Case Report

Lung cancer masquerading as a paraneoplastic neurologic syndrome without a primary lung mass: Case report and review of literature

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ABSTRACT

Paraneoplastic and autoimmune encephalitis (AIE) syndromes describe a range of inflammatory disorders of the brain. “Classic” paraneoplastic encephalitis syndromes occur due to a remote neoplasm and are associated with antibodies that target intracellular neuronal proteins while the more recently described AIE syndromes are not always paraneoplastic and occur in association with antibodies that target cell-surface neuronal receptors (e.g., anti-NMDA receptor, anti-LGI1, anti-GABA<sub>B</sub> receptor). Diagnosis can be difficult and delayed due to nonspecific clinical, imaging, and laboratory findings, and in those syndromes associated with a neoplasm, the neurologic syndromes often precede the cancer diagnosis. We present a case of a 64-year-old patient diagnosed with anti-GABA<sub>B</sub> receptor encephalitis that subsequently revealed an underlying small cell lung cancer without a primary lung tumor. This case highlights the clinical challenge in diagnosing immune-mediated encephalitis, its methodical work up, and subsequent management.

KEY WORDS: Autoimmune encephalitis, encephalopathy, paraneoplastic encephalitis, small cell lung cancer

INTRODUCTION

Paraneoplastic and autoimmune encephalitis (AIE) are rare neurological syndromes characterized by acute or subacute onset of personality changes, cognitive decline, short-term memory loss, and seizures. Many of these cases are associated with antineuronal antibodies secondary to an underlying cancer. Patients with AIE previously referred to as “seronegative” may test positive for autoantibodies to neuronal extracellular epitopes, such as the voltage-gated potassium channel (VGKC) complex, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, N-methyl-D-aspartate receptor, and gamma aminobutyric acid B receptor. The management includes immunotherapy and treatment of the underlying cancer.

CASE REPORT

A 64-year-old patient with the past medical history of hypertension, bipolar disorder, anxiety, untreated hepatitis...
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C, and extensive tobacco use presented to our county hospital with several days of word-finding difficulties, disorientation, and memory problems at home. The patient was initially admitted to an outside hospital a few days prior for newonset seizures attributed to abrupt discontinuation of her home benzodiazepines and started on valproic acid. On physical exam, the patient was oriented only to self, delirious, and following some commands though without any focal neurologic deficits. Preliminary work-up was overall unrevealing and included no significant laboratory abnormalities and urine drug screen only positive for cannabinoids. Magnetic resonance imaging (MRI) of the brain [Figure 1, arrow] showed encephalomalacia of the anterior right temporal lobe and right frontal lobe without evidence of meningoencephalitis, and electroencephalogram (EEG) showed continuous symmetric diffuse 4–7 Hz theta background and superimposed beta frequencies without any specific localization.

The patient’s encephalopathy was initially attributed to a medication side effect from valproic acid versus a manifestation of her underlying psychiatric disorder, and all medications were held. The patient remained confused and delirious, and on day 3 of hospitalization, she had a witnessed generalized tonic–clonic seizure lasting approximately 2 min and was started on antiepileptic drugs (AEDs). Etiology was again thought to be benzodiazepine withdrawal with encephalomalacia noted on MRI as the seizure focus, but despite being on multiple AEDs, the patient continued to have seizure episodes.

Autoimmune work-up was initiated and unremarkable, and lumbar puncture was performed to investigate possible infectious causes of her encephalopathy and seizures. The cerebrospinal fluid (CSF) studies revealed a lymphocytic pleocytosis, mild elevation in protein, normal glucose, negative cytology, and negative infectious studies (including VDRL, EBV, HSV). Given the lymphocytic pleocytosis, consideration was given to an autoimmune or paraneoplastic encephalitis, and the patient was empirically started on high-dose intravenous corticosteroids and intravenous immunoglobulin (IVIG).

Computed tomography (CT) of chest, abdomen, and pelvis did not reveal an underlying neoplasm.

Given the limitations of the laboratory at the hospital and the diagnostic uncertainty, the CSF studies were sent for the Mayo Clinic Encephalitis Panel, which returned positive for antibodies to the GABA<sub>B</sub> receptor, confirming the diagnosis of anti-GABA<sub>B</sub> receptor AIE. We had a high suspicion for lung cancer in our patient with a history of extensive tobacco use as prior studies have shown significant association of anti-GABA<sub>B</sub> receptor encephalitis and small cell lung carcinoma. Even though initial CT scanning was unremarkable, positron emission tomography – computed tomography (PET-CT) [Figure 2] confirmed increased fluorodeoxyglucose (FDG) uptake in the left hilar and subcarinal lymph nodes without a primary lung mass. An endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed on a station 11 L (left hilar) lymph node that revealed pathology consistent with small cell carcinoma positive for synaptophysin stain [Figure 3a and b].

