Clinical Case of the Month

Altered Mental Status and Headache in a Young Man

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INTRODUCTION

Central nervous system (CNS) toxoplasmosis can be a life-threatening disease in patients with human immunodeficiency virus (HIV) infection.[1] We describe a case of a young adult man with acquired immune deficiency syndrome (AIDS) who presented with altered mental status and headache secondary to toxoplasmosis.

CASE PRESENTATION

A 31-year-old man with advanced human immunodeficiency virus (HIV) infection presented to the emergency department with a chief complaint of worsening confusion for several weeks. He had been having headaches intermittently for about a year, which had progressively worsened over the last month. He denied cough, fever, chills, weakness, weight loss, tremors, or visual disturbances. He had a history of smoking tobacco and marijuana. He lived alone. He had not seen a provider for more than a year and had not taken antiretroviral therapy during this time. His CD4 cell count 18 months earlier was 299 cells/mm^3 (Normal Reference Range is 228-2,290), and CD4% was 18.1%(Normal Reference Range is 37%-63%).

Upon admission to the emergency department, his temperature was 97.3˚F, heart rate 64 beats/minute, blood pressure 120/83 mmHg, respiratory rate 16/minute, and oxygen saturation of 100% on room air. He weighed 52 kilograms. His height was 167 centimeters. His body mass index was 18.6. On physical examination, he was alert and oriented to place and person and was dysarthric. The rest of his physical examination revealed no reported abnormalities.

His laboratory workup revealed a normal complete blood count and comprehensive metabolic panel. His CD4 cell count was 30 cells/mm,^{3} and CD4% was 5%. His urine toxicology test was positive for marijuana and cocaine. A CT scan of the brain showed large left frontal and left temporal lesions with edema and a 3.8 cm heterogeneously enhancing

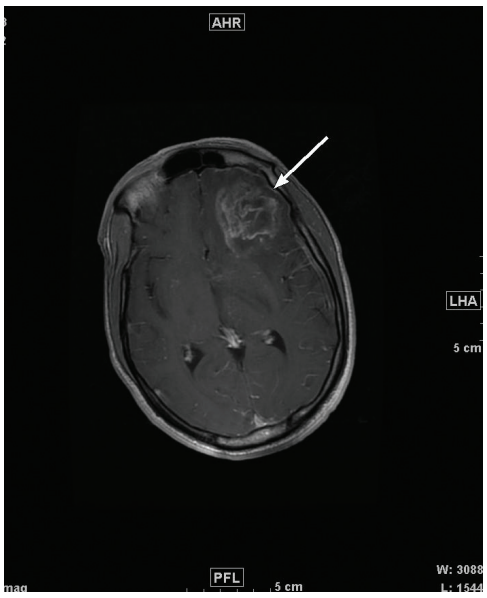

Figure 1: An axial T1-weighted post-contrast image with fat saturation demonstrates an irregularly enhancing left frontal lobe mass (arrow).

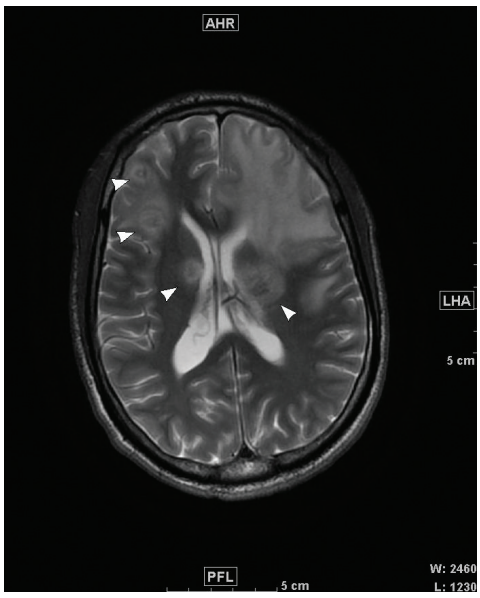

Figure 2: T2 FLAIR imaging at a slightly higher level reveals smaller lesions in the right hemisphere (arrowheads).

