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DIAGNOSTIC AND THERAPEUTIC PARADOXES IN PCR-POSITIVE, HISTOPATHOLOGY-NEGATIVE CNS ASPERGILLOSIS IN A PATIENT WITH HIV AND HODGKIN LYMPHOMA

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ABSTRACT

Background: Invasive central nervous system (CNS) aspergillosis is rare among human immunodeficiency virus (HIV)-positive patients due to preserved neutrophil function, despite significant CD4+ T-cell depletion. Diagnosis typically requires histopathologic confirmation, but polymerase chain reaction (PCR) testing has introduced new challenges due to its high sensitivity but limited specificity.

Case presentation: We describe a newly diagnosed 43-year-old HIV-positive male with concurrent Hodgkin lymphoma who presented with progressive neurological decline and a ring-enhancing brain lesion. While histopathological analysis of the brain biopsy demonstrated features of HIV-associated leukoencephalopathy, PCR testing paradoxically identified *Aspergillus fumigatus*; however, histopathological examination failed to demonstrate definitive fungal elements. Despite negative cerebrospinal fluid galactomannan and β-D-glucan assays, empiric voriconazole therapy was initiated in accordance with current treatment guidelines. Over the ensuing month, the patient returned with worsening neurologic status, radiographic lesion progression, and ultimately developed Torsades de Pointes, and multiorgan failure, resulting in death.

Discussion: This case underscores the diagnostic and therapeutic complexities of PCR-positive, histopathology-negative CNS aspergillosis in HIV. Overreliance on molecular results without confirmatory pathology may lead to unnecessary antifungal therapy and severe drug toxicity. Additionally, overlapping immunosuppressive conditions—such as HIV and lymphoma—complicate clinical interpretation and management.

Conclusion: In HIV-positive patients with CNS lesions, PCR detection of *Aspergillus* should not independently justify antifungal therapy. Histological confirmation and multidisciplinary evaluation are essential to avoid misdiagnosis and adverse outcomes. This case highlights the urgent need for more precise treatment guidelines on when to initiate and discontinue antifungal treatment in complex immunocompromised populations.

KEYWORDS

CNS Aspergillosis, Hodgkin lymphoma, human immunodeficiency virus, adverse drug reactions, Torsades de Pointes

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LEARNING POINTS

- Polymerase chain reaction positivity for *Aspergillus* in the absence of histopathologic confirmation presents a major diagnostic dilemma, particularly in human immunodeficiency virus (HIV)-positive patients, where overreliance on molecular diagnostics may lead to misdiagnosis, unnecessary antifungal exposure, and significant toxicity.
- Empiric antifungal treatment should be re-evaluated when central nervous system lesions progress or fail to improve, as prolonged use of agents like voriconazole can result in serious toxicity, including arrhythmias like Torsades de Pointes; clearer guidelines are needed to define when empiric treatment is appropriate in complex cases.
- HIV-positive patients with coexisting malignancy require a multidisciplinary, evidence-based approach, as overlapping immunosuppressive conditions can obscure diagnosis and complicate treatment decisions.

INTRODUCTION/BACKGROUND

Central nervous system (CNS) ring-enhancing lesions in patients with newly diagnosed human immunodeficiency virus (HIV) pose substantial diagnostic complexities. The differential diagnosis encompasses a wide range of pathologies, including opportunistic infections, malignancies, and immune-mediated processes[1]. CNS aspergillosis is rare in HIV-positive patients because HIV depletes T cells and usually preserves neutrophil function[2]. Neutropenic or myelosuppressed patients have the highest risk of invasive aspergillosis, its incidence in HIV-positive patients is comparatively low[1,2]. When it occurs, it has a high mortality rate, making prompt treatment essential[3]. The diagnosis of invasive CNS fungal infections conventionally relies on cerebrospinal fluid (CSF) analysis via polymerase chain reaction (PCR) for pathogen detection, with definitive confirmation predicated on histopathological visualization of fungal elements. Finding *Aspergillus fumigatus* on PCR without histologic evidence creates a difficult diagnostic dilemma, raising critical questions regarding the test's specificity, clinical significance, and implications for empiric antifungal therapy[3]. This report provides an in-depth exploration of these diagnostic and therapeutic paradoxes, highlighting crucial considerations for clinicians managing complex immunocompromised patients.

