

## Rhabdomyolysis and COVID-19 Infection: Is It Due to Statin Use or Anti-TIF1- $\gamma$ Antibodies?

Emmanuel C. Mantilla<sup>1</sup>, Mamatha Pasnoor<sup>2</sup>,  
Mazen M. Dimachkie<sup>2</sup>

<sup>1</sup>Department of Neurology, John Peter Smith Health  
Network, Fort Worth, TX, U.S.A

<sup>2</sup>Department of Neurology, Neuromuscular Division,  
University of Kansas Medical Center,  
Kansas City, KS, U.S.A.

### ABSTRACT

Coronavirus disease 2019 (COVID-19), now a global pandemic, has infected millions of people and caused hundreds of thousands of deaths. Neurological presentation of the novel coronavirus includes headaches, seizures, myalgias, hyposmia, ageusia, etc. Guillain-Barre Syndrome (GBS) and its variant, Miller Fisher Syndrome, have been reported in COVID-19 patients presenting with lower limb weakness, paresthesia, facial diplegia, and ataxia. Most recently, large vessel occlusion strokes were seen in infected younger patients without vascular risk factors. We present a novel case of rhabdomyolysis associated with COVID-19 infection in a patient on atorvastatin, in whom we detected positive anti-transcriptional intermediary factor 1 gamma antibodies (anti-TIF1- $\gamma$  Ab). Bilateral upper and lower extremity weakness improved with aggressive fluid administration and intravenous immunoglobulin (IVIg) at 0.4mg/kg for a total of 5 days. Interrupting a strong cytokine response with IVIg early on during the disease may have led to rapid improvement.

**Keywords:** COVID-19, SARS-CoV-2, rhabdomyolysis, myositis, inflammatory myopathy, anti-TIF1- $\gamma$  antibody.

### Background

Coronavirus disease 2019 (COVID-19), the disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has come a long way since it was first discovered in several patients in Wuhan, China on December 2019.<sup>1</sup> Now a global pandemic, it has infected millions of people and caused hundreds of thousands of deaths. Over a short span of time, the virus has revealed its nature, presenting with more than just severe respiratory symptoms. Neurological symptoms such as headaches, seizures, and loss of consciousness, hyposmia, myalgias, and ageusia have been reported to be associated with this novel virus.<sup>2-6</sup> In Italy, one of the most severely hit by the

pandemic, five patients with COVID-19 presented with lower limb weakness and paresthesia, with one patient presenting with facial diplegia and ataxia, consistent with Guillain-Barre Syndrome (GBS)<sup>7</sup>. Miller Fisher syndrome, a variant of GBS, was described on a patient in Spain.<sup>8</sup> Most recently, large vessel occlusion strokes have been seen in younger patients with COVID-19 who did not have significant risk factors<sup>9</sup>. Indeed, this novel virus has caused a myriad of neurological symptoms, and neurologists are presented with the challenge of managing these patients without specific guidelines and with limited current data. We present a novel case of rhabdomyolysis associated with COVID-19 infection in a patient on atorvastatin, no rash but a positive anti-TIF1- $\gamma$  antibody titer found on myositis panel.

### Case

A 69-year-old female was admitted to our hospital with a one-week history of progressive, severe arm and leg weakness and unsteadiness. She endorsed difficulty lifting her arms above her shoulders, with associated muscle pain. She had a recent normal mammogram. She also reported difficulty swallowing with both liquids and solid foods. She had a low grade fever at 99.1 F, tachycardia, as well as mild cough, which prompted a virus screen. Influenza A and B rapid testing were negative, but her PCR for SARS-CoV-2 came back positive. A computed tomography angiogram (CTA) scan of the chest was done, which revealed linear opacities involving the right upper lobe and both lower lobes, and several areas of minimal non rounded ground glass opacities involving the dependent aspects of both lobes. There was no evidence of pulmonary embolus. There were no physical or laboratory findings indicative of dehydration. Her inflammatory markers were elevated: D-dimer of 4,281 ng/mL (215-500 ng/mL), and C-reactive protein (CRP) of 1.6 mg/dL (0-0.3 mg/dL). Her creatinine kinase (CK) was elevated at 4,499 U/L (26-192 U/L), along with serum myoglobin at 2,132 ng/mL (13-17 ng/mL), and aldolase of 14.1 (1.5-8.1 U/L). She did not have any myoglobinuria, and her urine was negative for red blood cells (RBCs).

