

MuSK+ Myasthenia Gravis Presenting with Severe Sleep Apnea, Respiratory Dysfunction and Response to Rituximab

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Introduction

MuSK+ MG is a rare subtype of MG that affects predominantly female individuals and manifests with striking features of cranial, bulbar and respiratory muscle weakness during the disease course (1). Isolated or predominantly respiratory failure is rare at presentation, however progression to severe bulbar weakness and respiratory crisis are distinctive features of MuSK+ MG, which poses significant diagnostic challenges, considering the low prevalence of the disease (2-4). Furthermore, patients frequently have poor response to standard immunotherapies and higher rate of life-threatening crisis, adding significant challenges for disease management. We report a case of reversible respiratory muscle dysfunction at disease onset, leading to dyspnea, sleep apnea and hypoventilation in a patient with MuSK+ MG. While it is acknowledged that the current case is a rare presentation of a rare disease, it raises a number of treatment considerations and as such we wish to highlight these features through this report.

Case Report

Clinical presentation and initial investigations

A 53-year-old woman presented to the emergency

department with dyspnea and orthopnea that progressed over 5 months. Past medical history was relevant for type 2 diabetes (HbA1C of 6.4%, without any micro or macrovascular complications), hypertension and depression. She had recently been diagnosed with severe obstructive sleep apnea (OSA). The sleep study done at another facility showed a total apnea-hypopnea index (AHI) of 53.4/hour in NREM and 63.1/hour in REM sleep, along with sustained oxygen desaturation suggestive of hypoventilation (minimum saturation of 55.1% and 94.8% time spent below 90% saturation). On initial neurologic examination, cranial nerves were normal. There was no facial, or bulbar weakness, ptosis or restricted ocular movements and palate elevation was symmetric. Muscle power was mildly reduced in neck extension/flexion, arm abductors and hip flexors (4+/5 MRC - Medical Research Council muscle scale). She had an unremarkable cardio-respiratory examination and was of normal body mass index (BMI).

Nocturnal non-invasive ventilation with bi-level positive airway pressure ST (Resmed Stellar™ 150) plus supplemental oxygen was started following her admission to hospital. She required an inspiratory positive airway pressure (IPAP) of 21cmH₂O, an expiratory positive airway pressure (EPAP) of 9cmH₂O and a backup rate of 16 breaths per minute to abolish the obstructive events and improve gas exchange.

Chest CT was normal, with no mediastinal or pulmonary masses, infiltrative or infectious processes. Diaphragm M mode/two-dimensional B mode ultrasound imaging during quiet inspiration showed normal baseline thickness and a normal thickening fraction of 35% with inspiration. A transthoracic echocardiogram was normal. Forced vital capacity (FVC) was 1.18 liters seated and 0.69 liters supine (supine: seated FVC difference of 41.5%). Venous blood gas measurements showed pH of 7.38, pCO₂ of 60mm Hg, pO₂ of 52mmHg, HCO₃ of 36 mmol/L. Phrenic nerve conduction studies were normal. Repetitive nerve stimulation of the facial and accessory nerves showed no significant decrement in amplitude (4% in the frontalis, 2% in trapezius). Electromyography of the upper limb

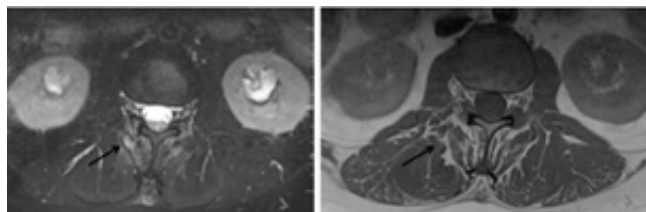


Figure 1. Axial T2 images with fat suppression of the lumbar paraspinal muscles showing atrophy of the intrinsic paraspinal musculature and fatty replacement at L3 spinal level (arrows).

muscles was normal, but there were myopathic motor unit action potentials and early recruitment in the hip flexors and paraspinal muscles, with fibrillation potentials and complex repetitive discharges. MRI spine showed atrophy and edema of the intrinsic paraspinal musculature, fatty replacement, with normal sign and muscle volumes in bilateral hip and thigh muscles (Figure 1). CK was 39 U/L (normal <149). A dried blood spot test for acid maltase deficiency was normal.

