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Clinical Reasoning: A 68-year-old man with a first presentation of status epilepticus

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SECTION 1

A 64-year-old man with transfusion-dependent myelodysplastic syndrome (MDS), hypertension, chronic obstructive pulmonary disease, hypothyroidism, blindness from treated syphilitic chorioretinitis, and no prior seizure history presented in generalized status epilepticus. His daily home medication regimen included prednisone 20 mg (chronic therapy for MDS), diltiazem 120 mg, digoxin 250 μg, tiotropium 80 μg, and levothyroxine 112 μg. On admission he was febrile to 39.9°C and in atrial fibrillation with rapid ventricular rate. Initial hematologic profile showed 11,910 leukocytes/mm^3 (12% immature forms, 46% neutrophils, 32% lymphocytes), hematocrit of 30.8%, and platelet count of 215,000/mm^3, with an otherwise normal serum chemistry.

Once the seizures were controlled with IV lorazepam, fosphenytoin, and levetiracetam, he was extubated. His examination at that time demonstrated bilateral blindness, normal strength/sensation, normal coordination/gait testing as his blindness would permit, brisk symmetric reflexes with flexor plantar responses, and no nuchal rigidity.

Given the patient's prior risk factors for new-onset seizures, initial laboratory abnormalities, and vital sign instability suggestive of the systemic inflammatory response syndrome, a broad diagnostic evaluation was pursued. Head CT demonstrated a hypodensity involving the splenium and parieto-occipital periventricular white matter bilaterally (figure, A).

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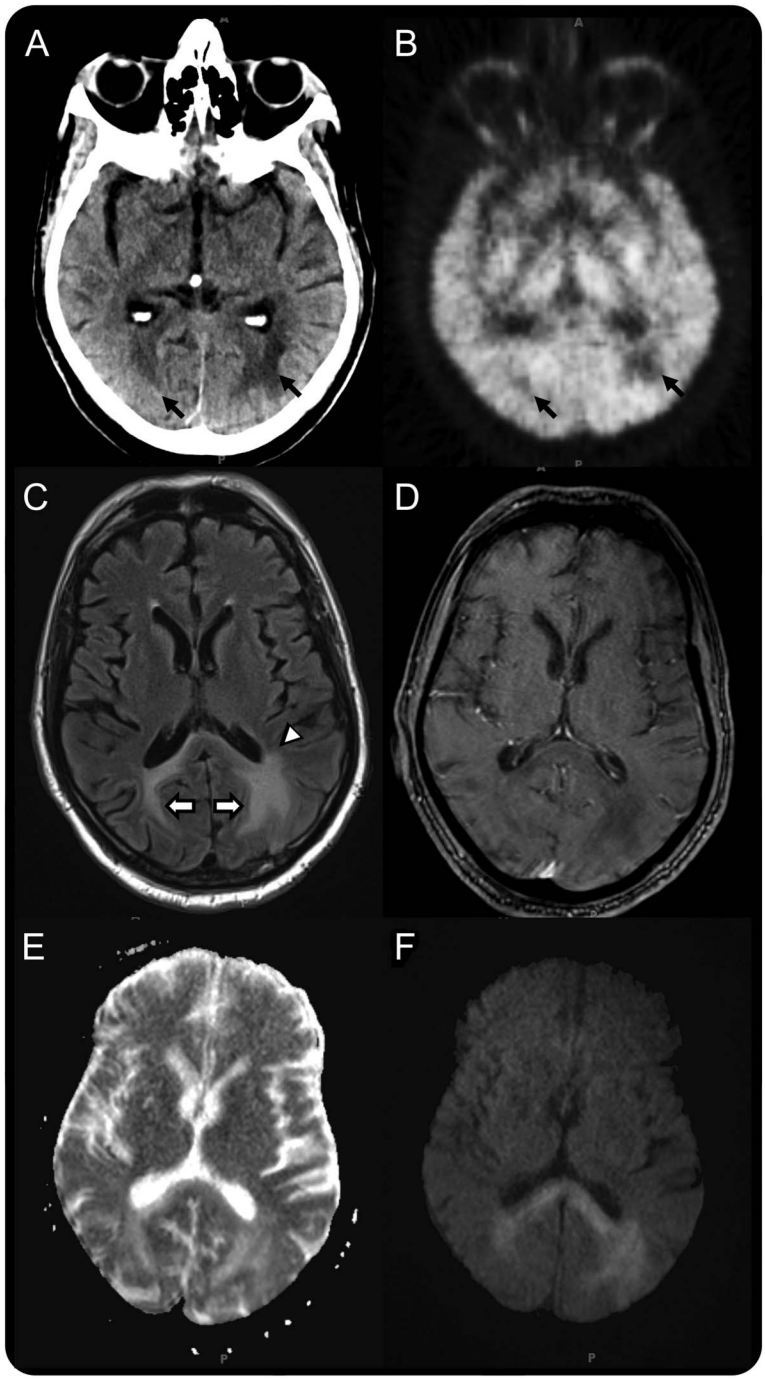
Figure Imaging of the brain