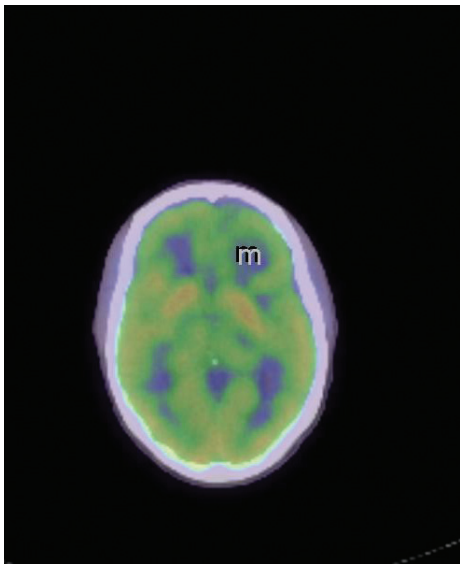

Figure 3: Fused PET-CT images at the same level as Figure 1 show no hypermetabolism in the region of the dominant mass (m). The smaller lesions in Figure 2 also were not hypermetabolic.

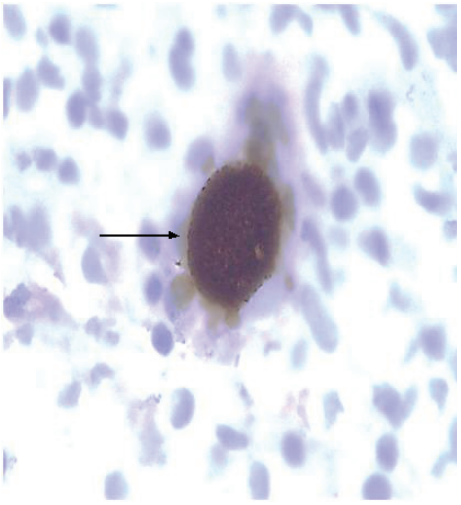

Figure 4: Anti-toxoplasma immunohisto-chemistry highlighting the toxoplasma oocyst (60x).

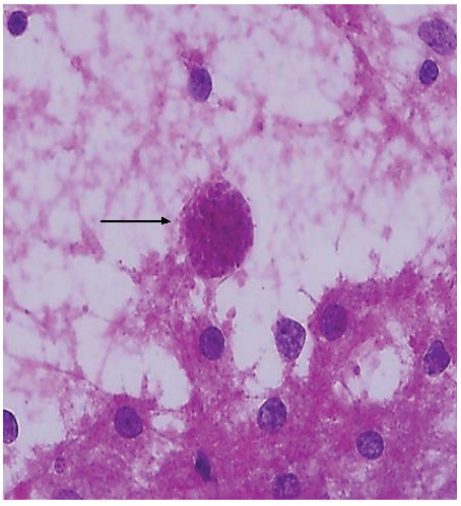

Figure 5: Toxoplasma oocyst with encysted toxoplasma bradyzoites (40x).

component in the left frontal lobe. There was a midline shift of 6 mm from the midline to the right.

The patient was initially admitted to the medical intensive care unit. He was started on dexamethasone to decrease the cerebral edema, levetiracetam for seizure prophylaxis, and empiric treatment with leucovorin, sulfadiazine, and pyrimethamine for possible toxoplasmosis. Of note, he had a positive toxoplasma serology five years prior. MRI of the brain demonstrated multiple heterogeneously contrast-enhancing lesions throughout both cerebral hemispheres. The largest of these lesions measured 4.1 cm x 4.0 cm x 3.5 cm in the left frontal lobe. The lesion and its associated edema resulted in a mass effect with sulcal effacement and intimal shift of the midline to the right side (Figures 1, 2). Rapid plasma regain and serum cryptococcal antigen were negative. A lumbar puncture was not performed due to the increased risk of herniation.

After 10 days of treatment with antitoxoplasmosis therapy, he had no change in his neurologic exam. A subsequent positron emission tomography of the brain did not show any significant changes and no areas of increased metabolic activity (Figure 3). A brain biopsy was performed. The tissue specimens were consistent with toxoplasmosis (Figures 4, 5).

