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Pembrolizumab-induced necrotizing diaphragmatic myositis

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Abstract

Pembrolizumab, an anti-PD1 antibody, is increasingly used for the treatment of non-small cell lung cancer. We report a severe and poorly described adverse effect of this therapy: necrotizing myopathy with diaphragmatic and myocardial involvement.

A 77-year-old male was diagnosed with metastatic lung adenocarcinoma and started a regimen with chemotherapy along with Pembrolizumab. Two weeks after the second cycle, he was admitted to the hospital due to acute myocarditis and hypercapnic respiratory failure. Treatment with glucocorticoids and Mycophenolate improved his cardiac condition. However, hypercapnic respiratory failure persisted, as well as orthopnea and generalized muscle weakness including bulbar musculature. After comprehensive evaluation including diaphragmatic ultrasound, electromyogram, and biopsy, he was diagnosed with autoimmune necrotizing myopathy with diaphragmatic and myocardial involvement. Treatment with intravenous immunoglobulins and non-invasive mechanical ventilation was added. However, he experienced respiratory deterioration, resulting in death.

This case exemplifies the importance of early recognition and intensive treatment of this serious adverse effect. Due to the increasing use of these therapies, it is expected to see a parallel increase in their adverse effects in the coming years.

Keywords: Pembrolizumab, necrotizing diaphragmatic myositis

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Introduction

Pembrolizumab is an anti-PD-1 antibody approved for the treatment of locally advanced or metastatic non-small cell lung cancer. The activation of cytotoxic T lymphocytes in this therapy can increase the risk of a wide variety of autoimmune adverse effects. [1] Neurologic adverse effects are less common than dermatologic, gastrointestinal or rheumatologic (prevalence of 1-4.2% vs 10-15%, respectively). [1] Myasthenia gravis (0,12-0,2%), autoimmune myopathies (0,58-0,76%) and Guillain-Barré syndrome (0,2-0,3%) are the most common adverse effects reported, with a mortality of 30.3%, 25% and 12.5%, respectively. Myocarditis and respiratory muscle myositis are the major causes of death due to adverse effects of checkpoint inhibitors like pembrolizumab. [2]

We report a rare and poorly described severe adverse effect of pembrolizumab: necrotizing myopathy with diaphragmatic and myocardial involvement.

Case

A 77-year-old male was diagnosed with stage IV lung adenocarcinoma and treated with a regimen of carboplatin, pemetrexed and pembrolizumab. He received a total of two cycles separated by one month.

Two weeks after the administration of the second cycle, he was admitted to the Coronary Care Unit due to heart failure and hypercapnic respiratory failure. Laboratory findings suggested acute myocarditis: elevation of troponin T (2445 ng/L), creatine kinase (3300 U/L) and NT-proBNP (4320 ng/L). An immune-mediated complication associated with pembrolizumab was suspected. Methylprednisolone was initiated at a dose of 1g/24 hours for 5 days, followed by a tapering dose of 2 mg/kg/day. Additionally, mycophenolate was initiated at a dose of 750 mg/12 hours. Three weeks later, mycophenolate was discontinued due to severe thrombocytopenia (33,000 platelets/µL).

During the following weeks of hospitalization, he showed improvement in his cardiac condition. However, hypercapnic respiratory failure and intolerance to supine position persisted. A CT-scan with contrast was performed and ruled out pneumonitis, pneumonia and pulmonary embolism. Neurologic exploration showed generalized muscle weakness, diplopia, ptosis and dysarthria. Non-invasive mechanical ventilation (NIV) was initiated due to suspected diaphragmatic involvement.

Diaphragmatic ultrasound showed right-predominant bilateral diaphragmatic hypokinesia. Pulmonary function tests revealed a severe restrictive disorder with 25% of theorical maximal inspiratory pressures. The patient tested positive for anti-titin antibodies against striated muscle. Antibodies against acetylcholine receptors and muscle-specific tyrosine kinase (Musk) were negative. Electromyogram showed a myopathic pattern suggestive of primary muscle fiber involvement. Finally, a biopsy of the left bicep's brachialis revealed mild inflammatory infiltrates with abundant necrotic and regenerating features (Figure 1).

These findings strongly suggested the presence of autoimmune necrotizing myopathy with diaphragmatic and myocardial involvement. As diaphragmatic biopsy was contraindicated due to the severe respiratory failure, the diagnosis of pembrolizumab-induced myositis in our case report was established based on the previous findings and through a multidisciplinary approach involving specialists in respiratory medicine, oncology and neurology. Treatment with intravenous immunoglobulins was added.

Initially, the patient responded well to NIV despite some intolerance to treatment at the beginning. Dyspnea, orthopnea and hypercapnic respiratory failure were corrected. Unfortunately, he had a respiratory infection with bronchospasm and rapid respiratory worsening. He consequently had a cardiac arrest with asystole due to severe hypoxemia. Cardiopulmonary resuscitation was done for 30 minutes without success, resulting in the patient's death.

