American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e932852
DOI: 10.12659/AJCR.932852

Received: 2021.04.23
Accepted: 2021.05.19
Available online: 2021.06.01
Published: 2021.07.10

# Diagnostic and Treatment Challenges in Cerebral Tuberculoma in a Patient with Morbid Obesity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Qi Ying Wong
ABCDEFG 1 Andy Sing Ong Tang
ABCDEF 1 Wei Huei Loh
BDEF 2 Xin Min Yong
BEG 1 Desmond Samuel
ACDEF 3 Wan Chung Law
ACDEF 4 Hock Hin Chua

1 Department of Internal Medicine, Miri General Hospital, Ministry of Health Malaysia, Miri, Sarawak, Malaysia
2 Department of Radiology, Miri General Hospital, Ministry of Health Malaysia, Miri, Sarawak, Malaysia
3 Neurology Unit, Department of Internal Medicine, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia
4 Infectious Disease Unit, Department of Internal Medicine, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia

**Corresponding Author:** Wong Qi Ying, e-mail: wong_qy89@hotmail.com
**Conflict of interest:** None declared

**Patient:** Female, 26-year-old
**Final Diagnosis:** Cerebral tuberculoma
**Symptoms:** Abdomen distension • cough • fever • loss of appetite • loss of weight
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Infectious Diseases

**Objective:** Challenging differential diagnosis

**Background:** Tuberculosis is prevalent, especially in low-income countries. The most devastating manifestation of tuberculosis is central nervous system (CNS) involvement, albeit rare.

**Case Report:** We report a rare case of a 26-year-old woman with morbid obesity and hepatitis C who had cerebral tuberculoma and was treated with an extended duration of anti-tuberculosis multi-drug therapy. This patient was initially diagnosed with disseminated tuberculosis of the lungs, liver, and peritoneum. After 4 months of anti-tuberculosis treatment, she developed new right temporal hemianopia and new cerebral tuberculoma, which was identified on repeated magnetic resonance imaging (MRI) and was attributed to tuberculosis-immune reconstitution inflammatory syndrome. The anti-tuberculosis treatment was continued; however, she gained large amounts of weight, which resulted in the failure of the anti-tuberculosis treatment of the cerebral tuberculoma. We decided to adjust the anti-tuberculosis drug dosage using her total body weight, and she responded well, with a decrease in size of the cerebral tuberculoma. The anti-tuberculosis treatment was subsequently stopped after 3 years because of clinical and imaging improvement.

**Conclusions:** This case illustrates the challenges faced in the treatment of cerebral tuberculoma, which, in this case, included a high body mass index affecting drug dosage and confounding an inadequate treatment response as seen on interim MRI, resulting in prolonged duration of anti-tuberculosis treatment. Persistent enhancement seen on brain MRI does not equate to treatment failure.

**Keywords:** Infectious Disease Medicine • Obesity • Tuberculoma • Tuberculoma, Intracranial

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/932852







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## Background

Tuberculosis is prevalent, especially in low-income countries. The most devastating manifestation of tuberculosis is central nervous system involvement, albeit rare. The diagnosis of tuberculoma is challenging despite the vast developments in current laboratory and imaging modalities [1]. We report the case of a patient with morbid obesity and disseminated tuberculosis of the lungs, liver, and peritoneum, and cerebral tuberculoma. There is a lack of published data reporting cases of tuberculosis treatment in patients with morbid obesity, with only 2 similar case reports in the literature [2,3].

## Case Report

A 26-year-old woman with newly diagnosed Child-Pugh class A hepatitis C presented with low-grade fever, productive cough, abdominal distension, and loss of weight and appetite for 2 months. On examination, she appeared alert with stable hemodynamic parameters. There was non-tender shifting dullness on abdominal examination, and other systemic examinations were unremarkable.

Laboratory investigations showed a normal complete blood count and renal profile, with mild transaminitis and albumin level of 26 g/L. The results of diagnostic peritoneocentesis showed a low serum ascites albumin gradient of 0.6 g/dL, with no evidence of infection or malignancy. Owing to suspicious chest X-ray findings, a computed tomography (CT) scan was performed and showed multiple miliary nodules in the lungs, with liver and kidney micro-abscesses. A sputum GeneXpert assay detected the presence of *Mycobacterium tuberculosis*, with no resistance to rifampicin. Other infective screenings were negative, including blood, sputum, and peritoneal fluid cultures, melioidosis serology, peritoneal fluid, and sputum acid-fast bacilli and *Mycobacterium tuberculosis* cultures. A final diagnosis of disseminated tuberculosis was made and the World Health Organization (WHO) category I anti-tuberculosis treatment was commenced, resulting in clinical and radiological improvement.

