

<b>TITLE OF CASE</b>
Paradoxical reaction to antitubercular treatment in a case of pulmonary tuberculosis
<b>SUMMARY</b>
<p>A 51-year-old male presented with intermittent fever, mild cough and loss of appetite since one-month. His sputum smear was positive for acid-fast bacilli and his chest radiograph revealed apical infiltrations. The patient was treated with antitubercular therapy (ATT) and recovered well for one month. Then, he suddenly developed focal seizures. A magnetic resonance imaging of the brain with gadolinium enhancement showed high intensity nodular foci in the frontal, parietal and occipital regions. The patient was diagnosed as a case of paradoxical reaction to ATT and was successfully managed with continued ATT and adjunctive steroid therapy.</p>
<b>BACKGROUND</b>
<p>Paradoxical response to ATT, defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions during appropriate treatment, creates a diagnostic difficulty. Central nervous system is one of the most common sites of involvement among non-HIV-infected patients.[1] High degree of suspicion is required when a patient presents with neurological symptoms over the course of successful tuberculosis treatment.</p>
<b>CASE PRESENTATION</b>
<p>A 51-year-old farmer presented to a local health facility in western Nepal with a one-month history of intermittent fever and decreased appetite. He had a mild, productive cough, but his physical exam was normal. Investigations revealed a chest radiograph (Fig 1) showing apical infiltrations in both lung fields. Three sputum smears were positive for acid-fast bacilli and the culture grew out mycobacterium tuberculosis sensitive to first line drug therapy. Antitubercular therapy (ATT) consisting of rifampicin, isoniazid, ethambutol, and pyrazinamide was started. The patient was taking his medications regularly. One month into his treatment, the patient was afebrile and his cough had subsided. The chest roentgenogram showed improvement and repeat sputum smears were negative. Then, he suddenly developed 4 episodes of focal seizures involving the right half of the body while working in his rice field. There was no history of trauma or toxic substance ingestion. At this time a complete physical exam (including neurological) revealed no abnormalities.</p>
<b>INVESTIGATIONS</b>
<p>Initial laboratory investigations (post seizure) revealed haemoglobin concentration of 10.1g/dL, leucocyte count of <math>11 \times 10^9</math> /L with 88 % neutrophils and 12% lymphocytes. Liver, renal, and electrolyte studies were normal. HIV test was negative. A non-contrast computed tomography (CT) scan of the head was normal with no midline shift. Cerebrospinal fluid analysis revealed cloudy fluid with a protein concentration of 271mg/dL, a glucose concentration of 29mg/dL (with a blood glucose concentration of 108mg/dL), red blood cells 145 per mm<sup>3</sup>, and white blood cells 7 per mm<sup>3</sup> (2 polymorphs &amp; 5 lymphocytes). Gram stain and acid-fast bacilli stains were negative. A magnetic resonance imaging (MRI) of the brain with gadolinium enhancement showed high signal intensity nodular foci in frontal, parietal</p>

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and occipital lobes (Fig 2).
<b>DIFFERENTIAL DIAGNOSIS</b>
Neurocysticercosis Pyogenic brain abscess Cerebral space occupying lesions Progressive and disseminated TB due to low adherence, drug resistant TB or low absorption of the drug Paradoxical reaction to antitubercular therapy manifesting as intracranial tuberculomas
<b>TREATMENT</b>
The patient was treated with a tapering dose 60 mg of prednisolone for 9 weeks. In addition, his ATT was continued for 18 months.
<b>OUTCOME AND FOLLOW-UP</b>
The patient had no further bouts of seizure and responded well to the treatment. A repeat MRI eight months after his neurological complications was normal. The patient completed his ATT regimen and was fine when last seen in March 2012.
<b>DISCUSSION</b>
<p>Neurological problems during the course of ATT in both immune competent and compromised patients are a recognized phenomenon.[2] Although neurocysticercosis is common in Nepal, the MRI findings were not in keeping with this disease. Similarly the history and radiological findings were also not in keeping with either pyogenic brain abscess or space occupying lesions. Our patient's neurological findings after the start of ATT may have been a new development or possibly a progression of intracranial tuberculomas.[3,4] Routine brain imaging is not indicated in non-symptomatic patients and was not required at baseline for our patient. Although the definite etiology of the paradoxical reaction, as seen in our patient is unknown, it is now generally believed that there might be an immunological basis for this reaction. The initiation of ATT for pulmonary TB may partly be responsible for immune enhancement that may have occurred at microscopic intracranial foci in the brain and lead to his clinical presentation with seizures.[2] It is difficult to differentiate a paradoxical reaction from treatment failure, drug resistance or a secondary infection. Our patient was under directly observed treatment, complaint to the regimen and the culture revealed no resistance to the first line of drugs. If our patient was HIV positive and therefore at a higher risk of other infectious or malignant processes, a brain biopsy for definitive diagnosis would be prudent.</p> <p>Paradoxical deterioration in the central nervous system clinically presents with headache, mental confusion, focal seizure, cranial nerve palsy, and cortical signs such as hemiparesis, paraparesis, and hemianesthesia as a result of enlargement or development of intracranial tuberculoma and hydrocephalus.[1,4] Paradoxical tuberculomas are observed in approximately 1% cases of active tuberculosis.[5] They are more commonly observed in tuberculous meningitis, reported in 4.5 – 28% of the cases,[5] where patients developed new intracranial lesions,[6] presented with paradoxical enlargement of previously verified intracranial tuberculomas during the ATT course,[7] or developed tuberculomas after completing ATT for tuberculous meningitis.[8]</p> <p>Deterioration during ATT therapy is clearly a challenging problem especially in the developing world.[1] A paradoxical reaction needs to be suspected and investigated in any patient on ATT who presents with neurological findings. The potential beneficial effect of steroids while continuing ATT in many of these patients has been well documented.[2] Hence early</p>

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recognition and treatment of this disease entity is of paramount importance especially in areas with widespread treatment for tuberculosis.

## LEARNING POINTS/TAKE HOME MESSAGES

- An initial improvement during ATT therapy followed by deterioration despite a definitive diagnosis, treatment and compliance to treatment should be suspected as paradoxical reaction to ATT even in an immunocompetent person.
- Discontinuation of in ATT therapy is not warranted in paradoxical reactions, and can be effectively managed with continuation of the same drug regimen.
- Adjunct systemic steroid therapy helps improve symptoms and reduces tuberculoma size.

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FIGURE/VIDEO CAPTIONS
<p>Figure 1: Heterogeneous, bilateral infiltrations in the upper lobes of both lungs.</p> <p>Figure 2: Gadolinium-enhanced, magnetic resonance images showing multiple high signal intensity foci in frontal, bilateral parietal and occipital lobes.</p>
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