Clinical Reasoning: An 18-year-old man with subacute mental status change

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SECTION 1

An 18-year-old man was brought to the emergency department (ED) by his parents because he was "not himself." Two days prior, he woke with a bloody tongue and no memory of biting it, decreased appetite, fever, and fatigue. His parents observed him to have impaired short-term memory, "jerky" flexion-extension movements of the arms, visual hallucinations, and confusion.

There was no recent travel, illness, animal or insect bites, prolonged outdoor exposure, or tobacco, drug, or alcohol abuse. He was afebrile with normal vital signs. There was bradyphrenia, poverty of speech, deficits in short-term memory, and poor attention. Cranial nerves, deep tendon reflexes, coordination, gait, strength, and sensation were normal and symmetric with downgoing toes. No abnormal movements were observed in the ED. Complete blood count, comprehensive metabolic panel, urine drug screen, and noncontrast head CT scan were normal. A lumbar puncture was performed and CSF analysis showed 23 white blood cells with 86% lymphocytes, 14% monocytes, 0% neutrophils, 187 erythrocytes, protein 46, glucose 94.

Questions for consideration:

1. What treatable diagnosis is at the top of the differential?
2. What diagnostic studies and empiric therapies should be considered?

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SECTION 2

Herpes simplex virus (HSV) encephalitis should be the primary concern and CSF was sent for HSV 1 and 2 PCR. MRI of the brain with gadolinium was normal. He was treated with acyclovir in the ED and phenytoin was started for what was thought to have been a seizure at home.

On the second day of hospitalization, he had a nonfocal examination, but became aggressive and violent, had constant visual hallucinations, and only recognized his mother. Psychotic behavior persisted for several days and he was started on haloperidol. An EEG showed diffuse slowing. HSV PCR of the CSF was negative, but acyclovir was continued. On the fifth day, he exhibited hypersalivation and chewing movements, and was nonverbal. His respiratory effort increased, and he was transferred to the intensive care unit.

His eyes were open and fixed forward with no blink to threat and his extremities were rigid. He did not speak, make eye contact, follow commands, or move spontaneously. Brainstem reflexes were intact. He had a generalized seizure and was intubated for deteriorating respiratory function. Fever, hypertension, rigidity, and haloperidol use made neuroleptic malignant syndrome a consideration. Dantrolene was started but stopped after creatine phosphokinase remained normal and other symptoms resolved.

He experienced fluctuating blood pressure, tachycardia, fever, hypersalivation, ileus, constipation, hyperhydrosis, and generalized seizures. Levetiracetam was added. Movements of the mouth and face were prominent with constant air swallowing. Acyclovir was discontinued after HSV PCR was negative twice.

Questions for consideration:

1. How has the differential changed, and what diagnostic considerations remain?
2. What are the salient physical signs and symptoms of his hospital course?

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HSV was our primary consideration due to his altered consciousness, seizures, psychiatric symptoms, and short-term memory loss, although there were no MRI abnormalities in the medial temporal or inferior frontal lobes, and HSV PCR was negative twice. Aside from a lymphocytic pleocytosis, CSF protein and glucose did not provide strong evidence for HSV or another infectious process. Other infections that may present with mental status change, including Epstein-Barr virus, cytomegalovirus, varicella zoster virus, West Nile virus, rabies, syphilis, tuberculosis, and cryptococcus, were negative. Vaccinations were up to date and measles infection leading to subacute sclerosing panencephalitis was not thought likely. HIV testing was negative. He was afebrile and there was a low suspicion for bacterial meningitis.

A rheumatologic process was unlikely due to unremarkable history and laboratory values including antinuclear antibodies, anti-double-stranded DNA, and anti-ribosomal-P to evaluate for systemic lupus erythematosus cerebritis, and negative SS-A and SS-B antibodies for Sjögren syndrome. Vasculitis was considered unlikely and therefore a CT angiogram was not performed. A vascular ischemic process was low on the differential because of his age, lack of risk factors, and normal diffusion-weighted imaging. Hashimoto encephalopathy can present with cognitive abnormalities and elevated thyroperoxidase and thyroglobulin antibodies despite a euthyroid state, although these were not checked.

A primary psychiatric or drug-related etiology was unlikely with a negative history and no use of neuroleptics or selective serotonin reuptake inhibitors prior to admission. There was no epileptiform activity to support a diagnosis of nonconvulsive seizures although continuous monitoring would have been more definitive. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes was unlikely because there was no history of migraines with vomiting, no stroke-like episodes, no growth or developmental abnormalities, and normal lactate levels. Porphyria typically causes abdominal pain and gastrointestinal symptoms, but neuropathy, behavioral changes, or frank psychosis may manifest. Our patient did not display ophthalmoplegia or ataxia or have a history of alcohol abuse or a malnourished state that might have supported a diagnosis of Wernicke-Korsakoff syndrome.

