Cryptococcal meningoencephalitis in an immunodeficiency virus positive patient coinfected with tuberculosis

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ABSTRACT

Background: Cryptococcal meningitis is an inflammation of the meninges due to Cryptococcus fungal infection which commonly invades people living with immunodeficiency virus (PLHIV) with impaired immunity. The disease has a high mortality rate and is frequently misdiagnosed in the early stages due to vague symptoms. This case report aimed to provide information regarding diagnosing and managing cryptococcal meningoencephalitis in patients with acquired immunodeficiency syndrome (AIDS) and tuberculosis.

Case presentation: We reported a case of 34-year-old woman that complained of headache and fever from one month ago. There were also oral white patches in the last two weeks. The patient was diagnosed with lung TB and human immunodeficiency virus (HIV) in February 2021, but the TB was just being treated in the past two months and HIV in last two weeks. Head CT-scan with contrast showed meningoencephalitis, brain edema, left frontal, left ethmoidal, left and right maxillary and left sphenoid sinuses. On the 9th day of hospitalization, the patient had seizures. Analysis of the cerebrospinal fluid culture revealed Cryptococcus neoformans. The patient’s comorbidities were leucopenia, hypoalbuminemia, pneumonia, brain edema which led to poor prognosis. On the 10th day, the seizures relapsed, followed by the drastically reduced SpO2, and death. Septic shock and multiorgan failure were considered the cause of the case’s death.

Conclusion: This case highlights the importance of early diagnosis and management to avoid unfavorable outcome.

Keywords: human immunodeficiency virus, tuberculosis, Cryptococcus neoformans, meningoencephalitis.

Case PRESENTATION

A 34-year-old female, came to Bhakti Dharma Husada (BDH) Hospital, Surabaya, by chief complaints were headache and pain in the back side of the neck in the last one month. The pain worsened since the last one week. The patient felt nauseous and vomited once a day before admission. Other complaints were fever since the last one month, oral white patches since the last two weeks and decreased body weight of ± 5 kg in one month (Figure 1). The patient was diagnosed with TB and HIV in February 2021 and started taking intensive regimens of antituberculosis drugs in the past two months, followed by

INTRODUCTION

The most common fungal infection of the nervous system among people with human immunodeficiency virus (PLHIV) is cryptococcosis, caused by Cryptococcus fungi, and is associated with CD4 cell depletion. The fungal infection could develop space occupying lesions (SOL), meningoencephalitis. Before antiretroviral (ARV) therapy was invented, fungal and other opportunistic infections were a major problem for HIV infection or acquired immunodeficiency syndrome (AIDS) patients. Since the advent of ARV’s, the number of fungal infections and deaths from fungal infections in HIV/AIDS patients has decreased substantially in the US and other developed countries. A study showed that the incidence of cryptococcosis in AIDS patients in the US decreased by about 90% in 1990. The decline in opportunistic infections is mainly due to early HIV diagnosis and initiation of ARV therapy which prevents HIV patients from reaching the stage where their immune systems are more exposed to the virus and susceptible to fungal and other infections.

Cryptococcal meningitis is an inflammation of the meninges (protective membranes of brain and spinal cord) due to Cryptococcus fungal infection. This fungus invades the central nervous system (CNS) and develops into an opportunistic disease related to AIDS, as listed by the Centers for Disease Control and Prevention (CDC). The disease mortality rate is high, ranging from 20-30%, even with the administration of antifungals. The diagnosis of cryptococcal meningitis in the early stages is often missed due to non-specific clinical and radiological features.

