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Immune checkpoint inhibitor-induced encephalitis with dostarlimab in two patients: Case series

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are being used increasingly in the treatment of several cancers and have been associated with neurological complications including immune checkpoint inhibitor-induced encephalitis (ICI-iE). We present two cases of ICI-iE with the novel agent dostarlimab, which to our knowledge are the first reported with this agent. These cases add to the growing body of literature on ICI-iE, demonstrating two cases of meningoencephalitis associated with the novel agent dostarlimab treated successfully with prednisone. As imaging studies may be unrevealing, clinicians must maintain a high index of suspicion for ICI-iE in any patient who develops altered mental status on ICI therapy, with low threshold to obtain lumbar puncture for evidence of inflammatory CSF and to exclude other causes. It is important to note that many neurological presentations of ICIs can also be secondary to tumor metastasis and other paraneoplastic syndromes, making the diagnosis challenging. Prognosis can be good with early recognition and treatment with corticosteroids. Whether patients can be rechallenged with ICI is to be determined in larger studies given the rarity of this complication.

1. Introduction

Immune checkpoint inhibitors (ICIs) are being used increasingly in the treatment of several cancers and have been associated with neurological complications including immune checkpoint inhibitor-induced encephalitis (ICI-iE). We present two cases of ICI-iE with the novel agent dostarlimab, successfully treated with prednisone, which to our knowledge are the first reported.

2. Case 1

A 79-year-old man with metastatic pancreatic cancer on week 23 of treatment after 6 cycles of dostarlimab presented with generalized weakness, lethargy, and fluctuating alertness over one day. He had undergone an uncomplicated dental extraction with pretreatment and continuation of amoxicillin 6 days prior, with low-grade fever and lethargy on the third post-operative day. He was recently diagnosed with hypothyroidism on screening bloodwork and started on levothyroxine 50 μg/d 10 days prior to presentation. His past medical history was otherwise remarkable for diabetes mellitus, hypertension, and tumor-associated superior mesenteric vein thrombosis requiring anticoagulation with apixaban. On examination his temperature was 39 degrees Celsius and he was drowsy but rousable, inattentive, oriented to self but not to place or date. He had bradyphrenia but could name high and low frequency words to confrontation and follow 3-step commands with prompting. Cooperation was limited however there were no lateralizing signs. He was initially treated with broad spectrum intravenous antibiotics and acyclovir for suspected infectious meningoencephalitis. EEG was performed the following day which was normal with no focal abnormalities. Lumbar puncture was performed on day 4 after anticoagulation was held, demonstrating elevated protein (1.68 g/L) and lymphocytic (76%) pleocytosis (75 cells/uL). CSF, blood cultures and virology remained negative after 5 days. MRI obtained on day 7 (Fig. 1) showed diffuse confluent periventricular, subcortical, and deep white matter T2/FLAIR hyperintensities with no abnormal enhancement. Given high suspicion for ICI-iE, he was treated concurrently with prednisone (1 mg/kg) on day 2 with return to baseline cognition after 9 days and discharged uneventfully on slow prednisone taper over 12 weeks with no relapses at 3-month follow-up. Repeat MRI 1 month after discharge showed minimal progression of white matter changes (Fig. 1C, D).

3. Case 2

A 75-year-old female with grade 4 endometrial cancer on week 52 of palliative immunotherapy after 10 cycles of dostarlimab presented with fevers, generalized weakness, and fluctuating level of consciousness over one week. Her past medical history was significant for remote right thalamic lacunar stroke, small cell carcinoma previously excised from the forearm, diverticulitis, radiation colitis and recurrent urinary tract infections. On examination her temperature was 38 degrees Celsius and she was drowsy but rousable to voice, alert and oriented to name, place, and date. Language and speech were normal with regards to comprehension, fluency, and repetition. There were no meningeal signs and neurological examination was otherwise unremarkable. Blood and urine cultures were negative for growth. EEG showed mild to moderate generalized slowing with no focal or epileptiform abnormality. Lumbar puncture was performed on day 5 which showed elevated protein (1.09 g/L) and lymphocytic (97%) pleocytosis (30 cells/uL) with normal glucose, negative culture and virology. MRI head on day 6 (Fig. 2) revealed ill-defined abnormal signal involving the basal ganglia and thalamus bilaterally with associated vasogenic edema, raising the possibility of autoimmune encephalitis. Dostarlimab was stopped and she was treated with prednisone (1 mg/kg) with a 6 week tapering regimen. Cognitive function and repeat MRI were stable at 3-week follow-up. 6 weeks after discharge, she developed constipation, abdominal pain,

