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SARS-CoV-2-induced myopathy: Clinical aspects, paraclinical changes, and therapeutic options

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made a considerable global effect, posing notable challenges for clinicians, the pandemic becoming one of the most imperative international health emergencies lately. Among other more frequent manifestations, SARS-CoV-2 disease may also give rise to skeletal muscle involvement. Viral-induced skeletal muscle involvement is a potentially severe manifestation of COVID-19 (Coronavirus Disease 2019) and may be either acute, or in the context of "long-COVID". The present review aimed to illustrate few aspects about pathomechanisms, clinical and paraclinical frames, and treatment options for SARS-CoV-2-induced muscle involvement. Notably, it has been stated that SARS-CoV-2 may have the ability to invade muscle myocytes directly, the disease having a variety of clinical manifestations, from myalgia and muscle weakness to rhabdomyolysis. Nevertheless, it is also important to take into account that most of patients with severe forms receiving mechanical ventilation for more than one week may have complications such as CIM (critical illness myopathy) and/or CIP (critical illness polyneuropathy) that may be clinically similar to SARS-CoV-2-induced myositis, yet may be differentiated paraclinically from it. Additionally, it was hypothesized that SARS-CoV-2 infection may constitute a trigger for autoimmune diseases such as polymyositis/dermatomyositis. Presently, there are no diagnosis criteria and no specific therapeutic strategy for SARS-CoV-2-induced myositis.

Keywords: myopathy, SARS-CoV-2, critical illness myopathy, critical illness polyneuropathy, myositis, rhabdomyolysis

INTRODUCTION

Trying to include everything in a universal frame, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made a considerable global effect, posing notable challenges for doctors. The pandemic rapidly became one of the most imperative universal health and economic emergency of late years [1-9].

Coronavirus disease 2019 (COVID-19) emerged as to be an unexplored condition with a large number of manifestations especially with the involvement of the lungs, kidneys, liver and gastrointestinal tract, among others. COVID-19, in these latter days, may have the capability to target multiple tissue types, with a high potential to affect skeletal muscle [1-3].

In addition to the common respiratory symptoms such as cough, high temperature, and sore throat, illustrated since the beginning of the pandemic, proximal muscle weakness is progressively being reported as a symbol of important risk of morbidity in SARS-CoV-2 infection. Myalgia is reported extensively in most of the recent studies as a common muscle involvement expression of COVID-19, starring in more than half of all SARS-CoV-2-infected people [1,10-12].

According to recent studies, COVID-19 can be associated with viral-induced muscle involvement, direct myocyte invasion or autoimmunity triggering being the pathophysiological processes. Myositis determined by SARS-CoV-2 may present in multiple forms, from myalgia and muscle weakness to rhabdomyolysis [13-15]. Exponential increases in enzyme parameters such as Creatin kinase (CK) may or may not ac-

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company the clinical manifestations. Secondary to both parts of the immune system, innate and adaptive, attributed to the angiotensin-converting enzyme 2 (ACE2) receptor, the virus-mediated muscle inflammation enters and affects the muscle fiber. It is also notable that almost half of patients with severe illness being on a controlled ventilation mode for more than one week progress to Critical illness myopathy (CIM) and/or Critical illness polyneuropathy (CIP) [8,9,16].

A generally accepted timeframe of the "Long-COVID" or "COVID long-haulers" is in general words describing those patients with COVID-19 who experienced symptoms for more than one month after diagnosis, whether laboratory or clinical confirmed. Patients who developed "COVID long-haulers" can test, but are not limited to, variety symptoms such as "lung burn" that can be traduced in breathing difficulties, chest ache, cognitive deficit ("brain fog"), vesicular or maculopapular rash, mood swings and thromboembolic disease [17,18].

Generally speaking, persistent muscle pain and long-drawn fatigue are considered to be significative invalidating manifestations post-recovery [1, 12]. When COVID-19 progress to acute myositis, approximatively 50% of the patients confront with an extended period of which may vary from weeks to months. It has been discovered that SARS-CoV-2 may injury muscle fibers directly [13-16].

The present review aimed to present the key pathomechanisms, clinical manifestations, and paraclinical changes associated with SARS-CoV-2-induced muscle involvement.