In this case-report, we present a patient with cryptococcal meningoencephalitis in HIV/AIDS patients with tuberculosis (TB). We highlight the approaches to diagnosis and management of cryptococcal meningoencephalitis in HIV/AIDS patients.
CASE REPORT

(GCS) 15, comatos mentis, blood pressure (BP) 156/117 mmHg, pulse 93x/minute, respiratory rate (RR) 20x/minute, axillary temperature 38°C and SpO₂ 98%. There were white patches in the oral cavity. Thoracic and cardiac examination revealed rhonchi in the right and left hemithorax with no wheezing. Abdominal and extremities examinations were within normal limits. The investigations revealed hemoglobin 10.1 g/dL, leukocytes 3200/mm³, platelets 385,000/mm³, neutrophils 66.9%, lymphocytes 11.1%, blood urea nitrogen (BUN) 5 mg/dL, serum creatinine 0.4 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 20 U/L, serum glutamic pyruvic transaminase (SGPT) 5 U/L, albumin 2.66 g/dL, random blood glucose (RBG) 108 g/dL, sodium 128 mEq/L, potassium 3.2 mEq/L, chloride 92 mEq/L and C-reactive protein (CRP) 0.7 mg/L. The blood gas analysis showed pH 7.5, pCO₂ 40, pO₂ 110, HCO₃ 31.3, base excess (BE) 8, SpO₂ 99% and PaO₂ to FiO₂ (P/F) ratio 524 mmHg. Lung x-ray showed pulmonary TB and hyperaerated lung (Figure 2A). Head CT-scan with contrast showed meningoencephalitis, brain edema, left frontal, left ethmoidal, left and right maxillary and left sphenoid sinusitis (Figure 2B).

Based on the history and physical examination, the patient was diagnosed with meningoencephalitis, oral candidiasis, AIDS, lung TB under intensive phase of category 1 treatment, hypovolemic hyponatremia (sodium 128 mEq/L), hypokalemia (potassium 3.2 mEq/L), hypoalbuminemia (albumin 2.62 g/dL) and alkalosis metabolic. The patient was treated with high carbohydrate and high protein diet in 2100 kcal/day and additional fruits and vegetables, IV dextrose and electrolyte infusion 1000 ml/24 h and IV aminofluid of 500 ml/24 hour, IV metoclopramide 10 mg every 8 hour, oral paracetamol 500 mg every 8 h, oral potassium chloride 600 mg every 8 h, oral antituberculosis drugs category 1 intensive phase, oral ARV and oral folic acid 1 mg every 24 hour. The patient was planned for examinations of procalcitonin, IgG and IgM of toxoplasma, Genexpert, culture of blood, sputum and cerebrospinal fluid (CSF).

On the 3rd day of treatment, the patient still had headaches in the back side and ate soft food. The vital sign examination showed BP 140/80 mmHg, pulse 92x/minute, RR 20x/minute, sodium 133 mEq/L, potassium 3.5 mEq/L, chloride 100 mEq/L, albumin 2.4 g/dL, leukocytes 2400/mm³ and Hb 9.5 g/dL. The results of IgG and IgM toxoplasma in blood serum were negative (1.574 and 1.57, respectively) and procalcitonin 0.18 ng/mL. Because the pain was 3-4, according to visual-analogue scale (VAS) score, the patient was still treated with paracetamol.

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500 mg every 8 h and IV dexamethasone 5 mg every 12 hour. The patient was also suspected of having an opportunistic bacterial infection from decreased leukocyte and therefore the patient was treated with IV ceftriaxone 2 grams every 12 hour.

On the 5th day of treatment, the patient complained of pain in the back of the head but decreased to a pain scale of 2 and the oral white patches were disappeared. The vital sign examination showed BP 140/90 mmHg, pulse 96x/minute, respiratory rate 20x/minute, Hb 10.3 g/dL, leukocyte 2450/mm³, albumin 2.9 g/dL. The culture of spinal fluid showed clear, no clots, pH 8, leukocytes 44 cells/mm³, no erythrocytes, no monocytes, polymorphonuclear 4 cells/mL, Nonne and Pandy positive, glucose 13 mmol/L, and protein 117.1 mg/dL. The sputum culture showed sensitive Klebsiella pneumoniae and Streptococcus viridans to ceftriaxone and sensitive Cryptococcus neoformans to fluconazole. The patient was suspected of having tuberculous meningoencephalitis (TBM), community-acquired pneumonia, AIDS, and pulmonary TB. Additionally, the patient was also given IV fluconazole 400 mg every 24 hour.

