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Letter to the Editor

Presence of antibodies to striated muscle and acetylcholine receptor in association with occurrence of myasthenia gravis with myositis and myocarditis in a patient with melanoma treated with an anti–programmed death 1 antibody

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Dear Editor,

The increasing use of immune checkpoint inhibitors (ICIs) for the treatment of solid tumours increase the importance of management of immune-related adverse events (irAEs) [1]. Myasthenia gravis (MG) infrequently occurs in patients receiving ICIs [2–6]. ICIs-related MG (iciMG) often shows concurrent elevation of the creatine kinase (CK) level, suggesting myositis and/or myocarditis, and results in higher frequencies of myasthenia crisis with a risk of death [4,5,7]. Anti-striated muscle antibodies (Str-Abs) may be useful biomarkers for iciMG with myositis and/or myocarditis because they appear in cases of idiopathic MG (iMG) associated with myositis and/or myocarditis [8,9]. We describe a patient with melanoma treated with pembrolizumab, who developed severe iciMG with myositis and myocarditis and concurrently had Str-Abs as well as anti-acetylcholine receptor antibody (AChR-Ab). This is the first report of elevated Str-Abs in iciMG with myositis and/or myocarditis.

An 83-year-old Japanese man was referred to us for primary melanoma on the scrotum with metastases in the bilateral lungs and inguinal lymph nodes. As the disease progressed rapidly, he was treated with pembrolizumab. His blood tests showed no remarkable findings before the administration of pembrolizumab. On the 25th day after first administration, he developed fatigable weakness and muscle pain. He visited our hospital on the 29th day. A physical examination revealed bilateral ptosis, diplopia, weakness of neck flexor and extensor, and bilateral thigh myalgia. On the next day, he felt dysphagia and dyspnoea. Various laboratory tests showed abnormal findings: aspartate transaminase, 328 U/l (normal range 13–30 U/l); alanine transaminase, 337 U/l (10–42 U/l); CK, 5567 U/l (59–248 U/l); CK–myocardial band, 177 ng/ml (1–5 ng/ml); troponin-T, 0.337 ng/ml (0–0.090 ng/ml); and brain natriuretic peptide, 42.1 pg/ml (0–20.0 pg/ml).

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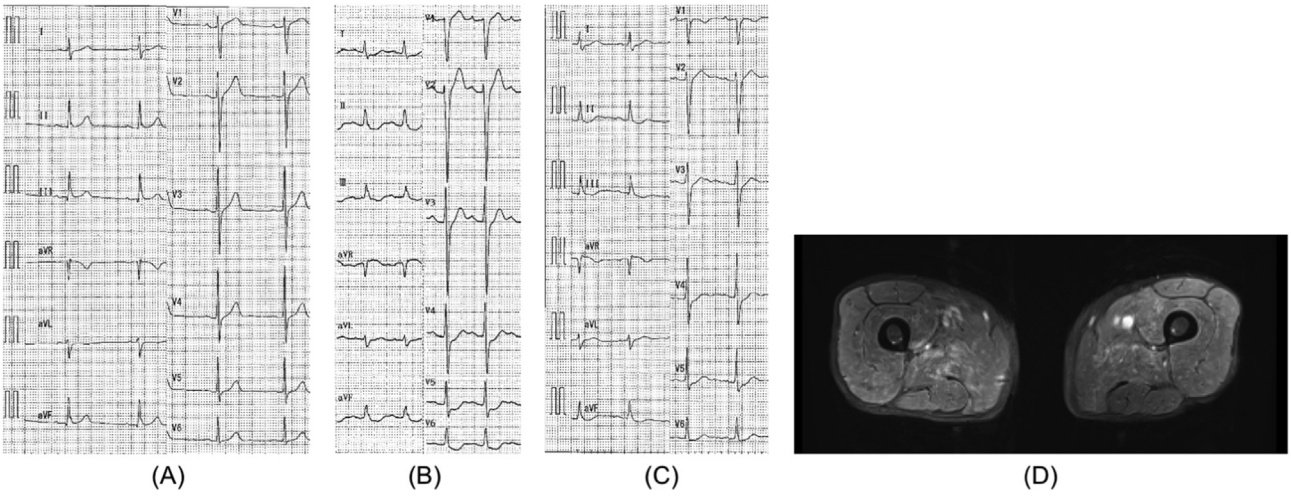

