JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : https://doi.org/10.14710/jkd (dmj).v12i1.36701
JKD (DMJ), Volume 12, Number 1, January 2023 :

CASE REPORT: LESSON LEARNED FROM DELAYED DEFINITIVE TREATMENT OF STAGE 4 HIV PATIENT WITH CEREBRAL TOXOPLASMOSIS

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ABSTRACT

Background: Cases of cerebral toxoplasmosis continue to burden people living with HIV/AIDS (PLWHA). This surge in cases is primarily due to patient's delayed definitive treatment, missed follow-up, and insufficient diagnostic equipment in some regions, particularly in developing countries such as Indonesia. **Case Presentation:** We report on a 35-year-old male with HIV stage IV referred to the emergency department with spastic impairment in four extremities from a secondary healthcare facility. Specific atypical symptoms that mimicked subacute meningitis were identified during the physical examination. The patient was subsequently given a daily dose of tenofovir (TDF), lamivudine (3TC), and efavirenz (EFC). Cotrimoxazole and clindamycin were also given to patient to treat the toxoplasmosis. These treatments had given for 14 days and the spastic motor deficit was improved due to the coordination between neurologist, rehabilitation doctors, and internists along the treatment. **Conclusion:** We suggest that improved early diagnosis and treatment of HIV patients to prevent opportunistic infections, including cerebral toxoplasmosis, is needed, particularly in primary healthcare facilities in developing countries.
Keywords: *cerebral toxoplasmosis, human immunodeficiency virus, Indonesia, treatment*

INTRODUCTION

Cerebral toxoplasmosis continues to be a burden living with HIV/AIDS (PLWHA). The disease caused by the protozoan *Toxoplasma sp.* is mainly driven by the reactivation of latent infection in patients with CD4+ T cell counts of less than 100 cells/μL.[1] As a single disease, toxoplasmosis significantly impacts healthcare services, individual healthcare, and health insurance companies.[2] Earlier estimation, published in 2012, suggested that toxoplasmosis accounted for nearly $3 billion of illness-related costs in United States.[2–4]

The prevalence of co-infection in low-income countries is the largest, at 55%, especially in Southeast Asia.[5,6] In Indonesia alone, the majority of cerebral toxoplasmosis increased to 45% in 2017.[7] This merits a proper investigation of cases of cerebral toxoplasmosis in developing countries. Several factors contribute to this, including delayed treatment, missed follow-up, and limited diagnostic tools in some areas.

Herein, we report an HIV patient with cerebral toxoplasmosis and the lessons that could be drawn from patient outcomes as a result of delayed treatment.

CASE PRESENTATION

A-35-year-old man with HIV infection and having experienced loss to follow-up two years was admitted to our hospital with a spastic motor impairment in four extremities, fever, headache, nausea, and vomiting for three weeks from a secondary health facility. In addition, there was no report of trauma, ingestion of raw food, or manipulation of snails and slugs during gardening. On physical examination, neck stiffness and spastic quadriparesis were observed. Brain Computed Tomography (CT) showed a cystic contras-enhancing lesion located in the right subcortical parietal lobe with perifocal edema (Fig.1).

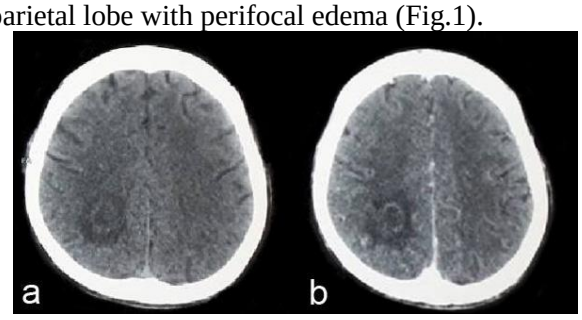

Figure 1. Head CT scan image of stage 4 HIV patient with toxoplasmosis cerebral. The picture shows a cystic lesion, ring enhancement, solitary in the subcortical right parietal lobe (measurement ± AP 1.9 x LL 1.4 x CC 1.8 cm) accompanied by perifocal edema

