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Educational Case: Opportunistic Infections of the Central Nervous System

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, central nervous system, infections, toxoplasmosis, human polyomavirus 2 (JC virus), cytomegalovirus, *Cryptococcus*, tuberculosis

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Primary Objective

Objective NSC2.2: Opportunistic Infections of the CNS. Discuss 5 common opportunistic infections that involve the CNS of immunocompromised individuals and describe their pathologic features.

Competency 2: Organ System Pathology; Topic NSC: Nervous System—Central Nervous System; Learning Goal 2: Infection

Patient Presentation

A 56-year old male health-care worker from Brazil with HIV presents to the clinic with complaints of right arm twitching and decreased sensation in the left arm. Back in Brazil, he lived on a farm with various animals which also provided the meat for family dinner. He has not been adherent with antiretroviral therapy for the past 5 years. He denies any other neurological deficits or loss of consciousness. His wife accompanies him and states that she has also noticed a sharp decline in his memory and attention span over the past few months and is concerned he is having "some dementia." During this same year, he has also had a chronic cough, weight loss, night sweats, and increasing fatigue over the past year.

Diagnostic Findings, Part 1

Laboratory Results

Blood tests revealed that the patient had a CD4+ cell count of 95 cells/μL, confirming this patient's diagnosis of acquired immunodeficiency syndrome. This diagnosis puts him at severe risk of various serious infections.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis?

This patient's blood tests confirm a diagnosis of Acquired Immunodeficiency Syndrome because of his noncompliance to antiretroviral therapy against HIV. He presents with focal neurologic deficits and potential cortical signs like memory

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Table 1. Comparison of Clinical Findings, Symptoms, and Diagnosis of Various CNS Infections.

Infection	Risk Factors	Symptoms	Diagnostic Technique	Clinical Findings
Toxoplasmosis	• Immunosuppression • <100 CD4+ cells/μL. • Eating undercooked or contaminated meat • Drinking unpasteurized goat's milk • Handling of cat's feces	• Constitutional signs like fever • Neurologic deficits (focal and diffuse) • Altered mental status • Seizures	• CT/MRI • Anti-toxoplasma antibodies • Biopsy	• Imaging reveals multiple ring enhancing lesions with surround erythema • Biopsy reveals tachyzoites
PML (JC virus)	• Immunosuppression (HIV/AIDS, immune-modulating therapies) • <100 CD4+ cells/μL	• Initial focal neurologic deficits • Steady progression to widespread neurologic deficits affecting all areas of the CNS	• JC virus DNA via PCR of CSF • CT/MRI • Biopsy	• MRI T2-weighted studies reveal increased signal in the white mater • On biopsy, intranuclear viral inclusions within infected oligodendrocytes
CMV encephalitis	• Immunosuppression for CNS disease to occur • <50 CD4+ cells/μL	• Rapid progression helps differentiate from HIV encephalitis, PML • See altered mental status/ delirium as well as diffuse neurologic deficits	• CMV DNA via PCR of CSF • CT/MRI • Biopsy	• Imaging reveals meningeal enhancement or periventricular inflammation • CMV inclusions ("owl's eye")
Cryptococcus meningitis/ encephalitis	• Immunosuppression • <100 CD4+ cells/μL • Handling of bird or bat droppings • Handling of soil	• Nonspecific constitutional symptoms, such as fever, headache, nausea, and vomiting often with altered mental status	• Lumbar Puncture • CT/MRI • Detection of cryptococcal capsular polysaccharide antigen in serum and CSF • PCR	• LP reveals a high opening pressure, low WBCs, low glucose, and elevated protein • Imaging reveals leptomeningeal enhancement • Detection of cryptococcal capsular polysaccharide antigen in the serum and CSF
Mycobacterium Tb	• Immunosuppression • <200 CD4+ cells/μL • Smokers • Health-care workers, prisoners	• Nonspecific constitutional symptoms such as fever, headache, nausea • Neurologic deficits (focal and diffuse)	• Acid fast staining • Cultures • PCR • Skin testing • CT/MRI	• Imaging reveals tuberculomas, meningeal enhancement, hydrocephalus, and basilar exudates

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; JC virus, human polyomavirus 2; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal encephalopathy.

impairment, which leads to concerns of central nervous system compromise. Other symptoms such as his chronic cough, fatigue, and weight loss raise concern for infection or malignancy.