The initial noncontrasted head CT (A) reveals areas of hypodensity that do not fit a vascular distribution. A comparison with the subsequent fluorodeoxyglucose PET reveals hypometabolism (black arrows) in the region of hypodensity, provided for comparison (B). Repeat MRI of the brain at approximately the same level shows persistence of the T2/fluid-attenuated inversion recovery hyperintensity (C) with a sharp demarcation at the gray-white border with U-fiber involvement (white arrows) and a nondescript border in the white matter (white arrowhead) and extension more anteriorly around the left occipital horn of the lateral ventricle. There is still no enhancement on the T1 postcontrast series (D). There appears to be high signal on the diffusion-weighted imaging (E), but there is no apparent restriction of diffusion when looking at the apparent diffusion coefficient (F).

SECTION 2

To assess the splenial hypodensity on CT, a brain MRI was performed and demonstrated an ill-defined, nonenhancing, T2/fluid-attenuated inversion recovery (FLAIR)–hyperintense lesion of the splenium and occipital lobes that was limited to the white matter and subcortical U-fibers, sparing the gray matter without evidence of mass effect or atrophy. Initial lumbar puncture (LP) revealed a lymphocyte-predominant pleocytosis (23 leukocytes/mm^3) in the CSF with elevated protein (103 mg/dL) and normal glucose (61 mg/dL; serum glucose 116 mg/dL). Bacterial and fungal cultures, Venereal Disease Research Laboratory, cryptococcal antigen, herpes simplex virus/varicella-zoster virus/Epstein-Barr virus/cytomegalovirus/enterovirus PCRs, and flow cytometry with cytopathology were nondiagnostic. He was later noted to be pancytopenic. Serial EEGs revealed left temporal epileptiform activity on a background of diffuse cerebral disturbance.

Question for consideration:

1. What is the differential diagnosis for lesions of the splenium?

There are many causes of splenial lesions (table), including convulsive status epilepticus. The splenium's hypersensitivity to cellular fluid mechanics and metabolic disturbances might result in diffusion-weighted imaging (DWI) and T2/FLAIR signal changes. Two possible mechanisms are decreased available glucose (similar to signal changes in hypoglycemic patients) and altered salt homeostasis with resultant myelin edema.

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Table Differential diagnosis for lesions of the splenium

Epilepsy
Seizure
AED overdose (e.g., carbamazepine)
Abrupt drug withdrawal
Vascular
Stroke
Posthypoxic cardiac arrest
Hypertension/hypertensive encephalopathy
Preeclampsia/eclampsia
Posterior reversible encephalopathy syndrome
Reversible cerebral vasoconstriction syndrome
Migraine with aura
Infections
Encephalitis
HHV-6
Malaria
Rotavirus
Measles
Salmonella
Escherichia coli O157
HIV
Progressive multifocal leukoencephalopathy
Demyelinating/inflammatory
Acute disseminating encephalomyelitis
Multiple sclerosis
Neuromyelitis optica
Lupus
Granulomatous disease (e.g., sarcoid)
Metabolic
Chronic alcohol usage and malnutrition (e.g., B_1, B_{12})
Hypoglycemia
Hyponatremia
Hypernatremia
Osmotic demyelination syndrome
Renal failure
Miscellaneous
Trauma: axonal injury
Leukodystrophy (e.g., ALD, MELAS, metachromatic)
Neoplasm (e.g., glioma, CNS lymphoma)
Chemotherapy (e.g., fluorouracil, cyclosporine)
Radiation therapy
Serotonin syndrome
Neuroleptic malignant syndrome
Altitude sickness

