Review of PD-1–Induced Myositis and a Case of Pembrolizumab-Induced Myositis in a Patient with Metastatic Melanoma

Kirollos S. Hanna, PharmD, BCPS, BCOP

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DISCUSSION: We discuss a case of an 86-year-old male patient with metastatic melanoma who developed myositis secondary to initiating pembrolizumab therapy. To our knowledge, this is the second reported case of myositis resulting from pembrolizumab. The patient received 2 cycles of therapy at 2 mg/kg and developed dysphagia and hoarseness 1 week later for which he was admitted to the hospital for further evaluation. After a complicated hospital course, steroid therapy, and plasma exchange, the patient failed to respond, aspirated, and died. We also review other cases of immune-mediated myositis reported in the literature.

CONCLUSION: Several immune-mediated adverse events, including myopathies, have been associated with immune checkpoint inhibitors, including programmed-cell death-1 and cytotoxic T-lymphocyte–associated protein-4 inhibitors. Adverse events often respond to discontinuation of therapy and initiating steroids. Tumor necrosis factor–alpha inhibitors and plasma exchange may be used for severe, unresponsive cases. Clinicians should be vigilant with such events and initiate therapeutic interventions rapidly to optimize patient safety and outcomes.

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gland and involving 1 intraparenchymal lymph node. The largest metastatic deposit measured 1.8 cm and was associated with extracapsular extension.

Postresection, the patient received adjuvant radiation therapy to the right neck and parotid, for a total dose of 6600 cGy in 30 fractions from July 2016 through September 2016. One month postradiation, adjuvant pembrolizumab therapy was initiated at 2 mg/kg intravenously every 3 weeks.

The patient tolerated cycle 1 of therapy well without any complications. Approximately 1 week later, starting with the second cycle, he presented to his outpatient provider complaining of dysphagia and hoarseness over several days. A magnetic resonance imaging scan of the brain, head, and neck did not show any evidence of metastases or any acute findings.

Video swallow studies demonstrated very poor swallowing function, with severe oropharyngeal dysphagia. Apart from severe oropharyngeal dysphagia and hoarseness, the patient denied any headache, visual disturbances, nausea and vomiting, or any other focal neurological deficits. At the time of presentation, his creatine phosphokinase was normal (ie, 180 U/L). The patient was admitted to the hospital for further evaluation.

After consultation with an otolaryngologist, a comprehensive examination of the patient’s upper airway was performed using flexible fiberoptic nasal laryngoscopy and no clear abnormalities were observed. A neurology consultation was ordered to evaluate for any central nerve involvement. The electromyography examination showed myopathic changes, with fibrillations, suggestive of proximal, bulbar myopathy with electrophysiological correlates of myonecrosis, fiber splitting, or vacuolization. A muscle biopsy was performed for further evaluation of the splenius capitis and send-out laboratory tests included a MyoMarker Panel 3, acetylcholine receptor (AChR) antibodies, and hydroxymethylglutaryl-CoA synthase antibodies to rule out myasthenia gravis or statin-induced myopathy. The observed inflammatory changes correlated of myonecrosis, fiber splitting, or vacuolization. He had been taking atorvastatin for years without any complaints.

Laboratory results all returned within normal limits for the MyoMarker Panel 3 (ie, Anti-Jo-1 Ab, PL-7, PL-12, EJ, Oj, SRP, M1-2, TIF1 GAMMA, MDA-5, NXP-2, Anti-PM/Scl Ab, anti-fibrillarin antibodies, U2 snRNP, Anti-U1-RNP Ab, Ku, and Anti-SS-A 52 kD Ab IgG), hydroxymethylglutaryl-CoA synthase antibodies to rule out myasthenia gravis or statin-induced rhabdomyolysis. He had been taking atorvastatin for years without any complaints.

Immunosuppression and T-cell inhibition results when PD-1, an immune checkpoint receptor, binds to its ligands PD-L1 and PD-L2, leading to tumor growth.

