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$GABA_BR$-Mediated Paraneoplastic Limbic Encephalitis Due To Thymic Small Cell Carcinoma

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We report the case of a 55-year-old male who presented with several weeks of seizures, agitation, progressive confusion, and receptive aphasia. CSF showed a monocytic pleocytosis and tested positive for $GABA_B$ receptor autoantibodies. Pathological examination of an excisional mediastinal lymph node biopsy showed thymic small cell carcinoma, supporting a diagnosis of paraneoplastic limbic encephalitis (PLE). PLE is a subtype of limbic encephalitis and is associated with an array of autoantibodies. Neurologic symptoms related to PLE may precede the detection of the primary cancer. Recognition of the constellation of clinical features of limbic encephalitis should prompt initiation of diagnostic testing for this condition as well as evaluation for an underlying malignancy. A review of the literature reveals that this is the first case report of a patient with thymic small cell cancer presenting with PLE.

KEY WORDS: paraneoplastic; limbic encephalitis; thymic small cell carcinoma; $GABA_BR$ antibody.

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CASE PRESENTATION

A 55-year-old male with a history of coronary artery disease, tobacco abuse, and anxiety presented with an episode of bilateral upper and lower extremity tremor associated with loss of consciousness and subsequent hour-long period of confusion. He was diagnosed with a benzodiazepine withdrawal seizure and he was discharged on levetiracetam. Over the following days, the patient's wife observed that he continued to have difficulty conversing as well as ongoing sleep disturbance, agitation, and hallucinations. He was readmitted and a lumbar puncture was performed which showed a monocytic pleocytosis. CSF culture and meningitis/encephalitis nucleic acid detection testing were negative for infectious etiology. EEG revealed epileptiform abnormalities in bilateral temporal lobes and a brief electrographic seizure in the right temporal region. Brain MRI showed a small meningioma and symmetric T2 prolongation within the hippocampi without abnormal enhancement. CT chest showed conglomerate lymphadenopathy encasing the pulmonary artery, right hilar lymphadenopathy, and a peripheral left lung mass that seemed to be consistent with a hamartoma. Mediastinoscopy and lymph node (LN) biopsy were performed. Post-operatively, the patient continued to be combative and agitated with hallucinations. He was intubated for airway protection and transferred to our hospital for further care.

On admission, he had normal vital signs. He was awake but not oriented and unable to follow commands. Neurologic exam was notable for dysarthria and global aphasia with perseveration. Viral testing and rheumatologic testing were unremarkable (Table 1). A serum autoimmune evaluation panel was notable for $GABA_B$ receptor Ab ($GABA_BR$) positivity (Mayo Medical Laboratories) (Table 2). Additionally, a CSF autoimmune evaluation panel was positive for $GABA_BR$ Ab with a 1:256 titer (normal < 1:2)(Mayo Medical Laboratories). Pathology from the excisional mediastinal LN biopsy showed sheets of neoplastic cells with scant cytoplasm, high nuclear to cytoplasm ratio, and round to oval nuclei with irregular nuclear membrane (Fig. 1). Tumor necrosis and > 60 mitotic figures/10 high-power fields were also present. IHC staining was positive for AE1/AE3, synaptophysin, CD56, and PAX-8, and negative for chromogranin-A and TTF-1. Additional in-house stains showed positivity to p-40, CD5, and CK5/6. Morphology, strong diffusely positive CD56 and synaptophysin IHC staining and negative IHC staining for p-40 and CK 5/6 were consistent with a diagnosis of small cell carcinoma. Positive PAX-8 staining in combination with negative TTF-1 staining was consistent with thymic origin of small cell carcinoma.

The patient was treated with two courses of IVIG, plasma exchange, and two doses of rituximab with the goal of reducing autoantibody titers. Four cycles of cisplatin plus etoposide chemotherapy were administered to treat the underlying malignancy with the intention of treating the inciting etiology. He continued to have episodes of agitation and hallucinations, requiring intermittent restraints, constant direct supervision, and psychotropic medications. Radiation treatment of mediastinal lymphadenopathy was precluded by difficulty controlling the patient's behavior and his inability to follow instructions reliably. The hospital course was further complicated by status epilepticus requiring intubation and intensive anti-epileptic medication escalation. Ultimately, he was transitioned to comfort care and died.

