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The Diagnostic Conundrum and Treatment Dilemma of a Patient With a Rapidly Progressive Encephalopathy

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A 45-year-old man of the Yakama Nation tribe without significant medical history had an abrupt onset headache that progressed over a week. He presented to an emergency department and a noncontrast head computerized tomography (CT) was unremarkable except for mild ethmoid sinus disease. One week later, the patient developed neck stiffness, fever to 101.6 degrees F, chills, and body aches. The patient's partner reported episodes of confusion with auditory and visual hallucinations, seeing things on the wall, and thinking he was covered in chocolate.

After 2.5 weeks into the course of illness, the patient sought care from his primary care physician who referred him to a local emergency department. In the emergency department, the patient was afebrile though ill appearing with diaphoresis. He had fluent speech, normal comprehension, and intact memory and concentration. He was noted to have an unsteady tandem gait and positive Romberg sign. The rest of the neurologic examination was unremarkable.

He was admitted to the hospital where cerebrospinal fluid (CSF) analysis revealed a significant neutrophil-predominant pleocytosis with a low glucose (Table 1, column Day of Illness 17). An infectious etiology was suspected, and empiric treatment was initiated with intravenous administration of ceftriaxone, vancomycin, acyclovir, and dexamethasone. Extensive serum and CSF infectious and autoimmune workup was unrevealing (Table 2). Repeat imaging with a contrast-enhanced brain magnetic resonance imaging (MRI) about 3 weeks after symptom onset demonstrated hyperintensities in the deep gray and white matter as well as basal leptomeningeal enhancement (Figure 1). An atypical viral meningoencephalitis was presumed and antibiotics, antivirals, and steroids were discontinued.

The hospital course was characterized by a progressive encephalopathy, and approximately 1 month after initial symptom onset, the patient began having episodes of unresponsiveness concerning for seizures and required intubation. In between the episodes, he was drowsy and followed simple commands.

His clinical progression and episodes of depressed consciousness prompted transfer to our institution for further evaluation. On arrival, repeat CSF analysis revealed a persistent neutrophilic pleocytosis and hypoglycorrhachia (Table 1, column Day of Illness 27). Intravenous acyclovir, ceftriaxone, vancomycin, and enteral doxycycline were initiated. As CSF cultures, antibody tests, and viral polymerase chain reactions (PCRs) returned negative, these treatments were again discontinued. Continuous electroencephalogram (EEG) monitoring over a 3-day period revealed diffuse slowing but no epileptiform activity. Contrast-enhanced CT of the chest, abdomen, and pelvis and testicular ultrasound were normal. Whole-body [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scan from the base of skull to upper thighs revealed no evidence of primary malignancy or metastases. A nonlesional brain biopsy from the right frontal lobe demonstrated nonspecific findings of scattered rare perivascular lymphocytic infiltrates with no evidence of neoplasm or a specific infection (Figure 2).

Due to the persistent CSF pleocytosis, hypoglycorrhachia, and elevated protein, as well as brain imaging with basal leptomeningeal enhancement, antituberculous medications and dexamethasone were started and continued for an 8-week course. The patient had no known exposure to tuberculosis (TB). The CSF fungal cultures and broad-based PCR tests for fungal elements and TB were negative (Table 2).

Six weeks after the symptom onset, the patient progressed to a deep coma, unresponsive to both verbal and painful stimuli and with no purposeful movements. He also began

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Table 1. Cerebrospinal Fluid Analysis.

	Day of Illness							
	17	27	31	38	47	79	150	Normal Values
Red cells/μL	15	1	20	5	0	0	0	None
White cells/μL	1046	493	329	143	39	14	4	0-5
Neutrophils, %	67	69	56	07	01	00	00	
Lymphocytes, %	25	27	38	67	86	94	75	
Monocytes, %	08	04	6	26	13	06	25	
Protein, mg/dL	127	111	101	95	55	51	41	15-45
Glucose, mg/dL (% of serum glucose)	36 (28)	37 (36)	34 (32)	56 (39)	51 (54)	59 (39)	51 (52)	40-80

Table 2. Blood, Urine, and Cerebrospinal Fluid Testing.

