

HIV and Cryptococcal Meningitis: A Case Report

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Abstract — Cryptococcal Meningitis (CM) has caused high morbidity and mortality rate among people living with HIV infection (PLWH). This case report showed a 32 years old female with HIV infection who came with chief complaint headache since 1 month before hospital admission (SMRS). Her headache had become worse in the past 2 days SMRS. Had been taking antiretroviral (ARV) therapy for 2 weeks and anti-toxoplasmic therapy for 3 weeks SMRS could not alleviate her complaints. Although the cerebrospinal fluid (LCS) examination has shown high probable Tuberculosis and Cryptococcal meningitis, specific examination for these infections only showed a positive result for CM. Few days after hospital admission, the patient experienced generalized seizures, monoplegia and sixth nerve palsy. Two months after high dose fluconazole therapy, the specific examination for Cryptococcal infection in CSF showed a negative result. This case report will show the difficulties in diagnosing and managing CNS opportunistic infections. Diagnosing CNS opportunistic infections, such as CM, has been a great challenge because of the low sensitivity and positive prediction value of the tests available, especially among PLWH. Managing these infections also poses some limitations, especially for the availability of their medications. Time to start ARVs has also been a big issue since ARVs were being given before 1 definite diagnosis was established. This case study also showed that fluconazole alone can be used as an alternative therapy to amphotericin B and flucytosine for C.M. Therefore, this case report has shown the difficulty in diagnosing and managing CM in Indonesia.

Keywords — *Cryptococcus, HIV Infection, IRIS, Indonesia*

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INTRODUCTION

After the discovery of antiretroviral drugs (ARVs) over 30 years ago, opportunistic infections in the central nervous system continue to cause morbidity and mortality in patients infected with Human Immunodeficiency Virus (HIV) [1,2]. Among patients with HIV infection, opportunistic infections in the central nervous system (CNS) that commonly occur include cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis, cryptococcal meningitis, and cytomegalovirus (CMV) encephalopathy [1]. Furthermore, the initiation of ARV treatment at the time of definitive diagnosis is often not established, making it difficult to differentiate the diagnosis of opportunistic infections in the central nervous system from the unmasking symptoms of Cryptococcal Meningitis Immune Reconstitution Inflammation Syndrome (CM-IRIS). Additionally, the lack of availability of the first-line drugs for managing cryptococcal meningitis poses a challenge in such cases. This case report will discuss the challenges in diagnosing and managing cryptococcal meningitis.

CASE ILLUSTRATION

A 32-year-old woman with a history of previous HIV infection presented to the Emergency Department of the Hospital with a complaint of headache that had been ongoing for 1 month prior to admission. The headache was reported to have worsened over the past 2 days before admission and was described as a continuous, sharp, stabbing pain throughout the head. The headache was accompanied by nausea and vomiting since 1 day before admission. The episodes of nausea and vomiting occurred three times a day and consisted of previously consumed food or drink without any evidence of blood. The patient also reported having a fever since 1 month before admission, with the highest temperature observed 2 days prior to admission. The fever was

continuously high throughout the day but could be reduced with antipyretic medication. The temperature reduction was reported not to return to the patient's normal body temperature prior to the onset of headache symptoms.

Despite having a history of HIV infection since 3 years ago, the patient only took antiretroviral (ARV) FDC (Tenofovir 300 mg, Lamivudine 300 mg, Efavirenz 600 mg) once because of intolerable side effects. Three weeks ago, the patient came to a regional general hospital (RSUD) and was suspected of having toxoplasmic meningitis. The patient was given methylprednisolone 4 mg twice a day and toxoplasma treatment (clindamycin 600 mg four times a day and pyrimethamine 75 mg once a day). The patient then restarted ARV treatment 2 weeks ago with the Duviral regimen (Zidovudine 300 mg and Lamivudine 150 mg) and Neviral (Nevirapine 200 mg) twice a day. The administration of ARV and anti-toxoplasma drugs was done without checking the CD4 count and HIV viral load in the blood due to limited resources at the RSUD.

Due to the patient's condition not improving, the patient sought treatment at the author's hospital. The patient works as a trader and has been married for 5 years with 2 children (both children are not infected with HIV). The patient's husband was also diagnosed with HIV infection and received the same treatment (one tablet of FDC daily). The patient's husband regularly takes ARV medication. Before marriage, the patient had sexual intercourse with a man other than her husband. The patient's husband also stated that he often had unprotected sexual intercourse with multiple women, especially 2 years before marriage. The history of drug use was denied by both the patient and her husband. The patient and her husband do not keep any specific animals.

