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Recognising immunotherapy-induced meningoencephalitis: a case during treatment for primary metastatic melanoma of the bladder neck

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SUMMARY

Although novel immunotherapy has shown promise for patients with melanoma, a more activated state of the immune system may lead to adverse systemic effects. Immunotherapy-induced meningoencephalitis is a rare and seldom reported adverse effect of immunotherapy but with the expanding role of immunotherapy in cancer treatments it must be recognised. Patients receiving immunotherapy should receive a proper warning about the potential for this life-threatening condition. Herein, we report a patient in his 70s with neurological changes after his second treatment with dual immunotherapy for a primary metastatic melanoma of the bladder neck.

BACKGROUND

In 2021, there will be an estimated 106 110 new melanomas diagnosed in the USA.¹ Ipilimumab and nivolumab are human immunoglobulin programmed death 1 (PD-1) immune checkpoint inhibitor (CPI) antibodies that selectively block interactions between PD-1 expressed on activated T cells with ligands programmed death-ligand 1 (PD-L1) and PD-L2 expressed on antigen-presenting cells and cancer cells that result in significant enhancement of T-cell function.² These drugs are used to treat melanomas that cannot be treated surgically or that have already metastasised.³

Immune-related adverse events caused by novel immunotherapy such as CPIs, are a rare but complex and clinically important subject.^{4,5} These may manifest in various compromised neurological states such as aseptic meningitis and encephalitis.⁴ Often, patients' presentations encompass a wide range of diseases and differential diagnoses. Diagnosing immune therapy-related adverse events is important due to the potential life threatening sequelae and the complexity of management. Physicians may delay proper treatment or may not know whom to refer for assistance in the management of this complex disorder.

Here, we report an exceedingly rare case of a patient undergoing immunotherapy treatment for primary metastatic melanoma of the bladder neck who exhibited significant cognitive decline following treatment with ipilimumab and nivolumab. These effects were observed in this patient only and research is required to the prove causation. The distinctive presentation, differential diagnosis, management and treatment of immunotherapy-induced meningoencephalitis (IIM) is discussed.

CASE PRESENTATION

A white male above the age of 70 (height: 6' 0" (1.83 m); weight: 216.1 lbs (98.0 kg); body mass index: 29.3 kg/m²) was found to have a rare primary malignant melanoma of the bladder neck without evidence of metastatic disease after several episodes of haematuria and urinary obstruction. The patient was referred to a national comprehensive cancer institute and was started on immunotherapy. He received a dual ipilimumab and nivolumab (anti-PD1, PDL1, anti-CTLA4) infusion within 2 months of his initial hospitalisation for urinary obstruction. Adverse events included increased fatigue and he slept for most of the week at home after his second round of immunotherapy. Indeed, his wife reported that the patient experienced an episode of sleep for 20 hours without interruption. On awakening from this, he stood up and fell to the ground shortly after, prompting a visit to the hospital emergency department. The patient was noted to be confused on admission to the hospital.

DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

The patient had diabetes but was not hypoglycaemic on arrival, ruling out a hypoglycaemic event. Patient was noted to have an elevated temperature of 37.8°C and so an infectious cause for confusion was suspected. Urinary tract infection was suspected secondary to melanoma of the neck of the bladder prompting a urine culture and intravenous antibiotics were started. A multidisciplinary team consisting of infectious disease, urology and endocrinology led by the patient's primary care physician convened to treat the patient. The patient's oncologist was remotely based but informed and included in the decision-making process.

The following day there was no improvement in patient's mental state. CT scan of the head without contrast was performed for suspected stroke, metastatic malignancy or other acute intracranial pathology. CT scan showed no evidence of acute intracranial pathology. Hypopituitarism, likely immune-related was noted and endocrinology advised on proper replacement therapy.

