

Paraneoplastic limbic encephalitis associated with small-cell lung cancer

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Limbic encephalitis is a disorder characterized by personality changes, irritability, depression, seizures, memory loss, and sometimes dementia. In more than half of cases, limbic encephalitis is paraneoplastic and indicates the presence of an underlying cancer. Symptoms of limbic encephalitis often precede the diagnosis of cancer or mimic other complications of cancer or its treatment, confusing the differential diagnosis. It is believed that cytotoxic T-cell responses and antibodies that target neuronal proteins usually expressed by the underlying tumor cause the neurologic symptoms. The detection of these antibodies has provided diagnostic tests that allow for recognition of the disorder as paraneoplastic and direct the search for the tumor to selected organs. Treatment of the tumor is critical to improving or stabilizing the neurologic disorder.

A 65-year-old man developed short-term memory problems over a 3-day period. He repeated comments and asked the same question several times. Evaluation demonstrated severe impairment of short-term memory with preservation of other cognitive functions. The patient's speech was fluent, and he followed commands without problems. However, after a few minutes he could not remember the doctor's name, the date, or the reason why he was being evaluated. The patient was oriented to person and was aware that he was in a doctor's office. When asked to state the time and date, he looked at his watch to get the answer. Except for decreased sensation in the first 3 fingers of both hands, results of the neurologic examination were normal. General medical examination was unremarkable. Medical history included hypertension and adult-onset diabetes. The patient had a 45-pack-year history of cigarette smoking.

The combination of neurologic symptoms and the strong smoking history suggested a paraneoplastic neurologic syndrome; this diagnosis was confirmed by serologic studies, which revealed the presence of the anti-Hu antibody. Computed tomography (CT) of the chest followed by bronchoscopy revealed a small-cell lung carcinoma (SCLC). Staging of the tumor showed local disease in the chest. The patient had a complete response to etoposide and carboplatin (Paraplatin). He was then treated with oral cyclophosphamide ([Cytosan] 1 mg/kg/day for 5 months, then 0.5 mg/kg/month for 5 months) and oral prednisone (70 mg every other day for 5 months and then slowly tapered off

over 5 months). Within a few weeks after the patient started cyclophosphamide and prednisone, he experienced a slight but noticeable improvement in memory function, which stabilized after 3 months; the mild sensory neuropathy of the fingers also stabilized. The patient's condition remains stable, with moderately severe memory deficits and without evidence of recurrent cancer, 36 months after symptom presentation.

Paraneoplastic neurologic disorders

The paraneoplastic neurologic syndromes are an extensive group of disorders that can affect any part of the central or peripheral nervous system. Evidence indicates that many of these syndromes are mediated by immunologic responses triggered by the presence of a cancer.¹ Paraneoplastic encephalomyelitis is a syndrome characterized by multifocal involvement of the nervous system, including the brain, brainstem, cerebellum, and spinal cord.² It is often associated with dorsal root ganglia and autonomic dysfunction.³ The clinical features of paraneoplastic encephalomyelitis depend on the area(s) predominantly involved; the case described above was a limbic encephalitis accompanied by mild sensory neuropathy.

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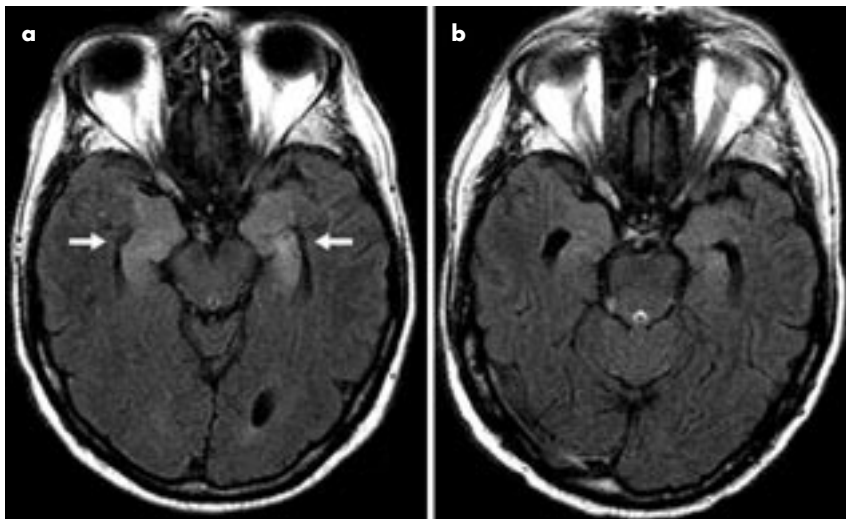


