

Ischemic Stroke: A Complication of Tuberculous Meningitis

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Authors' contributions

This work was carried out in collaboration between all the authors. Author WG designed the study. Author MA managed the literature search and wrote the first draft of the manuscript. Author IL wrote the second draft with assistance from author DD. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

We report a case of a 45-year old Hispanic male who was diagnosed with tuberculous meningitis (TBM) presented to the emergency department (ED) with altered mental status, confusion, and violent behavior. Computed tomography (CT) scan of the head was normal and repeated lumbar puncture (LP) did not yield new findings. Magnetic resonance imaging (MRI) of head showed multiple ischemic infarcts. Non-tPA stroke protocol was followed and anti-TB medicines were continued. With continuous cardiac monitoring, echocardiogram (ECHO) was normal so arrhythmia was less likely. Soon he was more responsive and alert with no further episodes of agitation and behavioral changes. Then, he was able to walk with assistance and was discharged to acute rehabilitation facility.

Keywords: Tuberculous meningitis; stroke; aspirin; steroids.

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1. INTRODUCTION

Tuberculous meningitis (TBM) is a very severe form of tuberculosis, which affects not only meninges but also adjacent parenchyma of the brain [1,2]. Deep gray nuclei are also often involved, since tuberculous angiopathy mainly affects the perforating vessels [1]. TBM commonly causes subacute or chronic meningitis in developing countries, making up about 10% of all TB cases [3].

Stroke is a well-known complication of TBM, and is regarded as a complication of duration of TBM [4]. Several studies have observed that about 20% of TBM patients develop a stroke during the illness [4]. Infection represents 16% of first-ever ischemic strokes of unusual cause in a clinical series [5]. Vascular complications are more common in chronic meningitis than in acute meningitis. TBM duration may depend on clinical presentation; small vessel obstruction commonly occurs in the early phase of TBM causing monoplegia, while middle cerebral or internal carotid arterial infarcts usually occur in later stages causing hemi or quadriplegia [1,4]. Stroke caused by TB-associated vascular disease can result in higher mortality and morbidity rate, but the more progressive disease stages are associated with increased risk of stroke. Despite having stroke, TBM patients have attributes that are closely linked with stroke, including: polymorpho-nuclear leukocytosis in the cerebrospinal fluid (CSF); meningeal growth on computed tomography (CT); and the progressive stage of disease [3].

Common characteristics of tuberculosis patients include: having diabetes and coronary heart disease, living in the less urbanized areas, and having lower monthly income. The link between tuberculosis and coronary heart disease may be facilitated by diabetes, or chronic infections may take part in the pathophysiology of atherosclerosis and cardiovascular disease [6].

TBM-associated stroke is a serious complication, with high morbidity and mortality [7]. The purpose of this case report is to emphasize the rarity of TBM leading to ischemic strokes, since it is rarely seen today in immunocompetent adults in North America. In addition, this study highlights that TBM-associated stroke is difficult to diagnose early, and that proper treatment regimen is essential [8].

2. CASE REPORT

A 42-year-old Hispanic male came to the emergency department (ED) complaining of headache for one day. CT head was negative for hemorrhage, he was diagnosed of primary headache and was discharged to home with Tylenol. Three weeks later, he came back to the ED with continued generalized tonic clonic seizure, and was intubated and transferred to intensive care unit (ICU). He was extubated successfully on the second day. Video electroencephalogram (EEG) was normal, but on clinical suspicion, he was diagnosed with a new onset of seizure and discharged to home on Levetiracetam. However, five days later he returned to the ED with headache again. Headache was intermittent, 10/10 in intensity, in occipital region, two to three episodes per day, lasting for 30-60 minutes, associated with left facial numbness and left arm weakness for one day. Headache did not respond to any medications. Computed tomography (CT) head was normal. He developed fever of 101.6 Fahrenheit and also complained of photophobia. CSF analysis showed elevated white blood cells (WBC) of 515, high lymphocyte of 92, elevated protein of 233, increased lactic acid level of 9.9, and low-normal glucose of 45. Lymphoma and cerebrovascular accident (CVA) was ruled out through CT chest, abdomen and pelvis and MRI brain with/without IV contrast, which was also negative. Quantiferon tuberculosis (TB) test came out positive, and the patient was started on anti-TB meds (Isoniazid, Rifampin, Pyrazinamide, Levofloxacin, Vitamin B6 and Dexamethasone). Later, the acid-fast bacilli (AFB) culture came out positive for TB. During extensive workup, deep vein thrombosis (DVT) was found in the right common iliac and external iliac vein. Thus, low-molecular weight heparin was started and bridged with warfarin, until therapeutic INR was achieved. All hypercoagulable workup was negative and patient was discharged home with anti-TB medication and other home medication. After one week of discharge, his family brought him back to the ED with complaint of sudden onset of confusion and behavioral changes for one day. Patient was talking inappropriately, was agitated and violent, and also complained of weakness on the left side of his face. During admission, vitals were normal, he was alert and oriented to self only, but not oriented to time or place. No focal neurological deficit was seen, and power was 5/5 in all extremities. The patient's NIHSS score was not able to be assessed since he was severely