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Table 1 Viral Testing and Rheumatologic Testing

Test Name	Test result
Hepatitis serology (A-C)	Negative
Epstein Barr virus (EBV)	Negative
Cytomegalovirus (CMV)	Negative
Herpes Simplex Virus (HSV)	Negative
HIV	Negative
DS-DNA	Negative
Rheumatoid Factor (RF)	Negative
SCL-70 antibody	Negative
Anti-Smith antibody	Negative
SS-A/Ro antibody	Negative
SS-B/La antibody	Negative
Antineutrophil antibody (ANA)	Negative
Antineutrophil cytoplasmic antibodies (ANCA)	Negative

DISCUSSION

Limbic encephalitis (LE) is characterized by memory loss, confusion, seizures, behavioral disturbance and personality changes. Initial workup of LE includes evaluation for infection, primary autoimmune disorders and toxic-metabolic causes. Evaluation of occult malignancy by imaging (CT or PET/CT) may be indicated in absence of alternative etiology. CSF analysis is often normal but can show a pleocytosis. Brain MRI may show increased T2 signal in the medial temporal lobes (unilateral or bilateral) but is not reliably sensitive or specific enough to make the diagnosis. It has been suggested that FDG-PET/CT may be more sensitive than MRI in early detection of limbic encephalitis; however, characteristic patterns have not been fully delineated.[1–3] EEG can be helpful in diagnosing subclinical seizures and in excluding other diagnoses that may have characteristic findings. Testing for autoantibodies in serum and CSF should be performed if an alternative etiology is not identified.

Autoimmune limbic encephalitis is caused by autoantibodies directed towards extracellular or intracellular antigens resulting in either a humoral or T cell–mediated inflammatory response. Over the past several years, a variety of antibodies have been described in the literature with a spectrum of clinical phenotypes. Antibodies can be directed against onconeuronal and neuronal cell surface antigens. Examples of antibodies associated with paraneoplastic limbic encephalitis include Hu (ANNA-1), Ma2, CV2/CRMP5, AMPA receptor, $GABA_B$, GluR5, and NMDA receptor.[4, 5]

Table 2 Mayo Clinic Laboratories Encephalopathy, Autoimmune Evaluation Panel (Serum)

Test name	
GAD65 Ab, S	Anti-neuronal nuclear Ab, type 1
NMDA-R Ab CBA, S	Anti-neuronal nuclear Ab type 2
Neuronal (V-G) K+ channel Ab, S	Anti-neuronal nuclear Ab type 3
LGI1-IgG CBA, S	Anti-glial nuclear Ab, type 1
CASPR2-IgG CBA, S	Purkinje cell cytoplasmic Ab type 1
GABA-B-R Ab CBA, S	Purkinje cell cytoplasmic Ab type 2
AMPA-R Ab, CBA, S	Purkinje cell cystoplasmic Ab type Tr
Amphiphysin Ab, S	N-type calcium channel Ab
CRMP-5-IgG, S	P/Q-type calcium channel Ab
AChR ganglionic neuronal Ab, S	Ach receptor (muscle)-binding Ab

$GABA_BR$ antibody–associated encephalitis was first described in 2010 in a retrospective evaluation of serum and CSF from patients suspected to have limbic encephalitis.[6] Since then, several case series have been published further characterizing the disorder.[7–10] While patients may test positive for additional autoantibodies, it is the $GABA_B$ receptor antibody that is believed to confer the symptoms associated with paraneoplastic limbic encephalitis (PLE). The hippocampal and temporal regions of the brain are most affected resulting in the phenotype of altered behavior, memory deficits, mood disturbance, and epilepsy. While data is limited to several case series, severe seizures are a prominent presenting feature. A high $GABA_BR$ antibody titer has correlated with the risk of status epilepticus.[6]

Evaluation for associated cancer is recommended even before antibody testing has resulted. One case series of 50 patients demonstrated that the diagnosis of PLE preceded the diagnosis of cancer in about 60% of patients.[11] Malignancies that have been associated with PLE include lung cancer, testicular germ cell tumors, breast cancer, lymphoma, neuroendocrine tumor, ovarian teratomas, and thymoma.[4, 11] Up to one half of the patients reported with $GABA_BR$-mediated PLE were diagnosed with small cell lung cancer (SCLC).[6, 8] This is the first published case of thymic small cell cancer presenting as PLE.

