



# Emergence of Myasthenia Gravis with Myositis in a Patient Treated with Pembrolizumab for Thymic Cancer

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Dear Editor,

A 34-year-old woman presented with a 4-week history of diplopia, dysphagia, and dyspnea. She had no previous history of a neuromuscular disorder. However, she had been diagnosed with thymic cancer (squamous cell carcinoma) 2 years previously, with metastasis to the pericardium, pleura, and lung, which had not been successfully treated with conventional chemotherapy (cyclophosphamide, vincristine, doxorubicin, and cisplatin). She had been treated with four cycles of 100-mg pembrolizumab every 2 weeks, which reduced the size of the tumor.

A physical examination revealed bilateral ptosis, ophthalmoplegia, dysarthria, facial diplegia, hypophonia, and weakness of the palatal and neck flexor muscles. Her deep tendon reflexes were symmetrically decreased. Laboratory studies showed a markedly elevated serum creatine kinase (CK) level of 2,125 U/L and seropositivity for acetylcholine-receptor antibodies (0.86 nmol/L). The findings of nerve conduction studies, repetitive nerve stimulation, and brain MRI were normal. Electromyography findings were suggestive of active myopathy.

Based on the clinical and laboratory findings, we made a clinical diagnosis of myasthenia gravis (MG) with myositis associated with pembrolizumab. Pembrolizumab was discontinued and the patient underwent a 5-day course of intravenous immunoglobulin (IVIg). She was then subsequently treated with a 3-day course of 1-g intravenous methylprednisolone (IVMP), followed by prednisolone (1 mg/kg). The CK level normalized (230 U/L) and her neck weakness improved after IVMP treatment. However, five cycles of plasmapheresis were applied due to aggravation of dyspnea. The dysphagia and ptosis had improved at the 6-month follow-up, but ophthalmoplegia and mild dyspnea persisted even though she was on continuous prednisolone treatment. Additionally, the thymic cancer remained the same even without additional chemotherapy.

Pembrolizumab is a monoclonal antibody targeting the programmed cell death 1 (PD-1) that is clinically beneficial in the treatment of malignancies such as metastatic melanoma and other advanced solid tumors, for which conventional therapies are only weakly effective.<sup>1</sup> Pembrolizumab binds to PD-1, which is an inhibitory signaling receptor expressed on the surface of activated T cells, resulting in pembrolizumab preventing the binding of PD-1 to other ligands, thereby increasing the effectiveness of the T-cell-mediated immune response against tumor cells. However, enhanced immune activation by a PD-1 inhibitor may induce adverse side effects. It is particularly notable that autoimmune events in the neuromuscular system have also been reported in patients with metastatic melanoma who were treated with pembrolizumab (Table 1).<sup>2-9</sup>

Unlike the previously published cases in which metastatic melanoma was the underlying cancer, our patient had a thymic carcinoma. It is well known that thymic abnormalities and

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**Table 1.** Case reports of neuromuscular disorder after pembrolizumab administration

Age/sex reference	Underlying disease	Symptom onset* (weeks)	Symptoms	Diagnosis	CK (U/L)	AChR ab*	Immuno-therapy	Outcome
34/F (our case)	Thymic cancer	8	EOM limitation, ptosis, neck weakness, dyspnea, dysphagia, and hypophonia	MG with myositis	2,125	+	IVIg, IVMP, PLEX, prednisone	Partial recovery
86/F <sup>2</sup>	Metastatic melanoma	6	EOM limitation, ptosis, proximal limb weakness, fatigue, and dysphonia	Necrotic myositis	1,499	-	IVMP, PLEX	Recovery
69/F <sup>3</sup>	Metastatic melanoma	9	EOM limitation, ptosis, dyspnea, and general weakness	MG	↑	-	IVMP, PLEX	No significant recovery, died due to brain metastasis
75/M <sup>4</sup>	Metastatic melanoma, well-controlled MG	5	Ptosis, dyspnea, and neck and proximal limb weakness	Exacerbation of MG	NR	+	IVIg, prednisone	Recovery
59/F <sup>5</sup>	Metastatic melanoma, well-controlled MG	12	Dyspnea, dysphagia with dysarthria, and general weakness	Exacerbation of MG	NR	-	PLEX, IVIg, prednisone	Recovery
71/F <sup>6</sup>	Metastatic melanoma	12	EOM limitation, dysphagia, dysarthria, and neck and proximal limb weakness	MG	1,200	-	Prednisone	Recovery, died due to underlying cancer
78/M <sup>7</sup>	Metastatic melanoma	8	Ptosis, facial weakness, dyspnea, dysphagia, dysarthria, proximal limb weakness, and myalgia	Necrotic myopathy over a NMJ disorder	1,284	-	PLEX, prednisone	No significant recovery, passed away
63/M <sup>8</sup>	Metastatic melanoma	2	EOM limitation, ptosis, facial weakness, dyspnea, and periorbital edema with erythema	MG with myositis	10,386	+	IVIg, IVMP, PLEX, prednisone	No significant recovery, died
85/F <sup>9</sup>	Metastatic melanoma	4.5	Diplopia and ptosis	Ocular MG	NR	-	IVIg, prednisone	Recovery

\*After administering pembrolizumab.

AChR ab: acetylcholine-receptor antibody, CK: serum creatine kinase, EOM: extraocular muscle movement, F: female, IVIg: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, M: male, MG: myasthenia gravis, NMJ: neuromuscular junction, NR: not reported, PLEX: plasmapheresis.

thymic cancer can be associated with MG. It is therefore not clear in the present case whether MG with myositis was triggered by pembrolizumab or whether MG was a manifestation of the underlying thymic carcinoma. However, our case is similar to previous cases in terms of its clinical presentation and the temporal relationship between the administration of pembrolizumab and the development of clinical symptoms. Therefore, the present treatment with pembrolizumab may have induced MG or aggravated latent MG. The clinical outcomes of autoimmune complications induced by pembrolizumab vary from complete improvement to death.<sup>2-9</sup> After discontinuing the PD-1 inhibitor, early treatment comprising steroid pulse, plasmapheresis, or IVIg is important in suspected cases of neuromuscular impairment. Clinicians should be updated about the possibility that newly developed anticancer drugs can induce neuromuscular impairment.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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