620–1630. doi:10.1001/jama.2021.4152.

21. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, NiAinle F, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomized clinical trial. *BMJ.* 2021;375:n2400. doi:10.1136/bmj.n2400.

22. Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomized controlled trial. *Lancet.* 2021;397:2253–2263. doi:10.1016/S0140-6736(21)01203-4.

23. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46:1089–1098. doi:10.1007/s00134-020-06062-x.

24. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini I, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neuropathol.* 2020;1621:491–1494. doi:10.1007/s00701-020-04374-x.

25. Kanitakis J, Lesort C, Danset M, Jullien D. Chilblain-like acral lesions during the COVID-19 pandemic (“COVID toes”): histologic, immunofluorescence, and immunohistochemical study of 17 cases. *J Am Acad Dermatol.* 2020;83870–875. doi:10.1016/j.jaad.2020.05.145.