Testing	Fluid	Result	Day of Illness When Test Performed
Coccidioides immitis (Ig G/IgM)	Blood	Negative	17, 31
Cryptococcus antigen	CSF	Negative	17, 30
Histoplasma antigen	Blood and Urine	Negative	31
Mycoplasma pneumonia (IgG/IgM)	Blood	Negative	30
Toxoplasma gondii (IgG/IgM)	CSF	Negative	27
Treponema pallidum (FTA-ABS)	Blood and CSF	Negative	30
Treponema pallidum (VDRL)	Blood	Negative	27, 30
Treponema pallidum RPR	Blood	Negative	27
Herpes simplex virus PCR	CSF	Negative	17, 30
Cytomegalovirus PCR	CSF	Negative	27, 30
Bartonella henselae	Blood	Negative	27
Brucella	Blood	Negative	27
Borrelia Burgdorferi (IgG/IgM)	Blood and CSF	Negative	27
Epstein-Barr virus (IgG/IgM)	Blood and CSF	Negative	27, 30
Human herpes virus 6 PCR	CSF	Negative	30
Varicella zoster virus PCR	CSF	Negative	30
Human immunodeficiency virus (RNA PCR)	Blood	Negative	48
Human immunodeficiency virus (Western blot)	Blood	Negative	18, 48
Arbovirus (IgG/IgM)	CSF	Negative	17
Enterovirus PCR	CSF	Negative	17, 30
Parechovirus PCR	CSF	Negative	30
West Nile virus (IgG/IgM)	CSF	Negative	27, 30
Influenza A and B (optical immunoassay)	Nares	Negative	17
Mycobacterium tuberculosis PCR	CSF	Negative	17, 38
Mycobacterium tuberculosis (Quantiferon Gold)	Blood	Negative	20, 33
Acid fast Bacilli culture	CSF	Negative	30
Mycobacterium avium PCR	CSF	Negative	38
Aspergillus fumigatus PCR	CSF	Negative	37
Creutzfeldt-Jakob (14-3-3, and tau amount)	CSF	Negative	30
Cytology	CSF	Negative	27, 30, 37
Anti-nuclear antibody	Blood	Negative	27
Extractable nuclear antigen panel (dsDNA, SM, ribosomal P, chromatin, RNP, Sm RNP, Scl-70, centromere B, SSA, SSB, and Jo-1)	Blood	Negative	27
Paraneoplastic antibody panel (antineuronal nuclear antibody, anti-glial nuclear antibody, Purkinje cell cytoplasmic antibody, amphiphysin antibody, and CRMP-5 IgG)	CSF	Positive for unidentified anti-neuronal antibody	38

Abbreviations: CSF, cerebrospinal fluid; FTA-ABS, fluorescent treponemal antibody-absorption; Ig, immunoglobulin; VDRL, Venereal Disease Research Laboratory; RPR, rapid plasma regain; PCR, polymerase chain reaction; dsDNA, double-stranded DNA; SM, Smith antibody; RNP, ribonucleoprotein; SSA, Sjögren antibody A; SSB, Sjögren antibody B; CRMP-5 IgG, Collapsin response mediator protein 5.

exhibiting limb and orofacial choreoathetoid movements with dystonia. He had severe dysautonomia, including hyperthermia, tachycardia, and hypertension. Multiple medications were trialed—including benzodiazepines, propranolol, baclofen, trihexyphenidyl, and botulinum toxin injections to the masticatory muscles—which had little improvement.

