# Pembrolizumab-induced Autoimmune Encephalitis: A Case Report and Discussion

Maher Almatrafi, MBBS and Katy LaLone, MD
University Hospitals Cleveland Medical Center, Cleveland OH

## BACKGROUND

Over the past decade, immune checkpoint inhibitors (ICPis) have revolutionized the treatment of advanced lung cancers. Among them anti-programmed cell death protein 1 (PD-1) and programmed-death ligand 1 (PD-L1) inhibitors have demonstrated remarkable clinical responses with improvement in overall survival in patients with advanced non-small cell lung cancer (NSCLC). [Figure 1] As such, anti-PD-1 inhibitors like pembrolizumab are now considered first-line treatments for patients with PD-L1-positive tumors. However, ICPis may be associated with immune-related adverse events, including autoimmune encephalitis (AIE), which is rare but a potentially fatal complication.

## CASE REPORT

A 61-year-old male with history of alcohol abuse, COPD, was diagnosed May 2019 with widely metastatic stage IVB NSCLC complicated by cerebral vasogenic edema requiring urgent whole brain radiation therapy (WBRT). He was subsequently treated with three cycles systemic chemotherapy plus pembrolizumab and then continued maintenance therapy with pemetrexed and pembrolizumab from October 2019 to November 2020 then transitioned to pembrolizumab monotherapy due to functional decline and falls.

Referred to outpatient psycho-oncology in August 2019 for management of alcohol use disorder, anxiety, and was noted to have some mild short-term memory deficits following WBRT. [Figure 2] He was treated with gabapentin and naltrexone with improvement in anxiety as well as reduction in alcohol and tobacco use.

In December 2020 at follow-up visit, noted to have somber mood, weight loss, increasing fatigue, cognitive decline, missing medications 2-3 days per week. He notably weaker, reported multiple falls, and now requiring a cane.

In January 2021, he presented to ED with worsening confusion, poor PO intake, new urinary incontinence, decreased responsiveness, staring, wandering around the house, bizarre behavior. Initial workup unremarkable apart from suspected UTI and abnormal TSH/T4. MRI Brain without contrast revealed a punctate area of diffusion restriction in right putamen and post radiation therapy white matter changes. [Figure 3] Clinical impression was multifactorial encephalopathy due to metabolic derangements, previous brain radiation, chronic alcohol use and UTI.

**Week 1 of Hospitalization:** Empirical treated with antibiotics for UTI, thiamine, lorazepam for presumed alcohol withdrawal, and levothyroxine for hyperthyroidism. He did not show any clinical improvement.
**Week 2:** immune-mediated encephalitis suspected by oncology team who empirically started IV methylprednisolone on day 8. His cognition notably improved after couple days.
**Week 3:** IV methylprednisolone transitioned to prednisone taper and patient was discharged to acute rehab.
**6 weeks Post-discharge:** Patient seen for follow up in psycho-oncology clinic ambulating with walker, in good spirits, with marked improvement in mentation noted on Montreal Cognitive Assessment (MoCA). [Figure 4]