Fig. 1. Electrocardiogram (ECG) and magnetic resonance imaging. (A) ECG reveals normal findings before pembrolizumab administration. (B) ECG shows T-wave abnormality, wide QRS, and first-degree atrioventricular block on admission. (C) Wide QRS and first-degree atrioventricular block were improved 3 d after the beginning of steroid pulse therapy. (D) Fat-suppressed T2-weighted magnetic resonance imaging shows high-intensity areas in the thighs.

Autoantibody tests were as follows: anti-nuclear antibody, 1:160 (<1:40); AChR-Ab, 11.2 nmol/l (0–0.3 nmol/l); Str-Abs, 1:61440 (<1:120); anti-titin antibody, positive (negative); and anti-Kv1.4 antibody, positive (negative). Serological tests of hepatitis virus were negative. Computed tomography imaging revealed no finding of thymoma. Electrocardiography revealed T-wave abnormality, wide QRS, and first-degree atrioventricular block, which were not previously documented (Fig. 1A–C). However, echocardiography revealed no abnormality, and his serum brain natriuretic peptide did not increase further. The thyroid function test and electrolyte levels were within normal limits. Fat-suppressed T2-weighted magnetic resonance imaging of his thighs revealed diffuse bilateral high-intensity lesions (Fig. 1D). Electrophysiologic neuromuscular junction tests, including edrophonium test and repetitive nerve stimulation test, were negative. The patient was finally diagnosed with pembrolizumab-induced MG, classified as IIIb according to the Myasthenia Gravis Foundation of America Clinical Classification, with myositis and myocarditis. In addition, he was affected by ICI-related hepatitis. We commenced 3 d of steroid pulse therapy (methylprednisolone 1000 mg/d) followed by prednisolone at a dose of 1 mg/kg/d, which were gradually tapered to 30 mg/d. In addition, four cycles of plasma exchange therapy were carried out simultaneously with steroid pulse therapy. His electrocardiogram and blood

