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CASE STUDY

Myasthenia gravis associated with anti-MuSK antibodies developed after SARS-CoV-2 infection

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Abstract

Introduction: Since the onset of the novel coronavirus pandemic, several neurological complications secondary to SARS-CoV-2 infection have been reported, affecting central nervous system, peripheral nervous system and neuromuscular junction.

Case report: We present the case of a 77-year-old man who developed bulbar myasthenia gravis (MG) eight weeks after SARS-CoV-2 infection. The search for serum antibodies against the acetylcholine receptor and the muscle-specific tyrosine kinase (MuSK), performed by radioimmunoassay (RIA), and the search of low-density lipoprotein receptor-related protein 4 antibodies, performed by immunohistochemistry, resulted negative, while anti-MuSK antibodies were detected by cell-based assay (CBA). The patient was treated with pyridostigmine (60 mg four times a day) with unsatisfactory clinical response, followed by immunosuppressive therapy (azathioprine 1.5 mg/kg/day) with improvement of MG symptoms after two months of treatment.

Discussion: Several viral diseases have been described as associated with the onset of MG, although the underlying mechanisms are not yet fully understood. Similarly, a growing number of scientific reports suggest a correlation between SARS-CoV-2 infection and autoimmune diseases. The interest of our case lies in the timing of the MG onset (after 2 months from infection), together with the unusual late onset of anti-MuSK MG. These elements suggest that coronavirus infection may act as a trigger of the disease. We confirm the importance of CBA in the serological diagnosis of RIA-negative MG.

KEYWORDS
anti-MuSK antibodies, cell-based assay, myasthenia gravis, SARS-CoV-2

INTRODUCTION

Some cases of myasthenia gravis (MG) associated with anti-acetylcholine receptor (AChR) autoantibodies following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported (range of ages, 21–65 years) [1–3]. Moreover, cases of SARS-CoV-2 infections have been reported in patients already diagnosed with anti-muscle-specific tyrosine kinase (MuSK)-MG [4]. In this report, we describe an anti-MuSK-MG case with onset 8 weeks after SARS-CoV-2 infection.

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CASE REPORT

We describe the case of a 77-year-old man without relevant past medical history, who was diagnosed with SARS-CoV-2 infection in March 2020. He presented with bilateral interstitial pneumonia, dyspnea, and fever. His clinical conditions slowly improved,

Abbreviations: AChR, anti-acetylcholine receptor; CBA, cell-based assay; LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific tyrosine kinase; NMJ, neuromuscular junction; RIA, radioimmunoassay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

and the oropharyngeal swab turned negative after 42 days from diagnosis. Eight weeks after the onset of SARS-CoV-2 infection, the patient complained of chewing difficulty, dysphonia, diplopia, and eyelid ptosis, worsened by muscular activity, and suggestive for MG. No weakness of limbs or respiratory muscles was evident. The diagnosis of MG was confirmed by electrophysiological study (repetitive nerve stimulation and single-fiber electromyography). Chest computed tomography was negative for thymic changes. Radioimmunoassay (RIA) for anti-AChR and anti-MuSK antibodies was performed twice, at disease onset and after 1 month, and resulted negative, as were low-density lipoprotein receptor-related protein 4 (LRP4) antibodies tested by immunohistochemistry. Therefore, the patient's serum was tested by cell-based assay (CBA)[5] approximately 3 months after disease onset, which was positive for anti-MuSK antibodies (Figure 1). Because the response to pyridostigmine (60 mg four times a day) was unsatisfactory, immunosuppressive therapy with azathioprine was started, reaching the final dosage of 1.5 mg/kg body weight/day, with improvement of chewing and eyelid ptosis after 2 months of treatment. No further increase of azathioprine dosage was needed. Steroids were avoided due to a history of severe arterial hypertension upon steroid administration. At the last visit in September 2020, the patient's only complaint was mild chewing fatigability. Clinical features, electrophysiological findings, antibody positivity, and the lack of response to pyridostigmine were all consistent with the diagnosis of MuSK-MG (grade IIb, according to the MG Foundation of American Clinical Classification) [6].

