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CASE REPORT

Small-Cell Lung Cancer Presenting with Personality Change

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Introduction: Paraneoplastic limbic encephalitis is a syndrome characterized by autoimmune inflammation of the limbic system in the setting of underlying malignancy. The syndrome presents with acute to subacute neuropsychiatric clinical findings, often before the cancer diagnosis.

Clinical findings: A 57-year-old woman with a 30 pack–year smoking history presented to an acute care hospital after multiple generalized tonic-clonic seizures. Her family reported that she periodically showed odd behavior, including confusion, disinhibition, and paranoia. All of these symptoms preceded her first seizure by 2 weeks.

Diagnoses, Interventions, and Outcomes: Brain magnetic resonance imaging revealed T2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) signal hyperintensity of the right amygdala and hippocampus, with sparing of the right insular cortex and cingulate gyrus. Electroencephalogram showed frequent right-temporal simple partial seizures. Her cerebrospinal fluid indicated mild pleocytosis and was positive for γ-aminobutyric acid-B receptor (GABA-BR) antibodies with a titer of 1:32 (reference range <1:2). Levetiracetam, fosphenytoin, lacosamide, and benzodiazepines were required to control seizure activity. Computed tomography of her chest, abdomen, and pelvis revealed a 4-millimeter subpleural parenchymal nodule in the left hilum. Positron emission tomographic-computed tomography showed hypermetabolic density in the left hilum and a left-sided enlarged lymph node in the mediastinum. Bronchoscopy with transbronchial needle biopsy confirmed small-cell lung cancer. After remission, the patient remained free of recurrent seizures.

Conclusions: This case illustrates the importance of early diagnosis and treatment of paraneoplastic limbic encephalitis. Because paraneoplastic limbic encephalitis is often associated with undiagnosed malignancy, recognizing the condition early can lead to timely initiation of tumor treatment.

Keywords: limbic encephalitis, small-cell lung cancer, paraneoplastic syndromes, nervous system

CASE PRESENTATION

A 57-year-old woman with a 30 pack–year smoking history presented with 2 generalized tonic-clonic seizures in the prior 3 days. Her family reported that during the previous 2 weeks, the patient periodically showed odd behavior, including confusion, disinhibition, and paranoia.

On admission to the hospital the patient’s hematologic and chemistry results were within normal ranges. Her neurologic exam revealed fluctuating orientation and short-term memory deficits, and her psychiatric exam showed pressured speech, hyper-emotionality, and inattention. Her cerebrospinal fluid indicated 16 leukocytes/mm³ with 90% lymphocytic predominance and was positive for γ-aminobutyric acid-B receptor (GABA-BR) antibodies with a titer of 1:32 (reference range <1:2). Her brain magnetic resonance imaging (MRI) showed T2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) signal hyperintensity of the right amygdala and hippocampus, with sparing of the right insular cortex and cingulate gyrus. Electroencephalogram (EEG) revealed frequent right-temporal simple partial seizures. These findings were consistent with paraneoplastic limbic encephalitis.

During her hospitalization, the patient required levetiracetam, fosphenytoin, and lacosamide to manage refractory right-temporal lobe seizures.
She was given 1,000 mg methylprednisolone for 3 days. After her symptoms improved, she was evaluated for underlying malignancy. Computed tomography (CT) of her chest, abdomen, and pelvis revealed a 4-mm subpleural parenchymal nodule in the left hilum and two adrenal nodules in the left adrenal gland. To help determine the biopsy site, she underwent a positron emission tomographic (PET)-CT, which revealed hypermetabolic density in the left hilum and a left-sided enlarged lymph node in the mediastinum. Bronchoscopy with transbronchial needle biopsy confirmed small-cell lung cancer. One year after remission of her cancer, she remained without recurrent seizures on a regimen of antiepileptic drugs for paraneoplastic epilepsy.

