Clinical Problem-Solving: Lethargy and Fever in an Immunocompromised Patient

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Abstract

We present the case of a 63-year-old woman with a glioblastoma multiforme on immunosuppressive steroid doses who developed lethargy and fever. We review the differential diagnosis and emphasize the importance of reframing the case when the clinical course differs from expectation. Once the diagnosis is evident, we discuss the incidence and clinical course in different patient populations.

A 63-year-old woman with a history of a right temporal glioblastoma multiforme (GBM) was admitted to the neurological intensive care unit with fever, lethargy, and worsening left-sided weakness and neglect. Four months previously, she developed left-sided weakness and was found to have a right temporoparietal GBM. She underwent subtotal resection followed by fractionated radiation. As part of a clinical trial, she received a novel immunotherapy, nivolumab, a humanized immunoglobulin-G4 (IgG4) anti-programmed cell death protein 1 (PD-1) monoclonal antibody. After receiving two-thirds of her 6000 centigray (cGY) radiation and 2 doses of nivolumab, she developed worsening left-sided weakness and difficulty ambulating. Magnetic resonance imaging (MRI) of her brain with gadolinium contrast demonstrated increased nodular enhancement in the right temporal lobe near the residual tumor (Figure 1A) and a significant increase in adjacent frontotemporoparietal T2 signal, causing 1 cm of right-to-left midline shift (Figure 1B, C). These findings were suggestive of either recurrent tumor or treatment effect. Her radiation and nivolumab were suspended, and she was started on 6 mg of dexamethasone every 6 hours, with rapid improvement in motor function.

She was discharged home from the hospital, but 7 days later, she became progressively sleepier and weaker on her left side over 24 hours. She was readmitted to the neurological intensive care unit, where she was found to have a temperature of 38.7°C. She was lethargic with a right gaze preference, left-sided neglect, and a mild left hemiparesis. Laboratory testing was notable for new hyponatremia to 127 mg/dL and a white blood cell (WBC) count of 16 000/μL with 83% neutrophils,

unchanged from prior hospitalization. A computed tomography (CT) scan showed improved frontotemporoparietal edema, with less midline shift (not shown).

The first important task is to determine whether this patient's presentation is due to her known tumor, treatment effect, or an entirely separate process. Her right gaze preference, left-sided neglect, and left hemiparesis localize to the right frontoparietal cortex, near the location of her known tumor and edema. Possible tumor-associated changes include progression, with or without worsening edema, or hemorrhage into the tumor bed. Additionally, seizures originating from her right frontal lobe could result in a postictal right gaze preference and a left-sided paresis. Treatment effects include radiation-induced pseudo-progression and nivolumab-induced edema. With her fever, leukocytosis, and altered mental status, central nervous system infection must be considered. Finally, recrudescence of her previous symptoms could be produced by a systemic infection, such as a pneumonia or urinary tract infection, or a toxic-metabolic insult, such as her new hyponatremia.

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Figure 1. A, Axial T1-weighted post-gadolinium sequence from prior hospitalization demonstrating enhancing tumor burden. B-C, Axial fluid attenuation inversion recovery (FLAIR) sequences from 2 rostrocaudal levels during her prior hospitalization. D-E, Axial FLAIR sequences on presentation demonstrating *reduced* peritumoral hyperintensity and *reduced* midline shift but *new* hyperintensity in the left insula, left mesial temporal lobe, and the cingulate gyri bilaterally. F, Apparent diffusion coefficient (ADC) and Diffusion weighted imaging (DWI) (inset) demonstrating restricted diffusion in the left insula and both cingulate gyri. G, Noncontrast brain computed tomography (CT) scan 3 weeks after presentation, showing diffuse temporal and cingulate hypodensity and obliteration of the basilar cisterns.

To discriminate among these possibilities, the patient requires urgent imaging and cerebrospinal fluid (CSF) evaluation. Imaging should precede lumbar puncture to rule out impending herniation. An infectious evaluation should be performed including urinalysis and chest X-ray. Continuous electroencephalography (EEG) monitoring should be performed if there are clinical fluctuations or if the above evaluation is not revealing.

Her CT scan showed no acute findings. Cerebrospinal fluid analysis demonstrated 4500 red blood cells (RBCs) and 7 WBCs in tube 1, 510 RBCs and 0 WBCs in tube 4, protein of 62.3 mg/dL, and glucose of 88 mg/dL. A chest radiograph showed no evidence of pneumonia, and a urinalysis was negative for leukocyte esterase. A HIV 1 and 2 enzyme-linked immunosorbent assay (ELISA) test was negative. Her dexamethasone was increased to 10 mg every 6 hours to treat presumed symptomatic peritumoral edema. She continued to have daily fevers as high as 39.0°C. Her sodium normalized with hypertonic saline. Despite these interventions, her level of consciousness deteriorated to coma, and she was intubated for airway protection. She demonstrated preserved respiratory drive and brain stem reflexes but no withdrawal in any extremity to noxious stimuli. Continuous EEG monitoring showed multiple left temporal seizures with generalization to the left hemisphere, continuous left temporal lateralized periodic discharges (LPDs), brief runs of right parietal

LPDs, and bilateral delta and theta slowing. Brain MRI demonstrated improved peritumoral edema and reduced mass effect, stable enhancement in the right temporal lobe, and a new area of T2 hyperintensity and diffusion restriction in the contralateral left insula, mesial temporal lobe, and cingulate gyrus (Figure 1D-F).

