Case Report

Paradoxical miliary tuberculomas in the brain in an immunocompetent case of pulmonary miliary tuberculosis: A case report

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ABSTRACT

Paradoxical reactions are immune-mediated *de novo* or worsening manifestations after initial improvement in a tubercular case during antitubercular therapy (ATT). Here, we report a young immunocompetent female diagnosed with miliary tuberculosis (TB), complicated by new and acute onset headache, vomiting, and left-sided weakness on the 15th day of ATT. Neuroimaging revealed multiple new ring-enhancing lesions consistent with miliary intracranial tuberculomas in the cortex, basal ganglia, and cerebellum. Treatment failure, drug resistance, alternative infections, malignancy, and drug toxicity were excluded. A paradoxical reaction as military tuberculoma in the brain was diagnosed. Initiation of corticosteroids resulted in rapid neurological improvement and radiological resolution by 8 weeks. Recognizing paradoxical intracranial tuberculomas early is essential to avoid misclassification as drug-resistant TB. Continued ATT with timely corticosteroid therapy leads to favorable outcomes.

Key words: Immunocompetent, Intracranial tuberculomas, Miliary tuberculosis, Paradoxical reaction

Paradoxical reactions in tuberculosis (TB) have been defined as either *de novo* clinical or radiological manifestations in a tubercular case already on antitubercular therapy (ATT) or worsening manifestations after initial improvement on ATT [1]. They occur in 6–30% of patients with TB, especially in extrapulmonary disease [2]. Central nervous system (CNS) involvement is one of the most serious paradoxical manifestations [3]. Although immune reconstitution inflammatory syndrome (IRIS) is common in human immunodeficiency virus (HIV)-infected individuals, it also occurs in immunocompetent patients [4]. Paradoxical reactions can be seen regardless of immune status in many other mycobacteria besides *Mycobacterium tuberculosis*, such as *Mycobacterium avium* [5], *Mycobacterium marinum* [6], *Mycobacterium ulcerans* [7], and *Mycobacterium leprae* as erythema nodosum lepra reaction [8]; and other bacteria as Jarisch Herxheimer reaction in leptospirosis, such as Syphilis and Lyme disease seen on ongoing treatment [9]. Paradoxical reactions in immunocompetent patients stem from rapid restoration or unmasking of cell-mediated immunity soon after starting ATT [10]. Early development of intracranial tuberculomas during ATT is uncommon, with disseminated military tuberculoma all over the brain being even sparser and can be mistaken for treatment failure, multidrug-resistant TB, or progression of primary disease. Paradoxical reactions require continuation of the same ATT regimen along with adjunctive corticosteroids, whereas treatment failure or drug resistance warrants alternative regimen modification.

We report a case of a young immunocompetent female with miliary TB who developed early paradoxical multiple miliary intracranial tuberculomas within 15 days of initiating ATT. This case underscores the clinical relevance of recognizing paradoxical reactions in non-HIV tubercular patients and emphasizes the importance of timely diagnosis to prevent unnecessary investigations, avoid inappropriate therapy changes, and ensure optimal patient outcomes.

CASE DESCRIPTION

A 22-year-old previously healthy, immunocompetent female presented to the outpatient department with a 3-month history of intermittent high-grade fever, associated with progressive loss of appetite and unintentional weight loss. The symptoms were insidious in onset and gradually worsened over time. She denied hemoptysis, night sweats, altered sensorium, headache, seizures, or recent travel. There was no history of TB, diabetes, corticosteroid use,

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or immunosuppressive therapy. Family history was non-contributory.

On examination, the patient appeared pale and mildly cachexic. Her vitals showed tachycardia with low-grade fever; blood pressure and oxygen saturation were within normal limits. Respiratory examination revealed reduced air entry with faint vesicular breath sounds bilaterally and fine crepitations in all areas. The rest of the systemic examination was normal.

Initial laboratory investigations revealed normocytic normochromic anemia, elevated erythrocyte sedimentation rate (ESR), and mildly raised C-reactive protein levels. Liver and renal function tests were within normal limits. HIV-1 and 2 Enzyme-Linked Immunosorbent Assay was negative (Table 1). Sputum AFB smear and GeneXpert testing were negative, likely due to the low bacillary load typical of miliary TB.

