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Case report

AUTOIMMUNE ENCEPHALITIS RELATED TO NIVOLUMAB FOLLOWED BY TUMOR REGRESSION

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Abstract

Immune checkpoints inhibitors have shown a remarkable improvement in overall survival of stage IV renal cell carcinoma patients. Nevertheless, there is a wide range of immune-related adverse events (IRAE) that arise from these revolutionary treatments. Autoimmune encephalitis is a rare but severe central nervous system IRAE in these cancer patients. The severities of these IRAEs preclude patients from continuing immunotherapy treatment. Few cases of autoimmune encephalitis with immunotherapy have been described in the literature and optimal clinical management of these events as well as patient's immune-mediated response after treatment suspension is still unclear. Here, we report a case of a 67 years-old woman with stage IV renal cell carcinoma under treatment with nivolumab who developed autoimmune encephalitis. After high doses of corticosteroids patient's condition improved significantly with full recovery after 5 days of treatment. Even though nivolumab was not reinstalled, a persistent response of her oncologic disease was evidenced. We expect that this case can contribute to the existing literature of both subjects, the management of autoimmune encephalitis as grade IV immune related adverse event and the responses of immune checkpoint inhibitors after IRAE.

Key words: encephalitis, nivolumab, immunotherapy, adverse events

Resumen

Encefalitis autoinmune relacionada con nivolumab seguida de regresión tumoral

Los inhibidores de puntos de control inmunológico han mostrado una importante mejoría en la supervivencia global de los pacientes con carcinoma de riñón estadio IV. Sin embargo, existe una amplia variedad de efectos adversos inmunomediados que surgen a partir de estos tratamientos revolucionarios. La encefalitis autoinmune es un infrecuente pero grave efecto adverso inmunomediado del sistema nervioso central en estos pacientes. La gravedad de este cuadro impide que los pacientes continúen con el tratamiento de inmunoterapia. Se han descrito pocos casos de encefalitis autoinmune con inmunoterapia en la literatura y aún no está claro el manejo clínico óptimo de estos eventos, ni cómo continua la respuesta inmunomediada después de la suspensión del tratamiento. Presentamos el caso de una mujer de 67 años con carcinoma de células renales estadio IV que desarrolló encefalitis autoinmune durante el tratamiento con nivolumab. La paciente mejoró significativamente luego del inicio del tratamiento con altas dosis de corticoides, con una recuperación completa después de 5 días del mismo. Si bien el nivolumab no se reinició, se evidenció una respuesta persistente de su enfermedad oncológica. Esperamos que este caso pueda contribuir a la literatura existente de ambos temas, el manejo de la

encefalitis autoinmune como efecto adverso inmunomediado grado IV y las respuestas que se obtienen con la inmunoterapia luego de estos efectos adversos.

Palabras clave: encefalitis, nivolumab, inmunoterapia, efecto adverso

With the advent of immunotherapy many changes have been made in cancer treatment. Particularly, it has revolutionized the treatment of metastatic renal cell carcinoma (mRCC) with immune checkpoint inhibitors (ICIs), being commonly administrated in combination with tyrosine kinase inhibitors (TKIs), other ICIs or as monotherapy[1]. Second line therapies in mRCC were established after several studies. Treatment with the programmed death protein 1 (PD1) checkpoint inhibitor nivolumab alone in second line was first introduced in Checkmate 025, a randomized study that compared everolimus and nivolumab in pretreated patients (without mTOR inhibitors at first line). Primary end point was overall survival (OS), which was 5.4 months longer in the nivolumab arm (median 25 vs. 19.6 months)[2].

The immune system is tightly regulated by a network of cells, molecules, signal pathways and receptors. ICIs prevent T lymphocytes attenuation by blocking the binding of inhibitory signals or enabling activating signals. This mechanism allows a more reactive immune system response against the tumor, but this disruption of immunological tolerance results in a lower response of Treg lymphocytes, a rise of auto antibodies, proinflammatory cytokines and complement activation, which explains the variety of immune related adverse events[3]. This mechanism of action is far from that of chemotherapy with a hugely different toxicity profile. Therefore, clinical oncologists should be aware of all the new spectrum of adverse events associated with immunologic treatment.

