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(CASE REPORT)

When Tuberculosis Strikes Twice: Cerebral Tuberculoma as a paradoxical reaction during antituberculous therapy in an immunocompetent patient: A case report

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Abstract

Cerebral tuberculoma is an uncommon manifestation of central nervous system tuberculosis (CNS-TB) and may develop as a paradoxical reaction during antituberculous therapy, even in immunocompetent individuals. Its clinical and radiological presentation poses a significant diagnostic challenge because it closely mimics other intracranial space-occupying lesions. We report the case of a 36-year-old immunocompetent man with pulmonary tuberculosis confirmed by Xpert MTB/RIF, demonstrating rifampicin susceptibility. Human immunodeficiency virus (HIV) infection and diabetes mellitus were excluded. Two months after initiating standard first-line antituberculous therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE), he developed progressive headache and left-sided hemiparesis. Brain computed tomography revealed two ring-enhancing lesions in the right frontoparietal region associated with marked vasogenic edema, consistent with cerebral tuberculomas. Cerebrospinal fluid analysis, including Xpert MTB/RIF testing, was negative for tuberculous meningitis. Toxoplasmosis, primary central nervous system lymphoma, and other infectious and neoplastic etiologies were excluded through comprehensive clinical, microbiological, and radiological evaluation. Given the high suspicion of a paradoxical inflammatory reaction, antituberculous therapy was continued without modification, and adjunctive dexamethasone was initiated, resulting in progressive neurological recovery without the need for neurosurgical intervention. This case highlights the importance of recognizing paradoxical reactions as a cause of newly developed intracranial lesions during otherwise effective antituberculous treatment. The integration of clinical, microbiological, and neuroimaging findings, together with the systematic exclusion of alternative diagnoses, allowed an accurate diagnosis and prevented unnecessary modifications to antimicrobial therapy. Early recognition of this entity may improve neurological outcomes and optimize the management of patients with central nervous system tuberculosis.

Keywords: Tuberculosis; Cerebral tuberculoma; Paradoxical reaction; Central nervous system tuberculosis; Antituberculous therapy; Case report

1. Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading infectious causes of morbidity and mortality worldwide. Despite substantial advances in molecular diagnostics, standardized treatment regimens, and global TB control strategies, the disease continues to represent a major public health challenge, particularly in low- and middle-income countries. According to the World Health Organization (WHO), more than 10 million new cases of

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tuberculosis and over one million deaths were estimated worldwide in 2024, reaffirming TB as one of the leading causes of death from a single infectious agent. Persistent socioeconomic disparities, increasing antimicrobial resistance, unequal access to healthcare services, and HIV coinfection continue to hinder progress toward the WHO End TB Strategy, which aims to dramatically reduce TB incidence and mortality by 2035. (1)

Central nervous system tuberculosis (CNS-TB) represents one of the most severe forms of extrapulmonary tuberculosis because of its high mortality rate and the substantial risk of permanent neurological sequelae. CNS-TB encompasses a spectrum of clinical entities, including tuberculous meningitis, cerebral tuberculomas, tuberculous brain abscesses, and spinal arachnoiditis. Among these manifestations, cerebral tuberculoma is characterized as a focal granulomatous lesion resulting from hematogenous dissemination of M. tuberculosis followed by a host immune response that produces central caseous necrosis surrounded by inflammatory tissue and a fibrous capsule. Although solitary lesions are common, multiple tuberculomas occur in approximately one-third of patients and predominantly involve the corticomedullary junction because of its rich vascular supply. (2, 3)