With the biopsy demonstrating toxoplasmosis, the patient was discharged to complete a course of pyrimethamine, sulfadiazine, and leucovorin. Antiretroviral therapy was to be initiated as an outpatient.

DISCUSSION

Epidemiology and Etiology

Toxoplasmosis, an infection with a worldwide distribution, is caused by the intracellular protozoan parasite, *Toxoplasma gondii*. Feline cats are the only animals in which *T. gondii* can complete its reproductive cycle.[2] Following feline ingestion of any form of *T. gondii*, the parasite infects the gut epithelial cells and reproduces. The feline then excretes infectious oocysts in feces. When non-felines, including humans, ingest *T. gondii* oocysts, the organisms invade intestinal epithelium and disseminate throughout the body. They then encyst in any type of nucleated cell and can lie dormant within tissues for the life of the host. There are four means of acquiring toxoplasmosis in humans: ingestion of infectious oocysts from the environment (usually from soil contaminated with feline feces); ingestion of tissue cysts in meat from an infected animal; through vertical transmission from an infected mother to her fetus; or via blood transfusion or organ transplantation from an infected donor.[2]

Immunocompetent persons with primary infection are usually asymptomatic, but latent infection can persist for the lifetime of the host.[3] Seroprevalence rates of toxoplasmosis vary substantially among different countries (eg, approximately 15% in the United States to more than 50% in certain European countries).[4] Among HIV-infected patients, seroprevalence of antibodies to *T. gondii* mirror rates of seropositivity in the general population.[5] In patients with

AIDS, there is no higher incidence of toxoplasmosis in cat owners compared to non-cat owners.[6]

Patients who are HIV-infected with <100 CD4 cells/mm^3, and are toxoplasma seropositive have an approximately 30% probability of developing reactivated toxoplasmosis in absence of prophylaxis.[7,8] The mechanism by which HIV induces susceptibility to toxoplasmosis appears to be multifactorial, including depletion of CD4 T cells; impaired production of IL-2, IL-12, IFN-gamma; and impaired cytotoxic T-lymphocytic activity.[9]

The introduction of anti-toxoplasma prophylaxis and potent antiretroviral therapy (ART) has altered the occurrence of toxoplasmic encephalitis.[10] In the Multicenter AIDS Cohort Study (MACS), the incidence of CNS toxoplasmosis decreased from 5.4 per 1,000 people in years 1990 to 1992 to 3.8 per 1,000 people in years 1993 to 1995, and 2.2 per 1,000 people in years 1996 to 1998.[11]

It is much harder to determine the incidence of extracerebral toxoplasmosis. Most of the available data is from before the introduction of ART and from France, where the seroprevalence to *T. gondii* is high. The most prominent risk factor for the development of extracerebral toxoplasmosis is advanced immunosuppression (mean CD4 cell counts of 57 and 58 cells/mm^3).[12,13] Concurrent CNS disease was present in 41% of patients in the report of 199 extracerebral cases.[13]

CLINICAL PRESENTATION

Eighty to ninety percent of acute *T. gondii* infections in immunocompetent hosts are asymptomatic. When symptomatic infection does occur, the most common manifestation is bilateral, symmetrical, non-tender cervical lymphadenopathy.[14,15] Twenty to thirty percent of symptomatic patients will have generalized lymphadenopathy. Constitutional symptoms, such as fever, chills, and sweats may be present but are typically mild. Headaches, myalgias, pharyngitis, diffuse non-pruritic maculopapular rash, or hepatosplenomegaly may also occur. Most immunocompetent patients have a benign, self-limited course lasting from weeks to months, but rarely longer than a year.[16]

T. gondii usually reactivates in patients with AIDS, most commonly doing so in the CNS leading to cerebral abscesses. Patients with cerebral toxoplasmosis typically present with headache, confusion, and fever.[6] This disease is an important cause of focal brain lesions in HIV-infected patients.[8,17] Characteristically, toxoplasma-associated encephalitis has a subacute onset with focal neurologic abnormalities frequently accompanied by headache, altered mental status, and fever.[18,19] The most common focal neurologic signs are motor weakness and speech disturbances. Patients can also present with seizures, cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus, movement disorders, and neuropsychiatric manifestations.[18,19] Toxoplasmosis rarely presents as a rapidly fatal form of diffuse encephalitis.[20]

