A case of sudden psychosis

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After her mother dies, Ms. T develops mania and disorganized behavior. She has a seizure and becomes increasingly agitated. Is this grief or something else?

CASE New-onset psychosis

Ms. T, age 26, presents to the psychiatric emergency room after a 1-week change in behavior. According to her family, Ms. T began to experience hyperactivity, increased rate of speech, and decreased sleep after her mother passed away 1 week ago. On the day of presentation, Ms. T had returned to work after a week's hiatus. Coworkers brought her to the hospital when Ms. T threw herself on the floor and flailed about. Family members report that Ms. T had been complaining of headache that day and during the preceding week. In the emergency room, the patient is intrusive and easily distractible, although able to give a history.

Ms. T has no psychiatric history. Her family history is positive for bipolar spectrum illness. Our initial consideration is that Ms. T is experiencing mania or psychotic symptoms triggered by the recent loss of her mother. Ms. T is evaluated in the medical emergency room to rule out a primary medical illness. Standard labs and head CT are normal, so she is returned to the psychiatric emergency room. She becomes severely agitated and requires multiple IM antipsychotics—2 courses of haloperidol, 10 mg; 2 courses of ziprasidone, 20 mg; and olanzapine, 10 mg. She is admitted to the inpatient psychiatric service with a diagnosis of psychosis not otherwise specified.

Soon after admission, Ms. T suffers a witnessed generalized tonic-clonic seizure and is transferred to the internal medicine service. After the seizure she is awake but minimally responsive. She does not display purposeful movements, opens her eyes but can follow the examiner only on occasion, and displays periodic facial grimacing. In addition, Ms. T is intermittently hypoxic—requiring supplemental oxygen via nasal cannula—and febrile, with persistent tachycardia. Electroencephalography (EEG) shows nonconvulsive status epilepticus involving the bilateral temporal regions.

Ms. T is transferred to the neurosurgical intensive care unit for monitoring and IV anticonvulsants. Subsequent EEGs demonstrate generalized slowing but no epileptiform activity. An infectious workup is negative. Head MRI shows bilateral cerebellar T2/FLAIR increased signal, which is a nonspecific finding. Cerebrospinal fluid (CSF) studies show lymphocytic pleocytosis and oligoclonal bands. These findings suggest a CSF humoral immune response; an extensive laboratory workup is otherwise largely unremarkable (*Table 1, page 67*).

Which disorder most likely accounts for Ms. T's presentation?

a) schizophrenia
b) bipolar disorder

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continued on page 67

continued from page 62

c) paraneoplastic syndrome
d) complications from a primary seizure disorder

The authors' observations

We consider that Ms. T may have schizophrenia. Schizophrenia onset is insidious, often with prodromal symptoms occurring months to years before diagnosis.[1,2] In Ms. T, the onset of the disturbance was brief; her family noted a change in behavior for only 1 week before presentation. Given this history, brief psychotic disorder remains high on the differential diagnosis because Ms. T's disorganized speech and behavior occurred seeming in relation to her mother's death.

Bipolar disorder is characterized by strong heritability, with risks increasing if there is a first-degree relative with the illness. The hallmark of bipolar I disorder is a manic episode, which presents as:

- decreased need for sleep
- grandiosity
- flight of ideas
- reckless or thoughtless behaviors
- increased energy
- increased productivity
- expansive or irritable mood.

This diagnosis seems to fit well with our patient, who for 1 week had increased rate of speech, hyperactivity, and decreased need for sleep. She also has a positive family history of bipolar illness. Often patients with bipolar disorder experience a prodrome characterized by periods of depressed mood and periods that appear similar to mania but are not as obvious or severe.[1,2] Ms. T lacks this history.

Psychiatric symptoms secondary to seizure disorder are well documented. Cognitive, mood, anxiety, and psychotic phenomena may occur in up to 50% of patients with seizures.[3] Typically, these symptoms are categorized as occurring during a seizure, after a seizure (post-ictal), or between seizures (interictal).

Manic syndromes secondary to seizure disorders present in an atypical manner with irritability and hyperactivity. Psychotic syndromes, on the other hand, appear with more classic schizophrenia-type symptoms:

- paranoia and persecutory delusions
- auditory and visual hallucinations
- amotivation
- apathy
- flattened affect
- disorganization.[3]

Ms. T had no history of witnessed seizure activity; however, the observed seizure early in her admission warranted exploring a possible underlying general medical condition.

Paraneoplastic syndromes may be associated with mood changes and other psychiatric symptoms.[4-6] Diagnosis is contingent on discovering the primary neoplasm, with or without specific paraneoplastic antibodies. Treatment is tailored to the oncologic process.