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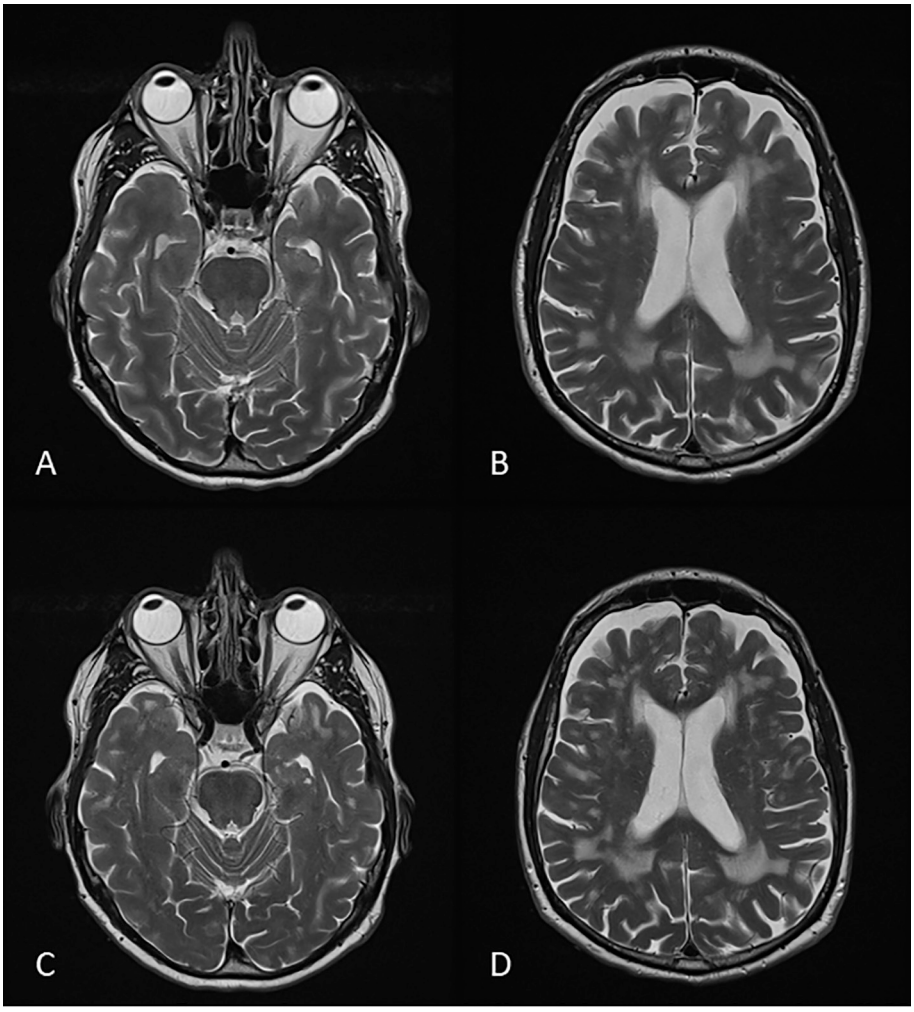

Fig. 1. Axial MRI Brain of Case 1 demonstrating non-enhancing patchy and confluent T2 hyperintensities in the periventricular deep white matter and subcortical bilateral cerebral hemispheres with some minimal progression from pre-treatment (A, B) and post-treatment with corticosteroids (C, D).

anorexia, and generalized weakness and was palliated in line with her advance directives (Table 1).

