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Brachial Plexus Neuritis Associated With Anti–Programmed Cell Death-1 Antibodies: Report of 2 Cases

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Abstract

Recently, guidelines have been outlined for management of immune-related adverse events occurring with immune checkpoint inhibitors in cancer, irrespective of affected organ systems. Increasingly, these complications have been recognized as including diverse neuromuscular presentations, such as demyelinating and axonal length–dependent peripheral neuropathies, vasculitic neuropathy, myasthenia gravis, and myopathy. We present 2 cases of brachial plexopathy developing on anti–programmed cell death-1 checkpoint inhibitor therapies (pembrolizumab, nivolumab). Both cases had stereotypic lower-trunk brachial plexus–predominant onsets, and other clinical features distinguishing them from Parsonage-Turner syndrome (ie, idiopathic plexitis). Each case responded to withholding of anti–programmed cell death-1 therapy, along with initiation of high-dose methylprednisiolone therapy. However, both patients worsened when being weaned from corticosteroids. Discussed are the complexities in the decision to add a second-line immunosuppressant drug, such as infliximab, when dealing with neuritis attacks, for which improvement may be prolonged, given the inherent slow recovery seen with axonal injury. Integrated care with oncology and neurology is emphasized as best practice for affected patients.

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Chemotherapy-induced peripheral neuropathy historically has occurred secondary to direct neurotoxic effects, which are most commonly associated with platinum compounds, vinca alkaloids, taxanes, or proteasome inhibitors.[1] We are entering an era of immune checkpoint inhibitor chemotherapies with neurological toxicities by immune-mediated mechanisms.[2] Two important drugs in this category are pembrolizumab and nivolumab, which are both human IgG4 antibodies against programmed cell death ligand 1 (PD-L1). These drugs were first recognized as being effective against melanoma, non–small-cell lung cancer, and renal cell carcinoma.[3] Many other clinical trials have been reviewed since then and reveal efficacy against head and neck cancers, lymphoma, bladder cancer, and Merkel cell cancer.[4,5]

The programmed cell death 1 (PD-1) pathway plays an important role in tumor-induced immunosuppression. Activated T cells encounter the PD-1 ligands PD-L1 (B7-H1) and programmed cell death ligand 2 (B7-DC) expressed by both immune and tumor cells, and this interaction leads to decreased T-cell receptor signaling, as well as reduced T-cell activation, cytokine production, and target-cell lysis.[6] Programmed death ligand 1 (also known as CD274 and B7-H1)[7] is more broadly expressed than programmed cell death ligand 2 on both hematopoietic and non hematopoietic cells, including tumor cells,[8] where it functions to down-regulate effector T-cell activity and thereby protect tumors from immune attack.[9,10] Because cancer cells often have overexpressed PD-L1 antigens, PD-1 favors propagation of the metastatic state. Antibodies directed against PD-1 can selectively enhance T-cell activity against tumor antigens.[3] However, a global shift in cellular reactivity by pro inflammatory

Th1/Th17 response and disinhibition of the host's immune-regulating mechanisms also occurs.[11] This shift can ultimately manifest itself with "immune-related adverse events" involving multiple systems, with significant morbidity and functional impairment.[12]

The peripheral nervous system is especially vulnerable to immune-mediated neuromuscular complications caused by misdirected T-cell reactions.[13] Increasingly, case series have emerged that highlight the often severe peripheral nervous system complications that occur with these agents, including neuromuscular junction defects (myasthenia gravis),[14,15] muscle disease (necrotic myositis),[16,17] peripheral nerve vasculitis,[18] and acute demyelinating (Guillain-Barré syndrome) neuropathies.[19] Their identification and proper management are crucial in reducing morbidity and avoiding improper therapy for clinical mimics.[12,14]

METHODS

We reviewed 2 patients prospectively, in our oncology and neurology clinics, who developed brachial plexus neuropathy while undergoing anti–PD-1 inhibitor therapy for cancer. The study was approved by the institutional review board at Mayo Clinic, Rochester, Minnesota.

Case 1

Case 1 is a 56-year-old man with metastatic melanoma positive for B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) V600E mutation taking pembrolizumab. Previous systemic therapy included a dabrafenib-trametinib (BRAF/EMK inhibition) combination, in addition to a previous history of bilateral axillary lymph node dissection and adjuvant radiation therapy, with a total dose of 3000 Gy at the time of original diagnosis. After his ninth pembrolizumab infusion, he developed sudden (<8 hours to maximal deficit) weakness of the left hand associated with loss of sensation and neuropathic pain in the medial hand, forearm, and back of hand. Pain was rated 7 of 10 (0 = no pain; 10 = worst possible pain), and weakness on the Medical Research Council scale included 75% weakness and sensory loss (Figure). The left brachioradialis reflex was reduced, and the left triceps reflex was absent. Horner syndrome was absent.

His immediate work-up, including computed tomography angiography of the left upper extremity, was unremarkable, with patent vasculature and no thrombus. A nerve conduction study (NCS) performed 4 days from onset revealed low-amplitude median compound muscle action potential recorded from the abductor pollicis brevis, with unobtainable F waves, and symmetric medial antebrachial sensory responses. Electromyographic examination (EMG) revealed mildly long-duration motor unit potentials in left C7-innervated muscles with no elicitable motor unit activation in the left abductor pollicis brevis and first dorsal interosseous muscles. Recruitment of motor units in muscles innervated by the lower trunk was markedly reduced. A repeat NCS-EMG 3 weeks after onset of symptoms with persistent weakness revealed fibrillations in lower trunk– and posterior cord–innervated brachial plexus muscles, with new loss of medial antebrachial sensory responses, consistent with a lower trunk–predominant brachial plexopathy. Magnetic resonance imaging (MRI) of the left brachial plexus did not reveal metastasis but rather features suggestive of a lower-trunk plexitis, as evidenced by a bright T2 signal without contrast enhancement. A whole-body positron emission tomography (PET) scan revealed no evidence of melanoma recurrence.

Pembrolizumab therapy was witheld at neurological presentation, and on day 3 from onset, we initiated intravenous (IV) methylprednisolone at 500 mg daily for 5 days, followed by 1 g daily for an additional 6 days. After the first week of receiving corticosteroids, his finger flexion strength improved to 4 of 5 and his interossei to 4- of 5, compared with earlier measurements of 2 of 5 and 3 of 5, respectively. Both the strength of other previously weak muscles and sensory deficits remained unchanged. The patient's left arm and forearm pain rating decreased to 4 of 10. Intravenous methylprednisolone was discontinued, and oral dexamethasone was initiated at 20 mg daily (ie, a prednisone equivalent of 1.5 mg/kg per day). He did not experience muscle atrophy, even in weak muscles, in combination with this or his subsequent attack.

Approximately 4 weeks after onset of initial symptoms and 3 weeks after a switch