CASE REPORT

Bali Medical Journal (*Bali MedJ)* 2021, Volume 10, Number 1: 314-319
P-ISSN.2089-1180, E-ISSN: 2302-2914

Bali Medical Journal
www.BaliMedicalJournal.org
Published by Bali Medical Journal

Myasthenia gravis and arrhythmias in COVID-19: a case report

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Received: 2021-01-04
Accepted: 2021-04-20
Published: 2021-04-30

ABSTRACT

Background: Myasthenia Gravis (MG) is an autoimmune disorder, which autoantibodies against postsynaptic (muscle) nicotinic acetylcholine receptors (nAChR). MG patients have a higher prevalence of cardiac manifestations in the presence of thymoma. It is not known whether Coronavirus disease 2019 (COVID-19) can cause more severe illness in patients with chronic neuromuscular disorders such as MG, which can cause respiratory muscle weakness, or in those who are immunosuppressed. This case report will discuss patient with MG, thymoma, atrial fibrillation, and COVID-19.

Case presentation: A 60-year old man came to the hospital with difficulty of swallowing. He had nasal voice and dropping of eyelids. These complaints were happened repeatedly, worsened at night and got better in the next morning. From the neurological examination, it was also obtained Wartenberg test (+), counting test (+), and prostigmine test (+). Atrial fibrillation was found with normal ventricular response and decreased systolic left ventricular function on the electrocardiogram and echocardiography. On the chest MSCT, a lobulated homogeneous solid mass was found in anterior mediastinum which supported the image of thymoma, and there was the imaging of typical viral pneumonia. The patient also had the positive result of COVID-19 PCR test.

Conclusion: MG patients have been shown with abnormal manifestations of heart rhythm. This may reflect as a complication of myocarditis or autonomic nervous system dysfunction. COVID-19 infection in MG can be challenging for many reasons. Current guidelines recommend continuing the current standard care treatment of MG during hospitalization.

Keywords: atrial fibrillation, autoimmune, COVID-19, myasthenia gravis, thymoma.
Cite This Article: Tugasworo, D., Kurnianto, A., Retnaningsih., Andhitara, Y., Ardhini, R., Daynuri., Budiman, J. 2021. Myasthenia gravis and arrhythmias in COVID-19: a case report. *Bali Medical Journal* 10(1): 314-319. DOI: 10.15562/bmj.v10i1.2168

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disease that autoantibody against nicotinic acetylcholine receptor (nAChR). This blockade and downregulation of nAChR reduce nerve impulses that can generate muscle action potentials.[1–3] The incidence of MG is 5-30 cases per 1 million per year with a prevalence of 10-20 cases per 100,000 population. MG mostly occur at the age of 30-50 years with the majority gender is woman.[1–c] Myasthenia gravis is a progressive disease with high mortality rate in the first 2 years, which is about 5%.[1–4]

Thymus abnormalities are common in MG patients. About 10% of MG patients are associated with thymoma. Most thymomas can produce T cells.[6-8] MG is an autoimmune disorder related to T cells and B cell-mediated. MG requires CD4+ T cells (T helper cells) for the production of autoantibodies against nAChR. T helper cells produce inflammatory cytokines that induce autoimmune reactions to self-antigens and eventually activate B cells. nAChR antibodies will activate the post-synaptic complement sequence of muscle surfaces.

Furthermore, nAChR antibodies will react with nAChR and increasing endocytosis and degradation. nAChR antibodies will then inhibit nAChR activation by blocking nAChR binding sites or inhibition of ion channel gate opening. The decrease of nAChR activation will decrease the motor endplate. Skeletal muscle weakness arises from a reduced potential in the motor endplate so that the muscle cannot generate an action potential and cannot stimulate muscle fiber contraction.[6,7,9] MG is known to involve other body systems including the heart. MG patients have a higher prevalence of cardiac manifestations in the presence of thymoma.[10] The cardiac manifestations of MG are associated with immunological response against myocardium and interfering cardiac conduction.[10-12]

Coronavirus disease 2019 (COVID-19) has rapidly developed into a global pandemic. Respiratory failure and COVID-19-related death were driven in part by a massive inflammatory response.[13] Neurological sequelae, including cerebrovascular events, impaired consciousness, skeletal muscle injury, and meningoencephalitis, can complicate the disease.[14] It is not known whether COVID-19 causes more severe disease in patients with chronic neuromuscular disorders such as MG, which can lead to

respiratory muscle weakness, or in those who are immunosuppressed. In addition, if there is concurrent respiratory muscle weakness, MG patients may increase the risk of complications related to COVID-19. Existing guidelines for the management of COVID-19 in patients with MG are based on expert consensus.[15,16]

The case reports about MG with thymoma, heart disorder, and COVID-19 are still limited. This case report will discuss about a 60-year old man with MG, thymoma, atrial fibrillation, and COVID-19.

