CASE REPORT

Pembrolizumab-induced Ocular Myasthenia Gravis with Anti-titin Antibody and Necrotizing Myopathy

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Abstract:
A 73-year-old man developed diplopia after the administration of pembrolizumab for lung adenocarcinoma. He had ptosis and external ophthalmoplegia without general muscle weakness. Serum CK levels were elevated. Although autoantibodies to acetylcholine receptor and muscle-specific kinase, the edrophonium test, and the repetitive nerve stimulation test were all negative, anti-titin autoantibody was positive, leading to the diagnosis of myasthenia gravis (MG). Muscle pathology showed necrotizing myopathy with tubular aggregates. Unlike previously reported cases of pembrolizumab-associated MG, the present case showed ocular MG. This is the first case of pembrolizumab-associated MG with anti-titin antibody, as well as the first case with tubular aggregates.

Key words: pembrolizumab, ocular myasthenia gravis, anti-titin antibody, necrotizing myopathy, tubular aggregates

(Intern Med 58: 1635-1638, 2019)  
(DOI: 10.2169/internalmedicine.1956-18)

Introduction

Pembrolizumab is an anti-programmed cell death 1 (PD-1) monoclonal antibody that is used for therapy against lung cancer. Increasing evidence suggests that it can cause myasthenia gravis (MG) and necrotizing myopathy, although the detailed clinicopathological features are still unclear (1).

Case Report

A 73-year-old man with hypertension and mitral valve regurgitation with no relevant family history of neuromuscular disorders was found to have a lung nodule on a regular medical checkup in 2016. Subsequently, a diagnosis of lung adenocarcinoma with brain and bone metastases was made by pulmonologists. The tumor proportion score of the programmed cell death-ligand 1 (PD-L1) expression was 85%, so he was started on pembrolizumab in July 2017 (day 1). On day 23, he was found to have diplopia, and his CK level had increased from 55 to 600 U/L. He was admitted to our hospital on day 30 with stable vital signs.

On a physical examination, he had diplopia and ptosis in the left eye with daily fluctuation. He had no easy fatigability or weakness in the limbs and trunk. On laboratory testing, his creatine kinase (CK) level was 7,311 U/L, aldolase 16.5 IU/L, aspartate aminotransferase (AST) 172 U/L, alanine aminotransferase (ALT) 74 U/L, lactate dehydrogenase (LDH) 631 U/L, creatinine 1.17 mg/dL, C-reactive protein (CRP) 0.68 mg/dL, erythrocyte sedimentation rate (ESR) 34 mm/h, and D-dimer 1.4 μg/mL. His thyroid function was within the normal range [thyroid stimulating hormone (TSH) 1.75 μIU/mL, FT3 2.61 pg/mL, FT4 1.05 ng/dL]. Rheumatoid factor, antinuclear antibody, anti-double stranded DNA (dsDNA) antibody, anti-ribonucleoprotein (RNP) antibody, anti-histidyl transfer RNA synthetase (Jo-1) antibody, anti-aminocyl transfer RNA synthetase (ARS) antibody, anti-mitochondrial M2 (M2) antibody, anti-signal

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Received: August 10, 2018; Accepted: November 4, 2018; Advance Publication by J-STAGE: February 1, 2019
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potentials were recorded in all muscles, indicating myogenic
ceps muscle. Low-amplitude and short-duration motor unit
stimulation test (right accessory nerve, axillary nerve, me-
nerve, and ulnar nerve) and the edrophonium test were
show ocular MG, there is the possibility of general inflam-
There have been four cases of anti-PD-1-associated MG that
showed a relatively severe generalized type (3), the present
case showed ocular MG without generalized symptoms.
On electromyography of the right deltoid, biceps brachii,
and iliopsoas, fibrillation potentials were seen only in the bi-
ceps muscle. Low-amplitude and short-duration motor unit
potentials were recorded in all muscles, indicating myogenic
changes. Magnetic resonance imaging of the thigh muscles
showed no evidence of myopathy. A muscle biopsy from the
left biceps brachii showed scattered necrotic and regenerat-
ing muscle fibers with minimal reactive mononuclear cell in-
filtration (Fig. 1A, B). Tubular aggregates were seen in
some fibers (Fig. 1C, D). On immunohistochemistry, major
histocompatibility complex (MHC)-I was mildly expressed
in fibers in some areas (Fig. 1E), and membrane attack com-
pact (MAC) was deposited on the sarcolemma of some non-
necrotic fibers, in addition to the cytoplasm of necrotic fi-
bers (Fig. 1F).

Based on the above results, a diagnosis of ocular MG
(Myasthenia Gravis Foundation of America I) with anti-titin
antibody and necrotizing myopathy with tubular aggregates
and inflammatory cell infiltration only around necrotic fibers. A:
scale bar 100 μm, B: scale bar 50 μm. C: Gomori trichrome
staining. D: dihydronicotinamide adenine dinucleotide (NADH)
staining. Tubular aggregates can be seen. C, D: scale bar 20
μm. E: Major histocompatibility complex (MHC)-I staining
demonstrates light staining of muscle fibers. Scale bar 100 μm.
F: Membrane attack complex (MAC) staining demonstrates
the deposition of necrotic fibers, with light deposition of non-
necrotic fibers. Scale bar 50 μm.