A latissimus dorsi biopsy was done in the seated position as she could not tolerate prone position due to respiratory distress. A Next Generation Sequencing gene panel including 90 genes encompassing limb-girdle muscular dystrophies, rigid spine, nemaline, myofibrillar and centronuclear myopathies, inclusion myopathies, metabolic myopathies and congenital myasthenic syndromes was also done and did not find any pathogenic gene mutations or variants of unknown significance. Single-fiber EMG of the frontalis muscle was abnormal, showing 56% abnormal pairs, 44% blocking and mean elevated jitter at 270.1µs. Acetylcholine receptor (AChR), low-density lipoprotein receptor-related protein 4 (LRP4), and Anti-MUSK antibodies were requested.

Clinical Progression and Treatment

Symptoms progressed over the next month with increased dyspnea and orthopnea, new-onset diplopia, mild dysphagia and dysarthria, mild left-sided fatigable ptosis, mild bilateral facial weakness and restricted extra-ocular movements with diplopia on extreme gaze. The patient developed a constant head drop (neck extension 3/5 MRC), and strength was reduced in the hip and shoulder girdle muscles. Myasthenia Gravis Foundation of America (MGFA)(5) class was IVb, as defined as severe weakness predominantly affecting oropharyngeal and respiratory muscles. Myasthenia Gravis Impairment Index (MGII)(6) was 46 out of 84 possible points (higher scores meaning more severe disease) and she was again admitted to the

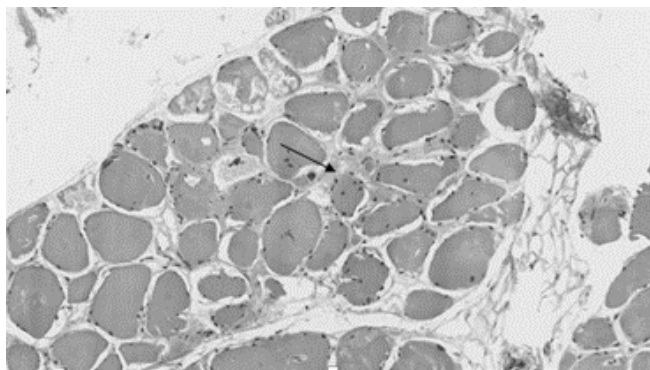


Figure 1. Morphological findings in latissimus dorsi muscle biopsy showing moderate variability in fiber size, scattered atrophic fibers and focal endomysial fibrosis (arrow).

hospital to facilitate treatment and for monitoring.

A formal clinical swallowing assessment was not suggestive of pharyngeal propulsion impairment and there were no signs of laryngeal penetration. Muscle biopsy showed focal endomysial fibrosis, fatty infiltration, normal glycogen content and no inflammatory changes (Figure 2). Gomori trichrome did not show any ragged red fibres, nemaline bodies or rimmed vacuoles. NADH showed normal checkerboard pattern without cores. PAS showed normal glycogen content and ORO showed normal lipid content. Congo red did not demonstrate any amyloid deposit. Immunostain for TDP-43 was negative.

Acetylcholine receptor (AChR) and low-density lipoprotein receptor-related protein 4 (LRP4) were negative. Anti-MUSK antibodies were positive, with high titers at 52 nmol/L (normal <13nmol/L), confirming the diagnosis of MUSK+ MG.

During this hospitalization she received a 5-day course of intravenous immunoglobulin (IVIg, 2g/Kg), and started a course of oral prednisone at a dose of 50mg/day (0.6mg/Kg/day). This therapy was chosen due to the recent progression of weakness, head drop, respiratory and bulbar symptoms given the likely favorable/fast response in severe sudden clinical deterioration. Plasmapheresis was considered, but given the restricted availability, this treatment was deferred and would be considered in case of further deterioration. Over the following two weeks, she had a significant improvement in diplopia/ptosis, however, no effect on respiratory and bulbar dysfunction, which prohibited safe discharge from hospital.

