Pembrolizumab-induced Myositis in the Setting of Metastatic Melanoma: An Increasingly Common Phenomenon

ABSTRACT

Pembrolizumab, an anti-programmed cell death protein 1 (PD-1) antibody, has demonstrated efficacy in treating metastatic melanoma. However, a handful of case reports have been published reporting autoimmune phenomena weeks after administration of the first dose of this immunomodulator. Although immunotherapy complications are not well known among dermatologists, they should be cognizant of this association between anti-programmed cell death protein 1 immunotherapy and autoimmune symptomology, since pembrolizumab has become a common therapy for metastatic melanoma. Here, the author presents a case of a patient with metastatic melanoma and a family history of autoimmune disease who presented with myositis in the weeks after receiving pembrolizumab.

KEY WORDS: Pembrolizumab, adverse effects, monoclonal antibodies, metastatic melanoma

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Pembrolizumab is an anti-programmed cell death protein 1 (PD-1) antibody recently approved by the United States Food and Drug Administration for the treatment of metastatic melanoma.[1] Since the first report in 2016, multiple published case reports have described myopathies induced by this immunomodulator, none of which, to our knowledge, have been reported in the literature specific to dermatology.[2] Here, the author presents a case of a patient with metastatic melanoma and a family history of autoimmune disease who presented with myositis in the weeks after receiving pembrolizumab.

CASE PRESENTATION

A 77-year-old male patient with Stage IV melanoma with metastases to the lung, adrenal gland, and bone and a family history of myasthenia gravis presented to the hospital with acute weakness and fatigue that had developed over the previous three days. The patient's wife noted that he had developed drooping eyelids and appeared easily fatigued when walking. He had received his first dose of pembrolizumab three weeks prior to the onset of his symptoms, but had not yet received his second dose due to transaminitis.

Upon examination, the patient showed an elevated troponin level with concerning electrocardiogram changes (T-wave inversions in III, AVR, and V1), along with elevated creatine phosphokinase (CPK), liver function, and creatinine findings. Unremarkable laboratory results included those concerning rheumatoid factor, antinuclear antibody, thyroid-stimulating hormone, anticholinesterase receptor titers, and acetylcholine binding activity. Transthoracic echocardiogram and magnetic resonance imaging of the brain occurred without identifying abnormalities.

The patient was intubated due to impending respiratory crisis and pre-emptively administered a course of intravenous immunoglobulin (IVIg) and prednisone 1g for five days before tapering to 95mg, per the 2018 National Comprehensive Cancer Network guidelines.[3] However, the patient continued to show poor negative inspiratory force, so tracheostomy and gastrostomy tube were placed. The patient also experienced several episodes of paroxysmal bradycardia with hypotension that were temporized with fluid resuscitation. Cardiac magnetic resonance imaging was unable to be completed due to the patient's condition. Additionally, although the patient's creatinine normalized, the CPK level continued to fluctuate. Muscle biopsy

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revealed necrotic myopathy and a positive striated muscle antibody titer 1:480, findings that were consistent with pembrolizumab-induced myositis.

The patient was treated with a five-day course of apheresis and discharged to a long-term acute care facility for the completion of the prednisone taper over six weeks while requiring mechanical ventilation. The patient was followed up with in the multidisciplinary cancer clinic two months later, having successfully participated in acute rehabilitation. Over the following three months, the patient developed confusion and lethargy, ultimately revealing the presence of brain metastases.

DISCUSSION

Pembrolizumab has demonstrated efficacy in treating metastatic melanoma refractory to ipilimumab.[1] However, since 2016, several case reports have been published suggesting autoimmune phenomena as an adverse effect that appears several weeks after the administration of the first dose of this immunomodulator.[1,2,4]

Patients have shown a rapid onset of muscle weakness akin to myasthenia gravis, with diaphragmatic necrotic myopathy.[2,4] As with our patient, reports of episodes of hypotension and bradycardia have been consistent with myocarditis-induced non-ST segment elevation myocardial infarction, with some leading to death.[5] High-dose steroids, IVIg, and plasmapheresis have been reported as mainstays of treatment by authorities, with patients showing near-complete recovery.[1,2,4,5]

In our patient, a family history of autoimmune diseases was known about prior to the initiation of pembrolizumab. Studies evaluating the relationship of pre-existing autoimmune history and use of anti-PD-1 immunotherapy have been conducted, but have not reported increasing adverse effects or deaths.[6] However, with the increasing reports of myopathies and/or fatalities related to these agents over the past three years, use of these agents in these patients should be reconsidered.

Although immunotherapy complications are not well known among dermatologists, they should be cognizant of this association between anti-PD-1 immunotherapy and autoimmune symptomology, since pembrolizumab has become a well-recognized therapy for metastatic melanoma. In addition to 40 percent of patients displaying cutaneous adverse effects, such as autoimmune dermatitis, after the administration of pembrolizumab, new cases of cutaneous squamous cell carcinoma have been reported and will likely appear more frequently in dermatology clinics.[7] Standardized screening for myositis induced by anti-PD-1 immunotherapy with creatinine phosphokinase and autoantibody levels might improve clinical outcomes for patients and should be considered upon the initiation of treatment.

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