The Canadian Journal of Neurological Sciences (2023), **50**, 635–636
doi:10.1017/cjn.2022.71

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Clinical Case Conference

Nivolumab-Induced Limbic Encephalitis Associated with Glutamic Acid Decarboxylase 65 Antibodies

Al-Alya AlSabah[1] and Robert Altman[2]

[1]Department of Neurology and Neurosurgery, McGill University; Jewish General Hospital, Montreal, QC, Canada and [2]McGill University, Montreal, QC, Canada

A 40-year-old woman known for posterior scalp melanoma, otherwise healthy, was diagnosed in November 2018 and subsequently treated with wide local excision. However, in January 2020, a routine surveillance Positron Emission Tomography (PET) scan revealed nodal metastases, confirming relapse and conferring a diagnosis of stage IV disease. One month after her first cycle of nivolumab, she developed abrupt confusion and short-term memory loss. One week into her admission, she developed a bilateral tonic clonic seizure of unknown onset and was treated with levetiracetam. Her EEG was normal; however, brain MRI demonstrated areas of FLAIR hyperintensity and diffusion restriction (not pictured) in the right (more than left) medial aspect of the temporal lobe involving the hippocampus (Figures 1 and 2); which also enhanced post gadolinium administration. Brain PET scan showed intense bilateral fluorodeoxyglucose (FDG) avid activity in both medial temporal regions (Figure 3). Cerebrospinal fluid analysis demonstrated pleocytosis, with WBC 19 ($0–5 \times 10^6$/L), mainly lymphocytes, with normal RBC, glucose and protein. Also, PCR of the Cerebrospinal fluid (CSF) was negative for herpes simplex virus and varicella-zoster virus. All bacterial cultures (routine and atypical) also were unremarkable. The diagnosis of neurological immune-related adverse events (irAEs) encephalitis was then made and she was started on intravenous (IV) steroids, 1g IV methyl prednisone for 5 d. A week after, her anti-neuronal antibody testing in the CSF using radioimmunoassay (RIA) returned positive at 48.5 nmol/L, which is over 2000-fold higher than the upper limit of normal (≤0.02). We did not test for GABA(A/B) receptor antibodies.

Despite high dose steroids, 1 g IV methylprednisolone for 5 d, a 5-day course of IVIG and lastly five therapeutic plasma exchanges, the patient did not improve. Because the CSF flow study showed > 92% T cells and 0% B cells, natalizumab was prescribed. Natalizumab is an alpha integrin inhibitor which can decrease T cells and decrease leukocyte migration across the blood–brain barrier. It was previously reported to be useful in immune checkpoint inhibitors (ICI)-induced anti-Hu limbic encephalitis patient.[1] Unfortunately, the serum John Cunningham virus (JC virus) antibody index was more than 0.4 thus, the drug was discontinued after its first dose for fear of developing CNS progressive multifocal leukoencephalopathy.

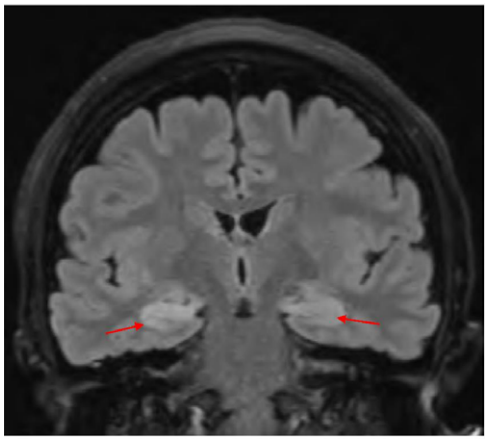

Figure 1: Coronal sequence – asymmetric hyperintense signal in both medial temporal lobes (red arrow), right > left side associated with oedema.

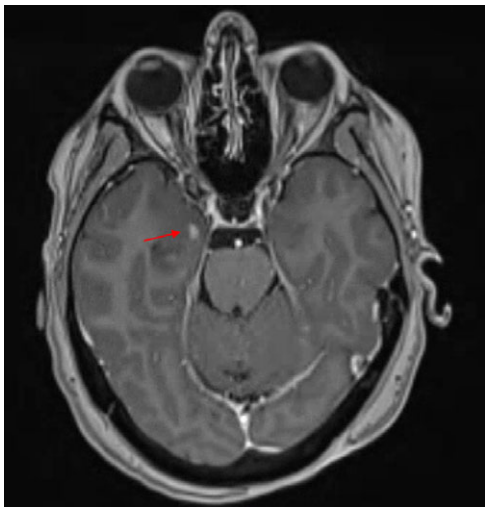

Figure 2: Axial T1, post gadolinium contrast. Enhancement is noted in the mesial right temporal lobe (red arrow).

Corresponding author: Al-Alya AlSabah, Department of Neurology, McGill University, Montreal, CA, Canada. Email: Al-alya.alsabah@mail.mcgill.ca

Cite this article: AlSabah A-A and Altman R. (2023) Nivolumab-Induced Limbic Encephalitis Associated with Glutamic Acid Decarboxylase 65 Antibodies. *The Canadian Journal of Neurological Sciences* **50**: 635–636, https://doi.org/10.1017/cjn.2022.71

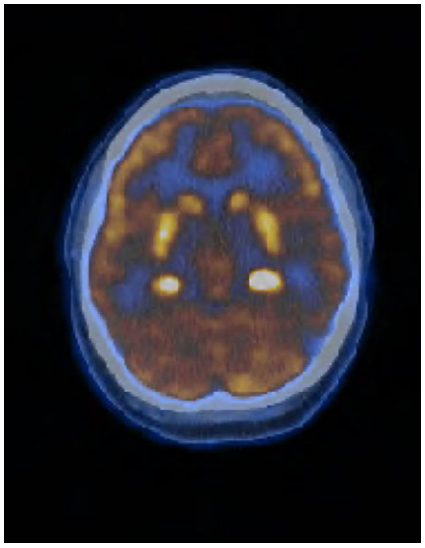

Figure 3: Cerebral PET scan, showing intense symmetric medial temporal lobe FDG activity.