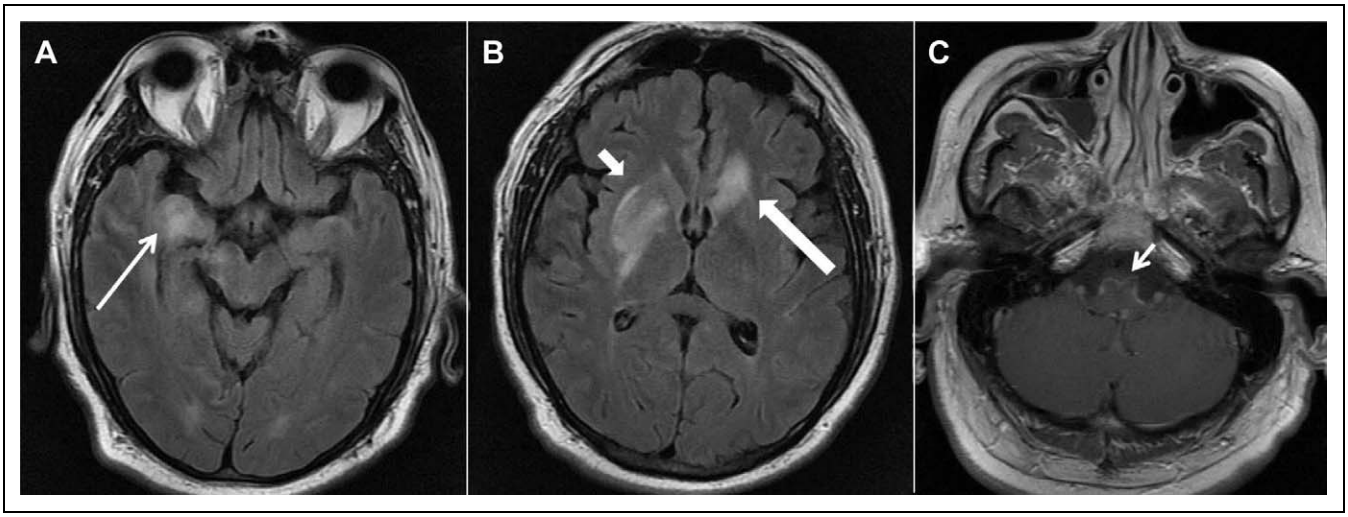

Figure 1. Magnetic resonance imaging (MRI) scans of the brain on day 27 of illness. A and B, Fluid attenuated inversion recovery (FLAIR) axial images of the lesions in the medial right temporal lobe (thin long arrow), right basal ganglia (short thick arrow), inferior left frontal lobe, and left caudate nucleus (long thick arrow). C, T1 postcontrast axial image demonstrating leptomeningeal enhancement involving the medulla (short thin arrow).

A diagnostic test result was obtained.

Differential Diagnosis

Discussant: Sandeep Khot

Neurohospitalists often encounter cases in which seizures and encephalopathy can follow a complex clinical course. This case demonstrates the difficulty in diagnosis, where a clinical syndrome involves fluctuating symptoms over many weeks and over multiple clinical institutions. The patient's presentation to our institution was characterized predominantly by episodes of depressed consciousness with concern for subclinical seizures. He was appropriately started on antiepileptic medications and monitored with continuous video EEG. However, the initial development of fever and neck stiffness with headache was highly suspicious for infectious meningitis. In our patient, the presence of these symptoms in the setting of an altered level of consciousness, possible seizures, and hyperintense signal within the temporal lobe suggested the development of encephalitis. Patients with encephalitis typically have fever and headache along with confusion, behavioral abnormalities, depressed level of consciousness, focal neurologic deficits, or new-onset seizure activity.[1]