FIGURE 1 Magnetic resonance imaging (MRI) scans obtained at symptom presentation and follow-up in a 65-year-old man with anti-Hu-associated limbic encephalitis. The MRI scan obtained at symptom presentation (**a**) demonstrates a fluid attenuated inversion recovery (FLAIR) signal abnormality involving the medial aspect of the temporal lobes. In the follow-up MRI scan obtained years later (**b**), after successful treatment of the underlying small-cell lung carcinoma, note that the signal abnormality is less intense and that there are atrophic changes (increased size of the temporal horns of the ventricles).

Paraneoplastic limbic encephalitis

In an adult, the acute to subacute onset of short-term memory deficits, with relative preservation of other cognitive functions, is characteristic of limbic encephalitis.⁴ The memory deficits may be noticed after several weeks of depression, personality change, or irritability. Seizures can occur and are most often partial complex seizures with or without motor involvement of the face and extremities. Olfactory and gustatory hallucinations are common. Some patients also develop signs of diencephalic-hypothalamic dysfunction, including drowsiness, hyperthermia, hyperphagia, and, less frequently, pituitary hormonal deficits.⁵ The asymmetric loss of sensation in the extremities affecting the hands preferentially over the legs is typical of paraneoplastic sensory neuronopathy, but not drug- or toxic-induced neuropathy.⁶

In 60% of cases, limbic encephalitis is a paraneoplastic disorder and indicates the presence of an underlying cancer; the most common under-

lying malignancy is SCLC, followed by testicular cancer, thymoma, and Hodgkin's lymphoma.⁷ Regardless of the tumor type, the neurologic dysfunction usually precedes the diagnosis of cancer.

Differential diagnosis

Due to the diversity of symptoms of limbic encephalitis, this disorder is likely underdiagnosed. In patients without a known cancer, limbic encephalitis may be mistaken for a viral encephalitis or a rapidly developing dementia secondary to a neurodegenerative disorder.⁸ When the patient is known to have cancer, symptoms of limbic encephalitis may be attributed to other more common complications of cancer, including intracranial metastases, metabolic abnormalities, infections, and cerebrovascular events, or to adverse effects of cancer treatment.⁹ For example, patients with miliary metastases or disseminated intravascular coagulation may present with seizures, memory problems, and other mental status changes that resemble limbic encephalitis.¹⁰ An

adverse effect of some chemotherapeutic agents or radiation-induced encephalopathy should be considered in the differential diagnosis.^{4,7,11} The close temporal association between chemotherapy and symptom onset or the chronic and slow progression of memory problems in patients with post-radiation encephalopathy helps to establish these diagnoses. Vitamin B₁ deficiency, which is not unusual in patients with leukemia or lymphoma, can result in a Wernicke-Korsakoff syndrome that can mistakenly lead to the diagnosis of limbic and brainstem encephalopathy.¹²

Establishing the diagnosis

In contrast to patients with other paraneoplastic neurologic syndromes, in whom magnetic resonance imaging (MRI) is of limited usefulness in helping to establish the diagnosis, patients with limbic encephalitis may present with early MRI changes suggestive of the disorder.¹³ Typically, the MRI shows hyperintense abnormalities in the medial aspect of the temporal lobes; these abnormalities are best seen in T2 and fluid attenuated inversion recovery (FLAIR) sequences and usually do not enhance after contrast administration (Figure 1). Over time, the hyperintense abnormalities may revert to a normal signal, leaving only atrophic changes.¹⁴ These MRI abnormalities should be differentiated from those in patients with herpes simplex encephalitis, in whom the MRI usually shows signs of edema, mass effect, contrast enhancement, and, sometimes, areas of hemorrhage. In about 20% of patients with limbic encephalitis, the MRI shows no abnormalities.¹⁵