agitated and violent. However his modified Rankin scale score was 2. The patient was admitted with non-tissue plasminogen activator (non-TpA) stroke protocol, and was given aspirin, statin, and other home medication were continued. Repeat LP did not show any new findings, but MRI head showed acute infarction of the right aspect of the splenium of the corpus callosum with surrounding edema (Fig. 1). 2D Echocardiogram within normal limits and cardiology as there was a consideration for endocarditis. Endocarditis was ruled out as transesophageal echocardiography (TEE) and blood culture both were negative. After four days, the patient became more alert and oriented, with appropriate speech and no agitation. His sensation was intact, cranial nerve was intact, and all extremities had a power of 5/5. The patient was discharged to rehabilitation facility with ischemic stroke with TBM and continued all the home medications. He was followed for 6 weeks after discharge, in which he remained alert, oriented, with normal behavior and speech, and with no focal or residual deficit during examination.

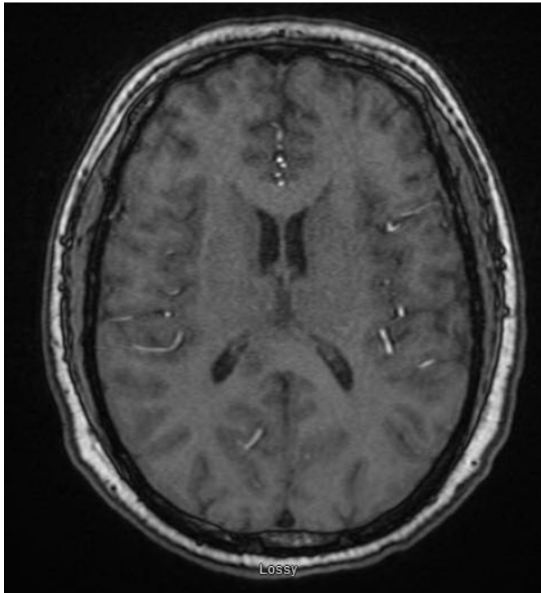


Fig. 1. MRI of brain without contrast
Arrow pointing at acute infarction of the right aspect of the splenium of the corpus callosum

3. DISCUSSION

Infarcts are one of the common imaging defects of TBM. Infarcts can either be asymptomatic or symptomatic. Symptomatic strokes in TBM

usually have dense hemiplegia. TBM patients with infarcts are reported to be three times more fatal than patients without infarcts [9]. The vasculopathy takes place in the vessels crossing the pool of exudate [1]. Cerebral infarction after infection commonly occurs in chronic meningitis, both in the acute and advanced stages of treatment [7].

Since TBM-related stroke is rare and has undefined clinical signs, it is difficult for developing countries to diagnose it in the clinic, and therefore treatment is delayed [10,11]. Other reasons why stroke may also be difficult to diagnose in TBM patients include: 1) the stroke is in a silent part of the brain, 2) the patient is heavily comatose to notify or display signs or symptoms 3) the preexisting weakness due to other lesions may obstruct the clinical picture [3,4]. Several studies show significant connections between long physician delay and poor outcome, and between physician delay and progression of stage during hospital stay [10]. Similarly in this case, there was a prolonged delay for TBM diagnosis, which led to patient returning to the hospital with a stroke.

TBM clinical image and outcome are regulated by basal exudates, tuberculoma, hydrocephalus, vasculitis, and stroke. Small and medium vessels crossing the basal exudates may show vasculitis, which causes strokes [3,12]. Vasculitis and/or intimal proliferation cause stroke in TBM, with or without overlying thrombosis or spasm [6]. In an autopsy study on TBM, vasculitis was reported in 41% [2,13]. Vasculitis in TBM can cause strokes usually located in the basal ganglia, in the middle cerebral arterial territory, resulting in full or partial vascular obstruction [9]. TBM usually causes ischemic stroke but hardly forms hemorrhagic infarcts that are linked to arterial and venous thrombosis [1,9,8].