On the 8th day of treatment, the patient was able to sit up on her own, headache still persisted with VAS 1-2. The blood analysis revealed Hb 11.7 g/dL, leukocyte 1660/mm³, platelet 135,000/mm³, procalcitonin 0.21 ng/mL, sodium 131 mEq/L and potassium 3.0 mEq/L. The culture of CSF showed yeast and no acid-fast bacteria (AFB). No bacteria or fungi were found in blood culture.

The patient experienced 2-minute-long seizures twice in 5 minutes on the 9th day of treatment. The patient was not conscious between the seizures and was also not conscious when having a seizure. The seizures manifested as the stomping hands and feet, and the eyes were staring upward. A gradual intravenous bolus of 5 mg diazepam was administered during a seizure, along with supplementary O₂ delivered through a simple mask (8 L/min), followed by a loading dose of phenytoin 600 mg in 0.9% NaCl solution 100 ml which was inserted in 15 minutes and its maintenance dose of 100 mg orally every 8 hour. On physical examination, the patient had a fever of 39°C and a BP 160/100 mmHg, additional IV paracetamol 1 grams was given every 8 hour and oral amldipine 10 mg every 24 hours orally.

The results of spinal fluid culture showed Cryptococcus neoformans (Figure 3), leading to the additional diagnosis which is cryptococcal meningoencephalitis. Amphotericin B 30 mg every 24 hour intravenously and increased dose of fluconazole to 1200 mg every 24 hour intravenously were added to the treatment. The intravenous dexamethasone was stopped and the intravenous ceftiraxone was reduced to 1 grams every 12 hour.

On the 10th day of treatment, the patient had a seizure for 5 minutes. The patient was given 10 mg diazepam in slow intravenous bolus and a loading dose of 300 mg of phenytoin in 0.9% NaCl 100 ml administered for 10 min intravenously during the seizure. It was followed by SpO₂ 80%, measured with simple mask. The oxygen mask was replaced with a Jackson Rees with an oxygen flow of 15 L/min. We also consulted the patient to anesthesiologist for intubation and the use of ventilator machine. The patient's SpO₂ fell to 67% 30 min after seizure. In the following 30 min, the patient was declared dead due to septic shock and multiorgan failure.

DISCUSSION

HIV, which belongs to the genus Lentivirus and family Retroviridae, can enter the human body through intact mucous membranes, injured skin and parenteral inoculation.10 HIV can be detected throughout the body including the nervous system in 10–14 days, while transmission of the virus through the blood can occur in 5–6 days.11 Clinical symptoms begin to appear after 3–6 weeks, including non-specific clinical symptoms such as fever, enlarged lymph nodes, malaise, or gastrointestinal symptoms and weight loss.5,12 As the immunodeficiency condition worsens, which generally appears when CD4 <300/µL, the body’s immune response will weaken, leading to opportunistic infections. The time between infection and the appearance of immunodeficiency symptoms can vary between 2–25 years.13

The clinical symptoms of the patient in this study led to AIDS. On physical examination, there was oral candidiasis and decreased body weight ± 5 kg in one month, and crackles in both lungs. Laboratory examination revealed leukopenia and hypoalbuminemia which could be related to infection or inflammatory processes. The three types of HIV test were positive. Chest X-ray showed pulmonary TB and hyperaerated lung. Head CT scan with contrast showed the impression of meningoencephalitis and brain edema. Based on clinical symptoms, physical and laboratory examinations, the patient had AIDS in clinical stages 3–4.