A day later, nursing staff noted he had an episode of emesis and vigorous coughing, which resulted in a code call for the rapid response team. Because of concerns for aspiration, a chest x-ray was obtained, which revealed a new left lower-lobe infiltrate. He started treatment with IV antibiotics and was transferred to the intensive care unit (ICU) for further care. In the ICU, his systolic blood pressure measurements were ranging in the 50s mm Hg and his blood pressure was resistant to phenylephrine boluses. His treatment was escalated to a combination of vasopressin, norepinephrine, and epinephrine drip, but he remained hypotensive. The care team initiated a discussion with the patient and his family regarding goals of care. The following morning, the patient died.

Pathological findings from the patient’s muscle biopsy results indicated severe necrotizing myopathy associated with a mild inflammatory reaction likely secondary to pembrolizumab exposure.

Discussion
Cancer immunotherapies have demonstrated positive outcomes in the treatment of many cancers, and their use continues to expand. Despite their clinical efficacy, immune-mediated AEs have led to increased morbidity and mortality. Immunosuppression and T-cell inhibition results when PD-1, an immune checkpoint receptor, binds to its ligands PD-L1 and PD-L2, leading to tumor growth.

Immune checkpoint inhibitors activate cellular immunity against cancer cells; however, their novel mech-
anism of action also affects normal host tissues leading to immune-mediated AEs.\textsuperscript{7,13} PD-1 inhibitor–induced myositis has been reported in less than 1% of patients. A summary of these cases is provided in Table 1.\textsuperscript{5-10}

Of note, similar CTLA-4 immune-mediated AEs of autoimmune inflammatory myopathy, demyelinating polyneuropathy, myelitis, myositis, myasthenia gravis–type syndrome, and dermatomyositis have been reported.\textsuperscript{14,16} Myositis is defined as an idiopathic inflammatory myopathy and can further be subcategorized as dermatomyositis, inclusion-body myositis, juvenile myositis, and polymyositis. These diseases are poorly understood and do not always completely respond to current medications, because of the rarity of the disorders, complex clinical phenotypes, and the limited number of clinical trials. The exact mechanism of PD-1–induced myositis remains unclear; however, several of the published case reports outline different mechanisms or patients with increased risk for complications.\textsuperscript{5,10} One report proposed that patients with elevated antistriated muscle antibody titer who receive immune checkpoint inhibitors may be at an increased risk for rhabdomyolysis and

