Dual checkpoint inhibitor induced autoimmune encephalitis

Natalie Elkayam[1], Shaurya Sharma[1]

SUMMARY

Immune checkpoint inhibitor therapy has become increasingly more used as a treatment modality for solid organ tumors. Nivolumab, anti-PD-1 and Ipilimumab, anti-CTLA-4 monoclonal antibodies are checkpoint inhibitors with well described immune related toxicities. Immune specific neurotoxicity is rare and not well elucidated in literature. We present a case of severe autoimmune encephalitis in a patient with metastatic renal cell carcinoma treated with both Nivolumab and Ipilimumab. A 53-year-old man with metastatic renal cell carcinoma presented due to visual and auditory hallucinations of sudden onset, confusion and weakness. Initial imaging and diagnostic workup did not demonstrate a clear source. However, a neurological etiology was suspected. It was concluded that the patient had autoimmune encephalitis induced by dual check point inhibitor therapy. This was further strengthened by his rapid response to systemic corticosteroid therapy. We present a summary of this case and its management and a review of literature on dual checkpoint inhibitor induced neurological adverse effects.

KEY WORDS: Immunity; Encephalitis; Autoimmunity; PD-1 monoclonal antibody, CTLA-4 monoclonal antibody; Metastatic Cancer

Arch Oncol 2019; 25(2):22-4

Published Online
May 17, 2019
https://doi.org/10.2298/AOO181230003E

[1] Maimonides Medical Center, Department of Medicine, Brooklyn, New York, USA

Correspondence to:
Maimonides Medical Center, Department of Medicine, Brooklyn, New York, USA

Received **2018-12-30**
Received in revised form **2019-03-10**
Received in revised form **2018-03-24**
Accepted **2019-03-27**

INTRODUCTION

The use of immune checkpoint inhibitors (ICI) has become a routine in clinical treatment of melanoma, renal cell carcinoma, urothelial carcinoma and non-small cell lung cancer (1). Since this contemporary therapeutic method has become increasingly more common, new toxicities are being recognized. Neurological complications have been reported and are increasingly being recognized with an estimated frequency of 3.8%-4.2%. These neurological complications most commonly include neuromuscular ones (1, 2). Autoimmune encephalitis is an extremely rare complication attributed to administration of ICI. We will discuss a case of a patient with checkpoint inhibitor induced encephalopathy.

CASE PRESENTATION

A 53-year-old man with a past medical history of metastatic renal clear cell carcinoma presented due to an unwitnessed fall. He was found by his family - on the floor, awake and in pain. According to his family, he presented with altered mental status - visual and auditory hallucinations, weakness and decreased appetite. The family endorsed that over the week preceding his admission he began having these hallucinations. Previous to these episodes, the patient was fully baseline functional and lucid.

The patient has a history of right clear cell renal cell carcinoma that was diagnosed in 2015. In early 2016 he underwent a total right nephrectomy. Nine months after the surgery, a mass in his right psoas muscle was found, as a result of disease progression. He has been treated with Cabozantinib, but progressed under this treatment. Three weeks prior to his current presentation he started receiving Ipilimumab and Nivolumab.

Upon admision in the emergency room the patient was afebrile,with vital signs, cardiovascular and respiratory parameterswithin normal limits. Physical examination revealed a well appearing male, that was alert but not oriented in place or time. He was disoriented and talked in a confused manner.

Initial laboratory tests results showed significantly altered levels of calcium (3.35 mmol/L), white blood cell count (15.4 10^9/μL), hemoglobin (5.03 mmol/L), albumin (22 g/L) and parathyroid hormone (0.21 pmol/L). Serum TSH, vitamin B12 levels and ammonia were within normal limits. Results for respiratory viruses (from viral panel) and bacteria and yeasts (from blood cultures) were negative. Radiography of the chest showed no acute lung infiltrate. Computed tomography (CT) of the spine showed no acute fractures or dislocations. A head CT showed no acute intracranial pathologies. The patient was admitted based on hypercalcemia of malignancy and altered mental status and received saline infusion and calcitonin.

Due to the continuation of the patient's confused and altered mental state in spite of improved calcium levels, a magnetic resonance imaging (MRI) of the brain was performed to evaluate possible presence of metastases. Results of MRI showed no acute intracranial pathology and ruled out brain metastases.

