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CASE REPORT

Diagnosis and Treatment of Tuberculous Meningoencephalitis and Toxoplasma Encephalitis in Positive HIV Patient: Case Report

Laporan Kasus : Diagnosis dan Tatalaksana Meningoensefalitis Tuberkulosis dan Ensefalitis Toksoplasma pada Pasien dengan HIV Positif

Della Septa[1], Yudhisman Imran[2], Ronny Yoesyanto Pragono[3]

[1] Internship of General Practitioner Program of Dr. Adjidarmo Hospital, Banten, Indonesia
[2] Neurology Department of Faculty of Medicine Trisakti University, Jakarta, Indonesia
[3] Neurology Department of dr. Mintohardjo Naval Hospital, Jakarta, Indonesia

yudhisman.imran @trisakti.ac.id

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ABSTRACT

Background

Tuberculous meningoencephalitis (TBME) and toxoplasma encephalitis (TE) are the most frequent cerebral opportunistic infections in positive HIV patients in developed countries. This study aims to determine a presumptive diagnosis of TBME and TE based only on clinical, CD4-count, and radiology features and to attend suitable early treatment for better patient outcomes.

Case Description

A 40-year-old presented to the emergency unit of dr. Mintohardjo Naval Hospital with decreased consciousness. History of positive HIV status, pulmonary tuberculosis for six months and anti-tubercular-treatment (ATT) drop-out. The GCS was E2M5V2, lung crackles, nuchal rigidity, positive Babinski reflex, and duplex hemiparesis. CD4-count: 4 cells/mm^3. Multiple hypodense lesions, "finger-like-oedema", featured on non-contrast head CT-scan. A lumbar puncture was not performed. Treatment of TBME included an ATT regimen, pyridoxine, cotrimoxazole, anti-oedema, and TE treatment included clindamycin and pyrimethamine. Based on the clinical and radiological diagnosis of TBME (nuchal rigidity, history of ATT drop-out, multiple hypodense lesions on CT-scan) and TE (altered mental status, duplex hemiparesis, CD4-count, "finger-like-oedema" projections on CT-scan), ATT and TE treatment were given for ten days. There were significant clinical improvements by GCS E4M6V3, negative nuchal rigidity after being treated early by ATT and TE treatment.

Conclusions

Presumptive Diagnosis of TBME and TE in HIV patients can be determined only based on clinical, CD4-count, and radiology examination. However, there are significant clinical improvements in giving ATT along with TE treatment immediately in positive HIV patients.

Keywords: tuberculous meningoencephalitis; toxoplasma encephalitis; HIV; ATT; TE treatment

ABSTRAK

Latar Belakang

Meningoensefalitis tuberkulosis (METB) dan toxoplasma encephalitis (TE) adalah infeksi oportunistik serebral yang paling sering terjadi pada pasien HIV positif di negara maju. Penelitian ini bertujuan untuk menentukan diagnosis suspek Meningoensefalitis tuberkulosis dan toxoplasma encep halitis berdasarkan fitur klinis, CD4-count dan gambaran radiologi. Hal ini bertujuan agar dapat diberikan pengobatan dini yang sesuai sehingga akan diperoleh hasil pengobatanyang lebih baik.

Deskripsi Kasus

Seorang laki laki berusia 40 tahun dibawa keluarganya ke unit gawat darurat Rumah Sakit Angkatan Laut Dr. Mintohardjo dengan penurunan kesadaran. Pasien memiliki riwayat status HIV positif, tuberkulosis paru selama enam bulan dan putus pengobatan anti-tubercular . Pada pemeriksaan fisik didapatkan GCS adalah E2M5V2, *lung crackles*, kakuk kuduk, refleks Babinski positif, dan hemiparesis dupleks. Hasil Pemeriksaan laboratorium CD4: 4 sel/mm3. CT-scan kepala non-kontras: multipel lesi hipodens, berbentuk " finger-like-oedema ", lumbal pungsi tidak dilakukan. Pasien diberikan pengobatan METB termasuk rejimen OAT, piridoksin, kotrimoksazol, anti-edema, dan pengobatan TE termasuk klindamisin dan pirimetamin. Berdasarkan diagnosis klinis dan radiologis TBME (kaku kuduk, riwayat OAT putus obat, multiple lesi hipodense pada CT-scan) dan TE (penurunan kesadaran, hemiparesis dupleks, CD4-count, proyeksi "finger-like-oedema" pada CT-scan). Pengobatan OAT dan toxoplasma encephalitis diberikan selama sepuluh hari. Didapatkan perbaikan klinis yang signifikan dalam perawatan, dan pengobatan pengobatan OAT dan TE lebih awal berupa GCS E4M6V3 dan kaku kuduk negatif.