Both thymic and small cell/neuroendocrine tumors from almost all sites can be associated with autoimmune neurologic sequelae, as was seen in this patient.[7, 12] Thymic neuroendocrine tumors are exceedingly rare neoplasms (1 case per 5 million cancers diagnosed) that present as an anterior mediastinal mass, and are sometimes associated with the hereditary MEN1 cancer syndrome.[13, 14] They are aggressive tumors that are associated with poor prognosis. One study of 254 patients with thymic neuroendocrine tumor showed a 5-year survival of 56%.[15] The mechanism by which these tumor types mediate humoral autoimmunity is unclear, but may relate to loss of negative selection of alloreactive clones in thymic malignancies, or abnormal neural self-antigen expression from neuroendocrine-derived malignancies.

Histology and immunohistochemical (IHC) staining were critical in making the diagnosis of primary thymic small cell carcinoma. Thymic neuroendocrine tumors (NETs) are classified as low/intermediate grade (typical carcinoid (TC) and atypical carcinoid (AC)) and high grade (large cell carcinoma and small cell carcinoma).[16, 17] Less than 5% of thymic neoplasms are classified as thymic NETs; of this subset, small cell carcinomas account for approximately 10%.[16] Although thymic small cell NETs are very rare, they portend a poor prognosis. Morphologic criteria are essential to differentiate between the subtypes of thymic NETs. Both TC and AC tumors have < 10 mitoses/10 high-power fields while small cell tumors have > 10 mitoses/10 high-power fields.[16] TC tumors lack necrosis, have uniform cells with identifiable

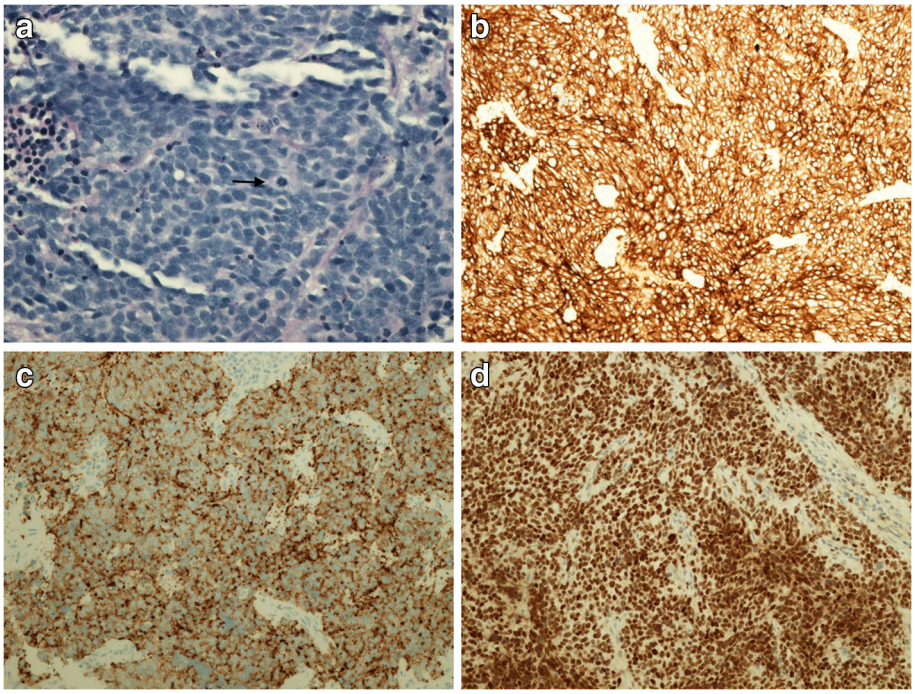

Figure 1 Excisional mediastinal lymph node biopsy. a H&E, × 40, with mitotic figure (arrow) and sheets of neoplastic cells with round to oval nuclei and high N/C ratio. b Strongly positive CD 56; representative of neuroendocrine differentiation. c Strongly positive synaptophysin staining; representative of neuroendocrine differentiation. d Positive PAX-8 staining favoring thymic carcinoma rather than lung carcinoma.