However, 4 months into treatment, the patient developed new-onset right temporal hemianopia, which progressively worsened. Urgent brain magnetic resonance imaging (MRI) showed caseating tuberculomas with optochiasmatic arachnoiditis (**Figure 1A-1C**). Cerebrospinal fluid analysis, including bacterial and fungal cultures, cytology, and tuberculosis work-up, was noncontributory. We decided to continue the anti-tuberculosis maintenance treatment (a fixed-dose combination of rifampicin and isoniazid) for 18 months. Her hemianopia improved gradually; however, a repeat MRI revealed an inadequate treatment response, with a residual lesion and perilesional edema (**Figure 1D**).

The patient had a drastic weight gain (from 67 kg to 110 kg) throughout the maintenance phase. Considering the procedure risks and related perioperative morbidity and mortality, the patient refused a diagnostic brain biopsy. We attributed the unsatisfactory treatment response to the possible underdosing of the anti-tuberculosis agent, decided to adjust the anti-tuberculosis treatment dosage based on the patient's total body weight, and added pyrazinamide into the regimen, which comprised rifampicin (9.6 mg/kg), isoniazid (4.6 mg/kg), pyrazinamide (18.2 mg/kg), and pyridoxine 50 mg once daily, owing to the higher dose of isoniazid. This regimen was given for 2 months, followed by another 16 months of isoniazid and rifampicin maintenance, with directly observed short-course supervision to ensure patient compliance. We conducted close monitoring of the patient's liver function tests, and no adverse events were observed. Serial brain imaging showed significant improvement. After cessation of treatment, the patient was followed up closely for 12 months. She had minimal residual right temporal hemianopia, which did not interfere with her daily life activities. A repeat MRI 1 year after treatment completion showed a stable lesion (**Figure 1E**).

## Discussion

The cornerstone in treatment of disseminated tuberculosis and cerebral tuberculoma is anti-tuberculosis drugs with or without surgical intervention. Our patient's clinical and radiological findings were highly suggestive of tuberculosis. Owing to the high prevalence of tuberculosis in our region, we decided against performing a brain biopsy, which is indicated in events of uncertain diagnosis or failed medical therapy [4].

Our patient had co-existing hepatitis C with grade 2 transaminitis, even before the commencement of anti-tuberculosis treatment. Her liver function remained stable throughout treatment, consistent with the fact that anti-tuberculosis treatment can be safely given in patients with liver disease [5]. Hepatitis C treatment was deferred in our patient owing to the concern of a drug-drug interaction and possible worsening hepatotoxicity [6].

Tuberculosis immune reconstitution inflammatory syndrome (IRIS), found in HIV-infected and uninfected individuals, results from a heightened inflammatory response, secondary to the reversal of immunosuppression by anti-tuberculosis treatment. This usually develops around 3 months after the initiation of anti-tuberculosis treatment, with a higher incidence in disseminated or extrapulmonary tuberculosis because of a higher bacillary load [7]. Two types of tuberculosis IRIS have been identified, paradoxical and unmasking. Paradoxical tuberculosis IRIS is defined by the worsening of pre-existing disease status or the emergence of new lesions in patients