C. neoformans and C. gattii are the main cause of cryptococcal meningitis. C. neoformans is found mainly in soil contaminated with poultry droppings such as: pigeons and chickens while C. gattii is more often found in weathered eucalyptus trees, so it is initially considered to be only limited to tropical and subtropical areas.13,14 The incidence of cryptococcal meningitis increased significantly in the mid-1980s during the HIV/AIDS pandemic and accounts for more than 80% of cryptococcal cases.
The disease is more common in people with impaired cellular immunity and is an AIDS-associated opportunistic infection with a CD4+ T cell count <100 cells/μL. Since the combinations of three or more ARVs existed, the incidence of cryptococcal meningitis has decreased, in particular in developed countries but has not had much effect in developing countries. The global cryptococcal meningitis incidence is estimated at 223,100 cases per year with 70% of annual mortality rates for low-income countries and 40% for middle-income countries. This disease spreads throughout the world, with the highest incidence in the African continent. The incidence of cryptococcal meningitis in Sub-Saharan Africa is estimated at one million cases per year, with at least 100,000-500,000 deaths per year. The second highest incidence of cryptococcal meningitis occurs in Asia-Pacific countries. In Indonesia, the prevalence of cryptococcal meningitis is increasing along with the increasing number of HIV patients. A study estimated the incidence of HIV-related cryptococcal meningitis reached 6600 cases in Indonesia, indicating that the prevalence of cryptococcal meningitis in PLHIV in 2018 was 7.1% in Bandung and 7.3% in Surabaya.

The clinical manifestation of cryptococcal disease in PLHIV can vary widely with the most dissemination was from the lungs to the CNS. The clinical spectrum of cryptococcal meningitis is generally due to intracranial hypertension caused by obstruction of CSF flow. The mechanism of intracranial hypertension in cryptococcal meningitis is not fully understood, one of which is thought to be due to the deposition of Cryptococcus yeast cells and their polysaccharide capsules in the arachnoidal villi which results in blockage of CSF flow.

Cryptococcal meningitis patients usually present with subacute or chronic clinical symptoms (more than a week to months). Common clinical symptoms include: subacute headache, fever, nausea, vomiting, seizures, visual disturbances (diplopia, decreased vision) and hearing. Changes in mental status may also be present and are usually associated with a poorer prognosis. Some patients may experience signs and symptoms of focal neurologic deficits due to involvement of the brain parenchyma. Signs of meningeal irritation such as stiff neck can be found in a quarter to a third of cryptococcal meningitis patients.

Our patient complained of headaches, nausea and vomiting in the last one month, the headache was worsened in the last one week. Seizures happened since the 8th day of hospitalization. The patient also complained of fluctuating fever and weight loss of ±5 kg in one month. On physical examination, no neck stiffness was found. The laboratory examination showed leukopenia and hypoalbuminemia and CD4 cells count was 72 a month before hospital admission. Sputum culture positive with C. neoformans. The head CT-scan revealed meningoencephalitis and brain edema.

Patients with HIV are suspected of suffering from cryptococcal meningitis should undergo laboratory and radiological investigations. Lumbar puncture is highly recommended. This action is not only for CSF laboratory examination but also to reduce intracranial pressure which usually increases in cryptococcal meningitis patients. Brain imaging should be performed before a lumbar puncture procedure, especially in patients who have focal neurological deficits or impaired consciousness. The CSF can be used for CSF parameters, culture, staining with Indian ink, Cryptococcus antigen detection. The CSF parameter of cryptococcal meningitis patients with HIV usually show mild or even normal pleocytosis, slightly elevated protein levels and low/normal glucose level. The CSF culture on Sabouraud Dextrose Agar (SDA) or Bird Seed Agar (BSA) medium is still one of the gold standards for diagnosing cryptococcal meningitis, but it takes about 7 days to find out and up to 10 days to know the quantity.

Microscopic examination of CSF using Indian ink is the simplest method but the sensitivity is rather low (<86%) and even decreases by 42% if the fungal load is less than 1,000 colony forming units (CFU)/mL in quantitative CSF cultures. Currently, the positive Cryptococcus antigen (AgCr) detected in CSF or blood is a definitive diagnostic criterion for cryptococcosis. In addition, this examination can also produce semiquantitative results (titers) using the serial dilution method. AgCr test with lateral flow assay (LFA) is more recommended than latex agglutination because it has advantages such as: stable at room temperature, does not require a cooling chain or centralized laboratory, more affordable and provides results in around 10 minutes only. The LFA AgCr test is an immunochromatographic technique that has a sensitivity of 99.3% with a specificity of 99.1% in CSF samples, and the sensitivity can reach 99% in serum with positive CSF results.