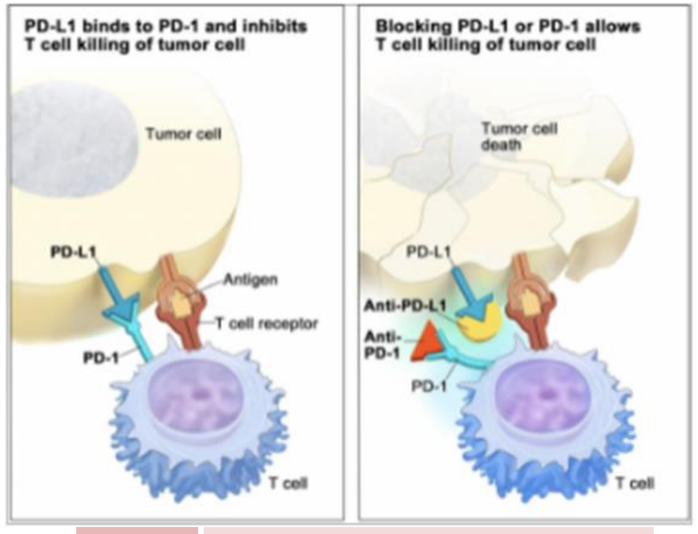



**FIGURE 1** Immune checkpoint inhibitors, PD-1, PD-L1

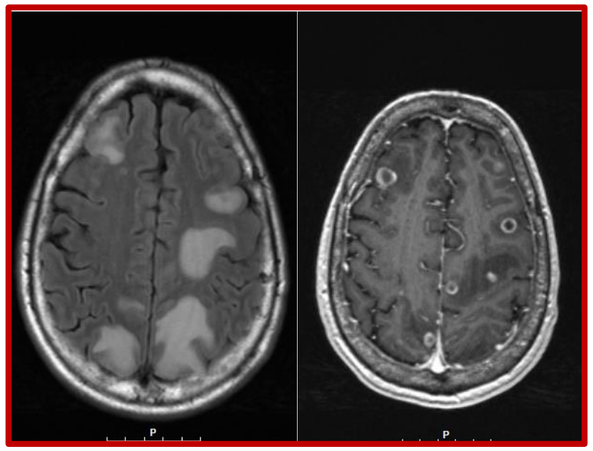


**FIGURE 2**

**MRI Brain May 2019:** Peri-tumoral edema but no white matter changes; innumerable metastases

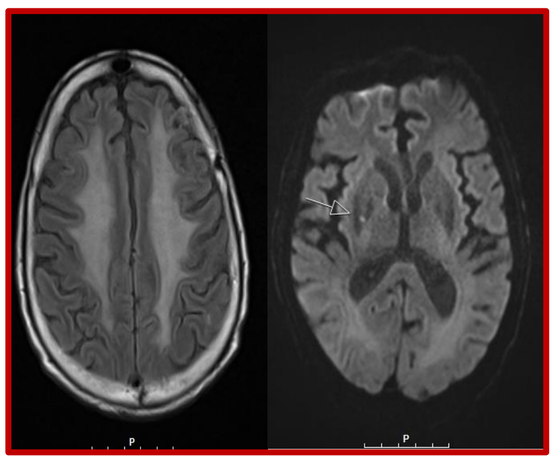
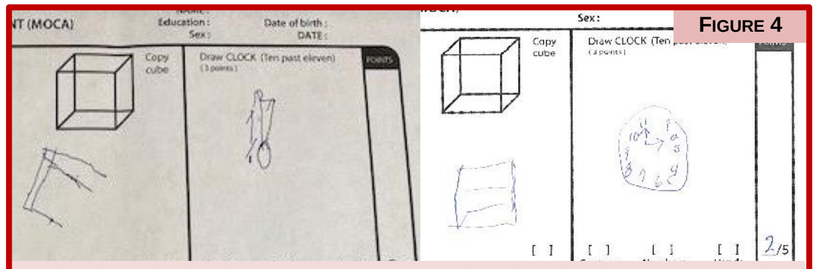


**FIGURE 3**

**(Left)** White matter changes; leukencephalo-pathy)

**(Right)** Right putamen infarct

**FIGURE 4**




**During hospitalization MoCA 14/30** **6wks after discharge MoCA 21/30**

## DISCUSSION & CONCLUSIONS

- Our literature search revealed only a few published case reports of autoimmune encephalitis in patients with lung cancer following anti-PD 1 inhibitor therapy. Immune checkpoints function to maintain self-tolerance and prevent autoimmunity. Due to their unique mechanism of action, ICPIs may be associated with immune-related adverse events although fortunately neurologic complications like AIE occur in less than 1% of patients.

- The diagnosis of AIE can be challenging and is largely based on clinical history and presentation. Onset may be acute or subacute occurring months to even years into treatment course. Management includes cessation of anti-PD-1 inhibitor therapy and initiation of immunosuppressive therapy with corticosteroids, plasma exchange, IVIG, and/or tumor necrosis factor-alpha inhibitors. Responses to treatment appear to vary and not all patients will have a meaningful recovery.

- While autoimmune encephalitis following anti-PD-1 inhibitor therapy is rare, prompt recognition and initiation of treatment can be life-saving.

- As anti-PD-1 inhibitors are becoming standard therapy for an increasing number of oncologic diseases, the consult-psychiatrist should be familiar with its clinical presentation and management.

- Clearly, more research is needed to help clarify diagnostic criteria and optimal management guidelines.

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