cytoplasm, < 2 mitoses/10 high-power fields, and often have identifiable architectural patters. AC tumors have focal areas of necrosis, 2–10 mitoses/10 high-power fields and architecture similar to typical carcinoid. Small cell NETs are composed of sheets of small round to oval cells with scant cytoplasm, high nuclear to cytoplasm ratio, frequent areas of necrosis, and numerous mitoses.[16, 17]

Positive IHC staining for neuroendocrine markers is helpful but is not mandatory for differentiating primary thymic small cell carcinoma from primary lung small cell carcinoma. TTF-1 positivity is noted in the majority of small cell lung carcinomas and absent in most thymic carcinomas.[16, 18–20] Almost all small cell lung carcinomas are negative for PAX-8 while PAX-8 staining is often positive in thymic carcinomas.[21, 22] Other malignancies on the differential were thymic squamous cell carcinoma, NUT carcinoma, or basaloid carcinoma, but they were determined to be less likely in this case given negative p-40 and CK 5/6 staining.

Given the dearth of randomized control trials, treatment recommendations of PLE are based on principles derived from case series and expert opinion.[23] Results of advanced antibody testing can be delayed, so treatment of PLE is usually initiated prior to serologic confirmation of the diagnosis. A dual-armed treatment approach is generally recommended, targeting both the underlying malignancy (if identified) and the autoimmune encephalitis. Treatment of the associated cancer is a priority in order to reduce the antigenic stimulus driving PLE.[23] If an associated tumor is not found, cancer screening at regular intervals has been recommended.[24] Concurrent immune modulation targeting paraneoplastic antibody production is also a mainstay of treatment. Intravenous steroids, IVIG, and plasma are first-line therapies.[23, 24] For those patients that do not respond to these measures, second-line treatments with immunosuppressant medications such as cyclophosphamide, cyclosporine, and rituximab are indicated.[23, 24] Chronic maintenance therapy can include IVIG and steroid taper over 6–8 months and an additional immunosuppressant such as azathioprine or mycophenolate mofetil.[23]

Clinical outcomes of LE are variable, and prognosis may depend on the cellular location of the antigenic target. One study of 77 patients with varying antibody-driven autoimmune encephalitis showed that nearly half had poor neurologic outcomes when assessed at long-term follow-up (mean duration 4.4 years).[25] Anti-NMDAR encephalitis is associated with better outcomes; with some studies demonstrating that > 80% of patients were classified as having good neurologic outcomes at long-term follow-up.[25, 26] The prognosis of PLE is difficult to characterize owing to its rarity, the limited availability of published data, and inherent variable outcomes of associated malignancies. However, the general consensus among experts is that neurologic recovery hinges on early identification and ability to successfully treat the underlying tumor.[11] Expedient initiation and subsequent escalation of treatment is also associated with better clinical outcomes.[24]

CONCLUSION

Altered mental status is a common condition for which patients are admitted to the hospital and encompasses a wide

spectrum of etiologies. Recognition of the constellation of seizure, cognitive changes, and behavioral disturbance should prompt consideration of diagnostic testing for limbic encephalitis. Early treatment and evaluation for an associated malignancy is critical because (1) treatment of the encephalitis with immunosuppressive agents may result in symptom improvement and (2) recovery to cognitive baseline is ultimately dependent on cancer-directed therapy.

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Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

Consent for Publication: *Informed consent was obtained from the patient's wife for publication of this case report and any accompanying images.*

