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Pyridostigmine-induced complete atrioventricular block in a patient with Musk antibody-negative myasthenia gravis a case report

Pyridostigmine-ind advanced AV block in MG patient with MuSK-neg

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Abstract

Background Myasthenia gravis (MG) is a rare autoimmune neuromuscular disorder in which autoantibodies impair neuromuscular junctions. MG can be associated with thymoma and with antibodies to the acetylcholine receptor (AChR), and is less commonly associated with antibodies to muscle-specific tyrosine kinase (MuSK). Treatment of AChR antibody-positive myasthenia gravis with the cholinesterase inhibitor, pyridostigmine, has known cardiac conduction side effects. Some reports indicate these cardiac effects, including bradyarrhythmias, occur more often with MuSK-ab positive MG. This report is of a 62-year-old man with recent onset muscle-specific tyrosine kinase (MuSK)-negative thymomatous myasthenia gravis presenting with bradycardia due to pyridostigmine-associated atrioventricular (AV) block.

Case report A 62-year-old man presented with fluctuating muscle weakness, unilateral ptosis, mild dyspnea, and mild dysphagia. Laboratory testing was positive for acetylcholine receptor antibodies (AChR-ab), but negative for MuSK antibodies. Due to his symptoms, treatment with intravenous immunoglobulin (IVIg) and pyridostigmine was initiated. Mediastinal computed tomography scan (CT scan) revealed a thymoma. During thymectomy surgery, the patient experienced intraoperative asystole. After he was stabilized, episodes of high-degree atrioventricular (AV) block were seen on postoperative ambulatory rhythm monitoring. Therefore, a permanent pacemaker (PPM) was implanted before repeat thymectomy, which was performed without complications Histopathological examination of the thymic tissue demonstrated a type B1 thymoma.

Conclusion This report has highlighted the importance of accurate diagnosis of MG and its autoimmune subtypes, and if treatment is required with pyridostigmine, the importance of follow-up and electrocardiographic monitoring to ensure the rapid diagnosis and management of cardiac conduction abnormalities, even if they are MuSK antibody-negative.

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Keywords Pyridostigmine bromide, Myasthenia gravis, Atrioventricular block, Thymoma

Background

Myasthenia gravis (MG) is a neuromuscular disorder affecting skeletal muscles due to autoantibodies directed against postsynaptic components, such as the acetylcholine receptor antibody (AChR) and muscle-specific kinase antibody (MuSK-Ab) [1]. The classic presentation of MG is fluctuating muscle weakness, typically involving the ocular, bulbar, and limb muscles, which tends to worsen as the day progresses [2]. The worldwide prevalence of MG is estimated to be around 12.4 per 100,000 population [3].

The diagnosis of MG is primarily based on the clinical presentation, but laboratory findings can help confirm the diagnosis [4]. MG is categorized into subtypes according to the clinical manifestations and detected autoantibodies [2]. The clinical subtypes include ocular MG, early-onset generalized MG, and late-onset MG [2]. The serological subtypes comprise AChR-Ab positive MG, MuSK-Ab positive MG, low-density lipoprotein receptor–related protein 4 antibody-positive MG, seronegative MG and MG with coexisting autoimmune [2].

Using cholinesterase inhibitors, which inhibit cholinesterase from hydrolyzing acetylcholine, is one of main therapeutic strategy in MG [5]. Pyridostigmine is a reversible acetylcholinesterase inhibitor that is well-studied and generally use for treating the symptoms of myasthenia gravis (MG). Cholinesterase inhibitors cause increase in amount of available acetylcholine that may cause symptoms of overstimulating parasympathetic nervous system like miosis, hypersecretion, diarrhea, bradycardia and hypotension [6]. Moreover, some reports indicate an increased risk of pyridostigmine-induced cardiac complications such as persistent sinus bradycardia or high-degree sinoatrial block among MuSK-antibody positive MG patients [7, 8]. This report is of a 62-year-old man with recent onset MuSK-negative thymomatous myasthenia gravis presenting with bradycardia due to pyridostigmine-associated high-degree atrioventricular (AV) block.