Encephalitis can be characterized as either infectious or noninfectious, with or without associated CSF inflammation. Historically, the most common identifiable causes of encephalitis have been infectious, including reactivation of latent herpes virus infection, including herpes simplex virus 1 (HSV-1) and varicella zoster virus, tick-borne bacterial infections, and arthropod-borne viral infections, including West Nile virus.[1] Noninfectious etiologies are typically autoimmune disorders, which may or may not be related to an underlying tumor. Limbic encephalitis, an inflammatory disorder with demonstration of MRI and EEG abnormalities in the temporal lobe with a typically mild CSF pleocytosis, can be either infectious or autoimmune. Limbic encephalitis classically involves the rapid development of irritability, depression, sleep disturbances, hallucinations, and short-term memory loss.[2] Our patient's clinical presentation was suspicious for subacute-onset limbic encephalitis, and he was appropriately started on acyclovir. Patients with HSV-1 encephalitis typically progress rapidly with depressed consciousness, focal neurologic deficits, and evidence of hemorrhagic inflammation on MRI and CSF evaluation.[3] The MRI finding of medial temporal lobe abnormalities was particularly concerning for HSV-1 infection, although basal ganglia involvement and basal meningeal enhancement were atypical (Figure 1). Given that the HSV PCR can be falsely negative when obtained within the first 72 hours of disease onset, restarting acyclovir and repeating the PCR testing were appropriate.

Although the initial suspicion in our patient was for an infectious meningoencephalitis, the findings of negative CSF testing and the development of new symptoms such as dyskinesias and dysautonomia led to further consideration for autoimmune limbic encephalitis. The diagnoses of autoimmune limbic encephalitis can be broadly categorized into those classic syndromes associated with antibodies to intracellular neuronal antigens (anti-Hu, anti-Ma proteins, and less frequently anti-CV2/CRMP5 and amphiphysin), which are often associated with a tumor, and antibodies to cell membrane antigens (voltage-gated potassium channel, N-methyl-D-aspartate receptor, and others that remain uncharacterized), which may or may not be related to a tumor.[2] Cancer screening with body CT, testicular ultrasound, and FDG-PET scan were obtained to evaluate for the presence of a tumor, and paraneoplastic antibody testing was obtained in both the serum and the CSF. The severity of CSF pleocytosis in our patient was unusual for

