7. Rasool MN. Ulnar nerve injury after K-wire fixation of supracondylar humerus fractures in children. J Pediatr Orthop 1998;18:686–690.
8. Lucchetta M, Briani C, Liotta GA, Martinoli C, Coraci D, Padua L. Ultrasonographic Tinel sign: comment. Muscle Nerve 2010;41:570–571.
9. Coraci D, Tsukamoto H, Granata G, Briani C, Santilli V, Padua L. Fibular nerve damage in knee dislocation: spectrum of ultrasound patterns. Muscle Nerve 2015;51:859–863.
10. Padua L, Di Pasquale A, Liotta G, Granata G, Pazzaglia C, Erra C, *et al.* Ultrasound as a useful tool in the diagnosis and management of traumatic nerve lesions. Clin Neurophysiol 2013;124:1237–1243.
11. Ristic S, Strauch RJ, Rosenwasser MP. The assessment and treatment of nerve dysfunction after trauma around the elbow. Clin Orthop 2000;370:138–153.
12. Brown IC, Zinar DM. Traumatic and iatrogenic neurological complications after supracondylar humerus fractures in children. J Pediatr Orthop 1995;15:440–443.
13. Ramachandran M, Birch R, Eastwood DM. Clinical outcome of nerve injuries associated with supracondylar fractures of the humerus in children: the experience of a specialist referral centre. J Bone Joint Surg Br 2006;88:90–94.
14. Erra C, Granata G, Liotta G, Podnar S, Giannini M, Kushlaf H, *et al.* Ultrasound diagnosis of bony nerve entrapment: case series and literature review. Muscle Nerve 2013;48:445–450.
15. Lee J, Bidwell T, Metcalfe R. Ultrasound in pediatric peripheral nerve injuries: can this affect our surgical decision making? A preliminary report. J Pediatr Orthop 2013;33:152–158.
16. Coraci D, Luchetti R, Paolasso I, Santilli V, Padua L. Intermittent ulnar nerve compression due to accessory abductor digiti minimi muscle: crucial diagnostic role of nerve ultrasound. Muscle Nerve 2015;52:463–464.
17. De Franco P, Erra C, Granata G, Coraci D, Padua R, Padua L. Sonographic diagnosis of anatomical variations associated with carpal tunnel syndrome. J Clin Ultrasound 2014;42:371–374.

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## FACIAL DIPLEGIA AFTER PEMBROLIZUMAB TREATMENT

Immune checkpoints are inhibitory molecules in the immune system that play pivotal roles in promoting self-tolerance and preventing autoimmunity. Increased expression of immune checkpoints on tumor-related immune cells has been observed during cancer progression, and upregulation of these checkpoints hinders the immune attack targeting cancer cells.[1] In recent years, immune checkpoint blockade has shown promise in treating advanced cancers. Programmed cell death protein-1 (PD-1) is an immune checkpoint that is highly expressed on T cells, and its ligand is also expressed on several solid tumors, including melanoma. Pembrolizumab is an anti-PD-1 monoclonal antibody that is increasingly used in advanced melanoma. The inhibition of immune checkpoints unleashes the immune system to attack self-antigens and promote autoimmunity.

### CASE REPORT

A 64-year-old man with a history of metastatic BRAF wild-type melanoma presented with a 5-day history of progressive fatigue, bilateral facial weakness, and dyspnea, without preceding infection or immunization. His melanoma had been treated with the peptide vaccine as part of a clinical trial, ipilimumab, and most recently with pembrolizumab. He entered remission after 14 months of pembrolizumab and had been cancer free for 9 months. Pembrolizumab was held for 3 months prior to presentation.

Results of the neurologic exam were notable for symmetric, bifacial weakness in a lower motor neuron pattern, diffuse areflexia, and flaccid dysarthria. There was no limb weakness, gait disturbance, or sensory abnormality. Brain MRI showed subtle enhancement of the facial nerves bilaterally. Results from a cerebrospinal fluid (CSF) analysis showed elevated protein (195 mg/dL) and 12 total nucleated cells per milliliter (82% lymphocytes). Negative or normal results were obtained from serum comprehensive paraneoplastic antibody panel, acetylcholine receptor antibodies (binding, blocking, and modulating), serum GQ1b and antiganglioside antibodies, HIV-1 and HIV-2 antibodies, CSF polymerase chain reaction for cytomegalovirus and Epstein-Barr virus, CSF cytology, CSF Gram stain, and bacterial culture. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated at 5 times and 2 times the upper limit of normal, respectively. Results of nerve conduction studies were remarkable for mildly slow lower limb motor conduction velocities, normal sural response, and normal facial motor studies, as shown in Table 1. Blink reflexes showed absent R1 and bilateral R2 responses despite paired stimulation. Needle electromyography (EMG) showed reduced recruitment and mildly complex motor unit potentials of the orbicularis oris and frontalis muscles. Motor unit potentials in limb and thoracic paraspinal muscles were normal. Sparse fibrillation potentials were observed only in thoracic paraspinal muscles.

The patient was diagnosed with the bifacial weakness variant of Guillain-Barre syndrome (GBS) and received 2 g/kg intravenous immunoglobulin (IVIG). He was subsequently given prednisone 1 mg/kg/day for 14 days for autoimmune hepatitis. Two weeks after initiation of IVIG and steroids, there was marked improvement in facial muscle strength, resolution of dysarthria, and normalization of liver enzymes. Repeat nerve conduction studies were unchanged except for the presence of delayed R1 responses, borderline R2 latencies, reduced facial motor amplitudes, and prolonged ulnar and tibial F-wave latencies (Table 1). Needle EMG revealed reduced recruitment of mildly large, sometimes complex motor unit potentials not only in the orbicularis oris and frontalis muscles but also in the vastus medialis, tibialis anterior, medial gastrocnemius, and thoracic paraspinal muscles. Sparse fibrillation potentials were observed only in thoracic paraspinal muscles.

