CLINICAL IMAGE

Seizures in an Immunocompromised Patient

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A 37-year-old female with a past medical history of human immunodeficiency virus (HIV) presents to the emergency department with tonic-clonic seizures. The patient experienced two tonic-clonic seizures at home earlier that day and was brought to urgent care by family members. She was evaluated by urgent care and was then transferred to the emergency department, where she underwent a brain computed tomography (CT) without contrast and magnetic resonance imaging (MRI) with and without contrast *(Figures 1 and 2)*. The patient stated she had a cough for the past week that was productive and clear in nature. Other than an abrasion to her bottom lip, she suffered no injuries. She has a prior history of seizures but was not taking any anti-epileptic medications. The patient was diagnosed with HIV approximately ten years prior to this presentation and was temporarily on highly active antiretroviral therapy (HAART), but then became non-adherent to the regimen. She smokes a half a pack of cigarettes per day and is a "regular" drinker. She would not disclose the exact quantity of her alcohol consumption. The patient had no other significant medical history. Her surgical history consisted of a caesarian delivery and tubal ligation. Her family history is significant for hypertension. She denied headache, dizziness, fever, chills, neck stiffness, numbness, gait disturbance, weakness, vision changes, abdominal pain, chest pain, and labored breathing.

FIGURE 1:

Axial T2-weighted MRI of the brain depicting T2 hyperintensities involving the subcortical U fibers most notably at the right occipital lobe and to a lesser extent the left occipital lobe and the left temporal lobe with associated atrophy (yellow arrows).

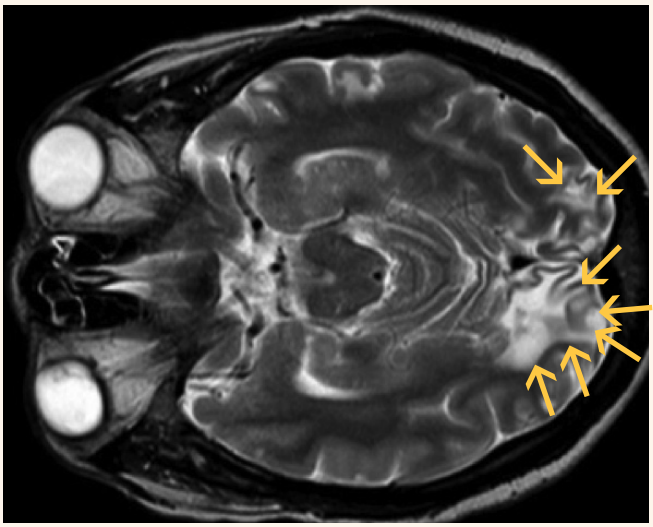
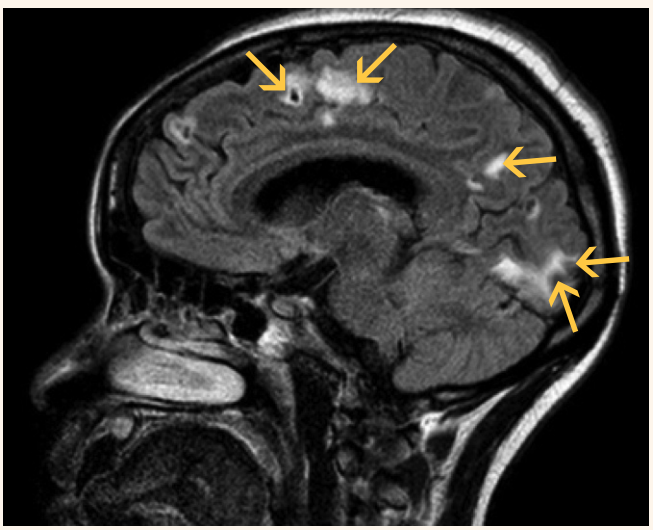


FIGURE 2:

Sagittal fluid-attenuated inversion recovery (FLAIR) image depicting multiple FLAIR signal hyperintensities involving subcortical U fibers (yellow arrows).



