

## CLINICAL VIGNETTE

# Cat Bugs vs Brain Cancer: The Diagnostic Difficulties of Distinguishing between Toxoplasma Encephalitis and Primary CNS Lymphoma in an AIDS Patient

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### *Case presentation*

A 36-year-old female with a past medical history of HIV infection was brought by her father to the emergency department (ED) for vomiting, anorexia, and progressive loss of ambulation and social skills. She had been feeling vaguely unwell for a year but became acutely worse three months prior to admission when she began vomiting after every meal and reported decreased appetite. Her ability to ambulate progressively declined, and she became completely bedbound one month prior to admission. During this time, she also exhibited symptoms of urinary and fecal incontinence. In addition to her physical symptoms, the patient also deteriorated psychosocially. She progressively stopped speaking, although she would occasionally hum or speak to herself. Her father also noted she occasionally had difficulty with word-finding. Prior to this acute illness, she had no obvious cognitive or expressive deficits. She had not been taking any medications or using illicit substances.

On presentation, the patient was somnolent but arousable. She was febrile to 103°F and urine toxicology screen was negative. She was unable to answer questions and only occasionally followed commands. On head and neck exam, her pupils were reactive to light, and her extraocular movements were intact. She had notable seborrheic dermatitis at her hairline. Her biceps reflexes were 2+ bilaterally but no patellar reflex could be elicited. She was able to plantarflex weakly with her left foot but was unable or unwilling on the right. Her laboratory values were significant for a white blood cell (WBC) count of 3,000 cells/mm<sup>3</sup> and a CD4 count of 16 cells/mm<sup>3</sup>. A non-contrast CT in the ED showed multifocal edema, so an MRI with contrast was performed.

The MRI showed multiple intraparenchymal peripherally enhancing masses (Figure 1), which were located in the right frontal lobe, left basal ganglia, left lateral ventricle temporally, and left splenium, as well as innumerable foci of nodular enhancement in the cerebellum suggestive of meningeal involvement. Enhancement of the lateral ventricle walls was also found, suggestive of ventriculitis. Based on these imaging findings, the diagnoses of toxoplasmosis encephalitis (TE) or central nervous system (CNS) lymphoma (PCNSL) were

considered but could not be differentiated based on imaging alone.

### *Diagnosis of toxoplasma encephalitis*

The differential diagnosis of a ring-enhancing lesion in a patient with AIDS is primarily toxoplasmosis vs. primary CNS lymphoma. Historically, up to 50-70% of AIDS patients with brain lesions had TE and 20-30% had PCNSL with the remainder made up by progressive multifocal leukoencephalopathy and other viral, bacterial, or fungal infections.<sup>1</sup> MRI alone is insufficient to differentiate between toxoplasmosis and lymphoma.<sup>2</sup> Although there are characteristics that are more likely to occur in one disease over the other, the two diseases share significant overlap on imaging.

Toxoplasma encephalitis is more likely to present as multiple CNS lesions, although 31% presented as single lesions in one study.<sup>3</sup> By contrast, a study of CNS lymphoma found a single lesion in 62% of the sample.<sup>4</sup> Whereas TE tends to have a predilection for the basal ganglia,<sup>5</sup> PCNSL tends to be found on the brain periphery or corpus callosum, although up to 25% may be found in deep structures including the basal ganglia.<sup>6</sup> In addition to overlap in number and location of lesions, there is also significant overlap in apparent diffusion coefficient (ADC) ratios of TE and PCNSL lesions on MRI; although for lesions with ADC ratios below 1, there is a much greater proportion of PCNSL compared to TE (34% vs. 2%).<sup>7</sup>

PET scans can also be used to help differentiate between TE and PCNSL. Primary CNS lymphoma tends to consistently have higher fluorodeoxyglucose (FDG) uptake compared to TE, especially after initiation of toxoplasmosis therapy.<sup>8</sup> Specificity and sensitivity of FDG PET-CT can approach 100% for the diagnosis of PCNSL, although most study samples have been small.<sup>9</sup> As evinced above, conventional neuroimaging is of limited utility in the differentiation between TE and PCNSL, whereas PET imaging appears to have greater accuracy but requires further empiric validation.

Given the difficulty of diagnosing toxoplasma encephalitis from conventional imaging alone, an alternate diagnostic approach must be used. Definite diagnosis of TE with exclusion of PCNSL requires stereotactic brain biopsy, optimally with immunoperoxidase staining.<sup>5</sup> Brain biopsy yielded definitive diagnosis of brain lesions in AIDS patients in almost 94% of the cohort in one study.<sup>10</sup> Nonetheless, as an invasive procedure, brain biopsy carries a non-negligible risk of morbidity and mortality<sup>11</sup> and is not used for first-line diagnosis. For suspected toxoplasmosis in AIDS patients, the clinical picture and response to treatment are considered sufficient for diagnosis.