On physical examination when the patient arrived, the patient was conscious with a temperature of 38°C, and there was no neck stiffness or cranial nerve palsy. Other neurological examinations were within normal limits. Laboratory tests during the recent medical history showed lymphopenia (absolute lymphocyte count: 440/ μ l), low CD4 count (24 cells/ μ l [404-1612] and 14.3% [33-58%]), low CD8 count (32 cells/ μ l [404-1612] and 19.5% [33-58%]), low CD4/CD8 ratio (0.73 [<2]), and non-reactive anti-toxoplasma IgG. HIV RNA viral load test showed 193 copies/ml (335 IU/ml). Chest X-ray showed normal findings for the heart and lungs. Computed tomography (CT) scan of the head with contrast showed no signs of bleeding, infarction, or significant mass. Initially, the patient was diagnosed with stage IV HIV infection on ARV therapy with suspected cerebral toxoplasmosis. The patient then received Duviral 300 mg and Nevirapine 200 mg twice a day, clindamycin 600 mg four times a day, pyrimethamine 75 mg once a day, dexamethasone 20 mg three times a day, and other supportive treatments. Due to the patient's condition not improving, a cerebrospinal fluid (CSF) examination was performed on the fourth day of treatment. The CSF examination showed high opening pressure (25 cm H₂O), strongly positive Pandy reaction and None reaction in the CSF, high number of cells in the CSF (170 cells/ μ l), low glucose ratio in the CSF compared to blood glucose (17% of blood glucose), high mononuclear to polymorphonuclear (PMN) leukocyte ratio (60%:40%), and high total protein to microsomal triglyceride transfer protein (MTP) ratio in the CSF (125.8 mg/dl). The CSF India Ink staining test showed positive results. India Ink staining of the CSF (on the fourth day of treatment and before fluconazole administration) showed the presence of *Cryptococcus Neoformans* cells with round budding and thick capsule walls (Figure 1). The yeast cells were found up to 3 per high-power field in several fields of view. Gram staining, Ziehl-Neelsen staining (ZN), mycobacterial culture, and adenosine deaminase (ADA) test on the CSF showed negative results. *Candida* culture in the CSF showed non-*Candida albicans* yeast. Lipoarabinomannan (LAM) test to detect *Mycobacterium tuberculosis* antigen in urine could not be performed due to limited resources. Since the specific tests for cryptococcal meningitis showed positive results, the patient was diagnosed with stage IV HIV infection on ARV therapy with cryptococcal meningitis. On the fifth day of treatment, the patient experienced recurrent seizures in all four extremities. The seizures occurred twice with a duration of 4 minutes each. Immediately after the

Based on the provided information, here is a summary of the patient's case:

The patient is a trader who has been diagnosed with HIV infection for the past 3 years. They initially started antiretroviral therapy (ART) but discontinued it due to intolerable side effects. Recently, the patient presented at a regional general hospital with suspected toxoplasmic meningitis and received treatment with methylprednisolone, clindamycin, and pyrimethamine. Two weeks ago, the patient restarted ART with the Duviral regimen (Zidovudine and Lamivudine) and Neviral (Nevirapine). The patient's condition did not improve, so they sought treatment at another hospital.

On examination at the new hospital, the patient had a fever but no neck stiffness or cranial nerve palsy. Laboratory tests showed low CD4 count, low CD8 count, low CD4/CD8 ratio, and lymphopenia. The patient's HIV viral load was detectable. Chest X-ray and head CT scan were unremarkable. The initial diagnosis was stage IV HIV infection on ART with suspected cerebral toxoplasmosis.

The patient received treatment for cerebral toxoplasmosis and continued with ART, dexamethasone, and supportive care. However, the patient's condition did not improve. A CSF examination was performed, showing high opening pressure, positive Pandy reaction, elevated cell count, low glucose ratio, elevated mononuclear to polymorphonuclear leukocyte ratio, and elevated total protein to MTP ratio. The CSF India Ink staining test revealed the presence of *Cryptococcus Neoformans* cells, indicating cryptococcal meningitis. The patient was then diagnosed with stage IV HIV infection on ART with cryptococcal meningitis. On the fifth day of treatment, the patient experienced recurrent seizures in all four extremities.

