Small Cell Lung Cancer-Associated Paraneoplastic Autoimmune Encephalitis with Isolated Anti-Zic4 Antibodies

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Introduction

• Paraneoplastic autoimmune encephalitis (PAE) is a rare and serious manifestation of paraneoplastic syndromes (PNS), in which the immune system erroneously targets neuronal tissues, leading to brain inflammation.

• This condition is often associated with small-cell lung cancer (SCLC), a malignancy known for its rapid progression and early metastasis.

• Several neuronal antibodies have been associated with PAE, including anti-Yo, anti-Hu, anti-Tr/DNER, and more rarely, anti-Zic4.

• Zic4 is a zinc-finger protein that plays a part in cerebellar development, and they are expressed during the development and maturation of the central nervous system.

• Anti-Zic4 antibodies have been affiliated with paraneoplastic cerebellar degeneration (PCD).

• Patients with isolated Zic4 antibodies are more likely to develop severe cerebellar dysfunction than those with concurrent immunities.

• Here we present a case of SCLC-associated autoimmune encephalitis with isolated positive anti-Zic4 antibodies who presented with signs and symptoms of PCD, highlighting the challenges in diagnosis and management.

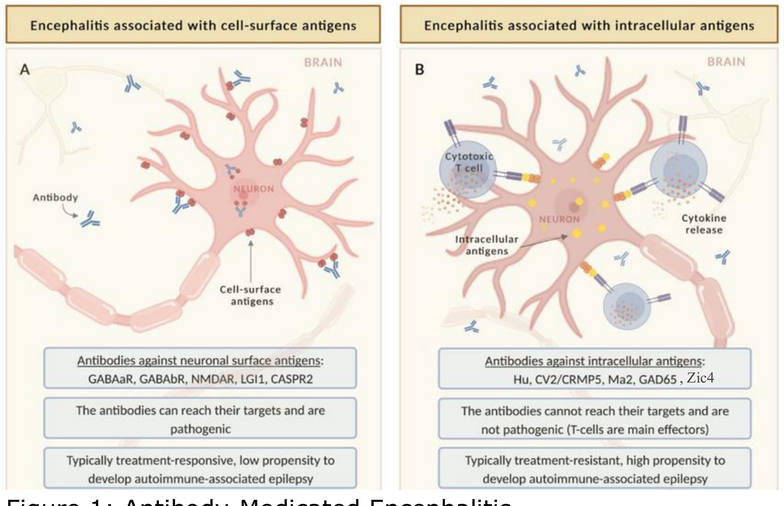

Figure 1: Antibody-Medicated Encephalitis

Physical Exam

Initial physical exam findings were generally unremarkable other than for intermittent dysarthria and buccal oral dyskinesias. She was alert and oriented x 4, and her initial vitals were stable with a blood pressure 126/85, heart rate 94, afebrile, and saturating well on room air.

Case

A 56-year-old woman with a past medical history of small cell lung cancer with metastasis to the liver and diabetes presented to the emergency department with tongue numbness and encephalopathy. The patient stated that she was having abnormal tongue movements with numbness and tingling for a few days. She endorsed symptoms of dysarthria and buccal oral dyskinesias. The patient was also recently hospitalized at a different hospital for similar symptoms but was discharged home, considered to be in stable medical condition. The family described a progressive cognitive decline for a few days, along with intermittent bilateral tremors. Regarding her current presentation, she denied any fevers, chills, or sick contacts. She denied starting any new medications. The patient was initially admitted to the observation unit, but after discussion with neurology and the medical team, the decision to admit the patient to the general medical floor was made.

Clinical Course

- Initial CT and MRI of the brain were unremarkable, and EEG did not demonstrate seizure activity.
- Labs just demonstrated a slight leukocytosis, with no metabolic derangements.
- Neurology was consulted and suggested possible PNS, and she was empirically treated for metabolic and infectious encephalopathy.
- Her condition worsened despite seizure prophylaxis and medical therapy. She developed opsoclonus, nystagmus, and severe agitation.
- Eight days after hospitalization, the patient developed hypoxic respiratory failure, was intubated, and admitted to the ICU.
- She was prophylactically covered with ceftriaxone, ampicillin, vancomycin, and acyclovir due to concerns of meningitis.
- The patient then underwent a lumbar puncture, and CSF analysis showed pleocytosis and extensive workup for infectious causes were negative. High-dose steroids were administered without effect.
- Paraneoplastic antibody testing was ultimately positive for isolated anti-Zic4 antibodies.
- Other complications during her hospital stay included ventilator-associated pneumonia and unsuccessful weaning from the ventilator requiring a tracheostomy.
- IVIG and plasmapheresis were considered, however, given her poor prognosis, her family chose comfort measures, and she expired shortly afterward. A brain biopsy was also performed and was negative for prion disease.

Discussion

- This case illustrates the diagnostic complexity and rapid progression of PAE, particularly when associated with rare and isolated anti-Zic4 antibodies.
- While anti-Zic4 antibodies are often seen with other paraneoplastic antibodies, isolated positivity can independently cause severe cerebellar dysfunction.
- Our patient's nonspecific early symptoms delayed definitive diagnosis and immunotherapy.
- Her course emphasizes the importance of early suspicion and expedited antibody testing in cancer patients with ambiguous neurologic symptoms.

Conclusion

There has to be a high level of suspicion for paraneoplastic autoimmune encephalitis in patients with previously diagnosed malignancy presenting with nonspecific neurological symptoms. The nonspecific nature of presentation and overlap with metabolic derangements or psychiatric illness often leads to delayed diagnosis. Early diagnosis and treatment with immunomodulatory therapy may improve outcomes. This case emphasizes the importance of early recognition, multidisciplinary management, and therapeutic challenges in treating a patient with paraneoplastic autoimmune encephalitis.

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