Almost all patients with TE are seropositive for anti-toxoplasma IgG.<sup>5</sup> Given that the seroprevalence of anti-toxoplasma is around 11% in the United States and as high as 80% in other countries,<sup>5,12</sup> positive serology is insufficient for TE diagnosis. The vast majority (80-95%) of patients with TE have a CD4 T cell count of less than 100 cells/mm<sup>3</sup>,<sup>13</sup> thus early biopsy should be considered in patients with CD4 count greater than 100-200.<sup>13,14</sup> Cerebrospinal fluid (CSF) analysis can be used to further support a TE diagnosis with a specificity of 100%; however, sensitivity is significantly less.<sup>15</sup>

*Sande's HIV/AIDS Medicine* management reference recommends empiric toxoplasmosis treatment be started in all patients with a clinically consistent presentation: neuroimaging with multiple enhancing lesions while not on toxoplasma prophylaxis, positive toxoplasma serology, and CD4 count <100-200.<sup>13</sup> The 2013 *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* suggest diagnostic criteria of (1) identification of one or more mass lesions on neuroimaging and (2) detection of the organism in a clinical sample, such as by CSF PCR.<sup>5</sup> Clinicians may use a combination of these recommendations in deciding to begin empiric treatment.<sup>14</sup> With first-line anti-toxoplasma treatment, pyrimethamine and sulfadiazine, patients should demonstrate clinical improvement within 14 days and radiologic improvements within 3 weeks<sup>3</sup>.

### **Clinical course**

Given the patient's MRI findings, a full infectious disease workup was performed, including lumbar puncture. Treatment for toxoplasmosis with pyrimethamine, sulfadiazine, and leucovorin was empirically started with the goal of reassessing clinical status and MRI after two weeks to decide if diagnostic brain biopsy was necessary. She was also started on cefotaxime and azithromycin until extracerebral sources of infection could be ruled out. Her serum microbiology labs were significant for an HIV viral load of 172,000 copies/mL as well as positive toxoplasma IgG but negative IgM. Her initial cerebrospinal fluid (CSF) analysis showed elevated WBCs of 95/UL, elevated lymphocytes of 82/ UL, and

elevated protein to 529 mg/dL with normal glucose. Lumbar puncture was repeated two days later for additional infectious disease analysis and showed xanthochromia with a red blood cell (RBC) level of 50/UL, as well as low glucose (29mg/dL), in addition to the elevated WBCs and protein. Although the toxoplasma PCR was negative on analysis of the initial CSF, the toxoplasma DNA was positive on the repeat CSF analysis, helping support the presumptive diagnosis of toxoplasma encephalitis.

Clinically, the patient improved rapidly following initiation of fluids, antibiotics, and the anti-toxoplasma regimen. She was responsive and able to follow commands. Over the course of two weeks before her repeat MRI, she regained the ability to speak with minimal word-finding difficulty, although her memory waxed and waned. From her initial non-oriented state, she became consistently oriented to self and location, but she continued to struggle with date.

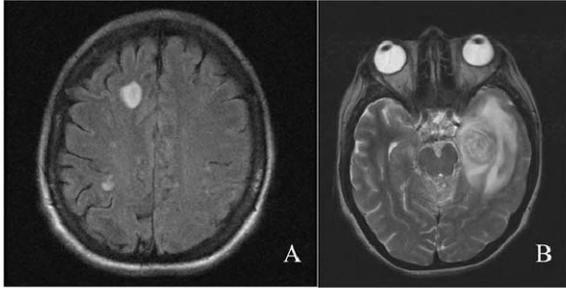
An MRI was repeated two weeks after starting the toxoplasma regimen. The images continued to show multiple contrast-enhancing lesions of the brain; however, reduction in the sizes of the temporal and basal ganglia lesions was noted. Furthermore, reduction in enhancement of the cerebellar lesions and global reduction in edema was appreciated. The large lesion of the splenium was mostly unchanged. The general reduction of the brain edema and multiple lesions after two weeks of toxoplasmosis therapy, in conjunction with the patient's clinical improvement, supported our initial diagnosis of toxoplasma encephalitis. The patient was discharged to a skilled nursing facility on continued 6-week toxoplasma therapy and antiretrovirals.

### **Conclusion**

Although average presentations differ, there is significant overlap between the imaging findings of toxoplasma encephalitis and primary CNS lymphoma. These similarities, coupled with the high seroprevalence of anti-toxoplasma antibodies, can make distinguishing between the two entities difficult. This patient serves as a classic example of this difficulty with diagnosis further complicated by an initially negative CSF toxoplasma PCR. Nonetheless, her imaging and serology more supported the diagnosis of toxoplasma encephalitis, and an empiric trial of an anti-toxoplasma regimen with imaging follow-up in two weeks was an appropriate course of action.

## Images

**Figure 1.** A) Axial flair image showing several intraparenchymal lesions. B) T2 image showing large peripherally enhancing mass in the left lateral ventricle with surrounding edema



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