

Case Report

Unusual Presentation of a Rare Case of Immunotherapy Combination-Induced Encephalitis: A Case Report

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Keywords

Immune checkpoint inhibitors · Immune-related adverse events · Encephalitis · Cancer

Abstract

Introduction: Immune checkpoint inhibitors have revolutionized cancer treatment owing to their ability to activate cellular immune checkpoint pathways and mediate an antitumor activity. Due to their immunological actions, immune-related adverse events (irAEs) have become a concern. Neurological adverse events are rarely seen whether in the central or peripheral nervous system and can be potentially life-threatening. We present a rare case of occipital encephalitis following dual immunotherapy treatment in a patient with melanoma. **Case Presentation:** A 41-year-old man diagnosed with nodular melanoma of the right torso with axillary lymphadenopathies was treated with dual immunotherapy: nivolumab and ipilimumab. After 24 weeks, patient developed right homolateral hemianopia, and imaging findings correlated with occipital encephalitis. Autoantibodies were not detected. The patient was treated with steroids and exhibited radiological improvement of his encephalitis but maintained his right hemianopia. **Conclusion:** Neurological side effects of immunotherapy are not very common and range from mild to severe life-threatening symptoms. Previous analyses have shown that combination immunotherapy has a higher risk of side effects than monotherapy. Diagnosis of neurological manifestations is usually made by imaging, mainly brain magnetic resonance imaging or detection of autoantibodies in the CSF. The gold standard treatment is usually corticosteroids or rarely other molecules such as IVIg or monoclonal antibodies. The prognosis is usually favorable.

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment owing to their ability to activate cellular immune checkpoint pathways in order to reactivate the T-cell-mediated antitumor immunity and counteract immune evasion by cancer cells [1]. The two most commonly used molecules are programmed cell death receptor (PD1/PDL1) inhibitors and cytotoxic T-lymphocyte-associated protein inhibitors [2]. They are nowadays widely used in the treatment of many types of cancers with a remarkable efficacy either as monotherapy or in combination with each others [2] or with chemotherapy.

Due to their immunological actions, immune-related adverse events (irAEs) have become a concern. They can involve multiple organs and the most common reported adverse effects are as follows: silent thyroiditis which manifest itself as severe hypothyroidism if not screened for early; second most frequently reported side effect is hypoadrenalism which should also be screened for with simply cortisol level; more of a concern, pneumonitis, colitis, hepatitis, hypophysitis [1], and many others. They warrant a high index of clinical suspicion for early initiation of appropriate management since reversibility can be attained.

Neurologic adverse events are rarely seen but when encountered, they are difficult to diagnose, fatal, and potentially life-threatening [3]. The mechanism of the neurotoxicity is still unclear but can be attributed, according to several studies, to cytokine-mediated inflammatory reactions, production of autoantibodies as in paraneoplastic syndromes, or systemic depletion of regulatory T cells [4]. The symptoms can affect the central or peripheral nervous system. We hereby present a case of occipital encephalitis following dual immunotherapy treatment in a patient with melanoma which left him with severe sequelae.

Case Report

A 41-year-old gentleman with a history of seizures since childhood at the age well controlled on medications (valproic acid, levetiracetam, and rivotril) with no documented new seizure activity, good performance status (KPS 100%), presents diagnosed with a nodular melanoma on the right torso that had developed on a dermal melanocytic nevus. Following resection, anatomic pathology report described the melanoma as Clark III, Breslow 7 mm, ulcerated pT4b cN1 M0. He had upfront ipsilateral axillary lymphadenopathies evident clinically and on PET scan. No other metastases detected. He was started on dual immunotherapy: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. After 24 weeks of immunotherapy (4 cycles) and 1 week after the fourth cycle, patient developed anaphylaxis which was well treated. Shortly after this event, he started complaining of right homolateral hemianopia. No other neurologic symptoms were detected. A gadolinium-enhanced brain MRI scan was obtained and showed on the T2 and mainly Flair sequences left occipital cortical hyperintensity correlating with occipital encephalitis (Fig. 1).