The most common IRAEs are rash, colitis and pneumonitis[4]. Neurologic events are infrequent but may be serious and potentially life-threatening complications requiring immediate immunosuppressive therapy. These include cases of immune encephalitis which is a rapidly progressive encephalopathy caused by brain inflammation and cannot be distinguished from other encephalitis etiologies based on clinical symptoms[5]. Diagnosis process includes physical examination with new focal CNS findings, seizures not explained by a previously known seizure disorder, lumbar puncture (LP) with cerebrospinal fluid (CSF) pleocytosis, MRI features suggestive of encephalitis[6] with the suspicion of immune etiology in the context of ICI treatment. It also includes ruling out other causes such as infectious, paraneoplastic and metastatic. Auto antibodies may be present and support diagnosis, but they are not part of the early diagnostic criteria as results can take several weeks. Standard treatment in these cases is immunosuppressive therapy, primarily with high-dose corticosteroids. If no clinical improvement is achieved, immunosuppressants such as immunoglobulins or rituximab are added. Also, antibiotic treatment is necessary from the beginning since viral or bacterial encephalitis could be fatal without treatment.

Paraneoplastic encephalitis mimics the neurologic symptoms but commonly precedes cancer diagnosis and does not respond to immunosuppressive treatment[7]. The faster treatment is initiated the better is the recovery.

Larkin et al analyzed neurologic immune related adverse event (IRAE) from 12 studies, including 3763 patients with metastatic melanoma, treated with ipilimumab plus nivolumab or nivolumab alone. The rates of severe neurologic adverse events were 0.93%. Encephalitis was present in 6 patients (less than 0.2%), with a unique fatal event[8].

Although IRAEs may be severe, they are correlated with response. The rationale for this association is that blocking the inhibition of the immune system activates an hyperreactive immune system that could affect to both tumor response and autoimmunity[9].

We present a case of autoimmune encephalitis with treatment interruption and subsequent major long-term response that even lasts till today.

Clinical case

In November of 2017, a 67-year-old woman with stage IV clear cell renal cell carcinoma on second line treatment with nivolumab, was admitted at the emergency department, a week after her 18th application, with a two-week progression of a subacute confusional syndrome that add urinary incontinence and a single fever episode.

Her kidney cancer was diagnosed in February of 2014 in a localized stage so partial nephrectomy was performed. Pathology was consistent with stage 1 clear cell renal cell carcinoma Fuhrman grade 3. Pulmonary relapse was evidenced in the oncological control of March 2016, thus first line treatment with pazopanib was initiated, and due to the progression in the size of the lesions, second line with nivolumab started in January 2017 with partial response (Fig. 1). She had no history of neurological disorders, was not on any medication. Her background was being a former smoker, hypertension and had a mechanical aortic and a mitral valve replacement in 2015.

Physical examination at emergency entrance evidenced fever 38 degrees Celsius, Glasgow Coma Scale score of 15, minimental state of 11, apraxia, temporal and spatial disorientation, bradypsychia, perseveration, inattention and slow speech.

No signal of motor or sensitivity affection, cranial nerves were conserved, no pyramidal or extrapyramidal signs, neck was supple, fundoscopy was normal.

Complementary studies: Laboratory tests showed no abnormalities, with negative HIV and VDRL, TSH 0.9 (within normal range). Brain CT showed no mass, intracranial bleeding or hydrocephalus, no major vessel vascular territory infarct and MRI showed T2, FLAIR and DWI bilateral hyperintensity at posterior periventricular white matter (Fig. 2A). The EEG with occasional activity of sharp waves that were observed in centrotemporal areas in both hemispheres. A LP was performed, CSF evidenced: hyperproteinorrachy 0.6mg/L, WBC 15/µL most mononuclear cells, glucose 60, lactate acid 1.9 mmol/L.