Pathomechanisms of muscle involvement in COVID-19

Binding to the ACE2 receptor on human cells, SARS-CoV-2 has a viral structural spike (S) protein being known as a functional place of binding for SARS-CoV-1 and SARS-CoV-2 [19]. This virus depends on the presence of host cellular ACE2 in order to bind through S1 spike domain receptor, while using host surface-protein enzymes (transmembrane protease serine 2 (TMPRSS2) and lysosomal cathepsins) to promote S2 spike domain exposure. Hoffman, Ferrandi and Shang et al. emphasized the crucial role of TMPRSS2 expression for membrane fusion [20-22]. It is well-known that a elevated levels of the ACE2 receptor can be found in lung simple squamous epithelium and also in organs that are being part of cardiovascular, gastrointestinal, renal and skeletal muscle system [23-27]. It has been noted the presence of ACE2 in voluntary muscles suggesting the affinity of SARS-CoV-2 towards skeletal muscle, hence the muscular injuries. Viral multiplication inside human host cells results in multiple viral copies which are released in the system. The inflammatory reaction can rapidly turn into an aggressive cytokinic response with multi-systemic consequences, a process called "cytokine storm" [24,25].

Following the infection, high levels of interleukin-6 (IL-6) can determine alterations of metabolic homeostasis of muscles and accelerate cell damage [28-30]. Hyperlactatemia develops the effect of the cell damage and exacerbates the damage inside muscle cell. In addition to metabolic acidosis, hyperlactatemia inhibits the oxygen-carrying capabilities of erythrocytes contributing and because of that appears hypoxemia. In hypoxemic conditions, production of high amounts of lactate dehydrogenase (LDH) secondary to muscular anaerobic glycolysis results in elevated concentration of lactate, therefore stimulating hypoxic ischemia [31]. A self-sustaining myocytic cascade will result in necrosis of the muscular fibers leading to discharge muscle components of the blood stream: rhabdomyolysis [32]. It was also illustrated that SARS-CoV-2 may be the initial stimulus a chronic auto-immune mediated muscle damage [33-35].

Presenting a significant plasticity, the relevance of skeletal muscle activity can be demonstrated by the function of respiratory ventilation [36]. The diaphragm and parasternal intercostal muscles, two very important elements in the breathing process, work in a synergic manner while ventilating [37]. In this particular situation, any pathologies which damage severely skeletal muscle can affect pulmonary ventilation [38-40].

As it was mentioned above, ACE2 is well represented in skeletal muscle. In some studies, it is emphasized that ACE2 levels are found in various types of cells from skeletal muscle satellite cells to mesenchymal stem cells [20], this finding explaining the high sensitivity of different muscle cells to SARS-CoV-2 [41].

Cross-reactivity is an immune phenomenon that can also explain muscle injury. In this process antibodies initially targeted towards specific pathogens will destroy self-structures, in this case muscle cells, through molecular mimetism; the production of T and B-lymphocytes populations will lead to excessive inflammation with important myocyte destruction. Recent studies have revealed 3 different T-cell receptor epitopes with high sensitivity for SARS-CoV-2: O-ribose methyltransferase, RNA-dependent RNA polymerase, and 3'-to-5' exonuclease proteins in dermatomyositis patients which may suggest that the virus has the capability of excessive activation of cytotoxic T-lymphocytes (CD8), inducing COVID-19 myositis [1].

Clinical aspects of muscle involvement in COVID-19

Taking into consideration how the COVID-19 pandemic started, fever, cough, and dyspnea was the classic triad. Moreover, it was immediately confirmed that infection can be associated with a wide range of complications [14-17].

SARS-CoV-2-induced myositis can present in a multitude of ways, most often being reported in males over 30. The clinical manifestations of SARS-CoV-2-induced myopathy may be diverse and vary in severity, typically including myalgia and symmetric muscle weakness in both proximal and distal extremities [1]. A life-threatening complication in SARS-CoV-2 infection is illustrated by severe acute myopathy. Additionally, some patients may develop weakness due to muscle fiber atrophy and/or CIM and/or CIP. Recent studies have revealed that almost all patients infected with SARS-CoV-2 who were intubated for more than 2 weeks were at risk of developing either CIP, CIM or both complications [5,9,10].

Furthermore, severe rhabdomyolysis may be a rare and late complication associated with COVID-19 [5,9,10].

Rhabdomyolysis is known as an infrequent and severe complication of SARS-CoV-2 infection and can be defined as a violent destruction of the skeletal muscles resulting in discharging huge amounts of muscle elements in the blood stream extra-cellular space [14,42-44]. In such cases, patients can illustrate the typical frame of COVID-19 consisting in symptoms such as myalgia, fever, shortness of breath which can rapidly progress to rhabdomyolysis [45-48].

