

Paradoxical Reaction in Tuberculous Meningitis and Tuberculoma: Diagnostic Challenges Following Incomplete Treatment

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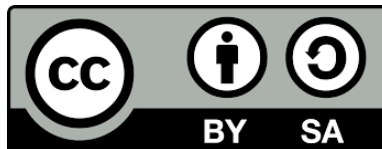
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ABSTRACT

Introduction: Exacerbation of clinical or radiological findings in tuberculous meningitis (TBM) may result from a paradoxical reaction (PR), an immune-mediated response occurring in 6–30% of cases during or after anti-tuberculosis treatment (ATT). This case highlights the potential for PR to occur in the context of an incomplete ATT regimen. **Case Illustration:** A 20-year-old female presented with a 1-month history of headache, fever, double vision, nuchal rigidity, and bilateral abducens palsy. Cerebrospinal fluid analysis revealed pleocytosis and elevated protein, while brain MRI demonstrated leptomeningeal enhancement with multiple tuberculomas. She received standard ATT (RHZE), but discontinued therapy before completion due to symptom resolution and medication burden. One year later, she developed altered sensorium and behavioral changes; MRI showed new tuberculomas with edema despite negative serology. A diagnosis of PR was made, and high-dose intravenous corticosteroids were administered, resulting in clinical and radiological improvement. **Discussion:** PR remains a diagnostic challenge, often mistaken for microbiological relapse, drug resistance, or treatment failure. It arises from a distinct immune response to mycobacterial antigens, distinguishing it from relapse or drug resistance. **Conclusion:** Clinicians should suspect PR in worsening TBM cases, even in the setting of incomplete ATT, to prevent misdiagnosis and initiate prompt treatment.

1. INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis, often leading to significant morbidity and mortality despite appropriate therapy. Its management remains challenging due to its variable presentation, delayed diagnosis, and unpredictable treatment response. Exacerbation of clinical or radiological findings in patients with tuberculous meningitis (TBM) following anti-tuberculous treatment (ATT) is known as a paradoxical reaction (PR).¹ While the precise pathophysiology remains unclear, it is believed to result from an exaggerated immune reconstitution phenomenon, in which previously suppressed immune cells mount an intensified inflammatory response against residual mycobacterial antigens or their cell wall components.² This immune hypersensitivity leads to worsening inflammation despite effective microbial control.²

PR is observed in 6-30% of patients with tuberculosis (TB), with a higher incidence in disseminated disease and extrapulmonary disease, particularly TB of the central nervous system (CNS).³ This phenomenon may occur within days to one year after the initiation of ATT, often mimicking a microbiological relapse, drug resistance, or treatment failure.^{2,4} The risk of developing permanent neurological damage and death highlights the significance of timely recognition by clinicians and early treatment with corticosteroids.

Although PR has been well described in patients adherent to ATT, reports of individuals with incomplete or prematurely discontinued treatment are scarce. This highlights a knowledge gap in understanding the incidence, presentation, and management of PR in patients with treatment