The patient's hospitalization was complicated by his acute decline. He was found non-responsive to verbal stimuli, hypotensive (90/40 mmHg), with a high heart rate (140 beats/min) and tachypneic (45 breaths/min). The patient then underwent a lumbar puncture due to suspicion of bacterial meningitis. The cerebral spinal fluid (CSF) showed no cells after Gram staining. Bacterial and fungal cultures were negative, as well as levels of Cryptococcus antigen, Lyme disease antibodies and also herpes simplex levels. After cytological examination CSF was found negative for malignant cells. The CSF was colorless with a total protein of 0.39 g/L, and glucose of 4.22 mmol/L. N-Methyl-D-aspartic acid (NMDA) antibodies or other neuronal antibodies were not evaluated in the cerebrospinal fluid.

Electroencephalography (EEG) was performed and ruled out subclinical seizures. The patient was treated with high doses of dexamethasone, but had only mild improvement under this treatment. The treatment was switched to methylprednisolone resulting in significant improvement in his mental status. He became alert and oriented in place, but not in time. His mental status improved, but fluctuated.

DISCUSSION

Nivolumab, a PD-1 monoclonal antibody, and Ipilimumab, a CTLA-4 monoclonal antibody are immune checkpoint inhibitors. Immune checkpoint inhibitor therapy (ICIT) is becoming a common treatment modality for solid organ tumors, including melanoma (3), renal cell carcinoma (4), urothelial carcinoma (5) and non-small cell lung cancer (6, 7).

These checkpoint blockades enhance T-lymphocyte mediated anti-tumor immune response which can in turn lead to immune related adverse events (irAEs) (8). More commonly documented irAEs include thyroid dysfunction, colitis, pneumonitis and hepatitis (9). There has been an additional increase in the number of reported neurological adverse events likely due to increasing usage of ICIT for the treatment of various types of cancer. The full spectrum of neurological complications, their severity, evaluation and treatment are not completely elucidated.

Our patient presented with an acute change in his mental status. Other causes were evaluated such as infectious etiologies, space occupying lesions, toxins, subclinical seizures, hypercalcemia of malignancy and metabolic/toxic encephalopathy, which were all ruled out. Neurological irAEs could only be diagnosed by exclusion and in our opinion should be evaluated in all patients with similar presentation.

The diagnosis of autoimmune encephalitis can be obscured due to a combination of the rarity of its presentation (they are still rarely documented in literature) and also due to the varying range of symptoms. Neurological adverse events can affect central or peripheral nervous system and include non-specific symptoms such as fatigue, headache, vertigo, paresthesia, and dysgeusia, or specific symptoms that resemble clinical syndromes of myasthenia gravis (10), Guillain-Barre syndrome (11), peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy, transverse myelitis, meningitis (8), limbic encephalitis (12), and posterior reversible encephalopathy syndrome (13). The pathophysiology of neurological irAEs is unclear and may involve multiple mechanisms.

The diagnosis of neurological irAEs is difficult due to their presentation at various points during immunotherapy and also due to varying symptoms that do not fit to a particular diagnosis. Atypical features, memory loss, cognitive impairment, gait disturbance, neck rigidity, encephalitis and a variety of different manifestations that have been documented in literature can obscure its diagnosis (1). Clinical vigilance is paramount for diagnosis. In this particular case, presentation of patient was within two weeks of initiation of therapy. Patient presented with confusion, auditory and visual hallucinations, without any focal neurological deficits. The patient's condition significantly improved after steroid based therapy, supporting the diagnosis of autoimmune encephalitis.

No reliable markers or autoantibodies have been identified to be associated with irAE, with only rarely reported cases of anti N-methyl-D-aspartate antibodies titer (NMDA) in this matter (14, 15). NMDA receptors are expressed on the surface of melanocytes and tend to be associated with paraneoplastic syndrome in patients with melanoma (16). Anti-Ma2 antibodies are associated with paraneoplastic neurological syndrome causing autoimmune encephalitis; however, they have been associated with testicular cancer and small cell lung cancer, and have no known association with metastatic renal cell carcinoma (17). Cerebrospinal fluid of our patient was negative for both of these antibodies. In our opinion, irAEs should be considered as highly possible effect triggered by ICIT in cases of new onset of neurological syndromes of unknown or unclear etiology. It has already been confirmed that combination of PD1 and CTLA-4 ICIT increases the risk of incidence of neurological adverse events from 2.4 to 14 % (18).

The index of suspicion should be high in patients on ICIT. Prompt treatment should be initiated even if the symptoms are not conclusive towards a single diagnosis, with recommended treatment for severe neurological adverse events consisting of high doses of corticosteroids administered intravenously. Escalation of therapy may be indicated with anti-TNF α antibody agent (Infliximab), anti-CD20 antibody (Rituximab), or cyclosporine (19). Permanent discontinuation of ICIT is recommended in severe or life threatening irAEs.

