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Case report

Rabdomyolysis as a serious complication of COVID-19

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Abstract: Rhabdomyolysis is an acute condition with skeletal muscle damage and release of toxins produced by myocytes with variable clinical presentation. Laboratory diagnosis is based on an increase in serum creatine phosphokinase (CPK), which can trigger irreversible renal impairment. The aim was to describe the association of COVID-19 with rhabdomyolysis as a serious complication, in order to promote early diagnosis and treatment. Case description: Female patient, 18 years old, grade 3 obesity, complaining of dry cough for 7 days, associated with continuous fever for 4 days, myalgia of the lower limbs and moderate dyspnea for 2 days, was admitted to the emergency room and sent to the Intensive Care Unit (ICU), with positive PCR-RT. After 12 hours of admission, the patient developed severe hypoxemic acute respiratory failure. On the second day of hospitalization, an exponential increase in CPK was found and measures of volume optimization were initiated. On the seventh day of hospitalization, associated with increased CPK, a decline in renal function was observed, evolving to the need for renal replacement therapy. On the ninth day of hospitalization, she presented with multiple organ dysfunction and death. In conclusion, COVID-19 can generate rhabdomyolysis by direct myocyte injury by SARS-CoV-2, an exacerbated immune response to the virus resulting in a cytokine storm with concomitant muscle damage and through

direct injury by circulating viral toxins. However, as it is an uncommon manifestation and presents a nonspecific clinical condition, early diagnosis is not always performed. This conclusion was based on the case report presented and not only on the results of the literature review, since the clinical case is in accordance with the literature and can contribute to the recognition of these conditions, leading to better management in the treatment.

Keywords: rhabdomyolysis; COVID 19; intensive care; obesity; creatine phosphokinasey

1. Introduction

In the province of Wuhan, China, at the end of 2019, atypical cases of pneumonia were identified that progressed abruptly to Severe Acute Respiratory Syndrome (SARS) and with large-scale transmission, leading to alarming contagion rates at local level and subsequently reached pandemic proportions. It was found that the etiologic agent of this disease is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a virus that is part of the set of coronaviruses, single strand RNA virus, causing coronavirus disease 2019 (COVID-19) [1,2].

This disease develops with variable clinical manifestations depending on the health status and age of the infected person, and can develop asymptomatic, mild and severe conditions. The most common symptoms are atypical pneumonia with dry cough, progressive dyspnea, fever, asthenia, anosmia, odynophagia, runny nose and sneezing (one of the symptoms that indicate prevention with the use of masks). It is known that the disease incubation period is from 1 to 7 days and the clinical manifestations occur between 7 and 11 days of infection, the infected droplets can spread up to two meters and have the ability to deposit on surfaces, remaining viable for days if in favorable atmospheric conditions. Contamination occurs by inhaling these droplets or by contact with a contaminated surface followed by touching the airways and eyes [3,4].

COVID-19 has a wide spectrum of complications in different systems; however, these correlations have not been well elucidated so far. Complications such as thromboembolic manifestations, encephalitis, Guillain-Barré syndrome, acute kidney injury and even rhabdomyolysis have been reported, the latter being the target of the present study. Rhabdomyolysis is an acute condition with skeletal muscle damage and release of toxins produced by myocytes, with varied etiology and clinical manifestations.

Few cases of association between COVID-19 and rhabdomyolysis have been described so far, however, it is known that infections by SARS-CoV-2 can develop with nonspecific myalgia and medical knowledge of this possible manifestation is of paramount importance in order to prevent severe kidney injuries and their possible complications, in order to reduce the morbidity and mortality of this comorbidity [2,5–7].

Thus, the aim of this study is to describe the association of COVID-19 with rhabdomyolysis as a serious complication, in order to promote early diagnosis and treatment for better clinical treatment and prognosis.

2. Case description

Information contained in this report was obtained by reviewing the medical records of the inpatient, as well as evaluating the conducts, laboratory and imaging tests requested and other diagnostic methods, with a review of the available literature.