Case report

A 62-year-old man with a past medical history significant for type 2 diabetes mellitus and hypertension was referred to our hospital for evaluation of fluctuating muscle weakness, unilateral ptosis, mild dysphagia, and dyspnea. Electromyography (EMG) and nerve conduction studies performed on the patient were negative for myasthenic testing and did not show any significant findings consistent with neuropathy. On physical examination, the ice pack test was positive.

Brain MRI and spirometry were performed to rule out lung and central nervous system (CNS) disorders. The brain magnetic resonance imaging (MRI) without contrast was normal, allowing us to exclude CNS tumors, multiple sclerosis (MS), and cerebrovascular accident (CVA). Spirometry did not indicate any lung disorder responsible for the dyspnea. Due to the presence of dysphagia in the setting of myopathy, the patient was treated with intravenous immunoglobulin (IVIg) at 0.4 gr/kg daily for 5 days. After this course, the patient's symptoms resolved.

Laboratory testing revealed positive results for acetylcholine receptor antibodies (AChR-ab) which was 3.1 nmol/L (>0.5 nmol/L was positive), but radioimmunoprecipitation assay (RIA) for muscle-specific kinase antibodies (MuSK-ab) was reported negative. Based on the patient's presenting signs and symptoms along with these immunology results which was positive for AChR-Ab, a diagnosis of myasthenia gravis (MG) was made.

Due to the high prevalence of thymic disorders in MuSK-ab negative MG patients, a mediastinal computed tomography scan (CT) scan was performed. This showed a 21 × 23 mm mildly lobulated, homogeneously enhancing anterior mediastinal mass concerning for thymoma (Fig. 1). The patient was discharged on pyridostigmine 60 mg every 8 h and an elective thymectomy was scheduled.

During Pyridostigmine therapy for patient, electrocardiography and echocardiography were performed because of potential risk of this drug for cardiac conduction abnormalities. The electrocardiogram (ECG) showed a consistently prolonged PR interval of 220 ms, indicative of first-degree AV block, along with a heart rate of 65 beats per minute (Fig. 2). Echocardiography revealed normal left ventricular ejection fraction (LVEF) but mild tricuspid and mitral regurgitation. For the thymectomy procedure, anesthesia was induced with Fentanyl, Isoflurane, Sodium thiopental, and Atracurium. Suddenly, the patient's heart rate dropped and he went into asystole. Following successful cardiopulmonary resuscitation, he was admitted to the cardiac care unit (CCU). Cardiac monitoring revealed sinus rhythm with prolonged PR-interval (about 320 mS) along with 2 non-conducted P-wave which represent High-degree (advanced) AV block (Fig. 3).

While the short half-lives of anesthetic agents may have contributed to the intraoperative asystole, episodes of CHB were noted more than 36 h after surgery. We believed Pyridostigmine was likely the primary culprit responsible for these postoperative bradyarrhythmias.

