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Restricted Diffusion in Cerebral Toxoplasmosis Mimicking Primary Central Nervous System Lymphoma in Newly Diagnosed Advanced HIV: A Case Report

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Abstract

Cerebral toxoplasmosis is an important cause of intracranial mass lesions in patients with human immunodeficiency virus (HIV) infection and may be difficult to distinguish radiographically from primary central nervous system lymphoma (PCNSL). Although diffusion-weighted imaging may assist in the differential diagnosis, substantial overlap exists between these entities. We describe a 47-year-old man who presented with two weeks of progressive weakness beginning in the right lower extremity and subsequently progressing to profound bilateral lower-extremity weakness and generalized fatigue. Noncontrast computed tomography of the head demonstrated extensive vasogenic edema centered in the posterior left parietal lobe with compression of the left lateral ventricle and approximately 6 mm of midline shift. Magnetic resonance imaging (MRI) demonstrated multiple enhancing supratentorial lesions involving both cerebral hemispheres, including a dominant 3.9-cm left parietal lesion with extensive surrounding vasogenic edema and prominent restricted diffusion. Further evaluation revealed a new diagnosis of HIV with severe immunosuppression and a CD4 count of 26 cells/µL. *Toxoplasma gondii* serology demonstrated IgG greater than 400 IU/mL with negative IgM. Although cerebral toxoplasmosis was favored, PCNSL remained an important diagnostic consideration because of the marked diffusion restriction and absence of cerebrospinal fluid or tissue confirmation. Empiric trimethoprim-sulfamethoxazole therapy was initiated for a six-week course. Repeat MRI 15 days after initiation of therapy demonstrated interval reduction in the enhancing lesions, substantially decreased vasogenic edema, and improvement in associated mass effect, supporting a presumptive diagnosis of cerebral toxoplasmosis. This case highlights that prominent restricted diffusion does not exclude cerebral toxoplasmosis and emphasizes the importance of integrating immune status, lesion distribution, serologic findings, and response to empiric therapy when differentiating toxoplasmosis from PCNSL in patients with advanced HIV.

Categories: Neurology, HIV/AIDS, Infectious Disease
Keywords: aids, cerebral toxoplasmosis, diffusion-weighted imaging, hiv, primary cns lymphoma, restricted diffusion, toxoplasmic encephalitis

Introduction

Toxoplasma gondii is an intracellular protozoan that usually causes asymptomatic or minimally symptomatic infection in immunocompetent hosts. In individuals with advanced HIV-associated immunosuppression, reactivation of latent infection can result in toxoplasmic encephalitis (TE), a potentially life-threatening opportunistic infection and an important cause of intracranial mass lesions [1,2].

TE most frequently presents with a subacute neurologic syndrome characterized by headache, altered mental status, seizures, or focal neurologic deficits. Neuroimaging classically demonstrates multiple contrast-enhancing lesions with surrounding vasogenic edema, often involving the basal ganglia or corticomedullary junction [1,2]. However, imaging appearances are heterogeneous, and atypical findings may complicate differentiation from other opportunistic infections and neoplastic processes.

Primary central nervous system lymphoma (PCNSL) is one of the most clinically important alternative diagnoses in patients with advanced HIV who present with enhancing intracranial lesions. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements have been evaluated as tools to distinguish the two entities. PCNSL commonly demonstrates diffusion restriction because of high tumor cellularity, whereas the necrotic portions of toxoplasmosis lesions have traditionally been described as demonstrating relatively increased diffusion [3,4]. Nevertheless, restricted diffusion has been documented in cerebral toxoplasmosis, limiting the specificity of this imaging characteristic [4,5].

We describe a patient with newly diagnosed advanced HIV infection and multifocal cerebral toxoplasmosis whose lesions demonstrated prominent core diffusion restriction, initially raising concern for PCNSL. A marked radiographic response to empiric anti-*Toxoplasma* therapy subsequently supported the diagnosis of

TE despite the atypical MRI appearance.

This case was previously presented in abstract form at the 2026 American Academy of Neurology Annual Meeting and published in the Neurology meeting supplement [6].