To note, this patient did not receive any radiotherapy to the brain nor had undergone any central nervous system surgeries, and staging prior to therapy showed no CNS involvement. A PET-CT scan done showed pathological changes suggestive of left occipital decreased normal brain avidity limited to the right occipital cortex (Fig. 2). A lumbar puncture was done and returned with negative studies and cytology. No autoantibodies were tested unfortunately.

The patient was started on steroid (prednisolone 1 mg/kg daily) tapered over 16 weeks and immunotherapy discontinued. A repeat MRI brain after 1 month showed improvement in the flair signal abnormalities involving the left occipital cortex, and increase ventricular dilatation and involution of the brain. Despite this radiological improvement, patient retained a right hemianopia. Prednisone was stopped after 4 months of tapering. Patient was switched

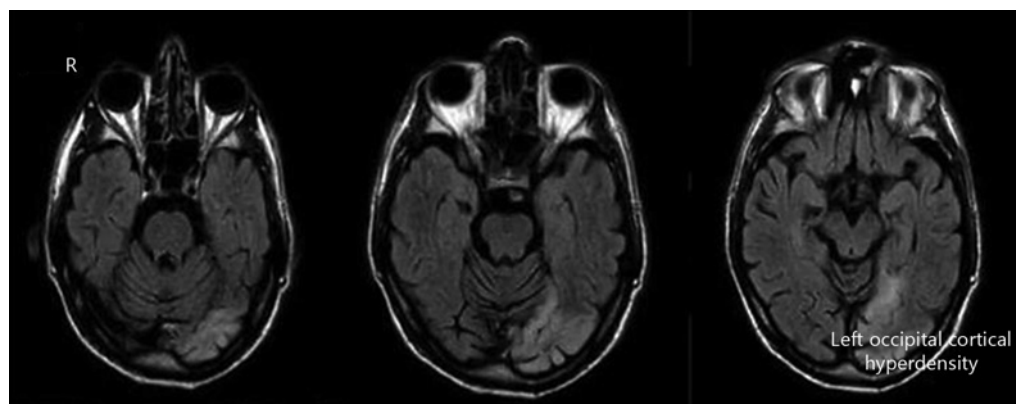


Fig. 1. Brain MRI showing T2 hyperintense region of the occipital area correlating with encephalitis.

to dabrafenib for his melanoma therapy (since his tumor harbored the BRAF V600E mutation) owing to the severe and disabling side effects of immunotherapy in his case. He had presented to the Neuro-Oncology Division at Mount Lebanon University Hospital for management of the immunotherapy side effects then he was sent back to pursue therapy with his primary oncologist.

Discussion

Neurological adverse events of immunotherapy are variable. They can involve the central or the peripheral nervous system. The mechanism is not well known, but it is assumed that the lymphocytes are activated to produce cytokines that disrupt the regulatory T-cell function and the humoral immunity [5]. These side effects can range from mild nonspecific neurologic symptoms to severe grade 3 and 4 diseases manifested as inflammatory myopathies; myasthenia gravis, vasculitis, neuropathies, aseptic meningitis, autoimmune encephalitis, multiple sclerosis, and hypophysitis. They can also simply be a reactivation of a preexisting autoimmune neurological disorder [5].

In a study done by Man et al. [6], the adverse events were higher and much more severe with PD1/PDL1 inhibitors than with cytotoxic T-lymphocyte-associated inhibitors (13.4% vs. 22.8%, $p < 0.001$) and higher with combination immunotherapy versus monotherapy (55.3% vs. 21.9%, $p < 0.001$) [7]. Difference should be made between irAEs of ICIs and neurologic paraneoplastic syndromes related to the underlying known malignancy that are usually subacute and progressive and develop before the diagnosis of the disease [2].

When suspecting a neurological irAEs, a thorough workup is indicated starting with history, detailed description of symptoms, detection of paraneoplastic antibodies that can be predictive of an increased risk of ICI-associated encephalitis [7]: anti-NMDAR (anti-N-methyl-D-aspartate receptor) reported in a case by Williams et al. [2], neurofilament light chain IgG [8] and phosphodiesterase 10A IgG [9]. Other studies have reported detection of Ma2 IgG. The majority of encephalitis is until now seronegative [3]. The study of Graus et al. [10] sets guidelines for diagnosing autoimmune encephalitis based on clinical symptoms and imaging-related findings with exclusion of other diagnosis that can cause encephalitis. Testing for antibodies is not a must in their study. Criteria for possible autoimmune encephalitis include:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms.