The clinical presentation of cerebral tuberculomas is highly variable and largely depends on lesion size, number, anatomical location, and the extent of surrounding vasogenic edema. Patients may present with progressive headache, seizures, focal neurological deficits, cognitive impairment, signs of increased intracranial pressure, or altered consciousness. On neuroimaging, particularly contrast-enhanced magnetic resonance imaging (MRI), tuberculomas typically appear as ring-enhancing or nodular lesions associated with vasogenic edema and, in some cases, significant mass effect. However, these imaging characteristics are not pathognomonic and overlap with numerous intracranial disorders, including cerebral toxoplasmosis, neurocysticercosis, pyogenic brain abscess, metastatic tumors, primary central nervous system lymphoma, and other granulomatous diseases. Consequently, epidemiological context, microbiological findings, and therapeutic response play a pivotal role in establishing the correct diagnosis. (4, 5)

A particularly challenging manifestation is the paradoxical reaction, defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in patients receiving appropriate antituberculous therapy after an initial period of clinical improvement. Before establishing this diagnosis, alternative causes of treatment failure—including poor adherence, drug resistance, medication toxicity, opportunistic infections, and alternative diagnoses—must be carefully excluded. Paradoxical reactions usually occur within the first weeks to months of therapy and are currently believed to result from an exaggerated host inflammatory response triggered by the release of mycobacterial antigens during bacillary destruction, a mechanism analogous to immune reconstitution inflammatory syndrome (IRIS) described in HIV-infected individuals. (6, 7)

Although paradoxical reactions have been extensively reported among patients with HIV following initiation of antiretroviral therapy, increasing evidence indicates that they may also occur in immunocompetent individuals. Clinical series have demonstrated that approximately 6% to 29% of patients with CNS tuberculosis experience paradoxical clinical deterioration, while longitudinal neuroimaging studies have reported an even higher incidence of newly developed or enlarging cerebral tuberculomas during treatment. Recognizing this phenomenon is crucial because the appearance of new intracranial lesions during otherwise appropriate therapy may be mistakenly interpreted as treatment failure or multidrug-resistant tuberculosis, potentially leading to unnecessary modifications of the antituberculous regimen. (7, 8)

The optimal management of paradoxical reactions remains an area of ongoing investigation. Current WHO recommendations advocate continuation of standard antituberculous therapy after excluding drug resistance and other causes of clinical deterioration, with adjunctive systemic corticosteroids recommended to reduce cerebral edema and excessive inflammatory responses in patients with significant neurological involvement. Neurosurgical intervention is generally reserved for selected cases complicated by refractory intracranial hypertension, obstructive hydrocephalus, severe mass effect, or persistent diagnostic uncertainty. Nevertheless, important questions remain regarding the optimal duration of therapy, the ideal corticosteroid regimen, and the prognostic factors associated with radiological resolution and long-term neurological recovery. (3, 5, 7)

Herein, we report the case of an immunocompetent patient with microbiologically confirmed pulmonary tuberculosis who developed multiple cerebral tuberculomas during standard antituberculous therapy as a manifestation of a paradoxical reaction. This case underscores the diagnostic challenges posed by this uncommon entity, highlights the importance of systematically excluding alternative diagnoses, and emphasizes the need for early recognition of paradoxical inflammatory reactions to avoid unnecessary changes in antimicrobial therapy and optimize neurological outcomes.

2. Case Presentation

A 36-year-old male agricultural worker with no significant past medical history presented to our institution. He denied alcohol consumption, illicit drug use, and any history of chronic medical conditions, including diabetes mellitus or hypertension. Metabolic evaluation revealed a glycated hemoglobin level within the normal range, with no evidence of metabolic immunosuppression. He also reported no family history of neurological or infectious diseases.

Two months before the current neurological presentation, the patient had been diagnosed with microbiologically confirmed pulmonary tuberculosis based on a positive Xpert MTB/RIF assay demonstrating rifampicin susceptibility. He was initiated on standard weight-based first-line oral antituberculous therapy consisting of fixed-dose combination tablets containing rifampicin, isoniazid, pyrazinamide, and ethambutol (HRZE). At the time of the initial diagnosis, HIV infection was excluded by three independent serological tests. The CD4+ T-lymphocyte count was within normal limits, and HIV viral load testing revealed undetectable RNA levels, effectively ruling out HIV-associated immunosuppression. Baseline renal and hepatic function tests were within normal limits, with no clinically significant biochemical abnormalities.