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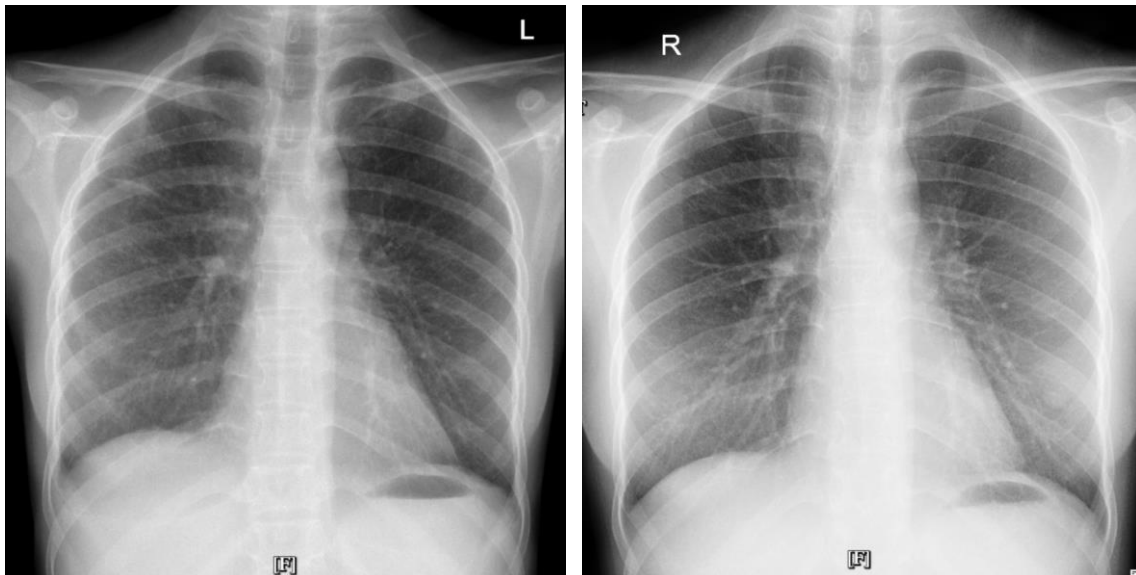
non-compliance or interrupted therapy. To the best of our knowledge, most reported cases of PR occur in patients who were either on ATT or had completed the regimen. The objective of this report is to emphasize the importance of recognizing PR even in the setting of treatment non-compliance, rather than attributing such manifestations solely to reinfection. We report a case of PR in a 20-year-old female with TBM and tuberculoma.

2. CASE ILLUSTRATION

A 20-year-old Southeast Asian female presented with a 1-month history of headache, fever, and double vision. General examination findings were unremarkable, and her vital signs were within normal limits. Upon neurological examination, nuchal rigidity and bilateral abducens nerve palsy were observed. Laboratory work-up was significant for mildly elevated leukocytes (11.300 / μ L) and hyponatremia (122 mmol/L). Serological testing for HIV was negative. Chest radiograph revealed miliary opacities bilaterally, suggestive of miliary tuberculosis (Fig. 1).

Figure 1.

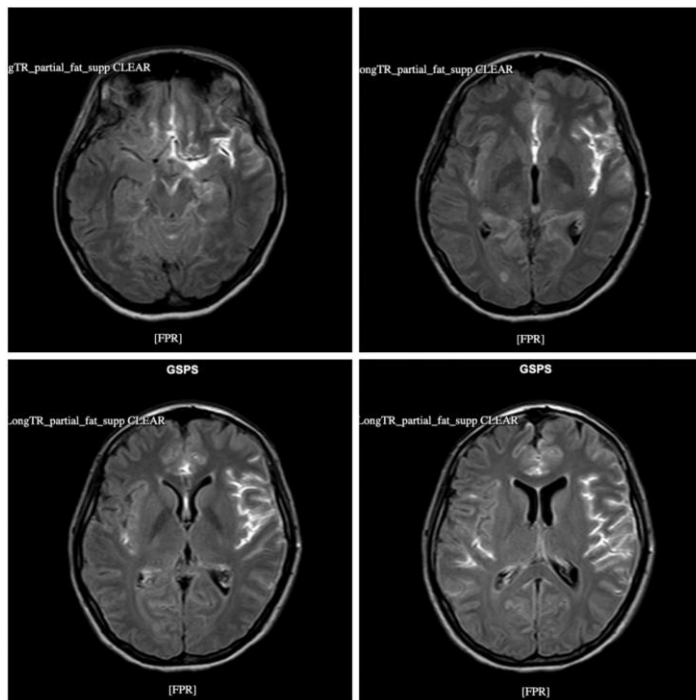
(a) Chest X-ray (CXR) at presentation showing miliary opacities and bilateral pleural effusion. (b) CXR one year after the initial diagnosis with normal findings



A contrast-enhanced brain magnetic resonance imaging (MRI) revealed diffuse sulcal enhancement in the leptomeninges, left Sylvian fissure, basal cistern and cerebellar vermis, with multiple contrast-enhancing nodules in the bilateral frontal lobe, right occipital lobe, and right cerebellar hemisphere (Fig. 2). Cerebrospinal fluid (CSF) analysis revealed pleocytosis, low glucose levels (29.0 mg/dL), and elevated protein levels (0.97 g/L). CSF GeneXpert MTb/RIF was positive for *Mycobacterium tuberculosis* with no rifampicin resistance. A diagnosis of TBM with tuberculoma was made, and the patient was started on an ATT regimen. Clinical improvement and weight gain were demonstrated, with complete resolution of symptoms within three months. However, she did not adhere to her medication and discontinued the treatment after 8 months, due to the complete resolution of symptoms and medication burden.