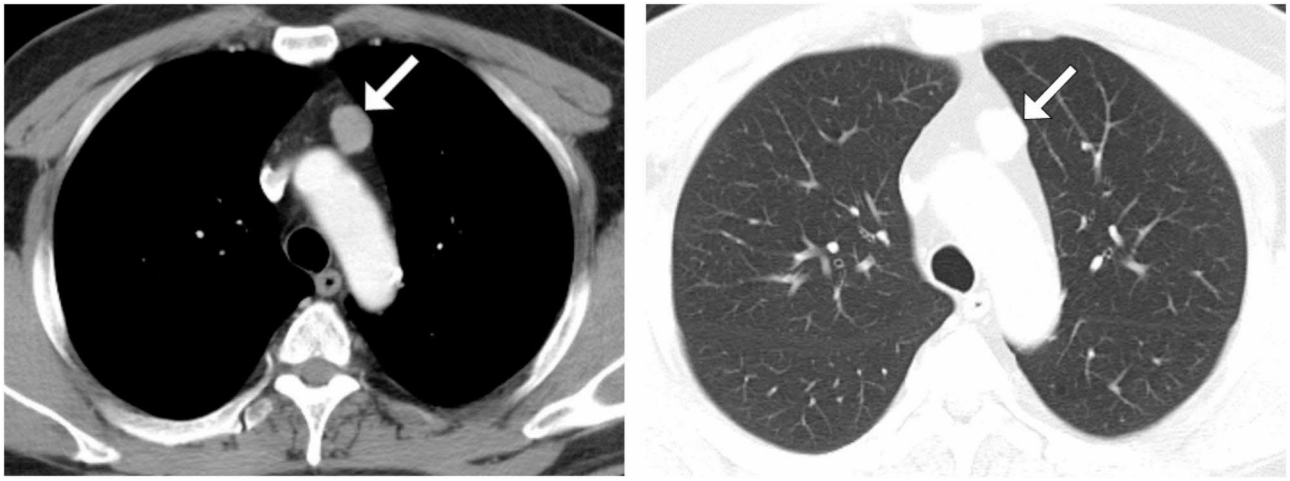

Fig. 1 Contrast-enhanced mediastinal CT scan demonstrating a 23*21 mm soft tissue mass with homogeneous in the anterior mediastinum, consistent with thymoma

