

Case Report

Pandora's Box: Not Every Box Unleashes Harm - Brain Biopsy Unmasks Cerebral Nocardiosis and Redirects Therapy in a Woman with Advanced HIV and Pulmonary Tuberculosis

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Abstract

Cerebral nocardiosis is a rare cause of brain abscess in people with advanced human immunodeficiency virus infection and is easily mistaken for cerebral toxoplasmosis or tuberculoma. We report a woman in her mid-thirties with advanced human immunodeficiency virus infection (CD4+ T-cell count 10 cells/mm³), poor adherence to antiretroviral therapy and rifampicin-sensitive pulmonary tuberculosis, who presented with headache and vomiting. Magnetic resonance imaging showed multiple ring-enhancing lesions with an eccentric target sign, Toxoplasma gondii IgG was reactive, cerebrospinal fluid studies identified no pathogen, and positron emission tomography-computed tomography argued against primary central nervous system lymphoma. She was treated empirically for cerebral toxoplasmosis alongside anti-tuberculosis and antiretroviral therapy, with initial improvement. During corticosteroid taper she deteriorated with right upper limb weakness,

focal motor seizures and radiological progression, initially attributed to immune reconstitution inflammatory syndrome. After three non-diagnostic cerebrospinal fluid examinations, stereotactic biopsy of the left parietal lesion showed branching filamentous organisms, and 16S ribosomal RNA sequencing identified *Nocardia farcinica*. Intravenous meropenem and amikacin, added to high-dose trimethoprim-sulfamethoxazole, produced sustained clinical and radiological improvement. In advanced human immunodeficiency virus infection, ring-enhancing brain lesions that progress despite appropriate empirical therapy should prompt early tissue diagnosis with molecular sequencing, and immune reconstitution inflammatory syndrome should remain a diagnosis of exclusion.

Key words

CNS nocardiosis; *Nocardia farcinica*; HIV/AIDS; cerebral toxoplasmosis; ring-enhancing brain lesions; immune reconstitution inflammatory syndrome; stereotactic brain biopsy; 16s ribosomal RNA sequencing.

Introduction

Multifocal ring enhancing intracranial lesions in people with advanced HIV are common but they remain a major diagnostic challenge. The main possibilities are cerebral toxoplasmosis, tuberculoma and primary central nervous system lymphoma. These conditions often look similar on imaging, majority of centres rely on serology and MRI to guide treatment when a biopsy cannot be done right away [1, 2]. *Nocardia* accounts for only 1–2% of all brain abscesses, but the risk increases sharply in people with impaired cell mediated immunity. In the largest pooled series publication CNS nocardiosis was seen in immunocompromised HIV patients which was reported as a smaller but recognized risk factor [3]. The clinical, imaging features are non-specific, so nocardiosis is often mistaken for toxoplasmosis, tuberculoma, pyogenic abscess [4, 5, 6]. We present a patient who was thought to have cerebral toxoplasmosis, tuberculoma, or IRIS at different times before a stereotactic biopsy but mNGS identified a nocardial brain abscess. This case shows the limits of empirical treatment, the value of unbiased molecular sequencing, and the need for early tissue sampling when standard therapies do not work [7, 8, 9].

Case presentation

An African woman in her mid-thirties was referred to our tertiary neurology service. Two

months earlier, she had low-grade fever, significant weight loss, poor appetite. In her home country, she was diagnosed with rifampicin-sensitive pulmonary tuberculosis, confirmed by bronchoalveolar lavage GeneXpert MTB (Rifampicin sensitive) and was concurrently found to be HIV-positive, was initiated on standard four-drug anti-tuberculosis therapy comprising rifampicin, isoniazid, ethambutol, and pyrazinamide, along with a dolutegravir-based antiretroviral therapy (ART) regimen. However, her adherence to ART was poor.

Two weeks before presentation to our center, she developed holocranial headache and multiple episodes of non-projectile vomiting. She denied cognitive impairment, altered sensorium, loss of consciousness, seizures, visual disturbances, cranial nerve symptoms, limb weakness, sensory symptoms, gait imbalance, bladder and bowel disturbances. No significant family history of neurological illness/ tuberculosis/ intravenous drug use, multiple sexual partners, smoking, alcohol consumption, recent travel apart from her medical journey, animal contact, occupational exposure to soil. On examination, she appeared chronically ill and cachectic, was conscious, alert, and cooperative, with stable vital signs, with normal fundus, no signs of meningeal irritation or any focal neurological deficits.