Table 1

Ms. T's laboratory workup*

Test	Result
C-reactive protein	0.7
Erythrocyte sedimentation rate	5
Cryptococcal antigen (serum)	Negative
Antinuclear antibody	Negative
CSF lymphocytes	88
CSF nucleated cells	200
CSF RBC	33
CSF glucose	44
CSF protein	45
CSF igG index	1.2
CSF oligoclonal bands	Present

CSF: cerebrospinal fluid; igG: immunoglobulin G; RBC: red blood cell
*Results were negative for gonorrhea, chlamydia, lupus, human immunodeficiency virus, syphilis, Lyme disease, varicella zoster virus, West Nile virus, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, tuberculosis, and California, St. Louis, eastern equine, and western equine encephalitis

EVALUATION A medical cause

The psychiatry consultation-liaison service is asked to further evaluate Ms. T for psychiatric contributions to her continued altered mental status. Ms. T remains in restraints

Clinical Point

Mania syndromes secondary to seizure disorders present atypically with irritability and hyperactivity

Clinical Point

Neurobehavioral symptoms predominate early in the course of paraneoplastic illness

Table 2

Anti-NMDA receptor encephalitis: Symptoms, findings, and treatment

Typical presentation
Young female
Prodromal symptoms
New onset psychosis, anxiety, or mood symptoms
Catatonia
Coma
Seizure activity (typically bilateral temporal lobe activity on EEG)
Hypoventilation
Autonomic instability
Dyskinesia
Laboratory and radiologic findings
CSF or serum antibodies
CSF pleocytosis and elevated protein, normal glucose
Background slowing or sharp-wave activity on EEG
Temporal lobe abnormalities
Treatment
Tumor resection
Immunosuppressants (typically corticosteroids)
Intravenous immunoglobulin
Plasmapheresis

CSF: cerebrospinal fluid; EEG: electroencephalography; NMDA: *N*-methyl-D-aspartate

and receives fosphenytoin, 200 mg bid; levetiracetam, 1,000 mg bid; and lorazepam as needed for agitation. Following consultation, the team considers a working diagnosis of an autoimmune encephalopathy based on the negative infectious workup, the patient's demographics, and the clinical picture (psychiatric symptoms, seizure, and encephalopathy). Ms. T undergoes 5 courses of plasma exchange with no effect. Catatonia is considered, but the patient does not demonstrate significant change with numerous doses of lorazepam.

Because Ms. T does not improve, the team starts a more specific paraneoplastic workup. MRI reveals a 9-mm lesion on her right ovary. Corticosteroids, including IV methylprednisolone, 1 g/d, are started. Ms. T's clinical presentation improves; soon after scheduled corticosteroid dosing, she is taken to the operating room for right salpingo-oophorectomy. Surgical pathology later confirms the lesion as a mature teratoma. A standard paraneoplastic panel is negative; a separate test for anti-NMDA (*N*-methyl-D-aspartate) receptor antibodies is positive, however, and confirms the diagnosis of ovarian mass-associated anti-NMDA receptor limbic encephalitis.

Paraneoplastic syndromes are most often associated with which type of cancer?

a) breast
b) lung
c) ovarian
d) colon

Paraneoplastic syndromes

This case represents the interface between a complicated medical phenomenon and psychiatric symptomatology. Mood changes (typically depression), memory problems, paranoia, hypersomnolence, aggressive behavior, agitation, and catatonia have been associated with paraneoplastic syndromes.[4-6]

Common malignant associations include small cell lung carcinoma (most common) and breast, stomach, colon, renal, bladder, ovarian, uterine, testicular, cell line, and thymic cancers. Research strongly suggests an autoimmune mechanism: tumor-related antibodies cross-react with similar antigens in the neurologic system. Paraneoplastic symptoms often precede symptoms of the malignancy, and the diagnosis is suggested by positive imaging and a paraneoplastic panel.

Definitive treatment is that which is appropriate for the specific neoplasm. Other successful therapies include immunosuppressants (including corticosteroids) and, less often, intravenous immunoglobulin (IVIg) or plasma exchange (when laboratory testing confirms known antibodies).[7] Prognosis is highly variable, from complete

continued on page 71

continued from page 68

recovery to death; antibody-positive cases may portend a more guarded prognosis.[4]

Anti-NMDA receptor limbic encephalitis is a paraneoplastic syndrome associated with ovarian teratomas and antibodies specific to the glutamate receptor. It is thought to be an autoimmune phenomenon whereby tumor-related antibodies elicit an immune response within certain parts of the neurologic system. Ms. T represents a typical clinical presentation of this syndrome—she is a young, otherwise healthy woman with:

- preceding headache
- new-onset psychotic symptoms
- seizure activity (particularly in the temporal lobes)
- central hypoventilation
- hyperthermia and tachycardia
- dyskinesia and catatonia-like symptoms.[5]

The course of anti-NMDA receptor limbic encephalitis typically progresses in distinct phases from prodromal symptoms to psychosis to unresponsiveness and hypoventilation to dysautonomia and dyskinesia.[4,5] Anti-NMDA receptor antibody identification is not included in standard paraneoplastic panels but can be specifically ordered from the University of Pennsylvania and Mayo Medical Laboratories.

