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COVID-19

Anti-HMGCR myopathy misdiagnosed as motor neuron disease and complicated with COVID-19 infection

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Dear Editor-in-Chief,

Inflammatory myopathy (IIMs) are a large group of potentially treatable myopathies in children and adults; necrotizing autoimmune myopathy is a distinct clinicopathologic entity, accounting for up to 19% of all IIM, and it is clinically characterized by proximal muscle weakness of acute or subacute onset and high creatine kinase levels (CK) [1]. Most patients with necrotizing autoimmune myopathy have antibodies against signal recognition particle (SRP) or against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) [2].

The severe acute respiratory syndrome-correlated new coronavirus (SARS-CoV-2) is spreading worldwide since the beginning of 2020. The major clinical manifestations of the SARS-Cov-2 infection are due to pulmonary complications, and although most have mild symptoms, such as fever, headache, cough, dyspnea, myalgia, and anosmia, some develop acute respiratory distress syndrome that can result in death. Several neuromuscular symptoms were identified as part of the COVID-19 spectrum, and myalgias are reported in up to a half of patients with SARS-CoV-2 infection; instead, CK elevations depend on the disease severity, ranging from mild to severe rhabdomyolysis. Even if electromyography, muscle imaging, and muscle histopathology are not available to date, coronavirus infections may cause an IIM; few cases [3, 4] have described myositis triggered by SARS-CoV-2, and to date little is known [5] about the role of SARS-CoV-2 infection to determine relapse in previously affected patients.

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Here we present a case of a patient who was firstly diagnosed with a "lower motor neuron disease", in which further assessment revealed the presence of necrotizing autoimmune myopathy. After a few weeks on steroid treatment, symptoms worsened and only subsequently this was proved to be a relapse triggered by SARS-CoV-2 infection.

The patient is a 64-year-old male who came to our attention for a rehabilitation program due to a recent diagnosis of "lower motor neuron disease". His first symptoms started 6 months before admission to our Centre, and they were characterized by a progressive weakness in his lower limbs with difficulty climbing stairs and walking for long distances, along with difficulty raising his arms over his head. He did not complain of any cramps or myalgias. No sensory or autonomic symptoms were reported. Three months after the onset of symptoms, the patient was admitted to a Neurology Clinic where he underwent several assessments including an EMG test which showed a diffuse increased spontaneous activity at rest; during voluntary contraction, polyphasic motor unit action potentials (MUAPs), with normal amplitude, duration and pattern of recruitment, were registered. CK level was> 4000–5000 U/L in three serial blood draws. Brain and spinal MRIs were all unremarkable. He was discharged with a diagnosis of "atypical motor neuron disease with predominant involvement of lower motor neuron". The patient was started on riluzole. When the patient was admitted to our Centre for a neurorehabilitation program, neurological examination revealed a normal muscle bulk and tone without any fasciculations. He was unable to raise his arms above his head, and he required to push himself out of a chair using both hands and with a widened base. Gait was pretty stable. On manual strength testing, a significant symmetric loss of strength in his proximal muscles in both upper (UL) and lower limbs (LL) was evident. Specifically, according to the Medical Research Council (MRC) Scale, deltoid was 2+, biceps and triceps brachii 4+, iliopsoas 2+, hamstrings 4−, quadriceps 4+ and gluteus maximus 2+ bilaterally. Sensory and cerebellar systems were within normal limits. Deep tendon reflexes

(DTRs) were diffusely reduced. Cranial nerves were apparently intact. General examination did not reveal any rash or dermatitis, especially over face, neck or hands. His past medical history was remarkable for benign prostatic hypertrophy and for a perivascular dermatitis of trunk and neck which occurred about 3 months before the onset of motor symptoms (and which had regressed with a few weeks of oral steroid treatment). The patient was on tamsulosin and had apparently never been exposed to statins.

Blood tests were normal except for CK levels which were still significantly elevated (4890 U/L). Routine screening for SARS-CoV-2 with a nasopharyngeal swab was negative. Spirometry and transthoracic echocardiography were normal. Results of a new EMG test showed the presence of spontaneous activity characterized by fibrillations and positive sharp waves which were evident mostly in proximal muscles both in the ULs and LLs, also involving paraspinal muscles and tongue. During voluntary contraction small, short and polyphasic MUAPs were detected in the same muscles, with an early recruitment. The patient underwent a muscle MRI with STIR sequences which revealed the presence of a hyperintense signal in the thighs, especially in the adductor muscles and hamstrings. A muscle biopsy was performed on the left deltoid (Fig. 1). Several fibral splittings, scattered necrotic fibres, macrophagic infiltration and mild increase of connective tissue were observed. To exclude a paraneoplastic aetiology, a PET of the whole body was performed, which did not identify any suspected mass; a diffuse hypercaptation of F18-fluorodeoxyglucose was observed in all muscles of the trunk and girdles (Fig. 2). Serological tests for common antibodies associated to inflammatory myopathies revealed the presence of anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase antibodies. (anti-HMGCR). So a final diagnosis of necrotizing autoimmune myopathy with anti-HMGCR antibodies was made.