Case Presentation

A 47-year-old Creole-speaking man with a history of hypertension but no other significant known medical history presented to the emergency department after approximately two weeks of progressive neurologic symptoms. He had initially developed pain in the right lower extremity, followed by progressive weakness of the right leg and subsequently profound weakness involving both lower extremities. During the several days preceding presentation, he also developed worsening generalized weakness and fatigue. On admission, he was alert and oriented to person, place, and time, with a flat affect and normal speech. Muscle tone was normal without spasticity. Strength was 4/5 in the right deltoid and 3/5 in the right biceps and triceps, compared with 5/5 in the corresponding left upper-extremity muscles. Bilateral hip flexion, knee extension, knee flexion, ankle dorsiflexion, and plantar flexion were 0/5. Biceps, brachioradialis, and triceps reflexes were 2+ bilaterally; patellar reflexes were absent, Achilles reflexes were 1+ bilaterally, and plantar responses were downgoing. Sensation was decreased in both lower extremities. Finger-to-nose testing was intact; heel-to-shin testing could not be assessed.

Noncontrast computed tomography of the head demonstrated extensive vasogenic edema centered within the posterior left parietal region, with local mass effect, compression and effacement of the left lateral ventricle, and approximately 6 mm of rightward midline shift. MRI of the brain with and without intravenous contrast demonstrated multiple enhancing supratentorial lesions involving both cerebral hemispheres. The dominant lesion measured approximately 3.9 cm in the left parietal lobe and was associated with extensive surrounding vasogenic edema, effacement of the left lateral ventricle, and approximately 6 mm of subfalcine shift. DWI demonstrated prominent hyperintensity within portions of the lesion core with corresponding low signal on ADC mapping, confirming true restricted diffusion. The images are shown in Figure *1*.

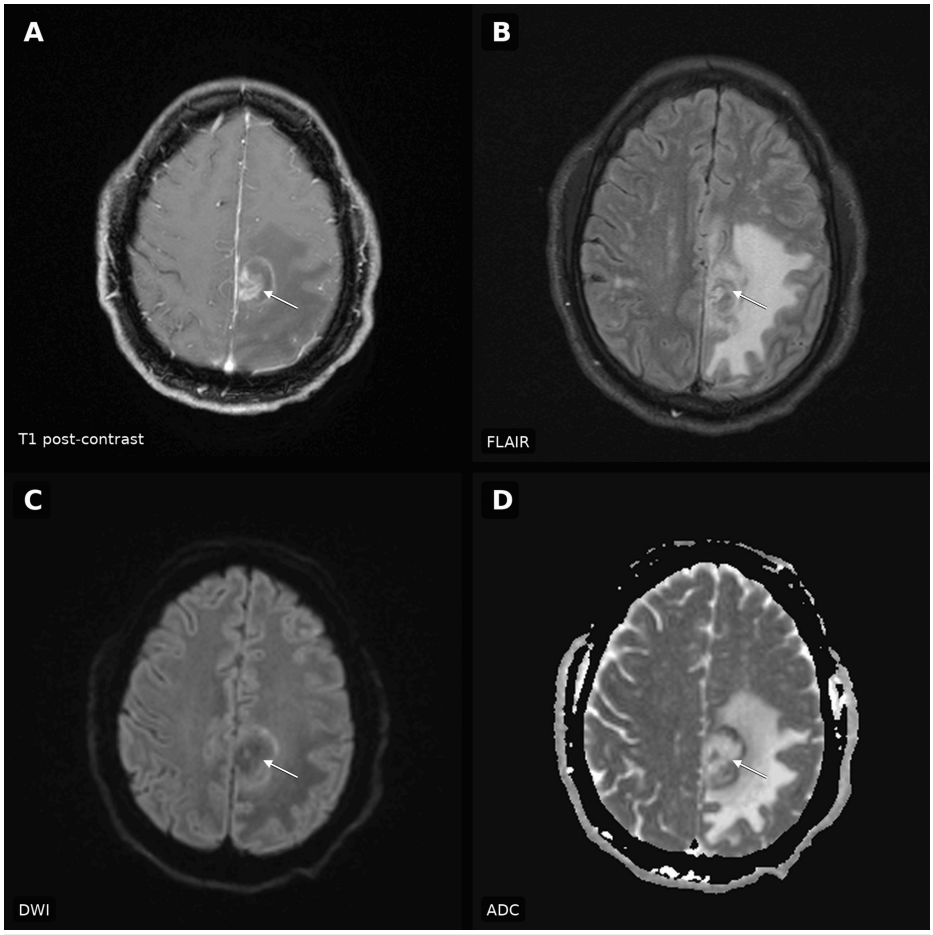


FIGURE 1: Initial MRI demonstrating the left parietal lesion, surrounding vasogenic edema, and diffusion findings.