Which of the following are treatments for anti-NMDA receptor limbic encephalitis?

a) corticosteroids
b) plasma exchange
c) surgical excision
d) all of the above

TREATMENT Rapid improvement

After removal of the dermoid lesion and IV corticosteroids, Ms. T exhibits rapid improvement. She begins acknowledging others in the room, making eye contact for nearly the first time during this hospitalization, and starts recognizing family members. She also begins verbalizing, responding appropriately to questions in 1 or 2 words. After a 34-day hospital stay, Ms. T is transferred to another facility for rehabilitation; her medication list consists of a corticosteroid taper from prednisone, 20 mg/d, over 2 weeks; fosphenytoin, 200 mg bid; and levetiracetam, 1,000 mg bid.

She eventually is discharged from the rehabilitation facility with noted improvement in multiple domains: she demonstrates cognitive improvement and can walk short distances. She

Box

Paraneoplastic syndromes: Case reports show common patterns

Neurology. Several case reports in neurologic literature describe presentations similar to Ms. T's.

Sansing et al[8] described a 34-year-old woman with prominent psychiatric symptoms who had an immature ovarian teratoma with positive anti-NMDA (*N*-methyl-D-aspartate) receptor antibody. She was treated with tumor resection, plasmapheresis, and corticosteroids and experienced significant improvement.

Nasky et al[7] describe a 23-year-old woman with paranoia, agitation, and delusions. A neoplasm was not identified, but she was anti-NMDA receptor antibody positive and improved with IV corticosteroids and IV immunoglobulin.

Dalmau et al[5] compiled a case series analysis of 100 cases of anti-NMDA receptor encephalitis. Tumor removal with IV corticosteroids, IV immunoglobulin, and plasma exchange were the most common treatments. Patients with tumors that were identified and resected had better functional recovery than those without tumor resection.[5]

Psychiatry. A search of psychiatric literature yielded only 2 pertinent case reports. Lee et al[9] described an 11-year-old girl with acute confusion, agitation, paranoia, hallucinations, and later malignant catatonia that improved after removal of an ovarian teratoma. Seki et al[10] reported on an 18-year-old woman who presented with schizophrenia-like symptoms of disorganization and loss of self awareness. This patient's symptoms resolved almost completely after unilateral salpingo-oophorectomy, corticosteroid administration, and plasma exchange.

Clinical Point

Anti-NMDA receptor limbic encephalitis is associated with ovarian teratomas and antibodies specific to the glutamate receptor

Related Resource

• Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol. 2008;7(4):327-340.

Drug Brand Names

Fosphenytoin • Cerebyx
Haloperidol • Haldol
Levetiracetam • Keppra
Lorazepam • Ativan
Methylprednisolone • Medrol, Depo-Medrol, others
Olanzapine • Zyprexa
Prednisone • Deltasone, Meticorten
Ziprasidone • Geodon

Disclosures

Drs. Cavalieri and Southammakosane report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. White is a consultant for Pfizer Inc.

Clinical Point

Treatment for paraneoplastic illness may include tumor removal and immunosuppressants

continues to require 24-hour care and exhibits intermittent agitation.

The authors' observations

We present the case of a patient with a specific paraneoplastic disorder—anti-NMDA receptor limbic encephalitis—with symptoms mimicking those seen in psychiatric disorders such as schizophrenia and bipolar disorder. These similarities complicate recognition and treatment of the underlying disorder.

Ms. T had a complicated yet typical presentation of anti-NMDA receptor limbic encephalitis (***Table 2, page 68***) that was initially mistaken for a manic episode with psychotic features. The diagnosis was made more complex by the death of her mother 1 week before presentation, which could have precipitated her symptom onset. Similar case reports have appeared in neurologic and—less frequently—psychiatric literature (***Box, page 71***).[5,7-10]

Commonly, patients with paraneoplastic limbic encephalitis experience a protracted hospital stay and extensive medical workup with long inpatient psychiatry stays before more severe physical manifestations—such as seizure activity and autonomic instability—prompt transfer to medical or neurologic services.[5] Ms. T spent time on psychiatric, internal medicine, and neurologic services before her team established a definitive diagnosis.

Because neurobehavioral symptoms predominate early in the course of paraneoplastic illness,[5] psychiatrists should prepare to be the first medical point of contact for these patients.

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Bottom Line

Patients with paraneoplastic limbic encephalitis commonly present with behavioral or mood changes that mimic those of psychiatric illnesses such as schizophrenia and bipolar disorder, which often delays diagnosis. Definitive treatments are specific to the neoplasm and include surgical excision, corticosteroids, and IV immunoglobulin or plasma exchange when laboratory testing confirms the presence of antibodies.