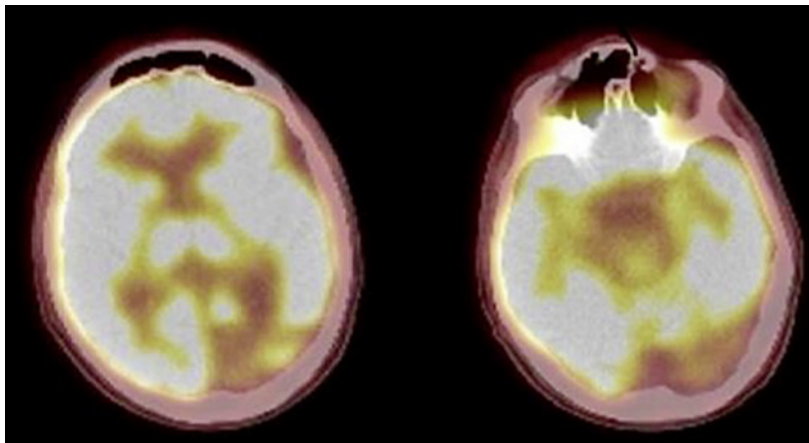


Fig. 2. PET-CT showing pathological changes of occipital encephalitis.

2. At least one of the following:

- New focal CNS findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis (white blood cell count of more than 5 cells per mm³), or MRI features suggestive of encephalitis.

3. Reasonable exclusion of alternative causes.

Our case reports a patient with new focal CNS disorder, homolateral hemianopia, and MRI findings suggestive of encephalitis and exclusion of other diagnosis by imaging studies and LP analyses. Our patient has a unique type of encephalitis not related to any of the known syndromes reported in the study of Graus et al. [10]. But it met the criteria for an autoimmune encephalitis according to the guidelines suggested in the study.

Imaging is used in the diagnosis of neurological events. MRI is usually normal in 60% of patients or present otherwise nonspecific findings with enhancement of leptomeninges or white matter [11] as opposed to the case presented in here where MRI findings were typical of encephalitis. Exclusion of other differential diagnosis is mandatory, including sepsis, intracerebral hemorrhage, ischemia, leptomeningeal dissemination, metabolic disturbances, nonconvulsive status epilepticus, paraneoplastic limbic encephalitis, PRES, or vasculitis [12].

ICI-induced encephalitis, as reported in this case, is a rare severe autoimmune condition presenting usually with memory deficit, psychiatric disorders, or seizures. Our case reported hemianopia, a very rare manifestation of autoimmune encephalitis. Table 1 shows a small literature review of the ICI combination-induced autoimmune encephalitis.

The treatment of ICIs encephalitis is highly grade-dependent; grade 1 does not require immunotherapy discontinuation, whereas grades 2 (moderate) and 3 (severe) require discontinuation of the medication. Nearly all the neurological adverse events present in advanced grades, and treatment is needed in most of the times. The gold standard treatment of ICI-induced encephalitis remains corticosteroids at a dose of 1–2 mg/kg given over several days to reach doses >1,000 mg/day of methylprednisolone [12]. Steroids should be tapered down very slowly for at least 4 weeks to meet the long half-life of ICIs [22]. Pneumocystis pneumonia prophylaxis with trimethoprim-sulfamethoxazole should be considered and potential steroids side effects anticipated and managed. In cases of refractoriness to steroids, workup should be repeated to rule out other causes of encephalitis. Other molecules can be used for treatment such as IVIg, plasma exchange therapy, monoclonal antibody (rituximab), or an α4β1 integrin antibody (natalizumab) as mentioned in the case of Hottinger et al. [16].