4. Discussion

Immune checkpoint inhibitors (ICIs), such as anti-programmed death-1 (PD-1) agents are being used increasingly in the treatment of several cancers [1]. Dostarlimab is an experimental humanized anti-PD-1 immunoglobulin G4 monoclonal antibody against the PD-1 receptor and is under investigational use in clinical trials [2] and have been a significant advancement in cancer care. ICIs have been associated with immune-related adverse events with a reported incidence of neurological complications in 2–6% [3]. Although ICI-iE is overall considered a rare complication, encephalitis has been found to be the most frequent neurological presentation with positive anti-Ma2 and anti-Hu antibodies, occurring in nearly half of these cases [4,5] although they were negative in both of our cases. A review in 2017 found that the median time of onset from start of therapy was 6 weeks [6] whereas in our cases it was 23 and 52 weeks, respectively. Interestingly, the MRI features of our second case with abnormal signal around the basal ganglia and thalami with associated edema (Fig. 1) has been reported with other cases of ICI-iE [5]. Other imaging findings of ICI-iE remain non-specific and include mesial temporal lobe or basal ganglia hyperintensities, or other areas of cortical and subcortical increased signal [6,7].

Treatment of ICI-iE includes stopping the ICI and often corticosteroids although the optimum dose and duration of therapy are not known. In line with many reported cases, our cases were treated successfully with oral prednisone 1 mg/kg with a slow taper and rapid resolution of symptoms. Both our cases did not experience any relapse of encephalopathy at 12 and 3 weeks follow-up. Our second case was transitioned to palliative care at 6-weeks with ICI therapy having been discontinued and repeat MRI remaining stable suggesting her deterioration was more likely related to cancer progression and possible bowel obstruction. Our first case has successfully weaned off prednisone with no recurrence of any neurological symptoms. An overview of the approach to management of ICI-iE is illustrated in Fig. 3.

