

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 cause life-threatening 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-1 γ , 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 fibres 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 im-

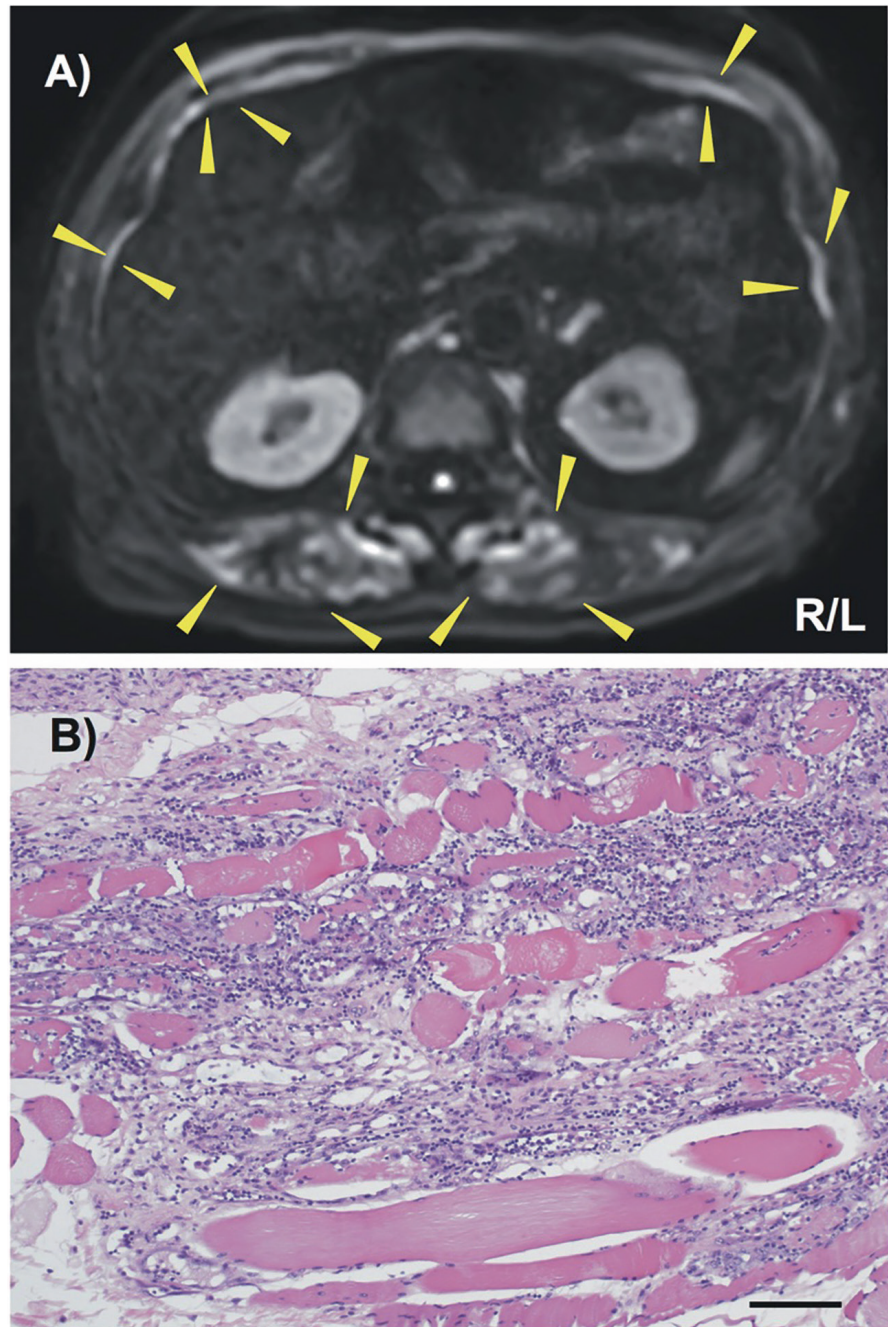


Fig. 1. A) Muscle MRI findings on admission. Hyperintense signal and enhancement in the entire diaphragm and paraspinal erector muscles in axial diffusion-weighted images.

B) Biopsies taken at autopsy from the diaphragm. Active necrotic myositis and with haematoxylin and eosin staining. Scale bars: 100 μ m.

munoglobulin 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 myofibres with necrotic and regenerative changes without tumor invasion (Fig. 1b). IrMyositis is often complicated with myas-

thenia 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 favoured 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-threatening respiratory failure, so the therapeutic strategy needs to be improved.

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