It is well-known that CIM and SARS-CoV-2-related myopathy are two pathologic entities with clinical similarities, therefore the physician must be familiar with differential aspects between these two processes. The following arguments point mainly to CIM: first, an episode of acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, and second the use of specific medication (muscle relaxants and corticosteroids) [11,49-52].

It has been established the association between SARS-CoV-2 infection and its myotoxic effect. Bearing this in mind, it is of critical importance to pay a particular attention to patients with severe forms of COVID-19 [11].

As a primary myopathy, CIM has not yet a well-known pathophysiology. From recent studies we can find that there are some factors that put the patient at risk, such as premorbid health status, with the length of mechanical ventilation, and severity of the acute disease. There is a number of factors which may put the intensive care unit (ICU) patient at risk of developing a severe form of CIM: age, hyperglycemia for more than 72 hours, delirium, and controlled ventilation for more than five days [53,54]. Trying to understand the pathophysiology, there is in both conditions, a sort of association of severe damage to the body due to the "cytokine storm" affecting the microvascular circulation and metabolic disturbances [55]. Even if it is possible that they may be present at the same time in patients, every condition has specific mechanisms. CIM is an entity which resembles both cachectic and acute necrotizing myopathy (ANM), defined by lack of myosin. Cachectic myopathy usually means atrophy and is marked by lack of type 2 muscle fibers [56].

TABLE 1. Comparison between CIM, CIP and SARS-CoV-2 myopathy; CIM-critical illness myopathy, CIP-critical illness polyneuropathy, IL-6-interleukin-6, EMG-electromyography

	CIM	**CIP**	**SARS-CoV-2-induced myopathy**
Start	within days	2/more weeks	within days
Recovery	complete	slower/ incomplete	depends on severity; poor prognosis for rhabdomyolysis
Mortality risk	↓	↑	depends on severity
Ventilatory dysfunction	present	present	present
Myalgia	absent	absent	present
Limb muscle weakness	present	present	present
Flaccid limb weakness in proximal extremities	↑	↓	↓
Facial muscle weakness	↑	↓	↓
Potential association with the use of drugs with myotoxic adverse effects	present	absent	absent
Level of IL-6	↑	↓	absent
EMG aspect	myogenic	neurogenic	myogenic
Muscle biopsy	"gold standard" – acute myopathy, necrosis, loss of normal muscle	absent	absent
Inflammatory markers	absent	absent	↑

We must take into consideration that, CIM has a better prognosis than CIP and, especially in elderly patients, it can have a bad prognosis with negative impact if not caught and treated in time [53,57-59].

However, there is a percentage over 50% of patients who will recover completely from CIM, CIP, or critical illness polyneuromyopathy (CIPNM), those suffering from muscular weakness may continue to experience symptoms from 4 weeks to two years after ICU discharge. Among critically ill patients, ventilated in the ICU, muscle atrophy develops in early stages specifically in the first 10 days of COVID-19 [8,11].

Trying to differentiate the two paths of myopathy, CIM can be characterized by the impossibility of ventilator support weaning, flaccid limb weakness in proximal extremities and facial muscle weakness more frequently than in CIP. Common manifestations of CIM and CIP consist in ventilatory and limb muscles weakness with extraocular and facial muscles remaining intact and diminished osteotendinous reflexes. When it comes to the onset of the symptoms, CIM tends to manifest after a couple of days, while in CIP the patient develops signs after a period extended from 14 days to several weeks. [54,60]. It was also a clear distinction between CIP and CIM, where patients with CIP have a slower or incomplete recovery, and higher mortality rate, whereas patients with CIM often show complete recovery within 6 months [54].

Another important issue to discuss is the fact that it was hypothesized that SARS-CoV-2 infection may be a trigger for autoimmune diseases such as polymyositis and dermatomyositis, which are especially challenging, notable in the case of positive autoantibodies (antinuclear antibodies, anti-Mi2, anti-melanoma differentiation-associated protein 5 (anti-MDA5) [61].