What Infectious Organisms May Be Affecting Our Immunocompromised Patient's Central Nervous System, and What Risk Factors for Each Infectious Agent Are Present in This Patient (see Table 1 for Comparisons)?

- Toxoplasmosis
  - Exposure to animals (possibly cats) on his farm
  - Exposure to undercooked meat from farm animals
- JC virus
  - Five-year history on noncompliance with antiretroviral therapy
- Cytomegalovirus
  - Five-year history on noncompliance with antiretroviral therapy
- Cryptococcus
  - Exposure to soil and bird droppings on the family farm
- Tuberculosis
  - Foreign travel
  - Health-care worker

What Is Toxoplasmosis?

Toxoplasmosis is an intracellular protozoan. It infects humans that ingest food contaminated with oocytes from cat feces or undercooked meat. Cysts can then invade extensively into skeletal muscle, eye tissue, and brain gray and white matter (Figures 1 and 2).

How Does Toxoplasmosis Present in Immunocompetent and Immunocompromised Patients?

In individuals that are immunocompetent, the disease may remain completely asymptomatic or produce a mononucleosis-like

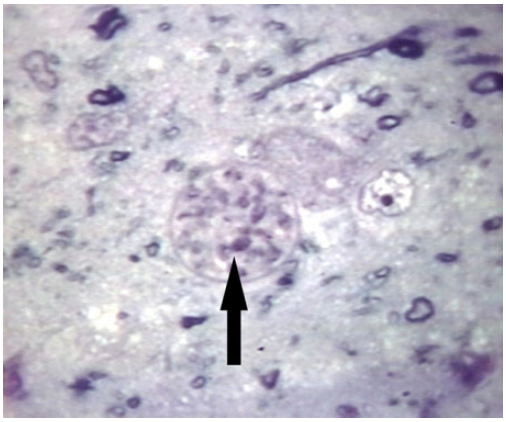

Figure 1. Large toxoplasmosis cyst in a brain histological sample of a patient with AIDS. Arrow points to large circle with purple points indicated the cyst, ×400 magnification. Reproduced with permission from Dr Peter G Anderson and the University of Alabama at Birmingham (UAB) Pathology Education Information Resource (PEIR) Digital Library.

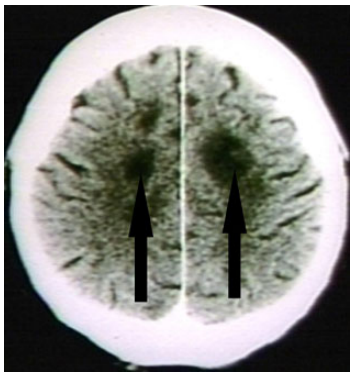

Figure 2. Hypointense areas on brain MRI. Arrow points to blacked out circular areas representative of toxoplasmosis lesions. Gadolinium enhancement can result in ring enhancement (not seen here), and active lesions are often surrounded by edema. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library. MRI indicates magnetic resonance imaging.

illness. In immunocompromised individuals, reactivation of a latent infection can lead to unifocal, multifocal, or even diffuse central nervous system (CNS) disease. Although it is the most prevalent HIV-associated opportunistic CNS infection, the incidence of Toxoplasmosis has significantly decreased with better treatment of HIV and use of prophylactic medications. When it does arise, it can present as a cerebral abscess, diffuse encephalitis, or chorioretinitis, and individuals often have a <100 CD4+ cells/μL. Along with headaches and fevers, clinical manifestations of the disease include neurological deficits, both focal and diffuse, including cortical and cerebellar signs, cranial nerve deficits, focal neurologic deficits or arm weakness and decreased sensation, seizures, and altered mental status.[2]

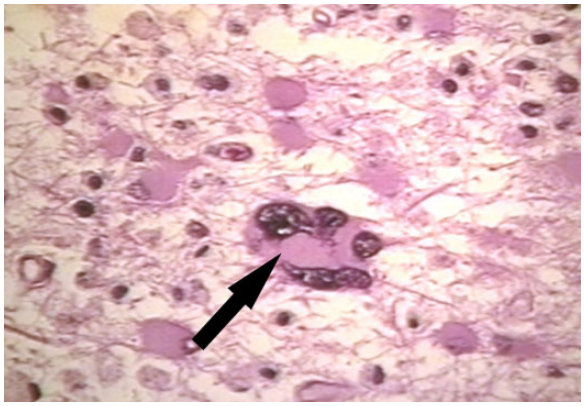

Figure 3. White matter damage in brain. Specimen from white matter area with multinucleated astrocyte, indicating undigested damaged brain matter (arrow); ×400 magnification. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library.

