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Short Communication

A case series of PD-1 inhibitor-associated paraneoplastic neurologic syndromes

AlexanderJ. Gill*, Michael A. Perez, Christopher M. Perrone, Charles J. Bae, Amy A. Pruitt, Eric Lancaster

Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, United States of America

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are highly efficacious for treating many solid tumor types. Because of their immune-activating mechanism of action, ICIs can trigger various immune-mediated toxicities. We present three cases: *i)* a woman with anti-Ri brainstem encephalitis; *ii)* a man with anti-Hu sensory neuronopathy; and *iii)* a woman with suspected combined anti-Hu and anti-NMDA paraneoplastic syndromes associated with the initiation of the ICIs pembrolizumab and nivolumab. These cases suggest that ICIs can induce both humoral and cell-mediated paraneoplastic neurologic syndromes. Identifying biomarkers that predict risk of developing ICI-associated paraneoplastic syndromes and the development of efficacious treatment strategies for neurologic ICI-toxicities are critical unmet needs.

1. Introduction

Recent advances in cancer immunotherapy have led to the development of immune checkpoint inhibitors (ICIs). These novel agents have significantly increased survival and they are becoming the standard of care in many malignancies. Immune checkpoints function to maintain self-tolerance and prevent autoimmunity. Accordingly, ICIs enhance the immune system's ability to selectively eliminate cancer cells, but ICIs can also trigger cell-mediated and humoral immune responses against self-antigens. ICIs have been associated with numerous immune-mediated complications affecting the peripheral and central nervous systems. The ICIs pembrolizumab, nivolumab, and cemiplimab are monoclonal antibodies that target the inhibitory T-cell surface receptor programmed cell death protein-1 (PD-1). These ICIs have been associated with acute and chronic autoimmune demyelinating polyneuropathies, myasthenia gravis, limbic encephalitis, and other neurologic complications (Graus and Dalmau, 2019; Hottinger, 2016; Touat et al., 2017).

2. Case 1

A 71-year-old woman with metastatic lung adenocarcinoma receiving pembrolizumab presented with diplopia, unsteady gait, and urinary incontinence. Stage IIa non-small cell lung cancer was diagnosed in 2013 and she underwent lung resection and adjuvant chemoradiation the following year. She was in remission for three years and then developed recurrent metastatic disease (EGFR and ALK wild-type, negative PDL1 expression) for which she received four cycles of induction therapy (pemetrexed/carboplatin/pembrolizumab) then transitioned to maintenance therapy of pemetrexed/pembrolizumab. After her sixth dose of pembrolizumab she presented with several weeks of diplopia, tremors, urinary incontinence, and unsteady gait. Her examination showed rotary jerk nystagmus toward her right shoulder in primary gaze, mixed upbeat and rotary nystagmus in upward gaze, right hypertropia and esotropia in all gazes, gait ataxia, and lower-extremity paresthesias. MRI head and full C/T/L spine showed neither signal abnormality nor enhancement. Her CSF showed lymphocytic pleocytosis (10 cells/ul) and elevated protein (40 mg/dL). Over concern for ICI-mediated autoimmunity, pembrolizumab was discontinued and dexamethasone was administered (12 week tapering course). Subsequent CSF paraneoplastic panel demonstrated an ANNA titer of 1:5 and the presence of anti-Ri antibodies. After an additional 8 weeks, and while continuing her dexamethasone taper, her gait instability, tremor, incontinence, and diplopia had resolved. However, 3 weeks after completion of her dexamethasone taper, her diplopia returned and she was admitted for IV steroids, rituximab, and a gradual prednisone taper over months. Again her diplopia initially improved, but then worsened 4 months into her prednisone taper. Cyclophosphamide

* Corresponding author at: Department of Neurology, Hospital of the University of Pennsylvania, 3 W. Gates Building, 3400 Spruce Street, Philadelphia, PA 19104, United States of America.
E-mail address: alexander.gill2@uphs.upenn.edu (A. Gill).

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therapy is now being considered. A PET scan one year after initiating treatment for her recurrent metastatic disease showed no evidence of persistent or recurrent tumor.