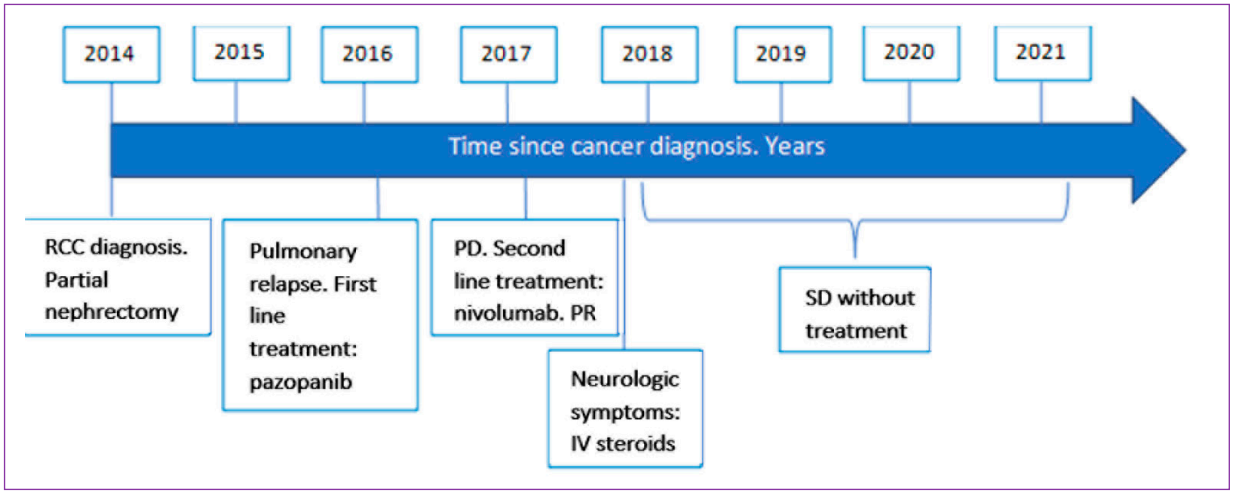
Infectious encephalitis was suspected and couldn`t be discarded in the first place so antibiotic scheme with acyclovir 600 mg/d, ampicillin 2 gr/4 hs, ceftriaxone 2 g/12 h and dexamethasone 8 mg/8h was initiated. Because of EEG alterations she was medicated with levetiracetam 500 mg/12 h.

Blood, urine, and CSF cultures results were negative, including VDRL, FTA-ABS, HSV, enterovirus, cytomegalovirus, and varicella zoster PCR in CSF. Onconeural antibodies were studied: anti-HU, anti-RI, anti-YO, with negative results. Same as multiple other autoantibodies anti-NMDA, anti-VGKC and anti JO1.

The symptoms persisted. Without fever, negative infectious results, not progression of cancer disease and brain MRI without metastases but compatible with inflammatory status, the suspected diagnosis was autoimmune encephalitis, then high doses of methylprednisolone corticosteroid were administrated (1 g IV daily for 5 days) with frank improvement of neurological symptoms, and subsequent complete resolution, not requiring other immunosuppressive therapy as immunoglobulin or rituximab. Nivolumab was terminated interpretating it as the original cause of the encephalitis.

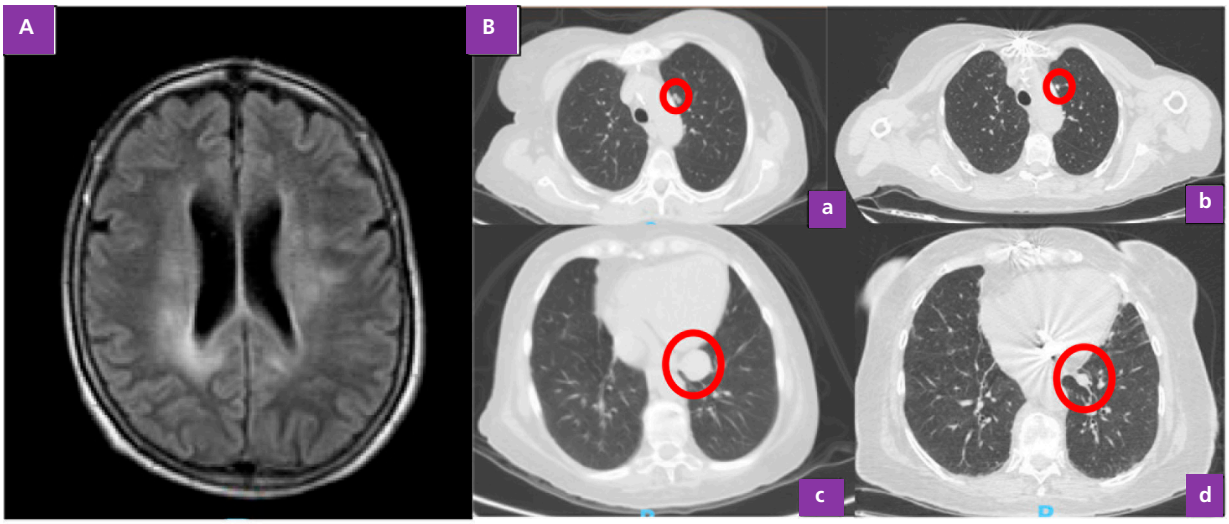
After the patient's discharge, subsequent CT controls showed a greater partial response of the kidney cancer lesions, which are stable without progression even after 4 years of the suspension of nivolumab, without the need for any oncological treatment (Fig. 2B).