Chest radiograph demonstrated diffuse, fine, uniformly distributed miliary nodules throughout both lung fields (Fig. 1a). High-resolution computed tomography of the thorax further confirmed the presence of multiple micronodules in a random pattern, suggestive of miliary TB (Fig. 1b).

Based on clinicoradiological correlation, a diagnosis of miliary TB was established, and the patient was initiated on standard first-line ATT (HRZE regimen) along with pyridoxine. She was advised to have a close follow-up.

Table 1: Laboratory parameters at the time of presentation

Parameters (Unit)	Values	Reference range
Hemoglobin (gm/dL)	9.0	11.5–15.5
Total leukocyte count (cumm)	6600	4000–11000
Platelet count (lac/cumm)	1.21	1.5–4.0
Erythrocyte sedimentation rate (mm/h)	44	0–20
C-reactive protein	Reactive	
Serum glutamic-oxaloacetic transaminase (U/L)	49	<40
Serum glutamic pyruvate transaminase (U/L)	46	<34
Alkaline phosphate (U/L)	121	<240
S Urea (mg/dL)	25	13–43
S Creatinine (mg/dL)	10	0.6–1.2
HIV I and II	Non- reactive	

HIV: Human immunodeficiency virus

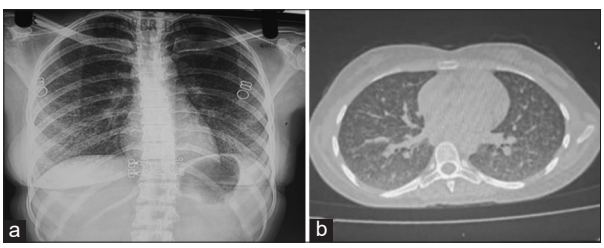

Figure 1: (a) Chest X-ray showing diffuse, uniformly distributed miliary nodules; High-resolution computed tomography thorax showing randomly distributed micronodules consistent with miliary tuberculosis

On the 15th day of ATT, the patient returned with new symptoms: Persistent, dull aching headache, recurrent vomiting, and a feeling of imbalance for 1 day. In view of persistent vomiting, liver function tests were carried out, which came out to be normal. Over the next 24 h, she developed numbness in her left upper and lower limbs with mild left-sided weakness, prompting neurological evaluation. Repeat general examination showed no signs of meningeal irritation. Neurological examination revealed grade 4/5 motor weakness in the left upper and lower limbs, with preserved cranial nerve functions. For these acute-onset focal neurological deficits, an urgent NCCT Head was performed. Imaging revealed multiple well-defined ring-enhancing lesions in the basal ganglia, cerebral hemispheres, and cerebellum, surrounded by significant vasogenic edema (Fig. 2). Magnetic resonance imaging (MRI) Brain was performed, which showed multiple well-defined, rounded, peripherally enhancing lesions; few of them appeared conglomerated and coalescing; present in the bilateral cerebral hemispheres, cerebellum, and basal ganglia, suggestive of military tuberculomas (Fig. 3).

The sudden appearance of *de novo* CNS lesions shortly after initiating ATT raised concerns for the differentials, such as paradoxical reaction, treatment failure, drug-resistant TB, additional superadded infections, and neoplastic lesions. However, the timing, the patient's good adherence, absence of drug resistance risk factors,

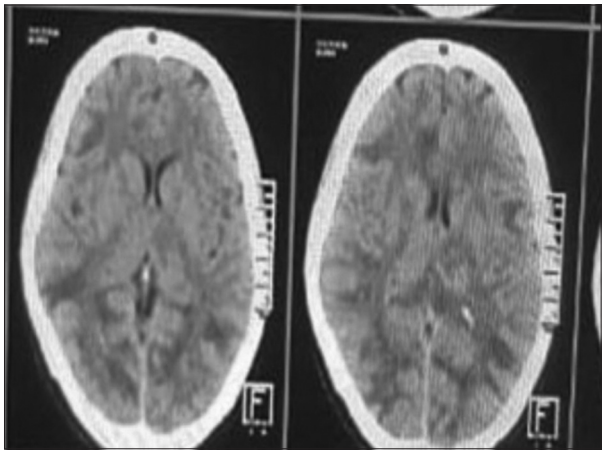

Figure 2: Non-contrast computed tomography brain showing multiple ring-enhancing lesions with surrounding edema