Molecular detection method with polymerase chain reaction (PCR) for diagnosing cryptococcal meningoencephalitis, may use the meningitis/encephalitis FilmArray panel (Biofire, Utah). This panel is a multiple PCR test that can detect 14 meningitis-causing pathogens (bacteria, viruses, and fungi), including Cryptococcus with a sensitivity of 96% and specificity of 100%. However, this method is not suitable for developing countries due to its expensive cost.

The analysis of CSF showed colorless, no clots, pH 8, WBC 44 (normal: 0-5), RBC 0, MN 40, PMN 4, cell count 46, Nonne and Pandy positive, glucose 13 mg/dL (normal: 50-80 mg/dL), total protein 117.1 mg/dL (normal: 15-45 mg/dL). C. neoformans identified from spinal fluid culture. AgCr assay was not performed due to unavailability of reagents. The results of the cerebrospinal fluid examination confirmed cryptococcal meningoencephalitis.

Brain imaging examinations for cryptococcal meningoencephalitis, either with CT-scan or magnetic resonance imaging (MRI), did not all result positive findings. Normal brain imaging was found in 47% of CT scans and 8% of MRIs. Many features are similar to cryptococcal meningoencephalitis, especially in patients with AIDS. In lesions that increase in the basal ganglia, toxoplasmosis or primary lymphoma should be considered. Subependymal contrast lesions may represent primary lymphoma or cytomegalovirus encephalitis. Approximately 21-27% of cryptococcal meningoencephalitis cases show typical
features on MRI. Typical cryptococcal meningoencephalitis imaging features include perivascular space dilatation, pseudocysts, cryptococcomas, leptomeningeal enhancement and hydrocephalus.25

On radiological examination, the head CT-scan with contrast of the patient showed a hypodense lesion in the right and left temporoparietooccipital region with gyral enhancement accompanied with leptomeningeal enhancement, sulci and gyri effacement and the presence of a ventricular and cystic system outside the normal lesion which leads to a common finding of meningoencephalitis and brain edema.

The administration of ARV in HIV patients with cryptococcal meningoencephalitis is risky in causing clinical deterioration that can be life-threatening. This is related to the occurrence of immune recovery syndrome (IRS) or immune reactivation inflammatory syndrome (IRIS). The IRS mechanism is not yet fully understood. However, the possibility is due to a partial recovery of the immune system resulting in an exaggerated immunological response to certain antigenic stimuli.20 The mechanism of SPI in HIV patients with cryptococcal meningoencephalitis can be divided into two, namely paradoxical and unmasking. The main difference between the two SPIs is whether cryptococcal meningoencephalitis infection is diagnosed and treated before or after the initiation of ARVs. Paradoxical immune recovery syndrome occurs in HIV patients who are diagnosed with cryptococcal meningoencephalitis and respond to antiretroviral administration before antiretroviral therapy, but after starting ARVs the symptoms of cryptococcal meningoencephalitis relapse worsen.23 The unmasking mechanism was asymptomatic before the administration of ARV and only showed obvious clinical signs of cryptococcal meningoencephalitis after ARV was started. In HIV patients with cryptococcal meningoencephalitis, ARV drugs should be delayed before antifungal administration and initiated 4-6 weeks afterward.4

The patient was treated with intravenous therapy of ceftriaxone 2 grams every 12 hours, dexamethasone 5 mg every 12 hours and gradually reduced to 2.5 mg every 24 hours on 9th day of treatment, intravenous amphotericin B 30 mg and intravenous fluconazole 1200 mg every 24 hours on day 9 of treatment.

