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## Paradoxical Reaction in a Patient with Co-Occurring Tuberculous Meningitis and Pott's Disease

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Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Patient:** Male, 36  
**Final Diagnosis:** TB paradoxical reaction  
**Symptoms:** Back pain • diplopia • Headache  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Infectious Diseases

**Objective:** Unusual clinical course  
**Background:**

Paradoxical reactions to tuberculosis (TB) are clinical or radiological worsening of prior tuberculous lesions or the development of new lesions upon treatment with appropriate anti-tuberculosis therapy (ATT). This phenomenon has been described in both HIV-seropositive and HIV-seronegative patients. Although historically estimated to occur in 6–30% of HIV-seronegative patients with TB, the phenomenon is often under-recognized in the current era, particularly in countries of low TB prevalence. We describe a case of a TB paradoxical reaction affecting the CNS and spine in an HIV-seronegative individual who received clinical care in the U.S.

**Case Report:** A 36-year-old HIV-seronegative refugee from Eritrea presented to the hospital with fever, back pain, and headache shortly after arriving to the U.S. He was diagnosed with TB meningitis and Pott's disease and was started on ATT. He developed worsening clinical symptoms, including headaches, transient diplopia, and mood disturbances, as well as new radiologic abnormalities in the brain (tuberculomas) and spine (abnormal enhancement) despite appropriate ATT. He received prolonged 4-drug ATT and steroids as well as changes in his ATT regimen, and multiple attempts were made to biopsy the brain and spine to address concerns for radiologic changes. Eventually, he was discharged 1 year later with clinical improvement and full neurologic recovery.

**Conclusions:** Radiologic and clinical findings due to paradoxical reactions may be unfamiliar to clinicians in countries with low TB prevalence and inadvertently lead to either inadequate management such as the underappreciation of the clinical signs and symptoms indicating potential severity of CNS paradoxical reaction, or conversely overly invasive approaches in a patient who is otherwise clinically improving. Increasing awareness about extrapulmonary paradoxical reactions in such patients is crucial for ensuring appropriate diagnostic approaches and timely clinical management.

**MeSH Keywords:** Immune Reconstitution Inflammatory Syndrome • Tuberculosis, Central Nervous System • Tuberculosis, Osteoarticular

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/909194>



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## Background

A paradoxical reaction (PR) to tuberculosis (TB) is a clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient receiving appropriate anti-tuberculosis therapy (ATT) [1]. Although the exact pathophysiology remains uncertain, it is thought to be due to an exaggerated inflammatory reaction to mycobacterial cell wall antigens in an improving immune system [2]. While such reactions are now commonly reported in human immunodeficiency virus (HIV)-seropositive patients starting antiretroviral therapy, the literature has few reports of paradoxical reactions in HIV-seronegative patients, based mostly on anecdotal case reports or small series [3,4]. These reports have shown that paradoxical reactions occur in about 6–30% of HIV-seronegative patients who receive ATT [5].

Risk factors for developing paradoxical reactions include disseminated disease – defined as multiple sites of TB – and extrapulmonary TB, presumably due to greater mycobacterial antigen loads [6,7]. In particular, TB in the central nervous system (CNS) appears to place patients at higher risk for developing paradoxical reactions [8]. Other predictors include low baseline lymphocyte count and an upsurge in lymphocyte count after treatment initiation [5]. Gupta et al. reported that among 58 patients with central nervous system (CNS) tuberculosis in India, 10 had paradoxical reactions manifesting as TB meningitis and/or tuberculomas on neuroimaging [9].

Paradoxical reactions may present with or without symptoms. When the CNS is affected, complications can potentially be serious because of spatial limitations in the cranium. CNS symptoms may include headache, mental confusion, focal seizure, cranial nerve palsy, and cortical signs due to enlarging tuberculomas [5]. While these symptoms may occur during development of the tuberculomas, overall long-term outcomes are poorly described. One study concluded that the presence of tuberculomas did not significantly affect prognosis [10]. In a series of cases with interval development of tuberculomas or documented enlargement of tuberculomas while on ATT, the majority of patients eventually had clinical improvement, although 25% had residual neurological symptoms [11]. Such long-term complications include paraplegia, blindness, or, rarely, death [8,11,12]. The optimal management of such complications is not yet clear.

