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Case Report

DILEMMATIC INTERSECTION IN CRYPTOCOCCAL MENINGITIS TREATMENT: SIDE EFFECTS, DRUG RESISTANCE, AND EFFICACY

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ABSTRACT

Introduction: Fluconazole resistance in Cryptococcus neoformans is progressively increasing over the past 10 years, particularly in developing countries, which reaches 43.6% resistance rate. This case demonstrates the emerging dilemma of cryptococcal meningitis management with antifungal resistance.

Case Report: A 31-year-old male with HIV presented with severe headache, hearing loss, and fever. Brain imaging was within normal limits, and CSF analysis showed increased cell count (86, PMN 10, MN 76), elevated protein, glucose ratio <0.4, positive India ink, and positive Cryptococcus Ag, leading to a diagnosis of cryptococcal meningitis. He was treated with IV Amphotericin B for 14 days and Fluconazole, but developed acute kidney injury (AKI), delaying further fluconazole therapy. One month later, he returned with a severe headache; CSF re-analysis showed positive Cryptococcus culture and fluconazole resistance. The patient was treated again with IV Amphotericin B for 14 days.

Discussion: Azole resistance in Cryptococcus spp is associated with ERG11 gene mutation which is the fluconazole's target. Interruption of fluconazole in cryptococcal meningitis during the therapy phase could be the risk factor for acquired resistance. The minimum inhibitory concentrations (MIC) test can help in the selection of therapy with Cryptococcus breakpoint for fluconazole susceptibility is MIC < 8 µg/mL. In previous cases, itraconazole and voriconazole were proven to replace fluconazole. However, in this case, there were limitations in costs and treatment coverage.

Conclusion: Drug evaluation in parallel with treatment in Cryptococcal meningitis, with prior fluconazole use or delayed therapy, is recommended.

Keywords: cryptococcal meningitis; HIV; fluconazole resistance

INTRODUCTION

Cryptococcal meningitis remains a significant cause of morbidity and mortality among immunocompromised individuals, particularly those living with advanced HIV infection. Despite advancements in antifungal therapy, challenges such as drug toxicity, limited access to optimal medications, and the emergence of antifungal resistance continue to complicate

management and prognosis.[1,2,3] Fluconazole resistance, in particular, has emerged as a growing concern, especially in resource-limited settings where diagnostic and therapeutic options are constrained.[3,4] This case report describes a 31-year-old HIV-positive male with a history of pulmonary tuberculosis who presented with cryptococcal meningitis complicated by fluconazole-resistant Cryptococcus spp. infection. The case highlights the clinical course, therapeutic challenges including amphotericin B-induced acute kidney injury (AKI), delayed fluconazole maintenance therapy, and the critical importance of fungal culture and susceptibility testing in guiding management. Through this case, we aim to underscore the growing need for resistance surveillance and tailored antifungal strategies in the era of rising fluconazole resistance.

CASE REPORT

A 31-year-old male with a history of HIV and pulmonary tuberculosis on anti-tuberculosis therapy for two months presented with a two-week history of persistent headache and fever, followed by progressive hearing impairment over five days and blurred vision.

Upon physical examination, he was febrile (38.5°C) and cachectic, with a GCS score of 15, reactive pupils (2/2 mm), and bedside visual acuity >2/60 bilaterally. Neurological findings included neck stiffness, positive Kernig's sign, and right-sided sensorineural hearing loss. Cranial nerves were otherwise intact. Motor and sensory functions were intact, with normal tone, strength, reflexes, proprioception, and no bowel or bladder dysfunction. Cardiopulmonary examination was unremarkable with normal heart and lung sounds. Abdominal examination showed no organomegaly. Renal assessment was normal with adequate urine output.

Investigations revealed an elevated lumbar puncture (LP) opening pressure

of 55 cmH_2O. Cerebrospinal fluid (CSF) analysis showed a cell count of 10.0/μL (N <5/μL) with 40% polymorphonuclear (PMN) and 60% mononuclear (MN) cells, markedly low glucose (1.2 mg/dL), and elevated protein (1.39 g/L; N = 0.15–0.45 g/L). India ink staining and cryptococcal antigen (CrAg) testing were positive for Cryptococcus spp**.** Brain MRI demonstrated pathological intensity lesions in the left caudate nucleus, left lentiform nucleus, and posterior right lentiform nucleus without significant contrast enhancement. Haematology results were unremarkable. Renal function was normal, with a creatinine level of 0.86 mg/dL and an eGFR of 119 mL/min/1.73m².

The patient was initiated on induction therapy with amphotericin B (35 mg/day) and fluconazole (800 mg/day), with continuous renal function monitoring. Amphotericin B was administered for a full 14-day course, after which renal function deteriorated. Therefore, consolidation therapy with fluconazole was temporarily suspended. Over two months, renal function progressively improved, permitting reintroduction of fluconazole. However, two weeks after resuming fluconazole therapy, the patient developed a severe headache and required hospital readmission. Cerebrospinal fluid analysis and culture confirmed the presence of Cryptococcus spp. resistant to fluconazole and voriconazole but remaining sensitive to amphotericin B, necessitating retreatment with amphotericin B.