CONCLUSION

There is limited information regarding the neurological adverse effects of immune checkpoint inhibitors. There are also varying information regarding the onset and progression of autoimmune encephalitis as a complication of immune checkpoint inhibitors, since adverse effects are not reported in great detail in phase III clinical trials. It is important to recognize such adverse effects in order to be timely caught and adequately treated. Although a rare side effect, neurological irAEs could become more frequent as immune checkpoint inhibitors are becoming more routinely used in the treatment of various solid tumors. Due to increased usage and prevalence of ICIT, prompt diagnosis of neurological irAEs requires clinical awareness and watchfulness. This case showed the importance of understanding this adverse event and catching it early in its course. Patients on treatment with ICIT should be educated and made aware of the possible adverse events. New neurological symptoms, even if nonspecific and atypical should be observed closely, and investigated in a proactive manner.

Declaration of Interests

Authors declare no conflicts of interest

REFERENCES

1 Feng S, Coward J, McCaffrey E, Coucher J, Kalokerinos P, O'Byrne K. Pembrolizumab-Induced Encephalopathy: A Review of Neurological Toxicities with Immune Checkpoint Inhibitors. Journal of Thoracic Oncology 2017;12(11):1626-1635. doi: 10.1016/j.jtho.2017.08.007

2 Kao JC, Liao B, Markovic SN, Klein CJ, Naddaf E, Staff NP, Mauermann ML. Neurological Complications Associated With Anti–Programmed Death 1 (PD-1) Antibodies. JAMA Neurology 2017;74(10):1216. doi: 10.1001/jamaneurol.2017.1912

3 Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Hamid O. Pembrolizumab versus Ipilimumab in Advanced Melanoma. New England Journal of Medicine 2015;372(26):2521-2532. doi: 10.1056/nejmoa1503093

4 Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Gurney H. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. New England Journal of Medicine 2015;373(19):1803-1813. doi: 10.1056/nejmoa1510665

5 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J, Fong L, Quinn DI. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. New England Journal of Medicine 2017;376(11):1015-1026. doi: 10.1056/nejmoa1613683

6 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, Arén FO. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. New England Journal of Medicine 2015;373(2):123-135. doi: 10.1056/nejmoa1504627

7 Decatris MP, O'Byrne KJ. Immune checkpoint inhibitors as first-line and salvage therapy for advanced non-small-cell lung cancer. Future Oncology 2016;12(15):1805-1822. doi: 10.2217/fon-2016-0086

8 Bot I, Blank CU, Boogerd W, Brandsma D. Neurological immune-related adverse events of ipilimumab. Practical Neurology 2013;13(4):278-280. doi: 10.1136/practneurol-2012-000447

9 Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, Chow LQ. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. The Lancet Oncology 2016;17(7):956-965. doi: 10.1016/s1470-2045(16)30066-3

10 Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro-Oncology 2014;16(4): 589-593. doi: 10.1093/neuonc/nou001

11 Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barre syndrome in a melanoma patient. Annals of Oncology 2011;22(4):991-993. doi: 10.1093/annonc/mdr028

12 Salam S, Lavin T, Turan A. Limbic encephalitis following immunotherapy against metastatic malignant melanoma. BMJ Case Reports 2016:2016215012. doi: 10.1136/bcr-2016-215012

13 Posterior reversible limbic encephalopathy syndrome during ipilimumab therapy for malignant melanoma. Maur M, Tomasello C, Frassoldati A, Dieci MV, Barbieri E, Conte P. 2012, J Clin Oncol, Vol. 30, pp. 76-78.

14 Williams TJ, Benavides DR, Patrice K, Dalmau JO, de Ávila ALR, Le DT, Mowry EM. Association of Autoimmune Encephalitis With Combined Immune Checkpoint Inhibitor Treatment for Metastatic Cancer. JAMA Neurology 2016;73(8) doi: 10.1001/jamaneurol.2016.1399

15 Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, Carpentier AF. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. European Journal of Cancer 2017;73:1-8. doi: 10.1016/j.ejca.2016.12.001

16 Wei X, Walia V, Lin JC, Teer JK, Prickett TD, Gartner J, Samuels Y. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. Nature Genetics 2011;43(5):442-446. doi: 10.1038/ng.810

17 Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. Journal of Neurology 2010;257(4):509-517. doi: 10.1007/s00415-009-5431-9

18 Neurotoxicity from immune checkpoint inhibition in the treatment of melanoma: a single center experience and review of literature. Spain L, Walls G, Julve M, et al. 2016, Ann Oncol, Vol. 28, pp. 377-385.

19 Blackmon J, Viator T, Conry R. Central nervous system toxicities of anti-cancer immune checkpoint blockade. Journal of Neurology and Neuromedicine 2016;1(4):39-45. doi: 10.29245/2572.942x/2016/4.1040