3. Case 2

A 58-year-old man with Merkel cell carcinoma receiving pembrolizumab developed severe ataxia and loss of proprioception with pseudoathetosis. In 2016 in the setting of slowly progressively foot and hand pain and numbness of unclear etiology, a nerve conduction study showed moderately to markedly delayed sensory latencies with normal amplitudes. A year later, a left thigh mass was found, which was diagnosed as Merkel cell carcinoma. He was treated with carboplatin, etoposide, and radiation, but within several months the carcinoma returned with lymph node metastases. He was then treated with Topotecan and additional radiation, but his metastases did not fully respond. His serum paraneoplastic panel (Quest Diagnostics) revealed anti-Hu antibodies (titer 1:1600), anti-CV2 antibodies (titer 1:3200), and anti-VGKC antibodies (672 pmol/L). No anti-LGI1 and anti-CASPR2 antibodies were detected. He underwent left inguinal lymph node dissection in March 2018 and was started on pembrolizumab. Up until this point, his ascending numbness, paresthesias, and difficulty walking progressed very slowly over several years with recent worsening likely secondary to carboplatin–induced toxic sensory neuropathy. After his first dose of pembrolizumab, his sensory loss, paresthesias, and sensory ataxia rapidly progressed over two weeks leaving him wheelchair bound. Neurologic exam two months after his third pembrolizumab dose showed full strength, but bilaterally reduced vibratory sensation to mid-shins and distal hands, loss of proprioception with pseudoathetosis in his hands and feet, a positive Lhermitte's sign, and severe gait unsteadiness consistent with a severe sensory ataxia. A cervical spine MRI revealed abnormal T2 prolongation within the posterior cord from C2/C3 to C7/T1 without pathologic enhancement. MRI of his brain was unremarkable. A nerve conduction study showed absent sensory responses, normal motor responses, and acute and chronic denervation of the left arm and leg. He had a normal B12, methylmalonate, and copper levels. Pembrolizumab-induced anti-Hu sensory neuronopathy was suspected. Pembrolizumab was discontinued with the expectation of a sustained pembrolizumab oncologic remission. He indeed remained in oncologic remission by recent PET imaging with non-progressing but severe sensory neuronopathy.

4. Case 3

A 68-year-old woman with recently diagnosed and resected right breast Merkel cell carcinoma presented with sensory paresthesias, ataxia, subacute encephalopathy, pharyngeal weakness, and episodes of acute respiratory failure after initiating nivolumab. PET imaging after local resection but prior to nivolumab treatment revealed right axillary FDG-avid adenopathy without evidence of additional sites of disease. Within days after her first nivolumab dose she developed lower extremity paresthesias and several weeks later after her second dose of nivolumab she developed progressively altered mental status, truncal ataxia, and vertical nystagmus. She then suffered recurrent episodes of encephalopathy, unresponsiveness, and acute respiratory failure requiring intubation. At an outside hospital, her brain MRI was unrevealing and her CSF analysis showed the following: 3 wbc/ul, protein 33 mg/dL, glucose 115 mg/dL, > 5 oligoclonal bands, negative autoimmune encephalitis panel, and presence of anti-Hu antibodies. Her neurologic exam upon transfer to our hospital confirmed bilateral upper extremity ataxia, abnormal nystagmoid eye movements, pharyngeal weakness, and orofacial dyskinesias. EEG monitoring revealed no seizure activity. A brain MRI revealed T2/FLAIR hyperintensities bilaterally in the medial temporal lobes. A nerve conduction study showed absent sensory responses in her arms and legs with relatively preserved motor nerve amplitudes consistent with a severe sensory neuronopathy. Given concern for a nivolumab-induced autoimmune complication, nivolumab was discontinued and she was treated with daily 1000 mg intravenous methylprednisolone daily for 5 days, 3 days of intravenous immunoglobulin, and 2 doses of rituximab without clinical improvement. Per her wishes and after family discussion, she was transitioned to comfort care and extubated and she subsequently expired. Her laboratory analyses revealed the following: *i)* positive anti-Hu antibodies (serum titer 1:15360, CSF titer 1:256, Mayo Clinic Laboratory paraneoplastic panel); *ii)* negative CSF autoimmune encephalitis antibody panel (NMDAR, LGI1, Caspr2, AMPAR, GABA-B-R, and GAD65 antibodies, Hospital of the University of Pennsylvania clinical laboratory); and *iii)* In our research laboratory, CSF NMDAR antibody response at 1:1 dilution living cells and 1:2 on fixed cells with no reactivity in rodent brain sections following our published methods (McCracken et al., 2017). Ultimately, her clinical condition and serology were consistent with an anti-Hu sensory neuronopathy and anti-NMDA encephalitis.

5. Discussion

Paraneoplastic disorders result from pathological nervous system immunologic responses in the presence of benign or malignant tumors (Dalmau and Rosenfeld, 2008; Graus and Dalmau, 2019). They are often associated with specific autoantibodies, such as anti-Ri and anti-Hu. Some antibodies (e.g. anti-NMDAR) have a direct pathogenic effect, while some paraneoplastic disorders (e.g. anti-Hu syndromes) are mediated by T-cell immune responses targeting the same antigen as the associated onconeuronal antibody (Lancaster, 2017). The temporal relationship between ICI-initiation, acute neurologic syndromes, and clinical improvement following ICI cessation and immunotherapy (in the anti-Ri case) supports a cause-effect relationship. Recent studies strongly support the conclusion that ICIs can trigger both antibody-mediated and T-cell mediated paraneoplastic neurologic syndromes (Graus and Dalmau, 2019). Additionally, our third case suggests that ICIs may trigger concurrent paraneoplastic syndromes (both antibody and T-cell mediated) in a treated patient as she had clinical signs and symptoms, brain imaging, and neurophysiology studies are consistent with concomitant anti-Hu and anti-NMDA paraneoplastic syndromes.