The patient presented with a two-week history of progressive left-sided weakness, initially affecting the upper extremity and subsequently progressing to complete paralysis of the left arm. The neurological deficit was accompanied by a gradually worsening moderate-intensity headache without circadian variation or identifiable precipitating factors. He denied nausea, vomiting, fever, neck stiffness, seizures, visual disturbances, or alterations in consciousness.

Upon hospital admission, the patient was hemodynamically stable, afebrile, and fully alert, with a Glasgow Coma Scale score of 15/15. Neurological examination demonstrated left-sided hemiparesis predominantly involving the upper extremity, with muscle strength graded as 1/5 on the Medical Research Council (MRC) scale at initial assessment. There were no meningeal signs or cranial nerve abnormalities. Sensory examination was unremarkable, and no cerebellar dysfunction was identified. The remainder of the physical examination revealed no clinically significant abnormalities.

A contrast-enhanced brain computed tomography (CT) scan demonstrated two ring-enhancing intracranial lesions located in the right frontoparietal region, each measuring less than 1 cm in diameter. Both lesions were predominantly situated at the corticomedullary junction and were associated with marked surrounding vasogenic edema. No midline shift, hydrocephalus, or radiological evidence of severe intracranial hypertension was observed. In the clinical context, these findings were considered highly suggestive of granulomatous lesions of infectious origin.

To establish the underlying etiology, an extensive diagnostic workup was performed to exclude other causes of ring-enhancing intracranial lesions. Toxoplasma serology was negative. HIV infection remained excluded by repeated serological testing, with persistently normal CD4+ T-cell counts and an undetectable HIV viral load, making acquired immunodeficiency highly unlikely. Cerebrospinal fluid (CSF) analysis revealed a negative Xpert MTB/RIF assay for Mycobacterium tuberculosis, normal cytology, absence of pleocytosis, no significant hypoglycorrhachia, and no elevation in protein concentration suggestive of bacterial or tuberculous meningitis. Blood cultures were negative. Furthermore, the available investigations showed no evidence suggestive of primary central nervous system lymphoma. Flow cytometric analysis was not performed because of limited local availability, and magnetic resonance spectroscopy was unavailable at our institution.

Based on the integration of clinical, microbiological, and radiological findings, a diagnosis of multiple cerebral tuberculomas associated with active pulmonary tuberculosis was established. Because the initial molecular assay had confirmed rifampicin susceptibility and there was no clinical, microbiological, or radiological evidence of treatment failure or drug-resistant tuberculosis, the standard first-line antituberculous regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol [HRZE]) was continued without modification.

The development of intracranial lesions following initiation of antituberculous therapy, in the setting of an otherwise favorable clinical response and without microbiological evidence of disease progression, was interpreted as a paradoxical reaction to antituberculous treatment. This immune-mediated inflammatory phenomenon is believed to result from restoration of host immune responses against residual mycobacterial antigens and is considered the immunopathological counterpart of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) occurring in immunocompetent individuals. Given the extensive perilesional vasogenic edema and the presence of focal neurological deficits, adjunctive dexamethasone was initiated at a dose of 12 mg/day, followed by gradual tapering according to the patient's clinical response. The patient experienced progressive neurological improvement with partial recovery of motor function and did not require neurosurgical intervention. Antituberculous therapy was therefore

maintained without modification, resulting in a favorable clinical outcome and supporting the diagnosis of a paradoxical inflammatory reaction rather than treatment failure.