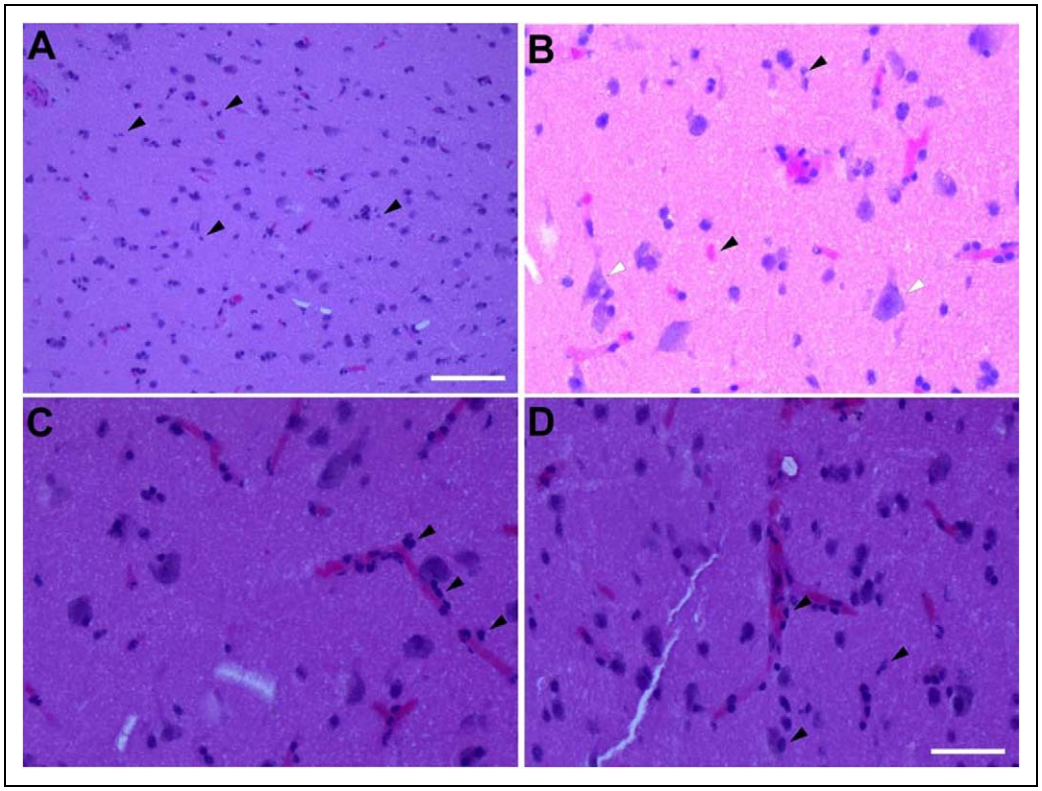

Figure 2. Nonlesional brain biopsy. A-D, Hematoxylin and eosin-stained sections show activated microglia (black arrowheads). B, Background neurons (white arrowheads) are identified. Scale bar in A = 250 μ; B-D = 100 μ.

autoimmune encephalitis, where typically only a mild to moderate lymphocytic pleocytosis is found.

Diagnostic challenges

As in this case, the lack of a specific diagnosis leaves the clinician uncertain how to predict or alter the course of the disease. The clinical picture of rapidly progressive coma suggested either infectious or autoimmune-mediated encephalitis, but the CSF profile was more concerning for an infectious etiology. Further immunosuppression for presumed autoimmune or paraneoplastic limbic encephalitis was considered though not initiated early on due to concern for potential TB meningoencephalitis.

Diagnosis of TB meningoencephalitis

Infectious causes of meningoencephalitis are frequently considered in the differential diagnosis of progressive encephalopathy with CSF pleocytosis. Most bacterial, fungal, and specific viral etiologies of meningitis can be evaluated by antibody or PCR testing or CSF cultures. The TB meningitis is particularly difficult to diagnose definitively, given the insensitive testing for acid-fast bacilli (AFB) in CSF. The CSF pleocytosis and hypoglycorrhachia, as well as basal meningeal enhancement on brain MRI, raised concern for TB meningitis. The TB meningitis is the most severe form of extrapulmonary TB with a broad and nonspecific presentation of disease, necessitating a high index of suspicion among providers and making an early diagnosis difficult. Characteristically, CSF shows a lymphocytic pleocytosis, an elevated protein level greater than 100 mg/dL, a low CSF glucose with a ratio of CSF-blood glucose <0.5 or some combinations of these findings.[4]

Neuroradiologic findings in TB meningitis include meningeal inflammation, basal exudates, infarcts, or hydrocephalus.[5,6] Parenchymal involvement can present with a localized tuberculoma, abscess, or cerebritis, as well as ischemic stroke,[7] typically involving the deep gray matter of the thalamus or basal ganglia.[8] Our patient developed hyperintense lesions on T2 and fluid attenuated inversion recovery (FLAIR) sequences within the basal ganglia and medial temporal lobe though without evidence of ischemia.

The demonstration of *Mycobacterium tuberculosis* in CSF smear or culture is required to confirm the diagnosis, though both the methods are insensitive and can be associated with a treatment delay. The sensitivity of CSF culture for TB meningitis in most Western countries is only between 52% and 78% and may take up to 6 weeks.[9] Diagnostic tests such as nucleic acid amplification, including PCR, are also limited by low sensitivity (60%) for CSF AFB.[10] Tuberculin skin testing or interferon-γ release assays, such as the Quantiferon-TB gold,

have limited utility for a rapid diagnosis and do not distinguish between prior exposure and active disease nor confirm central nervous system TB. In suspected cases of TB meningitis, treatment with antituberculosis medications should be promptly initiated while awaiting definitive diagnostic testing, because treatment delay has been associated with poorer outcome.[11] The use of dexamethasone has also been shown to decrease mortality in the treatment of TB meningitis.[12]

Diagnostic Results

Approximately 6 weeks after the symptom onset, serum and CSF anti-N-methyl-D-aspartate receptor (NMDAR) antibodies returned positive by indirect immunofluorescence. The CSF also demonstrated a nonspecific antineuronal antibody. Given the positive anti-NMDAR antibodies in the setting of the later clinical features of facial dyskinesias, rigidity, and autonomic instability, 5 plasmapheresis treatments were completed over 2 weeks. The patient had slow improvement in the abnormal movements and dysautonomia over the following month. He remained unresponsive to commands or a painful stimulus though was noted to resist eye opening and occasionally attend to the examiner. He had completed a 2-month course of antituberculous treatment, and these medications were discontinued before completion of a full course of the therapy in favor of an alternative diagnosis. Rituximab infusions were subsequently initiated (weekly 800 mg for 4 weeks).