CASE DESCRIPTION

A previously healthy 43-year-old homeless African American male presented with acute right-sided weakness, confusion, headaches, and gait instability over one week. His initial evaluation identified severe pancytopenia, profound hyponatremia (sodium 123 mmol/l). During this admission he was found to have previously undiagnosed Hepatitis B and HIV with a CD4 count of 94 cells/µl. Imaging via magnetic resonance imaging (MRI) revealed left hyperintense intraparenchymal lesions with mass effect in subcortical regions *(Fig. 1)*, which was concerning for infection, lymphoma, or demyelination. Neurosurgical consultation was obtained, and intervention was deferred due to the diffuse and infiltrate nature of the lesions and high procedural risk in the setting of pancytopenia.

He was started on trimethoprim-sulfamethoxazole for toxoplasmosis prophylaxis, which was subsequently discontinued due to exacerbation of hyponatremia and new-onset seizures, attributed to drug-induced renal salt wasting syndrome. Lacosamide was chosen for seizure control because it has fewer effects on electrolytes. HIV management with bictegravir/emtricitabine/tenofovir alafenamide was also given.

Comprehensive infectious workup including CSF analysis was negative for toxoplasmosis, JC virus, Epstein-Barr virus (EBV), and malignancy. A brain biopsy demonstrated HIV-associated leukoencephalopathy. PCR analysis of brain tissue found *Aspergillus fumigatus* deoxyribonucleic acid (DNA), but no fungus was seen on histopathology. This prompted further investigation with CSF galactomannan and β-D-glucan assays which were negative. Due to significant diagnostic uncertainty and following guidelines advocating empirical therapy, voriconazole was initiated.

Subsequent systemic assessment demonstrated diffuse lymphadenopathy, prompting an excisional lymph node biopsy confirming mixed cellularity Hodgkin lymphoma (CD30+, CD15+, PAX-5+, and positivity for EBV). Following clinical improvement, the patient was discharged with plans for outpatient haematology-oncology follow-up to undergo

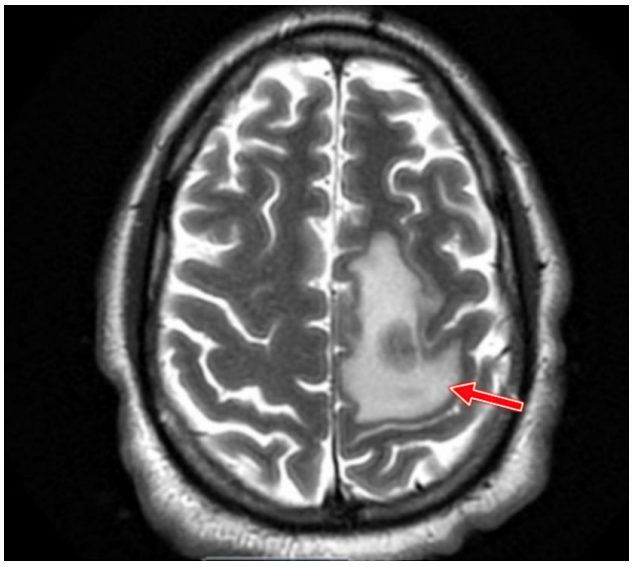


Figure 1. Magnetic resonance imaging revealed a 2.4 × 1.5 × 1.4 cm peripherally enhancing lesion in the left posterior frontal parietal lobe with increased surrounding vasogenic oedema (red arrow), concerning for a neoplastic, infectious, or demyelination process.

a bone marrow biopsy to evaluate for lymphoma invasion and to initiate chemotherapy.

One month later however, he returned with worsening confusion, weakness, gait instability, and fever. Labs showed persistent pancytopenia, electrolyte abnormalities including low sodium, potassium, and magnesium, and repeat brain imaging revealing increased CNS lesion growth with surrounding oedema. On day 2, he developed Torsades de Pointes (TdP) with pulseless cardiac arrest, from which he was successfully resuscitated. Electrocardiogram monitoring prior to arrest showed prolonged QTc (489 ms) with no ischemic changes and troponins came back normal. Despite stabilization, his overall clinical and neurological condition deteriorated significantly during his hospitalization. He developed severe sepsis with hypotension. Blood cultures and urine cultures obtained revealed no growth, and imaging showed no discrete abscesses or pneumonia. Nevertheless, his condition worsened and he succumbed to multiorgan failure. Sepsis was likely due to enteric translocation from gut mucosal barrier injury, exacerbated by pancytopenia and immunosuppression. Voriconazole levels were not measured, and no documented dose adjustments were made following initiation. Retrospectively, drug-level monitoring and risk-benefit reassessment may have influenced outcomes.

