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Letter to the Editor

PD-1 inhibitor-associated severe myasthenia gravis with necrotizing myopathy and myocarditis

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Dear Editor,

In recent years, immune checkpoint inhibitors are widely used to treat unresectable malignancies. Programmed cell death protein 1 (PD-1) inhibitors (i.e., nivolumab, pembrolizumab), although effective for treating melanoma, non-small cell lung cancer, and other malignancies [1], can have undesired neurological side effects including myasthenia gravis (MG), myopathy, and peripheral neuropathy [2,4]. To date, 44 cases of PD-1 inhibitor-associated MG (pMG) are reported, with only a few reports of this condition concomitant with myocarditis [2,4]. Here, we present a unique case of pMG with necrotizing myopathy and myocarditis, with a history of thymoma and acetylcholine receptor antibody (AChR Ab) positivity.

A 55-year-old woman with metastatic melanoma presented with a stiff neck, myalgia, and an increased creatine kinase (CK) level (953 IU/L) one day after the second infusion of nivolumab (2 mg/kg, every 2 weeks). Her medical history included a thymectomy for thymoma, 6 years prior, during which she tested seropositive for AChR Ab (72 nmol/L, normal range, < 0.3 nmol/L); however, she exhibited no MG symptoms. She then developed progressive ophthalmoplegia, ptosis, dysphagia, dyspnea, and limb weakness with an elevated CK level (maximum, 13652 IU/L). She also presented with wide QRS complex tachycardia and increased levels of CK-MB and troponin T and I. Echocardiography revealed dyssynchrony of the left ventricle and reduced ejection fraction (45%). She tested positive for AChR Ab (29 nmol/L) and negative for anti-signal recognition particle, anti-HMG-CoA reductase, and anti-striational Abs. A repetitive nerve stimulation study showed normal findings; however, single-fiber electromyography revealed evidence of neuromuscular junction dysfunction (increased jitter). Muscle MRI showed a patchy and diffuse high intensity area in the femur muscles on STIR (short-tau inversion-recovery) (Fig. 1A). Needle electromyography showed myogenic change without spontaneous activity. Biopsy of the quadriceps muscle demonstrated abundant necrotic fibers and scarce lymphocytic infiltration (Fig. 1B). The diagnosis of MG complicated by necrotizing myopathy and myocarditis associated with nivolumab was confirmed. Despite administration of intravenous immunoglobulin (IVIg, 0.4 g/kg/day, 5 days), she progressed to myasthenic crisis and required mechanical ventilation 9 days after the symptom onset; nivolumab was discontinued. Following immunotherapies (four cycles of IVIg and steroid pulse plus two cycles of plasma exchange), her symptoms improved gradually and the AChR Ab titer was reduced to 2.1 nmol/L. At day 180, she could walk, and her ventilatory support was weaned off.

Nivolumab is a monoclonal antibody that blocks the interaction of PD-1 on lymphocytes and PD-1 ligand on tumor cells, and induces T-cell activation and anti-tumor effects [5]. This T-cell activation appears to cause autoimmune disorders including MG, myopathy, and myocarditis. We analyzed 44 previously reported pMG cases, comprising 13 cases with myopathy, 3 with myocarditis, and 1 complicated by both (Table 1) [1–4,6,7].

It was observed that cases of pMG were frequently more severe than cases of MG not associated with PD-1 inhibitors [1–4]. Of the previously reported 44 pMG cases, mechanical ventilation was required in 16 (37%) out of 43 cases (no data for 1 case). Moreover, 16 (38%) out of 42 cases (no data for 2 cases) died (including deaths unrelated to MG). Some patients and/or their families had refused aggressive medical care including ventilatory support, suggesting that more patients may have required ventilatory support. Additionally, myocarditis and/or myopathy may contribute to the severity of pMG and further delay the diagnosis of weakness and hyperCKemia. Kao et al. suggested that the patients with pMG who presented with hyperCKemia were more likely to experience an MG crisis requiring ventilatory support than those without hyperCKemia [4]. In the present case, symptoms of myopathy and hyperCKemia preceded MG symptoms, suggesting that hyperCKemia may be a predictor of not only a more severe clinical course but also the development of MG in patients receiving PD-1 inhibitor therapy. In previous reports, the mean age of pMG onset (71.6 years, n = 42) was higher than that of MG not associated with PD-1 inhibitor; malignancy and older age at onset may also have contributed to the severity of pMG. Our patient was relatively young, which may explain the significant improvement at day 180.