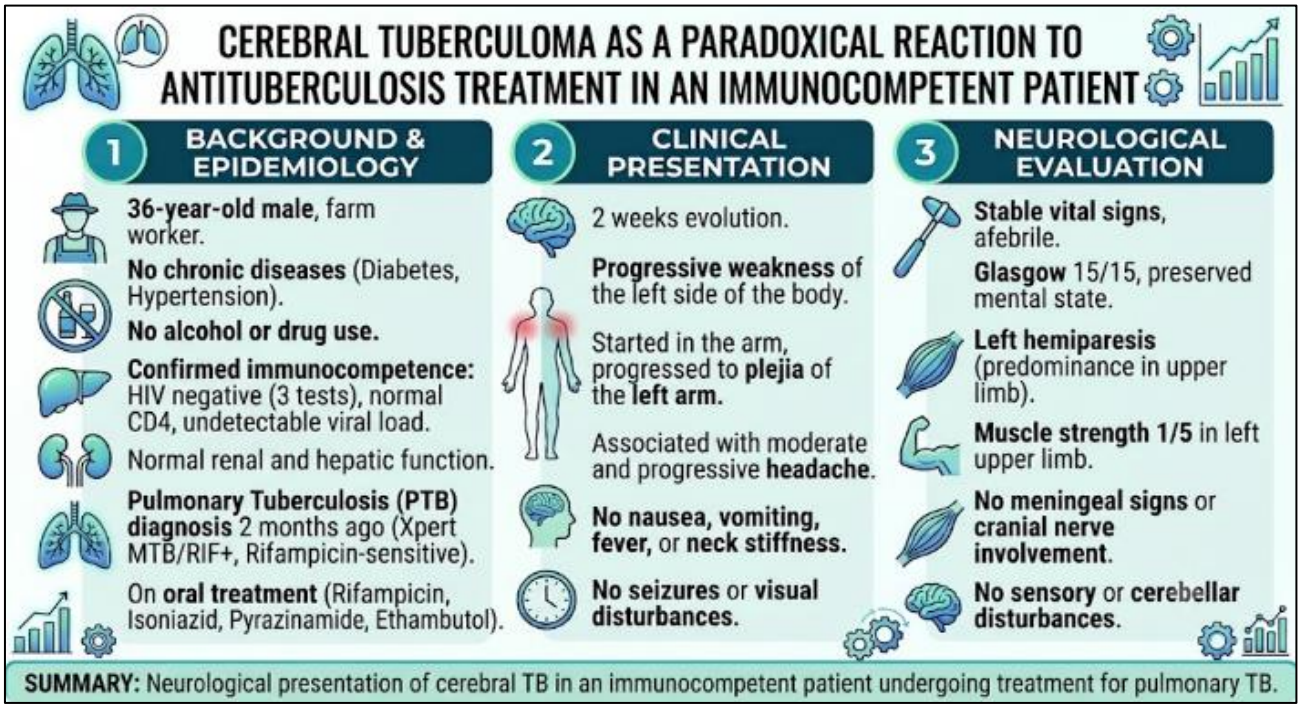

Figure 1 Case report summary

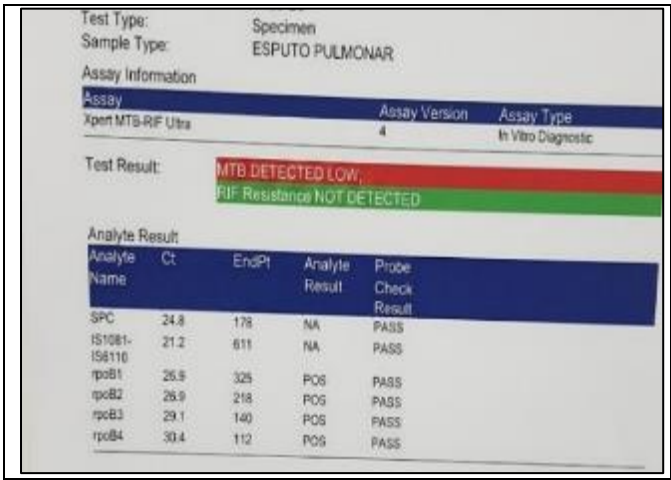

Figure 2 Xpert MTB/RIF sputum result showing detection of *Mycobacterium tuberculosis*