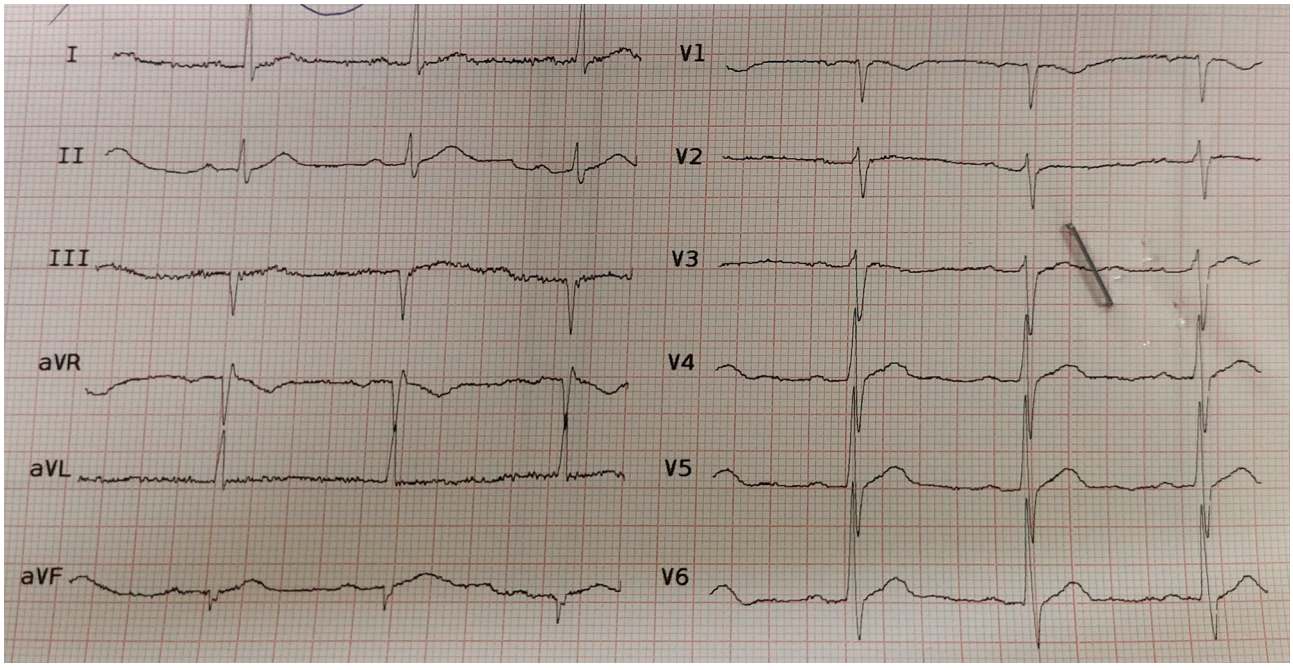

Fig. 2 Preoperative electrocardiogram (ECG) demonstrating sinus rhythm with a consistently prolonged PR interval of 220 ms, indicative first-degree atrioventricular (AV) block

Given the intraoperative asystole and postoperative episodes of CHB, the patient underwent permanent pacemaker implantation before thymectomy. The thymectomy surgery was then performed without any complications. The thymectomy specimen was sent to the pathology department for diagnostic histopathologic examination (Fig. 4). Histopathologic assessment confirmed a type B1 thymoma with a Masaoka-Koga pathologic stage of Ia (macroscopic complete encapsulation without microscopically detectable capsular invasion) and no assessment of nodal or distant metastatic spread (pathologic Nx Mx).

Discussion

This case report describes high-degree AV block in Musk-negative thymomatous MG. To our knowledge, this is the first report of pyridostigmine-induced high-degree atrioventricular block in a patient with MuSK-negative myasthenia gravis.

Myasthenia gravis is an antibody-mediated autoimmune disorder that affects the neuromuscular junction. The two primary autoantibodies involved are acetylcholine receptor antibodies (AChR-ab) and muscle-specific kinase antibodies (MuSK-ab). MuSK antibody-positive myasthenia gravis occurs more frequently in women and

