Limbic Encephalitis Presenting With Seizures, Anterograde Amnesia, and Psychosis in a Patient Seven Weeks Status Post Immature Ovarian Teratoma Removal

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ABSTRACT A paraneoplastic syndrome associated with anti-N-methyl-D-asparate (NMDA) receptors can initially present as a neurologic or psychiatric disturbance. Removal of the tumor is usually curative, and the syndrome is associated with the presence, rather than the history, of tumor. We present a case in which a 25-year-old, Hispanic woman presented with seizures, memory loss, and unusual behavioral changes. The woman had a teratoma removed 2 months earlier. Because of the time course, a paraneoplastic syndrome was initially considered unlikely. Brain imaging, electroencephalography (EEG) and neurologic work-up were negative. The patient was treated for a suspected somatoform disorder and psychosis. Based on the clinical picture, the working diagnosis was changed to delirium due to paraneoplastic limbic encephalitis. A course of intravenous immunoglobins (IVIg), and high dose steroids was administered. The patient's symptoms improved, and she was discharged home. After discharge, studies came back positive for antibodies against NR1/NR2 of the NMDA receptor.

INTRODUCTION

The patient is a 25-year-old Hispanic female, with a questionable past psychiatric history of depression and a past medical history of laparotomy for malignant immature ovarian teratoma removal 7 weeks before being taken to the emergency department because of two seizures. The patient was admitted to the Internal Medicine service and was evaluated by both Internal Medicine and Neurology staff. The patient was placed on an antiseizure medication, which was discontinued within a week from admission. Initial work-up, including CT, MRI, EEG, and a panel of labs (including routine paraneoplastic labs such as ANNA-1, PCA-1, amphibysin Ab, ANNA-2, PCA-Tr, PCA-2, ANNA-3, CRMP-5-IgG, and AGNA-1) was negative.

The patient's symptoms had a waxing and waning course with intermittent episodes of strange behavior, disinhibition (exhibiting hypersexual solicitation for sex from staff), and fluctuations in alertness, orientation, and concentration. The Psychiatry service was contacted after the patient became severely disinhibited, delusional, and combative.

Continued medical work-up was negative. The patient was transferred from the medical floor to a psychiatric ward primarily because it was considered the safest measure to take with the patient given her unusual behavior. The patient was accepted to the Psychiatry service with a working diagnosis of somatoform disorder not otherwise specified, psychotic disorder not otherwise specified, and dissociative disorder not otherwise specified.

The patient's concentration and mental status continued to wax and wane during the course of her stay on the inpatient mental health ward. Serial mental status exams showed a consistent short-term memory deficit and alternating orientation to time, place, and situation. The resident physicians on the inpatient psychiatry service started to consider the patient's seizures, short-term memory loss, and changes in mental status to clinically resemble a delirium with psychotic features. No standing antipsychotic was ordered.

A week after being transferred to the psychiatry ward, the patient suffered a series of generalized tonic-clonic seizures. The patient's condition continued to deteriorate. Her cognitive function declined. She started to display lingual-facial-buccal dyskinesias and sometimes displayed garbled and unintelligible speech and periods of mutism. The patient then became extremely agitated and hit staff. Psychiatry considered these symptoms atypical for any primary psychiatric disorder and requested further medical work-up.

A repeat of the initial work-up, to include labs and imaging, was reordered, in addition to drawing CSF for analysis of anti-NMDA receptor antibodies. These tests (aside from the CSF) all came back normal, and again, the presumption was made that the symptoms must be psychiatric in origin. Based on the clinical picture, however, the patient was empirically started on a 5-day course of intravenous immunoglobins (IVIg) for a presumed case of delirium due to paraneoplastic limbic encephalitis. The patient was also started on a standing dose of the atypical antipsychotic olanzapine (Zyprexa) for behavioral control.

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The patient and her husband gave verbal informed consent for publication of this case report.

Subjectively, the patient's condition began to improve, with normalizing speech, less erratic/psychotic-like behavior, and improving cognitive function. The patient's various providers debated whether improvement was due to the antipsychotic or to the IVIg. After completing the medical work-up, the antipsychotic was stopped, and the patient was given a 5-day course of high-dose solumedrol, again because of the change in the working diagnosis of delirium due to paraneoplastic limbic encephalitis.

The patient's mental status continued to wax and wane with regards to her orientation and short-term memory, but her mini mental status exams started an upward trend. Although the patient's symptoms had not completely resolved, the symptoms were felt to be improved to the point that the patient could not be hospitalized involuntarily. She was discharged to the care of her husband. After discharge, the CSF was found to contain anti-NMDA receptor antibodies. As the patient had not been receiving ongoing antipsychotic treatment, and the pattern of recovery was consistent with what is seen after treatment of paraneoplastic syndrome with IVIg and high-dose steroids, the presumptive diagnosis was changed to psychosis and delirium due to paraneoplastic, anti-NMDA receptor antibody limbic encephalitis.

The patient did not receive any follow-up therapy for her cancerous teratoma from military providers. The patient moved to Texas and was encouraged to have CT, U/S, and serologic blood work that would assist in detection of recurrent or measurable disease. At the patient's only documented psychiatry outpatient follow-up appointment after discharge, she scored a 30/30 on the mini-mental status exam, her behavior was noted to be normal, and she was largely considered to have had complete resolution of symptoms.

DISCUSSION

Although this has not previously been reported, this case illustrated that behavioral and neurologic consequences of a paraneoplastic limbic encephalitis syndrome can appear even after a tumor has been removed.[1–6] Caution is merited in assuming that the presentation of atypical behavioral changes must be psychiatric.