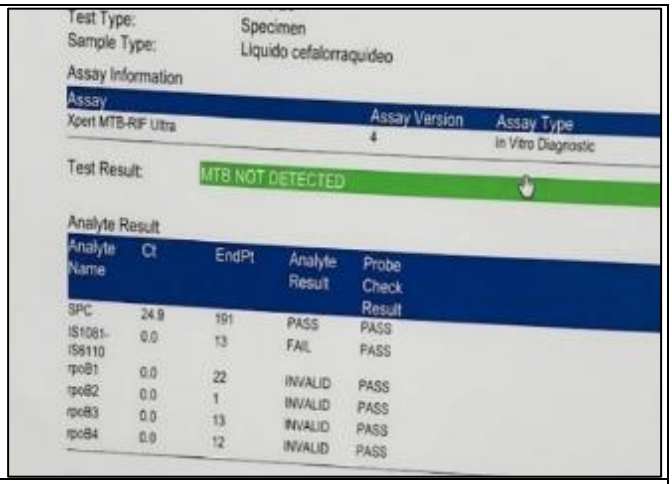

Figure 3 Xpert MTB/RIF result for cerebrospinal fluid: *Mycobacterium tuberculosis* not detected

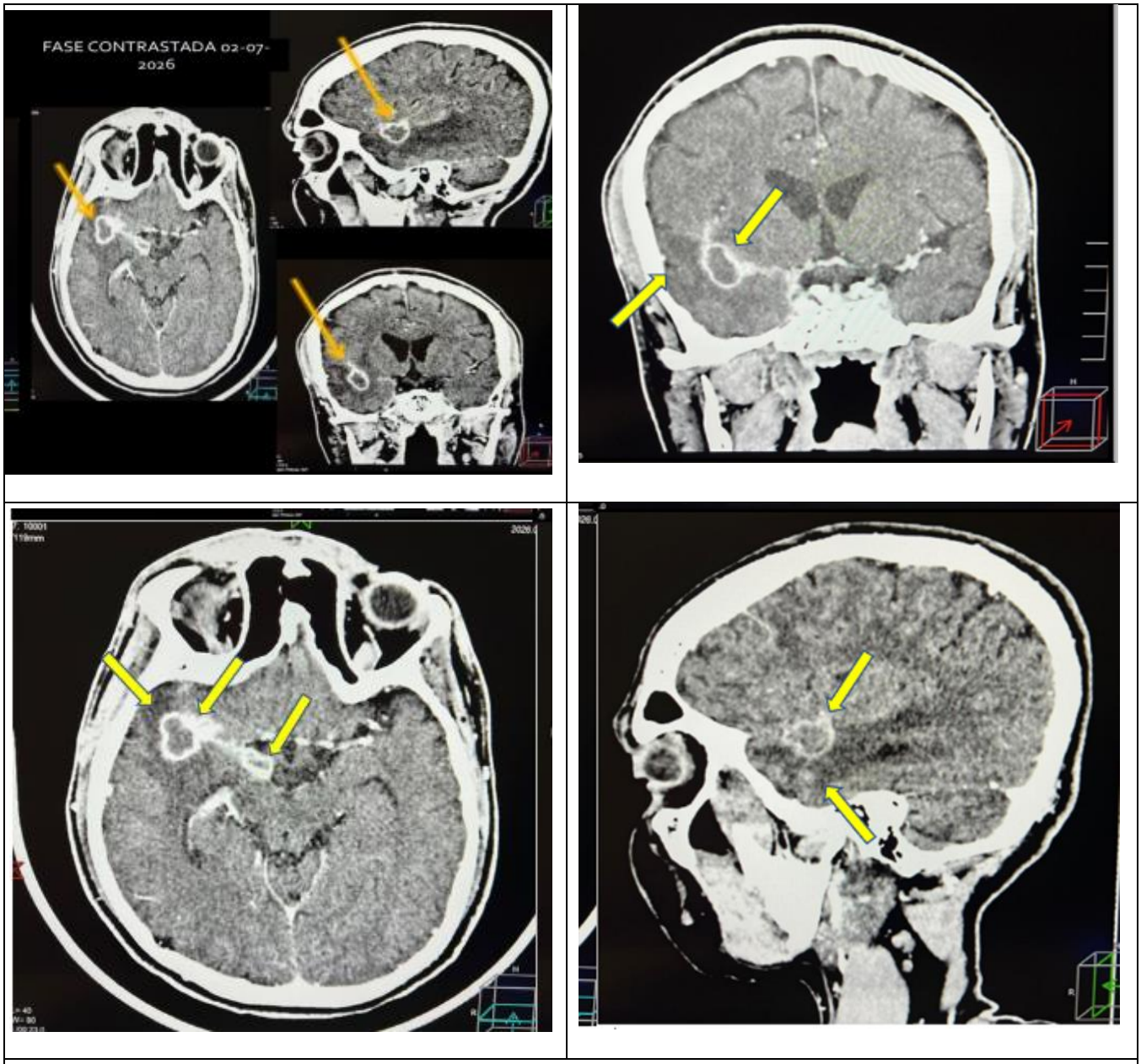

Figure 4 Contrast-enhanced CT scans in various sections showing a cerebral tuberculoma with perilesional edema (yellow arrows)

3. Discussion

The present case illustrates an uncommon manifestation of central nervous system tuberculosis (CNS-TB): the development of cerebral tuberculomas as a paradoxical reaction during appropriate antituberculous therapy in an immunocompetent patient. Although this phenomenon has been more frequently described in patients with HIV infection experiencing immune reconstitution inflammatory syndrome (IRIS), accumulating evidence over the past two decades demonstrates that paradoxical reactions may also occur in immunocompetent individuals. This entity represents a significant diagnostic challenge because it may closely mimic treatment failure, drug-resistant tuberculosis, or the emergence of alternative infectious or neoplastic diseases. (9,10)

Our patient shares several clinical characteristics with the cases reported by Mariño et al. and Lizarazo et al., who described immunocompetent patients developing new intracranial lesions between the second week and the first three months after initiation of antituberculous therapy. Similar to our case, neurological deterioration occurred despite good treatment adherence and in the absence of rifampicin resistance or any other identifiable cause explaining clinical

progression. These observations support the hypothesis that the appearance of cerebral tuberculomas during treatment reflects an exaggerated host inflammatory response to mycobacterial antigens released during bacillary destruction rather than true treatment failure. (2,11,6)