Kesimpulan

Diagnosis Presumtif Meningoensefalitis Tuberculosa dan toxoplasma encephalitis pada pasien HIV dapat ditentukan berdasarkan pemeriksaan klinis, CD4-count, dan radiologi. Terdapat perbaikan klinis yang signifikan setelah pemberian OAT dan terapi TE lebih awal pada pasien HIV positif yang dicurigai METB dan TE.

Kata Kunci: meningoensefalitis tuberculosis; toxoplasma ensefalitis; OAT; pengobatan toxoplasma encephalitis

INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis in the central nervous system (CNS), with a 5–15% incidence worldwide.[1] If the brain parenchyma is involved, it becomes tuberculous meningoencephalitis (TBME). The major risk factors of TBM are malnutrition, diabetes mellitus, immunocompromised status, including long-term corticosteroid therapy use and patients with human immunodeficiency virus (HIV).[2,3] Tuberculous co-infection with HIV is associated with low CD4 counts as well as toxoplasma encephalitis (TE) .[4-6]

Toxoplasma encephalitis is another CNS infection that became one of the most common opportunistic infections that cause focal brain lesions in HIV patients with CD4 counts of 51-100 cells/mm^3 or less.[4,6] *Toxoplasma gondii* (*T.* gondii) is a protozoan parasite that is particularly the causative agent of toxoplasmosis. The prevalence of toxoplasma infection varies, such as in Nigeria, Tunisia, and South Brazil, above 50%.[4] Diagnosis of TBME and TE are challenging due to variegated clinical manifestations, as well as an invasive procedure to obtain convenient culture specimens.[4,7,8]

The current basic diagnosis of both TBME and TE is based on the typical clinical presentation, neuroimaging features, and analysis of cerebrospinal fluid (CSF) characteristics examination with or without confirmed by definitive microbiological culture; nevertheless, the diagnosis could be delayed by the long, uncertain period of the culture, and in some instances, lumbar puncture (LP) may induce brain herniation.[2,7] Misdiagnosis, delayed diagnosis and treatment of TBM and TE result in poor outcomes and increased mortality rate.[1] Therefore, this study aimed to assess a presumptive diagnosis of TBME and TE based on clinical manifestations, CD4 count and neuroradiological findings without measuring CSF analysis and bacteria culture to initiate prompt treatment to provide a better outcome.

CASE REPORT

A 40-year-old male presented to the emergency unit of Dr. Mintohardjo Naval Hospital with decreased consciousness since a week ago. History of recurrent headache, persistent cough, night sweats, and weight loss for three months. History of confirmed pulmonary tuberculosis and anti-tubercular-treatment (ATT) drop-out for five months. He was diagnosed human-immunodeficiency-virus (HIV) 3 years before this admission but has defaulted anti-retroviral-treatment (ARV) for two years.

On physical examination, the *Glasgow Coma Scale* (GCS) was E2M5V2, pale-looking and malnourished with bilateral lung crackles. He had nuchal rigidity, positive Brudzinski, positive Babinski reflex on both sides, and duplex hemiparesis. CD4-count: 4 cells/mm^3. Bilateral infiltrates suggested active tuberculosis on the chest radiograph. We performed a non-contrast head CT scan (Figure 1), multiple hypodense lesions suspected of tuberculomas, and a "finger-like-oedema" feature appeared.

