Multiple Intracranial Tuberculomas: Diagnosis Difficulties in a Clinical Case

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Abstract

Intracranial tuberculoma is the second most common manifestation of central nervous system (CNS) involvement in immunocompetent tuberculosis (TB) patients and the major cause of death and disability in developing countries due to diagnostic difficulties. Tuberculosis is the most common infectious cause of CNS space-occupying lesions (SOLs) in Indonesia. However, we should consider other infectious causes for the differential diagnosis of CNS SOLs. Clinical presentations, histopathological and microbiological findings of brain biopsy specimens may confirm intracranial tuberculoma diagnosis. We discuss a case of multiple intracranial tuberculomas in a 23-year-old female with diagnosis difficulties at the early stage of illness.

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1. Introduction

Tuberculosis (TB) is still a major health problem. Indonesia is one of the six countries that stand out as having the largest number of TB incidents in 2013, positioned in fifth place. The average mortality rate of TB cases in Indonesia is 25/100,000 population. Tuberculosis in human is the result of infection with organisms of the Mycobacterium tuberculosis complex, which includes M. tuberculosis, M. bovis or M. africanum, a slender rod-shaped acid-fast bacterium with very slow growth. Initial infection is usually via the respiratory tract, following inhalation of the organisms within tiny aerosol droplets, predominantly produced by adults with cavitary TB.

Tuberculosis involving structures other than lung parenchyma, or extra pulmonary tuberculosis (EPTB), may occur as a result of spread of the organisms to pleura or pericardium, by lympho-hematogenous, or mucosal spread. It is closely associated with weakened cellular immunity. In the USA, there were about 20% cases of EPTB among all TB notifications between 2001 and 2003. In developing countries, the reported prevalence varied from 5% to more than 35% in 2004 and increased significantly in the wake of the HIV epidemic. Central nervous system (CNS) TB only makes up some 5% of notified cases of EPTB in developed countries, but it is the most serious form of EPTB. It is a major cause of death and disability in developing countries due to diagnostic difficulties and lack of treatment facilities. About 10% of immunocompetent TB patients manifest CNS involvement. The most common form is tuberculous meningitis (about 70-80%), followed by intracranial tuberculoma, and spinal arachnoiditis (rare). Tuberculoma may still account for up to 50% of intracranial mass lesions in undeveloped countries. It is a granuloma (i.e., a focal aggregate of activated macrophages) formed by the inflammatory response to M. tuberculosis infection. Macrophages induced by T-lymphocytes engulf the bacilli and form giant cells. Caseous material containing a few bacilli may appear at the center, surrounded by gliosis and lymphocytic infiltration. These lesions are slow-growing with variable perifocal edema, variable in size (up to 3-4 cm) and mostly intraparenchymal. It may involve any part of the CNS, more common in the cerebral hemispheres. Intracranial tuberculomas can cause focal neurological defects and seizures.

2. Methods

A private hospital in Medan city, Indonesia accepted a 23-year-old female with the complaint of weakness of both lower extremities. The symptoms began three months before she came to the hospital and progressively worsened. Review of her medical record revealed a history of a generalized seizure with five minutes duration, without consciousness impairment. Clinical diagnosis for her condition at that time was neurocysticercosis and her physician gave her anti-seizure medications as symptomatic treatment. The patient also complained of a headache followed by blurred vision that began eight months before she came to the hospital. Her physician diagnosed her with cerebral toxoplasmosis.