Cyclophosphamide was then started due to its ability to inhibit both B and T cells.

She continues to be followed in the complex neurology clinic with continued profound impairment in short-term memory 1 year after the diagnosis.

There have been several case reports of ICI antibody-associated encephalitis, such as encephalitis secondary to contactin-associated protein–like 2 (CASPR2),[2] anti-Ma2[3] antibodies and others. To the best of our knowledge, we report the fourth case of ICI-induced anti-GAD 65 encephalitis.[4–6]

Immune-related adverse effects (irAEs) due to ICI are numerous and can affect any organ. Also, irAEs symptoms can vary from mild (grades 1 and 2) to severe (grades 3 and 4). Most commonly affected systems are the dermatological and gastrointestinal systems. High grade (grades 3 and 4) neurological adverse effects are rare, representing less than 1% of irAEs.[7]

High levels of antibodies against GAD65, which is the rate-limiting enzyme in the synthesis of the inhibitory neurotransmitter GABA, have been associated with stiff-person spectrum disorders, cerebellar ataxia, temporal lobe epilepsy and limbic encephalitis.[8] The long-term clinical outcomes for GAD antibody-associated neurological syndromes are often suboptimal, and immunotherapy outcomes are typically incomplete.[8–10] The most likely explanation why this syndrome is so refractory to immunotherapy is because GAD is an intracellular enzyme. It is known that encephalitis associated with intracellular neuronal antigens-specific CD8 + Tcells causes irreversible neuronal cell death. In contrast, antibodies to neuronal cell surface antigens tend to be more responsive to immunotherapy due to reversible antibody-mediated disturbance of synaptic transmission and neuronal excitability with minimal neuronal damage.[11]

In a case series involving six patients, who developed anti-Ma2 (intraneuronal antigen) encephalitis after ICI, 4/6 patients died, and the remaining two showed a moderate to severe disability despite immunotherapy.[3] In contrast, a patient with anti-CASPR2 (membrane protein) encephalitis secondary to pembrolizumab therapy for metastatic melanoma improved significantly with high-dose steroids.[2]

There are three cases in the literature reporting of ICI-induced anti-GAD 65 limbic encephalitis, all of which responded to immunotherapy.[4–6] In contrast, our patient failed three lines of immunosuppression. We hypothesize that the anti-GAD 65 antibodies in the reposted patients may be associated with neuronal cell surface antibodies to GABA(A) receptors or GABA(b) receptors, which may more often respond to immunotherapy than in patients with anti-GAD65 antibodies.[12] Unfortunately, our patient was not tested for these antibodies. This emphasizes the importance of comprehensive neuronal antibody testing to determine whether the presence of co-existing neuronal antibodies may contribute to differences in treatment response.

Disclosures. Neither author has anything to disclose.

Statement of Authorship. Al-Alya AlSabah: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data.

Robert Altman: Drafting/revision of the manuscript for content, including medical writing for content.

References

1. Hottinger AF, De Micheli R, Guido V, et al. Natalizumab may control immune checkpoint inhibitor-induced limbic encephalitis. Neurol Neuroimmunol NeuroInflammation. 2018;5:e439.
2. Brown MP, Hissaria P, Hsieh AH, et al. Autoimmune limbic encephalitis with anti-contactin-associated protein-like 2 antibody secondary to pembrolizumab therapy. J Neuroimmunol. 2017;305:16–8.
3. Vogrig A, Fouret M, Joubert B, et al. Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. Neurol Neuroimmunol NeuroInflammation. 2019; 6;e604.
4. Chung M, Jaffer M, Verma N, et al. Immune checkpoint inhibitor induced anti-glutamic acid decarboxylase 65 (Anti-GAD 65) limbic encephalitis responsive to intravenous immunoglobulin and plasma exchange. J Neurol. 2020;267:1023–5
5. Shah S, Dunn-Pirio A, Luedke M, et al. Nivolumab-Induced Autoimmune Encephalitis in Two Patients with Lung Adenocarcinoma. Case Rep Neurol Med. 2018;2018:2548528.
6. Maniscalco GT, Zekeridou A, Allegorico L, et al. GAD65 autoimmunity after treatment with nivolumab: a multifocal presentation. Neurol Sci. 2021;42:4289–91.
7. Cuzzubbo S, Javeri F, Tissier M, et al. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer. 2017;73:1–8. doi
8. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: Clinical course, treatments, and outcomes. Arch Neurol. 2012; 69:230–8.
9. Budhram A, Sechi E, Flanagan EP, et al. Clinical spectrum of high-titre GAD65 antibodies. J Neurol Neurosurg Psychiatry. 2021;92:645–54.
10. Muñoz-Lopetegi A, de Bruijn MAAM, Boukhrissi S, et al. Neurologic syndromes related to anti-GAD65: Clinical and serologic response to treatment. Neurol Neuroimmunol neuroinflammation. 2020;7:e696.
11. Lancaster E, Dalmau J. Neuronal autoantigens-pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8:380–90.
12. Graus F, Saiz A, Dalmau J. GAD antibodies in neurological disorders — insights and challenges. Nat Rev Neurol. 2020;16:353–65.

https://doi.org/10.1017/cjn.2022.71 Published online by Cambridge University Press