Respiratory dysfunction as first presentation of myasthenia gravis misdiagnosed as COVID-19

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Abstract
Background The outbreak of the coronavirus disease 2019 (COVID-19) has had profound impact on health care not only for its direct effects, but also because it deeply influenced the whole clinical practice and diagnostic pathways, particularly in the acute setting.

Case report We present the case of a patient with respiratory dysfunction due to myasthenia gravis (MG) initially misdiagnosed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection due to ambiguity in the interpretation of radiological and microbiological findings during COVID-19 pandemic.

Discussion Respiratory dysfunction as first clinical manifestation of myasthenia gravis is rare, but potentially very harmful. Emergency physicians should always consider neurological diseases when dyspnea cannot be explained by cardiac or respiratory causes.

Keywords COVID-19 • SARS-CoV-2 • Myasthenia gravis • Dyspnea • Emergency medicine

Introduction
The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a sanitary emergency that has required massive public health efforts and introduced new diagnostic and therapeutic challenges in the everyday practice. Here, we present the case of a patient with fluctuant dyspnea as first presentation of seronegative myasthenia gravis (MG) that was initially misdiagnosed as COVID-19 for his respiratory disturbances.

Case report
A 46-year-old man, with hypertension and past history of cigarette smoking, presented to the emergency department (ED) on March 26 for symptoms consistent with upper respiratory infection (cough, sore throat, and fever). The patient had been put on azithromycin by the general practitioner 3 days before the presentation in the ED. Polymerase chain reaction (PCR) assay on nasal-pharyngeal swab sample was negative for SARS-CoV-2, while a chest X-ray was reported as suggestive for mild interstitial pneumonia. Thus, the patient was hospitalized in a COVID-19 ward and eventually discharged 3 days after, afebrile and without signs of respiratory dysfunction. The diagnosis at discharge was “mild SARS-CoV-2-related pneumonia.”

A few days after discharge, the patient suffered from shortness of breath, generalized weakness, and marked effort intolerance. Moreover, he occasionally found low values of arterial oxygen saturation on self-measurement at home (O2 saturation swinging from 91–97% over the day). For this reason, he presented to ED again on April 4, when another nasal-pharyngeal swab PCR for SARS-CoV-2 was negative. The chest CT scan showed modest bibasilar infiltrates (Fig. 1), and the arterial blood gases were within normal values. The diagnosis of SARS-CoV-2-related infection was confirmed, and the patient was discharged a few hours later in good general conditions.

On April 24, the patient returned to the ED for the third time complaining of persistence of asthenia and blood oxygen desaturation. He was hospitalized again and underwent another panel of investigations, including a PCR assay and a rapid Ig test for SARS-CoV-2 (both negative), an arterial gas analysis (SO2 97%; PO2 74 mmHg [9.8 kPa]; PCO2 44 mmHg [5.8 kPa]; lactate 1.6 mmol/L; HCO3- 26 mmol/L), an echocardiography (normal), a new chest CT scan (mild basilar
infiltrates), and a six-minute walking test (showing arterial oxygen desaturation down to 84%).

Because the prevailing clinical features were fatigue and dyspnea during effort, with only mild pathological findings on chest CT scan, a neurological evaluation was requested at this time to rule out a neuromuscular condition. The consultant neurologist outlined slight hypophonia after sustained speech, slight diplopia, and ptosis in one eye during sustained upward gaze and slight weakness in proximal lower limb muscles (scored 4/5 in the Medical Research Council scale), with normal deep tendon reflexes. Given the presence of mild signs of neuromuscular fatigability, repetitive nerve stimulation was performed, showing 15% decrement in the amplitude of compound muscle action potential registered in right nasalis muscle while stimulating at low frequency (5 Hz) the facial nerve (Fig. 2), strongly supporting a diagnosis of generalized myasthenia gravis (MG).

Quickly after the introduction of anticholinesterase therapy and oral steroid, dyspnea and fatigue significantly improved. Moreover, the 6-minute walking test did not show arterial blood desaturation. Serological testing for antibodies against acetylcholine receptor (AChR), muscle-specific kinase (MUSK), and ryanodin receptor (RyR) was negative. The chest CT scan previously performed was reviewed and no thymic residual tissue was identified. The patient was discharged in good medical condition and put on pyridostigmine 240 mg daily and oral prednisone 50 mg daily. He was instructed to promptly recognize symptoms of muscular fatigability and respiratory failure. At 1-month follow-up, the patient was minimally symptomatic, complaining only mild effort intolerance; he was put on azathioprine, and tapering of oral steroid was planned after 1 month.

Discussion

Respiratory dysfunction as the first clinical manifestation of MG has been rarely described, although no ad
A retrospective study on MG has estimated accurately the frequency of such clinical presentation [1].

Albeit respiratory failure in the context of MG can be extremely severe, in our case dyspnea was predominantly present during effort, and hypoxemia was never harmful. In our patient, MG was probably latent or paucisymptomatic (the patient previously complained of diplopia only if explicitly asked about it). Based on the presence of the symptoms at the very beginning of the clinical presentation including fever, we can hypothesize that the patient suffered an upper respiratory tract infection (not SARS-CoV-2-related) and shortly after developed respiratory muscles weakness due to MG. Azithromycin, which the patient took for 9 days when he had cough and fever, could have had a role in unmasking MG. Of note, hydroxychloroquine, which was widely used during the COVID-19 pandemic and is known to be associated with MG worsening [2], was not prescribed in this patient. Since we did not perform laryngoscopy to evaluate the function of vocal cords, we cannot rule out the occurrence of vocal cord paresis that may have both caused hypophonia and contributed to dyspnea in our patient. Ambiguity in the interpretation of radiological imaging (i.e., chest X-ray and chest CT scan) and microbiological testing (i.e., PCR assay and Ig rapid test), along with the due cautious approach to a case of acute dyspnea during the dramatic COVID-19 outbreak epidemic in an area severely hit by the disease, led to a delay in diagnosis. As it is well known, sensitivity of nasal swab PCR assay is moderate (estimated around 63-78%) [3]; thus SARS-CoV-2 infection could not be ruled out after multiple negative assays. The chest CT scan findings, however, were not specific for COVID-19; in fact, the bibasilar lung infiltrates likely depict atelectasis due to decreased respiratory muscles movement, hence representing a potential “radiological clue” of neuromuscular involvement [4]. In our case, antibodies against AChR and MUSK were tested negative: this condition, namely double-seronegative MG, occurs in about 15% of generalized MG and may be caused by rarer autoantibodies like anti-low-density lipoprotein receptor-related protein 4 (LRP4), and anti-cortactin. [5] Our case underlines the importance of considering neurological causes when dyspnea cannot be explained by cardiac or respiratory causes in the acute setting. Prompt recognition of MG in the case of acute respiratory dysfunction is crucial, and emergency physicians should always include MG in the differential diagnosis. Remarkably, looking for mild symptoms of neuromuscular fatigability such as fluctuant diplopia and ocular ptosis may improve diagnostic accuracy and help recognize generalized MG.

Authors’ contribution All authors contributed equally to the paper.

Compliance with ethical standards
Conflict of interest The authors have no relevant financial or non-financial interests to disclose
Ethical Approval None
Informed consent The participant has consented to the submission of the case report to the journal.

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