



Case Series

Non-Resolving Granulomatous Intracranial Lesions During Anti-Tubercular Therapy: A Case Series

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ABSTRACT

Background: Central nervous system tuberculosis (CNS-TB) is one of the most severe manifestations of extrapulmonary tuberculosis and remains associated with considerable morbidity and mortality despite effective anti-tubercular therapy (ATT). Intracranial tuberculomas may develop before treatment initiation or paradoxically during therapy. The appearance of new lesions or progression of pre-existing lesions despite adequate treatment presents a significant diagnostic and therapeutic challenge, often raising concerns regarding treatment failure, drug resistance, or alternative diagnoses.

Methods: This retrospective case series included 15 patients with tuberculosis who developed persistent or progressive intracranial granulomatous lesions during anti-tubercular therapy. Clinical presentations, radiological findings, cerebrospinal fluid analysis, treatment details, histopathological findings, and outcomes were reviewed. All patients underwent contrast-enhanced magnetic resonance imaging (MRI) of the brain and were followed clinically and radiologically during treatment.

Results: The mean age of the study population was 22.4 ± 7.1 years, with females accounting for 60% of cases. Headache (100%), vomiting (80%), and seizures (73.3%) were the most common neurological manifestations. MRI demonstrated multiple intracranial lesions in 86.7% of patients, with frontal lobe involvement being the most frequent finding. Perilesional edema was observed in 93.3% of patients, while significant mass effect was present in 40%. All patients received prolonged anti-tubercular therapy and corticosteroids. Five patients (33.3%) required neurosurgical intervention because of persistent symptoms or radiological progression. Histopathological examination of excised lesions demonstrated granulomatous inflammation in all operated cases. At final follow-up, complete clinical recovery was achieved in 40% of patients, partial improvement in 46.7%, and persistent neurological symptoms in 13.3%.

Conclusions: Paradoxical progression of intracranial tuberculomas may occur despite adequate anti-tubercular therapy and apparent improvement of systemic tuberculosis. Recognition of this phenomenon is essential to avoid misdiagnosis as treatment failure or drug resistance. Serial neuroimaging, adjunctive corticosteroid therapy, and selective neurosurgical intervention remain important components of management. Early identification and multidisciplinary care may improve neurological outcomes in affected patients.

Keywords: Central nervous system tuberculosis; Intracranial tuberculoma; Paradoxical reaction; Granulomatous lesion; Anti-tubercular therapy; Neurotuberculosis; Tuberculoma.

INTRODUCTION

Tuberculosis (TB) remains a major global health problem and one of the leading infectious causes of morbidity and mortality worldwide. According to the World Health Organization, approximately 10.8 million people developed tuberculosis in 2023, with India contributing the highest burden of disease globally [1]. Although pulmonary tuberculosis is the most common presentation, extrapulmonary tuberculosis remains an important cause of severe complications and disability.

Central nervous system tuberculosis (CNS-TB) is the most serious form of extrapulmonary tuberculosis, accounting for approximately 5–10% of extrapulmonary cases and nearly 1% of all tuberculosis cases [2,3]. CNS involvement may occur as tuberculous meningitis, tuberculoma, tuberculous abscess, or spinal disease. Among these, intracranial tuberculomas are localized granulomatous lesions resulting from hematogenous spread of *Mycobacterium tuberculosis* to the brain parenchyma and are associated with significant neurological morbidity and mortality [2].

Clinical manifestations of intracranial tuberculomas are often nonspecific and include headache, vomiting, seizures, focal neurological deficits, and signs of raised intracranial pressure [2,4]. Magnetic resonance imaging (MRI) is the preferred diagnostic modality and typically demonstrates single or multiple ring-enhancing lesions with surrounding edema and mass effect. However, these lesions may mimic neoplasms, fungal infections, neurocysticercosis, and pyogenic abscesses, making diagnosis challenging [4,5].

A major challenge in the management of CNS tuberculosis is the occurrence of paradoxical reactions during anti-tubercular therapy (ATT). These reactions are characterized by enlargement of existing lesions or development of new lesions despite appropriate treatment and microbiological response [3,6]. The proposed mechanism involves an exaggerated immune response to mycobacterial antigens released during treatment, resulting in persistent inflammation and granuloma formation [6,7].

Paradoxical intracranial tuberculomas often create diagnostic uncertainty because radiological progression may mimic treatment failure, drug resistance, or alternative intracranial pathology. Consequently, repeated neuroimaging, cerebrospinal fluid analysis, molecular testing, and occasionally histopathological confirmation may be required [3,8]. Although prolonged ATT and corticosteroid therapy remain the cornerstone of treatment, selected patients may require neurosurgical intervention because of persistent symptoms, progressive lesions, or diagnostic uncertainty.