Based on these findings, steroid therapy with high dose of methylprednisolone was initiated (1 g/day) with a gradual improvement of muscle strength; after 5 days of intravenous steroids, the therapy was shifted to oral steroid (prednisone 1 mg/kg/day). At discharge, the patient had regained a good motor function; he was independent in walking, climbing stairs and getting from supine to seated, and from seated to standing. However, after 14 days from discharge the patient started presenting a rapid worsening of his muscle strength with difficulty walking and getting up from sitting; he also reported marked asthenia along with occasional difficulty in swallowing and dry cough; no fever or other signs of respiratory infection were present. A possible inflammatory relapse was considered, and the patient was readmitted at our site to revisit treatment options. Neurological examination showed a decrease in muscle strength in all the muscles, especially in the proximal ones (deltoid 2, biceps and triceps 3, iliopsoas 2, quadriceps 3); the patient was not able to stand or walk without support, and he required assistance to get from supine to seated. CK level was >8000 U/L.

Routine screening for SARS-CoV-2 with a nasopharyngeal swab proved to be positive. A CT scan of the chest revealed a

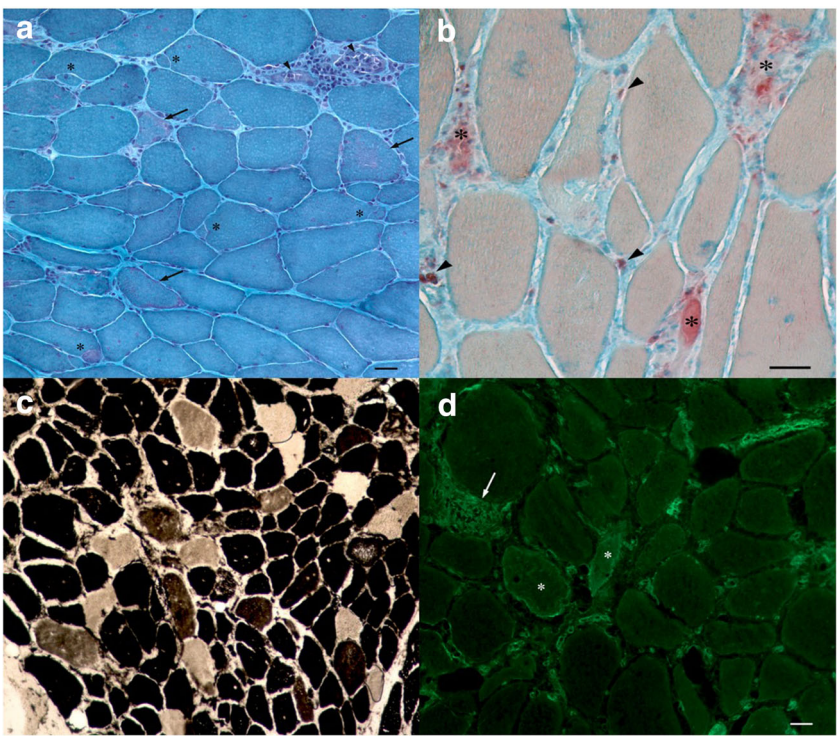

Fig. 1 Muscle histology (magnification ×200, scale bar 50 μm). **a** Gomori trichrome stain showing increased fibre diameter variability, mild endomysial connective tissue increase, numerous splitting fibres (asterisks), pale degenerating fibres (arrows), phagocyte invasion, and replacement of necrotic fibres (arrowheads). **b** Acid phosphatase stain showing phagocytes invading degenerating fibres (asterisks) and endomysial inflammatory cells (arrowheads). **c** ATPase pH 4.6 stain showing the normal checkerboard pattern of type 1 (dark) and type 2 (2a pale; 2b brownish) fibres. **d** MHC-1 immunofluorescence showing cytoplasmic and sarcolemmal positivity in some necrotic fibres (asterisks) and membrane staining of inflammatory cells (arrow)