CASE PRESENTATION

A 60-year old man came to the hospital with difficulty of swallowing for 1 month. He can only eat porridge and mushy rice. He had nasal voice especially when talk too much, and dropping of eyelids. These complaints were happened repeatedly, worsened at night and in excessive activity and got better in the next morning. The patient had the history of hypertension

The vital sign of the patient was blood pressure: 120/80mmHg, pulse rate: 92beats/minute, respiratory rate: 20 beats/minute, body temperature: 36.6^{0}C, and body weight: 60 kg. The neurological examination result was Glasgow coma scale (GCS): E4M6V5, ptosis in both eyelids and Wartenberg test had positive result (both eyelids became ptosis), dysphagia and dysphonia, counting test had positive result (the voice became nasal voice on the count of 9), paraparesis with motoric strength 3 (against gravity), prostigmine test had positive result (the muscle got better when the prostigmine was injected).

The interpretation of the electrocardiogram (ECG) was atrial fibrillation with normal ventricular response (NVR) that can bee is seen in figure 1. The result of the echocardiography examination was concentric left ventricular hypertrophy, region wall motion abnormality (+), decreased left ventricular systolic function with 48% left ventricular ejection fraction, normal right ventricle systolic function, tricuspid annular plane systolic excursion 19 mm, and normal heart valves. The result of chest X-ray examination was in normal limit (Figure 2). The result of chest MSCT

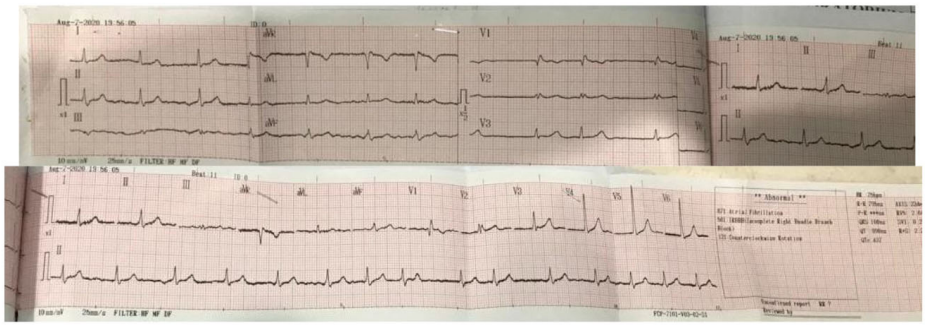

Figure 1. ECG shows atrial fibrillation with normal ventricular response.