Eighteen-year-old female patient, grade 3 obesity, with a history of dry cough for 7 days, associated with continuous fever for 4 days, myalgia of the lower limbs and moderate dyspnea for 2 days. She was admitted to the emergency room with hypoxemia, 88% pulse oximetry and tachypnea (25 incursions per minute), and admitted to the Intensive Care Unit (ICU). Thereafter, treatment with oxygen therapy with nasal catheter at 5 liters/minute, ceftriaxone, azithromycin, olsetamivir, hydroxychloroquine and nutritional support was started. Pulmonary ultrasound (Lung score 10), computed tomography scan of the chest evidenced approximately 50% ground-glass pattern (Figure 1) and positive COVID-19 PCR-RT.

After 12 hours of hospitalization, she presented with severe hypoxemic acute respiratory failure, requiring orotracheal intubation in rapid sequence with fentanyl, etomidate and succinylcholine and invasive mechanical ventilation. Sedation was performed with fentanyl and midazolam and neuromuscular blockade by cisatracurium. Due to the ratio of partial pressure of oxygen to fraction inspired of oxygen (PaO_2/FiO_2) less than 100, a prone position was performed, without satisfactory response. Two more attempts with prone position were performed due to P/F less than 100 and adjustments to the ventilator, but without satisfactory response and with a decline in lung injuries. On the second day of hospitalization, an increase in creatine phosphokinase (CPK) was observed exponentially (Table 1) and measures of volume optimization were initiated.

On the fifth day of hospitalization, the patient still had a continuous fever of 39 degrees, the piperacillin/tazobactam antibiotic was expanded and a new pulmonary ultrasound was performed (Lung score 15). On the seventh day of hospitalization, associated with increased CPK, there was a decline in renal function, evolving to the need for Renal Replacement Therapy despite protective measures such as volume optimization and adjustment of nephrotoxic drugs. Bicarbonate solution was initiated with the objective of alkalinizing urine and hemofiltration as a strategy to control the injury induced by myoglobin. On the ninth day of hospitalization, she presented with multiple organ dysfunction and death.

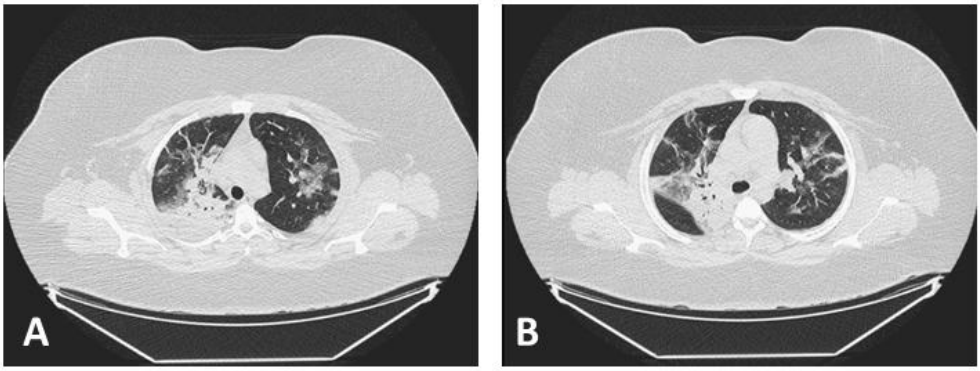

Figure 1. (A,B) Computed tomography scan of the chest of an 18-year-old female patient with SARS-CoV-2 infection on the day of admission, which revealed 50% ground-glass pattern.

Table 1. Biochemical parameters of the patient according to days of hospitalization.

Parameter (reference)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
CPK (24–174 U/L)	697	4,189	3,274	3,404	8,426	18,263	15,566	23,735
CR (0.4–1.3 mg/dL)	0.95	0.89	1.21	1.34	1.19	1.70	3.42	6.01
UR (15–40 mg/dL)	21	23	38	56	56	49	74	118
LDH (135–250 U/L)	455	522	592	627	893	1,061	1,080	1,062
AST (<31 U/L)	99	105	108	117	202	194	208	205
Phosphorus (4–7 mg/dL)	2.5	2.9	3.5	4.0	4.0	4.5	6.0	6.3

*Note: Laboratory findings: CPK (creatine phosphokinase), CR (creatinine), UR (urea), LDH (lactic dehydrogenase), AST (aspartate aminotransferase).