Investigations

Baseline laboratory profile

There was mild anemia, with a hemoglobin level of 11.1 g/dL. Total leukocyte count, platelet count, liver function tests, and serum creatinine (0.7 mg/dL) were within normal limits. But she had erythrocyte sedimentation rate (ESR) of 110 mm/hour and a C-reactive protein (CRP) level of 68.4 mg/L. The CD4+ T-cell count was profoundly reduced at 10 cells/mm³, fulfilling the criteria for AIDS. The HIV-1 viral load was 5,662 copies/mL, indicating ongoing viral replication, likely secondary to poor adherence to ART.

Initial neuroimaging

Magnetic resonance imaging (MRI) of the brain (**Figure - 1**) showed multiple cortical, subcortical lesions involving the left parietal lobe, bilateral parieto-occipital regions, the splenium of the corpus callosum, and the right cerebellar hemisphere with central diffusion restriction, suggestive of cerebral abscesses. T1-weighted images showed centrally hypointense with a peripheral rim that was isointense to gray matter. T2-weighted sequences showed central hyperintensity surrounded by a peripheral iso- to

hypointense rim, producing a eccentric target sign, a feature classically described in cerebral toxoplasmosis, albeit with low sensitivity. FLAIR images revealed iso- to hypointense lesion cores surrounded by marked hyperintense vasogenic edema. Susceptibility-weighted imaging (SWI) showed no evidence of blooming. Post-contrast T1-weighted images demonstrated multiple ring-enhancing, eccentric, studded conglomerate lesions in the left parietal lobe. Magnetic resonance spectroscopy (MRS) revealed prominent lipid and lactate peaks.

Microbiology, serology and PET-CT

Toxoplasma gondii IgG was reactive, which supports but does not confirm cerebral toxoplasmosis [1, 2]. The CSF showed lymphocytic pleocytosis (420 cells/ μ L, 100% lymphocytes), a significant increase in protein (~365 mg/dL), and a normal CSF-to-serum glucose ratio. Tests including India ink, cryptococcal antigen, bacterial and fungal cultures, GeneXpert MTB, *Toxoplasma* PCR were all negative. PET-CT of the brain (**Figure - 2**) showed reduced lesion uptake, arguing against primary CNS lymphoma.

Figure – 1: MRI brain at first admission.

Initial MRI brain showing multifocal cortical–subcortical ring-enhancing lesions involving left parietal lobe, bilateral parieto-occipital regions, splenium of the corpus callosum , right cerebellar hemisphere. Sequences shown: T1, FLAIR, T2 (target sign), SWI, DWI and post-contrast T1 demonstrating eccentric target sign with concentric rings.