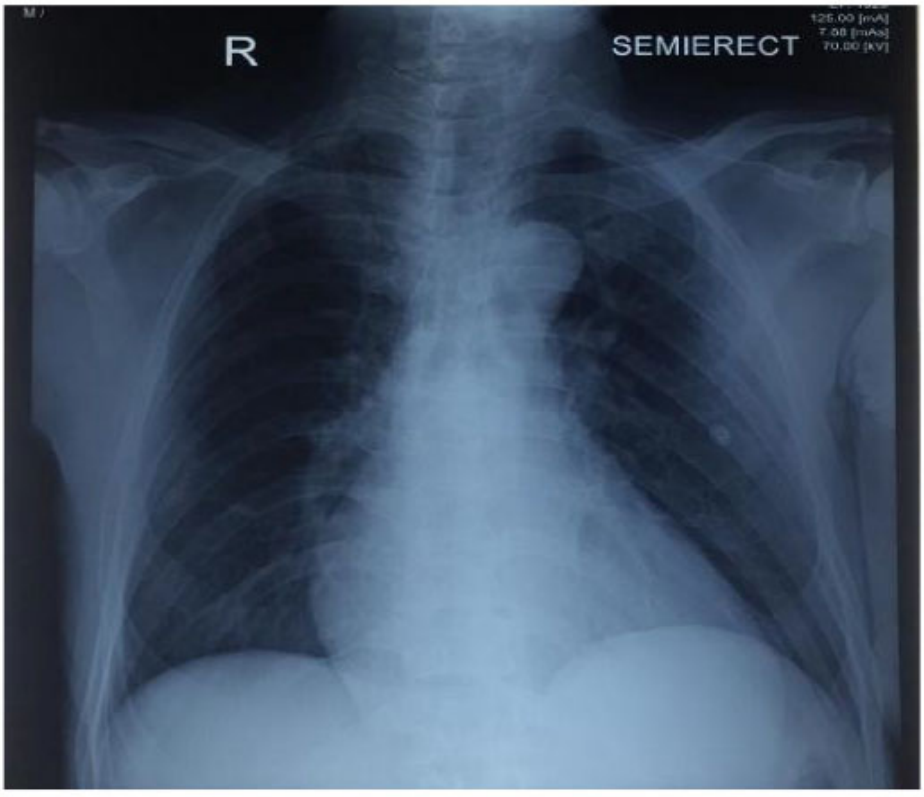

Figure 2. Chest X-ray

was a lobulated homogeneous solid mass was found in anterior mediastinum which supported the image of thymoma at the height of the vertebral body of thoracal 5 to thoracal 8 (AP1.8 X LL3.0 X CC6.2 cm) which partial part attached to the ascending aorta and there was subpleural infiltrates at segment 3 and 6 right lung, subpleural infiltrates of the segment 6 left lung and groundglass opacity of the subpleural segment 1, 2, and 3 of the left lung which correspond to typical viral pneumonia (Figure 3). The patient underwent a rapid test for COVID-19 and showed reactive results, and examined for the naso/oropharyngeal swab for Real Time-Polymerase Chain Reaction (RT-PCR) SARS-CoV-2 examination and the result was positive.

Patients were given infusion of ringer lactate 20 drops per minute, ranitidine injection 50mg/12hours intravenously, mestinone 60mg/8hours orally, ramipril 5mg/24hours orally, carvedilol 6.25mg/12 hours orally, warfarin 2mg/24 hours orally, and vitamin B1B6B12 1 tablet/8hours orally. The patient was programmed for therapeutic plasma exchange (TPE) and