Physical examination revealed a conscious patient with Glasgow coma scale (GCS) score of 15 (E4M6V5). Vital signs were normal. Exophthalmus (proptosis) was found on eye examination. Later there was deterioration in her neurological status, with GCS score of 13/15 (E3M6V4). The pupils were isocoric (four centimeters in diameter) with normal light reactions. Signs of increased intracranial pressure such as headache, projectile vomiting and seizure developed when her condition worsened. There were no meningeal and cerebellar signs. Motoric evaluations of both upper extremities were normal, but there were muscle strength reductions (grade 3/5) in them. There were no pathological reflexes and the sensory evaluation was normal. Her visual acuity was 1/60 (right) and 2/6 (left) with funduscopy showed papilledema. The rest of cranial nerves examination was unremarkable. The brain computed tomography (CT) scan showed supratentorial multiple space occupying lesions. There was no history of tuberculosis or human immunodeficiency virus (HIV) infection in her medical record. A biopsy of the mass was then performed by craniotomy and revealed the diagnosis. Grossly the biopsied tissue volume was three milliliters, consisting of an irregular white solid mass. Necrotic and hemorrhagic areas were found in the tissue.
Histopathological review of the mass demonstrated cerebral cortex tissue with multiple necrotizing granulomatous inflammation scattered throughout the tissue. The granuloma had a central caseous necrotic area surrounded by epithelioid histiocytes, Langhans giant cells, and lymphocytes. The epithelioid histiocytes contained single spindle shape nuclei with eosinophilic cytoplasm. The Langhans giant cells contained multiple nuclei with eosinophilic cytoplasm. The lymphocytes contained single basophilic nuclei with scanty cytoplasm. The surrounding brain tissue was gliotic. No malignancy process was found on the slides.

Fig. 2. Histopathological review of the mass, prepared using hematoxylin and eosin (H&E) stain. (A and B) Tumor consists of cerebral cortex tissue with multiple necrotizing granulomatous inflammation scattered throughout the tissue, 100x magnification; (C) The granuloma had a central caseous necrotic area surrounded by epithelioid histiocytes, Langhans giant cells, and lymphocytes, 200x magnification; (D) Langhans giant cells contain multiple nuclei with eosinophilic cytoplasm, 200x magnification.
Acid-fast stain of the mass by the Ziehl-Neelsen method showed only the tissue structures. There was no sign of acid-fast bacilli in the microscopic slide. Truant auramine-rhodamine acid-fast stain of the mass showed the cell structures and the tubercle bacilli. We were unable to obtain the fresh tissue for culture and instead, we obtained the paraffin embedded tissue for microscopic examination.

![Ziehl Neelsen staining](image1.png) ![Truant auramine-rhodamine staining](image2.png)

**Fig. 3.** (A and B) Ziehl Neelsen staining of the mass, 100x and 400x magnifications, respectively; (C and D) Truant auramine-rhodamine fluorochrome staining of the mass showed granuloma and tubercle bacilli, examined using WIG filter at 400x magnification and NIBA filter at 400x magnification, respectively.

### 3. Result and discussion

Indonesia is one of the TB endemic regions. Together with Bangladesh, China, India and Pakistan, Indonesia accounts for half of the new cases arising each year\(^6\). A prevalence survey found that lower detection of TB cases among women than men was most likely caused by lack of awareness, i.e., not knowing where to go for curative treatment and dependence on an accompanying person or a guardian\(^7\). The incidence rate is highest among young adults\(^6\). There is some evidence that young adult women (15–44 years) are more likely than men to develop active TB following infection\(^2,8\). In its endemic region, TB is the most common infectious cause of CNS space-occupying lesions in people with and without HIV\(^9\). The brain masses caused by TB are more often multiple\(^10\). Areas where blood flow is greatest are the chosen site of the tuberculous lesions. They can occur anywhere in the brain, though mainly in the cerebral or cerebellar hemispheres, and rarely in the brain stem and basal ganglia\(^11\). We report the case of a 23-year-old female with multiple intracranial tuberculomas in the cerebral hemispheres of supratentorial region.

The diagnosis of tuberculoma is often difficult. Up to two-thirds of patients will not have evidence of systemic TB and 50% of patients will have normal chest radiographs. Fever and signs of systemic infection are rare. Patients present with signs and symptoms of increased intracranial pressure or with focal neurologic deficits over months to years\(^5,11\). There was no evidence of systemic TB in this patient, otherwise we found headache, projectile vomiting and seizure that may indicate increased intracranial pressure. Complaints of bilateral weakness in the lower extremities and blurred vision may reveal a focal neurologic problem. A review of intracranial tuberculoma cases found that intracranial hypertension was the principal sign in 73% of patients, manifesting as headache and
papilloedema. She also showed papilledema on funduscopy. These findings guide to the conclusion that her clinical presentations are consistent with intracranial tuberculoma.