She was subsequently started on Rituximab infusions (710mg intravenous once a week, corresponding to approximately 375 mg/m²) and after the second infusion she had a significant improvement of her overall strength, shortness of breath and orthopnea; complete resolution of diplopia, ptosis, dysarthria and dysphagia. Given the clinical improvement and to minimize time in hospital, the remaining 2 weekly infusions were performed in an infusion centre, as the first wave of the COVID-19 pandemic accelerated in the Province of Ontario, including outbreaks in the hospital where she was admitted.

One month after the last rituximab infusion, she had a significant improvement of her neck weakness, without any need to support her head (MRC 4) and could ambulate for several blocks with no shortness of breath. There was minimal proximal weakness in her lower limbs (4+) and no fatigability. MGII score was 3 out of possible 64 points on the score questionnaire. MGFA class was now IIIb. Prednisone was progressively tapered to 10mg over the following 2 months to optimize type 2 diabetes mellitus control. Her IPAP settings were adjusted to 14cm H₂O,

EPAP to 8cmH₂O, improved since the initial adjustment, with complete resolution of her sleep apnea symptoms. Arterial blood gas measurements normalized: pH of 7.42, pCO₂ of 31mm Hg, pO₂ of 104 mm Hg, HCO₃ of 20 mmol/L. Additionally, at the 3-month mark, there was a significant improvement in FVC (3.3 litres), respiratory pressures were also normal (MIP 60cmH₂O, MEP 95cm H₂O, SNIP max 91cmH₂O). She could lie flat for longer periods and no longer experienced orthopnea.

Discussion

We report a 53-year-old woman presenting with dyspnea and sleep apnea for 6 months and mild proximal weakness on examination who demonstrated myopathic changes on paraclinical tests and was ultimately diagnosed with MuSK +myasthenia gravis. She exhibited partial response to IVIG and steroids and subsequent near complete response to Rituximab. Although there have been previous reports of MuSK + MG producing respiratory dysfunction, myopathic changes and response to Rituximab, our case is unique due to the early presentation with isolated sleep apnea and hypoventilation, followed by mild limb and bulbar weakness, severe neck weakness, the comprehensive clinical neuromuscular characterization, association with markedly high MuSK antibody titres and treatment decisions posed by the rapidly progressing COVID-19 pandemic.

Isolated respiratory dysfunction at presentation has been reported in a minority (2% of patients) in two large cohorts and in smaller case series of patients which included MuSK+ MG. (2-4). In spite of the rarity of a respiratory presentation, respiratory crisis (MGFA class V) can occur at some point in the disease course in 32 to 52% of MuSK+ MG cases reported in the literature (1, 7). Our patient developed mild limb and bulbar weakness and neck weakness only after presenting with respiratory dysfunction for 6 months, imposing significant challenges for clinical diagnosis and treatment.

In the only previously reported case of MuSK+ MG presenting with severe OSA (AHI of 31/hour), the patient had concurrent bulbar dysfunction as part of their presentation, something not observed in our case initially. An increased prevalence of sleep disordered breathing/OSA has been reported in some studies including patients who are AChR antibody positive as well as in children with MG (8, 9); however, not all studies have found this association (10). In a recent single-center study, the risk of OSA in MG patients was associated with the same risk factors as the overall population, including male sex and obesity (11). Risk factors leading to sleep apnea in MuSK+ MG are lacking in the literature, and notably our patient was

neither male nor obese. She also did not have prominent bulbar symptoms until later in the disease course, which has also been implicated as a cause of airway obstruction during sleep leading to apnea. As such, it is difficult to conclusively determine the mechanism leading to OSA in our patient, however, the marked improvement in OSA after immunotherapy implicates MG as the major reason for this finding.