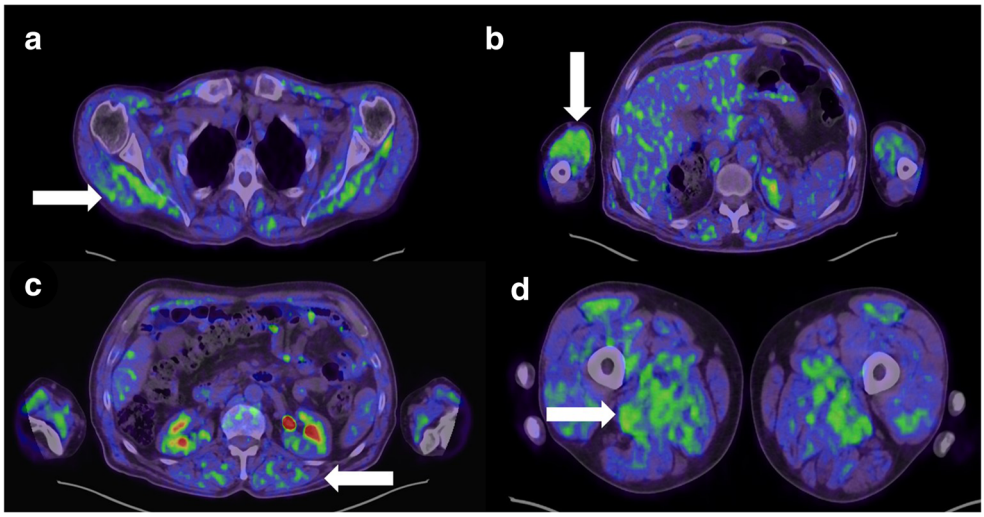

Fig. 2 Whole-body PET-CT scan with F18-fluorodeoxyglucose (F18-FDG). A significant hypercaptation (white arrow) is evident at scapular and deltoid muscles bilaterally (**a**) at muscles belonging to anterior compartment of arms (**b**), at paraspinal muscles (**c**), and thighs, especially posterior compartment (**d**)

bilateral interstitial pneumonia (Fig. 3). The patient was transferred to the infectious disease department where he continued his ongoing steroid therapy at the same dosage (1 mg/kg/day) along with prophylactic anticoagulation. During his stay, the vital signs remained within normal limits, including oxygen saturation. A few days after admission, muscle strength started to improve gradually along with CK levels which dropped to 800 U/L; 2 weeks later, the patient was discharged (after two negative nasopharyngeal swabs for SARS-CoV-2). Neurological evaluation at discharge revealed a marked improvement of muscle strength; gait was stable, and the patient did not require any assistance to stand or getting seated from supine.

Inflammatory myopathies are rare diseases, occurring at a rate of 9 to 14 cases per 100,000 people. They were first recognized in adults, but childhood onsets have been also described [6]. Anti-HMGCR myopathy is a subtype of IIM.

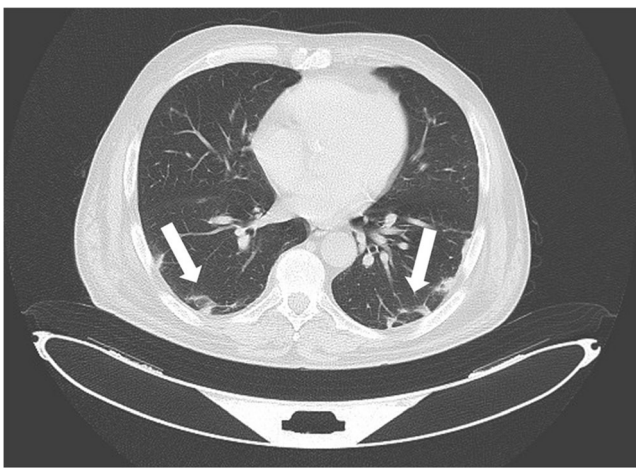

Fig. 3 Chest CT scan. Small ground glass opacities (white arrows) are evident at posterior level of the inferior lobes

What distinguishes anti-HMGCR myopathy from other IIM subtypes is the presence of anti-HMGCR autoantibodies and a strong association with statin use. Almost 90% of patients were exposed to statins [7]. Considering that statins can be found in foods and supplements, such as red yeast rice, it is conceivable that some statin-naïve patients may have unknowingly been exposed to statins [8].

Neurological practice is affected by the COVID-19 pandemic in several key ways. Patients with neuromuscular disorders may be particularly susceptible to SARS-CoV-2 infection and its complications, and this pandemic has forced a rapid reorganization of clinical care delivery, including telemedicine and telephonic contacts. A recent meta-analysis showed that the pooled percentage for having a pre-existing neurological disease in patients with severe COVID-19 was 8% [9]. Moreover, many patients with neurological autoimmune disease, such as inflammatory myopathies, are on a wide variety of immunosuppressive therapies, which can mask (as it happened in the patient presented above) symptoms related to a viral infection.