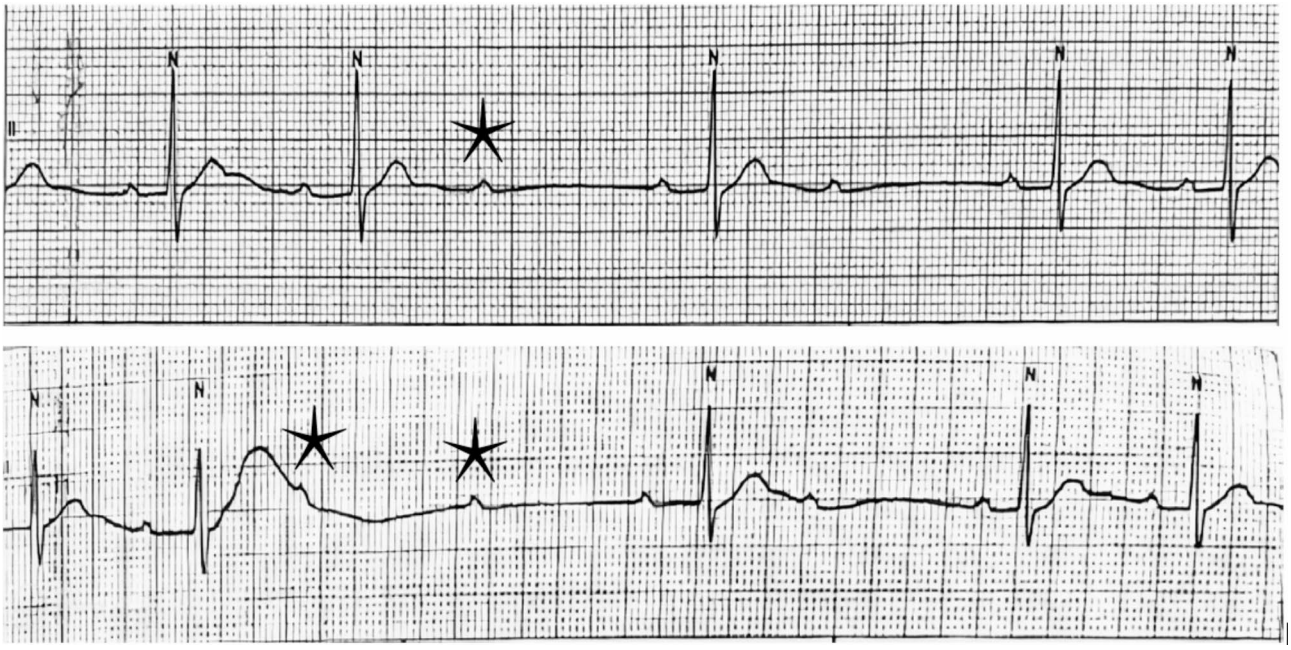

Fig. 3 Postoperative ECG demonstrating high-degree (advanced) AV block with a prolonged PR interval and 2 non-conducted P waves (asterisk) resulting in a 3-second pause

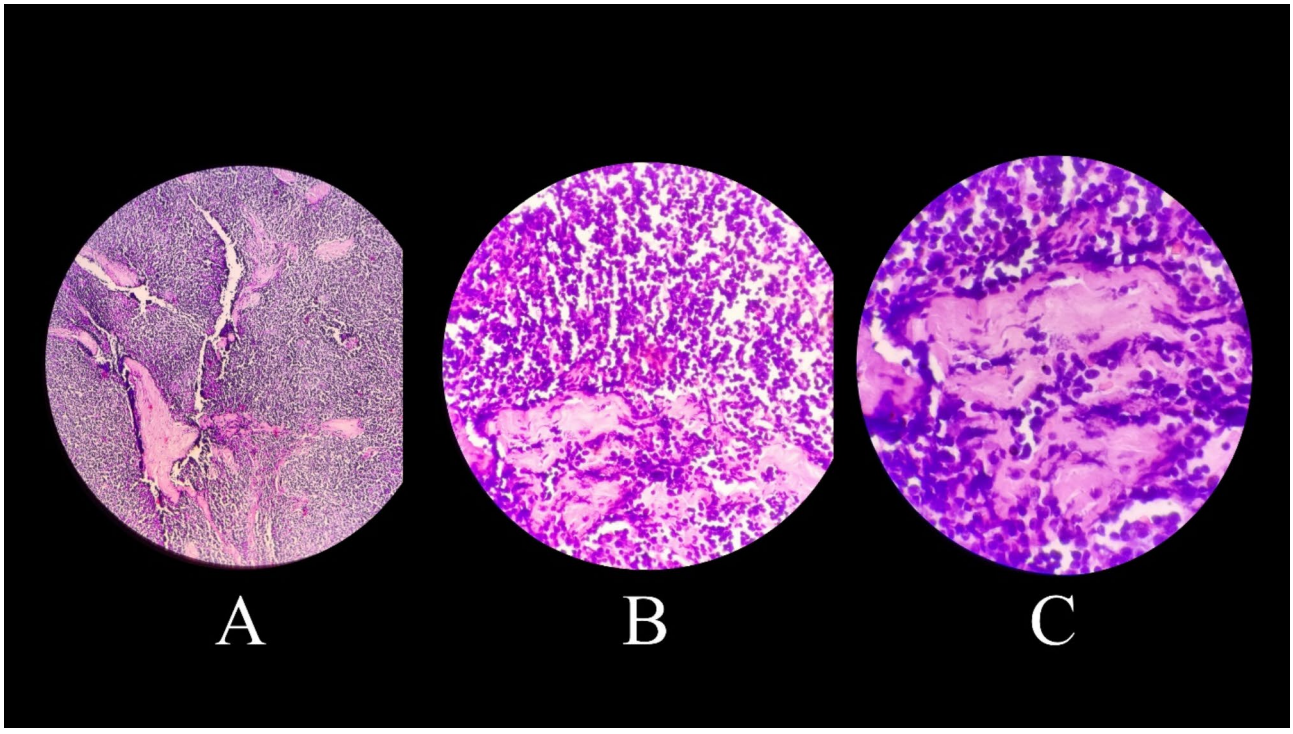

Fig. 4 Pathological images of thymoma. **A**: neoplastic tissue composed of sheets of epithelioid cells (hematoxylin-eosin staining ×100) **B**: mild pleomorphic nuclei admixed proliferation of small -sized lymphocytes (hematoxylin-eosin staining ×400) **C**: Proliferative fibrocollagenous tissue embedded within aggregates of fibroblast cells (hematoxylin-eosin staining ×1000)