In the present case, we speculated that the pathophysiology of myopathy was related to necrotizing myopathy rather than myositis or rhabdomyolysis. The muscle biopsy showed abundant necrotic fibers with sparse lymphocytic infiltration and human leukocyte antigen (HLA)-ABC and HLA-DR activity along both the necrotic and non-

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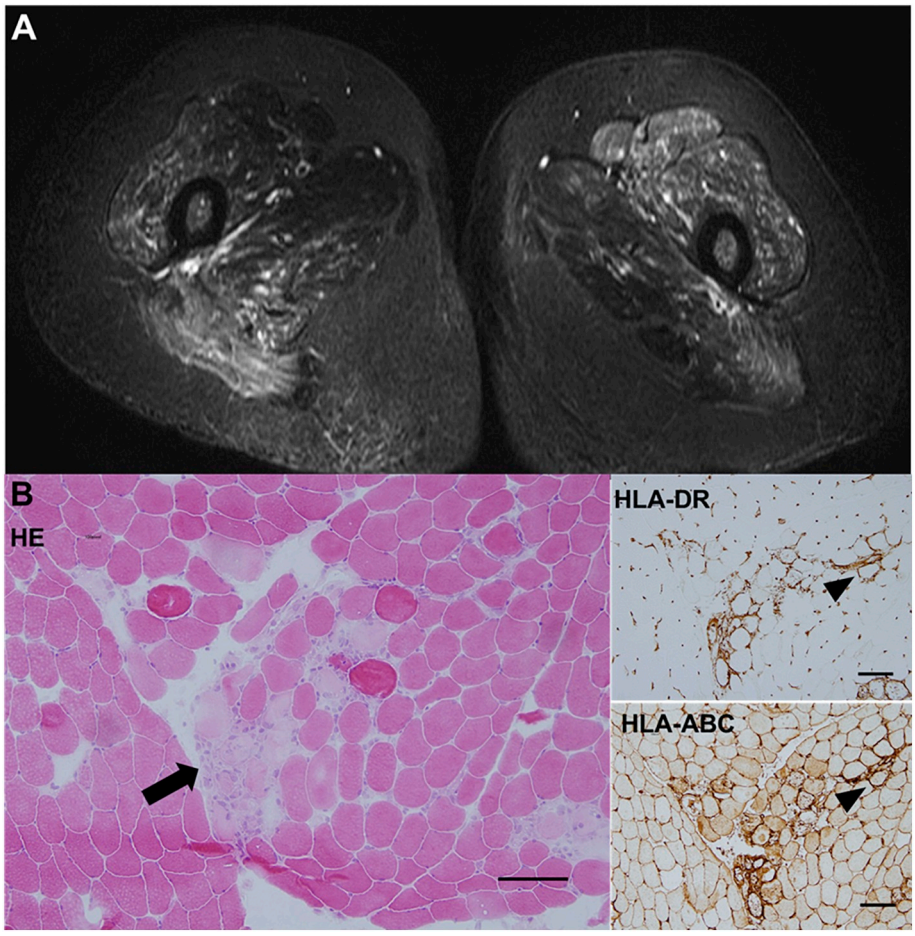

Fig. 1. (A) MRI of femur muscles (axial-STIR (short-tau inversion-recovery) sequence), showing diffuse high-intensity lesions. (B) Frozen section of the left quadriceps muscle biopsy. Abundant necrotic fibers with relatively sparse lymphocytic infiltrations are seen (black arrow) (HE: hematoxylin eosin stain). Immunohistochemistry results for human leukocyte antigen (HLA)-ABC and HLA-DR reveal positivity along both the necrotic and non-necrotic fibers (black triangle), suggesting an immune-mediated myopathy. Scale bars: 100 μm.

necrotic fibers, consistent with findings in immune-mediated necrotizing myopathy (Fig. 1B) [8]. Necrotic myofibers are typical findings in immune checkpoint inhibitor-associated myopathy [8,9]. Differences in the underlying pathogenesis of PD-1 inhibitor-associated myositis (typically with lymphocytic infiltration) and necrotizing myopathy (scarce lymphocytic infiltration) remain unclear and further study is needed.

