Case Report

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Title: Coexistence of anti-musk-positive bulbar myasthenia gravis and myotonic dystrophy Type 1: the first case report from Türkiye.

Short title: Myopathy and myasthenia overlap case report.

Abstract

Muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) is an acute-onset subtype of MG that primarily affects the fasciobulbar muscles and begins with progressive velopharyngeal and respiratory symptoms such as early respiratory crises, swallowing, and speaking difficulties. Myotonic dystrophy Type 1 (DM1) is an autosomal dominantly inherited autoimmune neuromuscular disease characterized by distal-dominant muscle weakness, cardiovascular pathologies, and corneal disorders. In this case report, we discussed a 42-year-old female patient with a previous diagnosis of DM1 and diagnosed with MuSK-MG as a result of electroneuromyographic and antibody tests upon the development of bulbar symptoms and thymus hyperplasia. The patient underwent video-assisted thymectomy, and medical treatment was started with a combination of pyridostigmine and methylprednisolone. The coexistence of anti-MuSK positive MG with thymoid hyperplasia and DM 1 has not been reported so far, and it has been predicted that both diseases may trigger each other through neuroinflammatory mechanisms on an autoimmunergic basis.

Keywords: Autoimmunity, muscle-specific tyrosine kinase myasthenia gravis, myotonic dystrophy Type 1, neuroinflammation, thymus hyperplasia.

Makale başlığı: Anti-musk pozitif bulbar myastenia gravis ve miyotonik distrofi Tip 1 birlikteliği: Türkiye'den ilk vaka sunumu.

Öz

Kas spesifik tirozin kinaz (MuSK) miyastenia gravis (MG), öncelikle fasyobulbar kasları etkileyen ve erken solunum krizleri, yutma ve konuşma güçlükleri gibi ilerleyici velofaringeal ve solunum semptomlarıyla başlayan, MG'nin akut başlangıçlı bir alt tipidir. Miyotonik distrofi Tip 1 (DM1), distal dominant kas zayıflığı, kardiyovasküler patolojiler ve kornea bozuklukları ile karakterize, otozomal dominant geçişli, otoimmün nöromüsküler bir hastalıktır. Bu olgu sunumunda, daha

önce DM1 tanısı alan, bulber semptomları ve timus hiperplazisi gelişmesi üzerine elektronöromiyografik ve antikor testleri sonucunda MuSK-MG tanısı alan 42 yaşındaki kadın hastayı tartıştık. Hastaya video yardımlı timektomi uygulandı ve piridostigmin ve metilprednizolon kombinasyonu ile medikal tedaviye başlandı. Anti-MuSK pozitif MG ile timoid hiperplazi ve DM 1'in birlikteliği şu ana kadar bildirilmemiş olup, her iki hastalığın otoimmünerjik temelde nöroinflamatuar mekanizmalar yoluyla birbirini tetikleyebileceği öngörülmektedir.
Anahtar kelimeler: Otoimmünite, kas spesifik tirozin kinaz miyastenia gravis, miyotonik distrofi Tip 1, nöroinflamasyon, timus hiperplazisi.

Introduction

Muscle-specific tyrosine kinase (MuSK) Myasthenia Gaves (MG) is an autoimmune neuromuscular junction disease characterized by acute onset bulbar symptoms and respiratory deterioration. Diagnosis is made by MuSK-Ab testing, edrophonium/neostigmine test, and electroneurophysiological studies such as repetitive nerve stimulation (RNS), single-fiber electromyography (SFEMG), and needle EMG. In anti-MuSK-Ab positive patients, minimal follicular hyperplastic thymus (remnant) or thymoma can rarely be observed [1, 2]. Myotonic dystrophy 1 (DM1) is an autosomal dominant inherited neuromuscular systemic disease that occurs after the unstable trinucleotide (CTG) repeat expansion in dystrophia myotonia-protein kinase (DMPK) gene [3] and usually affects somatic and smooth muscles, as well as systemic organ disturbance. It is characterized by low amplitude in compound muscle activation potential (CMAP), especially in distal muscles in EMG tests, and early recruitment pattern and myotonic discharges in needle EMG. In this case report, we evaluated DM1 and MG coexistence from neuroimmunologic and autoimmunergic perspectives in a patient diagnosed with DM1 who developed Anti- MuSK positive MG with thymic hyperplasia.