Discussion

Our case highlights that patients treated with pembrolizumab are at risk of developing necrotizing myositis. Respiratory failure due to myositis is a rare immune-related toxicity of checkpoints inhibitors that, if not early treated, can be fatal. [3]

To date, only a few case reports have been published regarding pembrolizumab-induced diaphragmatic myositis. [3,4,5] Compared to them, our patient had similar age and gender. In most of them, diaphragmatic myositis was suspected based on symptoms, laboratory findings and electromyogram; and diagnosis was confirmed after death by autopsy. Our case and the one from Haddox et al [3] are the only ones in which the diagnosis was suggested premortem by a biopsy of biceps brachialis and triceps, respectively. Haddox et al confirmed the diagnosis through a post-mortem diaphragmatic autopsy, which was not performed in our case due to the family's wishes.

As checkpoint inhibitors have become more widely used, close monitoring for prompt diagnosis and early management is crucial to prevent progression and

fatal complications. Diaphragmatic ultrasound, electromyography and antibodies against striated muscle are useful for diagnosis.

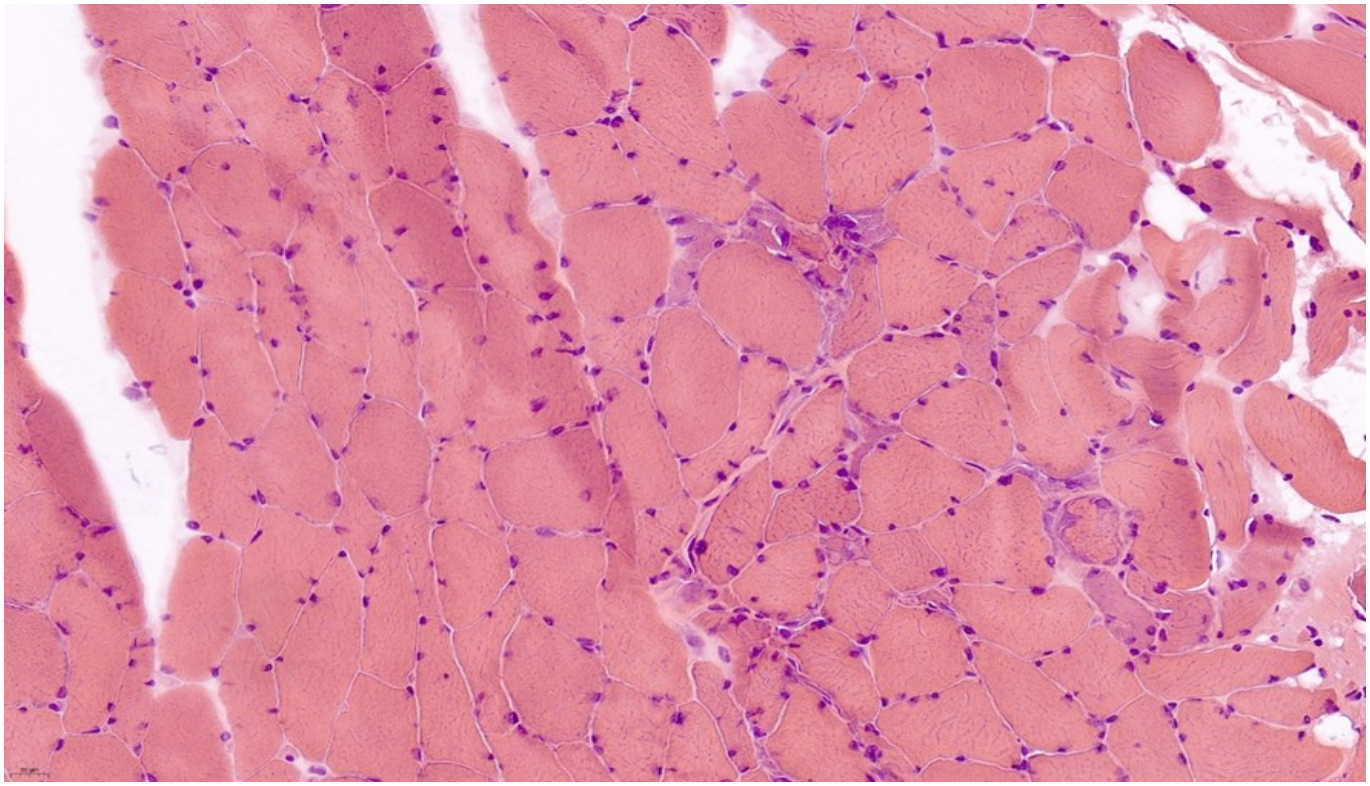

Figure 1: Muscle biopsy (Haematoxylin-eosin staining; x400) shows myofiber diameters and shapes are highly variable, with abundant necrotic and regenerative fibres, randomly distributed.

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