Clinical features and pathology of respiratory failure due to inflammatory myopathy induced by immune checkpoint inhibitors

Sirs,

Myositis induced by immune checkpoint inhibitors (irMyositis) is a representative neurologic immune adverse event (1-3), and may causes life-threating respiratory failure after steroid administration in severe cases (4-6). However, the detailed course of respiratory failure is unknown. We describe an autopsy case of irMyositis with fatal respiratory failure caused by inflammation of the diaphragm.

A 78-year-old Japanese man being treated with pembrolizumab (200 mg every 3 weeks) for metastatic bladder cancer (cT2N2M1) was admitted to our hospital presenting with diplopia, ptosis, and myasthenia of the proximal limbs without erythema, 10 days after the second injection of pembrolizumab.

Serum creatine kinase (CK) (7,657 U/L) was elevated. Antinuclear antibody and antibodies against ribonucleoprotein, aminoacyl transfer RNA synthetase, mitochondrial M2, anti-melanoma differentiation associated gene 5, Mi-2, transcriptional intermediary factor-1γ, signal recognition particle, and 3-hydroxy-3-methylglutaryl-coenzyme A were absent. Antibodies against acetylcholine receptor, muscle-specific kinase, low-density lipoprotein receptor-related protein 4, and Kv1.4 antibodies were also absent, and serum paraneoplastic antibody panels were negative. The edrophonium test revealed no improvement of diplopia, ptosis, and myasthenia. 3-Hz repetitive nerve stimulation revealed no decrements. Computed tomography showed no sign of interstitial pneumonia.

Magnetic resonance imaging (MRI) indicated systemic myositis in the femoral muscles, paraspinal erector muscles, and diaphragm (Fig. 1a). Muscle biopsy (right vastus lateralis) showed necrotic and regenerating fibers with inflammatory infiltration. The pulmonary function test on hospital day 1 showed a forced vital capacity (FVC) of 2.64 L (reference range: 2.25–2.81 L), and %VC was 92.0% (reference range: 80.0–100%). Echocardiography findings were normal.

We initiated 15 mg of prednisolone on hospital day 5, and titrated up to 30 mg, and began intravenous immunoglobulin (400 mg/kg for 5 days) on hospital day 7. The myasthenia of the extremities improved to normal and the serum CK levels gradually ameliorated to the normal range, while respiratory weakness progressively deteriorated. FVC and %VC were 1.71 L and 59.4%, respectively on hospital day 25. We started plasmapheresis three times on hospital day 25 and a second cycle of intravenous immunoglobulin on hospital day 33, which did not improve respiratory failure. On hospital day 36, FVC and %VC deteriorated further to 0.77 L and 29.5%, respectively. We suggested mechanical ventilation, but he refused, and died of hypercapnia on hospital day 37. We performed an autopsy and found that numerous CD8-positive T-lymphocytes and CD163-positive histiocytes had infiltrated the diaphragm between the myofibers with necrotic and regenerative changes without tumor invasion (Fig. 1b).