typically presents with more severe bulbar symptoms compared to AChR-positive cases [9].

In contrast, AChR-positive (MuSK-negative) patients, like our case, typically show direct antibody-mediated destruction of acetylcholine receptors. This might suggest a theoretically lower risk of cholinergic hypersensitivity. However, our case demonstrates that significant cardiac conduction abnormalities can still occur in these

patients. The mechanism may involve: (1) Cumulative cholinergic effects of pyridostigmine on cardiac tissue, (2) Potential cross-reactivity of AChR antibodies with cardiac tissue, (3) Underlying cardiac involvement associated with thymoma.

Our patient was newly diagnosed with MG, differentiating this case from previous reports of chronic MG patients developing cardiac complications [8, 10]. Serologic testing was negative for MuSK-Ab and positive for AChR-Ab, indicating AChR-positive MG. The presence of thymoma in our patient aligns with the higher prevalence of thymic abnormalities in MuSK-negative cases compared to MuSK-positive MG.

Treatment options for myasthenia gravis include non-immunosuppressive therapy (e.g., acetylcholinesterase inhibitors such as Pyridostigmine), immunosuppressive therapy (e.g., corticosteroids, azathioprine, Mycophenolate mofetil), and biological treatments like rituximab [11]. In cases of severe MG exacerbation, as seen in our patient presenting with dysphagia, treatment should be switched to intravenous immunoglobulin (IVIG) or plasma exchange [11].

Pyridostigmine is an acetylcholinesterase inhibitor that increases the amount of acetylcholine in the synaptic cleft, thereby stimulating nicotinic and muscarinic acetylcholine receptors. The muscarinic activity of Pyridostigmine can elicit some adverse effects, such as abdominal cramping [12].

Guglin et al. found cardiovascular involvement in 50% of MG patients with thymoma, suggesting a potential synergistic effect between thymoma-associated cardiac involvement and pyridostigmine-induced conduction abnormalities [13]. This may explain why our MuSK-negative patient developed severe cardiac conduction abnormalities despite the traditionally lower risk in this population.

The patient's follow-up data over 12 months demonstrated stable cardiac function. Serial ECGs showed appropriate pacemaker function with no episodes of high-grade AV block. Device interrogation at 3, 6, and 12 months revealed pacing dependency of 82%, 78%, and 75% respectively, confirming the ongoing need for permanent pacing. Follow-up echocardiograms at 6 and 12 months showed preserved left ventricular function (LVEF 55%) with no progression of the previously noted mild valvular regurgitation.

Several factors may have contributed to the development of severe cardiac conduction abnormalities in our patient: (1) Medication Interactions: The patient's antihypertensive medications, particularly beta-blockers, may have potentiated pyridostigmine's bradycardic effects. However, these medications had been stable for years without previous cardiac conduction issues. (2) Underlying Conditions: Type 2 diabetes mellitus may have contributed through autonomic dysfunction, Hypertension could have caused underlying cardiac remodeling, The presence of thymoma likely played a significant role through immune-mediated mechanisms. (3) Timing of Presentation: The recent onset of MG symptoms may have represented a period of particularly active autoimmune response, potentially increasing susceptibility to cardiac complications.