Our patient initially received high-dose intravenous corticosteroids and IVIG with minimal improvement in her encephalopathy. Even with later addition of plasma exchange (PLEX), she remained altered compared to baseline and unable to perform activities of daily living. Although tumor resection was not an option, our patient did receive one cycle of carboplatin and etoposide. However, given her poor functional status and poor prognosis, the patient was subsequently transitioned to hospice.

**DISCUSSION**

The clinical diagnosis of AIE can be challenging as it can manifest with several distinct syndromes and many cases

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**Figure 1:** Magnetic resonance imaging (T2 flare) showing encephalomalacia of the right anterior temporal lobe and right frontal lobe

**Figure 2:** Positron emission tomography – computed tomography images showing an ill-defined left hilar lymph node (station 11 L, dotted blue arrow) measures approximately 1.2 cm x 1.0 cm with a standardized uptake value of 11.5, and a subcarinal lymph node (white arrow) measuring 1.4 cm x 1.5 cm with a maximum standardized uptake value of 13.4
A large proportion of cases of anti-GABA<sub>B</sub> receptor, and anti-AMPA receptor encephalitis, Although seizures [13] B receptor AIE include loss of recent [8-11] receptor AIE is caused by antibodies In [1-3] [3,7] However, the relationship receptor AIE who do GABA<sub>B</sub> receptors in the limbic system and has a The most commonly reported symptoms receptor AIE, the percentage of cases with GABA<sub>B</sub> B receptor are G-protein-coupled receptors that represent inhibitory synaptic proteins in neurons. They are located in the central and peripheral nervous systems with high prevalence in the hippocampus, amygdala, thalamus, and cerebellum. The most commonly reported symptoms of anti-GABA<sub>B</sub> receptor AIE include loss of recent memory, seizures, personality changes, and altered level of consciousness. Occasionally, patients can manifest features of opsoclonus-myoclonus and cerebellar ataxia given the high prevalence of GABA<sub>B</sub> receptors in the cerebellum. [15,16] A large proportion of cases of anti-GABA<sub>B</sub> receptor AIE have an underlying malignancy with small cell lung cancer being the most common etiology. Other cancers often implicated in paraneoplastic encephalitis are lung cancers, testicular cancers, thymomas, teratomas, and Hodgkin’s lymphoma. In two small case series of anti-GABA<sub>B</sub> receptor AIE, the percentage of cases with a paraneoplastic etiology ranged from 30% to 50%. In another large case series of patients with anti-GABA<sub>B</sub> receptor AIE, 27 out of 47 patients (58%) had an underlying diagnosis of small cell lung cancer. [13,20,22] In this series, the median age of patients in the paraneoplastic group was higher when compared to the nonparaneoplastic group.

Work-up for malignancy should be initiated in any patient for which there is a strong suspicion for AIE. For patients with antibodies associated with the “classic” paraneoplastic encephalitis syndromes (e.g., anti-Hu, anti-Yo, anti-Ri), there is almost invariably an underlying neoplasm, but AIE can be paraneoplastic as well. Even in the absence of obvious malignancy like in this case, aggressive pursuit of possible malignancy with pathologic diagnosis is important to facilitate timely and appropriate treatment. Patients with anti-GABA<sub>B</sub> receptor AIE who do not have any underlying malignancy should be followed closely as the neurological syndrome may precede the development of malignancy. The mechanism of SCLC-associated autoimmune responses remains unclear; proposed mechanisms include abnormal self-antigen expression in tumor cells or mutation of the antigenic protein to those foreign to the immune system. [23] The optimal treatment for anti-GABA<sub>B</sub> receptor AIE remains unclear, and there are no randomized-controlled trials on the appropriate management. The main therapeutic strategies include immunomodulating therapy, immunosuppressive therapy, tumor resection,
and chemotherapy. In addition to appropriate treatment of underlying malignancy, first-line immunotherapy generally consists of a combination of corticosteroids, IVIG, and/or PLEX. In patients not responding to initial therapies, second-line therapies include rituximab, cyclophosphamide, or both. A systematic review of retrospective studies showed that AIE patients with immune therapy generally do better and relapse less than patients without therapy. However, a later study by Zhang et al. showed no significant difference in outcomes among patients treated with immunotherapy. Treatment for malignancy when present can include tumor resection and/or chemoradiotherapy.

The prognosis of GABA \(_B\) receptor-associated AIE also remains unclear. Most patients respond well to early diagnosis with institution of immunotherapy and treatment of underlying cancer, but others have a poor response to treatment resulting in poor prognosis. Most recently, a retrospective case series found status epilepticus, acute respiratory failure, and/or involvement of the limbic system are all associated with a worse prognosis.

**CONCLUSION**

This case presents a unique challenge in the diagnosis of a paraneoplastic neurological syndrome without a primary tumor and highlights the importance of a methodical work-up and high index of suspicion in the pursuit of underlying primary malignant process. The understanding of these syndromes is critical because delayed recoveries and suboptimal outcomes can result without treatment approaches to downregulate the immune response in the CNS.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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