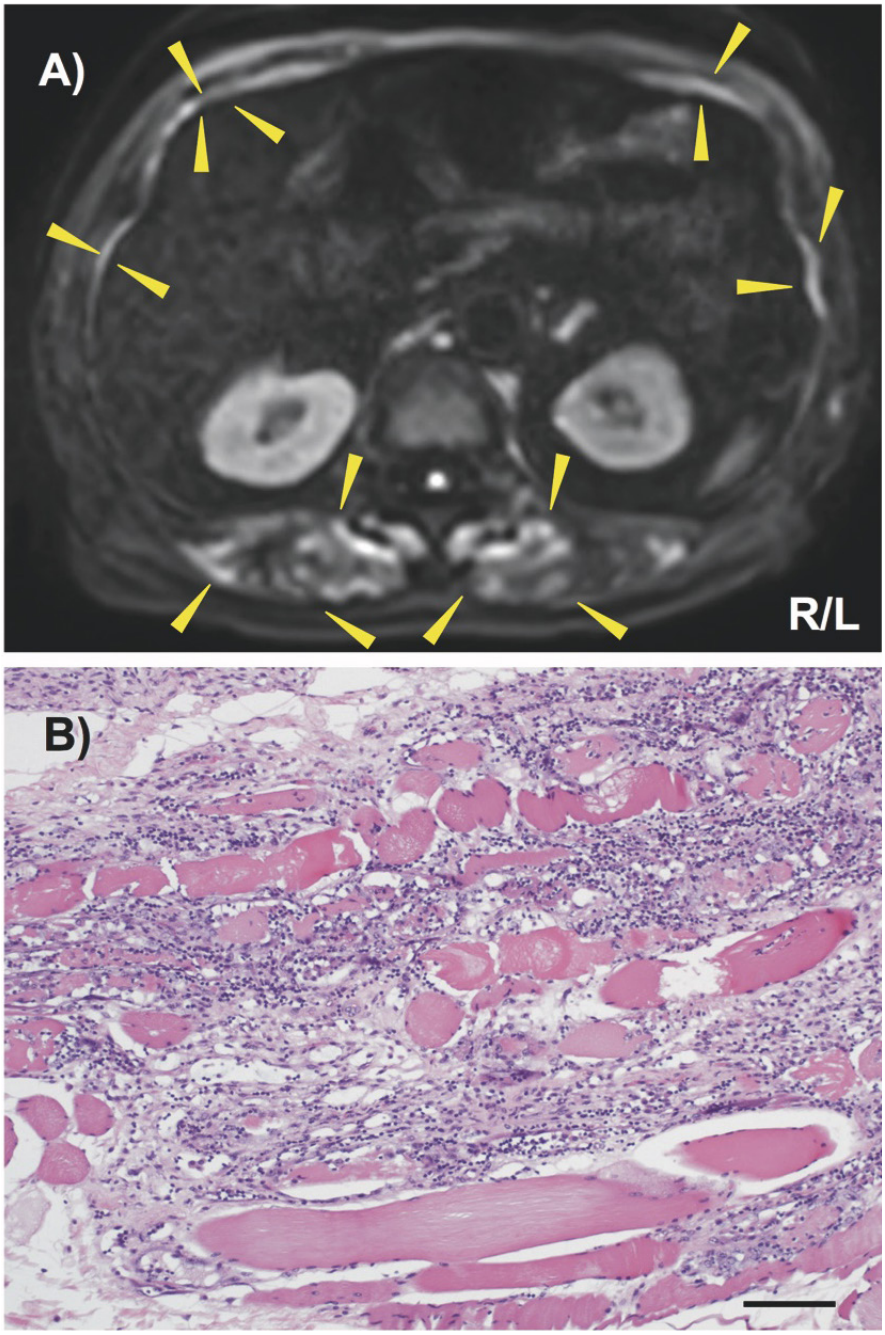

Fig. 1. A) Muscle MRI findings on admission. Hyperintense signal and enhancement in the entire diaphragm and paraspinal erector muscles in axial diffusion-weighted images.
B) Biopsies taken at autopsy from the diaphragm. Active necrotic myositis and with hematoxylin and eosin staining. Scale bars: 100 μm.

IrMyositis is often complicated with myasthenia gravis (MG) (7, 8). It characteristically presents not only with proximal myasthenia and myalgia of the limbs, serum CK level elevation, but also with ptosis and diplopia (7-9).

The overall fatality rate for irMyositis is 24% and is higher for irMyositis complicated with MG-like symptoms than that without (27.9% *vs*. 16%) (10). One of the most important causes of death in irMyositis is respiratory failure, but it is challenging to distinguish whether respiratory failure is due to myositis or MG crisis.

Our findings are consistent with the muscle pathology of irMyositis (9) and favored a diagnosis of myositis over neuromuscular junction disorder. Haddox *et al*. (5) also reported an irMyositis autopsy case showing active myositis of the diaphragm caused by cytotoxic T-lymphocytes, which is consistent with our report.

We speculate that steroids, immunoglobulin treatment, and plasmapheresis may have poor therapeutic effect on myositis of the diaphragm. In conclusion, active myositis in the diaphragm causes life-threating respiratory failure, so the therapeutic strategy needs to be improved.

Acknowledgement

We would like to thank Editage (www.editage.com) for English language editing.

Y. Aratake[1], *MD*
K. Obata[1], *MD*
K. Nishimura[2], *MD, PhD*
K. Shindo[1], *MD, PhD*

[1]*Department of Neurology, Kurashiki Central Hospital, Okayama;*
[2]*Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Okayama, Japan.*

Please address correspondence to:
Katsuro Shindo,
Department of Neurology, Kurashiki Central Hospital,
1-1-1 Miwa, Kurashiki-shi, Okayama, Japan.
E-mail: shindo@kchnet.or.jp

Funding. This study was supported in part by Intramural Research Grant (2-5) for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry.

Competing interests: none declared.

References

1. KAO JC, LIAO B, MARKOVIC SN *et al*.: Neurological complications associated with anti-Programmed Death 1 (PD-1) antibodies. *JAMA Neurol* 2017; 74: 1216-22.
2. MOREIRA A, LOQUAI C, PFÖHLER C *et al*.: Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. *Eur J Cancer* 2019; 106: 12-23.
3. MATAS-GARCÍA A, MILISENDA JC, SELVA-O'CALLAGHAN A *et al*.: Emerging PD-1 and PD-1L inhibitors-associated myopathy with a characteristic histopathological pattern. *Autoimmun Rev* 2020; 19: 102455.
4. LUECKE E, GANZERT C, VIELHABER S *et al*.: Immune checkpoint inhibitor-induced fatal myositis in a patient with squamous cell carcinoma and a history of yhymoma. *Clin Lung Cancer* 2020; 21: e246-9.
5. HADDOX CL, SHENOY N, SHAH KK *et al*.: Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm. *Ann Oncol* 2017; 28: 673-5.
6. MARTINS F, SOFIYA L, SYKIOTIS GP *et al*.: Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019; 16: 563-80.
7. SUZUKI S, ISHIKAWA N, KONOEDA F *et al*.: Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. *Neurology* 2017; 89: 1127-34.
8. SEKI M, URUHA A, OHNUKI Y *et al*.: Inflammatory myopathy associated with PD-1 inhibitors. *J Autoimmun* 2019; 100: 105-13.
9. TOUAT M, MAISONOBE T, KNAUSS S *et al*.: Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. *Neurology* 2018; 91: e985-94.
10. ALLENBACH Y, ANQUETIL C, MANOUCHEHRI A *et al*.: Immune checkpoint inhibitor-induced myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities. *Autoimmun Rev* 2020; 19: 102586.