The lack of inflammatory markers of CSF at the initial lumbar puncture is an indicator of a poor prognosis in cryptococcal meningitis. High intracranial pressure has been associated with a poor prognosis, and failure to control it has been associated with neurologic injury.2,20,26,27

Intracranial hypertension is one of the most severe neurological complications and has high morbidity and mortality. Approximately 50% of cryptococcal meningoencephalitis patients have ICH and an intracranial pressure greater than 200 mm H2O. The mechanism of intracranial hypertension may be related to occlusion of the CSF outflow of large amounts of yeast and polysaccharides residing in the arachnoid villi. Inadequate CSF drainage may be at risk for the development of brainstem herniation.28 CT or MRI of the head is capable of showing normal or reduced ventricular size. Sagittal MRI imaging may clearly detect brainstem herniation.2,29

Hydrocephalus is a frequent complication of fungal meningitis. The reason for obstructive hydrocephalus may be related to Cryptococcus in the choroid plexus or subependymal region that hamper the CSF flow. Intracranial calcifications rarely happens but detectable and considered as a sequel to chronic infection.35

Diffuse brain edema and status epilepticus were risk factors for poor prognosis of meningoencephalitis. The patient was declared dead after 10 days of treatment due to septic shock and multi-organ failure.

In patients with cryptococcal meningitis and HIV, treatment strategies are limited and relatively few.33 Adjuvant corticosteroids reduce the inflammatory response to infection and have been shown to improve outcomes in other central nervous system treatments such as bacterial meningitis and TB in adolescents and adults in several studies.9,22,23,30 Therefore sensitive diagnostic test to differentiate the types of meningitis is important and advanced technology such as next-generation sequencing (NGS) might increase the diagnosis time.31,32

A systematic review, conducted in Indonesia, Laos, Thailand, Uganda and Vietnam (n = 451), assessed whether systemic corticosteroids in the treatment of HIV-associated cryptococcal meningitis improve outcomes compared with standard care.23 The participants were randomized to receive six weeks of dexamethasone or placebo in addition to antifungal therapy like amphotericin B and fluconazole, cotrimoxazole prophylaxis and ARV. No differences were identified in mortality between the two groups at 10 weeks (danger-of-death ratio in dexamethasone group, 1.11, 95% CI 0.84-1.47) or at six months (risk-to-death ratio in dexamethasone group, 1.18, 95% CI, 0.91 to 1.53). Outcomes at 10 weeks were worse in the dexamethasone group: 13% of participants in the dexamethasone group had a positive result (no death or disability) at 10 weeks compared with 25% in the placebo group. Side effects were more common in the dexamethasone group, including grade 3 or 4 infections, cardiac, renal and gastrointestinal problems and biochemical abnormalities. The fungal clearance in the CSF during the first two weeks of treatment was slower in dexamethasone group than in placebo group.

This study excluded participants with clinical conditions in which corticosteroids might affect, such as in the treatment of mass-effect cryptococoma or acute respiratory distress syndrome (ARDS).23 The recommendation against the use of adjuvant corticosteroids applies specifically to routine use during the treatment phase of cryptococcal meningitis. If patients have a clinical condition for which the prescribed corticosteroid should be used in treatment, it is clinically appropriate.

CONCLUSIONS

HIV patients, especially who are treated late, frequently experience severe, unexpected complications involving fungal infections. Even with common symptoms like fever, headache, and vomiting, HIV patients who are also co-infected with TB should be given extra caution. The CNS is where lung infection in HIV patients
spreads most frequently. In addition to a comprehensive physical examination, a diagnosis must be confirmed by a radiological and laboratory examination. HIV patients with neurological deficits and symptoms must undergo brain imaging and lumbar puncture. A prompt diagnosis and effective therapy could produce a better outcome.

**PATIENT CONSENT**

Written informed consent was obtained from the patient to be included as case-report.

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**DISCLOSURE OF CONFLICT OF INTEREST**

The author stated that there is no conflict of interest.

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**AUTHOR CONTRIBUTION**

HW contributed to the study conceptual, data acquisition, clinical data assessment, follow-up of the patient and during manuscript preparation. MR, MVA and BB contributed to the study conceptual, data validation and during manuscript revision.

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CASE REPORT


