Clinical, electromyographical, histopathological characteristics of COVID-19 related rhabdomyolysis

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Abstract
Rhabdomyolysis is an uncommon complication of the coronavirus disease 2019 (COVID-19) infection. Previous reports have described its management and treatment in medical units, but have not discussed confirmatory tests or differential diagnosis. We report a case of a 58 year-old male patient, who was admitted for COVID-19 pneumonia and subsequently developed severe weakness, inability to move limbs, acute renal failure, significantly elevated myoglobin and creatinine kinase, and was diagnosed with rhabdomyolysis. Continuous renal replacement therapy, the treatment modality of choice over hyperhydration due to ongoing mechanical ventilation, was effective in resolving symptoms. No direct viral invasion of muscles was noted on biopsy. Here, we describe his symptoms, electromyography, and muscular biopsy results, and further discuss the possible differential diagnoses. Neuromuscular symptoms related to COVID-19 require careful clinical analysis. In addition, detailed reports of patients’ course of illness and diagnoses will assist in improving care for affected patients.

Keywords
Acute kidney injury, electromyography, biopsy, Guillain-Barré syndrome, critical illness, central nervous system, muscle weakness, intensive care units

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Introduction
The coronavirus disease 2019 (COVID-19) is caused by an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first diagnosed in late 2019; however, its clinical features are still being unveiled.

The general renal complications and their management in COVID-19 have recently been reviewed. The first case of rhabdomyolysis associated with COVID-19 was reported in March 2020.

SARS-CoV-2 attacks target cells of the body using angiotensin converting enzyme 2 (ACE2) receptors including striated and cardiac muscle cells. Until recently, SARS-CoV-2 has primarily been investigated for its effects on cardiomyocytes, even though myalgia and profound asthenia are two of the most frequent symptoms among infected patients. The virus’s affinity for striated muscles, and aggressive empirical treatment with toxic drugs, might explain the occurrence of rhabdomyolysis as an infrequent, severe complication of COVID-19. It may also present at the onset or course of the infection.

We reviewed 16 case reports of rhabdomyolysis in COVID-19 patients from existing literature. They primarily included pediatric and adult patients with only a single case series reported. Furthermore, previous reports have only described medical environments and treatment details, which included forced hyperhydration, alkalinization, and diuretics, but not second-line tests or plausible differential diagnoses.

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We describe a successfully treated clinical case, along with its electromyography (EMG), microscopic features, differential diagnoses, and etiologic analysis. These are important aspects for understanding the pathophysiologic mechanisms of organ damage underlying COVID-19.

Ethical approval was not required from our Institution as the described procedures fit with to-date best practice. Written informed consent was obtained from the patient for anonymized publication of the report.

Case report

A 58-year-old man with a medical history of hypertension, who was overweight (body mass index [BMI] 28 kg/m²), developed respiratory symptoms and fever on 23 February 2020. After testing positive for SARS-CoV-2 on a nasopharyngeal swab polymerase chain reaction (PCR) test, he was admitted to our hospital on 29 February with severe hypoxia and tachypnea. On presentation, the patient did not have any neurological or muscular symptoms. Continuous positive airway pressure, high flow nasal cannula respiratory support, and 7 days of lopinavir/ritonavir, hydroxychloroquine, and methylprednisolone were initiated based on our hospital protocol. On 2 March, he experienced severe hypoxia and tachypnea, and was put on mechanical ventilation following intensive care unit (ICU) admission. Sedation was reduced on 12 March following percutaneous tracheostomy. On 13 March, a septic episode related to a lower respiratory tract infection was diagnosed based on culture sensitivity, and 5 days of piperacillin-tazobactam was administered for multi-sensitive Enterobacter cloacae.

On 14 March the patient recovered from 2 days of sedation with generalized muscular weakness, including a lack of diaphragnic activity and respiratory trigger, and was placed under pressure support ventilation. We initially suspected critical illness myopathy (CIM); however, during the ongoing COVID-19 emergency, no physiotherapy support was available. Thus, passive mobilization was performed by an ICU nurse. On 16 March, the patient suddenly developed acute kidney injury (AKI) and became oligo-anuric with the following plasmatic levels: creatinine 310.35 µmol/L (normal range -n.r.- 74-107 µmol/L), myglobin 3,322 nmol/L (n.r. 1.3-3.7 nmol/L), and creatine kinase (CK) 3,309 U/L (n.r. 30-150 U/L).