Table 1. Combination ICI-induced autoimmune encephalitis, review of the literature

Case	Cancer	Immunotherapy	Grade	MRI finding	Treatment
Larkin et al. [13] (2017)	Malignant melanoma	Nivolumab + ipilimumab	>3	Normal or some areas of hypersignal on FLAIR	Steroids + plasma exchange
Bossart et al. [14] (2017)	Malignant melanoma	Ipilimumab + pembrolizumab	3	None	Steroids
Ito et al. [15] (2017)	Small cell lung cancer	Nivolumab + ipilimumab	3	None	Steroids + rituximab
Hottinger et al. [16] (2018)	Small cell lung cancer	Nivolumab + ipilimumab	3	Severe abnormalities in both hippocampi with contrast-enhancing lesions	Steroids and natalizumab
Williams et al. [2] (2016)	Melanoma Small cell lung cancer	Nivolumab + ipilimumab	3	None or none specific	Steroids
Elkayam and Sharma [17] (2019)	Metastatic renal cell carcinoma	Nivolumab + ipilimumab	3	None	Steroids
Keerty et al. [18] (2020)	Malignant melanoma	Nivolumab + ipilimumab	3	None	Steroids
Martínez-Vila et al. [19] (2021)	Malignant melanoma	Nivolumab + ipilimumab	3		
Bir Yucel et al. [20] (2022)	Malignant melanoma	Nivolumab + ipilimumab	3	Not done	Steroids and IVIg
Grunhut et al. [21] (2022)	Malignant melanoma of the bladder neck	Nivolumab + ipilimumab	3	Bilateral basal, ganglia hyperintensities on T2	Steroids

The prognosis of ICI-induced encephalitis is usually favorable due to early diagnosis and prompt management with nearly all patients having full recovery of their symptoms. This case emphasizes on the importance of early detection of new symptoms in a patient treated with immunotherapy, in order to establish a clear diagnosis and initiate the corresponding treatment. Clinicians should be aware of all the possible side effects of immunotherapy and the neurologic adverse events it can cause in order to withhold immunotherapy at the appropriate time. The article has important implications on clinicians practice when using immunotherapy in patients' treatment. The limitation of the study is mainly related to lack of autoantibodies testing due to unavailability of these tests.

Conclusion

ICI-induced encephalitis is a rare and severe life-threatening complication that warrants a high index of suspicion and whose diagnosis is directed by a thorough workup. With the initiation of early treatment nowadays, symptoms can be controlled and prognosis improved. Further studies are warranted to try to prevent and limit the onset of neurological side effects of immunotherapy and mainly the onset of a debilitating encephalitis.

Statement of Ethics

The article was reviewed and checked by the IRB Committee of Balamand University and was exempted from approval. Written informed consent was obtained from the patient for publication of data and images in this article. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000543215>).

Conflict of Interest Statement

The authors declare that there are no conflicts of interest to be mentioned.

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Author Contributions

Pamela Sfeir contributed to the writing of the original draft and editing with conceptualization of the work and data collection. Francois Kamar contributed in supervising the work and the final editing to the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries are to be addressed to the corresponding author.

References

- 1 Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol.* 2019;5(7):1008–19. <https://doi.org/10.1001/jamaoncol.2019.0393>
- 2 Williams TJ, Benavides DR, Patrice KA, Dalmau JO, de Ávila ALR, Le DT, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol.* 2016;73(8):928–33. <https://doi.org/10.1001/jamaneurol.2016.1399>
- 3 Albarrán V, Chamorro J, Rosero DI, Saavedra C, Soria A, Carrato A, et al. Neurologic toxicity of immune checkpoint inhibitors: a review of literature. *Front Pharmacol.* 2022;13:774170. <https://doi.org/10.3389/fphar.2022.774170>
- 4 Zhou Y, Li H. Neurological adverse events associated with PD-1/PD-L1 immune checkpoint inhibitors. *Front Neurosci.* 2023;17:1227049. <https://doi.org/10.3389/fnins.2023.1227049>
- 5 Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you “take the brakes off” the immune system. *Ther Adv Neurol Disord.* 2018;11:1756286418799864. <https://doi.org/10.1177/1756286418799864>
- 6 Man J, Ritchie G, Links M, Lord S, Lee CK. Treatment-related toxicities of immune checkpoint inhibitors in advanced cancers: a meta-analysis. *Asia Pac J Clin Oncol.* 2018;14(3):141–52. <https://doi.org/10.1111/ajco.12838>
- 7 Reynolds KL, Guidon AC. Diagnosis and management of immune checkpoint inhibitor-associated neurologic toxicity: illustrative case and review of the literature. *Oncologist.* 2019;24(4):435–43. <https://doi.org/10.1634/theoncologist.2018-0359>