There was a prodrome of fever, decreased appetite, and fatigue prior to hospitalization. While hospitalized, autonomic symptoms, oral dyskinesias, rigidity, and generalized seizures were observed, along with psychosis progressing to an unresponsive state, and ventilator-dependent respiratory failure. This diffuse and unique constellation of findings led us to explore an autoimmune paraneoplastic encephalitis.

CSF was sent for anti-Hu, anti-CRMP5 (anti-CV2), anti-Ma2, anti-amphiphysin, and anti-voltage-gated potassium channels (anti-VGKR). No neoplasm was identified on CT of the chest, abdomen, or pelvis, or a testicular ultrasound. Another MRI of the head with gadolinium was normal; repeat lumbar puncture showed 10 leukocytes with 98% lymphocytes, 2% monocytes, 0% neutrophils, 0 erythrocytes, 18 protein, 72 glucose, with 5 oligoclonal bands in the CSF but not the serum.

He was treated with a 5-day course of IV immunoglobulin (IVIg) for a presumptive autoimmune process without improvement. Serum and CSF were sent to test for NMDA receptor (NMDAR) antibodies and returned positive, while other paraneoplastic antibodies were later found to be negative. After 2 weeks under our care, he was transferred to another institution for further investigation. In retrospect, no abnormalities consistent with this disease were appreciated on the MRIs at our institution.

At the outside hospital, he was treated with rituximab without clinical improvement. Cyclophosphamide was given within the initial weeks to months and it is unclear what effect this had clinically although there was reportedly a dramatic decrease in CSF antibody titers in the first several months.

The patient had a tracheostomy and a percutaneous gastrostomy (PEG) tube placed. He remained on mechanical ventilation for 1 month. No tumor was identified on PET. He was hospitalized for 7 months and then discharged to rehabilitation, and as of 10 months he still requires 4 antiepileptics for generalized seizures. Repeat body CT scans and testicular ultrasounds have been negative. No surgical exploration has been performed in search of an occult tumor. He receives monthly maintenance IVIg and cyclophosphamide followed by CSF analysis to measure antibody titers, which reportedly continue to decrease. Autonomic stability has returned and oral dyskinesias have ceased. There is still a poverty of spontaneous speech although he frequently repeats or mimics others. He also uncharacteristically curses, and is emotionally labile with frequent laughing and crying. The PEG tube remains in place.

DISCUSSION Anti-NMDAR encephalitis is an immune-mediated syndrome most often diagnosed in young women from ages 20–50. It is typically associated with a mature or immature ovarian teratoma and less frequently a mediastinal teratoma or no tumor.[1-3] There have been fewer documented

cases in men, with testicular or mediastinal teratomas, small cell lung cancer, or no tumor identified.[3]

A prodrome consisting of fatigue, headache, fever, or a viral-like illness may last days to weeks and is followed by a psychotic phase. The usual presenting symptoms are personality or behavioral change, loss of short-term memory, or hallucinations.[1,3] Empiric treatment with acyclovir for herpes encephalitis is common. After several days patients become less responsive, and hypoventilation requiring mechanical ventilation can occur. The unresponsive phase may persist for months.[3]

Hyperkinesis is a prominent feature, consisting of rigidity, orofacial or extremity dyskinesias, myoclonus, ballism, dystonic postures, or movements of the pelvis and abdomen, sometimes psychogenic in appearance.[1-3,4,5] Because of rigidity, hypertension, fever, and recent exposure to neuroleptics or selective serotonin reuptake inhibitors, patients may be misdiagnosed with neuroleptic malignant or serotonin syndrome.[6] Seizures are also frequent, with generalized being the most common.[1-3]

In a case series of 100 patients with anti-NMDAR encephalitis, 55 patients had abnormal MRI findings on fluid-attenuated inversion recovery/T2 with contrast enhancement on T1, predominantly in the medial temporal lobes or cerebral cortex.[3] Ninety-five patients had lymphocytic pleocytosis, elevated protein, or oligoclonal bands in CSF. Ninety-two patients had an abnormal EEG; mainly diffuse or frontotemporal slowing, with the minority having epileptic activity.[3] Fifty-nine percent of patients had a tumor, with aberrant NMDAR expression as the likely inciting agent.[1-3]

Neurologic recovery correlates with a decrease in antibody titers, suggesting that the anti-NMDAR is pathogenic.[3] IVIg, plasmapheresis, steroids, cyclophosphamide, and rituximab have all been used with variable results.[3] Tumor resection followed by immunotherapy is most effective for clinical and radiologic resolution, although frontal-lobe dysfunction and sleep disturbances may persist.[3]

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DISCLOSURE

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