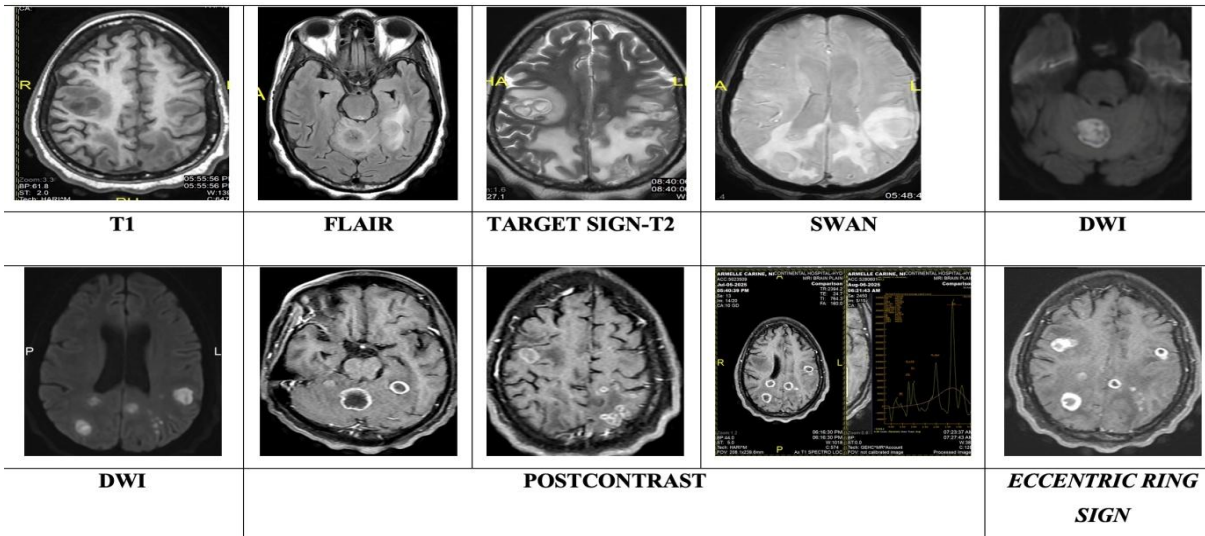
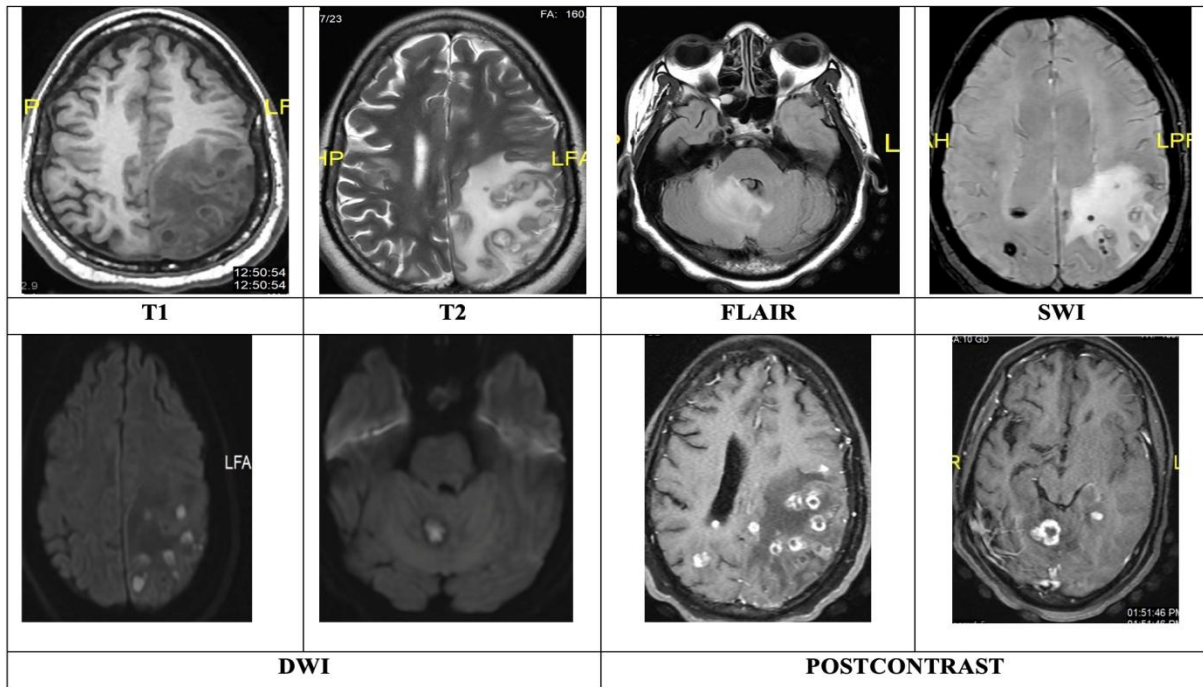


Figure – 4a: MRI brain in third admission showing interval progression of diffusion-restricted ring-enhancing lesions in the left parietal and pre-/post-central regions, with thicker irregular peripheral enhancement, increased perilesional oedema, mass effect and new focal meningitis. Sequences: T1, T2, FLAIR, SWI, DWI AND POST-CONTRAST T1.



Differential diagnosis

In a patient with multiple ring-enhancing brain lesions, severe immunosuppression, and positive Toxoplasma serology, the following diagnoses were considered, listed from most to least likely:

- Cerebral toxoplasmosis was the leading diagnosis, supported by a very low CD4 count, the presence of the eccentric target sign, and reactive IgG in the serum [2, 10].
- Tuberculoma was also strongly considered because the patient had microbiologically confirmed pulmonary TB. Intracranial tuberculomas can have MRI appearances that are hard to distinguish from other causes.
- Primary CNS lymphoma was possible but less likely because there were multiple lesions, and the lesions showed reduced uptake on PET-CT [1, 10].

Treatment

First admission: empirical therapy for presumed CNS toxoplasmosis

With advanced HIV, a very low CD4 count, reactive Toxoplasma IgG, matching neuroimaging, and no other microbiological diagnosis, she was treated for probable CNS toxoplasmosis on a background of pulmonary TB, which included ongoing ATT and ART, high-dose TMP-SMX, dexamethasone for perilesional oedema, antiseizure prophylaxis, and supportive care, consistent with current practice when biopsy is deferred [2, 11].

Second admission: suspected IRIS during steroid taper

About a month later, she was readmitted with a severe headache, fever, and vomiting. Her CD4+count increased slightly to 13 cells/mm³. A repeat MRI (**Figure - 3**) showed interval reduction in lesion size and number, but new peripheral SWI blooming appeared. Repeat CSF tests showed drop in her cell count to 9 cells/ μ L and protein to 71 mg/dL, with no organisms found. Since she was improving both clinically and on scans, her care continued conservatively with a gradual tapering of corticosteroids.