The above symptoms and MRI findings, in association with cerebrospinal fluid (CSF) changes characteristic of inflammation (eg, increased proteins, moderate pleocytosis, oligoclonal bands, intrathecal synthesis of proteins), are highly suggestive of paraneoplastic limbic encephalitis

and should prompt testing for anti-neuronal antibodies.⁴

Usefulness of antibody markers

When present in serum and/or CSF, antineuronal antibodies facilitate the diagnosis of limbic encephalitis and often allow for early detection of the associated tumor (Table 1). Among patients with SCLC, the anti-Hu antibody is present in about 50% of those with predominant or isolated symptoms of limbic encephalitis.^{7,16} A few patients with limbic encephalitis and anti-CV2 antibodies have been reported; the underlying tumors in these patients were SCLC and thymoma.¹⁷ Limbic encephalitis in association with antibodies to voltage-gated potassium channels (VGKC) is paraneoplastic in about 20% of patients; the most frequently associated tumors are thymoma and SCLC.¹⁸

Anti-Ma2 antibodies may be found in the serum and CSF of patients with limbic and/or brainstem encephalopathy; these patients usually have testicular cancer (either seminomatous or nonseminomatous germ cell tumors), but patients with other tumors such as breast and non-small cell carcinoma of the lung have been reported.¹⁹ Patients with anti-Ma2 antibodies frequently have additional involvement of the hypothalamus and brainstem and are more likely to have abnormal MRI findings than other patients with paraneoplastic limbic encephalitis.

A new category of paraneoplastic limbic encephalitis has recently been described in young women with ovarian teratoma (in one patient the tumor was in the mediastinum).²⁰ All of these patients had serum and CSF antibodies to NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR) that were highly enriched in the hippocampus. These patients often present with acute changes in behavior and personality, as well as paranoid thoughts and aggressive behavior, and may be misdiagnosed as

TABLE 1
Antibodies associated with limbic encephalitis

Antibody	Frequently associated cancers	Distinctive features of the limbic encephalitis
Anti-Hu	SCLC > others	Often part of a widespread encephalomyelitis
Anti-Ma2	Testicular > lung > others	May be associated with hypothalamic and brainstem encephalitis
Anti-amphiphysin	Breast, SCLC	With or without stiff-person syndrome
Anti-CV2/CRMP5	SCLC, thymoma	May be associated with striatal encephalitis, cerebellar findings, peripheral neuropathy, uveitis
Anti-NMDAR	Mature or immature teratoma	Predominant psychiatric component, seizures, central hypoventilation
Anti-VGKC	About 20% of cases are paraneoplastic; most commonly associated with thymoma	May be associated with peripheral-nerve hyperexcitability, autonomic dysfunction, sleep disturbances

SCLC = small-cell lung carcinoma; CRMP5 = collapsin response mediator protein 5; NMDAR = *N*-methyl-D-aspartate receptor; VGKC = voltage-gated potassium channel

having acute psychosis, malingering, or drug abuse. Other patients have clinical features more typical of limbic encephalitis, such as short-term memory loss and seizures. Most patients with this newly recognized form of paraneoplastic limbic encephalitis will progress to a decreased level of consciousness, with autonomic dysfunction and central hypoventilation, and will require prolonged ventilatory support.

If paraneoplastic antibodies are present but a cancer is not discovered, the patient should be assumed to harbor an occult neoplasm unless proven otherwise. Body PET scans may detect tumors that escape detection by other standard imaging methods.²¹ In patients with a history of cancer or with a cancer that has recently gone into remission, the development of a paraneoplastic neurologic syndrome frequently heralds tumor recurrence.

Treatment

When limbic encephalitis is part of a widespread encephalomyelitis, it is generally poorly responsive to treatment.³ Early recognition and treatment of the tumor, however, may result in stabilization or improvement of the neurologic symptoms.

A study of patients with SCLC and paraneoplastic limbic encephalitis suggested that the presence of anti-Hu antibodies was associated with a decreased likelihood of neurologic improvement.¹⁶ In contrast, about 35% of patients with limbic encephalitis associated with antibodies to Ma2 improved with immunotherapy and treatment of the tumor (usually a testicular germ cell tumor).¹⁹ Patients with antibodies to cell surface antigens (anti-VGKC or -NMDAR) are more likely to respond to immunotherapy and tumor removal than those with antibodies targeting intracellular antigens (anti-Hu, -Ma2, -CV2/CRMP5, or -amphiphysin).²²

General recommendations

Experience suggests that the best chance to affect neurologic outcome in patients with limbic encephalitis depends on: (1) the prompt diagnosis of the disorder; (2) if paraneoplastic, early discovery and treatment of the tumor; and (3) the use of immunotherapy. Likewise, any clinical features or test results suggesting that the patient's syndrome is not a paraneoplastic neurologic disorder are also important to avoid any delays resulting from unnecessary oncologic evaluations.

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