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The patient had a T-CD4+ lymphocyte count was 30 cells/µl. The patient's immunoglobulin M (IgM) level was 0.10, and immunoglobulin G (IgG) level was >300, according to serological testing. Hyponatremia was discovered via biochemical tests after an average complete blood count. The patient was subsequently given a daily dose of tenofovir (TDF) 300 mg, lamivudine (3TC) 300 mg, and efavirenz (EFC) 600 mg of a combination of antiretroviral therapy (cART). Cotrimoxazole, as well as toxoplasmosis treatments such as pyrimethamine and clindamycin, were given to patient.

After six days in the hospital, the patient had two general tonic seizures lasting 5-8 minutes each, with the patient conscious in between. The neurology team then administered intravenous diazepam, followed by phenytoin. To prevent muscle atrophy and pressure sores in patient, the medical rehabilitation team also intervened in proper body positioning, general ROM exercise, gradual mobilization, and bed rotations. During the treatment, the patient's overall condition improved. After ten days of treatment, the headache and nausea had resolved, and the quadriparesis improved; then, the patient was discharged to home to complete 17 days of treatment.

DISCUSSION

Patients with HIV stage IV frequently develop toxoplasmosis cerebri, a disease of the central nervous system, especially those whose CD4 counts are below 100 cells/l. In Indonesia alone, the prevalence of cerebral toxoplasmosis in HIV patients grew from 39.6% in 2016 to 47% in 2017. The mortality of HIV-associated cerebral toxoplasmosis during hospitalization, with appropriate anti-toxoplasma treatment, may be up to 30%. These conditions could be happened by environmental factors such as poor production system practices, water treatment, hygiene, and culinary practices. Other than that, the obedience patients with toxoplasmosis to their treatments are considered low. These facts describe why the mortality of patients with toxoplasmosis still increased even in the appropriate treatments.[8,9]

The majority of cerebral toxoplasmosis cases are the result of latent *Toxoplasma gondii* infection reactivation. People with HIV have this reactivation frequently because of a weakened immune system in the body. The study by L. Liu *et al.* in 2017 that found that the seroprevalence ratio in HIV stage IV patients was greater than that in healthy proband controls, namely 46.12% compared to 36.56%, supports this.[8,9] Subacute onset of headaches, fever, decreased muscle strength, ataxia, cranial nerve palsy, and decreased consciousness to convulsions are some of the disease's clinical signs. Some of them may exhibit potentially fatal signs of encephalitis, including fever, positive meningeal signs, and elevated intracranial pressure.[8]

The patient in this study also experienced fever, headache, nausea, and vomiting along with limb weakness that they had been complaining about for three days before to admission. GCS, vital signs, general neurological, and meningeal symptoms are all examined during a physical examination of a patient with cerebral toxoplasmosis. With a compos mentis GCS of 15, the patient in this study presented as frail. Blood pressure, heart rate, and pulse all fell within normal ranges, but the patient's body temperature was feverish. The results of a general neurological examination showed that the superior and inferior extremities were feeble, while the muscles were more toned and their physiological responses were more active. Meningeal symptoms were discovered in the nuchal stiffness, however the Brudzinski I-IV test was negative.

The CD4 test, complete blood count, leukocyte count, CSF cytology, and anti-toxoplasma IgM and IgG serological testing are laboratory procedures that support the diagnosis. 8 The patient's CD4 level is 30 cells per liter, which is less than 100 cells per liter. IgG of a 4x titer is positive and IgM serological testing is negative. The patient in this investigation did not have a primary *T. gondii* infection, as evidenced by the lack of IgM antibodies. IgM antibodies are typically used to diagnose active toxoplasmosis, but in individuals with HIV/AIDS, almost all cases are reinfections, and IgM antibodies are produced at undetectable levels because of a weak immune response.