White arrows identify the dominant left parietal lesion in each panel. (A) Axial post-contrast T1-weighted imaging demonstrates lesion enhancement. (B) Fluid-attenuated inversion recovery (FLAIR) imaging demonstrates the lesion and extensive surrounding vasogenic edema. (C) Diffusion-weighted imaging (DWI) and (D) corresponding apparent diffusion coefficient (ADC) mapping demonstrate the lesion's diffusion characteristics. These findings were considered in the differential diagnosis of cerebral toxoplasmosis and primary central nervous system lymphoma.

During the hospitalization, HIV testing was positive, representing a new diagnosis of HIV infection. The CD4 T-lymphocyte count was 26 cells/µL, consistent with profound cellular immunosuppression. Serum *T. gondii* testing demonstrated IgG greater than 400 IU/mL with negative IgM. Blood cultures were obtained and were negative. Lumbar puncture was deferred because of extensive cerebral vasogenic edema and associated mass effect, including compression of the left lateral ventricle and midline shift.

Spinal MRI was also obtained during evaluation of the bilateral lower-extremity weakness. Cervical and thoracic imaging demonstrated extensive long-segment spinal cord edema extending from the cervicomedullary junction through the thoracic cord toward the conus, with enhancing intramedullary lesions at T7-T9 and T11-T12. Assessment of cervical enhancement was limited by motion degradation, with no definite abnormal enhancement identified within those limitations. The radiologic differential favored an infectious process in the setting of immunosuppression, with inflammatory, neoplastic, and autoimmune demyelinating etiologies also considered.

In the setting of newly diagnosed advanced HIV infection, severe immunosuppression, multifocal enhancing intracranial lesions, and strongly positive *Toxoplasma* IgG, reactivation cerebral toxoplasmosis became the leading diagnostic consideration. However, PCNSL remained an important alternative diagnosis, particularly given the prominent diffusion restriction. Other considerations included pyogenic abscess and other opportunistic infectious processes. Empiric trimethoprim-sulfamethoxazole (TMP-SMX; Bactrim DS) was administered orally as two double-strength tablets every 12 hours for a total of six weeks. Each tablet contained 160 mg of trimethoprim and 800 mg of sulfamethoxazole. Brain biopsy was deferred to assess the response to empiric treatment for toxoplasmosis. The patient did not receive corticosteroid therapy before the follow-up MRI. Follow-up MRI obtained 15 days after initiation of TMP-SMX therapy and 17 days after

baseline imaging demonstrated reduction of the largest left parafalcine lesion from 3.9 × 1.7 cm to 3.5 × 1.5 cm. The largest left deep gray lesion decreased from 2.0 cm to 1.5 cm, and the left cerebellar lesion decreased from 0.9 cm to 0.5 cm. Surrounding vasogenic edema and left lateral ventricular effacement decreased, and the previously reported midline shift resolved. The follow-up MRI images are shown in Figure 2.