It's important for the patient to receive appropriate treatment for cryptococcal meningitis and HIV infection. Prompt initiation of antifungal therapy with drugs like amphotericin B and flucytosine is recommended for cryptococcal meningitis. Additionally, optimizing the patient's ART regimen and managing any complications or side effects are crucial. Close monitoring and follow-up care are essential for the patient's overall management and well-being.

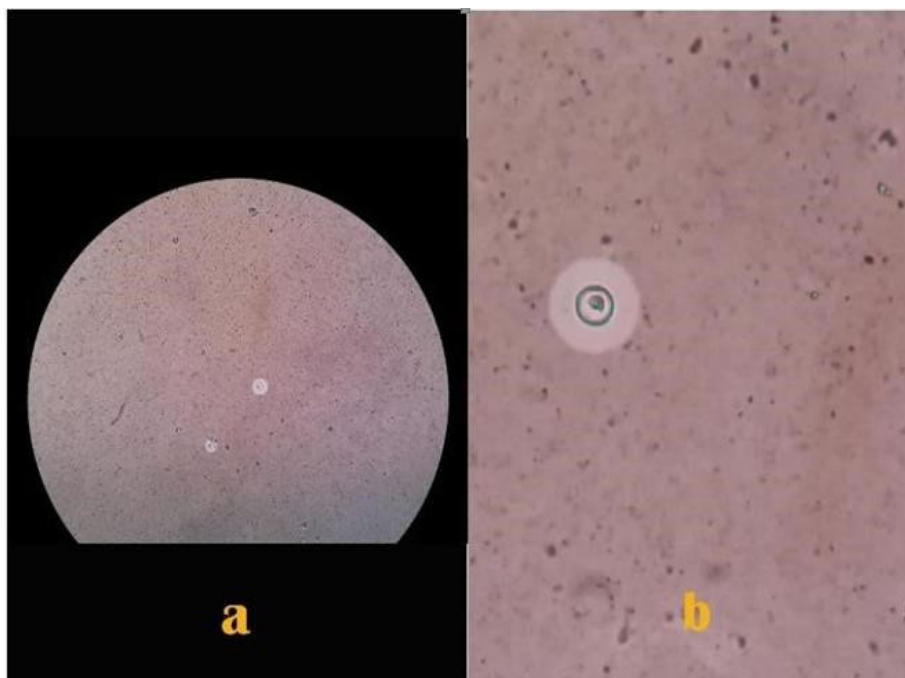


Figure 1. Fluid cerebrospinal fluid staining with India ink before intensive fluconazole therapy. (a) 10x magnification (b) 40x magnification.