Case report

A 42-year-old female patient presented with difficulty in swallowing and lisping for a month. Her complaints were diurnal and tended to increase in the evening. In medical history, she had a diagnosis of Myotonic dystrophy type 1(DM1) 10 years ago. The patient first applied to cardiology with complaints of fatigue, generalized weakness, and dyspnea, and transthoracic

echocardiography revealed grade 1 atrioventricular block, mild mitral insufficiency, and grade 1 interatrial septal aneurysm. During the examination, generalized asymmetrical decreased muscle tone and loss of dominant muscle strength in the lower extremities were observed, and she was referred to Electromyography (EMG). EMG nerve conduction studies detected decreased CMAP in the right peroneal, bilateral tibial, and right ulnar motor nerves. Needle EMG showed myotonic discharges (from 1+to 4+scales) in the distal muscles, which were more prominently seen in the lower extremity (Tibialis anterior, peroneus longus, gastrocnemius medius) muscles (Figure 1). In muscle biopsy, basophilic regenerating fibers and splittingfibers varying in shape and diameter, dominated by fibrosis and adipose tissue, were observed (Figure 1). The molecular genetic analyses revealed the number of cytosine thymine- guanine (CTG) repeats to be over 100 (cytosine-CTG repeats of the ZNF9 gene was <30) in the myotonic dystrophy DM protein kinase (DMPK) fragment gene. Four years after the first diagnosis, the patient developed blurred vision and dry eyes, and the Optical coherence tomography revealed corneal thinning (285-402 microns (threshold value for average minimum corneal thickness is 492 microns)) in pachymetry mapping. The Schirmer test was evaluated as negative. The current findings were assessed as significant regarding the eye and cardiovascular involvement of DM1. In the neurologic examination, soft palate paresis with marked dysphagia and rhinolalia, along with widespread a decrease in deep tendon reflex and markedly strength loss in distal extremities in lower extremities (lower extremity distal 4/5, proximal +4/5) were detected. In the myasthenic antibody screening protocol, anti-acetylcholine receptor antibody (anti-AChR Ab) and anti-titin were evaluated as negative. The patient's anti-muscle-specific tyrosine kinase antibody (anti-MuSK Ab) was detected positive. Other autoimmune disease antibody tests were concluded as negative. Partial improvement in orofaciobulbar dysfunction (especially swallowing dysfunction) was observed with the Edrophonium test.

In the repetitive nerve stimulation test (RNS), the trapezius and orbicularis oculi muscles showed evident amplitude decrements (21% and 35%, respectively). Positron Emission Tomography computed tomography was applied after a suspicious nodular lesion in the anterior mediastinum in the thorax CT, and a low-level FDG uptake in reticular densities was observed (Figure 2). The findings were evaluated as a thymic remnant, and thymus type B2 thymoma was detected in pathological investigation (T1N0M0). The

patient was diagnosed with anti-MuSK-MG (MuSK antibody-positive seronegative MG) with thymus hyperplasia accompanying the systemic involvement (cardiac and eye) of DM. The treatment was applied with oral methylprednisolone (16 mg/day) and pyridostigmine tablet (720 mg/day). She was operated on with video-assisted thoracoscopic thymectomy, and following the operation, two courses of intravenous methylprednisolone (IVMP) (1000 mg/day) were provided progressive improvement in bulbar complaints after medical and operational treatment was observed.

Discussion

The neuromuscular junction is a particular synapse formed between motor neurons and muscle fibers, and its association with different muscular diseases has been reported in a few rare cases [4, 5]. Clinically, it is challenging to distinguish neuromuscular junction pathologies from myopathies from each other because their coexistence incidence is infrequent, and their symptoms/findings are similar. However, making a differential diagnosis, which may affect the entire treatment process, is essential in terms of diagnosis and treatment and understanding autoimmunergic and neuroinflammatory interaction mechanisms. MuSK protein is responsible for the differentiation and aggregation of AChR by triggering low-density lipoprotein receptors (LRP-4) at the neuromuscular junction [6]. MuSK antibodies consist of the HLA DR14 and DQ5-related IgG4 isotype and prevent AchR aggregation by inhibiting the MuSK-LRP4 complex [7]. DMs are genetically inherited neuromuscular diseases characterized by generalized muscle weakness and degeneration. Disease etiopathogenesis is thought to be related to the interaction of antigen-presenting cells and tool-like receptors, which increase in the extracellular matrix as a result of CTG repeat increase, and this precipitates the release of a series of Danger Associated Molecular Patterns from damaged fibers that cause aggravation of the inflammation, and muscular dystrophy [8, 9]. DM has been associated with tumors, including thymoma, but it is not clear whether this is a part of the syndrome or occurs incidentally [10]. Different studies have reported changes in the expression of various immune mediators, such as CXCL10, CCL5, CXCL8, TNFAIP3, and TNFRSF9, in DM1-related glial cell lines [11]. Additionally, a significant increase in interferon-regulated genes (IRGs) and genes associated with the innate immune response was observed in DM1 patients compared to healthy controls [12]. These studies provide detailed

information to understand different aspects of immune system dysregulation, particularly in adaptive immunity and, to a lesser degree, innate immunity in DM1. In the Observational Prolonged Trial In DM1 to Improve QoL standards (OPTIMISTIC) [13] study, the correlation between blood transcriptome and DM disease severity was examined using a number of complementary pathways, gene ontology, and upstream regulatory analyses. It has been determined that symptom severity in DM1 is associated with transcriptomic alterations in innate and adaptive immunity, specifically macrophage priming, mitochondrial protein import, and Th2-cell expansion. Based on current findings, there is an immunologic dysfunction at the root of both diseases and immunoglobulin (IVIG) treatment can be shown as evidence that immunological dysfunction can be seen after IVIG treatment in both [14, 15].