DISCUSSION

This case illustrates several key diagnostic and therapeutic challenges in the management of CNS lesions in immunocompromised patients:

1. *Diagnostic uncertainty in PCR-positive, histopathology-negative CNS Aspergillosis:* While PCR testing is highly sensitive for detecting fungal DNA, it does not distinguish between active invasive infection, colonization, contamination, or non-viable fungal elements[3]. Histopathology remains the diagnostic gold standard of invasive CNS fungal disease. In this case, the positive PCR without fungal evidence on pathology or imaging, and negative fungal markers, suggests a false-positive result[4,5]. Relying solely on PCR results without histological confirmation risks significant overdiagnosis, inappropriate antifungal administration, potential drug toxicity, and development of antifungal resistance. The literature suggests PCR's high sensitivity but uncertain specificity, necessitating adjunctive confirmatory measures such as CSF galactomannan, β-D-glucan assays, and advanced molecular diagnostics[3].
2. *Rarity of Aspergillosis in HIV:* Invasive aspergillosis predominantly affected individuals with prolonged neutropenia or hematologic malignancies, particularly in patients undergoing chemotherapy or organ transplantation[5]. While HIV causes profound immunosuppression, it typically spares neutrophil function. The coexisting Hodgkin lymphoma in this patient may have contributed additional immunologic vulnerability, though this remains speculative.
3. *Alternative diagnostic considerations:* The patient's EBV-positive Hodgkin lymphoma raises concern for associated paraneoplastic neurological syndromes, characterized by immune-mediated neurological dysfunction secondary to tumour presence. The literature discusses a link between HIV and EBV in lymphomagenesis, leading to oligoclonal dysregulated B-cell expansion and subsequent lymphoma development[6]. It is rare for HL to manifest in brain parenchyma with an incidence of 0.02-0.5%, as it predominantly presents extra-axially[6]. HIV-driven immune dysregulation could also contribute to atypical CNS leukoencephalopathy and inflammatory lesions. Despite negative biopsy, primary CNS lymphoma cannot be fully ruled out given the patient's profound immunosuppression. Repeat biopsies or advanced diagnostics such as next-generation sequencing and positron emission tomography (PET)-MRI imaging could prove further insights[3].
4. *Risk-benefit analysis of empirical antifungal therapy:* Although guidelines support empirical antifungal treatment in certain high-risk cases, voriconazole poses significant risks, including hepatotoxicity, neurotoxicity, and QTc prolongation[7]. The development of TdP and subsequent cardiac arrest in this patient underscores the potential dangers of empirical treatment in the absence of definitive diagnostic confirmation. Notably, radiographic progression of CNS lesions despite antifungal therapy further argues against true invasive aspergillosis and suggest a need for re-evaluation of the treatment strategy.
5. *Complexity of multisystem disease:* The patient's course was further complicated by profound electrolyte imbalances, drug interactions, and overlapping syndromes from HIV, malignancy, and systemic infection. Management required nuanced adjustments in medication regimens and coordination across specialties, highlighting the importance of a multidisciplinary approach.

CONCLUSIONS

The diagnosis and management of CNS aspergillosis in HIV-positive patients with concurrent malignancies demand a cautious, multidisciplinary approach. PCR positivity alone—particularly in the absence of histopathological confirmation—should not be used in isolation to justify initiation of antifungal therapy, especially when radiographic and clinical features deviate from classic presentations. Empirical treatment with high-risk agents such as voriconazole carries significant toxicity risks, including hepatotoxicity, neurotoxicity, and QTc prolongation, which may be especially detrimental in immunocompromised individuals.

There is a critical need for more precise, evidence-based guidelines to inform the initiation and duration of antifungal therapy in such complex cases. Recommendations should define appropriate clinical contexts for empirical treatment, specify when radiographic reassessment (e.g., within 2–3 weeks) should be performed, and outline clear criteria for

discontinuation if no radiographic or clinical improvement is observed. This case underscores the importance of balancing timely therapeutic intervention against the potential harms of unnecessary antifungal exposure. Advancing diagnostic accuracy and refining treatment protocols will be essential to improving outcomes in patients with ambiguous CNS lesions and overlapping immunosuppressive conditions.

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