What Is JC Virus?

JC virus is a polyomavirus. A large majority of the population is latently infected with the virus and have no disease. Prior to the era of the AIDS epidemic in the 1980s, it was an exceptionally rare finding. Recent advancements in immune-modulating therapies, such as the monoclonal antibody natalizumab utilized in the treatment of multiple sclerosis and Crohn disease, have introduced a new cohort of immunosuppressed patients susceptible to active infection with JC virus. Patients with non-Hodgkin lymphoma receiving high-dose chemotherapy with hematopoietic stem cell transplantation incur a similar risk.[3]

What Disease Does JC Virus Cause in Immunocompromised Patients?

In immunocompromised individuals, JC virus causes a lytic infection of oligodendrocytes leading to the demyelination of the CNS. This is a process known as progressive multifocal encephalopathy (PML) which holds a 30% to 50% mortality rate in the first few months following diagnosis (Figures 3 and 4).[4]

What Are the Symptoms of Progressive Multifocal Encephalopathy?

Patients present with marked with visual and cognitive deficits, motor weakness, impaired coordination, seizures, and speech deficits. Individuals with the disease often have <100 CD4+ cells/μL.

What Is Cytomegalovirus?

Cytomegalovirus (CMV) is a common virus that infects people that often remains asymptomatic or causes a mild disease in

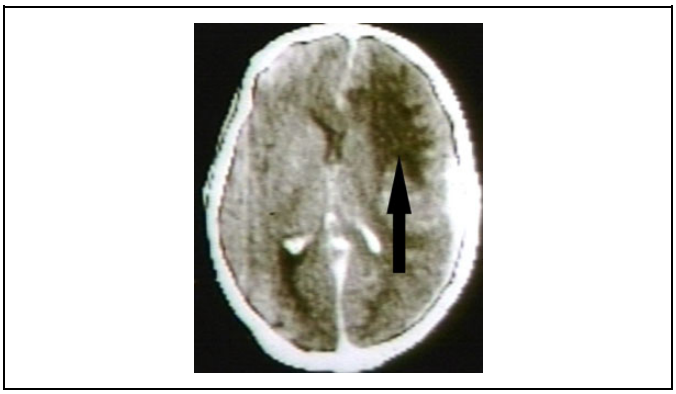

Figure 4. White matter destruction on brain MRI secondary to PML. Arrow points to blacked out area indicating white matter destruction. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library. MRI indicates magnetic resonance imaging; PML, progressive multifocal encephalopathy.

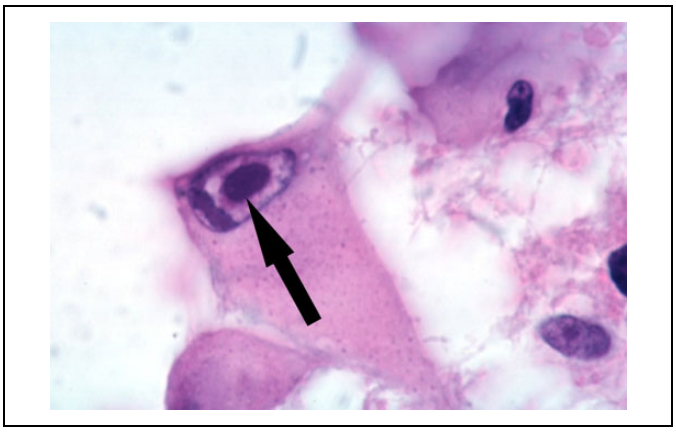

Figure 5. Cowdry body of cytomegalovirus in a brain histological sample. Arrow points to large purple oval representative of the cowdry body; ×400 magnification. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library.

immunocompetent individuals. Thus, it is extremely rare to see any neurologic disease resulting from CMV in immunocompetent individuals (Figure 5).

What Symptoms Can Cytomegalovirus Cause in Immunocompromised Patients?