This case report presents a neuroimmunological perspective on an autoimmunergic basis to anti-MuSK-MG and DM1 coexistence. Immune mechanisms may trigger both diseases in genetically predisposed individuals, and any study that will elucidate the etiopathogenesis in this field will guide immunological treatments for both diseases.

Conflicts of interest: The authors have no potential conflicts of interest to disclose.

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Before starting the study, the corresponding author obtained written consent from the participant. The consent form, patient demographic, and clinical and imaging information of each patient included in the study were recorded and stored in the patient forms by the corresponding author.

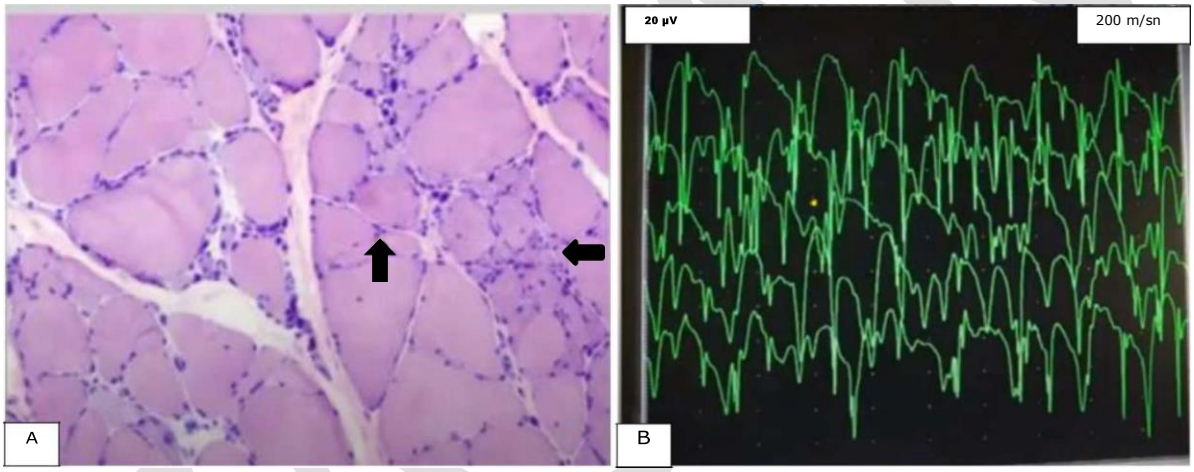

Figure 1. The histological features of muscle biopsy revealed a high number of central nuclei and a markedly increased variation in fiber diameter (black arrow) (A). Concentric needle electroneuromyography revealed myotonic discharges with variable amplitude andfrequency induced by mechanical stimulation (Tibialis anterior) (B)

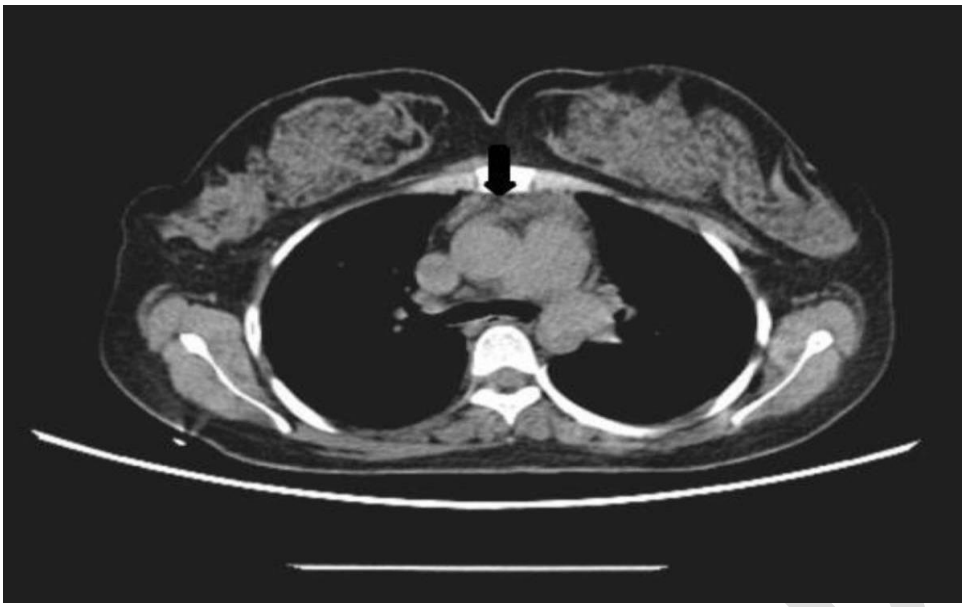

Figure 2. Thymic remnant causing low levels of FDG uptake was observed in reticular densities in the anterior mediastinum (black arrow)

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