It might be prudent for such patients to take extra precautions to prevent exposure to the virus and in selected instances to revaluate the dosages of the medications. Holding or suspending oral corticosteroids or subcutaneous immunoglobulins is not routinely recommended; on the contrary, they can contribute to reduce cytokine's damaging effects by limiting the formation of cytokine [10].

In conclusion, COVID infection must be taken into account as a possible trigger for relapse of an inflammatory myopathy (especially in this pandemic period); prompt recognition of infection may be delayed due to ongoing immunosuppressive therapies; holding or suspending oral corticosteroids is usually not recommended; and the resolution of the viral infection seems to result in a spontaneous patient recovery without adjustments of the ongoing steroid therapy.

Abbreviations ALS, amyotrophic lateral sclerosis; CK, creatine kinase; COVID-19, coronavirus disease 19; CT, computed tomography; DTRs, deep tendon reflexes; EMG, electromyography; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IIM, inflammatory myopathies; MRC, Medical Research Council; MRI, magnetic resonance imaging; MUAPs, motor unit action potentials; LLs, lower limbs; PET, positron emission tomography; SRP, signal recognition particle; STIR, short tau inversion recovery; ULs, upper limbs

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Author contribution DV and PC participated in the acquisition and analysis of data, and in the critical revision; AB, VAS, and CL participated in the acquisition and analysis of data, in the conception of the manuscript, in drafting the manuscript or figures, and in the critical revision.

Data availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics approval This case report is in accordance with the ethical standards laid down in the declaration of Helsinki and its later amendments.

Consent to participate Not applicable.

Consent for publication The participant has consented to the submission of the case report to the journal.

Conflict of interest CL received compensation for occasional scientific consulting from Neuraltus, Cytokinetics, Mitsubishi Tanabe Pharma Europe, and Italfarmaco and has received funds from ARISLA and Italian Ministry of Health. VAS participates in Advisory Boards or Teaching activities for Biogen, Roche, Avexis, PTC, Santhera, Sarepta, and Dyne. The remaining authors have nothing to declare.

References

1. van der Meulen MF, Bronner IM, Hoogendijk JE, Burger H, van Venrooij WJ, Voskuyl AE et al (2003) Polymyositis: an overdiagnosed entity. Neurology 61(3):316–321. https://doi.org/10.1212/wnl.61.3.316
2. Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR et al (2011) Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 63(3):713–721. https://doi.org/10.1002/art.30156
3. Beydon M, Chevalier K, Al Tabaa O, Hamroun S, Delettre AS, Thomas M et al (2020) Myositis as a manifestation of SARS-CoV-2. Ann Rheum Dis annrheumdis-2020-217573. https://doi.org/10.1136/annrheumdis-2020-217573
4. Zhang H, Charmchi Z, Seidman RJ, Anziska Y, Velayudhan V, Perk J (2020) COVID-19-associated myositis with severe proximal and bulbar weakness. Muscle Nerve 62(3):E57–E60. https://doi.org/10.1002/mus.27003
5. Bolig TC, Abdulaziz N, Schiopu E (2020) Complete recovery from COVID-19 bilateral pneumonia in an immunosuppressed man with immune-mediated necrotizing myopathy. Case Rep Rheumatol 2020:8886324. https://doi.org/10.1155/2020/8886324
6. Velardo D, Faravelli I, Cinnante C, Moggio M, Comi GP (2020) Pediatric anti-HMGCR necrotizing myopathy: diagnostic challenges and literature review. Neurol Sci 41(10):3009–3013. https://doi.org/10.1007/s10072-020-04491-6
7. Adler BL, Christopher-Stine L (2018) Triggers of inflammatory myopathy: insights into pathogenesis. Discov Med 25(136):75–83
8. Upreti S, Fayyaz B, Bongu RP (2019) Anti-HMG-CoA reductase myopathy, an undesirable evolution of statin induced myopathy: a case report. J Commun Hosp Intern Med Perspect 9(1):33–35. https://doi.org/10.1080/20009666.2019.1571882
9. Orsucci D, Ienco EC, Nocita G, Napolitano A, Vista M (2020) Neurological features of COVID-19 and their treatment: a review. Drugs Context 9:2020-5-1. https://doi.org/10.7573/dic.2020-5-1
10. Guidon AC, Amato AA (2020) COVID-19 and neuromuscular disorders. Neurology 94(22):959–969. https://doi.org/10.1212/WNL.0000000000009566