Neurology was consulted for her weakness and dysphagia. She was alert and oriented on initial examination, without dysarthria or aphasia noted, but her speech was hypophonic. Although there was no facial asymmetry nor ptosis at rest, she had some weakness of her facial musculature, with some air escaping when puffing cheeks. She had no trouble with eyelid closure. Bilateral shoulder flexors and the rest of her upper extremity proximal muscles were 3-/5 on manual

muscle testing, and 4+/5 distally for both wrists and fingers. Her hip flexors were bilaterally 3/5, and 4+ /5 on knee flexion, extension, as well as ankle dorsiflexion and plantarflexion bilaterally. She endorsed muscle pain on movement which may have somewhat influenced her effort during testing. Sensory examination was normal to light touch and temperature. Reflexes were 2 both for upper limbs, 1 for both knees, and were absent at the ankles bilaterally. She was able to walk with slow gait and with some assistance. MRI of her brain showed an incidental small meningioma with very minimal mass effect on the inferior frontal falx. Acetylcholine receptor antibody (Ab) and muscle specific antibody (MuSK) were both negative. Myositis panel was normal, except for anti-TIF1- $\gamma$  (p155/140) Ab (*Table 1*). She did not present with any rashes, nor does she have a history of cancer. As the patient was taking 40mg of atorvastatin for several years for dyslipidemia, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) Ab was obtained to evaluate for statin-associated autoimmune necrotizing myopathy (SANAM), which was negative. Atorvastatin was stopped on admission. Rheumatologic labs were also obtained and were negative, including ANA, Rheumatoid factor, ANCA vasculitis panel, RNP ab and anti-Smith ab.

Throughout the admission, the patient's respiratory status remained stable, her oxygen saturation levels well over 90% on room air. No antibiotics were given, and she was placed on IV fluids for her rhabdomyolysis. However, on Day 4 of admission, her CK levels continued to rise, reaching its peak of 5,456 (26-192) U/L, despite aggressive hydration and supportive care. She was then started empirically on immunoglobulin (IVIg) at 0.4mg/kg for 5 days.

The day after the first dose, her CK started to trend down. She denied any side effects with the IVIg treatment. After completing her immunotherapy on Day 8 of admission, the patient noted subjective improvement of her lower extremity weakness. On Day 12 of admission, her hip flexors were 3+ to 4/5 bilaterally approximately, and she had increased range of motion on shoulder flexion and abduction. Functionally, her walking was better, and she had increased use of her arms without significant pain. Her CK on Day 12 was 2,617 (26-192) U/L. She was discharged on Day 21 of admission, and has a follow up visit in the neurology clinic.

### Discussion

Our patient presented with the typical viral prodrome of myalgia and generalized muscle weakness while on chronic stable statin dosage. Rhabdomyolysis is not as widely reported with COVID-19 as myalgias. In fact, myalgia is a very common symptom in COVID-19, with up to 44% of confirmed cases in an institutional review of by Huang, et al.<sup>5</sup> However, Guan et al reported only 2 patients with rhabdomyolysis (muscle pain or muscle weakness, and CK > 10 times the upper limit of normal) out of 1099 with confirmed COVID-19 from 552 different hospitals in mainland China.<sup>4</sup> Beydon, et al presented another case in France, where the patient presented with myalgia and initial CK of 25,384 IU/L. MRI of the lower extremity showed muscle edema and their patient was treated with IV fluids.<sup>10</sup>