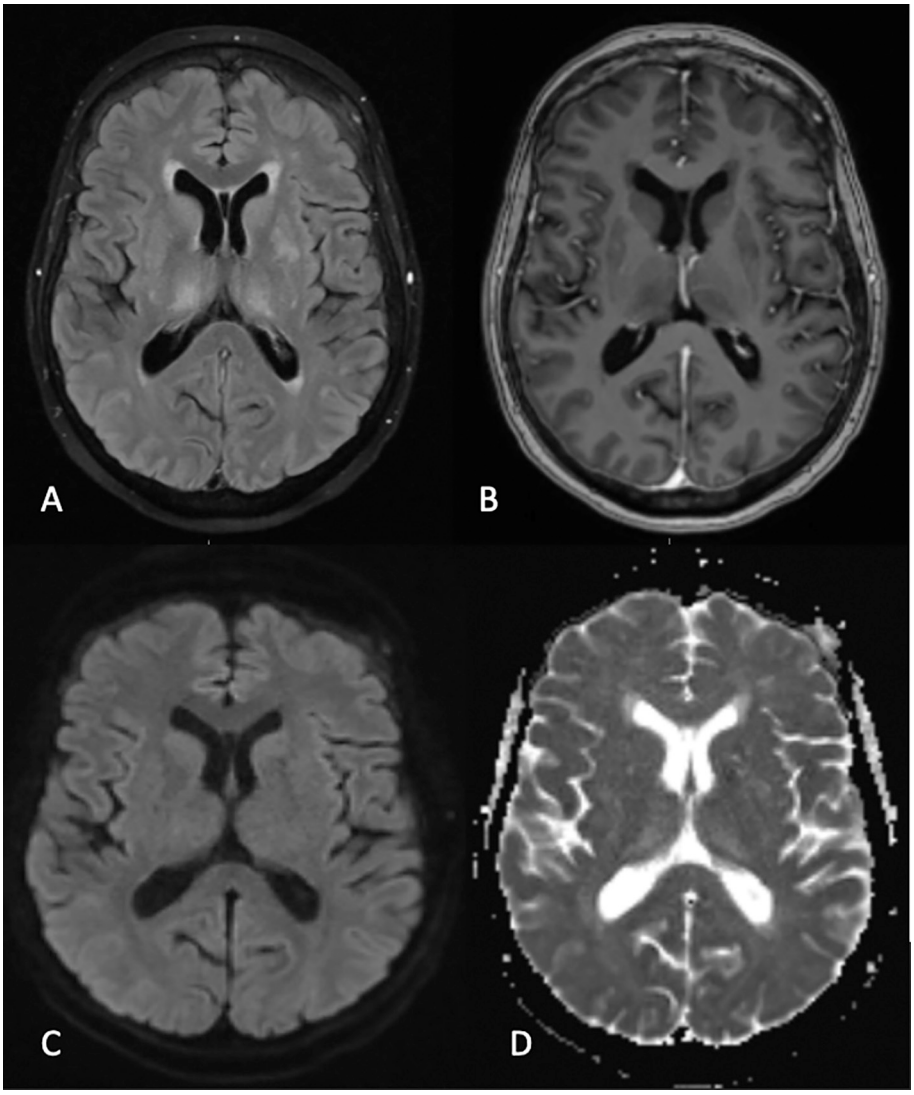

Fig. 2. Axial MRI Brain of Case 2 demonstrating T2-FLAIR hyperintensities around the basal ganglia and bilateral thalami (A). No abnormal enhancement was observed (B) and there were no areas of diffusion restriction (C, D).

5. Conclusion

These cases add to the growing body of literature on ICI-iE, demonstrating two cases of meningoencephalitis associated with the novel agent dostarlimab treated successfully with prednisone. MRI and EEG may be unrevealing, so clinicians must maintain a high index of suspicion for ICI-iE in any patient who develops altered mental status on ICI therapy, with low threshold to obtain lumbar puncture for evidence of inflammatory CSF and to exclude other causes. It is important to note that many neurological presentations of ICIs can also be secondary to tumor metastasis and other paraneoplastic syndromes, making the diagnosis challenging. Prognosis can be good with early recognition and treatment with corticosteroids, as demonstrated in both patients with resolution of encephalitis, although the second patient appeared to pass away from cancer progression rather than neurological sequelae. Whether patients can be rechallenged with ICI is to be determined in larger studies given the rarity of this complication.

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Non standard abbreviations

None.

Table 1
Outline of demographic and summary of investigations of the two cases presented.

	Case 1	Case 2
Age	79	74
Sex	Male	Female
Malignancy	Pancreatic	Endometrial
Checkpoint inhibitor	Dostarlimab	Dostarlimab
Onset of Symptoms (days after start date of therapy)	155 days	363 days
Week after first dose (cycle)	23 (cycle 6)	52 (cycle 10)
Clinical presentation	Fever, lethargy, decreased level of consciousness	Fever, nausea, vomiting, decreased level of consciousness
Magnetic Resonance Imaging (MRI)	Refer to Fig. 1	Refer to Fig. 2
Electroencephalogram (EEG)	Normal (Day 2)	Mild to moderate diffuse slowing (day 0)
Cerebrospinal Fluid Profile	*Day 4* Glucose 4.8 mmol/L Protein 1.68 g/L WBC 75 $\times$ 10^6 / L (76% lymphocytic)	*Day 5* Glucose 3.4 mmol/L Protein 1.09 g/L WBC 30 $\times$ 10^6 / L (97% monocytic)
Autoantibodies	*Encephalitis Panel*[a]: Negative (Mitogen Diagnostic Laboratories) *Paraneoplastic Panel*[b]: Negative (Mitogen Diagnostic Laboratories)	*Encephalitis Panel:* Negative (UBC neuroimmunology laboratories and Mitogen Diagnostic Laboratories) *Paraneoplastic Panel:* Negative (UBC neuroimmunology laboratories and Mitogen Diagnostic Laboratories)
Treatment	Prednisone 65 mg/d x 1 week (started on day 2) then 5 mg/week taper	Prednisone 70 mg/d x 1 week (started day 9) then 5 mg/week taper
Outcome	Resolved	Encephalitis resolved. Patient passed away secondary to cancer progression.
Follow-up period	12 weeks	6 weeks