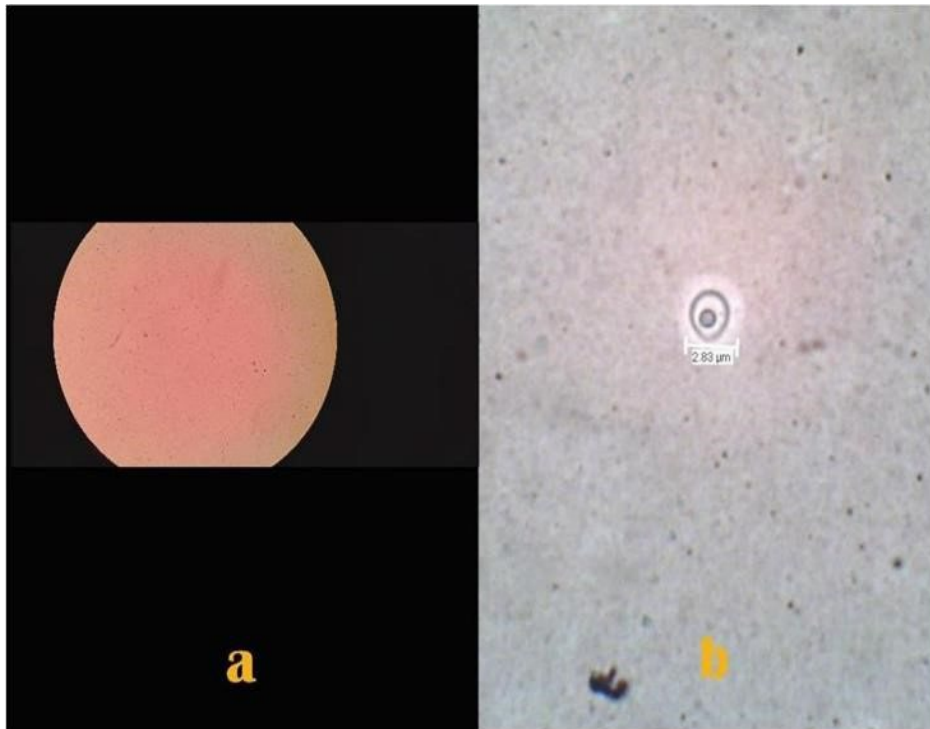


Figure 2. Cerebrospinal fluid staining with India ink before the administration of intensive fluconazole therapy on day 10. (a) 10x magnification (b) 40x magnification.

DISCUSSION

The case illustration above demonstrates the difficulties in establishing the diagnosis and management of cryptococcal meningitis in HIV-AIDS patients in developing countries with limited resources, such as Indonesia. Confirmatory diagnostic tests are required to diagnose cryptococcal meningitis as other opportunistic infections in the central nervous system (CNS), such as toxoplasmosis and tuberculosis meningitis, present similar symptoms. The management of cryptococcal meningitis also poses challenges due to limited availability of drugs [1]. In this case, the definite diagnosis of opportunistic infection in the central nervous system is difficult to differentiate from the symptoms of unmasking Cryptococcal Meningitis Immune Reconstitution Inflammatory Syndrome (CM-IRIS), as antiretroviral therapy (ART) was not initiated at the time of diagnosis. Therefore, the focus of this case report is on establishing the diagnosis and management of cryptococcal meningitis.

Cryptococcal Meningitis

Cryptococcal meningitis is a subacute meningoencephalitis caused by *Cryptococcus neoformans* infection. *Cryptococcus neoformans* is a saprophytic fungus found in the environment, and it can evolve to survive in humans, other mammals, and birds. Additionally, this organism is an intracellular and extracellular pathogen that can survive and replicate in acidic phagolysosomes of macrophages [3]. The yeast form of this fungus is round to oval-shaped with a diameter of 5-10 μm and possesses various virulence factors, such as the ability to grow at a temperature of 37°C, antiphagocytic polysaccharide capsule, and the ability to suppress cellular and humoral immune responses when adhering to host tissues [3]. Furthermore, the laccase enzyme produced by *Cryptococcus* can enhance the

production of melanin from l-dopa [3]. Studies have shown that *Cryptococcus* with low laccase enzyme production has weaker virulence because it cannot disseminate from the lungs to the bloodstream or the brain [4]. As a result of increased melanin production, *Cryptococcus* tends to spread to the central nervous system (CNS).

Cryptococcal meningitis is an opportunistic disease that commonly occurs in patients with advanced HIV infection, particularly in Southeast Asia, South Asia, and East Africa [3,5]. Besides HIV-infected patients, this disease can affect individuals with compromised immune systems [3,5]. The proportion of deaths caused by cryptococcal meningitis due to HIV infection varies from 30% in developed countries to 70% in developing countries [2,3]. The high mortality rate is attributed to the unavailability of antifungal treatments and complications arising from increased intracranial pressure [2, 3].

Diagnosis of Cryptococcal Meningitis in HIV-AIDS Patients

Cryptococcal meningitis in HIV-AIDS patients presents with similar typical symptoms as other opportunistic infections [1]. A similar situation was observed in this case where the patient was initially diagnosed and treated for toxoplasmosis meningitis at a general hospital because toxoplasmosis is the most common cause of focal brain lesions in patients with Acquired Immune Deficiency Syndrome (AIDS) [6].

In this case, the patient presented with a complaint of headache for 1 month prior to admission to the hospital. The headache worsened 2 days before admission and was accompanied by nausea and vomiting. Progressive headache is rarely found in patients with progressive multifocal leukoencephalopathy [1]. This type of headache can also be present in patients with tuberculous meningitis. Further diagnostic tests are required to differentiate between tuberculous meningitis and cryptococcal meningitis. Physical examination alone cannot distinguish between tuberculous meningitis and cryptococcal meningitis.