Abbreviations: AED = antiepileptic drug; ALD = adrenoleukodystrophy; HHV-6 = human herpesvirus 6; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

SECTION 3

Following extubation and transfer to the Neurology floor, the patient quickly returned to normal mentation without evidence of new focal abnormalities. A follow-up MRI was performed 1 week after the initial scan, demonstrating progression of the T2/FLAIR lesion (figure, C). The DWI signal changes persisted without apparent diffusion coefficient correlate (figure, E and F) and the lesion remained nonenhancing (figure, D).

A JC virus (JCV) PCR test was added on to the initial CSF analysis and 2 additional large-volume LPs were performed for assessment of CNS lymphoma by flow cytometrics and cytopathology. Repeat CSF demonstrated a persistent lymphocytic pleocytosis (13 leukocytes/mm^3, protein 101 mg/dL; 30 leukocytes/mm^3, protein 140 mg/dL) with normal glucose (53 mg/dL with serum glucose 76 mg/dL; glucose 48 mg/dL with serum glucose 94 mg/dL). The patient's peripheral blood profile revealed a gradual downtrend and eventual persistence of pancytopenia. This was confirmed to be baseline from his MDS, which required monthly transfusions for progressive anemia.

Question for consideration:

1. What are the differential considerations of a persistent CSF lymphocytic pleocytosis in the setting of systemic leukopenia?

The etiologic considerations for a persistent CNS lymphocytic pleocytosis in a patient with a leukopenia suggestive of a chronically immunosuppressed state are manifold due to the possibility of the apparently modest CNS involvement reflecting an impotent immune response. Atypical infections of bacterial (e.g., *Treponema pallidum* recurrence), fungal (e.g., *Cryptococcus* species), parasitic (e.g., *Toxoplasma gondii*), mycobacterial (e.g., *Microbacterium tuberculosis*), and viral (e.g., JCV, HIV, lymphocytic choriomeningitis virus) origin are key considerations. Neoplastic meningitis or primary CNS lymphoma should also be considered given the patient's history of MDS and additional risk factors. Finally, a parameningeal process may cause chronic aseptic meningitis in an immunosuppressed patient.

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The JCV PCR test returned positive and there was no growth on subsequent bacterial, fungal, and mycobacterial cultures or other viral pathogens isolated. All antibiotics were stopped without recurrence of fever or changes in mental status. Flow cytometric and cytopathology studies were unremarkable.

Question for consideration:

1. What are the causes of non-HIV-associated progressive multifocal leukoencephalopathy?

The association of progressive multifocal leukoencephalopathy (PML) with immunosuppressed states was first described in patients with hematologic malignancies (predominantly Hodgkin disease, chronic lymphocytic leukemia, and chronic myelogenous leukemia). In fact, lymphoproliferative disorders accounted for the majority of pre-HIV epidemic PML cases.[1] Rheumatic diseases, autoimmune vasculitis, MDS, and idiopathic CD4 lymphocytopenia are also associated with PML. Patients on immunosuppressive drugs or specific monoclonal antibodies (e.g., natalizumab, efalizumab, rituximab, brentuxiumab) have been found to be at increased risk of PML as a consequence of their therapies. The persistent CSF lymphocytic pleocytosis suggested that JCV infection was the basis of an ongoing inflammatory process in the CNS, likely as a consequence of the patient's chronic systemic immunosuppression.

Question for consideration:

1. What management options exist for non-HIV-associated PML?

There are few therapeutic options that have proven effective in treating PML. The mainstay of PML therapy is reconstituting the immune system through removal of offending agents, antiretroviral therapy in the case of HIV/AIDS, or stimulation of an altered immune system.