Third admission: paradoxical neurological deterioration

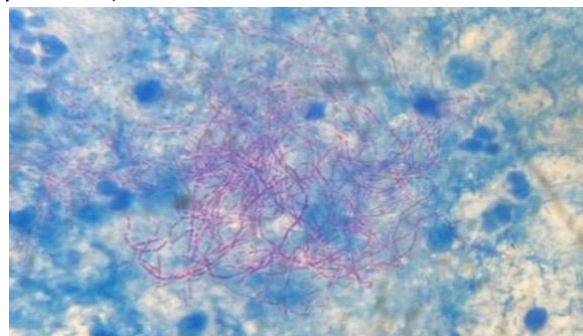
About two months later, she developed new-onset weakness in her right upper limb (4/5) and had focal right sided motor seizures with preserved awareness. Considering that her symptoms worsened due to steroids tapering, IRIS was strongly suspected, so dexamethasone was reinstated at the previous dose. A repeat MRI (**Figure - 4a**) showed clear interval progression, with an increased size and number of diffusion-restricted ring-enhancing lesions predominantly in the left parietal, precentral, postcentral gyrus regions, with increased perilesional oedema, mass effect, with new focal meningitis in the left parietal lobe lesion. Her repeat CSF showed rise in cell count to 57 cells/ μ L (lymphocytic), protein to 100 mg/dL, but again no organism was detected. Her CD4+ count increased to 35 cells/ mm^3 . Another antiepileptic was added, and EEG showed focal delta activity in the left parietal region.

Stereotactic brain biopsy and definitive diagnosis

When radiological findings worsened despite optimized empirical treatment and repeated non-invasive microbiological tests remained negative, a multidisciplinary team decided to perform a stereotactic biopsy of the left parietal lesion with a neurosurgeon, as there was a significant progressive increase in lesion burden in this area. Histopathology showed signs of infection, so a *Nocardia* stain was requested as her CD4+ count was <50 cells/ mm^3 . Imaging revealed multiple ring-enhancing brain abscesses, which matched cerebral nocardiosis. Brain tissue was tested using 16S ribosomal RNA sequencing with Oxford Nanopore Technology (ONT), which identified *Nocardia farcinica* (**Figure - 4b**) which confirmed the diagnosis of nocardial brain abscess and explained why empirical therapy had not worked. 16S ribosomal RNA sequencing (16S rRNA) has become a valuable tool for diagnosing CNS infections when standard cultures and antigen tests are repeatedly negative [7, 8, 9].

Figure – 4b: Modified acid fast stain and next generation sequencing

Nocardia stain and Bactfast metagenomic next-generation sequencing report of brain biopsy tissue confirming *Nocardia* species (*Nocardia farcinica*).



Targeted antimicrobial therapy

Antimicrobial therapy was changed to intravenous meropenem and amikacin, while high-dose TMP-SMX was continued, along with ongoing ART, ATT with gradual reduction of corticosteroids. This approach led to rapid, sustained clinical, radiological improvement, which matches expert recommendations for severe CNS nocardiosis that support using multidrug therapy with TMP-SMX, carbapenems, and aminoglycosides [11, 12].

N. farcinica is important to note because it is naturally resistant to third-generation cephalosporins; therefore, combination therapy based on susceptibility is essential [4, 11].

Outcome and follow-up

After switching to targeted therapy, patient showed steady clinical, radiological improvement, with a reduction in the overall lesion burden and no new lesions.

Prognosis: Although CNS nocardiosis usually has high morbidity, a historically reported case fatality rate of about 20–40% [3, 11], in this case, early tissue diagnosis and prompt targeted therapy led to a good outcome.

Long-term plan: Continued antimicrobial therapy with planned step-down to oral TMP-

SMX after parenteral therapy; periodic neuroimaging surveillance; serial CD4 + count, HIV viral load monitoring; ongoing ART; and structured neurology and infectious diseases follow-up.

Discussion

CNS lesions in advanced HIV, especially when the CD4+ count is <50 cells/mm³, are still some of the most challenging issues in neurology and infectious diseases. Cerebral toxoplasmosis, tuberculoma, primary CNS lymphoma are the main possibilities, as all three can cause multifocal ring-enhancing lesions that look similar on imaging [1, 2]. In our patient, the eccentric target sign on MRI and a positive Toxoplasma IgG test in the background of severe immunosuppression made cerebral toxoplasmosis the most likely diagnosis with TMP-SMX therapy aligned with widely used pragmatic algorithms in resource-limited or urgent settings [2, 10]. The diagnosis was complicated by pulmonary tuberculosis, since intracranial tuberculomas can closely mimic this picture in the background of IRIS. This is a paradoxical inflammatory reaction that usually appears within weeks of starting ART, where immune recovery actually worsens the symptoms of a pre-existing infection [13, 14]. Distinguishing IRIS from treatment failure or a separate diagnosis is one of the harder calls in HIV neurology, IRIS itself has been described in CNS nocardiosis, blurring the picture further [11, 15].