In cases of CNS paradoxical reactions, patients received adjunctive steroids or additional second-line ATT [9]. Use of corticosteroids has largely been agreed upon in the literature, particularly for patients with symptomatic paradoxical reactions [12,13]. Surgical management has also been described, including VP shunts and surgical debridement [5,14]. However, precise guidelines for diagnosis and treatment are not established,

making management of this condition challenging, particularly for those unfamiliar with paradoxical reactions.

## Case Report

A 36-year-old male Eritrean refugee presented to the Emergency Department (ED) complaining of chronic mid-back pain. He had been in a motor vehicle accident 7 years prior, but otherwise did not have any recent history of trauma. He denied fevers, chills, or headaches. On exam, he had full strength with flexion and extension, was able to raise his legs off the bed, had normal ambulation, and did not have focal midline back tenderness. No radiologic imaging was obtained. He was discharged from the ED with symptomatic management. He presented again to the ED 1 month later with persistent back pain, but this time with fevers and new frontal headache. He denied prior or current alcohol or illicit drug use. There was no significant family history. He had no known BCG administration or treatment for latent TB infection. Review of systems did not document recent weight loss.

On admission, his temperature was 38.6°C. His weight was 68.04 kg (BMI 23 kg/m<sup>2</sup>), which was below his ideal body weight of 77 kg. The chest and abdominal exams were normal. There was no nuchal rigidity, but he had vertebral tenderness at T6 through T8. His neurological exam was otherwise normal. His labs were as follows: WBC 3.9 cells/ $\mu$ l [26% lymphocytes]; hemoglobin 13.5 g/dL; platelets 194 000/ $\mu$ l; creatinine 0.71 mg/dL; AST 19  $\mu$ L; ALT 30  $\mu$ L; ESR 25 mm/hr; and albumin 4.6 g/dL. Malaria smear, HIV test, and blood cultures were negative.

An MRI spine (Figure 1A) showed discitis, osteomyelitis, and a paraspinal abscess at T8–T9. CT-guided aspirate of the abscess showed 3+ smear positive for acid-fast bacilli (AFB). Brain MRI (not shown) with contrast showed mildly increased leptomeningeal enhancement along bilateral Sylvian fissures. A lumbar puncture showed the following: opening pressure 23 mm of H<sub>2</sub>O; 137 wbc/mm<sup>3</sup> (81% lymphocytes, 6% granulocytes, 13% monocytes); protein 561 mg/dL; glucose <20 mg/dL; gram stain showed no organisms, and AFB smear was negative. The patient was diagnosed with concomitant Pott's disease and TB meningitis and was started on steroids (initially 60 mg of prednisone for 2 days and then switched to a dexamethasone taper starting at 15 mg daily) and 4-drug anti-tuberculosis therapy (ATT) with 600 mg daily of rifampin (RIF), 300 mg daily of isoniazid (INH), 1500 mg daily of pyrazinamide (PZA), and 1200 mg daily of ethambutol (ETB).

One month later, the paraspinal aspirate and CSF cultures returned with pan-sensitive *M. tuberculosis*. The patient developed double vision; Ophthalmology was consulted and noted



**Figure 1.** MRI Spine. (A) Sagittal T1 post-contrast image obtained at admission demonstrates discitis/osteomyelitis at T8–T9, with normal appearance of T5 and T7. (B) MRI spine sagittal T1 post-contrast image 7 months later demonstrates an interval collapse of T8–T9 and new subtle enhancement of the T5 and T7 vertebral bodies (edema was also seen on fluid-sensitive STIR imaging, not shown), as well as an interval compression fracture of the T5 vertebral body.