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To evaluate for potential malignancy, a body CT scan with contrast was performed, which revealed bilateral lung consolidations and mild right-sided pulmonary effusion, attributed to aspiration events following his seizures. Fluorodeoxyglucose (FDG)-PET scan was used to verify the nature of the pulmonary pathology. A peripheral right lung nodule and mediastinal lymph nodes showed mild FDG avidity, which was believed to be inflammatory or infectious in nature. The abnormal signal in the splenium and parieto-occipital white matter on brain MRI was found to be hypometabolic on this FDG-PET study (figure, B).

Further investigations were pursued to help elucidate whether a superimposed, indolent cancer or infectious/inflammatory disease was responsible for his immunosuppressed state. His CD4 count was 108 cells/mm^3 with normal peripheral flow cytometry. His cytopenia was ultimately attributed to his MDS, as he had a persistent pancytopenia and negative HIV testing. Without clearly reversible etiologies for lymphopenia, he was started on mirtazapine 30 mg daily and mefloquine 250 mg daily for 7 days, followed by weekly dosing thereafter, for treatment of his PML. A slow prednisone taper from 20 mg daily was initiated. Other therapies were being considered, including recombinant interleukin-2, especially if his clinicoradiologic syndrome progressed and his CD4 count remained low. However, he was lost to follow-up; therefore, no further interventions were undertaken.

DISCUSSION We present a patient with PML occurring in the setting of multifactorial immunosuppression, primarily the consequence of a CD4 lymphopenia from his MDS and compounded by his chronic prednisone treatment. He originally presented with seizure, which has been noted to occur in 18% of PML cases.[2] The imaging findings of T2/FLAIR hyperintensity of the subcortical U-fibers with borders sharply demarcated at the gray-white junction, while ill-defined toward the white matter, with minimal mass effect or enhancement (present in 15%–40% of cases), were highly suggestive of PML. The hypointensity on T1-weighted sequences and lack of restricted diffusion further corroborated PML as the diagnosis. The American Academy of Neurology Neuroinfectious Disease Section recently proposed an algorithm for diagnosing PML in the absence of histopathologic confirmation.[3] Our patient's clinicoradiologic syndrome taken in the context of his CSF JCV PCR positivity is sufficient for the diagnosis of definite PML.[3]

Ever since the burgeoning of PML cases prior to the HIV combination antiretroviral therapy (cART) era, the incidence of non-HIV-associated PML has continued to rise in settings of organ transplantation and biologic therapies that alter the immune system.[4,5] There are a number of case reports suggesting that rheumatologic illnesses and their treatments as well as rare cases of MDS—all with lymphopenia—are risk factors for the development of PML.[4,6] Due to the prevalence of JCV seropositivity reaching upwards of 90% by adulthood,[5] the pathogenesis is presumed to be multifactorial. The etiology of JCV's pathophysiology is believed to originate from mutation of the noncoding control region of JCV, which occurs in a reservoir of B cells as they mature, subsequently resulting in oligodendroglial tropism and finally CNS dissemination as a result of impaired immune surveillance.[7] Most diseases associated with PML seem to result in impairments at multiple points in this timeline. In the case of our patient, his marked CD4 lymphopenia combined with chronic prednisone therapy was likely sufficient to allow for CNS infection and propagation.

Therapeutic interventions for PML are limited, outside of attempts to bolster and reconstitute the immune system. Of note, contrast enhancement on MRI as well as evidence of an inflammatory response in pathologic sections are good prognostic factors paralleling improvements in CD4 and JCV-specific cytotoxic T-cell populations.[3,5] Due to improvements in survival from 10% at 1 year to 63.6% living longer than 2.2 years with the advent of cART, a focus on immune system recovery to promote immune system surveillance has become the mainstay of therapy.[8] Withdrawal of immunosuppressive therapies[9] has been employed successfully in circumstances of iatrogenically induced immunoincompetence. In the circumstances where the immunosuppression is the consequence of the primary disease or when immunosuppressive therapies cannot be discontinued, the treatment options are limited.

AUTHOR CONTRIBUTIONS

Logan Douglas Schneider: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval. John Calvin Probasco: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Scott Douglas Newsome: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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