The key turning point came when the patient did not improve, even though she received the best possible empirical treatment, with a serial increase in lesion burden and three CSF tests that did not identify any pathogen. A stereotactic biopsy showed weakly acid-fast, branching filamentous organisms suggestive of *Nocardia*, which was subsequently confirmed by mNGS.

Comparison with other studies

This case sits within a small but expanding literature on CNS nocardiosis. Anagnostou and

colleagues reviewed 84 published cases and found that corticosteroid use (54%), transplantation (25%) were main predisposing factors, while HIV was less common. *N. farcinica* was one of the species most often linked to brain abscess [3]. Sun and colleagues (2024), Stefaniak (2015) described HIV-associated cerebral nocardiosis with diagnostic delays due to misdiagnosis, which is similar to our experience [4, 5]. Yang, Zhou, and Wang (2022, 2021) demonstrated that mNGS can identify *N. farcinica* when standard cultures, acid-fast staining are negative which matches our case, as routine CSF microbiology was unhelpful after three lumbar punctures, and both ATT and anti-toxoplasma treatments were tried before the correct diagnosis was reached [6, 7, 8].

This case stands out for two reasons. First, the patient met both imaging and serological criteria for toxoplasmosis and also had microbiologically confirmed pulmonary tuberculosis, which supported two strong competing diagnoses before nocardiosis was considered. Second, timing of corticosteroid taper, partial immune recovery, clinical worsening matched IRIS so closely that it delayed the search for another pathogen which shows IRIS can conceal a developing infection [11, 13, 14, 15].

In the setting of advanced HIV with multifocal ring-enhancing CNS lesions (CD4+ <50 cells/mm³), a structured differential diagnosis extending beyond toxoplasmosis, tuberculoma, primary CNS lymphoma, with inclusion of atypical opportunistic infections such as cerebral nocardiosis, is essential and IRIS must remain a diagnosis of exclusion. Worsening during ART or steroid taper should prompt rigorous exclusion of treatment failure, alternative pathogens, or a new infection before being attributed to IRIS alone. Conventional cultures, antigen assays, and PCR frequently miss *Nocardia*; therefore, stereotactic brain biopsy with the use of 16S ribosomal RNA sequencing can substantially increase the diagnostic yield which may be life-

saving in atypical or non-responding CNS lesions.

Treating CNS nocardiosis involves a prolonged course of combination antimicrobial therapy, most often TMP-SMX with a carbapenem and/or an aminoglycoside [11, 12]. It is important to consider species-specific resistance; as *N. farcinica* is characteristically resistant to third-generation cephalosporins [4, 11]. In our patient, switching to meropenem and amikacin led to sustained recovery and highlights the importance of multidisciplinary care.

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Dr. Neelamraju Sai Mounika (NSM), DNB Neurology Resident, she conceived the case report, conducted the literature search and drafted the manuscript. Dr. Rahul Konduri (RK) supervised the overall neurological management, mentored the resident author and revised the manuscript critically for important intellectual content. Dr. Gattu Santosh (GS) led the infectious disease evaluation, microbiological interpretation and antimicrobial planning. Dr. Sudheer Kunkunuru (SK) reported the serial MR imaging and PET-CT scans and contributed to image curation and figure preparation. All four authors approved the final version for submission and agree to be accountable for all aspects of the work. Dr. K.V. Shivanand Reddy (Neurosurgery) performed the stereotactic brain biopsy that established the diagnosis, and Dr. Pradeep Simha (Pulmonology) contributed to the evaluation and management of the patient's pulmonary tuberculosis; both are gratefully acknowledged and special thanks to Dr Manoj Kumar Singh, HOD of neurology for helping us do this case report.

Data availability statement

All relevant data are included within this article. Additional anonymized data are available from the corresponding author on reasonable request.

Generative AI policy

During preparation of this case report, the authors used an AI-assisted language tool (Claude, Anthropic) to check grammar and improve the readability of the manuscript draft. The tool was not used for image generation, interpretation of clinical findings, and authors take full responsibility for the accuracy and originality of the final content.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical consent was also obtained in accordance with institutional requirements.

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