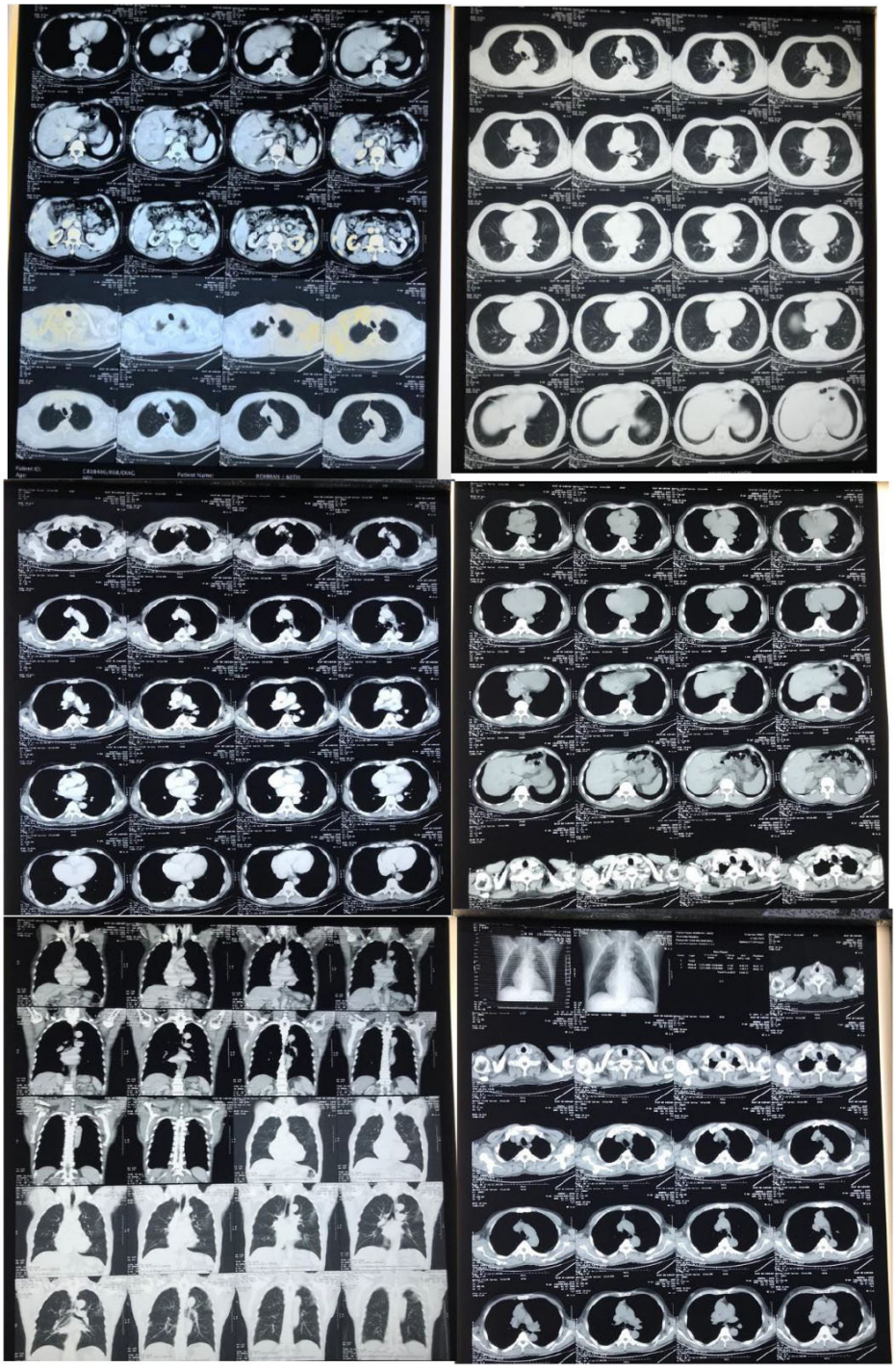

Figure 3. Chest MSCT

thymectomy surgery.

DISCUSSION

MG is clinically characterized by fatigue and weakness in body muscles. The muscle weakness increase throughout the day, worsen with activity and improve with rest. The other clinical characteristic can be found in MG including ptosis, diplopia, dysarthria, dysphonia, dysphagia, and weakness of the respiratory muscles. Ocular muscle weakness is usually bilateral and asymmetrical and results in diplopia (double vision) or ptosis (dropping of upper eyelid).[6,7,17] The quadriceps, triceps, and neck extensor muscle appear to be affected first in limb weakness. The most serious symptom is respiratory distress due to weakness of the diaphragm and intercostal muscles. These respiratory symptoms accompanied by severe bulbar symptoms, are called myasthenic crises and require mechanical ventilation.[6,7]

MG's most common cause is the abnormal development of antibodies to the immunogenic region (epitope) around the nAChR from the post-synaptic endplate region at the neuromuscular junction. These nAChR antibodies induce immune-mediated degradation of nAChR and the post-synaptic membrane.[1,17,18] The loss of a large amount of functional nAChR will decrease the amount of muscle fibers that can depolarize during motor nerve terminal activation, resulting in reduced formation of muscle fiber action potentials and muscle fiber contraction. Neuromuscular transmission blockage causes clinical weakness when it affects a large number of muscles. Fatigue or exhaustion occurs due to a decrease in the number of presynaptic vesicles along with continued activity.[1,18]

Patients who are suspected of having MG can be diagnosed based on several examinations, including simple clinical examination, namely Wartenberg test/ Simpson test (where the patient is asked to look at the object above the plane between the eyeballs >30 seconds, if ptosis occurs then the test result is positive) and a vocal cords test where the patient is asked to count 1-100, if the voice will gradually disappear then the test result is positive.[19-21]

In addition, you can do tensilon test, examination of acetylcholine receptor antibodies in serum, EMG, and chest MSCT. In the tensilon test, the patient will be given an injection of edrophonium chloride (tensilon) which is a short-acting anticholinesterase, which will have a temporary reduction or loss of muscle weakness. However, this test is not recommended in patients with heart problems because of its bradycardic effect. Meanwhile, the EMG can be assessed the amplitude of the action potential of a muscle group, which decreases when repeated stimulation of nerves to the muscles.[21,22]