Anti-NMDA Receptor Encephalitis

Discussant: Christopher Beatty

Anti-NMDAR encephalitis, first described in 2007,[13] is a well-characterized autoimmune condition with specific autoantibodies to the NMDAR. The majority of anti-NMDAR encephalitis cases are associated with an underlying tumor, frequently an ovarian teratoma.[14] The actual incidence of anti-NMDAR encephalitis is unknown, although multiple studies have demonstrated that it is a common causative agent of previously undiagnosed cases of encephalitis.[15-17] Approximately three-quarters of the affected individuals are women, and a tumor is detected in up to 59% of the adult patients.[14,18,19] In adult men, anti-NMDAR encephalitis is related to neoplasm in only 6% of the patients.[20] The mechanism initiating the disorder in those patients without neoplasm is unknown.

Clinical Course and Complications

Anti-NMDAR encephalitis can present with symptoms similar to infectious encephalitis, though patients usually develop a characteristic sequence of symptoms.[14,18,19] The typical clinical course, seen in up to 70% of the patients, begins with prodromal symptoms of headache, fever, nausea, diarrhea, or upper respiratory tract symptoms.[19] The clinical picture will commonly progress within the following 2 weeks,[19] with the development of behavioral and psychiatric symptoms, including agitation, hallucinations, bizarre behavior, and speech problems. The language disorder can vary from a reduction in speech output and echolalia to mutism.[19] After 10 to 20 days of initial symptoms, patients enter the second phase of illness.[18] Patients may develop orofacial and limb dyskinesias, catatonia, and a decreased level of consciousness.[14,18,19] Seizures, autonomic instability, and central hypoventilation, which may necessitate intubation, can occur during this period as well.[14,18,19] Dissociative responses to stimuli, such as resisting eye opening though remaining unresponsive to painful stimuli, have also been described in this latter phase of illness.[19]

The time course of our patient's symptoms was unusual. The subacute development of confusion and hallucinations, about 2 to 3 weeks after the onset of headaches, was intermittent and quickly overshadowed by episodes of unresponsiveness and later by a severe encephalopathy. The patient's movement disorder and autonomic dysfunction were not apparent until 40 days of illness. Such a delayed course of symptoms has been rarely reported with anti-NMDAR encephalitis.[18]

The majority of patients with anti-NMDAR encephalitis will recover fully or be left with mild deficits over time. Recovery is often hastened by immunosuppressive treatment. The best outcomes are seen when treatment is initiated within 40 days of the onset of disease.[18] In our case, the concern for infection made early immunosuppression a dangerous option. Patients typically require a prolonged hospitalization with a usual duration of 3 to 4 months of inpatient management (range of 1-14 months).[14,19] In a retrospective review of cases prior to the description of the disease where patients were subsequently confirmed to have anti-NMDAR encephalitis, recovery without immunosuppressive treatment took more than 3 years.[21] Immunotherapy and tumor removal result in a good recovery (slight disability or better on the modified Rankin scale) in 81% of the patients with anti-NMDAR encephalitis with a median follow-up of 24 months.[20] The majority of symptoms from the disease may resolve, though many patients continue to have difficulty with executive function, memory, and disinhibited behavior.[14,19,22] Relapses occur in 12% of the cases and are more common in patients without an occult tumor.[20] The estimated mortality rate in this grueling disease is 7% at 24 months.[20]