The present study was undertaken to evaluate the clinical profile, radiological characteristics, management strategies, and outcomes of fifteen patients with non-resolving intracranial granulomatous lesions developing during anti-tubercular therapy.

MATERIALS AND METHODS

This retrospective observational case series was conducted in the Department of Pulmonary Medicine in collaboration with the Departments of Neurology, Neurosurgery, Radiology, and Pathology at a tertiary care teaching hospital. The study included patients diagnosed with non-resolving or paradoxically progressive intracranial granulomatous lesions during anti-tubercular therapy (ATT).

A total of 15 patients with tuberculosis who developed neurological manifestations and radiologically proven intracranial granulomatous lesions while receiving anti-tubercular therapy were included in the study. Medical records, laboratory investigations, neuroimaging findings, treatment details, operative notes, and histopathological reports were reviewed retrospectively.

Inclusion and Exclusion criteria

Patients with confirmed pulmonary or extrapulmonary tuberculosis who developed neurological manifestations during ATT and demonstrated intracranial tuberculomas on magnetic resonance imaging (MRI) were included in the study. Patients with alternative intracranial diagnoses, incomplete records, or HIV infection were excluded.

METHODOLOGY

Baseline demographic characteristics, including age and sex, were recorded. Clinical presentation at the time of neurological involvement was documented. Neurological symptoms assessed included headache, vomiting, seizures, fever, weight loss, focal neurological deficits, and altered sensorium. A comprehensive neurological examination was performed in all patients at presentation and during follow-up.

Routine laboratory investigations included complete blood count, liver function tests, renal function tests, blood glucose estimation, and viral serology. Microbiological confirmation of tuberculosis was established using sputum smear microscopy for acid-fast bacilli (AFB), cartridge-based nucleic acid amplification testing (CBNAAT), TruNat MTB assay, or culture studies whenever available.

Lumbar puncture was performed whenever clinically indicated. Cerebrospinal fluid (CSF) samples were analyzed for protein concentration, glucose level, total and differential leukocyte count, AFB staining, CBNAAT/TruNat MTB detection, fungal culture, and fungal serology.

All patients underwent contrast-enhanced MRI of the brain at the onset of neurological symptoms. Radiological parameters assessed included the number of lesions, anatomical location, lesion size, pattern of enhancement, presence of conglomerate lesions, diffusion restriction, perilesional edema, mass effect, and appearance of new lesions during follow-up. Serial MRI examinations were performed to evaluate radiological progression, stability, or resolution of lesions during treatment.

All patients received anti-tubercular therapy according to National Tuberculosis Elimination Programme (NTEP) guidelines. Patients with CNS involvement received prolonged ATT for 12–18 months depending upon clinical and radiological response.

Adjunctive corticosteroid therapy was administered in patients with significant cerebral edema, mass effect, or paradoxical reactions. Antiepileptic medications were prescribed in patients presenting with seizures.

Patients demonstrating persistent neurological symptoms, progressive radiological lesions, significant mass effect, diagnostic uncertainty, or refractory seizures despite medical therapy were referred for neurosurgical evaluation. Surgical management consisted of lesion biopsy or excision through craniotomy when indicated.

Resected tissue specimens were subjected to histopathological examination. Additional investigations included AFB staining, bacterial culture, fungal staining, fungal culture, and molecular testing using CBNAAT or TruNat whenever feasible.

Outcome Assessment

Clinical outcomes were categorized as complete recovery, partial improvement, persistent neurological symptoms, or neurological deterioration. Radiological outcomes were classified as complete lesion resolution, partial regression, stable disease, or progressive disease based on serial MRI findings.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean \pm standard deviation, while categorical variables were expressed as frequencies and percentages.