Our patient did appear to show signs of diaphragmatic dysfunction which was worse in REM sleep and associated with supine changes in FVC of 41.5%, exceeding the 25% limit, which is usually associated with diaphragmatic weakness (12). In our patient, normal diaphragmatic ultrasound and evidence of myopathic changes in the paraspinal and proximal muscles tested indicates that the diaphragm was neither the sole driver of respiratory dysfunction nor severely damaged or atrophied (13). We could not directly assess whether myopathic changes in respiratory muscles could have contributed to her respiratory weakness, as we did not perform electromyography of the diaphragm or intercostal muscles. Hemidiaphragm atrophy has been reported in one patient with MuSK+ MG who presented with isolated dyspnea and had decreased diaphragmatic thickness and excursion with inspiration (12). This is in contrast to our patient with normal thickness and thickening fraction, and is not surprising given the reversible nature of the respiratory deficits.

Chronic myopathic changes including muscle atrophy and fatty replacement on MRI imaging in limb, facial and ocular muscles have been previously reported in patients with MuSK + MG (14, 15). Experimental studies suggest that MuSK plays a significant role in the development and maintenance of the neuromuscular junction, with anterograde and retrograde signaling roles, resulting in AChR clustering in the post-synaptic folds, a process essential for neuromuscular transmission (16). Histologic analysis in MuSK+ MG involved muscles shows increase in cytochrome c oxidase (COX)-negative fibres, mitochondrial aggregates and myofibrillar disarray, implicating mitochondrial dysfunction as a contributor to pathophysiology (14, 17, 18). Our patient had edema and fatty replacement of the intrinsic paraspinal muscles, along with chronic myopathic changes, which indicate that part of her weakness might be due to an underlying myopathic process. An extended genetic panel for myopathy was negative, and as such, the possibility of a concomitant hereditary myopathy is highly unlikely. After confirming the diagnosis of MuSK + MG, additional staining and electron microscopy were deferred.

We believe that the clinical presentation in our patient could be related to markedly elevated serum concentrations

of MuSK Immunoglobulin G4 (IgG4) antibodies, as those levels correlate with clinical changes (1, 19). High levels of MuSK antibodies have been associated with severe presentations, such as respiratory failure, as was the case in our patient. To our knowledge this is the highest reported antibody titer (52 nmol/L) as compared to other cases in the literature (4, 20). Also, improvement in response to Rituximab infusions seems to correlate with MuSK antibody titers as was the case in our patient (20). In recent years, there is growing evidence that Rituximab treatment in refractory MG, particularly MuSK+ MG leads to significant and sustained improvement and should be considered an early therapeutic option in severe cases (3, 21, 22).

Although steroids can induce early clinical remission in some MuSK+ patients, progressive deterioration often occurs in spite of prolonged, high dose steroids and can result in a fixed steroid-induced myopathy (1, 23, 24). Our patient experienced improvement in bulbar and respiratory function only after the first Rituximab infusion, in contrast to IVIG and steroid treatment, which only resulted in improvement of the ocular symptoms. Although some patients can have a delayed response to steroid or IVIG treatment, this is uncommon, and in our case, it was felt that the additional time spent in the hospital waiting for a response would confer additional risk of COVID-19 infection. Although the MGFA COVID-19 management recommendations (25) state that other immunomodulatory treatments should be considered prior to Rituximab, we propose this clinical scenario as one example where this treatment should be considered early, and ideally while self-isolating.

In summary, we highlight through this case that respiratory muscle dysfunction leading to dyspnea and hypoventilation can be an isolated presentation of MuSK + MG. Our case further provides evidence that myopathic changes can occur in MuSK + MG and contribute to respiratory symptoms through reversible dysfunction of diaphragm and accessory breathing muscles. Additionally, in patients being considered for neuromuscular causes of respiratory dysfunction including sleep apnea, single fiber EMG and reflexive MG antibody panels, including MuSK testing is necessary to completely exclude patients with MuSK+ MG who can present in this manner. Finally, we recommend that early treatment with Rituximab should be considered in bulbar and respiratory presentations of MUSK+ MG, as this can cause rapid improvement and avoid complications and ineffectiveness of more traditional immunotherapy.

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