In immunocompromised individuals, CMV encephalitis can present with altered mental status (including somnolence and lethargy), motor weakness, change in sensation, and impaired coordination. It can often be difficult to differentiate CMV encephalitis from HIV dementia; however, the rapid onset and signs of delirium often help differentiate the 2 disorders. Additionally, in the case of ventriculoencephalitis, cranial nerve involvement will often be present.[5]

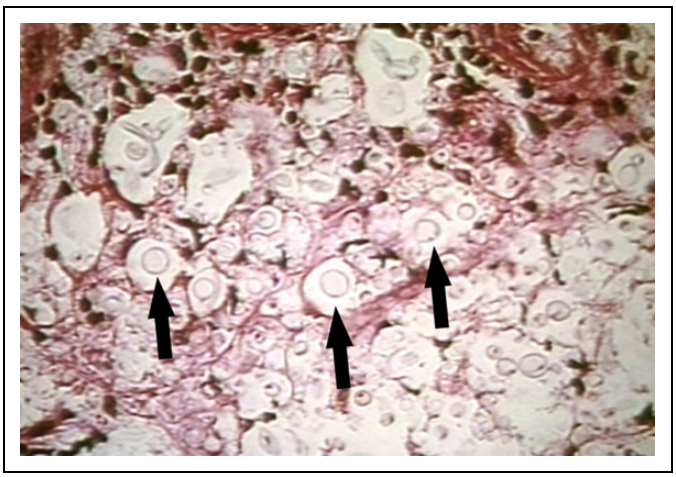

Figure 6. Encapsulated fungus *Cryptococcus neoformans* in a brain histological sample. Arrow points to the circles with a dark border and central clearing representative of the fungus; ×400 magnification. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library.

What Is Cryptococcus Neoformans*?*

Cryptococcal meningitis is an infection of the CNS with the fungus *Cryptococcus neoformans* found commonly in soil and bird droppings. The fungus is acquired through inhalation and, in the case of immunocompromised individuals, can disseminate hematogenously, leading to cryptococcal meningitis and cryptococcal encephalitis (Figure 6).

What Are the Symptoms of Cryptococcal Meningitis?

Clinical manifestations of the disease are often nonspecific and include fever, headaches, nausea, altered mental status, and memory loss. Even with proper antifungal therapy, mortality from cryptococcal meningitis approaches 30% to 50%.[6]

What Is Tuberculosis?

Tuberculosis is caused by a bacterium called *Mycobacterium tuberculosis* that primarily affects the lungs but can affect most parts of the body. Active infection of tuberculosis more often occurs in those with comorbidities, such as active smokers, as well as those who are immunocompromised. Additionally, persons who work in health care or in a prison environment are also more likely to be exposed to the bacteria (Figure 7).

What Are the Symptoms of Tuberculosis Meningitis?

In the case of immunocompromised individuals, dissemination of the bacteria to the brain can result in a Rich focus, a granuloma in the cortex or meninges, that can rupture into the subarachnoid space leading to tuberculous meningitis. The HIV-associated tuberculous meningitis accounts for 27% of meningitis cases in HIV-positive patients.[7] While most individuals with the disease typically have CD4+ cell counts <200

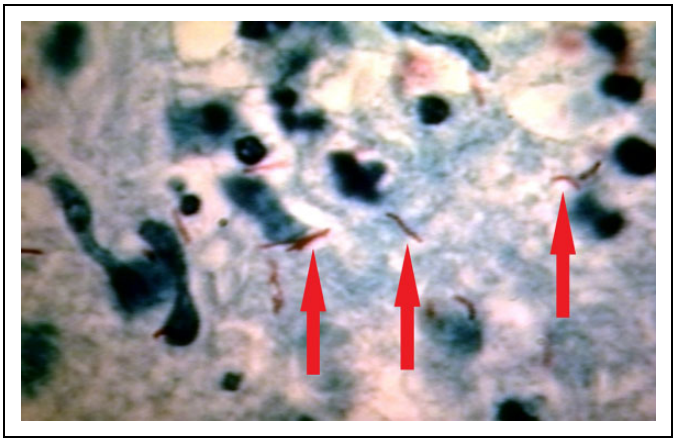

Figure 7. Tuberculosis of the brain. Arrow points to a fuchsia organism that represents acid-fast stained tuberculosis bacteria in a brain histological sample; ×400 magnification. Reproduced with permission from Dr Peter G Anderson and the UAB Pathology Education Information Resource (PEIR) Digital Library.

cells/μL, there have been numerous cases where dissemination to the CNS has occurred in individuals with normal CD4+ cell counts. Clinical manifestations of the disease are nonspecific and include fever, headaches, lethargy, and both focal and diffuse motor and sensory deficits.