Figure 2

Contrast-enhanced brain MRI (FLAIR sequence) during initial presentation demonstrating diffuse leptomeningeal enhancement and left Sylvian fissure, basal cistern, and cerebellar vermis enhancement, with multiple contrast-enhancing nodules

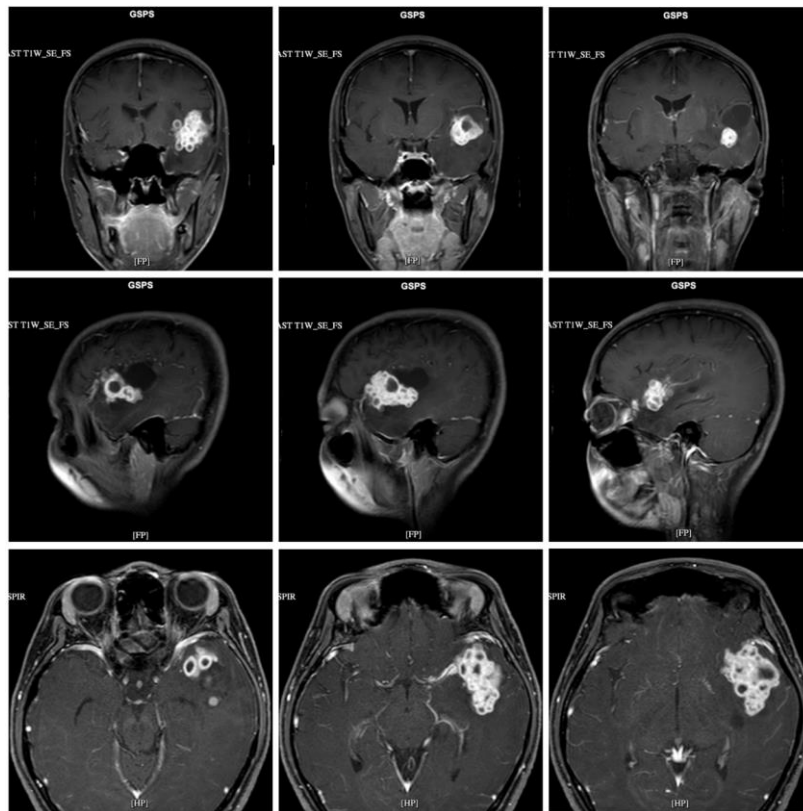


One year after the initial diagnosis, the patient returned with a 3-day history of altered sensorium, which included behavioral disturbances such as taking off clothing in public, scavenging rubbish, urinating in inappropriate places, and jumping off the second floor of a building. Prior to the onset of these symptoms, she experienced a 1-month history of olfactory hallucination, nausea, fever, and chills. The patient's mother also reported seizures, which occurred 2 weeks ago, accompanied by urinary incontinence. On admission, the patient was confused (GCS E4M6V3) and underweight (BMI 15.8 kg/m²). Vitals were unremarkable, and no neurological deficits were noted. Lacerations were observed on her extremities.

Diagnostics revealed elevated liver enzymes (SGOT 103 U/L, SGPT 45 U/L), hyponatremia (128 mmol/L), increased CRP (11.6 mg/dL), and a negative IGRA Quantiferon-TB. Contrast-enhanced brain MRI revealed a heterogenous, multiloculated lesion with rim enhancement (4.7x5.2x3.7cm) located in the left fronto-temporal lobe, with extensive perifocal edema and surrounding leptomeningeal enhancement, and multiple contrast enhancing nodules in the left parietal lobe, bilateral frontal lobe, and right temporal lobe (Fig. 3). High dose intravenous dexamethasone was commenced, with an initial dose of 0.4 mg/kg/day and tapered off over 8 weeks. Upon treatment, the patient's level of consciousness and cognitive behavioral symptoms improved. She is currently still on observation and continuing an 8-week course of corticosteroids.