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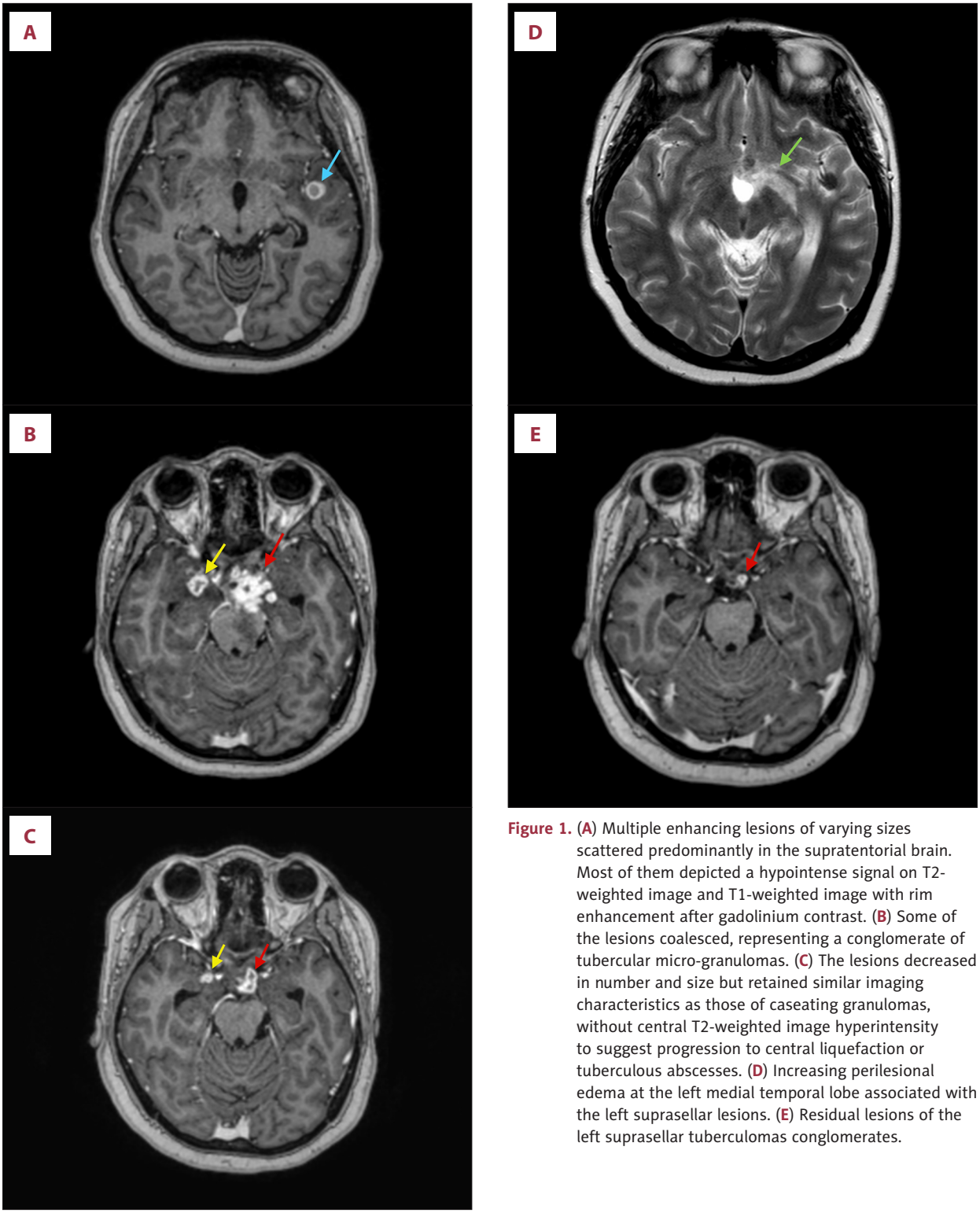


**Figure 1.** (**A**) Multiple enhancing lesions of varying sizes scattered predominantly in the supratentorial brain. Most of them depicted a hypointense signal on T2-weighted image and T1-weighted image with rim enhancement after gadolinium contrast. (**B**) Some of the lesions coalesced, representing a conglomerate of tubercular micro-granulomas. (**C**) The lesions decreased in number and size but retained similar imaging characteristics as those of caseating granulomas, without central T2-weighted image hyperintensity to suggest progression to central liquefaction or tuberculous abscesses. (**D**) Increasing perilesional edema at the left medial temporal lobe associated with the left suprasellar lesions. (**E**) Residual lesions of the left suprasellar tuberculomas conglomerates.





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who initially responded to anti-tuberculosis treatment, and it is not due to unsuccessful treatment or a new disease [8]. Similarly, in our patient, the cerebral tuberculoma developed after several months of treatment, with a new onset of hemianopia, likely attributable to paradoxical tuberculosis IRIS, as a consequence of a high mycobacterial antigen load released from the rapid killing of mycobacteria [8]. Diagnosis is mainly clinical, as there is no specific diagnostic tool for tuberculosis IRIS. The recommended therapy is to continue with the anti-tuberculosis treatment, and clinical improvements are generally seen 2 months into treatment [7].