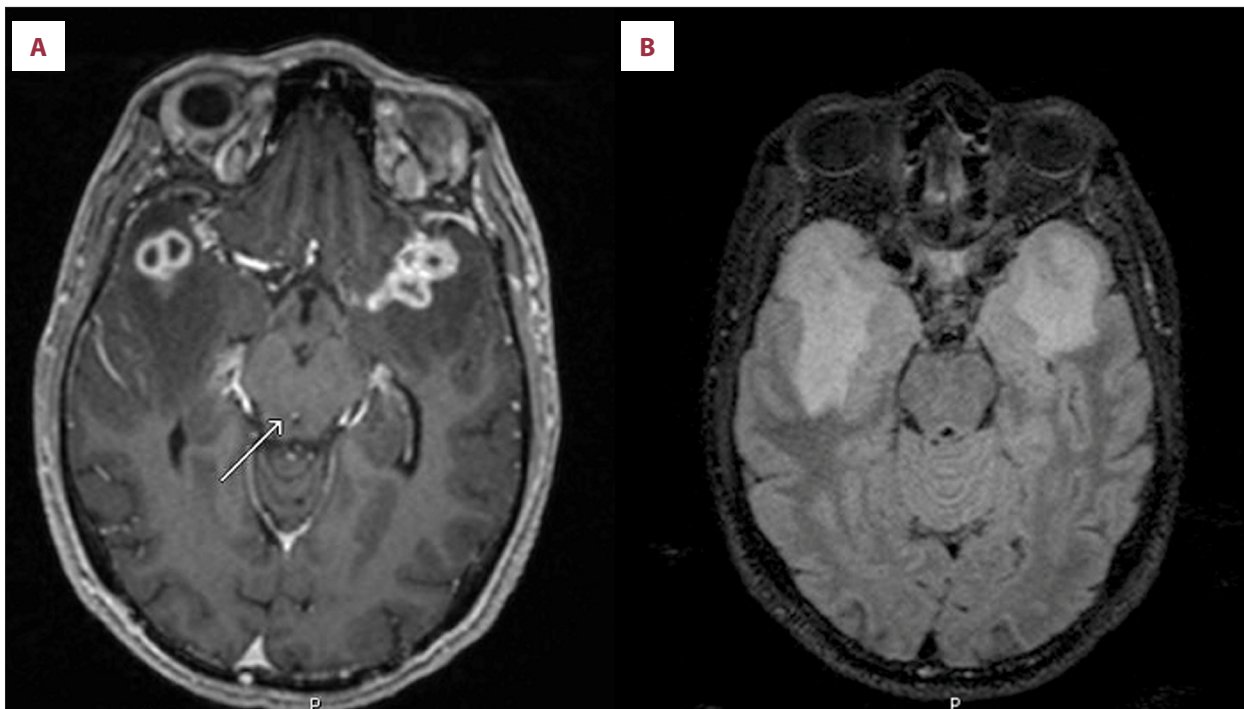
a decrease in visual acuity but no definite changes consistent with optic neuritis, and recommended discontinuation of ethambutol. A cranial nerve exam was not recorded. Repeat LP was not performed. Six weeks after diagnosis, he was transferred to our hospital for possible surgical management of spinal tuberculosis. During this time, he continued to have back pain and developed mood disturbances, suicidal ideation, persistent headaches, and seizures. Repeat brain MRI using Gadolinium reformat technique (MPRAGE) (Figure 2A) showed multiple new temporal lobe intracranial tuberculomas with edema (Figure 2B, FLAIR image). Repeat CSF analysis showed: 373 nucleated cells/ $\mu\text{L}$  (59% lymphocytes/41% segs); protein 600 mg/dL; glucose 38 mg/dL; opening pressure was not recorded; and AFB stain and TB-PCR were negative. An EEG showed no epileptiform activity. Moxifloxacin (400 mg daily) was added as a fourth drug since ethambutol had been stopped. A repeat spine MRI (not shown) showed mild-moderate collapse of T8-9 and spinal cord compression at multiple levels. A bone biopsy was performed at T8-9, showing chronic osteomyelitis with negative AFB stain. He was discharged on the aforementioned doses of INH, RIF, PZA, Moxifloxacin, and steroids (dexamethasone 6 mg daily with planned taper). Dosing was modified based on therapeutic drug level monitoring.