RESULTS

A total of 15 patients with non-resolving or paradoxically progressive intracranial granulomatous lesions during anti-tubercular therapy were included in the study. The mean age of the patients was 22.4 ± 7.1 years (range: 16–41 years). Females constituted 60% (n=9) of the study population, while males accounted for 40% (n=6). Pulmonary tuberculosis was the predominant primary disease and was present in 80% of patients. [Table 1]

Table 1. Baseline Demographic Characteristics of Patients

Variable	Value
Total patients	15
Mean age (years)	22.4 \pm 7.1
Age range (years)	16–41
Male	6 (40.0%)
Female	9 (60.0%)
Pulmonary tuberculosis	12 (80.0%)
Extrapulmonary tuberculosis	3 (20.0%)

Headache was the most common presenting neurological symptom and was observed in all patients (100%). Vomiting occurred in 80% of patients, while seizures were reported in 73.3%. Fever and weight loss were observed in 53.3% and 46.7% of patients, respectively. Focal neurological deficits were identified in 26.7% of patients, whereas altered sensorium was present in 13.3%. [Table 2]

Table 2. Clinical Presentation

Clinical Feature	n (%)
Headache	15 (100.0)
Vomiting	12 (80.0)
Seizures	11 (73.3)
Fever	8 (53.3)

Weight loss	7 (46.7)
Focal neurological deficit	4 (26.7)
Altered sensorium	2 (13.3)

The mean duration between initiation of anti-tubercular therapy and development of neurological symptoms was 3.9 ± 1.8 months. All patients underwent contrast-enhanced MRI brain examination. Neuroimaging revealed multiple intracranial lesions in 86.7% of patients and solitary lesions in 13.3%. Frontal lobe involvement was the most common radiological finding, followed by parietal lobe and cerebellar involvement. Perilesional edema was present in 93.3% of patients, while mass effect was observed in 40%. [Table 3]

Table 3. MRI Characteristics of Intracranial Lesions

MRI Finding	n (%)
Multiple lesions	13 (86.7)
Solitary lesion	2 (13.3)
Frontal lobe involvement	11 (73.3)
Parietal lobe involvement	7 (46.7)
Cerebellar involvement	5 (33.3)
Conglomerate lesions	8 (53.3)
Ring-enhancing lesions	15 (100.0)
Perilesional edema	14 (93.3)
Mass effect	6 (40.0)
Diffusion restriction	4 (26.7)

Cerebrospinal fluid examination was performed in 11 patients. Most patients demonstrated normal or mildly abnormal CSF findings. Microbiological confirmation from CSF was uncommon. [Table 4]

Table 4. Cerebrospinal Fluid Findings

Parameter	Mean \pm SD
Protein (mg/dL)	41.8 \pm 17.4
Glucose (mg/dL)	57.2 \pm 11.8
Total leukocyte count (cells/mm ³)	13.6 \pm 8.9
Investigation	Positive n (%)
CBNAAT MTB	1 (6.7)
AFB stain	0 (0.0)
Fungal culture	0 (0.0)

All patients received prolonged anti-tubercular therapy and corticosteroid treatment. Antiepileptic drugs were administered to patients with seizure episodes. Five patients required neurosurgical intervention because of progressive lesions, persistent neurological symptoms, or diagnostic uncertainty. [Table 5]

Table 5. Treatment Characteristics

Treatment	n (%)
Anti-tubercular therapy	15 (100.0)
Corticosteroids	15 (100.0)
Antiepileptic drugs	11 (73.3)
Neurosurgical intervention	5 (33.3)
ATT duration >12 months	15 (100.0)
ATT duration >18 months	8 (53.3)

Histopathological examination of excised lesions demonstrated granulomatous inflammation in all operated patients. Molecular testing detected *Mycobacterium tuberculosis* in the majority of surgically managed cases, and no rifampicin resistance was identified. [Table 6]

Table 6. Histopathological Findings in Operated Patients (n=5)

Finding	n (%)
Granulomatous inflammation	5 (100.0)
Casating granuloma	4 (80.0)
MTB detected on molecular testing	4 (80.0)
Rifampicin resistance detected	0 (0.0)
AFB stain positive	0 (0.0)

At the final follow-up, complete clinical recovery was observed in 40% of patients, while 46.7% demonstrated partial improvement. Persistent neurological symptoms were noted in two patients. Radiological follow-up showed complete lesion resolution in 26.7% and partial regression in 53.3% of patients. [Table 7]

Table 7. Clinical and Radiological Outcomes

Outcome	n (%)
Complete clinical recovery	6 (40.0)
Partial improvement	7 (46.7)
Persistent symptoms	2 (13.3)
Complete radiological resolution	4 (26.7)
Partial regression	8 (53.3)
Stable lesions	2 (13.3)
Progressive disease	1 (6.7)