There is no imaging technique that can differentiate tuberculoma reliably from other intracranial mass lesions. A report states that 80% of the cases diagnosed by CT appearance alone were false positive. Magnetic resonance imaging (MRI) is commonly inconclusive in tuberculosis and may not distinguish it from a brain tumor, so the diagnosis is usually established through brain biopsy. In this case, brain CT scan alone was not sufficient to confirm the diagnosis of tuberculoma, therefore her surgeons performed an open brain biopsy to accommodate histopathological diagnosis of the accessible lesion. Stereotactic brain biopsy is a less invasive technique compared with open brain biopsy, but some surgeons still consider the latter as the selected method because stereotactic brain biopsy has a high chance of picking up non-diagnostic tissue. We obtained a white solid mass for examination after the brain biopsy.

Histopathologically, microscopic examination of tuberculomas shows the typical caseous necrosis with a granulomatous reaction that includes Langhans giant cells, lymphocytes, and fibrosis. With time, the lesions become fibrotic and calcified and it is difficult to demonstrate presence of \(M.\) tuberculosis. In this case, we found similar histopathological characteristics of tuberculomas (Fig. 2). Then, we subjected the biopsy tissue to Ziehl-Neelsen and truant auramine-rhodamine fluorochrome stainings (Fig. 3). Approximately 60% of tissue specimens from tuberculomas have shown acid-fast bacilli on smear. It is often difficult to identify the organisms from histopathological specimens. Therefore, a negative acid-fast stain does not completely exclude the diagnosis. Nontuberculous mycobacteria may also produce granulomatous inflammation, but the granulomas are typically poorly formed. In this patient, multiple necrotizing granulomatous inflammation was well formed. Caseating granulomas presentation and consistent cellular morphology is invariable and is thus the gold standard of diagnosis. Our findings were relevant for the diagnosis of intracranial tuberculoma, and exclude the differential diagnosis such as nontuberculous mycobacterial infection, neurocysticercosis, cerebral toxoplasmosis and CNS cryptococcosis at once.

Antituberculous chemotherapy has given surgical intervention a decreasing role in management of CNS tuberculomas. The use of high dose steroids to reduce symptoms of increased intracranial pressure is successful with no reported incidence of overwhelming tuberculous infection. Intracranial tuberculomas usually grow without permanently destroying the surrounding neural tissue, thus enabling a good clinical recovery. In a study, patients treated only medically tended to achieve better functional recoveries than those in whom surgical exploration preceded commencement of antituberculous chemotherapy. The prognosis of the patient in this case is poor because of a late diagnosis and she failed to get antituberculous chemotherapy in the early stage of infection. She had a craniotomy before the antituberculous chemotherapy that may carry some potential risks. The most significant risks during the procedure are intracranial hemorrhage, brain edema, and new focal neurologic deficits. Other risks include cerebral infarction, infection, and scarring with formation of an epileptic focus.

Many lesions leave no radiological traces following successful treatment. However, despite proper antituberculous therapy, physicians may occasionally observe newly developing or enlarging intracranial tuberculomas. By the degree of contrast enhancement on follow-up CT or MRI studies, physicians may judge the tuberculoma activity. Therefore, patients on antituberculous therapy who develop signs of intracranial pressure or new neurological signs should have urgent neuroimaging to exclude development of new lesions or enlargement of the existing granulomas.

4. Conclusions

Central nervous system TB is the most serious form of extrapulmonary TB, and it is the most common infectious cause of CNS space-occupying lesions in TB endemic region such as Indonesia. We report a case of multiple intracranial tuberculomas in the cerebral hemispheres of a 23-year-old female with delayed treatment because of diagnosis difficulties. Diagnosis was only confirmed after histopathological findings and auramine-rhodamine staining of her brain tissue obtained via a craniotomy with the possibilities of some risks during and/or after the surgical procedure.
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References