### Table 1: Previously Reported Cases of Checkpoint Inhibitor–Induced Myositis

<table>
<thead>
<tr>
<th>Patient (reference)</th>
<th>Case report summary</th>
<th>Presentation and intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>73-year-old Chinese male with metastatic urothelial carcinoma and pulmonary metastasis (Bilen et al, 2016)\textsuperscript{4}</td>
<td>Initial treatment with 7 cycles of gemcitabine/carboplatin, but residual disease remained Patient then received 5 cycles of dose-dense MVAC without a significant response He entered a clinical trial and received 2 cycles of nivolumab 3 mg/kg, combined with ipilimumab 1 mg/kg, every 3 weeks</td>
<td>The patient presented with back pain and weakness with difficulty ambulating, eating, speaking, and opening his mouth He was diagnosed with acute rhabdomyolysis associated with severe polymyositis Over a 14-week course, he received hydration, methylprednisolone 1 mg/kg twice daily, infliximab, 2 doses of IV immunoglobulin, and 12 rounds of plasmapheresis His muscle strength improved; however, the disease was progressive, and he was referred to hospice</td>
</tr>
<tr>
<td>80-year-old male with cutaneous melanoma (BRAF wild-type) metastatic to lymph nodes and skin (Kimura et al, 2016)\textsuperscript{6}</td>
<td>Initial treatment with surgical resection Because the patient had metastatic disease, he received 1 dose of dacarbazine followed by nivolumab 2 mg/kg</td>
<td>The patient presented with anorexia, fatigue, dyspnea, and muscle weakness 3 days after nivolumab administration He was diagnosed with myositis, complicated with myasthenic crisis He received corticosteroids 1000 mg/day for 3 days, followed by prednisolone 1 mg/kg tapered to 20 mg/day, plasmapheresis, and IV immunoglobulin over 4 months The melanoma stabilized, the myositis continued to improve</td>
</tr>
<tr>
<td>84-year-old male with metastatic melanoma to left heel (Yoshioka et al, 2015)\textsuperscript{7}</td>
<td>Initial treatment with surgical resection followed by 6 cycles of dacarbazine, nimustine, and vincristine, with local injection of beta-interferon Patient had disease progression and nivolumab therapy was initiated</td>
<td>The patient presented 7 weeks after receiving nivolumab, complaining of muscle weakness from neck to shoulder The article does not mention any treatment modalities, but states that prednisolone 30 mg daily was ineffective</td>
</tr>
<tr>
<td>75-year-old female with metastatic melanoma (BRAF wild-type) of the right leg and sentinel lymph nodes (Fox et al, 2016)\textsuperscript{8}</td>
<td>Initial treatment with surgical resection, disease relapsed Nivolumab therapy was initiated at 3 mg/kg every 2 weeks for a total of 2 doses</td>
<td>The patient presented with myositis after her second cycle of nivolumab Prednisone therapy was started, and the symptoms resolved The patient was diagnosed with simvastatin-induced myositis years ago The author fails to mention the duration and dosing of the steroid treatment</td>
</tr>
<tr>
<td>79-year-old male with metastatic non–small-cell lung cancer (Mehta et al, 2016)\textsuperscript{9}</td>
<td>The patient received nivolumab therapy, but the article does not mention the dose or duration of therapy before presentation</td>
<td>The patient presented with acute back pain, weakness, dyspnea, arrhythmias, and a reduced left-ventricular ejection fraction Corticosteroid treatment was initiated (dose and duration not specified), and patient had mild improvement in muscle weakness A differential diagnosis of polymyositis was made</td>
</tr>
<tr>
<td>86-year-old female with acrrolentiginous melanoma (BRAF wild-type) of the right index (Vallet et al, 2016)\textsuperscript{10}</td>
<td>Initial treatment with surgical resection and no adjuvant chemotherapy 5 months later, she presented with pulmonary metastasis and started treatment with pembrolizumab 2 mg/kg every 3 weeks for a total of 2 cycles</td>
<td>The patient presented 4 days after the second cycle of therapy with fatigue, left ptosis, and ophthalmoplegia She received a 3-day course of corticosteroids 1000 mg/day and her symptoms improved by &gt;50% Plasma exchange was then initiated, resulting in a near complete clinical recovery</td>
</tr>
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IV indicates intravenous; MVAC, methotrexate, vinblastine, adriamycin, cisplatin.
polymyositis. The patient in that case report had acute rhabdomyolysis associated with severe polymyositis after 2 cycles of nivolumab. Pretreatment, the patient’s antistriated muscle antibody titer was already elevated, at 1:15360, and upon presentation, it was elevated to 1:61440. The authors conclude that PD-1 inhibitors may exacerbate autoimmune conditions in patients with elevations in antistriated muscle antibody titer.

Another report describes that subclinical anti-AChR antibody in patients receiving immune checkpoint inhibitors could be a prediction tool to avoid myasthenic crisis and myositis. PD-1 inhibition resulted in increased anti-AChR antibody and several cytotoxic T-lymphocyte clonotypes in their patient during his treatment period and decreased upon treatment discontinuation. This is further supported by a case of myasthenia gravis in a patient with low anti-AChR antibody who was initiated therapy with nivolumab. Disruption in immune tolerance leading to autoimmunity may also result from immune checkpoint blockade and may be exacerbated by aging immune systems in the elderly population. This was hypothesized in the case of an 86-year-old female patient who had necrotic myositis secondary to pembrolizumab. In this case, myasthenia gravis autoantibodies were all normal, which included anti-AChR.