Diagnosis and Treatment

Several descriptions[19] exist in the literature of milder or incomplete forms of anti-NMDAR encephalitis, a forme fruste of the disorder, such as isolated psychiatric symptoms, seizures, or dystonia. These pure monosymptomatic syndromes occur in less than 5% of anti-NMDAR encephalitis cases,[19] though patients may also present with a predominant symptom, such as headache in our case, with milder manifestations of other elements of the syndrome such as

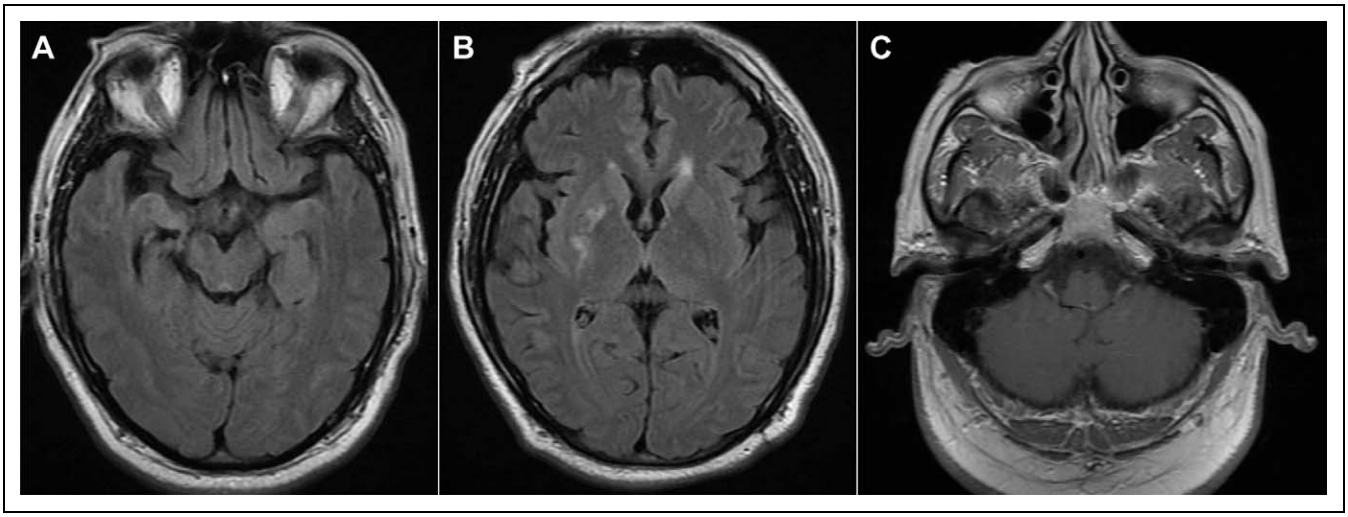

Figure 3. Magnetic resonance imaging (MRI) scans of the brain on day 150 of illness. A and B, Fluid attenuated inversion recovery (FLAIR) axial images demonstrating interval improvement in the previously visualized lesions at presentation. C, T1 axial postcontrast image with complete resolution of basal leptomeningeal enhancement.

confusion or hallucinations. Some of the classic behavioral symptoms of anti-NMDAR encephalitis may have also been overshadowed in our patient by symptoms of higher cortical dysfunction, decreased level of consciousness, or refractory seizures, as has been described in cases of limbic encephalitis.[2]

The CSF findings in our patient were also unusual for anti-NMDAR encephalitis, and suggested a potential infectious etiology. Initial CSF evaluation in anti-NMDAR encephalitis typically reveals only a mild pleocytosis with 25 to 35 cells/μL, though the highest reported value is 480 cells/μL.[14] The CSF protein may be mildly elevated, ranging from 20 to 70 mg/dL, and CSF glucose is typically normal.[14,15] To our knowledge, this degree of CSF pleocytosis, hypoglycorrhachia, and persistent elevation of protein more than 100 mg/dL has not been reported in anti-NMDAR encephalitis.

