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Concurrent Ocular Myopathy and Myasthenia Gravis After Zimberelimab Therapy in a Patient With Non-Small-Cell Lung Cancer

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Dear Editor,

Immune checkpoint inhibitors (ICIs) are promising candidates for cancer immunotherapy. Compared with conventional cytotoxic chemotherapy, ICIs are associated with higher rates of responses, overall patient survival, and tolerability.[1] However, there are well-documented ICI-related neuromuscular complications.[2] Here we report a rare case of concurrent ICI-related ocular myasthenia gravis (MG) and myopathy.

A 49-year-old female recently diagnosed with non-small-cell lung cancer (NSCLC) with lymph node metastasis (stage IIIC) was admitted to Seoul National University Bundang Hospital due to a 2-week history of fluctuating ptosis and diplopia. She had no comorbidities. The expression of programmed death ligand-1 in the tumor led to her receiving one cycle of zimberelimab, a monoclonal antibody targeting programmed cell death protein-1. After 16 days of zimberelimab therapy, she experienced ptosis and diplopia.

A neurologic examination revealed severe extraocular muscle (EOM) movement limitations and ptosis without orbital pain (Fig. 1A). The patient's pupils were isocoric, round, and exhibited a prompt light reflex. She did not report any weakness, dysarthria, or sensory symptoms. Deep tendon reflexes were symmetrical and normal. Her serum creatinine kinase (CK) level was slightly elevated at 343 IU/L (reference <270 IU/L). The acetylcholine-receptor-binding antibody level was also elevated, at 1.05 nmol/L (reference <0.4 nmol/L). Thyroid function test results were normal. While the ice-cube test was positive, the neostigmine test and antiganglioside antibody test were negative. Testing serum paraneoplastic antibodies revealed positivity only for the anti-CV2 antibody. Myositis-specific and myositis-associated autoantibodies were not tested. Nerve conduction studies, electromyography, and repetitive nerve stimulation tests produced unremarkable results. The patient showed no evidence of thymoma or myocarditis. We judged that MG alone could not explain the severe EOM limitations, and so orbital magnetic resonance imaging (MRI) was performed, which showed diffuse atrophy of the bilateral EOMs with heterogeneous enhancement of the bilateral medial and lateral rectus muscle bellies (Fig. 1B and D). Brain MRI performed 1 week prior to zimberelimab administration confirmed the absence of definite EOM atrophy with homogeneous enhancement, which is a normal finding (Fig. 1C and E).[3] These findings were consistent with a concurrent diagnosis of ICI-related ocular myopathy, which prompted the discontinuation of zimberelimab. Treatment with pyridostigmine and intravenous methylprednisolone (1 g daily for 5 days) followed by oral prednisolone (60 mg daily with slow tapering) resulted in partial improvements of ptosis and EOM limitations at the 6-month follow-up.

To the best of our knowledge, concurrent ICI-related ocular MG and myopathy has rarely been reported. Most patients undergoing treatment with ICIs experience general weakness

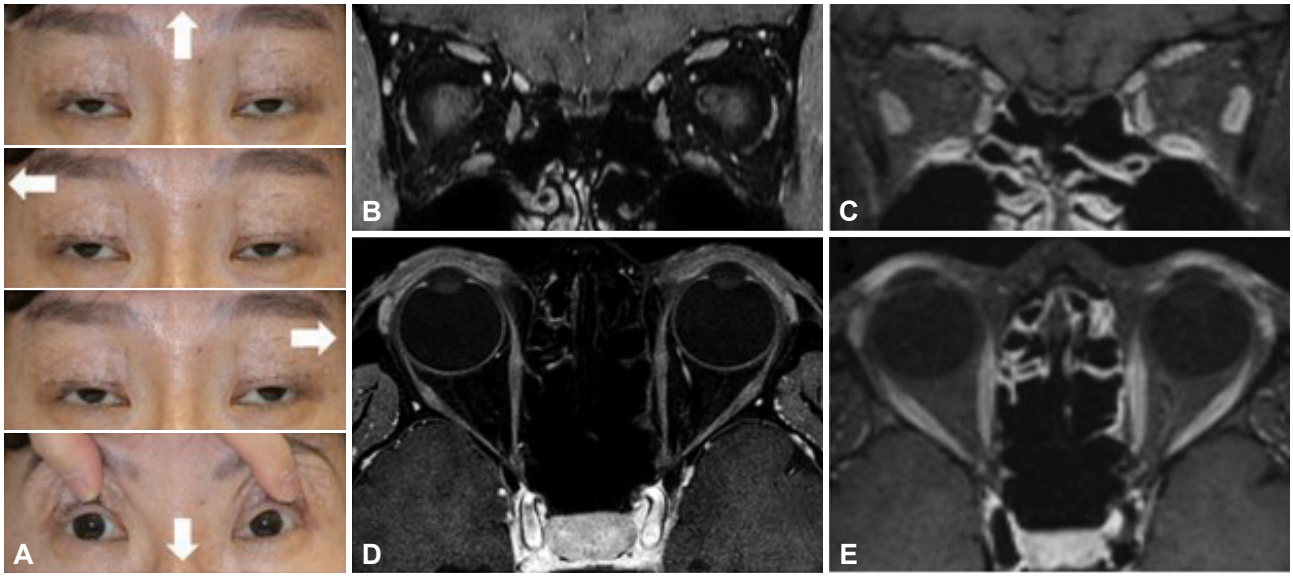

Fig. 1. Clinical (A) and radiologic (B–E) features of the patient. A: The patient had severe extraocular muscle (EOM) limitations. The arrows show gaze directions. Coronal and axial contrast-enhanced fat-suppressed T1-weighted magnetic resonance images of the orbit show diffuse atrophy and heterogeneous enhancement of the EOMs (B and D, respectively), which was homogeneous at baseline (C and E, respectively).

and high CK levels.[4,5] In addition, ICI-related MG often appears in the generalized form at onset and commonly manifests as a myasthenia crisis.[2] Unlike in previously reported cases, our patient had concurrent ocular MG and myopathy with only slight CK elevation. This study highlights that ICI-related MG and myopathy can have diverse clinical manifestations.

Unlike conventional ocular myopathy, ICI-related ocular myopathy can manifest as painless ophthalmoplegia.[6,7] Although EOM muscle biopsies were not performed in our patient due to the risk of permanent disability, the clinical and MRI findings were suggestive of EOM myopathy. Anti-CV2 seropositivity can be accompanied by MG with thymoma,[8] but paraneoplastic syndrome associated with anti-CV2 antibodies is a rare condition. Considering the high rate of the occurrence of ICI-related concurrent MG and myopathy, which along with NSCLC were present at our patient, we judged that the patient's symptoms were better explained by ICI-related toxicity than by paraneoplastic syndrome.

As far as we know, this is the first report of concurrent zimberelimab-related ocular MG and myopathy. Due to clinical trials investigating diverse ICIs and their targets,[9] healthcare practitioners should be updated about ICI-related neuromuscular adverse events and use this information to guide the management of NSCLC.

Ethics Statement

The patient provided informed consent.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Kyung Seok Park, a contributing editor of the Journal of Clinical Neurology, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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