The decision to implant a permanent pacemaker required careful consideration of potential complications and long-term management strategies. While necessary for our patient's severe conduction abnormalities, permanent pacing carries risks that warrant discussion: (1) Minimizing Right Ventricular Pacing: Chronic right ventricular pacing can lead to adverse cardiac remodeling and heart failure. Recent studies by Mei et al. demonstrate that algorithms minimizing right ventricular pacing can reduce risk of persistent/permanent atrial fibrillation, cardiovascular hospitalization and heart failure hospitalization [14]. Our patient's device was programmed with AV search hysteresis to promote intrinsic conduction when possible, though high pacing dependency limited its effectiveness. (2) Device-Related Complications: Lead dislodgement, Need for generator changes and Infection risk: The reported rate of cardiac device infections ranges from 0.6 to 6% [15]. Imberti et al. showed that end-stage chronic kidney disease requiring dialysis and corticosteroid therapy are independently associated with a higher risk of cardiac device infection [16].

Previous case reports have primarily focused on cardiac complications in MuSK-positive patients. Said et al. reported a case of MuSK antibody-positive myasthenia gravis without thymic abnormalities where pyridostigmine caused high-grade sinoatrial block requiring permanent pacemaker implantation [8]. While the prevalence of pyridostigmine-induced cardiovascular adverse effects is generally higher in MuSK antibody-positive patients, our case demonstrates that MuSK-negative patients may also be at risk for severe cardiac conduction abnormalities.

Gehi et al. reported a case of pyridostigmine-induced Mobitz type II block successfully managed with hyoscyamine without pacemaker implantation [17]. However, given the occurrence of intraoperative asystole and postoperative complete heart block in our patient, we proceeded directly to permanent pacemaker implantation. This aggressive approach was warranted by the severity of the conduction abnormalities and the need for definitive management before thymectomy.

This case expands our understanding of cardiac complications in MG by demonstrating that severe conduction abnormalities can occur in MuSK-negative patients, particularly in the setting of thymoma. The presence of thymoma may represent an additional risk factor for

cardiac conduction abnormalities in MuSK-negative patients treated with pyridostigmine, warranting careful cardiac monitoring in this population.

Conclusion

This report has highlighted the importance of accurate diagnosis of MG and its autoimmune subtypes, and if treatment is required with pyridostigmine, the importance of follow-up and electrocardiographic monitoring to ensure the rapid diagnosis and management of cardiac conduction abnormalities, even if they are MuSK antibody-negative.

Abbreviations

AChR	Acetylcholine Receptor
AChR-ab	Acetylcholine Receptor antibodies
AV block	Atrioventricular block
CCU	Cardiac Care Unit
CHB	Complete Heart Block
CNS	Central Nervous System
CT scan	Computed Tomography scan
CVA	Cerebrovascular Accident
ECG	Electrocardiogram
EMG	Electromyography
IVIg	Immunoglobulin
LVEF	Left Ventricular Ejection Fraction
MG	Myasthenia Gravis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MuSK	Muscle-Specific Tyrosine Kinase
MuSK-ab	Muscle-Specific Kinase antibodies
PPM	Permanent Pacemaker

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Author contributions

M.H and M.R and M.F: study design and data collection. M.H and M.R and S.A and M.S and N.N: Data interpretation. M.H and M.R and M.F: Literature search. All author: manuscript preparation and wrote the main manuscript.

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Data availability

The data supporting the findings of this case report are available within the article. Any additional data or materials not included in the manuscript are available from the corresponding author upon reasonable request, subject to privacy and ethical restrictions.This version acknowledges that: 1.Most of the relevant information is likely already included in the case report itself. 2.There may be additional materials (like detailed medical records) that aren't published but could be shared if needed. 3.Patient privacy and ethical considerations are paramount in case reports.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Babol University of Medical Sciences (Ethical code: IR.MUBABOL.HRI.REC.1402.067). Informed consent was obtained from all individual participants included in the study. All participants were informed about the purpose of the study, and they were assured that their participation was voluntary and that they could withdraw from the study at any time without consequences.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

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