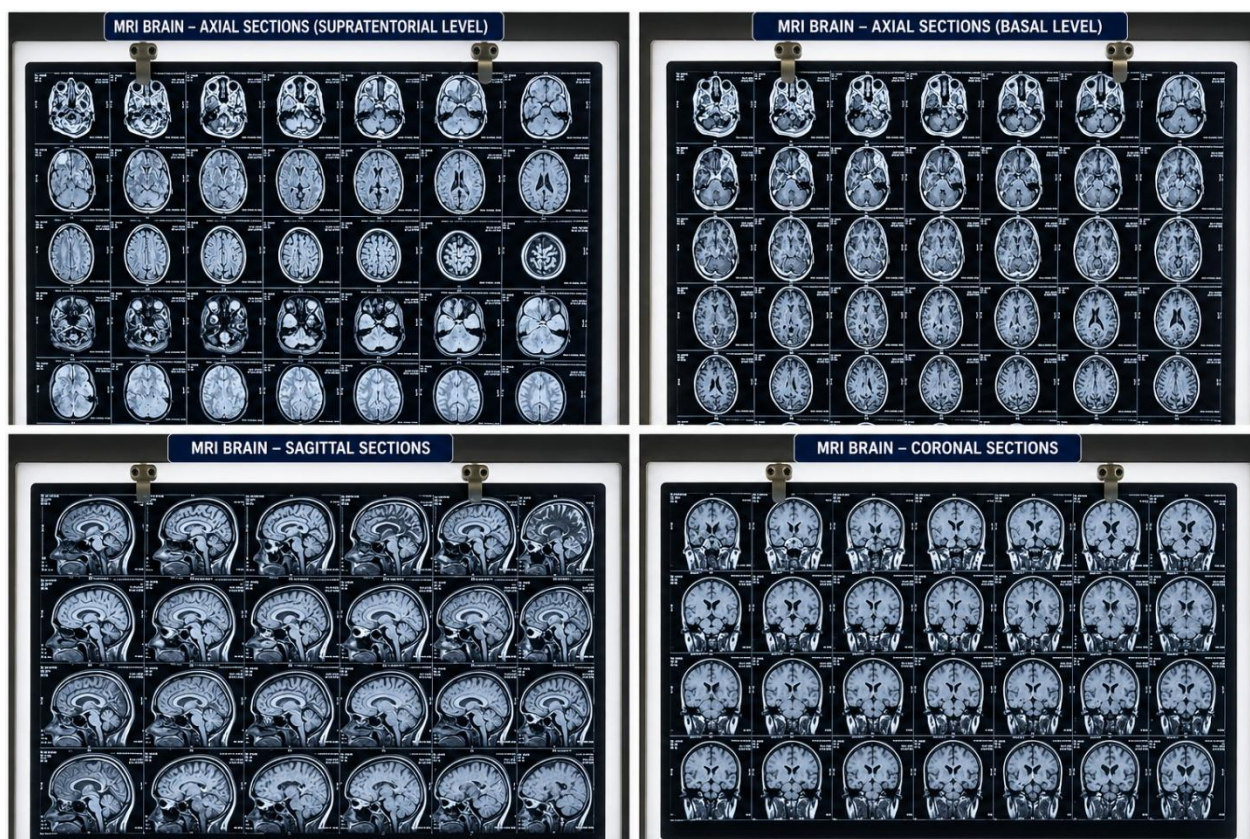


Figure 1. Serial MRI Brain Images Demonstrating Paradoxical Progression of Intracranial Tuberculomas During Anti-Tubercular Therapy

DISCUSSION

Central nervous system tuberculosis (CNS-TB) remains the most severe form of extrapulmonary tuberculosis and is associated with substantial mortality and long-term neurological disability despite effective anti-tubercular therapy (ATT) [2,3]. The development of intracranial tuberculomas during treatment presents a significant clinical challenge because radiological progression may occur despite adequate therapy and improvement in systemic disease. The present study evaluated 15 patients with non-resolving or paradoxically progressive intracranial granulomatous lesions and highlights the diagnostic and therapeutic challenges associated with this condition.

Headache, vomiting, and seizures were the most common clinical manifestations in our patients. Similar findings have been reported by Rock et al. and Cherian and Thomas, who identified headache and seizures as the predominant symptoms of intracranial tuberculomas, often resulting from raised intracranial pressure and perilesional edema [2,4]. The frequency of these symptoms in our study reflects the significant inflammatory response and mass effect associated with intracranial granulomatous lesions.

A notable observation was the appearance of neurological symptoms several months after initiation of ATT. The mean interval between treatment initiation and neurological deterioration was approximately four months. This finding is consistent with the phenomenon of paradoxical reaction, which has been increasingly recognized in CNS tuberculosis [3]. Wilkinson et al. described paradoxical worsening as clinical or radiological progression despite appropriate treatment, while Davis et al. suggested that this response is mediated by enhanced host immunity following destruction of mycobacteria during therapy [3,6].