From a clinical perspective, our patient presented with progressive headache and left-sided hemiparesis secondary to two right frontoparietal lesions associated with marked vasogenic edema. These findings are consistent with those reported in the systematic review by Velásquez et al., who analyzed 21 immunocompetent patients described in 20 published case reports. In their review, headache was the most common presenting symptom, followed by focal motor deficits and vomiting, while the majority of lesions were located within the cerebral hemispheres. The remarkable similarity between our case and this published series further supports the diagnosis of paradoxical cerebral tuberculoma and suggests that its clinical presentation in immunocompetent patients is relatively consistent. (13)

A particularly noteworthy feature of our case was the negative cerebrospinal fluid (CSF) Xpert MTB/RIF assay despite the presence of radiological findings highly suggestive of cerebral tuberculomas. This result does not exclude the diagnosis because tuberculomas are localized parenchymal granulomatous lesions characterized by a low bacillary burden and lack of obligatory communication with the subarachnoid space. Consequently, the microbiological yield of CSF studies is expected to be limited in the absence of concomitant tuberculous meningitis. Several published reports have described patients with negative CSF microbiological investigations in whom the diagnosis was ultimately established through the integration of compatible neuroimaging findings, microbiologically confirmed tuberculosis at an extracranial site, the appropriate clinical context, and a favorable response to antituberculous therapy. (3,5,6)