DIAGNOSTIC EVALUATION

A definitive diagnosis of central nervous system toxoplasmosis requires a compatible clinical syndrome, identification of one or more mass lesions by brain imaging, and detection of the organism in a biopsy specimen.[4] However, the majority of clinicians initially treat a seropositive patient with compatible symptoms, signs, and imaging for presumptive TE, reserving a biopsy in those who do not improve (clinically or radiographically) after two weeks of directed therapy. The vast majority of patients with toxoplasma encephalitis are seropositive for anti-toxoplasma IgG antibodies.[21] Anti-toxoplasma IgM antibodies are usually absent; quantitative IgG antibody titers are not helpful. The absence of antibodies to toxoplasma makes the diagnosis less likely but does not exclude it.[4] Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for identifying cerebral toxoplasmosis, which usually presents as multiple, ring-enhancing brain lesions often associated with edema.[22,23] Thallium single photon emission computed tomography (SPECT) and positron emission tomography (PET) can be useful in distinguishing toxoplasmosis or other infections from CNS lymphoma.[24,25] Lymphoma has greater thallium uptake on SPECT and greater glucose and methionine metabolism on PET than neurotoxoplasmosis or other infections.[26,27] Cerebrospinal fluid (CSF) may demonstrate a mild mononuclear pleocytosis and elevated protein level. Tachyzoites can occasionally be seen on cytocentrifuged cerebrospinal fluid samples stained with Giemsa. Detection of *T. gondii* by PCR has demonstrated high specificity (96% to 100%) but variable sensitivity (50% to 98%).[28,29] Thus, a positive PCR result establishes the diagnosis, but a negative test does not rule it out.

PROPHYLAXIS AND TREATMENT

Treatment usually consists of a combination of medications for six weeks. The regimen of choice is pyrimethamine and sulfadiazine.[4,30-32] Patients who are intolerant to sulfadiazine can take clindamycin.[4,33] Alternative regimens for those who do not tolerate more standard regimens include trimethoprim-sulfamethoxazole, or pyrimethamine plus azithromycin, or pyrimethamine plus atovaquone, or sulfadiazine plus atovaquone, or atovaquone.[4,34,35] All pyrimethamine-containing regimens should also include leucovorin (folinic acid) to prevent drug-induced hematologic toxicity. Adjunctive corticosteroids should be used for patients with radiographic evidence of midline shift, signs of critically elevated intracranial pressure, or clinical deterioration within the first 48 hours of therapy.[36] Anticonvulsants should be administered to patients with a history of seizures but should not be given routinely for prophylaxis to all patients with the presumed diagnosis of CNS toxoplasmosis.[4] Immune reconstitution inflammatory syndrome (IRIS) can lead to a paradoxical worsening of symptoms with development of worsening edema surrounding brain lesions as CD4 cell counts rapidly improve.[37-39] Management of IRIS includes

continuing treatment of toxoplasmosis and HIV and increasing the dose of steroids as needed to control symptoms.

After six weeks of treatment, secondary prophylaxis is instituted and can be safely stopped once the patient recovers and CD4 has been consistently >200/ul for at least six months on antiretroviral therapy.[4] It usually consists of the same regimen but with lower doses of pyrimethamine, sulfadiazine, and leucovorin. Alternative regimens include clindamycin, pyrimethamine, and leucovorin, or atovaquone with or without pyrimethamine, or atovaquone with sulfadiazine.[4,33,40,41]

Primary prophylaxis is indicated for patients with HIV and CD4 counts <100 cells/mm3 who are *T. gondii* IgG-positive.[4,42] The preferred agent is TMP-SMX.[4] Other options are dapsone plus pyrimethamine or atvaquone.[35] Primary prophylaxis may be discontinued if CD4 count is greater than 200 cells/mm3 for more than three months.[4]

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