Abnormalities on EEG are found in 80% to 100% of the patients with anti-NMDAR encephalitis, often with diffuse slowing, although epileptiform discharges can also be seen.[14,15,18,20,23] Brain MRI abnormalities are seen in up to 50% of the patients.[19] Most commonly, abnormal FLAIR and T2 signal can be seen in the medial temporal lobes,[24] similar to those seen in our patient, or the cerebral cortex.[14] Some reports have also described contrast enhancement in the meninges.[14,19]

Brain biopsy is generally not thought to be helpful with diagnosis. In a few patients who have undergone biopsy during the course of illness, specimens have shown nonspecific mild perivascular cuffing and microglial activation.[14]

Confirmatory testing for anti-NMDAR encephalitis is conducted through an indirect fluorescent antibody method in commercial laboratories. Testing is performed on both serum and CSF with higher titers in the CSF compared to the serum during active disease.[14,19] In rare cases, the serum has been negative, but the CSF has been positive, suggesting intrathecal antibody production.[14,19,23] There have been conflicting studies on whether anti-NMDAR antibody titers are associated with disease severity.[18,25]

Prior studies examining the presence of anti-NMDAR antibodies in the setting of viral meningoencephalitis have found little to no cross-reactivity,[14,15] though a recent study suggests that an inflammatory cascade in the setting of a viral meningitis could lead to false-positive test results.[26] Early in our patient's course, we suspected that the positive anti-NMDAR antibodies were the result of an inflammatory cascade, which was supported by the nonspecific CSF antineuronal antibody. As he developed symptoms with more characteristic of anti-NMDAR encephalitis, including dyskinesias and dysautonomia, he appeared to enter the second phase of illness albeit well after the typical 10 to 20 days.[18]. The pathogenic mechanism of anti-NMDAR encephalitis without an occult tumor remains unclear. The degree of pleocytosis present in our case could be the result of an unidentified infectious etiology with exposed antigens resulting in an autoimmune response. Alternatively, could the severity of CSF pleocytosis, higher than previously reported, be solely related to anti-NMDAR encephalitis? Clinicians should consider anti-NMDAR encephalitis in patients with a significant CSF pleocytosis that is not responding to typical infectious treatment.

Initial treatment of anti-NMDAR encephalitis should include removal of the offending tumor in paraneoplastic cases and immunosuppression in all cases. First-line immunosuppression includes corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange, or some combination of these interventions.[19] Evidence suggests that dual therapy with corticosteroids and either plasma exchange or IVIG is superior to steroids alone.[18] If first-line therapy fails, further immunosuppression with rituximab or cyclophosphamide is considered second line.[14,18,19,23,27] In many patients, second-line therapies have been used to prevent relapses.[20]

Case Follow-Up

The patient showed gradual improvement in his level of alertness and responsiveness approximately 3 months into his illness, although he developed considerable agitation. Multiple sedating medications for dysautonomia and abnormal movements were stopped. The patient began mouthing words but with confused and perseverative speech. He often required restraints and neuroleptic medications for severe agitation and to ensure safety, both for the patient and the hospital staff. He began to intermittently respond to simple commands. A final CSF analysis obtained nearly 2 months after initiation of the rituximab infusions was normal (see Table 1). A repeat brain MRI was also obtained with significant interval improvement and resolution of contrast enhancement (see Figure 3). He remained hospitalized at our facility for about 4 months before discharge to a skilled nursing facility. He was cognitively slow with poor memory and recall. Abnormal movements were gone. Monthly rituximab infusions were continued, and he became independent in all activities of daily living, returning home about 6 months after the onset of initial symptoms. A neuropsychological evaluation about 9 months after symptom onset documented cognitive and personality changes though no mood problems. Specifically, testing revealed poor focus with concentration, memory difficulty, and occasional child-like behavior that was also noted by the patient's partner. After 10 months from the onset of his illness, the patient has been unable to return to work due to the severity of his cognitive deficits.

Declaration of Conflicting Interests

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