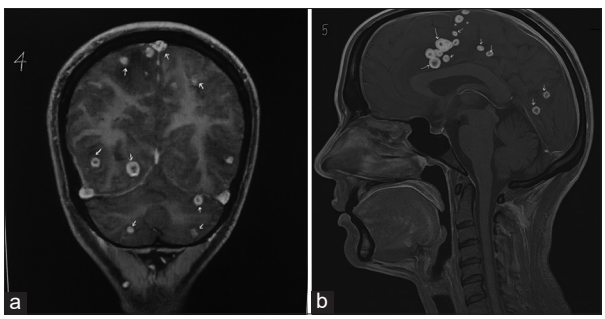

Figure 3: (a) Magnetic resonance imaging (MRI) brain (T1 post-contrast) showing multiple peripherally enhancing tuberculomas, (b) MRI brain showing conglomerated tuberculomas with surrounding edema

and rapid radiological progression after starting therapy strongly favored a paradoxical reaction.

Given the diagnosis of paradoxical miliary tuberculomas in the brain in a case of miliary pulmonary TB, the existing ATT regimen was continued unchanged. The patient was started on dexamethasone (0.4 mg/kg/day) to reduce intraparenchymal inflammation and cerebral edema. Over the next 5 days, she showed marked neurological improvement, with resolution of headache and vomiting and gradual restoration of limb strength. Oral corticosteroids were tapered gradually over 8 weeks. Routine blood monitoring remained stable throughout therapy. Follow-up CT brain after 4 weeks of therapy showed marked reduction in size of tuberculoma as well as edema (Fig. 4). Clinical course and recovery state with outcome of the case are depicted in Table 2.

DISCUSSION

Paradoxical reactions to ATT constitute a challenging and often misunderstood phenomenon, particularly in patients with disseminated or CNS TB. These reactions occur when a patient, initially responding to therapy, develops new or enlarging lesions or clinical deterioration due to an exaggerated immune response following partial immune restoration [1]. In the context of miliary TB, the high bacillary burden creates an intense antigenic environment, predisposing the patient to TB-associated IRIS once effective therapy is initiated [11]. In our case, the abrupt appearance of intracranial tuberculomas after commencement of ATT is consistent with *de novo* early paradoxical reactions. Other differentials are considered and ruled out as shown in Table 3 [12-14]. After excluding these possibilities, the presence of newer intracranial lesions during clinical improvement strongly supported the diagnosis of paradoxical intracranial tuberculomas secondary to immune reconstitution. Immunologically, the paradoxical reaction arises from a delayed but vigorous restoration of cell-mediated immunity, particularly an amplified Th1-driven response marked by elevated interferon-γ and TNF-α. This heightened immune activity enhances granulomatous inflammation around residual mycobacterial antigens [15].

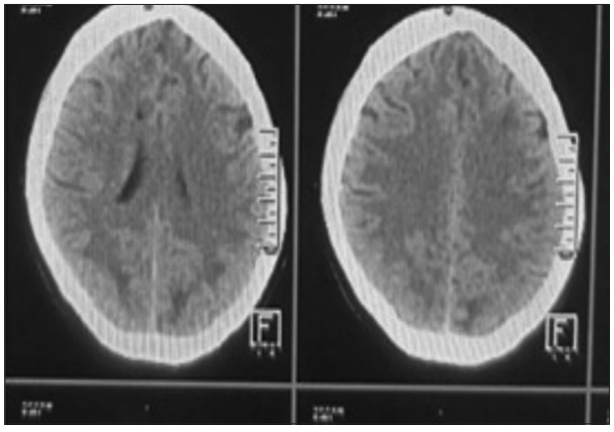

Figure 4: Follow-up computed tomography brain showing reduction in the number and size of tuberculomas and near complete resolution of edema

Management remained centered on continuing effective ATT and initiating corticosteroids to suppress the inflammatory surge. The patient exhibited both clinical stability and radiological improvement following the introduction of steroid therapy.

Although paradoxical intracranial tuberculomas have been documented sparsely in literature, the phenomenon remains uncommon, with only a small subset arising in the setting of pulmonary miliary TB and even sparser to have military intracranial tuberculomas as a paradoxical appearance. Even more infrequent are early-onset paradoxical reactions, as most published cases demonstrate CNS worsening after 6–12 weeks of therapy rather than within the first few weeks. The present case is therefore distinctive in several respects: It occurred unusually early in the treatment course, developed de novo intracranial tuberculomas rather than enlargement of pre-existing lesions, manifested in an immunocompetent host, and demonstrated a rapid and favorable response to corticosteroids-all features that collectively differentiate it from the majority of previously reported cases.