We did not perform LP because of the risk of cerebral herniation provoked by cerebral oedema, toxoplasma and tuberculoma masses. Directly after he was diagnosed based on clinical and CT-scan examination, we began to initiate both TBME and TE treatment, including ATT regimen (isoniazid 300 mg/rifampicin 450 mg/pyrazinamide 1000 mg/ethambutol 1000 mg), cotrimoxazole 960 mg b.i.d for pneumocystis carinii pneumonia (PCP) prophylaxis, anti-oedema (dexamethasone 0.4 mg/kg/day intravenous), along with TE treatment clindamycin 600 mg and pyrimethamine (200 mg at the start, then 25 mg daily). Each day GCS was gradually improved, and we found significant clinical improvements by GCS E4M6V3, negative neck stiffness, Brudzinski, and Babinski reflex on the tenth day he was hospitalized. Treatment of TBME and TE was continued, and on day 14, he was discharged.

DISCUSSION

Several studies have mentioned that clinical manifestations are the most predictive value for TBM diagnosis, leading to improved diagnostic scoring systems.[2] Diagnosis occasionally entrusts clinical features, laboratory, and neuroimaging findings. However, diagnostic guidance for tuberculous meningitis has not been standardized worldwide, and numerous reports still adopt different case definitions. In this study, we were using Marais *et al.* criteria to diagnose TBM.[8]

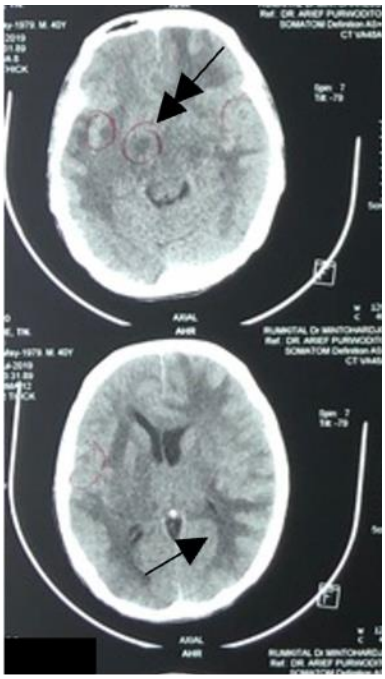

Figure 1. Axial non-contrast head CT scan: showed hypodense lesions in almost bilateral brain parenchyma causing sulci effacement, perilesional oedema "finger-like-oedema" appearances (arrow), and round multiple hypodense lesions in bilateral temporal cortical lobes suggested tuberculomas (double arrow).

A study by Marais *et al.* developed a case definition for TBM divided into three categories, definite, probable, and possible. Diagnosis is based on clinical criteria, CSF analysis, CNS biopsy, cerebral radiology, evidence of tuberculosis elsewhere and exclusion of other diagnoses. In our cases, we did not fulfil definite criteria because we did not perform a CSF culture or biopsy of the CNS system. However, we fulfilled the probable criteria only by the presence of clinical manifestations and neuroimaging features.[8] Their criteria helped us to diagnose this patient with clinical manifestations, scoring 6. Non-contrast head CT-scan result for multiple tuberculomas scored 2. Evidence of tuberculosis elsewhere included active tuberculosis on chest radiograph, and tuberculosis bacterial confirmed from GeneXpert scored 4. All scored 12. The number of points expected to diagnose probable tuberculous meningitis is≥12. In conclusion, this case is probably tuberculous meningitis. Therefore, we began the ATT regimen.

Neuroimaging has been a part of the assessment of TBM, with the sensitivity varying from 88 - 100%, while the specificity has a wider range of 69 - 97%.[9-12] Computerized tomography and magnetic resonance imaging (MRI) are both beneficial.[13] Head CT-scan is often used for differentiated TBM from another kind of meningitis, faster, more cost-effective, and more accessible than MRI, particularly in Indonesia.[4]

Basal areas meningeal enhancement such as prepontine cistern, basal cistern and tuberculomas are sensitive and specific for TBM.[9,10-12] Tuberculomas are represented as discrete or convalescing lesions, ring enhancement with an irregular thickness of the walls may appear solitary or multiple.[14] In TBM, meningeal pathology may spread into the cerebral parenchyma, cause encephalitis or vasculitis, lead to infarction or continue to end in vasogenic oedema.[15]