Figure 3

Contrast-enhanced brain MRI (T1-weighted sequence) one year later revealing a heterogenous, multiloculated lesion with rim enhancement in the left fronto-temporal lobe, with extensive perifocal edema and surrounding leptomeningeal enhancement, and multiple contrast enhancing nodules

**3. DISCUSSION**

In TBM, PR is typically observed in patients who show initial improvement following ATT, but later develop deterioration of neurological symptoms and radiological findings, as seen in this case.^{1,5} Although the exact pathophysiology behind it remains unclear, it is known that the administration of ATT triggers the dysregulation of delayed-type hypersensitivity response, causing the exacerbation of inflammation in a previously controlled TB infection.^{1,6,7} The onset of PR is divided into early and late, with approximately two-thirds occurring early (1-4 months of ATT initiation). Development of PR after completion of an ATT regimen has also been reported, making it difficult to distinguish from reinfection.⁸ Studies have shown that PR of CNS TB presents later compared to other sites, which may be associated with the differences in the immunological reaction dynamics caused by the blood-brain barrier.^{9,10}

Common manifestations of TBM include headache, meningeal signs, vision loss, neurological deficits, and raised intracranial pressure (ICP). Neuroimaging abnormalities include hydrocephalus, infarction, tuberculoma, and exudates. Such findings may worsen or emerge for the first time in a PR.⁴ Previous case reports have described similar manifestations of PR in TBM. A cohort study by Singh et al. reported common manifestations in PR include altered sensorium, fever, headache, reduced vision, and seizures, along with radiological changes such as enhancement of basal exudates, the formation of new or enlargement of existing tuberculomas, the development of infarcts, and progressive ventriculomegaly. They also reported significant predictors of PR in patients with TBM include disseminated or extrapulmonary disease, female gender, concomitant HIV infection, and a shorter duration of illness.^{2,11}

Our patient initially presented with a headache, fever, and double vision, with diagnostics consistent with TBM and tuberculomas. During the course of her ATT regimen, her symptoms completely resolved before reemerging one year later with new neurological deficits and

radiological worsening, thus excluding the possibility of drug resistance, which presents more progressively without prior improvement. Repeat brain MRI after 1 year revealed the formation of new tuberculomas, the most frequently reported radiological finding in PR-TBM.⁴ Despite medical noncompliance, her negative serological test, as revealed by the IGRA Quantiferon-TB test, strongly indicates a PR rather than a reinfection of TB. Repeat CSF analysis was not conducted, as findings are typically variable and nonspecific in PR and do not reliably distinguish PR from relapse or treatment failure.² Additionally, predictors of PR found in our patients include extrapulmonary disease and female gender.

According to the World Health Organization (WHO), patients with PR in TBM should continue their ATT regimen without alteration.¹² Corticosteroids remain a cornerstone of treatment for PR, according to the literature, particularly in symptomatic patients.^{11,13,14,15} Previous studies have reported successful management of PR with corticosteroids, with improvement after a few weeks of treatment. Alleviation of symptoms with corticosteroids may be attributed to an anti-inflammatory effect on the cerebral vasculature and/or a reduction in cerebral edema.^{7,9} Surgical interventions, such as VP shunts and surgical debridement, have also been reported and may be necessary in conditions such as hydrocephalus.^{6,16} Surgical adhesion lysis may be considered when medical management fails to yield improvement or if the diagnosis remains uncertain.¹⁷ Our patient was treated with high-dose intravenous Dexamethasone and showed improvement within a few days, indicating no requirement for surgical intervention. To date, consensus on the treatment of PR is not well established and requires further research, which has made its management difficult.¹⁸ Studies have shown that PRs in extrapulmonary TB do not adversely affect overall clinical outcomes.^{2,19} However, Geri et al. reported PR in CNS TB generally results in poorer outcomes as opposed to those with no CNS involvement.²⁰

4. CONCLUSION

The risk of developing PR underscores the importance of follow-up and close monitoring during TBM treatment, as patients may develop PR at any time during their ATT regimen. The inability to recognize and address PR promptly may lead to catastrophic complications and death. Hence, clinicians must be able to rule out other causes, such as drug resistance and reinfection. This case reinforces the urgency of timely diagnosis and early treatment to reduce morbidity in patients with PR in TBM.

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