The symptoms of limbic encephalitis usually involve seizures, rapidly progressive short-term memory deficits (which can progress to dementia), neuropsychiatric symptoms (irritability, depression, sleep disturbances, hallucinations, etc.) and possibly autonomic dysfunction.[7] This is due to neuronal inflammation and degeneration of the medial portion of one or both of the temporal lobes.[8] Limbic encephalitis has traditionally been considered a paraneoplastic neurologic disorder, with the term paraneoplastic referring to any symptom of unclear etiology but associated with the presence of a neoplasm.[9] Given the advances in technology, most specifically with the ability to test and identify antineuronal antibodies, limbic encephalitis is now regarded by some experts as an autoimmune disorder, often unrelated to cancer.[7,10] Having anti-NR1/NR2 antibodies of the NMDA receptor, however, can occur with or without cancer association.[9] In this patient's particular case, given that she had a history of an ovarian teratoma, her limbic encephalitis was likely paraneoplastic and not strictly autoimmune.

Many patients with limbic encephalitis have the demonstration of MRI and EEG abnormalities in the temporal lobes, cerebrospinal fluid inflammatory findings,[11] and a clinical picture as listed above. Diagnostic criteria of paraneoplastic limbic encephalitis has been reported by Gultekin and associates (See Table I).[8] Many patients (40–50%), like the female of this case, have normal MRI studies,[12] no inflammatory changes in the cerebrospinal fluid, and none of the classic paraneoplastic or antineuronal antibodies.[13]

After a viral etiology (such as Herpes simplex virus encephalitis and HHV-6 encephalitis) has been excluded, the onus on the physician is determining whether the limbic encephalitis is paraneoplastic or not.[7] Nonparaneoplastic causes have a differential that includes, but is not limited to, systemic lupus erythematosus, Hashimoto thyroiditis, Sjogren syndrome, antiphospholipid syndrome, and primary angiitis of the CNS. This presents a problem because the majority of paraneoplastic cases have neurologic manifestations before the detection of a tumor.[14,15]

Recent research now shows that a large majority of limbic encephalitis can be considered autoimmune (and not paraneoplastic) and these autoimmune cases are classified into two main categories: one associated with antibodies to intracellular neuronal antigens and the other with antibodies to cell membrane antigens, such as the NMDA receptor.[16] The treatment in these cases includes prompt tumor removal and immunotherapy (corticosteroids, plasma exchange, IVIg, and sometimes cyclophosphamide and rituximab).[7] In some cases patients do not respond to immunotherapy until the tumor is removed. Tumor removal is generally considered curative.

This case illustrates that behavioral and neurologic symptoms of a paraneoplastic syndrome can present well after the tumor itself is removed.

TABLE I. Diagnostic Criteria of Paraneoplastic Limbic Encephalitis

Criteria by Gultekin et al.[8]
(1) Pathological demonstration of limbic encephalitis, or (2) All four of the following: (a) Symptoms of short-term memory loss, seizures, or psychiatric symptoms suggesting involvement of the limbic system. (b) Less than 4 years between the onset of neurologic symptoms and the cancer diagnosis. (c) Exclusion of metastasis, infection, metabolic and nutritional deficits, stroke, and side effects of therapy that may cause limbic encephalopathy. (d) At least one of the following: (i) CSF with inflammatory findings. (ii) MRI FLAIR or T2 uni- or bilateral temporal lobe hyperintensities. (iii) EEG with epileptic or slow activity focally involving the temporal lobes.

The patient's history of cancer, an immature ovarian teratoma, is what likely caused her to produce antibodies against NR1/NR2 of the NMDA receptor. Another possible nidus for the antibodies may be micrometastasis that remained undetected with the PET scan. Literature suggests that the epitopes responsible for producing auto antibodies against the NMDA receptor originate from neural tissue ectopically expressed within a teratoma (usually of the ovaries).[7,9]

After a systematic literature search regarding limbic encephalitis and ovarian tumors, and teratomas in particular, was conducted by the authors, cases in which a paraneoplastic syndrome presents after the removal of the tumor have not been previously reported. As stated previously, having anti-NR1/NR2 antibodies of the NMDA receptor can occur with or without cancer association, making this patient's case of limbic encephalitis likely to be paraneoplastic in origin and not autoimmune.[9]

Although anti-NMDA receptor limbic encephalitis is potentially lethal, most individuals experience near-complete resolution of symptoms with immunosuppressive therapy. Improvement is often slow, and some patients (particularly those without a tumor) may have relapses. Patients, who do not improve, often respond to Rituximab (Rituxan) or intravenous Cyclophosphamide (Cytoxan). In a series of 100 patients, this approach leads to recovery or substantial improvement in 75% of cases.[17,18]

For much of this patient's hospital course, it was presumed that because lab work-up, imaging, and other tests were negative, the diagnosis must be psychiatric in origin. However, the patient's symptomatic presentation was always atypical for a primary psychiatric disorder. Rather, the clinical symptoms matched limbic encephalitis, a condition characterized by the development of seizures and extensive neuropsychiatric and autonomic dysfunction. The experimental lab test for anti NMDA receptor antibodies was what eventually determined the definitive diagnosis. However, this took an extended period of time to finalize, and it was the clinical rather than laboratory findings that pointed toward the correct diagnosis.[19]

Things can be confusing, as was evidenced by this case and the internal debate among the patient's various providers as to whether the cause of the patient's symptoms was strictly physiological or psychological. Even in today's era of technological prowess, giving credence to clinical symptoms should not be ignored even when laboratory and radiological results are negative. It is important to keep an open mind and continue a search for organic causes.

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