### DISCUSSION

Immune checkpoint inhibitors are increasingly used in cancer immunotherapy, and their immune-related adverse events are also increasingly recognized. Neurological autoimmunity was reported in only 1% of melanoma patients treated with pembrolizumab, which is relatively uncommon compared with dermatologic, endocrine, gastrointestinal, and rheumatologic autoimmunity that each were reported in approximately 10%–15% of patients.[2] Previously reported anti-PD-1 therapy-related neurologic conditions include seizures, polyradiculopathy, myasthenia gravis, cranial neuropathies, necrotizing myopathy[3,4] and GBS.[5] In addition to GBS, cranial neuropathies,

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**Table 1.** Nerve conduction studies before and after treatment

| Nerve conduction studies | Recording site | Normal value | Before treatment | After treatment |
|---|---|---|---|---|
| Right sural SNAP (DL/Amp/CV) | Ankle | <4.5/>6/>40 | 4/19/47 | 4.2/13/42 |
| Right fibular CMAP (DL/Amp/CV) | Extensor digitorum brevis | <6.6/>2/>41 | 4.7/5.6/37 | 4.1/2.1/37 |
| Right tibial CMAP (DL/Amp/CV/F-wave latency) | Abductor hallucis | <6.1/>4/>40/<58 | 4.5/8.7/36/57.5 | 5/7.4/39/58.9 |
| Right ulnar CMAP (DL/Amp/CV/F-wave latency) | Adductor digiti minimi | <3.6/>6/>51/<32 | 2.9/12.2/54/32 | 2.8/11.9/51/36.5 |
| Right antidromic median SNAP (DL/Amp/CV) | Digit II | <3.6/>15/>56 | 3/39/56 | 3.1/30/57 |
| Right facial CMAP (DL/Amp) | Nasalis | <4.1/>1.8 | 2.7/2 | 3.2/1.4 |
| Blink reflexes (R1/ipsilateral R2/ contralateral R2) | Orbicularis oculi | <13/<41/<44 | Absent | 14.6/39.9/40.4 |

*Amp, amplitude (motor in millivolts, sensory in microvolts); CMAP, compound muscle action potential; CV, conduction velocity (m/s); DL, distal latency (ms); SNAP, sensory nerve action potential.*

necrotizing myopathy, and myasthenia gravis may cause bifacial weakness in patients treated with pembrolizumab. Although the facial diplegia variant of GBS is uncommon and accounts for less than 1% of GBS cases,[6] the diagnosis of facial diplegia variant of GBS in this case is well supported with diffuse areflexia, elevation of CSF protein out of proportion to nucleated cells, subtle evidence of demyelination on nerve conduction studies, and good response to IVIG therapy.[7] Mild CSF pleocytosis has been recently described in another case of pembrolizumab-induced demyelinating polyradiculoneuropathy.[8]

The elimination half-life for pembrolizumab is estimated to be 29 days,[9] and adverse effects have been reported weeks after the last anti-PD-1 treatment.[5] Although GBS has been reported in association with anti-PD-1 inhibitors,[5,10] these patients developed GBS during treatment in contrast to our patient, and none of them had the facial diplegia variant. Sporadic GBS was considered, given the delay of onset after discontinuation of pembrolizumab, but the coexisting autoimmune hepatitis, another known complication of anti-PD-1 therapy, suggests that this facial diplegia variant of GBS is likely a part of anti-PD-1-associated autoimmunity. Whether prior treatment with ipilimumab or the peptide vaccine played a role in his presentation remains unknown.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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1. Turnis ME, Andrews LP, Vignali DA. Inhibitory receptors as targets for cancer immunotherapy. Eur J Immunol 2015;45(7):1892–1905.
2. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016;44:51–60.
3. Haddox CL, Shenoy N, Kao JC, Shah KK, Jain S, Halfdanarson TR, *et al.* Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm. Ann Oncol (to be published).
4. Vallet H, Gaillet A, Weiss N, Vanhaecke C, Saheb S, Touitou V, *et al.* Pembrolizumab-induced necrotic myositis in a patient with metastatic melanoma. Ann Oncol 2016;27(7):1352–1353.
5. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, *et al.* Neurological, respiratory, musculoskeletal, cardiac and ocular side effects of anti-PD-1 therapy. Eur J Cancer 2016;60:210–225.
6. Kim JK, Oh SY, Sohn EH, Hong YH, Jun SM, Bae JS. When is facial diplegia regarded as a variant of Guillain-Barre syndrome? J Peripher Nerv Syst 2015;20(1):32–36.
7. Susuki K, Koga M, Hirata K, Isogai E, Yuki N. A Guillain-Barré syndrome variant with prominent facial diplegia. J Neurol 2009;256(11):1899–1905.
8. de Maleissye MF, Nicolas G, Saiag P. Pembrolizumab-induced demyelinating polyradiculoneuropathy. N Engl J Med 2016;375(3):296–297.
9. Keytruda (pembrolizumab) [Package Insert]. Whitehouse Station, NJ: Merk & Co, Inc; 2015.
10. Johnson DB, Wallender EK, Cohen DN, Likhari SS, Zwerner JP, Powers JG, *et al.* Severe cutaneous and neurologic toxicity in melanoma patients during vemurafenib administration following anti-PD-1 therapy. Cancer Immunol Res 2013;1(6):373–377.

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