In previously reported pMG cases, 8 had a history of MG, 3 were seropositive for AChR Ab without MG symptoms, and none with thymoma before PD-1 inhibitor therapy initiation. In the present case, the patient had no MG symptoms, but was seropositive for AChR Ab and had a history of thymoma 6 years prior to nivolumab initiation. Thus a history of MG and AChR Ab positivity may be potential risk factors or predictors of MG onset in patients undergoing treatment with PD-1 inhibitors. Therefore, it may be beneficial to screen patients for AChR Ab and a history of MG prior to initiating PD-1 inhibitor therapy; PD-1 inhibitor therapy should be avoided for patients with AChR Ab positivity or MG. Of note, most patients (38/42, 90%) developed pMG before the fourth infusion of PD-1 inhibitor (mean 2.2, median 2). A previous study reported that T-cell activation by PD-1 inhibitors occurred within 2 weeks after the administration of the drug in an animal model of cancer, which may potentially explain the onset time of pMG in these patients [10].

The use of PD-1 inhibitors to treat unresectable cancer has now increased worldwide, though pMG is characterized by a severe clinical course when compared to MG not associated with PD-1 inhibitors. Although MG symptoms were severe in the present case, significant improvement was observed with intensive immunotherapy. Thus, a better understanding of pMG characteristics may improve clinical outcome in these patients.

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Ethical standards

Informed consent was obtained from the patient.

Disclosure of conflicts of interest

All authors report no conflicts of interest.

Authors contributions

Hayato So, conceptualized and designed study, treated the patient, drafted and revised the manuscript.

Ryotaro Ikeguchi: conceptualized and designed the study, treated the patient, drafted and revised the manuscript.

Masaki Kobayashi: performed histological analysis, revised the manuscript.

Miki Suzuki: performed histological analysis.

Yuko Shimizu: treated the patient, revised the manuscript.

Kitagawa Kazuo: conceptualized the study, critically revised the manuscript.

Table 1
Comparison of the present case and previously reported cases with pMG.

	Present case	Previously reported cases (n = 44)
Onset age of pMG, y, mean (range)[a]	55	71.6 (34–86)
Sex, M:F	F	26:18
PD-1 inhibitor regimen, n (%)		
Nivolumab	Nivolumab	27 (61)
Pembrolizumab		17 (39)
Malignancy, n (%)		
Melanoma	Melanoma	17 (39)
Lung cancer		16 (36)
Other cancers		11 (25)
Times of PD-1 inhibitor infusion before pMG onset, n (%)[b]		
One		8 (19)
Two	Two	21 (50)
Three		9 (21)
Four		3 (7)
Five		1 (2)
Other complications associated with PD-1 inhibitor, n (%)		
Myositis		13 (30)
Myocarditis		3 (7)
Both myositis and myocarditis	Both myositis and myocarditis	1 (2)
Rhabdomyolysis		3 (7)
AChR Ab-positive at pMG onset, n (%)	+	31 (70)
History of MG before PD-1 inhibitor use, n (%)	−	8 (18)
AChR Ab-positive before PD-1 inhibitor use without MG symptoms, n (%)	+	3 (7)
Bulbar palsy, n (%)[c]	+	21 (68)
Ventilatory support, n (%)[d]	+	16 (37)
Mortality rate, n (%)[e]		16 (38)

Ab: antibody; AChR: acetylcholine receptor; MG: myasthenia gravis; PD-1: programmed cell death protein 1; pMG: PD-1 inhibitor-associated MG.
[a,b]The numbers of patients with available data is 42.
[c]The number of patients with available data is 31.
[d]The number of patients with available data is 43.
[e]The number of patients with available data is 42.