Lesions in the central nervous system can also be found using imaging techniques like a CT scan or an MRI. An MRI examination provides a higher sensitivity for identifying intracranial infections-related abnormalities. Hypodense or iso-dense lesions in the corticomedullary junction or basal

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ganglia, single or multiple, and post-contrast injection ring enhancement accompanied by surrounding perifocal edema are typical characteristics of cerebral toxoplasmosis lesions. In this instance, a non-contrast and contrast head CT of the patient revealed a cystic hypodense lesion in the right parietal lobe of the subcortical brain, measuring AP 1.9 × LL 1.4 x CC 1.8 cm, along with ring enhancement and surrounding perifocal edema.

The most effective treatments for cerebral toxoplasmosis are pyrimethamine, clindamycin, and folic acid. Pyrimethamine is used orally in acute instances as a loading dosage of 200 mg, followed by daily doses of 50–75 mg. In order to lessen the bone marrow suppression caused by pyrimethamine, clindamycin 600 mg was also given orally every six hours, and folic acid 10 mg was administered orally every day. There was a six-week maximum for the duration of the main therapy. Additionally, HIV patients are given 960 mg of co-trimoxazole orally daily to avoid additional opportunistic infections. In this instance, the patient was treated using the aforementioned regimen in conjunction with ARV medication (TDF, 3TC, EFC), and on the 17th day, because the findings of the clinical examination were remarkably stable, the patient continued to receive outpatient treatment.[10]

It is also necessary to do interdisciplinary, comprehensive management that includes physical and neurological rehabilitation. According to research done in 2016 by Ryan Mattie *et al*, appropriate body alignment, general ROM exercise, incremental bed mobility, and bed rest can improve patient outcomes by 60% and reduce the length of stay for patients.

Thus far, few studies have described the relationship between proposed risk factors and poor outcomes among HIV-infected patient with cerebral toxoplasmosis. A retrospective cohort study conducted by Sonneville *et al*., showed that CD4+ T-cell counts <25 cells/μL (OR = 2.7) was independently associated with poor outcomes (modified Rankin Scale score ≥ 2) at 3 months.[10] Another retrospective study by Libório *et al*. found that AKI (OR = 8.3) and hyponatremia (OR = 9.9) were independent risk factors for death in HIV-infected patient with toxoplasma encephalitis (TE).[11] In addition, the significant statistical *difference* in overall survival between the time from symptoms onset to presentation ≥ 15 days and < 15 days in survivors and non-survivors, also reinforce the benefits of timeous treatment.[8] Several risk factors were discovered in this patient, including symptoms that began three weeks prior to hospital admission, delayed admission and definitive treatment, hyponatremia, and a low CD4+ T cell count.

Non-adherence to ARV medication and prophylaxis, in addition to the previously stated risk factors, is a societal risk factor that can increase the prevalence of cerebral toxoplasmosis. According to Jose Ernesto Vidal's research, recurrence occurred in 30% of cases due to poor adherence to secondary prophylaxis with TMP-SMX.[12] The patient was lost to follow-up for two years and did not take medicine because the patient did not realize that ARV was covered by the government and the family was unwilling to seek treatment because the social perception of HIV patient remained unfavourable.

Serological tests are useful for surveillance and research, but they have limitations when utilized in clinical practice.[13] Low IgG avidity, for example, can be misinterpreted as the absence of infection, and the possibility of both positive IgM and low IgG avidity makes it difficult to discriminate between chronic and acute infections.[14] PCR was found to be the most helpful diagnostic tool in European multicentric study than serology.[15] In Indonesia, PCR diagnostic techniques are not yet available in all health facilities, and there is no health insurance policy that includes PCR costs.

CONCLUSION

We suggest that improved early diagnosis and treatment of HIV patient to prevent opportunistic infections including cerebral toxoplasmosis is needed, particularly in primary healthcare facilities in developing countries. Further studies are necessary to better understand the diagnosis and collaborative management of cerebral toxoplasmosis in HIV patient.

ACKNOWLEDGMENTS

Best gratitude to parents of patient that willing to take a history of their illness, and our teachers especially in the Internal Medicine Department, Faculty of Medicine, Universitas Diponegoro.

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DECLARATIONS

Informed consent was obtained from patient included in the study. The authors affirm that research participants provided informed consent.

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