To establish the diagnosis of cryptococcal meningitis, further investigations such as cerebrospinal fluid (CSF) examination and other serological tests are necessary. The World Health Organization (WHO) divides the diagnostic approach for cryptococcal meningitis into two groups [2]. The first group includes cases with available access and no contraindication for lumbar puncture. The second group includes cases where lumbar puncture cannot be performed due to various reasons [2]. In the first group, CSF examination is conducted to assess the opening pressure and perform serological tests on the CSF [2]. If serological tests on the CSF are not available, an India ink test can be performed in the first group [2]. In the second group where CSF examination is not feasible, serological tests can be directly performed [2].

CSF examination in cryptococcal meningitis usually shows increased opening pressure, lymphocyte dominance in the CSF, elevated protein levels, and low glucose levels in the CSF [5]. Similar findings were observed in this case, with high opening pressure (25 cm H₂O) in the CSF, strongly positive Pandy and None reactions

Cryptococcal meningitis in HIV-AIDS patients has similar typical symptoms to other opportunistic infections [1]. A similar situation was found in this case where initially the patient was diagnosed and treated for toxoplasmosis meningitis at a local general hospital (RSUD) because toxoplasmosis is the most common cause of focal brain lesions in Acquired Immune Deficiency Syndrome (AIDS) patients [6].

In this case, the patient presented with a complaint of headache for one month prior to admission to the Hospital (SMRS). The headache worsened two days before admission and was accompanied by nausea and vomiting. Progressive headache is rarely found in patients with progressive multifocal leukoencephalopathy [1]. This type of headache complaint can also be found in patients with tuberculous meningitis. Further diagnostic tests are needed to differentiate between tuberculous meningitis and cryptococcal meningitis. Physical examination alone cannot distinguish between tuberculous meningitis and cryptococcal meningitis.

To establish a diagnosis of cryptococcal meningitis, additional diagnostic tests such as cerebrospinal fluid (CSF) examination and other serological tests are required. The World Health Organization (WHO) classifies the diagnosis of cryptococcal meningitis into two groups [2]. The first group is where access is available and there are no contraindications to lumbar puncture. The second group is where lumbar puncture cannot be performed due to lack of access or contraindications [2]. In the first group, CSF examination is performed to assess the opening pressure and serological tests on the CSF [2]. If serological tests on the CSF are not available, an India ink test can be performed in the first group [2]. In the second group, where CSF examination cannot be performed, serological tests can be done directly [2].

CSF examination in cryptococcal meningitis usually shows increased CSF opening pressure, lymphocyte dominance in the CSF, and elevated protein levels with low glucose levels in the CSF [5]. A similar situation was found in this case where the CSF opening pressure was high (25 cm H₂O), the Pandy reaction and None reaction in the CSF were strongly positive (indicating high protein levels in the CSF), the glucose ratio between the CSF and blood was low (17% of blood glucose), and there was a dominance of mononuclear leukocytes (lymphocytes and monocytes) in the CSF.

In addition to CSF examination, serological tests and India ink staining of the CSF are used to confirm the diagnosis of cryptococcal meningitis. Due to the unavailability of cryptococcal serological tests, India ink staining of the CSF was performed in this case. The use of India ink staining to support the diagnosis of cryptococcal meningitis has been recommended by the World Health Organization (WHO) in 2018, especially in conditions with limited access to cryptococcal antigen testing and no contraindications to lumbar puncture [2]. In the India ink staining preparation, the cryptococcal polysaccharide capsule does not absorb the ink, resulting in large refractile white circles against a dark background. India ink staining of the CSF in suspected cryptococcal meningitis has a 100% positive predictive value (PPV) and a 90.7% negative predictive value [7]. This indicates that if India ink staining shows a negative result, further testing with cryptococcal serological tests should be conducted if available. Conversely, a positive India ink staining indicates a definite diagnosis of cryptococcal meningitis. Cryptococcal meningitis can also be accompanied by other opportunistic infections such as tuberculosis and toxoplasmosis. Since the patient had previously received therapy for cerebral toxoplasmosis and did not show improvement, the diagnosis of toxoplasma infection can be ruled out. To establish a diagnosis of tuberculous meningitis, various supportive tests were performed on the CSF in this case, such as Ziehl-Neelsen staining (ZN) to detect acid-fast bacilli (AFB), Adenosine Deaminase (ADA) test, mycobacterial culture, and rapid tuberculosis molecular test (GeneXpert® TB) using CSF samples. Other tests, such as lipoarabinomannan (LAM) testing in urine, could not be performed due to

limited resources. This test also has similar sensitivity and specificity to other tests (Table 1) [8]. Since Ziehl-Neelsen staining, ADA test, mycobacterial culture, and GeneXpert® TB test on the CSF showed negative results, the possibility of tuberculous meningitis can be ruled out.