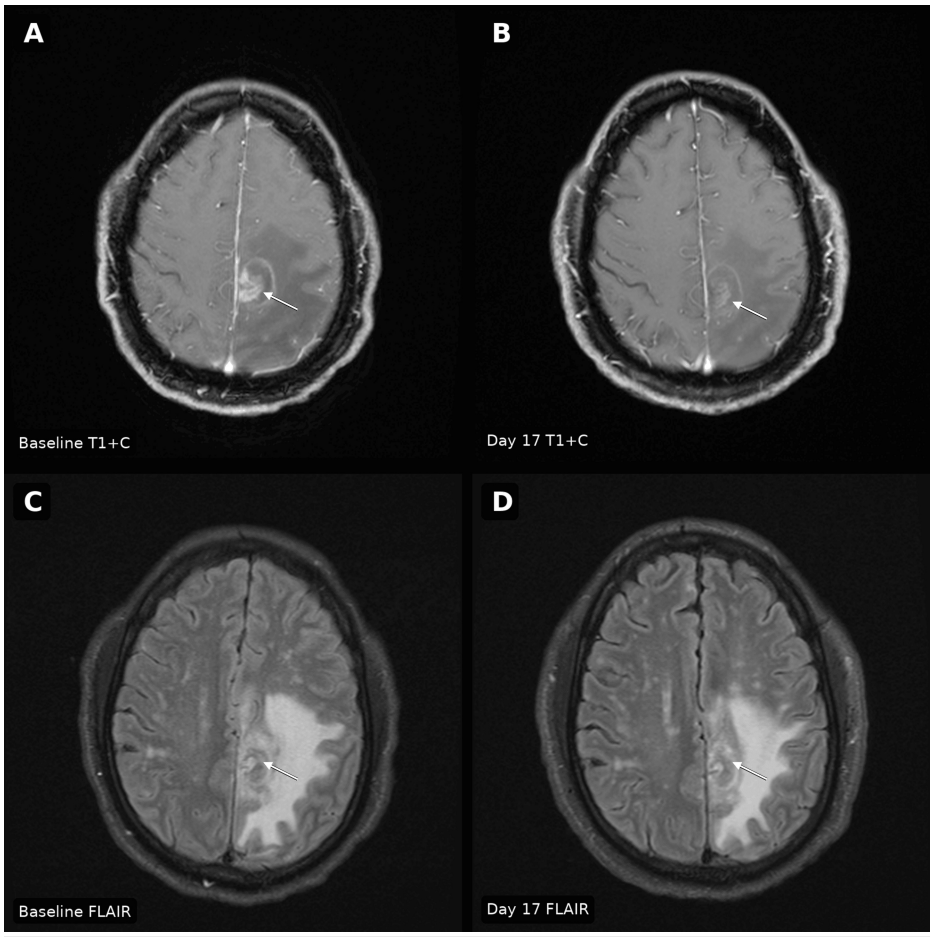


FIGURE 2: Radiographic response on follow-up MRI 17 days after baseline imaging.

Baseline post-contrast T1-weighted (A) and fluid-attenuated inversion recovery (FLAIR) (C) images are compared with corresponding post-contrast T1-weighted (B) and FLAIR (D) images obtained 17 days later. White arrows identify the left parietal lesion in each panel. Follow-up imaging demonstrates reduced lesion enhancement, decreased surrounding vasogenic edema, and improved associated mass effect following trimethoprim-sulfamethoxazole therapy.

Subsequent cervical MRI demonstrated marked decrease or resolution of the previously extensive cord edema, without abnormal cervical cord enhancement, interpreted as treatment response. Follow-up thoracic MRI likewise showed marked reduction in cord T2/STIR signal abnormality, with possible mild residual signal at T6-T8; this examination was terminated prematurely for patient comfort and was therefore limited. A later lumbar MRI demonstrated resolution of the previously seen enhancing T2-hyperintense lesions in the lower thoracic cord and conus, also interpreted as consistent with treatment response.

The objective radiographic response following initiation of anti-*Toxoplasma* therapy substantially strengthened the presumptive diagnosis of cerebral toxoplasmosis despite the atypical diffusion characteristics. Weakness persisted at discharge.

Discussion

Cerebral toxoplasmosis remains an important opportunistic neurologic infection in patients with advanced HIV and most commonly represents reactivation of previously acquired latent infection [1,2]. Individuals with severe cellular immunosuppression are at greatest risk, particularly those with CD4 counts below 100 cells/µL, with the highest risk occurring at CD4 counts below 50 cells/µL [1]. Our patient's CD4 count of 26 cells/µL placed him in this highest-risk group. *Toxoplasma* seroprevalence, reflecting prior infection rather than active encephalitis, is approximately 11% in the United States and 40-80% in certain European, Latin

American, Asian, and African countries [1].

Diagnostic approach to cerebral toxoplasmosis

The diagnosis of TE is frequently presumptive rather than tissue-confirmed. Most patients with HIV-associated TE have positive serum *Toxoplasma* IgG reflecting prior exposure, while IgM is generally absent because the disease usually represents reactivation rather than acute primary infection [1,2]. Importantly, the magnitude of the IgG titer alone does not establish active infection. The absence of cerebrospinal fluid or tissue testing limited diagnostic confirmation. Lumbar puncture was deferred because of cerebral edema and mass effect, whereas brain biopsy was deferred to assess the response to empiric anti-*Toxoplasma* therapy. Diagnostic interpretation therefore relied on the overall clinical, serologic, and radiographic findings and the response to empiric treatment.

A definitive diagnosis requires identification of *T. gondii* in tissue or another appropriate clinical specimen in the setting of a compatible clinical and radiographic syndrome. In routine clinical practice, however, a presumptive diagnosis may be established in a patient with compatible neurologic symptoms, characteristic imaging abnormalities, positive *Toxoplasma* IgG, and an appropriate response to empiric anti-*Toxoplasma* treatment [1]. The diagnosis in our patient is therefore most accurately described as presumptive cerebral toxoplasmosis, rather than microbiologically or histopathologically confirmed TE. The absence of tissue confirmation is particularly relevant because PCNSL could not initially be definitively excluded.