Continued cognitive decline pressed for a neurology consult in which the patient was found to have no spontaneous speech, inappropriate responses and apathy. Encephalopathy of a toxic metabolic or infectious cause was suspected. Cerebrospinal fluid (CSF) was obtained via fluorescent guided lumbar puncture. At this point, urine



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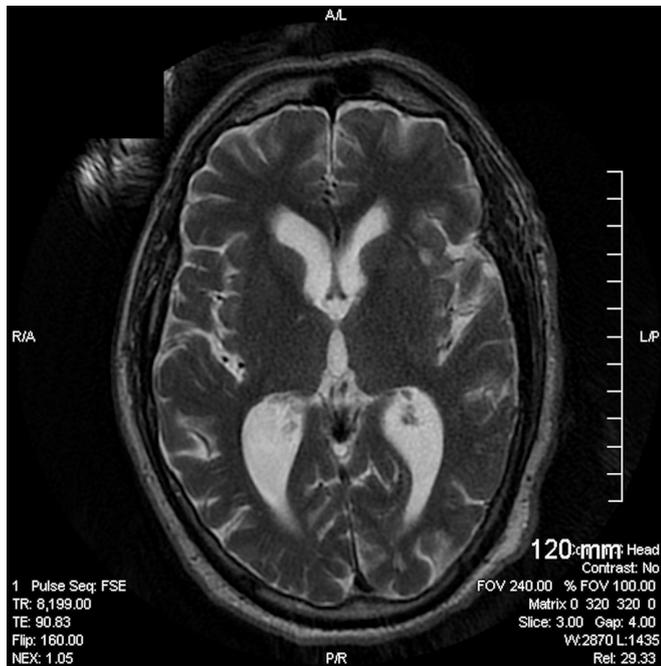


Figure 1 Initial MRI: axial T2-weighted image with hyperintensities in the bilateral basal ganglia.

cultures came back positive for *Staphylococcus aureus*, possibly from an indwelling Foley catheter. Intravenous antibiotics were continued according to sensitivities but mental state continued to decline. CSF cultures, viral panel and separate herpes simplex virus (HSV)-1 and HSV-2 CSF PCR tests were negative but CSF lymphocytosis was noted. MRI with and without contrast was performed but was difficult to interpret due to patient's movements and inability to remain still during the examination (figures 1 and 2). Toxic metabolic causes were ruled out with blood workup that included chemistry comprehensive studies,



Figure 2 Initial MRI: sagittal FLAIR-weighted image with mild but inconclusive hyperintensities seen in the meninges.

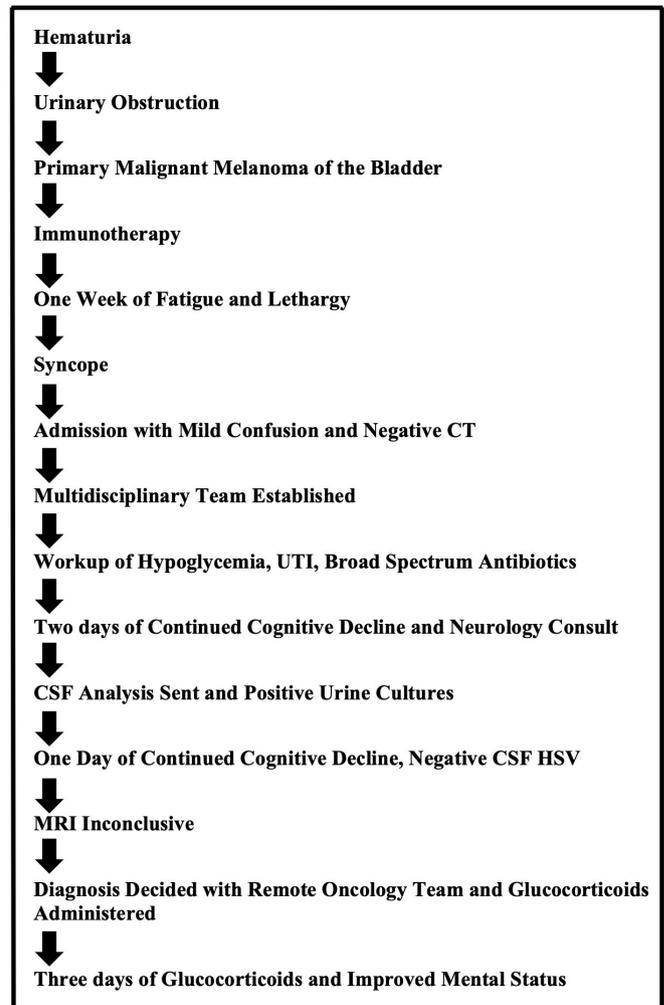


Figure 3 Timeline of clinical events. Figure author: Joel Grunhut.

basic haematology and thyroid studies. The team consulted the patient's oncologist once more and agreed on a diagnosis of immune mediated lymphocytic meningoencephalitis and hypophysitis. This was a diagnosis of exclusion due to the negative workup and consistent cognitive decline.