Therapy of TBM is based on the World Health Organization (WHO) regimens used for pulmonary tuberculosis. Antituberculosis therapy must be initiated directly after the diagnosis of TBM is considered.[2,16] Treatment, in this case, included the ATT regimen (isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1000 mg, ethambutol 1000 mg) and pyridoxine 50 mg. Isoniazid, rifampicin pyrazinamide and ethambutol for the first two months and isoniazid and rifampicin continue for the next ten months. However, extension and discontinuation of ATT are considered by the patient's condition and can be supported by evaluating a recent head CT scan.[17]

Intracerebral oedema is recognized as an essential consideration of TBM outcome.[2] Corticosteroids are used in HIV-negative people with TBM to reduce mortality. Although insufficient evidence to promote survival benefits in HIV-positive patients remains unclear.[10,17] In these circumstances, we provided corticosteroid: dexamethasone 0.4 mg/kg/day intravenous to resolve the vasogenic cerebral oedema and reduce the pressure inside the brain, lowering the risk of death.

Toxoplasmosis is the leading cause of focal neurological deficit in patients with HIV in developing countries. Vidal *et al.* study case description for cerebral toxoplasmosis divided into four categories, histology-confirmed by biopsy, laboratory-confirmed by LP (CSF nucleic acid amplification assays), probable case (clinical manifestations, neuroimaging features and responses of empirical anti-toxoplasma treatment) and possible case (single identification mass or multiple lesions by radiology, serum *T. gondii* immunoglobulin G (IgG) antibodies detected).[5,6]

The histology-confirmed and laboratory-confirmed cerebral toxoplasmosis is described as a definitive diagnosis. Probable cases associated with "presumptive" diagnosis in clinical practice, assuming the inessential use of histopathological inquiry and the inaccessibility of molecular diagnosis in low- or middle-income nations.[6] Typical CT-scan and MRI features in TE cases are several ring-enhancing lesions, perilesional oedema, oedema of surrounding white matter, or a "finger-like-oedema" which is also a common finding.[4,6,18,19] CT-scan sensitivity and specificity are >90%.[6,20]

In this case, we did not perform LP because of the risk of brain herniation due to cerebral oedema and intracranial masses. Although herniation after LP only occurred in 5% of patients in a study, it is contraindicated to perform LP if there is an intracranial space–occupying lesion with mass effect.[21,22] We also did not perform IgM and IgG antibodies test because of their unavailability, and it was not routinely tested in Indonesia. We relied on the CD4-count test that was far below 100 cells/ mm^3, classified as severely immunocompromised and indicated primary prophylaxis for cerebral toxoplasmosis.[6]

Although this patient was diagnosed with TE by presumptive diagnosis in clinical practice, furthermore LP and *T. gondii* immunoglobulin were not performed; one of the criteria to initiate empirical TE treatment is CD4-count <200 cells/mm^3 to lower the risk of neurological sequelae and mortality.[6,23-25] Therefore, with the high sensitivity and specificity of CT-scan imaging and CD4-count result, in this case, we initiated clindamycin 600 mg combined with pyrimethamine (200 mg at the start, then 25 mg daily), and folic acid to reduce hematopoietic toxicity of pyrimethamine as empirical TE treatment.[26,27] Afterward, the treatment should be evaluated within 10-14 days. If there was no clinical and radiological improvement, other diagnoses must be investigated.[4,6]

However, GCS gradually improved after being treated for ten days; we also found other significant clinical improvements. Those indicated the accurate diagnosis and early prompt treatment of TBME and TE in this case. Although we did not fulfil definite criteria of TBM, we started

the ATT regimen because of confirmed bacterial pulmonary tuberculosis and a high percentage of sensitivity and specificity of head CT-scan in TBME or TE. Unfortunately, we also did not fulfil the definite criteria of TE. Still, we initiated empirical treatment because of the criteria of the CD4-count cut-off. If there is confusion in diagnosing TE because of presumptive diagnosis, we still allow empirical TE treatment in a patient with HIV with a CD4 count <200 cells/mm^3.

CONCLUSION

Presumptive Diagnosis of TBME and TE in HIV patients can be determined only based on clinical, CD4-count, and radiology examination. However, there are significant clinical improvements in immediately giving ATT and TE treatment in positive HIV patients.

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AUTHORS CONTRIBUTION

All authors contributed to the preparation of this manuscript.

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CONFLICT OF INTEREST

There is no conflict of interest between the authors.

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