The exact mechanism of paradoxical tuberculoma formation remains incompletely understood. Current evidence suggests that bacillary destruction during treatment leads to the release of mycobacterial antigens, triggering an exaggerated cell-mediated immune response and subsequent granuloma enlargement [6,7]. Manyelo et al. further highlighted the role of pro-inflammatory cytokines, including tumor necrosis factor- α and interferon- γ , in the pathogenesis of paradoxical CNS tuberculosis [7]. Similar observations have been reported by Rohlwink et al., emphasizing the contribution of host inflammatory pathways to disease progression [9].

Magnetic resonance imaging was crucial for diagnosis and follow-up in our study. Most patients demonstrated multiple ring-enhancing lesions with surrounding edema, while frontal lobe involvement was the most common radiological finding. Bernaerts et al. described similar MRI characteristics, including ring enhancement, conglomerate lesions, and marked perilesional edema as typical features of intracranial tuberculomas [5]. Gupta et al. also demonstrated the superiority of MRI over computed tomography in assessing lesion morphology, edema, and treatment response [10].

An important finding in our study was the occurrence of radiological progression despite improvement in pulmonary disease and constitutional symptoms. Similar discordance between systemic and neurological responses has been reported by Dian et al., who emphasized that enlargement of intracranial lesions during treatment should not automatically be interpreted as treatment failure or drug resistance [8]. Thwaites et al. likewise reported that radiological worsening often reflects immune-mediated inflammation rather than ongoing infection [11].

Cerebrospinal fluid analysis showed limited diagnostic utility in our patients. CBNAAT positivity was observed in only one patient, while AFB staining and fungal cultures were negative in all cases. These findings are consistent with previous reports indicating that intracranial tuberculomas are often paucibacillary lesions and therefore yield low microbiological positivity rates [2,4]. Marais et al. demonstrated that conventional CSF investigations have limited sensitivity in isolated parenchymal CNS tuberculosis and should not be used to exclude disease [12].

All patients received prolonged ATT along with adjunctive corticosteroid therapy. Corticosteroids remain an important component of management because they reduce cerebral edema and inflammatory tissue injury. A landmark study by Thwaites et al. demonstrated improved survival with adjunctive corticosteroid therapy in CNS tuberculosis [13]. Subsequent studies have supported their use in patients with intracranial tuberculomas, particularly those with significant edema and mass effect [3,11].

Despite aggressive medical therapy, five patients required neurosurgical intervention because of persistent symptoms, progressive lesions, refractory seizures, or diagnostic uncertainty. Histopathological examination demonstrated granulomatous inflammation in all operated cases. Similar indications for surgery have been reported by Rajeswari and Chandy, who emphasized the value of surgical intervention in patients with enlarging lesions or uncertain diagnosis [14]. Surgical excision not only provides tissue confirmation but may also alleviate symptoms through decompression of mass lesions.

At follow-up, most patients demonstrated complete or partial clinical recovery. However, radiological improvement often lagged behind symptomatic improvement. Nicolls et al. reported similar findings and observed that enhancing lesions may persist for prolonged periods despite adequate clinical response [15]. Therefore, residual radiological abnormalities should not necessarily prompt modification of anti-tubercular therapy in clinically improving patients.

The present study highlights the importance of recognizing paradoxical intracranial tuberculomas as a distinct clinical entity. Early diagnosis, serial neuroimaging, appropriate corticosteroid therapy, and selective neurosurgical intervention are essential for optimizing outcomes. Although limited by its retrospective design and small sample size, this study provides valuable insight into the clinical spectrum and management of non-resolving intracranial granulomatous lesions during ATT. Overall, our findings emphasize that radiological progression during treatment does not necessarily indicate treatment failure or drug resistance and should be interpreted in conjunction with clinical and microbiological findings.

CONCLUSION

Non-resolving or paradoxically progressive intracranial tuberculomas represent a challenging manifestation of central nervous system tuberculosis and may occur despite appropriate anti-tubercular therapy. Headache, vomiting, and seizures were the most common presenting symptoms, while MRI played a crucial role in diagnosis and follow-up. Radiological progression did not necessarily indicate treatment failure or drug resistance and often reflected an exaggerated inflammatory response. Most patients responded favorably to prolonged anti-tubercular therapy, corticosteroids, and supportive management, although selected cases required neurosurgical intervention. Early recognition, serial neuroimaging, and multidisciplinary management are essential for achieving favorable neurological outcomes.

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