Lin, et al recently postulated that B lymphocyte reduction might occur during the early phase of severe COVID-19 infection, together with T lymphocyte reduction, as well as an increase in inflammatory cytokines and D-dimer.<sup>11</sup> This

Table 1: Myositis Panel

Antibody	Result
MI-2	Negative
PL-7 (threonyl-tRNA synthetase)	Negative
PL-12 (alanyl-tRNA synthetase)	Negative
P155/140 (TIF1-gamma)	Positive
EJ (glycyl-tRNA synthetase)	Negative
Ku	Negative
SRP (Signal Recognition Particle)	Negative
OJ (isoleucyl-tRNA synthetase)	Negative
SAE (SUMO activating enzyme)	Negative
NXP-2 (Nuclear Matrix Protein 2)	Negative
MDA5 (CADM-140)	Negative

immune response is the basis for their recommendation to initiate high dose IVIg at 0.3-0.5g/kg per day for 5 days, to potentially interrupt the storm of inflammatory factors and enhance immune function.<sup>11</sup> While our patient in retrospect had milder COVID-19 disease, she was initially treated with IV fluids but continued to have an increase in CK levels. After receiving IVIg, her CK declined and her myalgia and weakness improved. While D-dimer was highly elevated, our patient was anticoagulated. She did not experience any thrombotic or other adverse event as a result of IVIg. The administration of IVIg in COVID-19 patients presenting with other neurological conditions has been shown to be safe and effective as well with concomitant anticoagulation. The five COVID-19 patients earlier mentioned with confirmed GBS from Italy all received IVIg. Two had a second course of IVIg, and one had subsequent plasma exchange (PLEX).<sup>7</sup> A Miller Fisher case with COVID-19 infection described in Spain recovered completely following IVIg treatment.<sup>8</sup>

We initially did not consider an autoimmune muscle injury mechanism in this case given negative serologies (ANA, RF, etc.) and swift response to IVIg. An interesting later finding in this case, however, was the presence of anti-TIF1- $\gamma$  antibody on myositis panel. Anti-TIF1- $\gamma$  ab is one of the autoantibodies associated with inflammatory myopathies, particularly in dermatomyositis. Adult dermatomyositis patients with anti-TIF1- $\gamma$  have a higher frequency of cancer, up to 70%, as compared to those who are antibody negative.<sup>14</sup> Our patient did not present with the typical skin lesions associated with dermatomyositis. She also did not have a history of cancer, no evidence of cancer on chest CT or prior mammogram. Masiak et al, in a single center study of 80 patients with a positive autoimmune inflammatory myopathy profile, 11 were positive for anti-TIF1- $\gamma$  antibodies, 6 were diagnosed with dermatomyositis, and 2 had a neoplasm. Interestingly, one patient in that study presented with rhabdomyolysis with severe muscular weakness.<sup>12</sup> Therefore, we suspect that the immune response may have contributed to our patient's rhabdomyolysis.

We hypothesize that the immune activation in the setting of milder COVID-19 infection may have resulted in this positive antibody titer. This complex infection triggers the recruitment of macrophages and monocytes, the release of cytokines and adaptive T and B cells to target cells.<sup>15</sup> Most cases of COVID-19 are mild, as was the case in our patient, and this inflammatory process is capable of resolving this infection. This is thought to be the result of a well-functioning immune system. We think that our patient who had a

milder infection was able to generate an adequate immune response to COVID-19, part of which was the de novo production of anti-TIF1- $\gamma$  cross-reacting antibodies. Alternatively, that COVID-19 uncovered a predisposition to myositis in the setting of a mild infection cannot be excluded.

