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LETTER TO THE EDITOR

Discrepancy between Mild Muscle Pathology and Severe Muscular Compromise in COVID-19 Suggests Nonviral Etiologies

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To the Editor:

With interest, we read the article by Hooper et al about the histopathological and ultrastructural findings on autoptic muscle biopsy in a ∼60-year-old woman with a previous history of prediabetes, arterial hypertension, and hyperlipidemia, who experienced a fatal infection with SARS-CoV-2, manifesting as interstitial pneumonia requiring intubation and artificial ventilation (1). She died 1 week after having been tested positive for SARS-CoV-2 from intractable arterial hypotension, bradycardia, and respiratory and metabolic acidosis (1). Histology of the skeletal muscle revealed fibrin microthrombi, perimysial microhemorrhages, adjacent vacuolar degeneration and necrosis, and minimal inflammatory infiltration (1). Electron microscopy revealed degenerated cells with cytoplasmic condensation, degenerated mitochondria, and cytoplasmic clusters of SARS-CoV-2 particles (1). We have the following comments and concerns.

Involvement of the skeletal muscle in COVID-19 may not only manifest as myalgia, fatigue, or elevation of serum creatine kinase (CK) but also as muscle weakness, atrophy, dermatomyositis, critical ill myopathy, myasthenia, myasthenic syndrome, or rhabdomyolysis (2–4).

Missing in the report is the medication the patient received since hospitalization. Since some of the compounds given to treat COVID-19 are myotoxic (e.g., steroids, chloroquine, and azithromycin) (5), it is crucial to know the drugs given since admission. The influence of these compounds on muscle morphology should be discussed. Since SARS-CoV-2 may affect peripheral nerves and secondarily the skeletal muscle (6,7), we should know if the abnormalities detected on autopsy were attributable to neuropathy and concomitant myopathic changes. The results of nerve conduction studies (NCSs) and needle electromyography (EMG) should be provided.

We should know if the patient complained about any neuromuscular symptoms already on admission and the medication the patient was regularly taking prior to admission. Missing in this respect is the discussion about neuromuscular compromise already prior to admission. Did the patient suffer from a subclinical neuromuscular disorder (NMD) already before hospitalization?

Missing is a discussion about the discrepancy between the mild abnormalities on muscle histology and the sometimes-severe muscle compromise, even leading to muscle weakness and rhabdomyolysis. According to the presented morphological abnormalities, myopathy in COVID-19 patients is rather due to side effects from the treatment applied, pre-existing, subclinical muscle pathology, or due to secondary immune mechanisms than from viral myositis.

Thromboembolic events are a common complication of SARS-CoV-2 infections (8). We should know if pulmonary embolism, as detected on autopsy, was already detected *intra vitam* and if the patient received anticoagulation.

Overall, this appealing autopsy study has some limitations, which need to be addressed before drawing conclusions. Muscle damage due to drugs given for COVID-19 or prior to admission, previous NMD, and nerve damage with secondary muscle pathology need to be excluded. The findings suggest that severe muscular compromise in COVID-19 is rather due to nonviral pathophysiology than due to viral myositis.

COMPETING INTERESTS

The authors have no duality or conflicts of interest to declare.

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Authors' Reply

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To the Editor:

We thank the author for his interest in our report. Finsterer raises several important points when evaluating whether the muscle damage was truly attributable to COVID-19. In particular, the patient's history of the neuromuscular disorder (NMD), medications taken prior to admission or received for COVID-19 treatment, and concomitant neuropathy with secondary myopathic changes need to be considered. The author asserts that there is a discrepancy between the mild abnormalities on muscle histology and the sometimes-severe muscle compromise, even leading to muscle weakness and rhabdomyolysis. His primary question is whether severe muscular compromise in COVID-19 is rather due to nonviral pathophysiology than due to viral myositis.

To address these issues, it is worth emphasizing that the patient presented in the report did not have any known NMD history (1). Her initial presentation of flu-like symptoms was mild but was unfortunately followed by a fulminant process 1 week later which required intubation upon admission. She was not given specific medications or treatment for COVID as suggested by the author (2) since she was quickly transitioned to comfort care only and died 1 day later after admission. The pulmonary embolism, as detected on autopsy, was not known *intra vitam*. No nerve conduction studies or needle electromyography was attempted.

It has been known that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) in conjunction with other cell receptors to enter human host cells (3). A recent study did not find ACE2 and accessory proteases (TMPRSS2 and CTSL) coexpression in skeletal muscle tissue (4). This together with our findings that no overt viral particles were found by electron microscopy in the skeletal myocyte, argues against a direct viral infection of myofibers.

In severe COVID-19, SARS-CoV-2 induces a cytokine storm characterized by excessive release of cytokines such as IL-6 and IL-1β into the blood (5). Recent studies on critically ill patients and patients who have died from severe COVID-19 (6–8) indicate that the apparent discrepancy between the mild pathologic findings and severe muscle compromises are secondary to the storm of cytokine release (9). In addition, IL-6 activates the coagulation system and increases vascular permeability (5), which in combination with viral endotheliopathy (10), accounts for the well-documented COVID-19 associated microvascular damage as seen in this patient. In summary, accumulated evidence to date supports the notion that an interplay of these systemic derangements, rather than a direct infection of SARS-CoV-2 in myofibers, contribute to the pathologic changes seen in the skeletal muscle.

COMPETING INTERESTS

The authors have no duality or conflicts of interest to declare.

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