Diagnostic Findings, Part 2

Laboratory Results

Serological testing was performed for various infections. Only immunoglobulin (Ig)G for toxoplasma returned positive. The IgM for toxoplasma returned negative, indicating a likely chronic infection.

Imaging

The computed tomography (CT) head revealed a 4 × 3 cm^2 ring enhancing lesion in the right parietal lobe and 2 × 2 cm^2 ring enhancing lesion in the left parietal lobe, both with associated surrounding edema.

Questions/Discussion Points, Part 2

How Can Toxoplasmosis Be Detected?

Imaging studies with magnetic resonance imaging (MRI) or CT will reveal ring enhancing lesions with surrounding edema. Serology of anti-toxoplasma antibodies can be performed; however, many individuals around the world test positive due to latent, asymptomatic infection. Serology can also be done on specific body fluids such as cerebrospinal fluid (CSF), but these specimens can be difficult to acquire. Additionally, polymerase chain reaction (PCR) testing or direct visualization of the organism from lymph node biopsy or bronchoalveolar lavage (depending on location of infection) can also be performed.[8]

How Is JC Virus Detected?

Diagnosis of JC virus can be made through the identification of JC virus DNA via PCR of the CSF along with findings on imaging. Magnetic resonance imaging T2-weighted studies reveal increased signal in the white mater of cerebral hemispheres, cerebellum, and brain stem. Definitive diagnosis by biopsy is often not performed, but when obtained, is characterized by the presence of glassy, intranuclear viral inclusions within infected oligodendrocytes, which can be highlighted by immunohistochemical studies specific for JC virus.[9,10]

How Is Cytomegalovirus Detected?

Individuals with CMV encephalitis are almost always profoundly immunocompromised with <50 CD4+ cells/μL. Diagnostic studies include analysis of CSF for CMV DNA via PCR or CMV antigen, both highly specific for CMV infection. Imaging studies are often nonspecific; however, meningeal enhancement or periventricular inflammation in the case of ventriculoencephalitis can help aid diagnosis. Definitive diagnosis can be made by biopsy but is often avoided when clinical presentation and results from CSF analysis or imaging suggest CMV infection.[11]

How Is Cryptococcus Neoformans *Detected?*

Individuals with the disease have a <100 CD4+ cells/μL. Numerous methods are available to help confirm the diagnosis of cryptococcal meningitis. Lumbar puncture on the CSF reveal a high opening pressure, low WBCs, low glucose, and elevated protein. Cultures are considered the gold standard for diagnosis but take several days to result, which may lead to a delay in treatment. Additionally, detection of cryptococcal capsular polysaccharide antigen in the serum and CSF can be performed, which is useful due to its high sensitivity and specificity and can lead to early treatment. More recently, PCR is becoming more widespread and will likely be the test of choice within a few years.[12]

How Can Tuberculosis Be Detected?

Diagnostic studies with acid-fast staining, cultures, and PCR have traditionally been performed for detection of *Mycobacterium tuberculosis*. However, newer technology like the Xpert MTB/resistance to rifampin (RIF) assay has been shown to detect *Mycobacterium tuberculosis complex* and RIF in less than 2 hours.[13] Use of skin testing and IFN-γ release assay are unreliable in individuals with low CD4+ cell counts. Imaging studies can be useful, sometimes revealing tuberculomas, meningeal enhancement, hydrocephalus, and basilar exudates.[14]

What Is the Diagnosis Based on the Historical, Clinical, and Imaging Findings?

The historical (focal neurologic deficits with R arm twitching, exposure to potentially undercooked meat, nonadherent with

antiretroviral therapy, decline in memory, headaches, night sweats, increasing fatigue), clinical (CD4+ cell count of 95 cells/μL), positive serological testing, and imaging findings (4×3 cm^2 ring enhancing lesion in the right parietal lobe and 2×2 cm^2 ring enhancing lesion in the left parietal lobe, both with associated surrounding edema) are consistent with a diagnosis of toxoplasmosis.