He was readmitted 1 day later at an outside hospital due to difficulty obtaining medications from the pharmacy. During a subsequent prolonged hospital stay, a follow-up routine brain MRI (4 months after diagnosis) showed stable but persistent

ring-enhancing lesions despite documented adherence to 4-drug ATT and steroids. Gamma knife-guided stereotactic brain biopsy was performed, which showed abundant histiocytes and T cells with negative AFB stain. Brain biopsy cultures were negative. He was discharged to a rehabilitation facility to continue ATT and steroids.

Seven months after his initial diagnosis, he re-presented to the ED with worsening back pain, fall, and recurrent seizure-like activity. An MRI spine showed interval decrease in T8–T9 discitis/osteomyelitis, but new subtle enhancement of T5 and T7 along with a new T5 compression fracture (Figure 1B). He was transferred back to our hospital due to concern for progressive disease; Interventional Neuroradiology attempted to biopsy T5 but were unsuccessful due to a sclerotic vertebral body. A repeat CSF analysis showed 16 nucleated cells/ $\mu\text{L}$  (86% lymphocytes); protein 54 mg/dL; glucose 47 mg/dL; opening pressure was not recorded; AFB stain, TB-PCR, and AFB cultures were negative.

Over the ensuing 5 months, the patient remained in the hospital and was noted to have seizures thought to be consistent with psychogenic non-epileptic type (pseudoseizures); nonetheless, he was prescribed anti-seizure medications due to the intracranial masses seen on neuro-imaging. Eight months after original presentation, his ATT was simplified to INH 300 mg daily and RIF 600 mg daily. In total, the patient spent 1 year as an inpatient, ultimately completing 12 months of ATT: 8 months



**Figure 2.** MRI brain. Imaging obtained 6 weeks after ATT. (A) An axial T1 magnetization-prepared rapid gradient-echo (MPRAGE) post-contrast image demonstrates ring-enhancing tuberculomas in the temporal lobes bilaterally, as well as enhancement of the ependymal lining of the aqueduct of Sylvius (arrow). (B) An axial fluid-attenuated inversion recovery (FLAIR) image demonstrates areas of vasogenic edema adjacent to the tuberculomas.

of 4-drug therapy followed by 4 months of INH and RIF. He received 10 months of steroids, with doses of dexamethasone ranging from 0.5 mg every other day to 15 mg daily of dexamethasone. Periods of tapering were interspersed throughout his complicated hospital course. He had an overall 10-kg weight gain and his headaches and pseudoseizures resolved and he had no focal neurologic deficits. He remained depressed due to his prolonged hospital stay. Two months after completing therapy and an almost year-long hospitalization, he was seen in the clinic and noted to be healthy and to have significantly improved mood.

## Discussion

Prior studies have discussed paradoxical reactions in HIV-seronegative patients with pulmonary and extrapulmonary TB, particularly in cases of TB meningitis [1,2,6]. Our patient was originally diagnosed with TB meningitis, and follow-up MRI after 1.5 months of ATT showed new tuberculomas (Figure 2), the most frequently reported paradoxical reaction (PR) noted on imaging studies [15]. While tuberculomas may be asymptomatic and present as an incidental finding, serious CNS sequelae may ensue. In retrospect, our patient developed symptoms such as diplopia, headaches, mood disturbances, and seizures that were suggestive of PR, yet clinicians did not recognize the

potential seriousness of these symptoms. Specifically, clinicians did not consider the possibility of VI nerve palsy, which can present as a falsely localizing sign in the setting of increased ICP, particularly in patients with CNS TB who develop diplopia. Failure to recognize this could have resulted in permanent cranial nerve damage or death. We suggest that he should have been evaluated for increased ICP, including detailed neurological examination, and considered for interventions such as serial LPs or VP shunting earlier in his clinical course. It is possible that his prolonged symptoms of headaches and pseudoseizures may have been attributed to under-recognized increased ICP.