Figura 1 | Timeline showing the most important events since the diagnosis



RCC: renal cell carcinoma; PD: progression disease; PR: partial response; IV: intravenous; SD: stable disease

Figura 2 | A: Axial brain MRI, FLAIR sequence showing bilateral hyperintensity at posterior periventricular white matter. B: Comparison between CT at time of IRAE in Nov 2017 (a and c) with same area in Apr 2021 (b and d)



The patient gave verbal and written consent for the article to be published

Discussion

We present a rare case of tumor regression after nivolumab suspension because of a grade IV IRAE.

In this case, the symptoms began far from the start of treatment. With negative infectious results, magnetic resonance imaging compatible with an inflammatory pattern, ictal activity on EEG, no progression of the disease in the brain, and excellent response to immunosuppressive therapy, the diagnosis was autoimmune encephalitis. Absence of autoantibodies does not exclude the possibility of immune mediated disorder[6].

There are many other case reports of encephalitis as ICI adverse event, although generally they occur early on ICI treatment. Most of the patients had fatal resolution of the encephalitis, or partial response with progression of cancer disease after treatment hold[10, 11].

With this article we want to emphasize the low threshold of suspicion that must exist for an early recognition of the disease in patients with ICI treatment who develop alteration in mental status and the importance of a rapid establishment of treatment that greatly improves the results. Always being careful with differential diagnoses and excluding other potentially fatal diagnoses.

This article also highlights how long the tumor response can be in patients with metastatic renal cell carcinoma in the context of grade IV immune adverse events. After the suspension of treatment, of the multiple pulmonary metastases, only 2 of them persisted, which significantly reduced their size and have remained stable since then (Fig. 2B).

To the best of our knowledge this is the first case of mRCC tumor regression after stopping immunotherapy for a grade IV IRAE.

However, the better response of patients with IRAE is correlated with other reports and supports the idea of IRAE as biomarkers of response in patients with immunotherapy[9].

Two retrospective evaluations in metastatic RCC patients treated with ICIs evidenced that patients who experienced IRAEs were associated with improved OS[12, 13].

This phenomenon was also evidenced in other tumors. A prospective biomarker study of 106 patients with advanced non-small cell lung cancer treated with ICIs evidenced that the proportion of IRAEs was significantly higher in responders than nonresponders (65.2% vs. 19.3%, $p < .01$)[14].

In conclusion, some patients previously considered incurable are now achieving long-term remissions with these novel therapeutics, but at the expense of frequent and sometimes serious or even fatal IRAE. While increasing indications of immunotherapy, more and more patients are experimenting all kinds of IRAE. That's why medical doctors should be at the vanguard, tracking signs of toxicity and treat the patient as soon as possible to rise the odds of resolution.

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Conflict of interest: None to declare

References

1. Iris Y Sheng, Moshe C Ornstein. Ipilimumab and nivolumab as first-line treatment of patients with renal cell carcinoma: the evidence to date. *Cancer Manag Res* 2020; 12: 4871-4881.
2. Escudier B, Sharma P, McDermott DF, et al. CheckMate 025 Randomized phase 3 study: outcomes by key baseline factors and prior therapy for nivolumab versus everolimus in advanced renal cell carcinoma. *Eur Urol* 2017; 72: 962-71.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 78: 158-68.
4. Brahmer JR, Lacchetti C, Schneider BJ, 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: 1714-68.
5. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. *Curr Opin Neurol* 2016; 29: 806-12.
6. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15: 391-404.
7. Williams TJ, Benavides DR, Patrice KA, et.al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol* 2016; 73: 928-33.
8. Larkin J, Chmielowski B, Lao CD, 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: 709-718.
9. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer* 2019; 7: 306.
10. Jindřich Kopecký, Ondřej Kubeček, Tomáš Geryk, et al. Nivolumab induced encephalopathy in a man with metastatic renal cell cancer: a case report. *J Med Case Rep* 2018; 12: 262.
11. S. Galmiche, C. Lheure, N. Kramkimel, et al. Encephalitis induced by immune checkpoint inhibitors in metastatic melanoma: a monocentric retrospective study. *J Eur Acad Dermatol Venereol* 2019; 33(12): e440-e443.
12. Elias R, Yan N, Singla N, et al Immune-related adverse events are associated with improved outcomes in ICI-treated renal cell carcinoma patients. *J Clin Oncol* 2019; 37: 7 S645.
13. Verzoni E, Cartenì G, Cortesi E, et al. Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program. J Immunother Cancer 2019; 7: 1-99.
14. Akamatsu H, Murakami E, Oyanagi J, et al. Immune-related adverse events by immune checkpoint inhibitors significantly predict durable efficacy even in responders with advanced non-small cell lung cancer. Oncologist 2020; 25: e679-e683.