Autoimmune pancerebellitis associated with pembrolizumab therapy

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Checkpoint proteins reduce immune-mediated responses to promote self-tolerance and prevent autoimmunity. Programmed cell death protein 1 (PD-1) is a checkpoint receptor protein expressed on leukocytes that inactivates T cell-mediated immunity when bound to ligand PD-L1. Certain tumors can escape immune-mediated destruction by expressing high concentrations of PD-L1, evading host surveillance.¹ PD-1 pathway inhibitors effectively treat multiple malignancies including melanoma, non-small cell lung cancer, and squamous cell carcinoma.² However, there is increasing recognition of immune-related adverse events (irAE) associated with checkpoint inhibitor therapy due to dysregulated immune system activation.¹ We report immune-mediated cerebellitis following pembrolizumab.

Case report

A 70-year-old man with squamous cell cancer (SCC) of the neck presented with subacute ataxia and diplopia. He had been diagnosed with SCC 3 years prior, treated with cisplatin and radiation, then pembrolizumab after recurrence 2 years later.

Seven months after pembrolizumab initiation, he presented to an outside hospital with 8 days of diplopia. MRI of the brain demonstrated abnormal enhancement throughout the cerebellar parenchyma, particularly the left cerebellar deep nuclei, and corresponding T2 hyperintensities (figure, A and B). Lumbar puncture revealed 166 white blood cells (WBC) (lymphocyte predominant), 10 CSF oligoclonal bands, and an immunoglobulin G index of 0.9. He was treated with 4 days of 1 g methylprednisolone IV for presumed autoimmune cerebellitis. Repeat MRI revealed decreased abnormal enhancement and T2/fluid-attenuated inversion recovery signal, though he remained symptomatic and was transferred to our institution.

On transfer, the patient was inattentive and impulsive, with marked nystagmus, ataxia, and scanning speech. Steroids were held to maximize diagnostic yield. PET of the body revealed tracer uptake within his esophagus; biopsy showed nonspecific ulceration granulation tissue and reactive epithelium. Repeat brain MRI revealed ongoing bilateral cerebellar hemisphere and dentate nuclei T2 signal prolongation with reduced enhancement (figure, C and D); CSF likewise demonstrated improvement (WBC 31, protein 50, glucose 48). A broad infectious workup was negative, including HIV, coccidioides, syphilis, and Lyme serologies, PCR of the CSF for varicella, herpes simplex, and cytomegalovirus, and universal primers for fungal, mycobacterial, and bacterial organisms, including listeria. CSF cytology and flow cytometry were unremarkable, and a commercial panel of paraneoplastic autoantibodies, including anti-Yo, anti-Hu, and anti-Ma, was negative in CSF and serum.

Given the patient's nondiagnostic workup, cerebellar biopsy was performed 2 weeks off steroids. Pathology revealed a predominantly mature T cell perivascular lymphocytic infiltrate with microglial nodules and macrophages that were nonspecific though consistent with autoimmune process (figure, E and F). No neoplasm or infection was identified. He was treated with 5 days of methylprednisolone 1 g then an oral taper. Days later, his nystagmus and dysmetria

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MRI demonstrates abnormal enhancement on postgadolinium fat-saturated T1 (A) and increased fluid-attenuated inversion recovery (FLAIR) signal (B) throughout the cerebellum, especially affecting the left cerebellar deep nuclei. These signal abnormalities were substantially decreased on follow-up MRI 29 days later (postgadolinium [C] and FLAIR [D]) following cessation of pembrolizumab and steroid treatment. The specimen demonstrates a lymphohistiocytic inflammatory infiltrate involving the brain parenchyma. There is thick perivascular lymphocytic cuffing, although no vasculitis is identified. (E) A CD3 immunohistochemical stain confirms the presence of a predominantly mature T cell lymphocytic infiltrate (F).

improved, and by 2 months, vertigo and diplopia had resolved, although he experienced ongoing impulsivity and emotional lability.

Discussion

Immune checkpoint inhibitors are potent antineoplastic agents but carry the potential for irAE. We report a rare case of autoimmune cerebellitis related to pembrolizumab. Manifestations of cerebellar pathology include nystagmus, square wave jerks, scanning speech, dysmetria, ataxia, and impairments in personality, visuospatial, language, and executive functioning.³ Cerebellitis can be caused by infectious, post-infectious, neoplastic, paraneoplastic, and primary inflammatory processes.⁴ In our case, these etiologies were excluded through serum, CSF, imaging, and pathology results.

The most commonly reported PD-1 inhibitor toxicities in clinical trials were pruritus, diarrhea, fatigue, or rash; more serious reactions ranged from 7% to 17%.^{1,2} Frequently reported irAE include hypophysitis, pneumonitis, colitis, and hepatitis 1. Neurologic complications occur in 3% of patients given PD-1 inhibitor monotherapy and up to 14% of patients receiving concomitant cytotoxic T lymphocyte-associated protein 4 therapy.^{5,6} Most neurologic complications occur

outside of the CNS, including myasthenia gravis, neuropathy, and myopathy.^{5,6} CNS complications are uncommon but include aseptic meningitis, internuclear ophthalmoplegia, and autoimmune encephalitis.⁵⁻⁷ Kao et al.⁶ also described a patient with progressive dysarthria and ataxia following pembrolizumab, though imaging was normal and a lumbar puncture was not pursued due to improvement following therapy discontinuation. In contrast, our case provides compelling evidence of cerebellar autoimmune pathology on MRI, CSF, and biopsy.

Autoimmune cerebellitis is a rare consequence of PD-1 inhibitor therapy but is in keeping with growing recognition of neurologic immune-mediated adverse events. Our patient presented with motoric and nonmotoric symptoms consistent with a pancerebellar syndrome confirmed as inflammatory by imaging, CSF, and pathology. Although a single case association cannot prove causation, his negative exhaustive workup for alternate etiologies and pathology consistent with autoimmunity makes a PD-1 inhibitor irAE most likely. While commercially available autoantibodies were negative, it is possible that an uncharacterized antibody related to PD-1 inhibition with cerebellar tropism was involved. Our patient's clinical improvement following high-dose steroids is consistent with other reported irAE, though his persistent behavioral abnormalities suggest neurologic deficits may not be

entirely reversible.^{5–7} He also clinically deteriorated following his first steroid course but improved after a second treatment and taper, suggesting response to steroids may be delayed or require a more prolonged course. As the use of checkpoint inhibitors increases, heightened awareness of immune-mediated complications is warranted for prompt evaluation and treatment.

Author contributions

Jeffrey Vitt: primary manuscript writer. Collin Kreple: assisted in writing manuscript, editing manuscript. Nausheen Mahmood: assisted in writing manuscript, data collection. Elliot Dickerson: acquisition and preparation of images, editing manuscript. Giselle Lopez: acquisition and preparation of images, editing manuscript. Megan Richie: study concept and design, critical revision of manuscript.

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Disclosure

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