Because neurologic ICI-related toxicities are less common (and less studied) than systemic ICI-induced complications, optimum diagnostic and management guidelines are not well established. Our cases highlight the importance of recognizing ICI-induced neurologic complications, and our study raises the question as to whether the presence of a paraneoplastic antibody (e.g. anti-Hu) at the time of ICI initiation increases the risk for developing a paraneoplastic disorder or changes disease course. Notably, the anti-Hu antibody response is detectable in up to 40% of patients with small cell lung cancer, but the anti-Hu paraneoplastic syndrome is much rarer (< 1%) (Monstad et al., 2004). We believe that our patient (case 2) had a mild sensory neuropathy prior to the initiation of an ICI and then developed severe anti-Hu sensory neuronopathy afterwards. Clinical relevance of a pre-existing disease-associated antibody is supported by the observation that individuals with anti-GAD65 antibodies at the time of initiation of anti-PD-1 developed type I diabetes significantly sooner than individuals who were anti-GAD65 antibody negative (5 vs. 9 weeks) (Clotman et al., 2018). These data suggest that the presence of an auto-antibody linked to an autoimmune disease at the time of ICI initiation associates with accelerated autoimmune disease progression. Identifying clinical and paraclinical biomarkers that predict risk for developing ICI-induced paraneoplastic syndromes including potentially the presence of autoimmune/paraneoplastic antibodies prior to ICI treatment is critical for the development of effective diagnostic and management strategies.

Effective management strategies for systemic complications of ICI therapy include discontinuation of ICI therapy with or without concurrent corticosteroid therapy, but this strategy alone might be ineffective in ICI-induced neurologic syndromes. For example, autoimmune limbic and brainstem encephalitis often do not respond to

steroids or plasmapheresis or recur after therapy as in the case of our anti-Ri patient. In some cases sustained clinical responses have been observed with rituximab (Shah et al., 2018) or natalizumab (Hottinger et al., 2018) or other more potent immunosuppressants. Given the significant success of these ICIs in cancer therapy and with wider oncologic applications likely to be approved, there is an emerging need for further study and treatment of ICI-induced paraneoplastic disorders and other immune mediated neurologic toxicities.

Author contributions

A. Gill: patient care, acquisition and analysis of case data, review of the literature, drafting of the manuscript for intellectual content, and editing of the final text. M. Perez: acquisition and analysis of case data, review of the literature, drafting of the manuscript for intellectual content, and editing of the final text. C. Perrone, C. Bae, A. Pruitt, and E. Lancaster: clinical information, case discussion, intellectual contribution and critical review of the manuscript, and editing of the final text.

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Disclosures

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References

Clotman, K., Janssens, K., Specenier, P., Weets, I., De Block, C.E.M., 2018. Programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus: mini-review. J. Clin. Endocrinol. Metab. 1, 3144–3154.

Dalmau, J., Rosenfeld, M.R., 2008. Paraneoplastic syndromes of the CNS. Lancet Neurol. 7, 327–340.

Graus, F., Dalmau, J., 2019. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat. Rev. Clin. Oncol. https://doi.org/10.1038/s41571-019-0194-4.

Hottinger, A.F., 2016. Neurologic complications of immune checkpoint inhibitors. Curr. Opin. Neurol. 29, 806–812.

Hottinger, A.F., Micheli, R., Guido, V., Karampera, A., Hagmann, A., Pasquier, R.D., Mar 2018. Natalizumab may control immune checkpoint inhibitor–induced limbic encephalitis. Neurol Neuroimmunol Neuroinflamm. 5, e439.

Lancaster, E., 2017. Paraneoplastic Disorders. Continuum (Minneap Minn). vol. 23. pp. 1653–1679.

McCracken, L., Zhang, J., Greene, M., Crivaro, A., Gonzalez, J., Kamoun, M., et al., 2017. Improving the antibody-based evaluation of autoimmune encephalitis. Neurol. Neuroimmunol. Neuroinflamm. 4, e404.

Monstad, S.E., Drivsholm, L., Storstein, A., Aarseth, J.H., Haugen, M., Lang, B., et al., 2004. Hu and voltage-gated calcium channel (VGCC) antibodies related to the prognosis of small-cell lung cancer. J. Clin. Oncol. 22, 795–800.

Shah, S., Dunn-Pirio, A., Luedke, M., Morgenlander, J., Skeen, M., Eckstein, C., 2018. Nivolumab-induced autoimmune encephalitis in two patients with lung adenocarcinoma. Case Rep. Neurol. Med. 2018, 2548528.

Touat, M., Talmasov, D., Ricard, D., Psimaras, D., 2017. Neurological toxicities associated with immune-checkpoint inhibitors. Curr. Opin. Neurol. 30, 659–668.