References (Table 1)

[1] S. Suzuki, N. Ishikawa, F. Konoeda, et al., Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan, Neurology. 89 (2017) 1127–1134.
[2] A.I. Loochtan, M.S. Nickolich, L.D. Hobson-Webb, Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer, Muscle Nerve. 53 (2015) 307–8.
[3] D. Lopez, A. Calvo, A. Fershko, Myasthenia Gravis and Rhabdomyolysis in A Patient with Advanced Renal Cell Cancer Treated With Nivolumab: A Case Report And Review of the Literature, Br. J. Med. Health. Res. 2 (2015) 11–16.
[4] G. Sciacca, A. Nicoletti, L. Rampello, L. Noto, H.J. Parra, M. Zappia, Benign form of myasthenia gravis after nivolumab treatment, Muscle Nerve. 54 (2016) 507–9.
[5] P. Polat, P.D. Donofrio, Myasthenia gravis induced by nivolumab therapy in a patient with non-small-cell lung cancer, Muscle Nerve. 54 (2016) 507.
[6] Y.H. Chen, F.C. Liu, C.H. Hsu, C.F. Chian, Nivolumab-induced myasthenia gravis in a patient with squamous cell lung carcinoma: Case report, Medicine (Baltimore). 96 (2017) e7350.
[7] J.J. Mehta, E. Maloney, S. Srinivasan, P. Seitz, M. Cannon, Cureus. 20 (2017) e1702.
[8] Y. Hasegawa, S. Kawai, T. Ota, H. Tsukuda, M. Fukuoka, Myasthenia gravis induced by nivolumab in patients with non-small-cell lung cancer: a case report and literature review, Immunotherapy. 9 (2017) 701–707.
[9] E. Chang, A.L. Sabichi, Y.H. Sada, Myasthenia Gravis After Nivolumab Therapy for Squamous Cell Carcinoma of the Bladder, J. Immunother. 40 (2017) 114–116.
[10] D.S. Cooper, M.N. Meriggioli, P.D. Bonomi, R. Malik, Severe Exacerbation of Myasthenia Gravis Associated with Checkpoint Inhibitor Immunotherapy, J Neuromuscul Dis. 4 (2017) 169–173.
[11] A. Mitsune, S. Yanagisawa, T. Fukuhara, Relapsed Myasthenia Gravis after Nivolumab Treatment, Intern. Med. 57 (2018) 1893–1897.
[12] K.H. Kang, W. Grubb, K. Sawlani, Immune checkpoint-mediated myositis and myasthenia gravis: A case report and review of evaluation and management, Am J Otolaryngol. 39 (2018) 642–645.
[13] J. Bourgeois-Vionnet, B. Joubert, E. Bernard, et al., Nivolumab-induced myositis: A case report and a literature review, J. Neurol. Sci. 387 (2018) 51–53.
[14] J.H. Chen, K.Y. Lee, C.J. Hu, C.C. Chung, Coexisting myasthenia gravis, myositis, and polyneuropathy induced by ipilimumab and nivolumab in a patient with non-small-cell lung cancer: A case report and literature review, Medicine (Baltimore) 96 (2017) e9262.
[15] R.Y·C Tan, C.K. Toh, A. Takano, Continued Response to One Dose of Nivolumab Complicated by Myasthenic Crisis and Myositis, J Thorac Oncol. 12 (2017) e90-e91.
[16] A. Fellner, C. Makranz, M. Lotem, et al., Nivolumab-induced myositis: A case report and a literature review, J. Neurooncol. 137 (2018) 601–609.
[17] K.H. Lau, A. Kumar, I.H. Yang, R.J. Nowak, Exacerbation of myasthenia gravis in a patient with melanoma treated with pembrolizumab, Muscle Nerve. 54 (2016) 157–61.
[18] S.D. Phadke, R. Ghabour, B.L. Swick, A. Swenson, M. Milhem, Y. Zakharia, Pembrolizumab Therapy Triggering an Exacerbation of Preexisting Autoimmune Disease: A Report of 2 Patient Cases, J Investig Med High Impact Case Rep. 4 (2016) 2324709616674316.
[19] J. Zhu, Y. Li, Myasthenia gravis exacerbation associated with pembrolizumab, Muscle Nerve. 54 (2016) 506–7.
[20] L. Zimmer, S.M. Goldinger, L. Hofmann, et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy, Eur. J. Cancer. 60 (2016) 210–25.
[21] N.L. Gonzalez, A. Puwanant, A. Lu, S.M. Marks, S.A. Zivkovic, Myasthenia triggered by immune checkpoint inhibitors: New case and literature review, Neuromuscul. Disord. 27 (2017) 266–268.
[22] S.Y. Huh, S.H. Shin, M.K. Kim, S.Y. Lee, K.H. Son, H.Y. Shin, Emergence of Myasthenia Gravis with Myositis in a Patient Treated with Pembrolizumab for Thymic Cancer, J Clin Neurol. 14 (2018) 115–117.
[23] D. Makarious, K. Horwood, J.I. Coward, Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors, Eur. J. Cancer. 82 (2017) 128–136.
[24] I. Alnahhas, J. Wong, A case of new-onset antibody-positive myasthenia gravis in a patient treated with pembrolizumab for melanoma, Muscle Nerve. 55 (2017) E25-E26.
[25] D.E. Earl, A.I. Loochtan, R.S. Bedlack, Refractory myasthenia gravis exacerbation triggered By pembrolizumab, Muscle Nerve. 57 (2018) E120-E121.
[26] M. Hibino, K. Maeda, S. Horiuchi, M. Fukuda, T. Kondo, Pembrolizumab-induced myasthenia gravis with myositis in a patient with lung cancer, Respirol Case Rep. 6 (2018) e00355.
[27] S.M. Crusz, A. Radunovic, S. Shepherd, et al., Rituximab in the treatment of pembrolizumab-induced myasthenia gravis, Eur. J. Cancer. 102 (2018) 49–51.
[28] B.H. Nguyen, J. Kuo, A. Budiman, H. Christie, S. Ali, Two cases of clinical myasthenia gravis associated with pembrolizumab use in responding melanoma patients, Melanoma Res. 27 (2017) 152–154.
[29] T. Tozuka, T. Sugano, R. Noro, et al., Pembrolizumab-induced agranulocytosis in a pulmonary pleomorphic carcinoma patient who developed interstitial lung disease and ocular myasthenia gravis, Oxford Medical Case Reports. 11 (2018) omy094.
[30] K.L. March, M.J. Samarin, A. Sodhi, R.E. Owens, Pembrolizumab-induced myasthenia gravis: A fatal case report, al., J Oncol Pharm Pract. 24 (2018) 146–149.
[31] N. Uchio, K. Taira, C. Ikenaga, et al., Granulomatous myositis induced by anti–PD-1 monoclonal antibodies, Neurol Neuroimmunol Neuroinflamm. 5 (2018) e464.