Paraclinical investigations

SARS-CoV-2, a virus with a high myopathic potential, illustrates with the help of the paraclinical frame an overreacting inflammation, as the one illustrated by the well-known cytokine storm. On the occasion of the multitude of changes, some studies have investigated the contribution and the influence of CK in the unexpected evolution of the pandemic process. This phosphokinase was mostly found increased in severe SARS-CoV-2 infection, which indicates skeletal muscle damage precipitating limb weakness or even a failure in ventilation. In addition, in the near future it is important to be documented whether serum CK is a potential prognostic indicator for muscle weakness [11].

Notably, speaking about the muscle membrane dysfunction and/or alongside direct muscle damage, CK could be released directly from the muscular fibers. Finally, high levels of CK can also be present in the muscle injury, independent of the degree of inflammatory reaction (muscular dystrophy) [11,62-64].

However, the level of CK may not be always associated directly with illness severity regarding patients. Myositis related a considerable frame of important clinical symptomatology and paraclinical markers such as myositis-specific autoantibodies (anti-MDA5), CRP and erythrocyte sedimentation rate (ESR)). Besides all of these, specialists must take into consideration also the presence or the absence of elevated CK levels to diagnose the critical ill forms of myopathy [1]. It was also reported, in 16-33% of SARS-CoV-2 infected patients the association of muscle weakness and high levels of CK [65]. Some studies highlighted the fact that an elevated CK may not always be followed by a symptomatic evolution, that's why clinicians may pay a rigorous attention to all patients with muscle involvement in the context of COVID-19 [66,67].

In addition to elevated CK levels, the acute stage of myopathy could be pointed out by electromyogram, muscle magnetic resonance imaging (MRI) and muscle biopsy possibly due to skeletal myositis [11].

Being a marker with high potential, serum CK can anticipate respiratory collapse in SARS-CoV-2 infection some time before it is installed, as skeletal myopathy may affect chest muscles which can lead to ventilatory dysfunction [11].

Rhabdomyolysis, as a severe complication, may coexist with high levels of CK. A latter study illustrated an average value around 33,000 U/L, associated with an acute, profound, symmetric muscle weakness including the proximal extremities [44]. In the critically ill patients, the only significant manifestation may be myoglobinuria (dark urine), acute renal failure with elevated CK >5000 IU/L (which may need urgent hemodialysis), blood clotting disorders and lethal electrolyte imbalances. Therefore, rhabdomyolysis must be taken into consideration in all cases with an upsurge in muscle enzymes and acute renal failure, in the critical unit [45-48]. Rhabdomyolysis is standing out with high levels of CK, C-reactive protein (CRP) and negative myositis-specific autoantibodies [1,14].

Underlying the influence of the acute response in the pathogenesis of the critical illness, Langhans et al. illustrated substantial elevated levels of IL-6 in the skeletal muscle of CIM patients in comparison with non-CIM patients [57]. This conclusion has been used to treat patients for the acute respiratory distress syndrome and long-term ventilator dependence, mostly seen in older patients with SARS-CoV-2 [58].

It was also revealed that CK may have a potential clinical implication and may be useful in the process of predicting the progression of COVID-19. Furthermore, patients who died during hospitalization have

been reported to have elevated CK levels. Even if it was found in some recent studies a possible correlation between CRP and severe forms of COVID-19, there wasn't any coexistence of CK and other inflammatory biomarkers, such as CRP and ferritin [62].

Biopsy remains one of the most accurate methods for diagnosis of muscle involvement, a "gold standard" as the vast majority affirms.

Specialists considered unnecessary a muscle biopsy in COVID-19 patients with myalgias, stating that a clinical diagnosis is sufficient in the presence of a diagnosed viral infection [1,68,69]. In contrast to the majority, Almadani et al. studied a case of COVID-19-associated myositis complicated by compartment syndrome, and Bolig et al. a case of immune-mediated necrotizing myopathy, where both felt that a muscle biopsy was warranted [70,71].

When the patient has a critical form of COVID-19, on the biopsy specimen, areas of necrotic tissue or loss of healthy muscle tissue may be documented [72]. Interestingly, latter studies regarding autopsy, found ACE2 presence and SARS-CoV-2 viral RNA in diaphragm muscle of a subset of COVID-19 subjects, with a high degree of fibrosis of the diaphragm muscle and a unique myopathic phenotype [73].

Undoubtedly, neither inflammatory response in the myocytes nor SARS-CoV-2, could not be confirmed from cadaveric skeletal muscle tissue from positive SARS-CoV-2 patients, even if they had cardinal signs of severe myopathy, suggesting CIM/CIP, or indirect myotoxic effect of this virus [11,74,75]. Moreover, it was discovered that the cytokine storm demonstrated by SARS-CoV-2 has also been driven by Th1, which may also induce muscle inflammatory response [76-82].