Whenever the clinical course differs drastically from expectation, it is important to revisit initial assumptions and reframe a differential diagnosis. This patient progressed to febrile coma with seizures despite correction of metabolic abnormalities and peritumoral edema. Most importantly, her electrographic discharges and seizures originated from a site remote from her tumor. Such MRI changes could be seen as sequelae of the temporal lobe seizures, but the involvement of the cingulate gyrus suggests that they more likely represent encephalitis. She meets clinical criteria for encephalitis, which is operationally defined as altered mental status for least 24 hours and 2 of the following: fever, seizures, focal neurological findings, CSF pleocytosis, and EEG or MRI findings -suggestive of encephalitis.¹

Encephalitides are classified as infectious, immune-mediated, and idiopathic. In approaching a patient with suspected encephalitis, one needs to consider the age of the patient, immunologic status, time of year, location, and any environmental or occupational exposures. The list of viral, fungal, spirochetal, bacterial, mycobacterial, and protozoal causes is remarkably broad but may be narrowed after taking the above factors into consideration. Modern prospective

series on encephalitis in children and adults identify an infectious agent in 14% to 52% of cases,^{1,2} an immune-mediated etiology in 21%,³ and an unknown etiology in 37%.³ Herpes simplex virus (HSV) is the most common infectious agent identified, seen in 26% to 44% of cases.^{1,3} Varicella zoster virus (VZV) is the second most common occurring in 6% to 16% of infectious cases.¹⁻³

This patient, and any patient taking more than 10 mg of daily prednisone equivalents, has increased susceptibility to infection and should be considered immunocompromised.⁴ It is therefore important to consider atypical infectious encephalitis in addition to HSV and VZV. One series of encephalitis in bone marrow transplant recipients isolated the following pathogens in decreasing order of incidence: human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), HSV, VZV, JC virus, cytomegalovirus (CMV), and adenoviruses, with dual infection being a frequent occurrence.⁵ Rarer causes in the immunocompromised population include West Nile virus, BK virus, lymphocytic choriomeningitis virus, rabies virus, and *Balamuthia*, an amoeba causing rapidly fatal granulomatous encephalitis.⁶

In an immunocompromised patient with suspected encephalitis, a single normal CSF sample should not dissuade the physician from repeat testing and empiric treatment. This population is more likely to have noninflammatory CSF.⁷ Furthermore, the CSF polymerase chain reaction (PCR) test for HSV, the most common cause of encephalitis, has a 2% false-negative rate.⁸ The false-negative rate for other viral PCR tests is substantially higher.⁹ Given the high index of suspicion for encephalitis in this patient, repeat lumbar puncture with viral PCR testing is indicated, as is empiric therapy with intravenous acyclovir.

A repeat lumbar puncture demonstrated 12 RBCs and 2 WBCs in tube 4 with a total protein of 45.2 mg/dL and glucose of 71 mg/dL. Polymerase chain reaction testing for HSV-1 DNA was positive. Polymerase chain reaction tests for HHV-6, EBV, CMV, and HSV-2 DNA were negative. Despite treatment with acyclovir and control of her seizures, she remained comatose. A repeat CT scan later in her course showed diffuse hypodensity bilaterally involving the insulae, cingulate gyri, and the temporal and parietal lobes, suggesting significant tissue destruction (Figure 1G). After discussion with her family, her goals of care were redirected to comfort measures only and she died briefly after extubation.

This case illustrates the inherent challenges in diagnosing HSV encephalitis in a patient with a known brain tumor receiving immunosuppressive steroid doses. It also underscores the importance of revisiting the differential diagnosis when the clinical course does not conform to expectations.

Herpes simplex virus encephalitis is a long-studied clinical entity, but much remains to be understood about its pathology. The virus can remain dormant in sensory ganglia indefinitely, and both primary infection and reactivation of latent virus can cause encephalitis.¹⁰ Latent HSV is extraordinarily common;

one autopsy series of completely asymptomatic patients found HSV DNA in 65% of trigeminal ganglia and 34% of other brain tissues, including the medulla, olfactory bulb, pons, gyrus rectus, amygdala, and hippocampus in the order of decreasing frequency.¹⁰ In one-third of cases, there is no clinical history of HSV infection, but even in cases of presumed reactivation, it has not been definitively shown that the previously dormant strain is causing the encephalitis.¹¹

The signs and symptoms of HSV encephalitis are likely very similar in immunocompromised and immunocompetent patients.¹² However, the incidence of acellular CSF is higher in immunocompromised patients, occurring in 21% of 1 small case series,⁷ compared with 3% to 6% of their immunocompetent counterparts.^{7,13} In another particularly relevant but small series of patients with a high-grade glioma receiving radiation or steroids, as many as 57% lacked a pleocytosis.¹²

Herpes simplex virus encephalitis carries an estimated 70% mortality in any untreated patient.¹⁴ With acyclovir treatment, the mortality decreases to 5% to 19%,^{2,14} with 19% to 44% of survivors left severely disabled.¹⁴ In a very small series of immunocompromised patients, mortality with treatment was slightly higher, at 35%.⁷ In all populations, age, onset of coma before treatment, and time to acyclovir initiation are all associated with poor outcome.⁷

It is not fully understood why immunocompromised patients have a higher mortality, given that the immune reaction to the virus is thought to be primarily responsible for tissue damage. An intriguing possibility is an increased incidence of acyclovir resistance in this population. One series isolated acyclovir-resistant strains in 0.27% of immunocompetent hosts compared with 7% of the immunocompromised.¹⁵

The early recognition of HSV encephalitis, while potentially challenging in immunocompromised patients, is paramount, as delayed treatment significantly worsens prognosis.⁷

Authors' Note

Samuel Snider and Konstantin Stojanovic contributed equally to this work.

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