DISCUSSION

Epidemiology of Cryptococcal Meningitis and the increased prevalence of fluco-resistant cryptococcus

Cryptococcal meningitis is one of the major opportunistic infections causing morbidity and mortality in immunosuppressed patients such as people with HIV, those on glucocorticoid therapy or other immunosuppressive drugs. This serious opportunistic infection is caused by encapsulated yeast of

Cryptococcus genus mostly *Cryptococcus neoformans.*[1,2,3] An estimated 280,000 instances of cryptococcal infection in AIDS patients are reported globally each year, and the illness is thought to be responsible for 15% of AIDS-related mortality. Overall, individuals with HIV who have CD4 T lymphocyte (CD4) cell counts below 100 cells/mm³ represent 90% of cryptococcal cases.[4] The gold standard for treating Cryptococcal meningitis involves induction therapy with amphotericin B combined with flucytosine and followed by fluconazole as consolidation and maintenance therapy.[3] However, even after receiving therapy, patients may suffer disease relapse, poor prognosis, and high mortality due to antifungal drug resistance in Cryptococcus species.

Unlike other fungal infection, cryptococcus spp. displays an extraordinary genomic plasticity and physiological adaptability against antifungal intervention. These resistance traits can be inherited and are often transient.[5] Globally, there has been an increase in the percentage of cryptococcus isolates found to be some degree of fluconazole resistance. Increasing progressivity of fluconazole resistance is recorded over the past 10 years, especially in developing countries with approximately 43.6% rate of resistance.[6,7]

Research suggests that mutations in ERG11, a gene that codes for the FLC activity target enzyme lanosterol 14α-demethylase, are linked to azole resistance. Multidrug efflux pump proteins, reduced affinity for target enzymes, or generally decreased drug absorption are examples of the molecular foundation of resistance.[8,9]

Delayed Fluconazole Maintenance Therapy Due to AKI

Several risk factors causing acquired resistance are inadequate fluconazole treatment dose as monotherapy in cryptococcal meningitis and fluconazole discontinuations and noncompliance with medication throughout the consolidation and maintenance stages of treatment.[6]

Maintenance therapy was postponed for our patient due to acute kidney damage, which may have been brought on by amphotericin B-induced nephrotoxicity.

Importance of Fungal Culture and Resistance Testing

Fungal culture and resistance examinations are important to consider in order to assist in selecting therapy for cryptococcal meningitis, especially in cases of repeated relapse. Routine susceptibility testing is not indicated for the first occurrence of cryptococcal meningitis. Susceptibility testing should be pursued in those who have previously used fluconazole or have a history of pharmaceutical non-adherence with interruptions therapy, resulting in relapsed or chronic cryptococcal meningitis.[6] The minimum inhibitory concentrations (MIC) test can help in the selection of therapy in resistant patients. The Cryptococcus breakpoint for fluconazole susceptibility is MIC < 8 μg/mL, MIC 16-32 μg/mL (depending on dosage), and MIC > 64 μg/mL (resistant). The MIC value might be useful when deciding whether fluconazole treatment can be maintained.[6,10]

Alternative Antifungal Management Options

According to 2022 WHO guidelines, therapy administration in the consolidation phase and maintenance phase can be adjusted to each patient's condition, relying on expert opinions.[10] Repeat administration of Amphotericin B needs to be considered, however, monitoring of nephrotoxicity levels must be strict, especially in patients with a history of induced AKI. A previous report study showed successful therapy using liposomal amphotericin B (LampB) as consolidation therapy with weekly maintenance infusion. In addition, LampB also has a lower nephrotoxic effect compared to amphotericin B deoxycholate.[11] However, LampB is not available in Indonesia.

CONCLUSION

This case underscores the complexities involved in managing cryptococcal meningitis in immunocompromised patients, particularly in the context of antifungal resistance and treatment-related complications. The emergence of fluconazole-resistant Cryptococcus spp., coupled with amphotericin B-induced nephrotoxicity, significantly impacted the therapeutic course and patient outcomes. It highlights the importance of timely fungal culture and susceptibility testing, especially in cases of relapse or treatment failure, to guide appropriate antifungal therapy. Furthermore, the lack of access to safer antifungal alternatives such as liposomal amphotericin B presents a major limitation in resource-limited settings. Clinicians should remain vigilant for resistance development and consider early expert consultation for individualized treatment plans. Strengthening laboratory capacity for fungal diagnostics and expanding access to less toxic antifungal formulations are essential steps toward improving outcomes in cryptococcal meningitis, particularly in high-burden, low-resource regions.

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