There are several mechanisms involved in formation of cerebral infarctions in chronic meningitis, including: (i) vessels pass the exudates at the base of the brain, causing vessel suffocation and vasculitis formation with inflammation, spasms, constriction, and ultimately thrombosis; (ii) meningeal inflammatory exudate includes the adventitia which progressively spreads to the entire vessel wall, causing necrotizing panarteritis with secondary thrombosis and obstruction, and (iii) expanded ventricles stretching the affected vessel and forming a stroke [1,8,9].

The mechanism of TBM-associated stroke involves bacilli entering the subarachnoid space through initial subcortical or meningeal focus. The bacilli then activates a local T-cell-dependent response causing caseating granulomatous inflammatory exudate, which impacts the basal cisterns [8]. The exudate can result in hydrocephalus by various factors including blockage of CSF egress, absorption by exudates, and the damage of high protein level absorption [8]. Hydrocephalus can stretch affected vessels, leading to further ischemia [7]. The exudate can also impact efferent cranial nerves causing recurrent CN palsies, and suffocate the vessels crossing CSF, resulting in obliterative vasculitis and cerebral infarction. Cerebral infarctions in TBM are found to occur primarily in the "TB zone," which comprises of the heads of the caudate nuclei, the anteromedial thalami, the anterior limbs of the internal capsule, and the genua of the internal capsules. This zone is supplied by the medial striate, thalamo-tuberal, and thalamo-perforating arteries. Since these are medial arteries in the circle of Willis, the inflammatory basal exudate of TBM may impact medial areas more severely than lateral areas. MRI angiography can show a triad of a hydrocephalic pattern, arteries thinning at the base of the brain, and thin or blocked small-sized arteries with early draining veins [8].

Infections by *Mycobacterium tuberculosis* cause stimulation of a constant inflammatory response that initiates a chain of cytokines and chemokines. Inflammatory response is known to be pathogenic in the association between infection and atherosclerosis, and may be linked to endothelial dysfunction caused by bacterial endotoxins and cytokines. Increased C-reactive protein, a marker of systemic inflammation along with active tuberculosis, may also be linked to atherosclerosis and result in cardiovascular events [6].

Ischemic association with TBM has been studied in several ways including angiography, computed tomography (CT), color Doppler, and magnetic resonance imaging (MRI). CT scan studies show infarctions in 17% to 63% of patients. In a CT scan study, the strokes were in the TB zone in 75% of patients, which included the head of caudate anteromedial thalami, anterior limb and genu of internal capsule because of medial striate, thalamotuberal, and thalamoperforate artery involvement. Using MRI, infarctions were observed in 10 of 20 patients with TBM, with distribution of vascular involvement [13].

Compared to CT, MRI shows more hemorrhagic and non-hemorrhagic infarcts, meningeal development and granulomas [12].

There is no specific treatment of stroke in TBM. Patients are usually treated with standard anti-tubercular therapy with symptomatic and supportive treatments. Most studies recommend a total of 12 months of treatment, including intensive quadri-therapy for 2 months followed by biotherapy for 10 months [9]. The drug aspirin has antiplatelet, anti-aggregate, anti-inflammatory and antioxidant properties used to prevent ischemic stroke [4]. Aspirin causes gastrointestinal toxicity, gastric hemorrhage, thrombocytopenia and allergy, which results in slightly smaller strokes and greatly reduced 3-month mortality [2]. Despite the increased rate of stroke in TBM, the mechanism by which aspirin prevents stroke has not been studied [2]. In a randomized placebo controlled trial on 118 patients with TBM, aspirin caused absolute risk reduction of stroke by 19.1%, resulting in greatly reduced mortality compared to placebo [4]. One patient was administered aspirin 100 mg per day starting 48 h after stroke [3].

Adjunctive therapy by steroids (a dose of dexamethasone 0.6 mg / kg / d for 4 weeks, with a reducing course over 4 weeks) has also been proposed to improve the outcome of HIV-1 negative children and adults with TBM. Dexamethasone has an anti-inflammatory effect and may positively affect the outcome of TBM [4]. In a recent observational study, corticosteroids were proposed to be used routinely in TBM since it greatly reduces death, and inactivated residual neurological deficit in survivors. This study observed that corticosteroids may affect outcome of TBM by decreasing hydrocephalus and inhibiting infarction [1]. Previously in a large randomized study, adjunctive treatment with dexamethasone enhanced survival in adult patients with TBM [7].