DISCUSSION

Paraneoplastic limbic encephalitis is a rare disease characterized by inflammation of the limbic system. It typically manifests as neuropsychiatric clinical findings and is often associated with malignancy. Its clinical presentation includes subacute memory deficits, mood changes, hallucinations, paranoia, psychosis, sleep disturbances, or seizures. Due to the wide spectrum of disease presentation and sometimes challenging diagnosis, the time to treating the underlying malignancy is often delayed for a median of 4 months. This highlights the importance of promptly recognizing the combination of symptoms associated with paraneoplastic limbic encephalitis.

Classic paraneoplastic encephalitis is the result of antibodies against intracellular neuronal proteins, such as Hu, collapsin response-mediator protein-5 (CRMP5), Ri, Yo, or Ma2, as well as their associated paraneoplastic syndromes. These syndromes are often associated with malignancy and older age, and they may have a poorer response to immunotherapy. The antibodies directed against intracellular proteins elicit cytotoxic T-cell inflammation and often permanent neuronal damage. In contrast to classic paraneoplastic encephalitis, autoimmune encephalitis includes syndromes characterized by antibodies against neuronal or synaptic cell–surface proteins, such as the N-methyl-D-aspartate (NMDA) receptor, leucine-rich glioma-inactivated 1 (LG1), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), metabotropic glutamate receptor 5 (mGluR5), or contactin-associated protein-like 2 (Caspr2), as well as their associated autoimmune syndromes. These syndromes are less likely to be associated with malignancy, are associated with younger age, and often have a better response to immunotherapy. Antibodies targeting extracellular membrane domains of cell-surface antigens can regulate the function or quantity of the target protein, resulting in neuronal dysfunction, but not neuronal destruction.

Notably, a third group of antibody-associated encephalitis has emerged, shifting the classic paradigm of paraneoplastic and autoimmune encephalitis. This group includes mixed features of each syndrome, as seen in this case of small-cell lung cancer with associated antibodies to GABA-BR, a cell surface receptor. Another prominent example of cancer-associated autoimmune encephalitis is NMDA-receptor encephalitis, which is sometimes associated with ovarian teratoma. Several other autoimmune encephalitides (e.g., AMPAR, GABA-A, mGluR5) may be idiopathic or associated with underlying malignancy. For example, a recent review found that half of 20 patients with GABA-BR limbic encephalitis had associated paraneoplastic encephalitis and the other half had idiopathic or autoimmune encephalitis. The underlying malignancy was small-cell lung cancer, as seen in this case. This case further underscores the strong association of malignancy with both classic paraneoplastic encephalitis and autoimmune encephalitis, as well as the importance of pursuing screening for underlying tumors.

Paraneoplastic limbic encephalitis is diagnosed based on cerebrospinal fluid pleocytosis, positive antibodies, EEG with focal epileptiform activity, and hyperattenuation on T2/FLAIR of the limbic system with sparing of the insular cortex and cingulate gyrus. The differential diagnosis often includes acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and demyelinating syndromes. These diagnoses can exist concurrently. Treatment is largely supportive and involves modulating the immune system with steroids or intravenous immunoglobulin, as well as managing seizures with antiepileptic drugs. Ongoing evaluation for a diagnosis should not impede empiric treatment, as delayed treatment increases the risk of permanent sequelae. Definitive treatment of paraneoplastic limbic encephalitis is treatment of the underlying malignancy.
Figure 1. Brain MRI without contrast. Abnormal and asymmetric T2/FLAIR signal hyperintensity in the right amygdala and the entire right hippocampal formation. MRI, magnetic resonance imaging; T2/FLAIR, T2-weighted-fluid-attenuated inversion recovery.

Figure 2. PET-CT of mid-lung. The scan revealed a nodular density measuring approximately 10 x 9 cm at the left hilum, consistent with a borderline-enlarged left hilar lymph node. PET-CT, positron emission tomographic computed tomography.
Conflicts of Interest: None

REFERENCES