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QUESTIONS:

1. **What is the most likely diagnosis based on the patient's clinical presentation and imaging?**

   A. Toxoplasmosis

   B. Cytomegalovirus

   C. Progressive Multifocal Leukoencephalopathy

   D. Hodgkin Lymphoma

2. **What is the gold standard for diagnosing this disease?**

   A. Magnetic resonance imaging (MRI) of the brain

   B. Brain biopsy

   C. Polymerase chain reaction (PCR) of cerebrospinal fluid (CSF)

   D. Computed tomography (CT) of the head

3. **What is/are the treatment(s) for PML?**

   A. Antiretroviral therapy

   B. Interleukin (IL)-2

   C. Plasma exchange

   D. All of the above

ANSWERS:

1. **What is the most likely diagnosis based on the patient's clinical presentation and imaging?**

   Correct Answer:
   C. Progressive Multifocal Leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML) is a subcortical white matter disease of the brain. It is progressive in nature and results in demyelination in multiple foci of the brain. It is caused by the John Cunningham virus (JCV) which affects the oligodendrocytes of the central nervous system (CNS). PML is an AIDS-defining illness, with about 5% of HIV patients developing PML.[1,2] Clinical features may consist of motor weakness, ataxia, seizures, memory difficulties, and dementia. Classically, PML on MRI will depict bilateral, multifocal, irregular demyelinating white matter lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences.

Toxoplasmosis is another AIDS-defining illness caused by the parasite toxoplasma gondii. It can present clinically with flu-like symptoms, reduced or blurred vision, eye redness, and seizures. On T1-weighted precontrast MRIs, the lesions are typically hypointense in relation to the brain tissue.[3] On T2-weighted MRIs, the foci are usually hyperintense. After gadolinium is administered, ring enhancement occurs in most patients.[4] Cytomegalovirus is another AIDS-defining illness that is part of the human herpesvirus-5 family. CMV infection is most commonly asymptomatic, however, it can present as hepatitis, colitis, and pneumonitis.[5] The MRI may show subependymal signal changes along the lateral ventricles, septum pellucidum, corpus callosum and fornices.[6] Hodgkin lymphoma (HL) is a cancer that involves the immune system. Clinical features consist of B symptoms (weight loss, fever, fatigue, and night sweats) along with lymphadenopathy. It is uncommon to have CNS involvement in HL, consisting of only 0.2-0.5% of patients with HL.[7]

2. **What is the gold standard for diagnosing this disease?**

   Correct Answer:
   B. Brain Biopsy

Brain biopsy is the gold standard for diagnosing PML. The histopathologic hallmarks consist of a triad of multifocal demyelination, hyperchromic and amplified oligodendroglia nuclei, and enlarged astrocytes with lobulated hyperchromatic nuclei.[8] Brain biopsy carries a 93%-96% sensitivity, a 12% perioperative morbidity, and a 2% mortality.[8] Therefore, the diagnosis of PML is often made as a clinical diagnosis based on clinical judgment, imaging, and PCR for the JCV virus. MRI with and without gadolinium is most often used in imaging PML and is far more sensitive than a CT scan.[8]

3. **What is/are the treatment(s) for PML?**

   Correct Answer:
   D. All of the above

All of the answer choices above are possible treatment options for PML. Treatments with proven efficacy are lacking; however, through case reports and small clinical trials these treatment options have been used in clinical practice. IL-2 has been shown to play a part in stimulating T-cells which has been successful in treating PML; however, caution needs to be taken when using in patients with multiple sclerosis (MS) and PML.[9] Certain antivirals like acyclovir, cidofovir, brincidofovir, and ganciclovir have also been used in attempts to treat PML. In natalizumab-associated PML, plasma exchange is the standard of care because it accelerates the removal of the offending agent.[9] Clinical studies are underway and are analyzing different treatment modalities for PML along with prevention of JCV replication within cells. Education along with emphasis on initiation of HAART early on is key when talking to patients with HIV/AIDS.

DISCUSSION

Progressive Multifocal Leukoencephalopathy (PML) is a rare and potentially fatal neurological disorder most commonly seen amongst immunocompromised patients. PML occurs in approximately one in 200,000 people in the general population.[2] In the United States and Europe combined, an estimated 4,000 people are diagnosed with PML each year.[2] The pathogenesis involves a progressive, destructive, demyelinating process affecting the white matter parenchyma of the central nervous system (CNS). It is most frequently caused by the reactivation of

a virus known as the JCV in which approximately 85% of patients with PML are seropositive for antibodies against the virus.[10] JCV primarily infects the patient during childhood and remains latent within the kidney, lymphoreticular, or brain tissue until a setting of profound immunosuppression arises. The JCV will then cause lytic lesions of the CNS oligodendrocytes, sparing the optic nerves and spinal cord.[11] The immunocompromised populations most at risk for developing PML include those with HIV/AIDS (approximately 80% of cases), underlying hematologic malignancies, organ transplant recipients, and those on immunomodulating therapies such as Natalizumab for chronic inflammatory disorders such as Crohn's disease and Multiple Sclerosis (MS).[12] Currently, patients who developed PML following treatment with Natalizumab, make up the second largest group of patients with PML.[13]