DISCUSSION

Myasthenia gravis is the most common autoantibody-mediated autoimmune disease of the neuromuscular junction (NMJ). RIA represents the gold standard in the serological diagnosis of MG. Approximately 85% of MG patients have anti-AChR antibodies, and approximately 40% of those who are AChR antibody–negative have anti-MuSK antibodies [7]. More recently, antibodies directed against other proteins of the NMJ, such as LRP4 antibodies, have been described in a small number of patients [7]. The use of the CBA technique, which has a higher sensitivity than RIA but retains the same specificity, has proven helpful in the serological diagnosis of RIA-negative MG cases [7]. This patient was affected by mild MG symptoms that were easily managed with low-dose immunosuppression. This finding is in agreement with earlier observations that patients who tested positive with only CBA have milder MG than RIA-positive cases [5].

It has long been known that infections can both precede the onset of MG and trigger disease deteriorations, as with other autoimmune disorders [8]. Specifically, there have been several reports about SARS-CoV-2' potential for inducing autoimmune diseases including MG [9]. The mechanisms through which viral agents could trigger autoimmunity are not fully clarified. Increased release of type I interferons and other proinflammatory cytokines, T-cell activation, molecular mimicry, and epitope spreading may be involved [9]. The development of MG symptoms within 2 months after SARS-CoV-2 and the unusually late onset of MuSK-MG support the hypothesis that the viral infection represented a trigger for MG, even though we

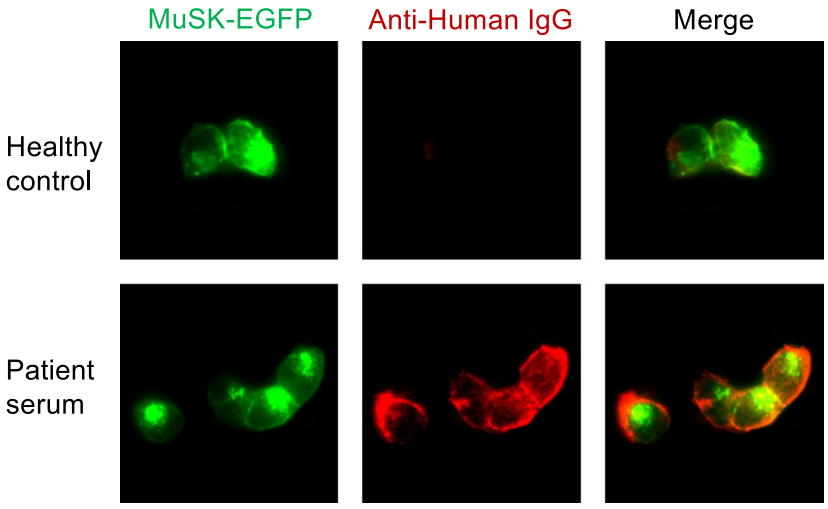

FIGURE 1 Cell-based assay results. IgG antibody binding (red) of the patient's serum (bottom) and healthy control serum (top) to human embryonic kidney 293 (HEK293) cells expressing MuSK-EGFP (green). For this study, HEK293 cells were transfected with complementary DNAs (cDNAs) expressing human acetylcholine receptor α, β, δ, and ε/γ subunits, and rapsyn-EGFP in a ratio 2:1:1:1:1; full length MuSK-EGFP [5], and cDNAs expressing human lipoprotein receptor-related protein 4 with a chaperone protein (low-density lipoprotein receptor–related protein associated protein 1) to enhance cell surface expression. Serum was diluted 1:20 and scored 3 based on a score system from 0 = negative to 4 = strong labeling of almost all transfected cells as previously described [4]. EGFP, enhanced green fluorescent protein; IgG, immunoglobulin G; MuSK, muscle-specific tyrosine kinase. [Colour figure can be viewed at wileyonlinelibrary.com]

cannot exclude that the viral infection unmasked latent MG. In conclusion, following SARS-CoV-2 infection, MG may present in elderly people and may not be easily recognized in the postinfection period because of comorbidities and when patients are seronegative on the standard RIA and immunohistochemistry. The prospective evaluation of patients with post–SARS-CoV-2 MG will provide valuable information about their long-term outcome, which could contribute to clarifying the association between SARS-CoV-2 and increased risk for development of autoimmune conditions.

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AUTHOR CONTRIBUTIONS

Andrea Assini: Conceptualization (lead); methodology (lead); writing–original draft (equal). **Ilaria Gandoglia:** Writing-original draft (lead). **Valentina Damato:** Methodology (equal). **Klaudio Rikani:** Methodology (equal). **Amelia Evoli:** Methodology (lead). **Massimo Del Sette:** Supervision (lead); writing–original draft (equal).

DISCLOSURE OF CONFLICT OF INTEREST

The authors declare no financial or other conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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