3. Discussion

3.1. Rhabdomyolysis x COVID-19: Clinical correlation

The new coronavirus, the etiological agent of COVID-19, is an enveloped single stranded RNA virus, of the family of β-coronaviruses, which has four main structural proteins: envelope (E), spike (S), nucleocapsid (N) and membrane (M) proteins. Spike protein has an affinity for the angiotensin-converting enzyme 2 (ACE-2) receptor. These receptors are expressed in a diversity of cells in different systems, which contributes to the understanding of the pathophysiology of the disease [8–10].

The virus has a cellular tropism in the respiratory tract, reaches the upper and lower tract areas, as well as invading cells of the pulmonary parenchyma, pneumocytes I and II, through contaminated saliva droplets. Therefore, respiratory disease can present with mild symptoms, flu-like symptoms, until extensive pneumonia that presents a ground-glass pattern on computed tomography and with exuberant respiratory symptoms, typical of respiratory failure [11–13].

After cell invasion, the virus starts its viral replication process and causes cell death after disrupting the host membrane. SARS-CoV-2 can suppress IFN-γ responses of the antiviral type in the early stage of infection, leading to uncontrolled viral replication. From there, an intense inflammatory process takes place, such as the production of cytokines and chemokines, such as IL-1, IL-6, TNF-α, which stimulate the formation of an auxiliary standard CD4+ T cells (Th1) response pattern, with activation of cytotoxic CD8+ T cells. Specific Th1/Th17 cells may be activated and contribute to increased inflammation. Furthermore, this storm of cytokines is not restricted to the respiratory system, but has a systemic repercussion. Thus, the host immune response promotes generalized inflammation, with endothelial activation, platelet aggregation and damage to vascular, renal and cardiac tissues [14–16].

However, other organs and tissues have ACE-2 receptors, allowing viral invasion by mechanisms similar to those occurring in the respiratory system. The main systems affected by viral injury and the immune response in COVID-19 are the renal and cardiovascular systems. Consequently, the complications of this infection extend beyond the respiratory organs, which

reflects the severity of this new pathology, the need for its understanding and the establishment of an effective treatment, which today does not have standardization and consensus, as well as unsatisfactory responses in the improvement of critically ill patients [3,17–19].

Rhabdomyolysis is a syndrome characterized by disruption of skeletal muscle integrity leads to the direct release of intracellular muscle components, including myoglobin, creatine kinase (CK), aldolase, and lactate dehydrogenase, as well as electrolytes, into the bloodstream and extracellular space. Ranges from an asymptomatic illness with elevation in the CK level to myalgia and life-threatening condition such as acute renal failure (ARF). It can be induced by autoimmune myopathies, substance abuse, alcohol use, infectious processes, electrolyte abnormalities, trauma, prolonged immobilization, strenuous exercise and seizures. Rhabdomyolysis may be associated with other viral infections such as infections by the human immunodeficiency virus (HIV), Epstein-Barr enterovirus (EBV), cytomegalovirus (CMV), adenovirus, herpes simplex virus (HSV) and varicella virus. However, these findings are more prevalent in the pediatric population compared to the adult population [20,21].

A possible bias in our study is that serology was not performed for these other agents, because in addition to COVID-19, the patient could have any of these agents contributing or triggering kidney injury. It manifests itself clinically with myalgia, fatigue, pigmenturia and can cause acute renal failure, however, the diagnosis is mainly based on the elevation of CPK levels above 1,000U/L in the laboratory exam. Although the pathophysiology of the correlation between SARS-CoV-2 infection and rhabdomyolysis is not clear, it is estimated that the mechanisms may consist of direct myocyte injury by SARS-CoV-2, an exacerbated immune response to the virus resulting in a cytokine storm with concomitant muscle injury and direct injury by circulating viral toxins [20–22].