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References

[1] M. Touat, D. Talmasov, D. Ricard, D. Psimaras, Neurological toxicities associated with immune-checkpoint inhibitors, Curr. Opin. Neurol. 30 (2017) 659–668.
[2] S. Suzuki, N. Ishikawa, F. Konoeda, et al., Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan, Neurology 89 (2017) 1127–1134.
[3] M. Touat, T. Maisonobe, S. Knauss, et al., Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer, Neurology 91 (2018) e985–e994.
[4] J.C. Kao, A. Brickshawana, T. Liewluck, Neuromuscular complications of programmed cell Death-1 (PD-1) inhibitors, Curr. Neurol. Neurosci. Rep. 18 (2018) 63.
[5] E. Simeone, A.M. Grimaldi, P.A. Ascierto, Anti-PD1 and anti-PD-L1 in the treatment of metastatic melanoma, Melanoma Manag. 2 (2015) 41–50.
[6] Y. Fukasawa, K. Sasaki, M. Natsume, M. Nakashima, S. Ota, K. Watanabe, Nivolumab-induced myocarditis concomitant with myasthenia gravis, Case Rep. Oncol. 10 (2017) 809–812.
[7] S.M. Crusz, A. Radunovic, S. Shepherd, S. Shah, V. Newey, M. Phillips, L. Lim, T. Powles, P.W. Szlosarek, J. Shamash, S. Rashid, Rituximab in the treatment of pembrolizumab-induced myasthenia gravis, Eur. J. Cancer 102 (2018) 49–51.
[8] Y. Allenbach, A.L. Mammen, O. Benveniste, W. Stenzel, Immune-mediated necrotizing myopathies working group, 224th ENMC international workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016, Neuromuscul. Disord. 28 (2018) 87–99.
[9] T. Liewluck, J.C. Kao, M.L. Mauermann, PD-1 inhibitor-associated myopathies: emerging immune-mediated myopathies, J. Immunother. 41 (2018) 208–211.
[10] A.D. Salama, T. Chitnis, J. Imitola, H. Akiba, F. Tushima, M. Azuma, H. Yagita, M.H. Sayegh, S.J. Khoury, Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis, J. Exp. Med. 198 (2003) 71–78.

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