As the name implies, PML is classically progressive in nature and characteristically affects multiple locations within the CNS. However, those treated with Natalizumab may frequently present with monofocal lesions, causing a diagnostic challenge for many physicians. The clinical presentation of the patient depends on the location of the disease. The most common neurological symptoms of PML include: altered mental status, vision loss due to occipital lobe lesions, motor weakness due to frontal lobe lesions, and ataxia from cerebellar lesions.[13] As the disease progresses, patients may also develop seizures. One study showed that 64% of patients experienced a seizure within the first year of diagnosis.[14]

The gold standard for diagnosing PML is via the histopathologic examination of a brain biopsy. However, with the advent of PCR detection of JCV DNA from CSF and the advances in neuroimaging technology, this combination in concordance with the appropriate clinical picture has supplanted the need for performing a brain biopsy.[15] Nevertheless, if neuroimaging and laboratory findings are reported as negative and the clinical suspicion for PML still remains high, a brain biopsy should be performed.[15] In regard to neuroimaging, magnetic resonance imaging (MRI) of the brain is preferred over computed tomography (CT) due to its much higher sensitivity. In some cases, MRI may even demonstrate pathologic lesions prior to the onset of clinical symptoms.[13] Classically, PML on MRI will depict bilateral, multifocal, irregular demyelinating white matter lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted (Image 1) and fluid attenuated inversion recovery (FLAIR) sequences *(Image 2)*.[13] In order to differentiate from other similarly appearing CNS pathologies such as MS, careful examination will show that PML primarily affects the subcortical region of the brain with involvement of the U-fibers.[9] In addition, PML characteristically spares the optic nerves and spinal cord.[11]

Before the widespread initiation of HAART for patients with HIV, the incidence of PML was higher in patients prior to HAART versus those once HAART was established as the standard of care. In a large nationwide population-based cohort of adult HIV-1-infected patients, it showed the incidence per 1000 person-years at risk. In the pre-HAART years (1995-1996), the incidence was 3.3 cases, while in the late-HAART period (2000-2006), the incidence decreased to 1.3 cases.[16] Along with the diminished incidence, the establishment of HAART in HIV-infected individuals with PML led to a one-year survival improvement from 10% to approximately 50%, and in some cases showed a slight improvement and stabilization of the disease.[17] Unfortunately, most patients who survive will continue to have progressive neurological sequelae.

Due to its high mortality rate, the approach towards managing patients with PML should be focused on prevention at the primary care level. Adequate preventative strategies require a multidisciplinary approach, starting with the role of the primary care physician (PCP). A delay in diagnosis can be harmful to the patients via increased healthcare costs through unnecessary tests and treatments, failing to modify the progression of the disease, and causing emotional stress due to an inaccurate diagnosis which can later result in the fracturing of the patient-physician relationship. One study showed that another diagnosis was considered before PML in nearly two–thirds of patients, and more than three–quarters of PML patients experienced a delay in their diagnosis greater than one month, regardless of their underlying immunosuppressive status.[18] Therefore, it is important for the PCP to recognize the early signs and symptoms of PML, and It is imperative for the PCP to build a trustworthy relationship with the patient as most cases of PML are due to immunosuppression from underlying HIV infection. The PCP can play an active role in educating HIV-infected patients on PML and maintaining close surveillance of the patient to ensure adequate HAART adherence. In addition, the PCP should be cognizant of patients in need of immunomodulating agents such as Natalizumab and should screen for seropositivity towards the JCV prior to the initiation of therapy.[9] Although there is no specific treatment for PML, the goal for therapy should be to manage the underlying etiology and work to restore the host's immune function against the JCV.[1] While medications such as cidofovir and cytarabine showed promise, later studies revealed these medications failed to improve patient survival.

AUTHOR DISCLOSURES:
No relevant financial affiliations or conflicts of interest.

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