The differential diagnosis represented one of the principal clinical challenges in this patient. Multiple ring-enhancing intracranial lesions warrant consideration of cerebral toxoplasmosis, neurocysticercosis, pyogenic brain abscesses, metastatic disease, and primary central nervous system lymphoma. In our patient, the absence of immunosuppression, repeatedly negative HIV testing, negative toxoplasma serology, exclusion of primary CNS lymphoma, microbiological confirmation of pulmonary tuberculosis, and progressive clinical improvement following continuation of antituberculous therapy made these alternative diagnoses considerably less likely. This diagnostic approach is consistent with recommendations from multiple case series emphasizing the importance of integrating clinical, epidemiological, microbiological, and radiological findings before pursuing invasive neurosurgical diagnostic procedures. (6,12,13)

Regarding management, the favorable clinical outcome observed after continuation of standard antituberculous therapy together with adjunctive dexamethasone is consistent with the majority of published reports. Available case series and literature reviews consistently conclude that continuation of appropriate antituberculous therapy remains the cornerstone of treatment, whereas systemic corticosteroids effectively reduce perilesional edema and attenuate the excessive inflammatory response responsible for neurological deterioration. Neurosurgical intervention should generally be reserved for carefully selected patients with refractory intracranial hypertension, obstructive hydrocephalus, significant mass effect, or persistent diagnostic uncertainty. None of these indications were present in our patient, and conservative medical management resulted in progressive neurological recovery, further supporting current evidence-based recommendations. (1,10,11)

This case provides additional evidence regarding a rare manifestation of tuberculosis in immunocompetent individuals and underscores the importance of recognizing paradoxical reactions as part of the natural clinical course in a subset of patients receiving appropriate antituberculous therapy. The principal strengths of this report include microbiological confirmation of pulmonary tuberculosis by rifampicin-susceptible Xpert MTB/RIF testing, systematic exclusion of alternative diagnoses, and favorable clinical recovery without modification of the antituberculous regimen. We believe this report contributes to the growing body of evidence supporting early recognition of this complication, particularly in countries with a high tuberculosis burden, where prompt identification may prevent unnecessary changes in antimicrobial therapy, avoid invasive procedures, and reduce diagnostic errors that could delay neurological recovery.

This case also highlights the diagnostic challenges frequently encountered in resource-limited healthcare settings. The lack of advanced neuroimaging techniques, including magnetic resonance spectroscopy, as well as the limited availability of stereotactic brain biopsy, often necessitates a diagnosis based on careful integration of epidemiological, microbiological, clinical, and radiological evidence. Under these circumstances, a favorable response to continued antituberculous therapy constitutes an additional diagnostic element supporting paradoxical cerebral tuberculoma once alternative etiologies have been reasonably excluded.

4. Conclusion

This case highlights that the development of cerebral tuberculomas during antituberculous therapy may represent a paradoxical inflammatory reaction rather than treatment failure, even in immunocompetent patients. Early recognition of this entity is essential to avoid misinterpretation as drug resistance, poor treatment adherence, or disease progression, all of which may lead to unnecessary modifications of antituberculous therapy or avoidable invasive procedures. Integration of clinical findings, microbiological evidence, and neuroimaging characteristics, together with the systematic exclusion of differential diagnoses such as cerebral toxoplasmosis, pyogenic brain abscesses, primary or metastatic brain tumors, and other opportunistic infections, allows a more accurate diagnosis and facilitates appropriate clinical management.

Furthermore, this case demonstrates that continuation of standard first-line antituberculous therapy combined with adjunctive corticosteroids in patients presenting with significant cerebral edema and focal neurological deficits can result in favorable neurological recovery without the need for neurosurgical intervention, provided that refractory intracranial hypertension or significant mass effect is absent. The favorable outcome observed in our patient supports current recommendations for the management of paradoxical reactions involving the central nervous system.

Finally, this report adds further evidence regarding an uncommon manifestation of central nervous system tuberculosis and emphasizes the importance of maintaining a high index of clinical suspicion in patients who develop new neurological symptoms during otherwise effective antituberculous treatment. Dissemination of well-documented cases will contribute to improving recognition of this condition, optimizing clinical decision-making, and expanding current knowledge regarding its pathophysiology, prognostic factors, and optimal therapeutic strategies, particularly in regions where tuberculosis remains highly prevalent.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest related to this publication.

