Clinical Vignettes

Renal Cell Carcinoma Presenting with Paraneoplastic Hallucinations and Cognitive Decline from Limbic Encephalitis

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We present a 66-year-old woman with 2 months of visual hallucinations, unintentional weight loss, and short-term memory decline, whose clinical presentation and EEG supported a diagnosis of limbic encephalitis. Subsequent evaluation for a paraneoplastic etiology revealed a renal mass, which was resected and identified as clear cell renal carcinoma. The patient's clinical condition improved after resection of the mass. When patients present with incongruous subacute neuropsychiatric symptoms, clinicians should be mindful of paraneoplastic neurological disorders, as early diagnosis and treatment of malignancy may lead to symptomatic improvement.

KEY WORDS: limbic encephalitis; paraneoplastic syndrome; renal cell carcinoma; visual hallucinations.

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CASE DESCRIPTION

A 66-year-old woman presented with 2 months of new visual hallucinations. She initially saw spiders on the walls; at the time of her presentation, however, she was having more vivid hallucinations, including seeing known deceased people harm her neighbors. While these visions were disturbing to her, she recognized that they were hallucinations and did not respond to them. Over the same period, her family also noticed short-term memory decline and an unintentional weight loss of 20 pounds. Her review of systems was otherwise normal, including a lack of symptoms suggestive of depression, and she had no medical, psychiatric, or relevant family history. She did not take medicines and denied use of tobacco, alcohol, and illicit drugs.

On physical examination, the patient was hemodynamically stable and had a normal cardiovascular, respiratory, abdominal, and pulmonary examination. Detailed neurological examination revealed no focal neurological deficits, including normal cranial nerves, intact and symmetric strength throughout, normal reflexes, no nystagmus, intact finger-to-nose testing, normal gait, and no dysidiadochokinesia with rapid alternating movement. She performed poorly on the Montreal Cognitive

Assessment¹, having particular difficulty with visuospatial skills, naming, and both immediate and delayed recall. Comprehensive laboratory assessment was performed and revealed normal urinalysis, complete blood count, basic metabolic panel, hepatic function panel, thyroid-stimulating hormone, free thyroxine, ammonia, folate, and vitamin B12. HIV testing and urine toxicology screen were negative. Cerebrospinal fluid (CSF) was colorless, with only one white blood cell (monocyte), one erythrocyte, glucose level of 65 mg/dL (normal range, 40–85 mg/dL), and protein level of 43 mg/dL (normal range, 15–45 mg/dL). CSF was negative for herpes simplex virus via PCR, fungal staining, and New York State Viral Encephalitis panel. CSF cytology was negative, and CSF protein electrophoresis did not identify any oligoclonal bands. Serum electrophoresis detected a distinct monoclonal band in the gamma region, but immunofixation was not performed. MRI of the brain, with and without contrast, revealed mild diffuse atrophy and subcortical hyperintensities on T2 and FLAIR imaging, findings which were nonspecific and possibly related to microvascular disease, but also potentially consistent with limbic encephalitis given the clinical setting. EEG showed a disorganized background with bitemporal slowing consistent with encephalopathy.

Because of concern for a paraneoplastic syndrome as a unifying diagnosis, CT scans of the thorax, abdomen, and pelvis were obtained, and an 8-cm exophytic mass was identified on the left kidney. The mass was resected and identified as clear cell renal carcinoma with sarcomatoid differentiation; there was no evidence of local extension or metastatic disease. Despite negative testing for the most common paraneoplastic antibodies, including anti-Hu, anti-Ri, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, and CRMP-5, a diagnosis of paraneoplastic limbic encephalitis was favored. A brief trial of risperidone caused increased agitation and was thus discontinued; however, after resection of the mass, resolution of her encephalopathic EEG abnormalities was noted, and her hallucinations subsided significantly.

DISCUSSION

When neuropsychiatric symptoms rapidly present in a patient who is 40 years of age or older, primary psychosis is unlikely, and thus an investigation for an underlying cause should be

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undertaken. In our patient, CSF studies and cytology did not support viral encephalitis or a carcinomatous process. Other diagnoses that were entertained included Lewy body dementia and rapidly progressive early-onset Alzheimer's dementia. The profound visual hallucinations and cognitive decline supported a diagnosis of Lewy body dementia; however, the patient did not exhibit bradykinesia, tremor, rigidity, or gait disturbance. The rapid onset of symptoms and the striking prominence of her hallucinations made a diagnosis of Alzheimer's less likely. MRI and EEG findings did not support frontotemporal dementia. Given the rapidity of symptoms onset prion disease was also considered, however the patient did not exhibit ataxia or myoclonus. Her unintentional weight loss in combination with the acute to subacute presentation of psychiatric symptoms and cognitive decline, with an otherwise normal neurological exam, created suspicion of an underlying malignancy-induced paraneoplastic neurological syndrome.