- 8 Basal E, Zalewski N, Kryzer TJ, Hinson SR, Guo Y, Dubey D, et al. Paraneoplastic neuronal intermediate filament autoimmunity. *Neurology*. 2018;91(18):e1677–89. <https://doi.org/10.1212/WNL.0000000000006435>
- 9 Zekeridou A, Kryzer T, Guo Y, Hassan A, Lennon V, Lucchinetti CF, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. *Neurology*. 2019;93(8):e815–22. <https://doi.org/10.1212/WNL.0000000000007971>
- 10 Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391–404. [https://doi.org/10.1016/S1474-4422\(15\)00401-9](https://doi.org/10.1016/S1474-4422(15)00401-9)
- 11 Müller-Jensen L, Zierold S, Versluis JM, Boehmerle W, Huehnchen P, Endres M, et al. Characteristics of immune checkpoint inhibitor-induced encephalitis and comparison with HSV-1 and anti-LGI1 encephalitis: a retrospective multicentre cohort study. *Eur J Cancer*. 2022;175:224–35. <https://doi.org/10.1016/j.ejca.2022.08.009>
- 12 Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–68. <https://doi.org/10.1200/JCO.2017.77.6385>
- 13 Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, et al. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. *Oncologist*. 2017;22(6):709–18. <https://doi.org/10.1634/theoncologist.2016-0487>
- 14 Bossart S, Thurneysen S, Rushing E, Frontzek K, Leske H, Mihic-Probst D, et al. Case report: encephalitis, with brainstem involvement, following checkpoint inhibitor therapy in metastatic melanoma. *Oncologist*. 2017;22(6):749–53. <https://doi.org/10.1634/theoncologist.2016-0366>
- 15 Ito M, Fujiwara S, Fujimoto D, Mori R, Yoshimura H, Hata A, et al. Rituximab for nivolumab plus ipilimumab-induced encephalitis in a small-cell lung cancer patient. *Ann Oncol*. 2017;28(9):2318–9. <https://doi.org/10.1093/annonc/mdx252>
- 16 Hottinger AF, de Micheli R, Guido V, Karampera A, Hagmann P, Du Pasquier R. Natalizumab may control immune checkpoint inhibitor-induced limbic encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(2):e439. <https://doi.org/10.1212/NXI.0000000000000439>
- 17 Elkayam N, Sharma S. Dual checkpoint inhibitor induced autoimmune encephalitis. *Arch Oncol*. 2019;25(2):22–4. <https://doi.org/10.2298/AOO181230003E>
- 18 Keerty D, Holmstrom B, Peguero E, Holmstrom B. Immunotherapy-mediated encephalitis in an oncological patient. *Int J Case Rep Imag*. 2020;11:101124Z01DK2020. <https://doi.org/10.5348/101124z01dk2020cr>
- 19 Martínez-Vila C, Laguna JC, Segui E, Ruiz G, Moreno FA, Fernandez-Morales LM, et al. Encephalitis associated with immune checkpoint inhibitor treatment in patients with melanoma. *J Immunother*. 2021;44(5):204–7. <https://doi.org/10.1097/CJI.0000000000000369>
- 20 Bir Yucel K, Sutcuoglu O, Yazici O, Yıldız Y, Şenol E, Uner A. Nivolumab–ipilimumab combination therapy-induced seronegative encephalitis; rapid response to steroid plus intravenous immunoglobulin (IVIG) treatment. *J Oncol Pharm Pract*. 2022;29(3):760–3. <https://doi.org/10.1177/10781552221118529>
- 21 Grunhut J, Brown S, Lutzky J, Skoczylas L. Recognising immunotherapy-induced meningoencephalitis: a case during treatment for primary metastatic melanoma of the bladder neck. *BMJ Case Rep*. 2022;15(7):e249411. <https://doi.org/10.1136/bcr-2022-249411>
- 22 Stuby J, Herren T, Naumburger GS, Papet C, Rudiger A. Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature. *Swiss Med Wkly*. 2020;150(4748):w20377. <https://doi.org/10.4414/smw.2020.20377>