Obesity affects the pharmacokinetics and pharmacodynamics of drugs by impairing drug binding to albumin, increasing cytochrome P450 2E1 activity, and increasing phase II conjugation activity [8]. Our patient had morbid obesity, with a body mass index (BMI) of 43 kg/m$^2$. The American Thoracic Society/Center for Disease Control and Prevention/Infectious Diseases Society of America tuberculosis treatment guideline advocates the use of the ideal body weight for calculating anti-tuberculosis treatment dosages [10]. Similarly, the WHO proposes capping the rifampicin and isoniazid dosages at 600 mg and 300 mg, respectively [11]. These recommendations can subject patients with obesity to underdosing, which can lead to treatment failure, as evidenced in our case. Total body weight, in contrast, is recommended by others and potentially has more adverse effects [2]. The use of a fixed-dose combination is challenging in patients with obesity because dose individualization is difficult. One case report describes a man with a weight of 92 kg and a BMI of 28.4 kg/m$^2$ who was prescribed the maximum dose of the fixed-dose combination, which resulted in treatment failure. Therapeutic drug monitoring that was done found the drugs were at subtherapeutic concentrations [2]. In the present case, owing to an inadequate initial response, the anti-tuberculosis treatment dosage was readjusted based on our patient's total body weight, with single-drug formulations, which resulted in a remarkable treatment response after 18 months, without significant adverse reactions.

Some experts suggest continuing treatment until the radiological resolution of enhancing lesions [12]. However, this practice can unnecessarily expose patients to the prolonged duration of potentially toxic drugs [13]. Most researchers did not agree that persistent enhancement seen on brain MRI beyond 18 months equates to treatment failure; thus, the extended duration of anti-tuberculosis treatment was not justifiable [14]. In our case, anti-tuberculosis treatment was initially continued because of residual perilesional edema and was subsequently stopped after a total of 3 treatments upon improvement of the lesions on MRI. There is a dire need for future prospective clinical trials to generate evidence-based guidelines with regards to the duration of treatment for patients with intracranial tuberculomas.

Our patient's initial MRI study showed multiple enhancing lesions of varying sizes, scattered predominantly in the supratentorial brain. Most of them depicted a hypointense signal on T2-weighted and T1-weighted images, with rim enhancement after gadolinium contrast (**Figure 1A**), suggestive of caseating granulomas with solid centers [15]. Some of the lesions coalesced, representing a conglomerate of tubercular micro-granulomas (**Figure 1B**), which parenchymal tuberculomas have the propensity to form [15]. The absence of pachymeningeal or leptomeningeal enhancement in the present case signified no concurrent meningitis. On subsequent MRI (**Figure 1C**), apart from decreasing in number and size, the lesions retained similar imaging characteristics as those of caseating granulomas, without central T2-weighted image hyperintensity to suggest the progression to central liquefaction or tuberculous abscesses. However, there was increasing perilesional edema at the left medial temporal lobe, associated with the left suprasellar lesions, hence anti-tuberculosis treatment was escalated (**Figure 1D**). A few subsequent follow-up studies showed improvement of disease, and the most recent MRI (about 3 years after the initial study) demonstrated residual lesions of the left suprasellar tuberculoma conglomerates (**Figure 1E**). The good response to anti-tuberculosis treatment on follow-up studies in the present case supports the diagnosis of parenchymal tuberculosis. However, there are broad differential diagnoses for rim-enhancing lesions, including toxoplasmosis, neurocysticercosis, pyogenic abscess, metastasis, and lymphoma of the central nervous system [15].

## Conclusions

Our case highlighted the dilemma posed in managing patients with morbid obesity with cerebral tuberculoma. There is no definite guideline on the dosing of anti-tuberculosis drugs for patients with obesity. Persistent enhancement after anti-tuberculosis treatment makes deciding the appropriate duration of therapy difficult. Clinical trials comparing the standard duration versus the imaging-guided duration of anti-tuberculosis would be ideal. Studies on appropriate weight-based dosing of anti-tuberculosis treatment for patients with obesity will be beneficial to clinicians managing such patients in real-world practice.

### Acknowledgements

The authors would like to thank the Director General of Health Malaysia and Clinical Research Center (CRC) Miri Hospital for the permission to publish this paper.

### Conflicts of Interest

None.





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### Ethical Approval

This article contains studies with human participants and was registered via the National Medical Research Register Malaysia with research ID no. NMRR-21-189-58632.

### Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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