About 10% of MG patients are associated with thymoma. Thymoma is a tumor in the thymus that originates from epithelial cells. Thymoma can be detected with chest MSCT, which can

be found as anteroposterior mediastinal mass. Macroscopically, the thymoma is a solid and lobulated gray-white mass with the longest size reaching 15-20 cm.[6,7,23] Most thymomas appear large and encapsulated, but in 20%-25% there is capsule penetration and tissue infiltration of structures around the thymus. Microscopically, almost all thymus cells consist of a mixture of epithelial cells and non-neoplastic lymphocyte infiltrates. In benign thymomas, the epithelial cells tend to be similar to those in the medulla and are often elongated or coiled. This is also known as thymoma medularis. Most of the patients with thymoma were asymptomatic, and 30%-40% only have local manifestations such as cough, shortness of breath, superior vena cava syndrome and others are associated with MG.[6,7]

The acetylcholine receptor has five units (2α, 1β, 1δ, 1γ or ε) around the central pore; α units contain acetylcholine binding sites and primary immunogenic sites.[2] Anti-AchR antibodies are positive in 85% of the common forms of myasthenia gravis and in 50% of the ocular forms, and negative results do not exclude the diagnosis, since so far 40% of cases with negative antibodies have anti-MuSK (specific muscle kinase) receptors, which play an essential role in post-synaptic differentiation of acetylcholine receptors. Positive anti-MuSK antibodies are more common in female patients and respiratory and also bulbar muscles are frequently involved. Other types of antibodies in myasthenia gravis are anti-smooth muscle antibodies (84% of patients younger than 40 years without thymoma or patients over 40 years with thymoma) and striational antibodies (anti muscle protein titin and anti ryanodinic receptor) which link themselves. itself in a cross-linking pattern at different epitopes in the skeletal and cardiac muscles.[10,11] Anti-Kv 1.4 antibodies have been associated with bulbar involvement, myasthenic crisis, thymoma, myositis, and myocarditis. Anti-Ach antibodies correlate with early onset of disease and seronegativity is associated with ocular form myasthenia. Almost all patients with myasthenia gravis and thymoma and half of the patients with myasthenia gravis (>50 years) have these antibodies.[10,11]

MG is known to involve other body organ, including the heart. MG patients have a higher prevalence of cardiac manifestations in the presence of thymoma, suggesting an autoimmune or paraneoplastic etiology.[7,24,25] The presence of all antibodies and as yet uncharacterized antibodies raises theoretical mechanisms for cardiac involvement in MG, by interfering with contractility, cardiac conduction, autonomic regulation or by immunological attack on the myocardium, involving complement activation, inflammatory cell infiltrates and consequently necrosis.[10–12,25,26] ECG abnormalities can be found in patients with MG and the most common forms are non-specific ST-T changes, abnormal T waves, prolonged QT interval, sinus tachycardia, arrhythmias, and bundle branch block.[10,27] A retrospective observational study involving 117 patients showed non-specific ECG changes. Sixty percent of those with anti-Kv 1.4 antibodies had ECG abnormalities, the most common of which were T wave abnormalities and QT prolongation. Anti-Kv 1.4 antibodies have also been associated with a more severe form of MG, a lethal arrhythmia including ventricular tachycardia, sick sinus syndrome, complete AV block and sudden death with prolonged QT intervals and non-specific ST-T changes.[10-12]

Another important part is the possibility of iatrogenic cardiac involvement during treatment with acetylcholine esterase (ACh-I) inhibitors which can cause bradycardia, hypotension, syncope, atrioventricular heart block due to increased amounts of acetylcholine at the synapse.[12] Several reports mention cases of vasospastic angina, acute myocardial infarction due to coronary artery spasm during a cholinergic crisis and the proarrhythmic effect of the ACh-I drug.[11] It is not clear whether the ACh-I effect is a direct pharmacological effect on the myocardium, whether it is an indirect effect that alters autonomic control of cardiac function or due to decreased receptor modulation in MG patients who are continuously treated with ACh-I. However, the effect of ACh-I on cardiac function in MG patients, suggests that there are changes in heart function responsive to AChI in some MG patients.[10,12]