REFERENCES

1. **Lee BY, Newberg AB, Liebeskind DS, Kung J, Alavi A.** FDG-PET Findings in patients with suspected encephalitis. Clin Nucl Med. 2004;29(10):620–5.
2. **Solnes LB, Jones KM, Rowe SP, et al.** Diagnostic value of 18 F-FDG PET/CT versus MRI in the setting of antibody specific autoimmune encephalitis. J Nucl Med. 2017;58(8):1307–1313.
3. **Guartuccio N, Caobelli F, Evangelista L, et al.** The role of PET/CT in the evaluation of patients affected by limbic encephalitis: A systematic review of the literature. J Neuroimmunol. 2015;284:44–48.
4. **Hoftberger R, Rosenfeld MR, Dalmau J.** Update on neurological paraneoplastic syndromes. Curr Opin Oncol. 2015;27(6):489–495.
5. **Jammoul A, Li Y, Rae-Grant A.** Autonantibody-mediated encephalitis: Not just paraneoplastic, not just limbic, and not untreatable. Clev Clin J Med. 2016;83(1):43–53.
6. **Lancaster E, Lai M, Peng X, et al.** Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9:67–76.
7. **Boronat A, Sabater L, Saiz A, Dalmau J, Graus F.** GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology. 2011;76(9):795–800.
8. **Höftberger R, Titulaer MJ, Sabater L, et al.** Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013;81(17):1500–6.
9. **Dogan OM, Deuretzbacher D, Haensch CA, et al.** Limbic encephalitis due to GABA b and MPA receptor antibodies: a case series. J Neurol Neurosurg Psychiatry. 2015;86:965–972.
10. **Guan HZ, Ren HT, Yang XZ, et al.** Limbic encephalitis associated with anti-γ-aminobutyric acid B receptor antibodies: a case series from China. China Med J. 2015;128(22):3023–8.
11. **Gultekin SH, Rosenfeld MR, Voltz R, et al.** Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumor association in 50 patients. Brain. 2000;123(7):1481–1494.
12. **Alexopoulos H, Dagklis IE, Akrivou S, Bostantjopoulou S, Dalackas MC.** Autoimmune encephalitis with $GABA_B$ antibodies, thymoma, and $GABA_B$ receptor thymic expression. Neurol Neuroimmino Neuroinflamm. 2014;1(4):e39.
13. **Yao JC, Hassan M, Phan A, et al.** One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):306–372.
14. **Ye L, Want W, Ospina NS, et al.** Clinical features and prognosis of thymic neuroendocrine tumours associated with multiple endocrine neoplasia type 1: a single-center study, systemic review and meta-analysis. Clin Endocrinol. 2017;87(6):706–716.
15. **Sullivan JL, Weksler B.** Neuroendocrine tumors of the thymus: analysis of factors affecting survival in 254 patients. Ann Thorac Surg. 2017;103(3):935–939.
16. **Travis W.D., Brambilla E., Muller-Hermelink H.K., Harris CC, eds.** World health organization classification of tumours. tathology and genetics of tumours of the lung, pleura, thymus and heart. IARC Press: Lyon; 2004:188–95.
17. **Fletcher CD**. Diagnostic histopathology of tumors, 2nd ed. Vol. 2. Edinburgh: Churchill Livingstone;2000. 1276–1295.
18. **Cai YC, Banner B, Glickman J, Odze RD.** Cytokeratin 7 and 20 and thyroid transcription factor 1 can help distinguish pulmonary from gastrointestinal carcinoid and pancreatic endocrine tumors. Hum Pathol. 2001;32:1087–1093.
19. **Folpe AL, Gown AM, Lamps LW, et al.** Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. Mod Pathol. 1999;12:5–8.
20. **Kaufmann O, Dietel M.** Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinomas and other neuroendocrine carcinomas of various primary sites. Histopathology. 2000;36(5):415–420.
21. **Asirvatham JR, Esposito MJ, Bhuiya TA.** Role of PAX-8, CD5, and CD117 in distinguishing thymic carcinoma from poorly differentiated lung carcinoma. Appl Immunohistochem Mol Morphol. 2014;22(5):372–6.
22. **Weissferdt A, Moran CA.** Pax8 expression in thymic epithelial neoplasms: an immunohistochemical analysis. Am J Surg Pathol. 2011;35(9):1305–10.
23. **Paul ML, Kleinig TJ.** Therapy of paraneoplastic disorders of the CNS. Expert Rev Neurother. 2015;15(2):187–193.
24. Lancaster. The diagnosis and treatment of Autoimmune encephalitis. J Clin Neurol. 2016;12(1):1–13.
25. **Yeshokumar AK, Gordon-Lipkin E, Arenivas A, et al.** Neurobehavioral outcomes in autoimmune encephalitis. J Neuroimmunol. 2017;213;8–14.
26. **Titulaer MJ, McCracken L, Gabilondo I, et al.** Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157–165.