Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–2

DOI: 10.1177/2324709621998472
journals.sagepub.com/home/hic
SAGE

SARS-CoV-2 as Well as Anti-COVID-19 Treatment May Cause Rhabdomyolysis

Josef Finsterer, MD, PhD[1]

With interest we read the article by Khosla et al about 5 patients with an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifesting as pneumonia (coronavirus disease 2019 [COVID-19]), who additionally developed rhabdomyolysis during hospitalization.[1] Four patients developed renal insufficiency during hospitalization and 2 patients died.[1] It was concluded that the pathophysiology of SARS-CoV-2-associated rhabdomyolysis requires clarification.[1] The study is appealing but raises comments and concerns.

The main shortcoming of the study is that the diagnosis "rhabdomyolysis" was not substantiated. It was neither reported that the urine in any of the 5 patients was dark-colored nor that myoglobin levels in the serum or urine were elevated. Diagnosing "rhabdomyolysis" not only requires documentation of hyper-creatine-kinase (CK)emia but also of a cola-colored urine and elevated serum or urine myoglobin. Additionally, patients with rhabdomyolysis frequently complain about fatigue, exercise intolerance, fever, myalgia, or muscle weakness. Hyper-CKemia in the absence of myoglobinurea does not justify diagnosing rhabdomyolysis. Many patients with a neuromuscular disorder have CK values similar to those of the presented patients over years without ever developing rhabdomyolysis. Renal insufficiency together with hyper-CKemia does not legitimate diagnosing rhabdomyolysis either. Renal insufficiency due to hyper-CKemia in the presented patients is rather unlikely given the low peak values. Additionally, other potential causes for renal insufficiency (eg, diabetes) were present in patients 2 to 5.[1]

A second shortcoming is that the medication the 5 patients were receiving during hospitalization was not considered as a trigger of hyper-CKemia. Patient 1 received azithromycin and tocilizumab. Patient 2 received chloroquine and steroids. Patient 3 received chloroquine, azithromycin, and steroids. Patient 4 received steroids and remdesivir, and patient 5 took azithromycin.[1] Unfortunately, it is not mentioned if the 5 patients received their home medication also during hospitalization or not. Azithromycin is known to cause rhabdomyolysis in some patients.[2] The odds ratio for azithromycin to cause rhabdomyolysis was 2.94 in a retrospective study of 7685 patients with rhabdomyolysis.[2] Rhabdomyolysis has been particularly reported in patients under statins who additionally received azithromycin for infectious disease.[3] From chloroquine it is known that it can be myotoxic and can cause permanent myopathy.[4] Steroids can induce mitochondrial myopathy. Tocilizumab has been reported to occasionally induce myositis.[5] Rhabdomyolysis has been reported even as an initial manifestation of COVID-19 without having started any myotoxic therapy yet.[6]

A third shortcoming is that the number of patients with hyper-CKemia on admission is different between Figure 1 (3 patients) and the first paragraph of the discussion (2 patients).[1] Anyhow, no explanation for hyper-CKemia already on admission is provided, but it is conceivable that it was due to statin therapy or due to the acute infection, which presumably started already prior to admission. There are several reports showing that acute infections can trigger hyper-CKemia[7] or even rhabdomyolysis in patients regularly taking statins.[8]

Overall, the study has limitations that should be addressed before drawing conclusions as those provided. The diagnosis "rhabdomyolysis" should be reconsidered, the onset of hyper-CKemia should be indicated, and the anti-COVID-19 treatment should be discussed as potential cause of hyper-CKemia. Isolated hyper-CKemia in the absence of typical features of rhabdomyolysis cannot be classified as rhabdomyolysis.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

The study was approved by the institutional review board.

[1]Klinik Landstrasse, Messerli Institute, Vienna, Austria

Received January 23, 2021. Accepted February 7, 2021.

Corresponding Author:
Josef Finsterer, MD, PhD, Klinik Landstrasse, Messerli Institute, Postfach 20, Vienna 1180, Austria.
Email: fifigs1@yahoo.de

Informed Consent

Informed consent was obtained.

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