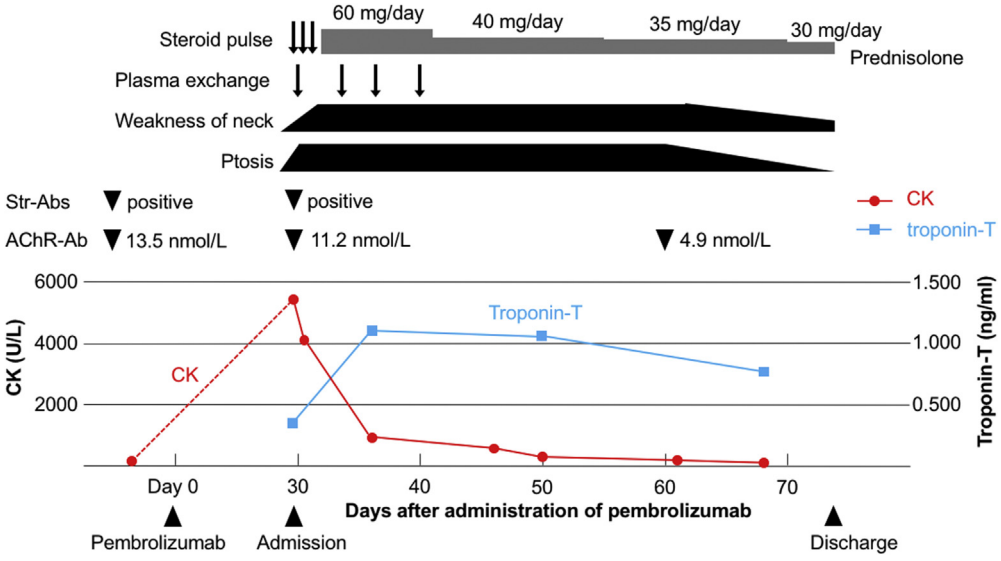

Fig. 2. Clinical course of an 83-year-old man with myositis, myocarditis, and myasthenia gravis after a single-dose administration of pembrolizumab. Creatine kinase and troponin-T were increased after pembrolizumab treatment. Steroid pulse and plasma exchange therapies decreased creatine kinase and troponin-T levels. Ptosis and muscle weakness were improved 6 weeks after the steroid pulse therapy.

tests were improved after the beginning of therapy, and clinical conditions including ptosis, external ophthalmoplegia, and weakness of the neck were also improved after 6 weeks. His primary tumour and metastases in the lungs and lymph nodes were stable, and no new lesions were found on computed tomography images 5 weeks later. A retrospective examination using his serum before pembrolizumab administration revealed positive results of anti-titin and anti-Kv1.4 antibodies, representing Str-Abs positivity. AChR-Ab was also positive (13.5 nmol/l). The patient's symptoms and the results of the examinations are summarised in Fig. 2.

The importance of monitoring and management for irAEs has been increasing alongside the use of ICIs for the treatment of solid tumours, and appropriate biomarkers are needed. Our patient with melanoma treated with pembrolizumab developed iciMG with myositis and myocarditis. We detected several autoantibodies including not only AChR-Ab but also Str-Abs, anti-titin antibody, and anti-Kv1.4 antibody. Str-Abs are heterogenous autoantibodies, which react with epitopes on the muscle proteins, including titin, and Kv1.4. Str-Abs are detected in iMG, especially in severe iMG associated with myositis, myocarditis, bulbar symptoms, and/or myasthenic crisis [8–10]. Str-Abs were positive in our iciMG patient with myositis and myocarditis. Because Str-Abs have been reported to be positive in ICIs-related myocarditis or polymyositis [11,12], they may be biomarkers for iciMG with myositis and/or myocarditis.

While Str-Abs are detected in iMG patients, they are generally negative in healthy individuals. However, Str-Abs were positive even before ICIs administration in a patient with ICIs-related myositis [11]. Our patient also had Str-Abs even before the administration of pembrolizumab. Irrespective of the pathogenicity of the autoantibodies, pre-existing antibodies to striated muscle suggest the presence of subclinical myositis and myocarditis before administration of ICIs. Furthermore, it is likely that iciMG progresses rapidly in cases of its onset immediately after ICI treatments, suggesting that ICIs elicit the pre-existing subclinical myositis and myocarditis. In addition, $CD8^+$ cytotoxic T cells prominently infiltrate in the striated muscle of iciMG [5,7,13], suggesting the participation of both cellular and humoral immunity. Indeed, cytotoxic T cells specific to shared antigens between striated muscle and autologous tumour were found in cases of iciMG with myositis [5].

Although the titre of AChR-Ab is relatively low in iciMG compared with iMG [7], iciMG is likely to be severe because of the coexistence of myositis and/or myocarditis. Based on our observation, Str-Abs may exist with AChR-Ab in iciMG and may be biomarkers for iciMG, especially that associated with myositis and/or myocarditis. We should consider iciMG with myositis and/or myocarditis when we encounter Str-Abs in patients treated with ICIs.

Clinicians should note the possibility of myositis and/or myocarditis leading to fatal irAEs in patients with iciMG. Str-Abs may provide useful information for diagnosis and management. Because there are few reports of Str-Abs examined in patients with iciMG, further studies are necessary to prove the association between Str-Abs and iciMG.

Conflict of interest statement

None declared.

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