[a] Encephalitis Panel = NMDA, VGKC (LGI1 and Caspr2), DPPX, AMPA, GABAB.
[b] Paraneoplastic Panel = Amphiphysin, PNMA2 (Ma2/Ta), CV2.1, Ri, Recoverin, SOX1, Titin, Yo, Hu, Zic4, GAD65 and Tr(DNER).

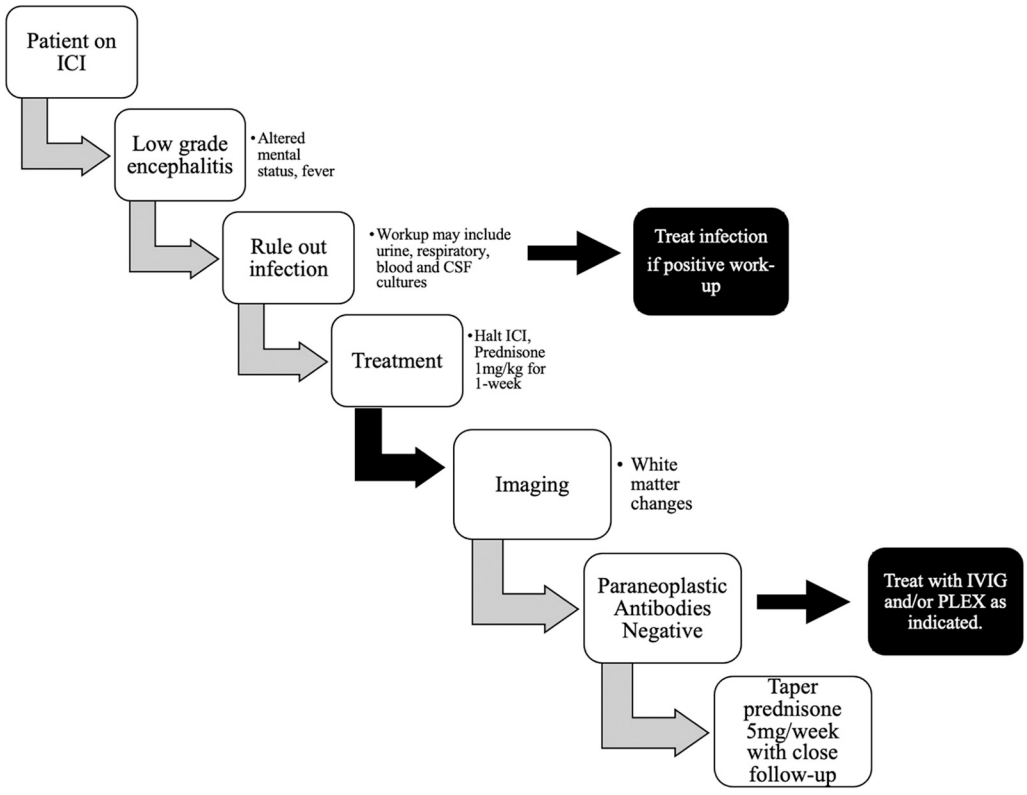

Fig. 3. Overview of the approach to diagnosis and treatment of immune checkpoint inhibitor related encephalitis.

Declaration of Competing Interest

Dr. Marzoughi has no competing interests or disclosures to report. Dr. Chen has no competing interests or disclosures to report.

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Sina Marzoughi*, Tychicus Chen
University of British Columbia, Department of Medicine, Division of Neurology, 8219-2775 Laurel St., Vancouver, BC V5Z 1M9, Canada

* Corresponding author.
E-mail addresses: Sina.marzoughi@ucalgary.ca (S. Marzoughi), tychicus@mail.ubc.ca (T. Chen).