In a classic review and series, Afghani and Lieberman reported development or enlargement of intracranial tuberculomas typically within the first 3 months of therapy; although most patients improved with continuation of ATT and adjunctive corticosteroids, a minority experienced residual neurological deficits (≈25%), some required surgical intervention (under one-third), and isolated deaths were reported [1]. Reiser *et al*. described a patient with miliary pulmonary TB who developed intracranial tuberculomas during chemotherapy and subsequently improved with continued first-line ATT and extended therapy, emphasizing that radiological progression in this setting does not necessarily indicate treatment failure [16]. Özer *et al*. similarly documented an early paradoxical CNS worsening in an HIV-negative patient, with clinical and radiological improvement after corticosteroid therapy while maintaining ATT, reinforcing that IRIS can affect immunocompetent individuals [17]. Compared with these reports, our patient, an immunocompetent young female with miliary TB, developed multiple intracranial miliary tuberculomas unusually early (day 15 of ATT) but demonstrated rapid clinical recovery and marked radiological resolution within 8 weeks after continuation of HRZE and initiation of dexamethasone (0.4 mg/kg/day, tapered over 8 weeks). This favorable course mirrors

Table 2: Timeline of events

Day	Event
0	Diagnosis of miliary TB; started HRZE
15	Headache, vomiting, left-sided weakness
15	NCCT Brain: multiple new ring-enhancing lesions
16	Dexamethasone initiated
20	Clinical improvement
28	Follow-up CT: reduced edema and lesions

TB: Tuberculosis, CT: Computed tomography, NCCT: Non-contrast computed tomography, HRZE: Hisoniazid, rifampicin, zyrazinamide, and ethambutol

Table 3: Showing differentials other than paradoxical reaction with excluding remarks

Other differentials	Excluding remarks
Multidrug-resistant or drug-resistant tuberculosis	The patient was afebrile for the first 2 weeks after treatment. The patient demonstrated strict adherence to therapy and maintained therapeutic dosing. There was no evidence of clinical decline in respiratory or systemic symptoms suggestive of uncontrolled primary disease
Poor compliance or inadequate drug absorption	The patient maintained excellent adherence, confirmed through history and pill counts. There were no gastrointestinal conditions impairing absorption. Steady clinical improvement in systemic TB parameters argued against inadequate drug levels.
Superadded intracranial infections	Absence of immunosuppression (HIV-negative) No clinical profile suggestive of fungal or parasitic infection Neuroimaging findings consistent with tuberculous granulomas
Malignancy (Primary CNS tumor or metastases)	The absence of a primary malignancy Imaging characteristics align more closely with granulomatous lesions
Drug toxicity or adverse neurological reactions	No ATT-associated neurotoxic profile was present Hepatic and renal parameters remained stable
Progression of untreated disease	Radiological worsening due to uncontrolled TB typically coincides with systemic deterioration, which was not observed. The patient's systemic symptoms improved, indicating therapy efficacy

ATT: Antitubercular therapy, TB: Tuberculosis, CNS: Central nervous system, HIV: Human immunodeficiency virus

the majority of published cases where continuation of effective ATT combined with timely anti-inflammatory treatment yields good outcomes, while underscoring the need to exclude drug resistance, alternative infections, or neoplasms before labeling deterioration as a paradoxical reaction.

Recognizing paradoxical reactions early not only prevents misclassification of treatment failure but also ensures that patients receive appropriate care without the non-judicious use of second-line antitubercular agents, safeguarding both individual outcomes and broader antimicrobial stewardship.

CONCLUSION

This case is rare as it is the occurrence of miliary tuberculomas in the brain occurring very early as a paradoxical reaction in an immunocompetent case of pulmonary miliary TB. This case underscores the essential principle that the emergence of new lesions during otherwise appropriate and adequately supervised treatment should immediately prompt clinicians to consider Paradoxical Reaction as a differential diagnosis. A high index of suspicion for paradoxical reaction allows for timely, targeted intervention-most notably corticosteroid therapy-which can yield excellent clinical recovery.

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