There are some cases of co-existing anti-striated muscle
antibody (anti-titin, anti-ryanodine, anti-Kv1.4 antibody) and
anti-AChR antibody in idiopathic MG with myopathy and
myocarditis (6). In the present case, anti-AChR antibody was
negative, but anti-titin antibody was positive. Appar-
etly, anti-striated muscle antibody was positive in previ-
ously reported cases of anti-PD-1-associated MG (7-9), but
the details were not described. To our knowledge, this is the
recognition particle (SRP) antibody, and anti-3-hydroxy-3-
methylglutary-coenzyme A reductase (HMGR) antibody
were all negative. Anti-acetylcholine receptor (AChR) anti-
body, anti-muscle-specific kinase (MuSK) antibody, and
anti-voltage-gated potassium channel Kv1.4 antibody were
also negative, but anti-titin antibody was positive, leading to
the diagnosis of MG, although both the repetitive nerve
stimulation test (right accessory nerve, axillary nerve, me-
dian nerve, and ulnar nerve) and the edrophonium test were
negative. The ice pack test was not evaluated.

Arterial blood gas analyses and spirometry showed no
evidence of respiratory insufficiency. Echocardiography
showed a good ejection fraction (70%) and no myocarditis.
On electromyography of the right deltoid, biceps brachii,
and iliopsoas, fibrillation potentials were seen only in the bi-
ceps muscle. Low-amplitude and short-duration motor unit
potentials were recorded in all muscles, indicating myogenic

Discussion

Immunotherapy is a recently established treatment method
for lung cancer. Representative agents include antibodies tar-
geting immune checkpoints, such as PD-1, PD-L1, and cyto-
toxic T-lymphocyte associated antigen-4 (CTLA-4). Pem-
brolizumab and nivolumab are anti-PD-1 monoclonal anti-
bodies. These agents connect with PD-1 expressed on acti-
vated T cells and exert their anticancer activity by eliminat-
ing the suppression of activated T cells (1). These immune
checkpoint inhibitors are reported to cause immune-related
adverse events (irAEs), including MG and myopathy (2),
though the pathomechanism is still unclear.

Although the previously reported cases of anti-PD-1 mon-
oclonal antibody-associated MG (anti-PD-1-associated MG)
showed a relatively severe generalized type (3), the present
case showed ocular MG without generalized symptoms.
There have been four cases of anti-PD-1-associated MG that
presented with the ocular type (Table) (3-5). Even if patients
show ocular MG, there is the possibility of general inflam-
mation, such as the elevation of the serum CK level and
myopathy on electromyography and a muscle biopsy

There are some cases of anti-striated muscle
antibody (anti-titin, anti-ryanodine, anti-Kv1.4 antibody) and
anti-AChR antibody in idiopathic MG with myopathy and
myocarditis (6). In the present case, anti-AChR antibody
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ously reported cases of anti-PD-1-associated MG (7-9), but
the details were not described. To our knowledge, this is the

Figure 1. Pathological features of necrotizing myopathy. A, B: Hematoxylin and Eosin staining demonstrates necrosis and regeneration of muscle fibers and necrotizing myopathy with inflammatory cell infiltration only around necrotic fibers. A: scale bar 100 μm, B: scale bar 50 μm. C: Gomori trichrome staining. D: dihydronicotinamide adenine dinucleotide (NADH) staining. Tubular aggregates can be seen. C, D: scale bar 20 μm. E: Major histocompatibility complex (MHC)-I staining demonstrates light staining of muscle fibers. Scale bar 100 μm. F: Membrane attack complex (MAC) staining demonstrates the deposition of necrotic fibers, with light deposition of non-necrotic fibers. Scale bar 50 μm.
first case of anti-PD-1-associated MG with anti-titin antibody. In idiopathic MG, 80% of patients have anti-AChR antibody, and 10% have anti-MuSK antibody (10). In anti-PD-1-associated MG, however, the positive rate for anti-AChR antibody differs widely, from 20% (9) to 73% (11). Anti-MuSK antibody has never been reported in a case of anti-PD-1-associated MG.

There have been several cases of anti-PD-1 monoclonal antibody-associated myopathy in which a muscle biopsy was performed. The reported pathological changes have varied, including necrotizing myopathy, nonspecific myopathy, and myopathy with complement-mediated microvasculopathy (2, 9). Serum CK is not elevated in all cases, but it is elevated in patients with necrotizing myopathy, as in the present case. This is the first case of anti-PD-1 monoclonal-antibody-associated myopathy that showed tubular aggreg-
gates on muscle pathology. Tubular aggregates are found in cases of periodic paralysis, congenital myasthenia, and myopathy due to abnormal store-operated Ca\textsuperscript{2+} channels (12), but the present case had neither clinical manifestations nor a family history suggesting any of these conditions. The relationship between tubular aggregates and anti-PD-1 monoclonal antibody therefore remains unclear.

**Conclusion**

We herein report a case of anti-PD-1-associated MG. Unlike other cases with anti-PD-1-associated MG, the present case showed ocular MG without limb or trunk weakness, although the serum CK level was high, and necrotic and regenerating fibers were seen in the muscle. Interestingly, anti-titin antibody was positive, and tubular aggregates were seen on muscle pathology, although the associations of these findings with PD-1 are still unclear. Similar cases will need to be accumulated in order to better understand this relationship.

The authors state that they have no Conflict of Interest (COI).

**References**


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