Our case report has several limitations including lack of outpatient follow up. In addition, electromyography and nerve conduction study (EMG/NCS) would have been a useful diagnostic tool to assist us in further characterization of the patient's muscle weakness. In addition, a muscle biopsy would also have been beneficial in describing the histopathological features. However, the limitations posed by isolation precautions, as well as strained health resources and organizational barriers due to the pandemic hindered us from performing any of these procedures.

In conclusion, rhabdomyolysis, as reported herein, is rare in the setting of acute COVID-19 infection. We cannot exclude that statin therapy may have triggered rhabdomyolysis. However, the elevation of anti-TIF1- $\gamma$  antibody titer suggests that COVID-19 infection has the potential to uncover or even trigger an autoimmune response targeting muscle. An international database is critically important to better capture rare neuromuscular complications of COVID-19 and to better characterize the acute and long-term neuromuscular sequelae of this pandemic.

### Acknowledgements

Department of Neurology, John Peter Smith Health (JPS) Network (Ambika Nair MD, Babak Rezaei MD, and Ratna Reddy MD); Steven Davis MD, Internal Medicine Chief, JPS Network; Timothy Kenny, MLS, Clinical Library Manager, JPS Health Network; Deepti Nagesh MD; Matthew Varon, MD, Neurology Department, University of Kansas Medical Center.

### References

- <sup>1</sup> Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*. 2020;382(8):727-733. doi:10.1056/nejmoa2001017
- <sup>2</sup> Bersano A, Pantoni L. On being a neurologist in Italy at the time of the COVID-19 outbreak. *Neurology*. 2020. doi:10.1212/wnl.00000000000009508
- <sup>3</sup> Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama*. 2020;323(11):1061. doi:10.1001/jama.2020.1585

<sup>4</sup> Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med*. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013 doi:10.1101/2020.02.06.20020974

<sup>5</sup> Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506. doi:10.1016/s0140-6736(20)30183-5

<sup>6</sup> Chen N, Zhou M, Dong X, et al. Epidemiological and Clinical Characteristics of 99 Cases of 2019-Novel Coronavirus (2019-nCoV) Pneumonia in Wuhan, China. *SSRN Electronic Journal*. 2020. doi:10.2139/ssrn.3523861

<sup>7</sup> Toscano G, Palmerini F, Ravaglia S, et al. Guillain–Barré Syndrome Associated with SARS-CoV-2. *New England Journal of Medicine*. 2020. doi:10.1056/nejmc2009191

<sup>8</sup> Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020. doi:10.1212/wnl.00000000000009619

<sup>9</sup> Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *New England Journal of Medicine*. 2020. doi:10.1056/nejmc2009787

<sup>10</sup> Beydon M, Chevalier K, Tabaa OA, et al. Myositis as a manifestation of SARS-CoV-2. *Annals of the Rheumatic Diseases*. 2020. doi:10.1136/annrheumdis-2020-217573

<sup>11</sup> Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerging Microbes & Infections*. 2020;9(1):727-732. doi:10.1080/22221751.2020.1746199

<sup>12</sup> Masiak A, Kulczycka J, Czuszyńska Z, Zdrojewski Z. Clinical characteristics of patients with anti-TIF1-γ antibodies. *Reumatologia/Rheumatology*. 2016;1:14-18. doi:10.5114/reum.2016.58756

<sup>13</sup> Okogbaa J, Batiste L. Dermatomyositis: An Acute Flare and Current Treatments. *Clinical Medicine Insights: Case Reports*. 2019;12:117954761985537. doi:10.1177/1179547619855370

<sup>14</sup> Dimachkie MM, Barohn RJ, Amato AA. Idiopathic inflammatory myopathies. *Neurol Clin*. 2014 Aug;32(3):595-628, vii. doi: 10.1016/j.ncl.2014.04.007. Review. PMID: 25037081

<sup>15</sup> Tay MZ, Poh CMI, Rénia L, MacAry PA Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020 Apr 28. doi: 10.1038/s41577-020-0311-8. [Epub ahead of print]