Due to the patient's history of seizures and inability to move the left eye and left leg, the patient was suspected to have experienced Unmasking Cryptococcus Meningitis Immune Reconstitution Inflammation Syndrome (CM-IRIS). CM-IRIS is an immune response to cryptococcal meningitis infection that is more severe (previously subclinical infection) caused by immune system recovery.^{12,13} There are two types of CM-IRIS, paradoxical and unmasking CM-IRIS. In paradoxical CM-IRIS, the immune response occurs when cryptococcal infection therapy has been given prior to ARV therapy [13]. In contrast to paradoxical CM-IRIS, cryptococcal meningitis infection only manifests subclinically, and cryptococcal therapy has not been administered in unmasking CM-IRIS [13]. Since CM symptoms were present prior to ARV administration, the diagnosis of unmasking CM-IRIS can be ruled out.

Management of Cryptococcal Meningitis in HIV-AIDS Patients

The management of cryptococcal meningitis in HIV-AIDS patients is divided into 3 parts: antifungal therapy, corticosteroids, therapy to reduce intracranial pressure, and antiretroviral therapy (ARV). According to the World Health Organization (WHO), antifungal therapy for cryptococcal meningitis is divided into 3 phases: induction, consolidation, and maintenance phases. In the induction phase, amphotericin B (1 mg/kg body weight/day) and flucytosine (100 mg/kg body weight/day) are given for a week, followed by fluconazole 1200 mg/day for a week. Another induction therapy that can be given is fluconazole 1200 mg in addition to flucytosine (100 mg/kg body weight/day) or amphotericin B (1 mg/kg body weight/day) [2]. In the consolidation phase, the administration of fluconazole 800 mg for 8 weeks after the induction phase is highly recommended [2]. In the maintenance phase, fluconazole (200 mg) is given after the consolidation phase [2]. However, amphotericin B and flucytosine are not available. Therefore, fluconazole 1200 mg daily for 14 days is used as the induction therapy for cryptococcal meningitis in this case. The use of fluconazole 1200 mg daily as induction therapy in the absence of amphotericin B and flucytosine availability is also recommended by the Infectious Disease Society of America [14]. Although the use of fluconazole as a monotherapy induction treatment for cryptococcal meningitis is considered less optimal, fluconazole has been proven to be useful in the management of *Cryptococcus neoformans* [15]. In addition, its low molecular weight, low protein binding, and moderate lipophilicity facilitate distribution to the central nervous system [15]. In the consolidation phase, the patient is given fluconazole 800 mg for 2 weeks. The administration of fluconazole 800 mg for 2 weeks is in accordance with the recommendations of the World Health Organization (WHO) [2]. In this case, the patient experienced progressive headache and left VI nerve paresis. The cause of the progressive headache and VI nerve paresis is increased intracranial pressure, which often occurs in patients with cryptococcal meningitis infection [5,14,16]. One way to reduce intracranial pressure is by performing cerebrospinal fluid (CSF) drainage. A similar procedure was performed in this case, where CSF decompression was done through lumbar puncture. Due to the occurrence of seizures during treatment, lumbar puncture was performed again, and a decrease in opening pressure from 25 cmH₂O to 22 cmH₂O was obtained. The next step in the management of cryptococcal meningitis in HIV-AIDS patients is the administration of ARV therapy. The Infectious Diseases Society of America recommends that Highly Active Anti-Retroviral Therapy (HAART) be

given 2-10 weeks after cryptococcal meningitis therapy [14]. However, in this case, ARV therapy was administered 2 weeks before antifungal therapy. The administration of ARV therapy poses a dilemma in antifungal therapy due to the possibility of developing Unmasking Cryptococcal Meningitis Immune Reconstitution Inflammation Syndrome (CM-IRIS). Grant and Komarow suggested that early ARV administration does not affect the occurrence of CM-IRIS events [17]. Further studies are needed to evaluate the ideal timing of ARV therapy in patients with cryptococcal meningitis.

CONCLUSION

This case report highlights the challenges in diagnosing and managing cryptococcal meningitis in developing countries with limited resources. Various diagnostic tests are required to rule out other opportunistic diseases that often present similar.

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