The toxoplasmosis-PCNSL diagnostic dilemma

PCNSL and cerebral toxoplasmosis may have overlapping clinical and conventional imaging characteristics in patients with advanced HIV. Both may present with focal deficits, multiple or solitary enhancing intracranial lesions, surrounding edema, and mass effect [3,7]. Certain features may shift the probability toward one diagnosis or another. Toxoplasmosis more commonly produces multiple lesions and has a predilection for the basal ganglia and corticomedullary junction, while PCNSL often demonstrates periventricular or deep cerebral involvement. However, neither lesion number nor location provides sufficient diagnostic specificity in isolation [2,7]. Diffusion imaging has therefore attracted particular interest as a potential discriminator.

Restricted diffusion as a diagnostic pitfall

Restricted diffusion is frequently associated with highly cellular tumors such as PCNSL and with viscous purulent material in pyogenic abscesses. Earlier studies suggested that ADC measurements might therefore help distinguish PCNSL from cerebral toxoplasmosis. Camacho et al. evaluated ADC values in patients with AIDS-related toxoplasmosis and lymphoma and found significantly greater diffusion in toxoplasmosis lesions compared with lymphoma [3]. However, substantial overlap in ADC ratios remained between the two groups. Schroeder et al. subsequently demonstrated that diffusion characteristics of toxoplasmosis and lymphoma overlap considerably and that ADC measurements alone cannot reliably distinguish the two conditions [4].

More importantly for the present case, restricted diffusion has been directly documented in neurotoxoplasmosis. In a retrospective series of 15 patients with neurotoxoplasmosis, Benson et al. reported a mean of 7.1 foci of restricted diffusion per patient [5]. This finding demonstrates that restricted diffusion can occur in toxoplasmosis, although this small, selected imaging cohort does not establish its population prevalence. Thus, although prominent diffusion restriction may appropriately increase suspicion for PCNSL or abscess, its presence should not exclude cerebral toxoplasmosis. The pronounced restricted diffusion within the core of the dominant lesion in our patient represented the major atypical imaging feature. The dominant left parietal lesion is marked by white arrows in Figure *1* and Figure *2*. In the setting of advanced HIV, this appearance created a genuine diagnostic dilemma between toxoplasmosis and PCNSL.

Potential mechanisms for restricted diffusion within toxoplasmosis lesions include increased inflammatory cellularity, viscous proteinaceous necrotic material, and variations in lesion stage and histopathologic organization [5]. Different lesions within the same patient may consequently demonstrate heterogeneous diffusion characteristics. The characteristic clinical and radiographic findings associated with cerebral toxoplasmosis and PCNSL are shown in Table *1*.

Feature	Cerebral toxoplasmosis	Primary CNS lymphoma	Present case
Immune status	Strongly associated with advanced HIV	Strongly associated with advanced HIV	Newly diagnosed HIV, CD4 26 cells/μL
Lesion number	Frequently multiple	Solitary or multiple	Multiple bilateral lesions
Enhancement	Commonly ring or nodular	Often solid; ring enhancement may occur in advanced HIV	Multiple enhancing lesions
Vasogenic edema	Common	Common	Extensive
Mass effect	May occur	May occur	6 mm subfalcine shift
DWI/ADC	Variable; restriction may occur	Restriction commonly present	Prominent core restriction
Toxoplasma IgG	Usually positive	May be incidentally positive	>400 IU/mL
Response to anti-*Toxoplasma* therapy	Expected	Not expected	Marked radiographic improvement at 17 days

TABLE 1: Selected features considered in differentiating cerebral toxoplasmosis from primary central nervous system lymphoma

References: [1-5,8]

Importance of the therapeutic response

One of the most important features supporting toxoplasmosis in this patient was the objective response to empiric treatment. In patients with advanced HIV and a clinical-radiographic presentation strongly suggestive of TE, empiric anti-*Toxoplasma* therapy is often initiated before invasive tissue diagnosis [1,2]. Clinical improvement is generally expected within 10-14 days of appropriate anti-*Toxoplasma* therapy; this benchmark does not imply a guaranteed radiographic response within the same interval. Brain biopsy should be strongly considered if clinical or radiographic worsening occurs during the first week despite adequate treatment, or if clinical improvement has not occurred by 10-14 days [1]. Our patient's follow-up MRI obtained 15 days after initiation of TMP-SMX therapy and 17 days after baseline imaging demonstrated decreased lesion size, substantially reduced vasogenic edema, and improved mass effect. In the absence of tissue confirmation, this temporal response to targeted therapy represents compelling evidence supporting the presumptive diagnosis of TE.