TREATMENT

Consult with the patient's remote oncology team led to a decision to treat as an adverse reaction to the immunotherapy and to begin a course of steroids. Methylprednisolone 40 mg=1 mL, intravenous push, every 8 hours and prednisone 5 mg=1 tab, oral, every morning, were administered. The patient immediately began to improve and was discharged 3 days later with continuous improvement in his mental and physical state (figure 3). Follow-up in the outpatient setting at the patient's primary care physician revealed continued and maintained improvement without any deterioration or adverse events. These effects were observed in this patient only and research is required to the prove causation.

OUTCOME AND FOLLOW-UP

Fortunately, 1-year follow-up with the patient found him to be back to his mental baseline, with no lasting effects from the hospitalisation. He continued to remain stable and did not receive additional immunotherapy treatments. His oncology

team is considering an additional round of immunotherapy with a single drug.

DISCUSSION

The clinical manifestations of IIMs are broad, atypical and encompass overlapping syndromes.⁶ This results in patients with IIM receiving treatment delays and possible consequential effects. There is a need to disseminate information regarding IIM in order to best inform physicians about recognition and management of such patients.

Before initiation of treatment with immune CPIs, patients should have a neurological evaluation to establish a baseline cognitive level.⁷ This will allow any future adverse neurological events such as IIM to be recognised earlier. This patient's care may have been expedited if a proper cognitive baseline was established before treatment.

Patients with suspected IIM must have a full workup to rule out other metabolic or infectious causes. A thorough investigation is warranted in a patient on immune CPIs with developing neurological involvement. Manifestations of neurological impairment vary widely although some presentations to consider are confusion or delirium, headaches, altered behaviour, short-term memory loss, speech abnormalities, fatigue, focal weakness, decreased level of consciousness, hallucinations, spastic tremors, fever and vomiting.⁸ Teams must take a thorough medical history, including evaluating current medications, and perform a thorough clinical neurological examination. Blood tests should assess metabolic abnormalities or signs of infection, followed by CSF analysis. Brain MRI can rule out metastasis and may pick up enhancement from encephalitis. Differentiation of IIM and aseptic meningitis requires a fine diagnostic workup as both conditions may present with lymphocyte pleocytosis, elevated protein, negative bacterial and viral cultures/serology in the

Patient's perspective

I believe this manuscript to be accurate in its entirety. I hope that doctors prescribing immunotherapy really understand the harmful effects it can cause. I would be very hesitant to ever take immunotherapy again because of my bad reaction.

Learning points

- ▶ Immunotherapy-induced meningoencephalitis is a rarely observed adverse event during treatment with immune checkpoint inhibitors such as ipilimumab and nivolumab.
- ▶ Physicians and patients alike should be educated about the possible neurological adverse effects that may arise with immunotherapy.
- ▶ Establishing a baseline cognitive level is necessary in older patients to help differentiate age-related changes from neuropathology.
- ▶ Early diagnosis and management with a multispecialty team are necessary to avoid potential life threatening sequelae.
- ▶ Rapid initiation of corticosteroids is recommended and patients may see quick and full recoveries if managed appropriately.

CSF analysis, abnormal leptomeningeal enhancement on brain MRI, and improvement with high-dose corticosteroids although altered mental status is less usual with aseptic meningitis.^{7,9}

In patients with presumed IIM, corticosteroids should be introduced rapidly, while continuing to treat with antiviral medications until negative CSF viral panels are returned.⁶ In this patient, treatment with corticosteroids helped improve his neurological status back to baseline.

This case exemplifies the importance of an experienced multidisciplinary team in recognising and treating IIM. In these rare and potentially harmful situations, accurate diagnosis and management must rely on an experienced multidisciplinary team. Future cases should continue to be disseminated through literature to enable future studies in understanding the pathophysiology and aetiology of IIM. Future research should identify if demographics, cancer type and other patient specific factors play a role in the onset of IIM.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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