Statement of ethical approval

Patient confidentiality was maintained through anonymization of all identifying clinical information in accordance with the ethical principles outlined in the Declaration of Helsinki.

Statement of informed consent

Written informed consent was obtained from the patient for publication of this case report.

Author Contributions

All authors participated in the clinical management of the patient, collection and analysis of clinical data, literature review, and preparation of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

References

[1] World Health Organization. (2025). *WHO consolidated guidelines on tuberculosis: Module 4: Treatment and care*. World Health Organization.

[2] Afghani, B., & Lieberman, J. M. (1994). Paradoxical enlargement or development of intracranial tuberculomas during therapy: Case report and review. *Clinical Infectious Diseases, 19*(6), 1092–1099. https://doi.org/10.1093/clinids/19.6.1092

[3] Bahr, N. C., Marais, S., Caws, M., van Crevel, R., Wilkinson, R. J., Tyagi, J. S., Thwaites, G. E., & Boulware, D. R. (2020). Management of intracranial tuberculous mass lesions: How long should we treat for? *Wellcome Open Research, 4*, 158. https://doi.org/10.12688/wellcomeopenres.15529.2

[4] Carter, E. C., Fernandez, C., Lim, C., et al. (2026). Incidence, risk factors and management of paradoxical reaction in central nervous system tuberculosis in the United Kingdom. *Journal of Infection, 93*(2), 106778.

[5] Chandrasiri, D. (2025). Paradoxical reactions in central nervous system tuberculosis: Insights into pathogenesis, diagnosis, and clinical management. *Sri Lanka Journal of Neurology*.

[6] Das, A., Das, S. K., Mandal, A., et al. (2012). Cerebral tuberculoma as a manifestation of paradoxical reaction in patients with pulmonary and extrapulmonary tuberculosis. *Journal of Neurosciences in Rural Practice, 3*(3), 350–354. https://doi.org/10.4103/0976-3147.102626

[7] Malhotra, H. S., Garg, R. K., Jain, A., Kumar, N., Kohli, N., & Sharma, P. K. (2016). Paradoxical reaction in tuberculous meningitis: Presentation, predictors and impact on prognosis. *BMC Infectious Diseases, 16*, Article 306. https://doi.org/10.1186/s12879-016-1625-9

[8] Mariño, E., Rodríguez-Pardo, J., et al. (2025). Paradoxical reactions of central nervous system tuberculosis: Report of three immunocompetent cases. *Case Reports in Infectious Diseases*.

[9] Nicolls, D. J., King, M., Holland, D., Bala, J., & del Rio, C. (2005). Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis. *The Lancet Infectious Diseases, 5*(12), 795–801. https://doi.org/10.1016/S1473-3099(05)70289-6

[10] Rajshekhar, V. (2015). Surgery for brain tuberculosis: A review. *Acta Neurochirurgica, 157*(10), 1665–1678. https://doi.org/10.1007/s00701-015-2524-5

[11] Rock, R. B., Olin, M., Baker, C. A., Molitor, T. W., & Peterson, P. K. (2008). Central nervous system tuberculosis: Pathogenesis and clinical aspects. *Clinical Microbiology Reviews, 21*(2), 243–261. https://doi.org/10.1128/CMR.00042-07

[12] Shah, I., & Borse, S. (2012). Paradoxical tuberculomas after completion of antituberculous treatment. *Tropical Medicine and Health, 40*(1), 15–17. https://doi.org/10.2149/tmh.2011-16

[13] Thakur, K., Das, M., Dooley, K. E., & Gupta, A. (2012). Cerebral tuberculoma as a manifestation of paradoxical reaction in patients with pulmonary and extrapulmonary tuberculosis. *International Journal of Mycobacteriology*.