Treatment

This patient should be immediately started on pyrimethamine and sulfadiazine to directly combat the infection. Leucovorin should also be started to avoid the toxic bone marrow effects caused by pyrimethamine. Clindamycin can be given in place of sulfadiazine in the setting of a sulfa allergy. Follow-up in 4 to 6 weeks for reevaluation of the condition. Additionally, the patient needs to be started on antiretroviral therapy for treatment of his HIV/AIDS diagnosis with close follow-up with an infectious disease clinician.[8]

Teaching Points

- Toxoplasmosis is an intracellular protozoan that comes from cat feces or undercooked meat that can cause cerebral abscess, diffuse encephalitis, or chorioretinitis in patients with <100 CD4+ cells/μL.
- The JC virus leads to demyelination of the CNS, causing PML.
- While the CMV is often asymptomatic in the immunocompetent, it can cause delirium and severe encephalitis in the immunocompromised.
- *Cryptococcus neoformans* causes a fungal encephalitis or meningitis with a 30% to 50% mortality rate despite proper treatment.
- Rupture of a tuberculosis into the subarachnoid space leads to tuberculosis meningitis.

Declaration of Conflicting Interests

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References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017:4. doi:10.1177/2374289517715040.
2. Flegr J, Prandota J, Sovičková M, Israili ZH. Toxoplasmosis—a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. Fernandez-Reyes D, ed. *PLoS One*. 2014;9:e90203. doi:10.1371/journal.pone.0090203.
3. Shishido-Hara Y. Progressive multifocal leukoencephalopathy and promyelocytic leukemia nuclear bodies: a review of clinical, neuropathological, and virological aspects of JC virus-induced demyelinating disease. *Acta Neuropathol (Berl)*. 2010;120:403-417. doi:10.1007/s00401-010-0694-x.
4. Progressive Multifocal Leukoencephalopathy Information Page. *National Institute of Neurological Disorders and Stroke*. 2019. https://www.ninds.nih.gov/Disorders/All-Disorders/Progressive-Multifocal-Leukoencephalopathy-Information-Page. Accessed May 20, 2019.
5. Maschke M, Kastrup O, Diener H-C. CNS manifestations of cytomegalovirus infections. *CNS Drugs*. 2002;16:303-315. doi:10.2165/00023210-200216050-00003.
6. Revankar S. *Cryptococcus*. Kenilworth, NJ: Merck Manuals; 2017. https://www.merckmanuals.com/professional/infectious-diseases/fungi/cryptococcosis. Accessed May 17, 2019.
7. Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. *BMC Infect Dis*. 2010;10:67.
8. Basavaraju A. Toxoplasmosis in HIV infection: an overview. *Trop Parasitol*. 2016;6:129-135. doi:10.4103/2229-5070.190817.
9. Saribaş AS, Özdemir A, Lam C, Safak M. JC virus-induced progressive multifocal leukoencephalopathy. *Future Virol*. 2010;5:313-323. doi:10.2217/fvl.10.12.
10. Muñoz-Mármol AM, Mola G, Fernández-Vasalo A, Vela E, Mate JL, Ariza A. JC virus early protein detection by immunohistochemistry in progressive multifocal leukoencephalopathy: a comparative study with in situ hybridization and polymerase chain reaction. *J Neuropathol Exp Neurol*. 2004;63:1124-1130.
11. Caliendo A. *Approach to the Diagnosis of Cytomegalovirus Infection*. April 2019. https://www.uptodate.com/contents/approach-to-the-diagnosis-of-cytomegalovirus-infection. Accessed May 17, 2019.
12. Abassi M, Boulware DR, Rhein J. Cryptococcal meningitis: diagnosis and management update. *Curr Trop Med Rep*. 2015;2:90-99. doi:10.1007/s40475-015-0046-y.
13. A new tool to diagnose tuberculosis: the Xpert MTB/RIF Assay. In: Atlanta, Georgia: Center for Disease Control. https://www.cdc.gov/tb/publications/factsheets/pdf/xpertmtb-rifassayfactsheet_final.pdf. Accessed May 15, 2019.
14. Singh AK, Malhotra HS, Garg RK, et al. Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. *BMC Infect Dis*. 2016;16:306. doi:10.1186/s12879-016-1625-9.