Importantly, treatment response should not be interpreted as absolute proof of toxoplasmosis. The lack of histopathologic confirmation remains a limitation of this case. Nevertheless, the combination of profound immunosuppression, multifocal enhancing lesions, positive *Toxoplasma* IgG, and objective radiographic improvement after targeted anti-*Toxoplasma* therapy makes TE considerably more likely than untreated PCNSL.

TMP-SMX for toxoplasmic encephalitis

Historically, pyrimethamine combined with sulfadiazine and leucovorin has been widely used for acute TE. TMP-SMX, however, is now an accepted treatment regimen and provides practical advantages related to availability, cost, and ease of administration [1,8]. A systematic review and meta-analysis by Prosty et al. found no significant difference in clinical or radiographic response between TMP-SMX and pyrimethamine-containing regimens, while treatment discontinuation because of toxicity was lower with TMP-SMX [8]. Current treatment recommendations include TMP-SMX as a preferred regimen for acute TE, with therapy generally continued for at least six weeks depending on clinical and radiographic response [1]. Our patient received a six-week course and demonstrated clear radiographic improvement early in treatment.

Clinical significance

The bilateral lower-extremity weakness should be interpreted in the context of both the bilateral cerebral lesions and the extensive spinal cord abnormalities. Long-segment cord edema and enhancing thoracic intramedullary lesions provided an additional potential anatomical correlate for the paraparesis; the deficits should therefore not be attributed solely to the dominant left parietal lesion. Subsequent marked improvement or resolution of the spinal MRI abnormalities during treatment supported a treatment-responsive process, but did not establish the specific cause of the cord lesions. Spinal involvement by toxoplasmosis remained a clinical consideration rather than a microbiologically or histopathologically

confirmed diagnosis.

The principal teaching point from this case is that restricted diffusion should alter the differential diagnosis but should not terminate it.

When a severely immunocompromised patient presents with enhancing brain lesions that demonstrate restricted diffusion, PCNSL and pyogenic abscess appropriately receive strong consideration. However, excluding toxoplasmosis solely because of diffusion restriction may lead to unnecessary invasive procedures or delay appropriate anti-*Toxoplasma* therapy. Instead, DWI findings should be interpreted in conjunction with the overall clinical probability, degree of immunosuppression, lesion number and distribution, serologic findings, and early response to therapy.

Our case also illustrates how an opportunistic central nervous system infection may serve as the initial presentation leading to a new diagnosis of advanced HIV infection. Recognition of the underlying immunocompromised state substantially changes both the differential diagnosis and the interpretation of otherwise atypical imaging findings.

Conclusions

Cerebral toxoplasmosis can demonstrate prominent restricted diffusion and may closely mimic PCNSL in patients with advanced HIV infection. Diffusion restriction should therefore not be considered exclusionary for toxoplasmosis. In our patient, newly diagnosed HIV infection with a CD4 count of 26 cells/μL, multifocal enhancing intracranial lesions, strongly positive *Toxoplasma* IgG, and substantial radiographic improvement 15 days after initiation of TMP-SMX collectively supported a presumptive diagnosis of cerebral toxoplasmosis despite prominent core diffusion restriction. This case emphasizes the importance of integrating neuroimaging with immune status, serologic findings, clinical context, and therapeutic response rather than relying on a single radiographic feature to differentiate toxoplasmosis from PCNSL. When diagnostic uncertainty persists or the response to empiric therapy is inadequate, tissue diagnosis by stereotactic brain biopsy should be considered following assessment of procedural risks, particularly in patients with significant cerebral edema and mass effect.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Lintu Ramachandran

Acquisition, analysis, or interpretation of data: Lintu Ramachandran, Hanna Malik, Junaid Essa

Drafting of the manuscript: Lintu Ramachandran, Hanna Malik, Junaid Essa

Critical review of the manuscript for important intellectual content: Lintu Ramachandran, Hanna Malik, Junaid Essa

Disclosures

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