Paraneoplastic neurological syndromes are rare—occurring in less than 1 % of patients with malignancies²—and are mediated by the patient's immune response against antigens shared by the tumor cells and components of the nervous system. They are frequently challenging to diagnose, as symptoms often precede the discovery of an underlying malignancy, and any level of the central or peripheral neurological system may be involved. Nevertheless, it is important to consider paraneoplastic syndromes such as limbic encephalitis early on when incongruous neuropsychiatric symptoms are present, as early diagnosis of malignancy and prompt initiation of treatment can lead to improvement in the neuropsychiatric manifestations.

Limbic encephalitis is an inflammatory process localized to structures of the limbic system, which includes the thalamus, hypothalamus, amygdala, and hippocampus. These structures are responsible for behavior, motivation, emotion, and memory. While most frequently paraneoplastic in origin, limbic encephalitis can also be strictly autoimmune-mediated without being associated with an underlying malignancy, with the classic example being voltage-gated potassium channel (VGKC) antibody-mediated disease.³ Patients with limbic encephalitis often present with relatively acute mood and behavioral changes, hallucinations, short-term memory decline, cognitive dysfunction, and seizures. Gultekin criteria for a clinical diagnosis of paraneoplastic limbic encephalitis include: (1) short-term memory loss, seizures, or psychiatric symptoms, (2) less than 4 years between symptom onset and cancer diagnosis, (3) exclusion of metastases, infection, metabolic or other causes, and (4) one of the following: inflammatory CSF findings, temporal lobe T2 or FLAIR hyperintensity on MRI, or EEG abnormality in the temporal lobes.⁴ Our patient's clinical presentation, malignancy, and bimodal EEG abnormalities support this diagnosis.

A number of associated antibodies have been identified in the serum or CSF of patients with presumed paraneoplastic neurological syndromes (Table 1); several of these antibodies

Table 1 Common Paraneoplastic Syndromes with their Classically Associated Antibodies and Tumors⁴⁻⁶

Antibody	Syndrome	Tumor
Classic paraneoplastic		
Anti-Hu (ANNA-1)	Limbic encephalitis, encephalomyelitis, subacute sensory neuropathy	SCLC
Anti-Ma	Limbic, brainstem, hypothalamic encephalitis	Testicular germ cell
Anti-CV2/CRMP5	Limbic, encephalomyelitis, uveitis, peripheral neuropathy	SCLC, Thymoma
Anti-amphiphysin	Stiff-man syndrome, encephalomyelitis	Breast, SCLC
Anti-Yo (PCA-1)	Cerebellar degeneration	Gynecological, Breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, opsoclonus	Gynecological, Breast
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
AGNA-1	Lambert-Eaton myasthenic syndrome, cerebellar degeneration, sensory neuropathy, limbic encephalitis	SCLC
PCA-2	Brainstem, limbic encephalitis, cerebellar degeneration, motor neuropathy	SCLC
Paraneoplastic & Non-paraneoplastic		
Anti-AChR	Myasthenia gravis	Thymoma
Anti-VGCC	Lambert-Eaton myasthenic syndrome	SCLC
Anti-NMDA	Encephalitis with psychiatric manifestations, dyskinesia, autonomic instability	Teratomas (ovarian & testicular)
VGKC antibodies (LGII)	Isaac's syndrome, limbic encephalitis, Morvan's syndrome, GI dysmotility, neuromyotonia	Thymoma, SCLC

SCLC small cell lung cancer

(anti-Hu, anti-Ma, and anti-CV2/CRMP5) are frequently identified in patients with paraneoplastic limbic encephalitis.^{7,8} However, it has been well-documented that the absence of classic antibody and CSF findings does not exclude the diagnosis of a paraneoplastic syndrome; a review of limbic encephalitis revealed that only about 60 % of patients have documented antibodies.^{5,6} Likewise, about 80 % of patients with limbic encephalitis are found to have CSF abnormalities, which mostly consist of mild protein elevations.^{5,6}