Although frank rhabdomyolysis is an uncommon finding, it is noted that COVID-19 tends to increase CPK levels, as seen in a cohort study (n = 1,099) in China, in which 13.7% patients had CPK at levels higher than expected. Thus, suggesting the existence of a component of muscle injury in the disease, fostered by common findings of myocardial injuries, representing a common mechanism between the two manifestations [2,23].

Rhabdomyolysis and its respective deposition of haem pigment generates acute tubular necrosis and therapies indicated for COVID-19 are not likely to alter the course of the already established renal injury. Discussion about this complication and its prevention should be emphasized by the high morbidity and mortality and important resource management, in view of the difficulty of managing devices for dialysis and trained staff during the pandemic [2,23].

3.2. Rhabdomyolysis x COVID-19: Correlation with reported cases

The case reported by Jin and Tong [24] showed a 60-year-old male patient, with a history of fever and cough for six days, with improvement of fever with antimicrobial treatment and progression of symptoms related to rhabdomyolysis. Because myalgia and fatigue are commonly reported in patients with COVID-19, as in the case of our patient, signs of rhabdomyolysis are often underreported. However, rhabdomyolysis should be clinically suspected when focal muscle pain is associated with fatigue. Laboratory tests for diagnosis of rhabdomyolysis are not performed routinely, thus generating difficult early diagnosis. Nevertheless, to avoid acute renal failure, early diagnosis is of paramount importance, together with its appropriate treatment.

The case reported by Samies et al. 2020 [20] showed a 16-year-old patient, obese, hypertensive,

with type 2 diabetes mellitus and obstructive sleep apnea. The patient sought care with fever, odynophagia, non-productive cough, myalgia and pigmenturia. Despite being a young and obese patient like the patient in the present study, this case, for presenting some classic manifestations of rhabdomyolysis, had an earlier intervention and, therefore, a progressive fall in CPK and hospital discharge after 14 days of hospitalization.

Gafen et al. 2020 [25] reported a case of a 16-year-old patient with autism spectrum disorder, attention deficit hyperactivity disorder, morbid obesity and obstructive sleep apnea who sought care with fever, myalgia, dyspnea and pigmenturia. He reported that 5 days ago he noticed asthenia that evolved to myalgia in the lower, upper limbs and trunk with dyspnea on exertion, he also reported hematuria, however, due to his cognitive ability, it was not possible to set exactly how long he had had this sign. Despite being a patient of similar age to the patient in the present study and similar obesity, again, this patient had classic signs of rhabdomyolysis, facilitating early diagnosis and better prognosis.

Rhabdomyolysis is a rare complication of succinylcholine administration during endotracheal intubation and Rapid Sequence Intubation (RSI), gold standard procedure in acute respiratory failure related SARS-Cov-2. Usually, hyperkalemia is more frequently, and in reported case, did not observe initially. RSI is a strategy implemented to enhance safety during intubation in patients with COVID-19, and it is mandatory to used muscle relaxants.

4. Final considerations

The report presented shows the need for an early diagnosis of rhabdomyolysis and its association as a serious complication of COVID 19 in order to reduce its morbidity and mortality. It is known that COVID-19 can cause rhabdomyolysis by direct myocyte injury by SARS-CoV-2, an exacerbated immune response to the virus resulting in a cytokine storm with concomitant muscle damage and through direct injury by circulating viral toxins. Nonetheless, because COVID-19 classically presents with fatigue and myalgia, it is difficult to diagnose rhabdomyolysis early and laboratory tests to confirm its diagnosis are not routinely requested. Few cases of rhabdomyolysis have been reported in the literature, however, an increase in CPK levels has been noted in patients diagnosed with COVID-19 and this should call attention to early recognition and interventions.

This conclusion was based on the case report presented and not only on the results of the literature review, since the clinical case is in accordance with the literature and can contribute to the recognition of these conditions, leading to better management in the treatment. We can consider that, for future perspectives, additional follow-up of similar cases is interesting, useful and will be carried out.

Conflict of interest

The authors have declared no conflict of interest.

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