To date, the role of these antibodies in drug-induced myositis is not clear, and at times, patients present with normal values as discussed above. However, these values have an established role in diagnosing myasthenia gravis. Three types of AChR antibodies exist and are classified as binding, blocking, and modulating.

Binding and modulating antibodies are detectable in 69% to 82% of patients with myasthenia gravis, and the latter is typically found in the absence of binding antibodies. Blocking antibodies are found in approximately 54% of patients. Striated muscle and MuSK antibodies are also found in patients with myasthenia gravis, and aid to identify specific epitopes on skeletal muscles in AChR antibody-negative myasthenia gravis. Furthermore, a key pathophysiological difference between myasthenia gravis and myositis is that myasthenia gravis involves autoantibodies that target the AChR, disrupting neuromuscular transmission and leading to progressive muscle weakness, whereas myositis involves destruction of myofibers, leading to stable weakness.

Because myositis is classified as an idiopathic inflammatory myopathy, treatment approaches focus on managing such inflammation. Defining the optimal treatment regimens for these disorders has been difficult, because of the rarity and complexity of these disorders. The main goals of treatment are enhancing muscle strength and avoiding the development of extramuscular complications. Although a standard regimen has not yet been established, steroids have been shown to improve strength, preserve muscle function, and normalize serum enzymes. For patients who do not respond to steroids or those who may not achieve a desirable response, azathioprine and methotrexate may be used, but the data are limited, and the response rates may not be seen for several months.

Other therapeutic modalities include PLEX, which aims to decrease circulating levels of autoantibodies and immune complexes and has been shown to be successful. This has conflicting responses in case reports, and the number of sessions and frequency is not established. In one report, infliximab demonstrated positive results but it was used in combination with steroids.

To evaluate the likelihood of pembrolizumab-induced myositis, we used the Naranjo Adverse Drug Reaction Probability Scale (Table 2). Using the provided metric in Table 2, we
concluded that pembrolizumab was the probable cause (total score, 6) of drug-induced myositis in our patient. Although postoperative radiation therapy could have contributed to some of our patient’s symptoms, we concluded that this was unlikely, because of the biopsy-confirmed diagnosis and the lack of surrounding muscular involvement. In addition, the onset of disease, supporting published evidence, and lack of changes in the patient’s medication profile, strongly suggest that this was the reason for the myositis.

It is unclear which patients may be at increased risk for these complications, but prompt management with steroids should be the initial treatment, and combined treatment modalities may benefit serious cases. Clinicians should be aware of these rare but serious immune-mediated AEs.

Conclusion

Pembrolizumab, in addition to other PD-1 inhibitors, has been associated with drug-induced myositis. Although rare, prompt diagnosis and treatment are necessary to prevent morbidity and mortality. In several reported cases, patients have shown a response to systemic therapy with corticosteroids and PLEX. In some patients, myasthenia gravis antibodies may be present, but deciphering the clinical meaning of these laboratory results remains a challenge in drug-induced myositis. It is unclear which patients may be at increased risk for these complications, but prompt management with steroids should be the initial treatment, and combined treatment modalities may benefit serious cases. Clinicians should be aware of these rare but serious immune-mediated AEs. With the increasing use of immunotherapies and the advent of newer agents, case reports will aid in the identification, management, and diagnosis of immune-mediated reactions.

Author Disclosure Statement

Dr Hanna is on the Advisory Boards and received funding from Takeda Oncology, Taiho Pharmaceuticals, Heron Therapeutics, and Amgen; is on the Speaker’s Bureau of Seattle Genetics; and is a Consultant for Hyloris Pharmaceuticals.

References