Jacobs DH (2020) explained about possible mechanism of atrial fibrillation in myasthenic crisis.[28] Sympathetic tone during severe illness may have stimulated cardiac conduction and caused arrhythmias.[25,28] A damaged baroreflex can lead to conduction abnormalities including atrial fibrillation and sudden death. This study demonstrated an increased incidence of atrial fibrillation, extra ventricular and supra-ventricular systole and prolonged QTc in MG with thymoma. Old studies cited in this study have shown low plasma noradrenergic activity and high compensatory adrenergic activity suggest sympathetic deficiency. One possible explanation for autonomic dysfunction is that 20% of cases of thymoma and about 3% of MG without thymoma have antibodies to ganglionic AChR. Ganglion AChR antibodies are seen in autoimmune autonomic gangliopathy but only in about 50%. The overlap of muscle and ganglionic AChR antibodies may be due to the alpha 1 subunit of muscle AChR and the alpha 3 sub-units of ganglionic AChR which are immunogenic.[10,28]

Cardiac examination in a patient with MG should consist of a physical examination including a third heart sound, holosystolic murmur, pulmonary crackles, or ankle swelling; laboratory findings including the increase of brain natriuretic peptide (BNP) and cardiac troponin; 6 minutes walk test; and echocardiography along with an ECG. An ECG can help as the first step in further examination of heart damage in MG patients. Diastolic disorders also affect exercise intolerance and are more likely to cause atrial fibrillation.[27,28]

The management of MG disease involves two groups of drugs, namely anticholinesterases and immunosuppressants (in thymoma), and in certain cases plasma transfusion, intravenous immune globin, and thymectomy are required.[22,25,29–31] For the group of anticholinesterase drugs that give the best results in improving muscle weakness in MG are neostigmine (prostigmine) and pyridostigmine (mestinone). In mild cases such as MG without tumors in the thymus,

patients with partial remission after thymectomy and pure ocular MG, the use of anticholinesterase drugs are only used for a certain period, (this is because ocular MG usually responds well to small doses of corticosteroid.[22] In MG with thymoma, the management that must be done is thymectomy, which removes the tumor and all thymus tissue. Thymectomy in MG without thymoma is also possible, although there is no scientific evidence of its effectiveness.[6,7] There is no specific treatment for atrial fibrillation in cases of myasthenia gravis. Arrhythmias associated with dysautonomia of antiganglionic Ach receptor antibodies will often improve with anticholinesterase or immunomodulatory treatment. The use of cholinesterase inhibitors is of concern given their potential to exacerbate bradyarrhythmias.[26]

COVID-19 infection in MG can be challenging for a variety of reasons: infection is known to trigger MG exacerbations/crisis, MG patients may be at a higher risk of developing such infection due to immunosuppressive drugs, and respiratory distress can be seen in both conditions that can confuse identification and management.[16] Recently, a panel of MG experts provided guidance on MG management during the COVID-19 pandemic. As per the recommendations, treatment decisions must be tailored to each patient; Immunosuppressive treatment should be continued, unless specifically discussed and approved by the health care provider.[17] In addition, they recommended continuing the current standard MG treatment treatment during hospitalization. There may be a need to increase the corticosteroid dose as is common with the steroid infection/stress protocol; however, if the symptoms of COVID-19 are severe, immunosuppression should be temporarily stopped. Immune depleting agents should be avoided, whereas standard immunosuppressive agents such as azathioprine and mycophenolate can be continued because they last longer. Additionally, there is currently no evidence to suggest that IVIG or PLEX increases the risk of infection with COVID-19.[15,16]

CONCLUSION

MG patients have been shown to have manifestations of abnormal rhythm. This may reflect a complication of myocarditis or alternatively, a malfunctioning of the sympathetic autonomic nervous system. Both of these mechanisms appear to be more common in myasthenic patients with thymoma. COVID-19 infection in MG can be challenging for many reasons. Treatment decisions must be tailored to each patient; Immunosuppressive treatment should be continued, unless specifically discussed and approved by the health care provider. In addition, current guidelines also recommend continuing the current standard MG treatment treatment during hospitalization.

ACKNOWLEDGMENTS

None.

DISCLOSURE (CONFLICT OF INTEREST)

The authors declare that there is no conflict of interest.

FUNDING

None.

ETHICAL CONSIDERATION

All patient had received signed informed consent regarding publication of their medical data in medical journal

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