Treatment

Even in the COVID-19-era, immunosuppressive medications are an important solution for inflammatory myopathies, although one of their adverse effects includes a higher risk of infection. Still being a hot-topic up to debate, the question whether to continue or withhold immunosuppressive therapeutic strategies in SARS-CoV-2-infected patients with myositis currently remains on hold [1]. Agents like human immunoglobulins, high-dose corticosteroids, JAK-inhibitors, T-cell modulators, IL-6 inhibitors (e.g., Tocilizumab), IL-1 inhibitors (e.g., Anakinra), anti-GM-CSF (Gimsilumab) and anti-IFNγ agents (e.g., Emapalumab) were used in the treatment of COVID-19 manifestations [83].

To continue with, besides the typical factors of risk for COVID-19 immunosuppressive therapy, the severity of the disease and the involvement of a multi-organ injury may have an important contribution to the rate of mortality [1].

Among some recent studies, these small specifications regarding therapeutic management during COVID-19 are of great significance, especially where medications suppressing the immune system has a huge impact on the patients survival. Furthermore, specialists seem to point out a valuable role of agents like Tocilizumab and Hydroxychloroquine, which maintain at a low level the mortality rate by avoiding a possible cytokine storm [84].

The administration of Hydroxychloroquine used for COVID-19 symptoms was also shown to cause a toxic myopathy that may also leads to muscle weakness during the pandemic. This was a certain way of which steps can be taken to diagnose this toxic myopathy earlier and help to differentiate it from COVID-19-related muscle involvement [85-87]. Hydroxychloroquine has his own anti-coronavirus properties and has been used either in patients with COVID-19 symptoms to ameliorate symptoms arising from autoimmune reactions or preventing the infection [87]. Furthermore, Hydroxychloroquine-myopathy can also induce respiratory failure which could erroneously be attributed to the SARS-CoV-2 infection [88,89].

It is essential to take into consideration that critically ill COVID-19 patients with possibly myotoxic medications administrated (corticosteroids and muscle relaxants) may trigger CIP/CIM and in part may contribute to the acute disease process [90]. Considering recent illustrations on CIP/CIM animal models, steroids may not have a substantial contribution to CIM [91,92].

In a world so advanced from a medical point of view, where thousands of studies are carried out every day, many therapies such as statins, antimalarial medications, antipsychotic medications, colchicine, antiretroviral medications, propofol, and TNF-α inhibitors may play an important role into the development of myopathies and may influence CK values [62,93,94]. Those that deserve a special attention are chloroquine and hydroxychloroquine, both of which were widely used in the treatment of SARS-CoV-2 infection [95].

Another antiviral therapy, Remdesivir (a nucleotide analogue prodrug that inhibits viral RNA polymerases) has demonstrated until now "in vitro" a significant reaction against SARS-CoV-2 [19,94]. In critical ill patients with severe inflammatory response, cytokine release may be diminished by the administration of Tocilizumab [96-100].

Until now, there is no evidence that the inflammatory myopathy itself makes patients more susceptible to COVID-19 or the immunosuppressive therapies they are receiving have such a potential [59].

CONCLUSIONS

Skeletal muscle involvement is a potentially severe manifestation of COVID-19 and may be either acute, or in the context of "long-COVID". Interestingly, it has been stated that SARS-CoV-2 may have the ability to invade muscle myocytes directly. SARS-CoV-2 -induced muscle involvement may vary greatly in terms of clinical manifestations, from myalgia and muscle weakness to rhabdomyolysis.

It is also notable that half of most of patients with severe forms receiving mechanical ventilation for more than one week may have complications such as CIM and/or CIP that may be clinically similar to SARS-CoV-2-induced myositis, yet may be differentiated paraclinically from the latter. Moreover, it was hypothesized that SARS-CoV-2 infection may constitute a trigger for autoimmune diseases such as polymyositis/dermatomyositis. Currently, there are no diagnosis criteria for SARS-CoV-2-induced myositis.

Regarding the therapeutic management it is important to mention that although the therapy was based on immunosuppressive medications and high-dose corticosteroids, no specific treatment has been established for the SARS-CoV-2-induced myositis.

SARS-CoV-2-induced muscle involvement poses numerous challenges for clinicians, both from a diagnostic point of view, as well as in terms of effective management.

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