Renal cell carcinoma is not classically associated with limbic encephalitis or other paraneoplastic neurological syndromes. While small cell lung cancer causes the majority of cases of limbic encephalitis, there have been at least two previously documented cases of limbic encephalitis associated with renal cell carcinoma.^{9,10} Both patients suffered from significant cognitive decline, and one had hallucinations. Similar to our case, neither patient was noted to have a detectable paraneoplastic antibody in their serum or CSF. After tumor resection, one of the patients was noted to have marked improvement in cognitive functioning,⁹ the other displayed slight improvement in visual-motor testing.¹⁰

When the clinical presentation and initial laboratory studies such as the CSF profile suggest a diagnosis of paraneoplastic neurological syndrome but do not help localize the potential

Table 2 Antibodies Classically Associated with Limbic Encephalitis—Treatment Responsiveness^{2,5,13}

Antibody	Tumor (Percentage of patients in which malignancy was discovered)	Treatment response
Anti-Hu (ANNA-1)	SCLC (>83 %)	Poor prognosis. 3-year survival 20 %
Anti-Ma	Testicular germ cell (>90 %)	33 % improve & 20 % stabilize with treatment of tumor & immunotherapy
Anti-CV2/CRMP5	SCLC, Thymoma	Response less well known. Thought to be poorer prognosis
Anti-NMDAR	Ovarian & Testicular Teratomas (50 %)	75 % improve with immunotherapy (and tumor resection)
VGKC antibodies (LGI1)	SCLC / Thymoma (10 %)	80–90 % improve with immunotherapy

malignant etiology, investigation for serum and CSF paraneoplastic antibodies should be the next step.¹¹ Preferably, this will include an entire panel of paraneoplastic antibodies rather than one or two specific antibodies, as overlap in syndrome presentation is common. Results of antibody testing should help guide further imaging studies (Table 1). If there is high suspicion for paraneoplastic limbic encephalitis, a CT scan of the thorax should be part of the initial work, as small cell lung cancer is frequently the etiology. If antibody testing is negative, age-based malignancy screening such as colonoscopy should be employed, and further imaging should be pursued to assess for the most common malignancies based on the clinical setting. Testicular examination and ultrasound should be included for younger males. Transvaginal ultrasonography and mammography can be considered for female patients. It is not uncommon for initial imaging to be negative, in which case a PET scan may be useful.^{11,12} If primary screening is negative, it is recommended to repeat screening in 3–6 months, and then every 6 months for up to 4 years.^{11,12}

The primary treatment of paraneoplastic neurological disorders is prompt removal and treatment of the tumor. Clinical outcomes vary, and appear to be influenced by the underlying malignancy and associated antibodies (Table 2). Limbic encephalitis is considered one of the more responsive paraneoplastic neurologic syndromes, with approximately half of patients experiencing neurological improvement with prompt treatment.⁵ While data describing clinical outcomes are largely limited to several case series,^{3,13–15} recent literature suggests that in contrast to paraneoplastic disorders with antibodies targeting intracellular antigens (anti-Hu, anti-Ma, anti-CV2), disorders related to antibodies against cell-surface antigens (VGKC antibodies, anti-NMDA) frequently respond quite well to immunotherapy.^{7,16} Immunotherapy to suppress the immune-mediated paraneoplastic process has proven beneficial, and especially should be considered when clinical remission from a known malignancy is not possible or if antibodies to cell-surface antigens are detected. While there

are no randomized controlled trials to guide treatment, corticosteroids, rituximab, plasma exchange, and intravenous immunoglobulin have also been shown to be effective.¹² Re-emergence of paraneoplastic manifestations may be the first indication that a recurrence of the underlying malignancy has occurred.

KEY POINTS

1. When patients present with incongruous subacute neuropsychiatric symptoms such as hallucinations, behavioral changes, memory loss, or cognitive decline, it is important to consider paraneoplastic neurological syndromes, such as limbic encephalitis.
2. Gultekin criteria for clinical diagnosis of limbic encephalitis include: (1) short-term memory loss, seizures, or psychiatric symptoms; (2) less than 4 years between symptom onset and cancer diagnosis; (3) exclusion of metastases, infection, and metabolic or other causes; and (4) one of: inflammatory CSF findings, temporal lobe T2 hyperintensity on MRI, or EEG abnormality in the temporal lobes.
3. With prompt diagnosis and treatment of the underlying malignancy (and consideration of concurrent immunotherapy), patients can experience significant improvements in their paraneoplastic symptom manifestations.

Conflicts of Interest: The authors each declare that they have no conflict of interest.

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