Our patient illustrates the challenge of managing paradoxical reactions because physicians must rule out other causes of clinical or radiological worsening, including drug resistance and poor medication adherence. In countries such as the U.S. where TB prevalence is low and technological interventions are readily available, it is tempting to image and biopsy new radiographic lesions, as was done with our patient, due to unfamiliarity with the presentations of PR. However, these interventions may cause more harm and delay other possible effective interventions.

The American Thoracic Society and the Centers for Disease Control and Prevention (CDC) guidelines for treating

drug-susceptible extrapulmonary TB recommend 2 months of 4-drug ATT followed by INH and RIF for a total of 9–12 months [10]. Steroids are recommended for 2–4 weeks, with a 6–8-week taper in patients who develop paradoxical reactions [16]. Treatment for paradoxical reactions is not well-established, but there seems to be some agreement as to the use of corticosteroids in paradoxical reactions involving the CNS. Our patient's treatment included 8 months of 4-drug ATT and 10 months of prednisone, which was not in line with guidelines, and reflected the clinicians' uncertainty and discomfort in treating paradoxical reactions.

While his behavioral issues may have been a part of the CNS-involved paradoxical reaction or other underlying psychiatric illness, prolonged steroid use may have also played a role, causing steroid-induced psychosis and/or depression. Interestingly, the paradoxical reactions developed in our patient while he was receiving steroids, raising questions about their role, efficacy, and recommended doses and duration in such reactions, which has yet to be established in the literature. Interestingly, prior reports show that treatment with ATT for such reactions has varied, with a range of treatment spanning 315–722 days [17].

He was also diagnosed with Pott's disease involving T8 and T9, and on follow-up MRI 7 months into ATT, manifested new, non-contiguous vertebral lesions at T5 and T7, suggestive of a paradoxical reaction. In contrast to the worsening of existing vertebral lesions described by Im et al. [19], our patient developed new enhancement and compression fractures at non-contiguous vertebrae. Non-contiguous spinal involvement is rare, although a prospective study in South Africa found that 16% of 98 patients with TB spondylitis had such lesions on spine MRI at diagnosis [18]. Nonetheless, our patient's case suggests that non-contiguous spinal TB can be seen not only at time of diagnosis, but also as part of a paradoxical reaction, even after 7 months of ATT. There have been few reported cases of paradoxical reaction involving TB spondylitis. Im et al. [19] reported 4 cases of paradoxical reactions in HIV-seronegative

patients that developed 2–12 weeks after starting 4-drug ATT; symptoms included worsening lower back pain and leg weakness, and T1-gadolinium-enhanced MRI showed worsening of vertebral enhancement [19]. All 4 patients underwent surgical decompression, finished 9–12 months of ATT, and recovered without sequelae [19].

## Conclusions

In summary, we report a patient with extrapulmonary TB manifesting as concurrent Pott's disease and TB meningitis, who subsequently developed paradoxical reactions in the brain and potentially in the spine during appropriate ATT and steroid therapy. This paradoxical reaction manifested with clinical symptoms – focal neurologic symptoms – and changes on radiological imaging. While multiple studies have found that some paradoxical reactions in extrapulmonary TB do not adversely affect overall clinical outcome [2,9], CNS lesions can have serious consequences and thus require more vigilance and potentially enhanced intervention, including surgical management. Conversely, better understanding of this clinical presentation can lead to avoidance of unnecessary invasive interventions such as multiple biopsies or unnecessarily prolonged antimicrobial and steroid treatment. However, there is at present no consensus on how to best manage these patients. In countries with low TB prevalence, we believe that increased awareness of extrapulmonary paradoxical reactions in HIV-negative patients should inform clinical decision-making, including guiding appropriate use of clinical diagnostics and interventions.

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## Conflicts of interest

None.

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