Anti-tuberculosis treatment prevents death or disability in less than 50% of the patients [9]. In a retrospective review of 175 patients with giant cell arteritis, stroke occurred in 3% patients with aspirin compared to 93% without, despite both groups receiving corticosteroids [9]. However, anti-tuberculous chemotherapy and corticosteroids were proposed to be ineffective in blocking cerebrovascular complications since three patients had stroke despite administration of these drugs [9]. The effects of steroids on preventing cerebral infarction remain

controversial, while some suggest that it may be beneficial for patients with severe disease [2]. While it is accepted that steroids lower cerebral edema and inflammatory exudates and prevent spinal block, the role in inhibiting cerebral infarcts after vasculitis is questioned. It is still not clear that steroids are associated with any prolonged benefit [7].

Prospective cases of this nature should be collected. Further studies should be done on the possible link between TBM-associated stroke and the synergistic effect of tuberculosis and smoking on vessel pathology [6]. In addition, evaluating recent developments on the molecular mechanisms of vascular injury may aid in fully understanding the mechanism of stroke in TBM. Other prospective studies should be done on: the association between established risk factors (i.e., genetic markers); new imaging techniques (i.e., MRI, MRA, SPECT, PET) to understanding changes in structure and function of stroke in TBM; development of therapeutic and preventive approaches for tubercular vasculitis; the role of antiplatelets (i.e., aspirin) in TBM; and, recent findings which associates higher rate of stroke among TBM patients with HIV infection, especially in low TB endemic countries [3,4].

4. CONCLUSION

This is a case of a 45-year old Hispanic male who was diagnosed with tuberculous meningitis associated with multiple ischemic infarcts. After six weeks, the patient recovered completely to normal baseline functional status. In summary, aspirin is known to slightly reduce strokes and significantly reduce 3-month mortality, and be more effective than anti-tuberculous therapy and corticosteroids in blocking cerebrovascular complications in TBM patients. Altered mental status, behavioral change, focal findings (i.e., speech difficulty, paralysis of limbs), and gait change could be a sign of stroke in TBM. Prompt chest radiography should be done in for all TBM patients. Clearly, there is a link between prolonged physician delay and poor outcome and progression of stage. Early recognition and empiric therapy of TBM may inhibit other complications. Early diagnosis and quick treatment before progression of stage is crucial for the outcome of TBM [7,8,11].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Singh B, Garg RK, Singh MK, et al. Computed tomography angiography in patients with tuberculous meningitis. *J Infect.* 2012;64:565-72.
2. Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: A randomized open label placebo controlled trial. *J Neur Sci.* 2010;293:12-7.
3. Pasticci MB, Paciaroni M, Floridi P, et al. Stroke in patients with tuberculous meningitis in a low TB endemic country: An increasing medical emergency? *New Microbiologica.* 2013;36:193-8.
4. Misra UK, Kalita J, Maurya PK. Stroke in tuberculous meningitis. *J Neur Sci.* 2011; 303:22-30.
5. Arboix A, Bechich S, Oliveres M, et al. Ischemic stroke of unusual cause: Clinical features, etiology, and outcome. *Eur J Neurol.* 2001;8:133-9.
6. Sheu J, Chiou H, Kang J, et al. Tuberculosis and the risk of ischemic stroke a 3-year follow-up study. *Stroke.* 2010;41:244-9.
7. Lan SH, Chang WN, Lu CH, et al. Cerebral infarction in chronic meningitis: A comparison of tuberculous meningitis and cryptococcal meningitis. *Q J Me.* 2001;94: 247-53.
8. Belorgey L, Lalani I, Zakaria A, et al. Ischemic stroke in the setting of tuberculous meningitis. *J Neuroimaging.* 2006;16:364-6.
9. Anuradha HK, Garg RK, Agarwal A, et al. Predictors of stroke in patients of tuberculous meningitis and its effect on the outcome. *J Med.* 2010;103:671-8.
10. Deiva K, Sothratanak S, Husson B, et al. Febrile brain stroke and tuberculous meningitis: Persisting threat in non-endemic countries. *Neuropediatrics.* 2010; 41:273-5.

11. Sheu J, Yuan R, Yang C. Predictors for outcome and treatment delay in patients with tuberculous meningitis. *Amer J Med Sci.* 2009;338.
12. Shukla R, Abbas A, Kumar P, et al. Evaluation of cerebral infarction in tuberculous meningitis by diffusion weighted imaging. *J Infect.* 2008;57:298-306.
13. Kalita J, Misra UK, Nair PP. Predictors of stroke and its significance in the outcome of tuberculous meningitis. *J Stroke Cerebro Dis.* 2009;18:251-8.

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