We suspected rhabdomyolysis; however, the hyperhydration strategy recommended by Jin and Tong in a similar case could have been potentially detrimental given the patient was on mechanical ventilation. Thus, continuous veno-venous hemo-diafiltration (CVVHDF) was the strategy of choice. Depending on its availability in the hospital, the patient was maintained on an HF1400 Prismaflex hemofilter with a polyarylethersulfone membrane (Baxter International, Deerfield, Illinois, USA). After 140 hours of CVVHDF, an additional 50 hours of continuous veno-venous hemofiltration (CVVH) was performed to improve the convective performance. The prescribed effluent dose remained over 30 mL/kg/h and a progressive normalization of biomarkers was obtained. After the treatment, the following plasmatic values were detected: creatinine 124.7 µmol/L, urea 22.9 mmol/L, CK 271 U/L, myoglobin 159.4 mmol/L and adequate urine output (more than 1500 mL per day) restarted on date 28 March with continuous infusion of furosemide 120 mL per day.

The antibiotic regimen was changed to 7 days of meropenem on 19 March, following a second septic episode and detection of Enterobacter cloacae—produced extended-spectrum beta-lactamase from bronchoaspiration sample. Nonetheless, absence of muscular recovery persisted, and we continued investigating the underlying cause. On 27 March, an EMG and subsequent muscle biopsy yielded negative results for myopathy with no signs of neuronal damage. The EMG reported: “normal nervous conduction, reduced compound muscle action potential of the motor nerves, likely compatible with the observed clinical myopathy.” The lack of axonal damage and the late onset with respect to the viral infection made Guillain-Barré syndrome unlikely. A biopsy might have been of scientific interest to investigate viral presence in the kidney; however, it was clinically inappropriate given the elevated chances of complications and progressive improvement of renal function. The muscle biopsy showed foci of cytolysis involving striated muscle fibers, isolated CD3-positive T-lymphocytes, and no signs of apoptosis (Figure 1(a)). These results were consistent with rhabdomyolysis. Both real-time reverse transcription PCR and immunohistochemistry techniques on paraffin-embedded tissue for viral myositis (Figure 1(b)), were negative. The patient was discharged to a rehabilitation hospital on 15 May, with spontaneous breathing, slow recovery of distal muscle activity, deglutition, and phonation, and complete recovery of renal function.

Discussion

Here, we describe the differential diagnosis discernment that guided our clinical, diagnostic and therapeutic choices. Rhabdomyolysis can be caused due to concurrent bacterial or viral infections. Underlying metabolic myopathies were excluded by the clinical anamnesis, while possible pharmacologic-causative agents were stopped a few days before the onset of rhabdomyolysis. The abrupt onset of extremely elevated CK and myoglobin levels, areas of muscular necrosis and inflammation, absence of apoptosis, EMG results, and positive clinical outcome suggest an infection-induced rhabdomyolysis, limiting the likelihood of CIM.

The negative results of viral detection might have been caused by the late stage of disease when the biopsy was effectuated, and viral clearance had probably already occurred. Myalgia is a known symptom even in mild forms of COVID-19, indicating potential direct or indirect virus-related muscle damage. No precise description of muscular symptoms related to COVID-19 has been provided to date.
Guillain-Barré syndrome was recently described in COVID-19 patients. However, the lack of axonal impairment and the onset of symptoms 23 days after viral infection were not consistent with this diagnosis. The involvement of the central nervous system has also been described, but our patient was alert and conscious after the cessation of sedation.

The existing literature on rhabdomyolysis in COVID-19 patients mainly describes the medical environment and common first-line treatments. Similar to earlier reports, our patient experienced an abrupt dramatic increase of CK and myoglobin, with consequent renal impairment. However, our patient was admitted for respiratory insufficiency and subsequently developed rhabdomyolysis and AKI requiring CRRT. Myoglobin and CK are heavy molecules (16.7 kDa and 81 kDa, respectively); myoglobin is only partially removed with convection techniques (CVVH) or with a high dose of convection (reinfusion) during CVVHDF treatment. Thus, the rationale of CVVHDF in this patient was mainly to manage AKI and avoid hydro-electrolytic complications (especially fluid overload and hyperkalemia), rather than myoglobin removal.

**Conclusion**

We intend to expand the understanding of COVID-19 associated complications by describing COVID-19 associated rhabdomyolysis, its management with CVVHDF, and differential diagnoses. Direct viral damage to myocytes was not detected, although an undetected dysregulated immune-response could be a plausible cause of muscle damage. The neuromuscular symptoms related to COVID-19 require careful clinical analysis and targeted treatments. Further studies on this complex and intricate scenario are warranted.

**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.

**Ethical approval**

Our institution does not require ethical approval for reporting individual cases or case series representing to-date best clinical practice.

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**Informed consent**

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