CASE REPORT

Paradoxical reaction to antitubercular treatment in a case of pulmonary tuberculosis

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Accepted 4 February 2016

SUMMARY

A 51-year-old man presented with intermittent fever, mild cough and loss of appetite of 1-month duration. His sputum smear was positive for acid-fast bacilli and his chest radiograph revealed apical infiltrations. The patient was treated with antitubercular therapy (ATT), recovered and was well for 1 month, after which he suddenly developed focal seizures. MRI 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.

and leukocyte count of $11 \times 10^9/L$ with 88% neutrophils and 12% lymphocytes. Liver, renal and electrolyte studies were normal. HIV test was negative. A non-contrast CT scan of the head was normal with no midline shift. Cerebrospinal fluid analysis revealed cloudy fluid with a protein concentration of 271 mg/dL, a glucose concentration of 29 mg/dL (with a blood glucose concentration of 108 mg/dL), red blood cells $145/mm^3$ and white cell counts $7/mm^3$ (2 polymorphs and 5 lymphocytes). Gram stain and acid-fast bacilli stains were negative. A MRI of the brain with gadolinium enhancement showed high signal intensity nodular foci in frontal, parietal and occipital lobes (figure 2).

BACKGROUND

Paradoxical response to antitubercular therapy (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. The central nervous system is one of the most common sites of involvement among non-HIV-infected patients.¹ A high degree of suspicion is required when a patient presents with neurological symptoms over the course of successful tuberculosis treatment.

CASE PRESENTATION

A 51-year-old man, a farmer, presented to a local health facility in western Nepal, with a 1-month history of intermittent fever and decreased appetite. He had a mild productive cough, but his physical examination was normal. Investigations including a chest radiograph (figure 1) revealed 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. 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 four episodes of focal seizures involving the right half of the body while working in his rice field. There was no history of trauma and no toxic substance ingestion. At this time, a complete physical examination (including neurological) revealed no abnormalities.

INVESTIGATIONS

Initial laboratory investigations (postseizure) revealed haemoglobin concentration of 10.1 g/dL,

DIFFERENTIAL DIAGNOSIS

- 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 ATT manifesting as intracranial tuberculomas

TREATMENT

The patient was treated with a 60 mg and tapering dose of prednisolone for 9 weeks. In addition, his ATT was continued for 18 months.

OUTCOME AND FOLLOW-UP

The patient had no further bouts of seizure and responded well to the treatment. A repeat MRI 8 months after his neurological complications was normal. The patient completed his ATT regimen and was fine when last seen, in March 2012.

DISCUSSION

Neurological problems during the course of ATT in both immune competent and compromised patients are a recognised phenomenon.² Although neurocysticercosis is common in Nepal, the MRI findings in this case were not in keeping with this disease. Similarly, the history and radiological findings were also not in keeping with pyogenic brain abscess nor with 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 aetiology of the paradoxical reaction, as seen in our patient, is unknown, it is now generally believed that there

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To cite: Paudyal B, Paudel K, Shakya M, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-214285

Figure 1 Heterogeneous, bilateral infiltrations in the upper lobes of both lungs.

might have been an immunological basis for this reaction. The initiation of ATT for pulmonary TB may partly have been responsible for immune enhancement that may have occurred at microscopic intracranial foci in the brain leading to his clinical

Figure 2 Gadolinium-enhanced, magnetic resonance images showing multiple high signal intensity foci in the frontal, bilateral parietal and occipital lobes.

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 and compliant with the regimen, and the culture revealed no resistance to the first line of drugs. If our patient had been HIV positive and therefore at a higher risk of other infectious or malignant processes, a brain biopsy for definitive diagnosis would have been prudent.

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 hemianaesthesia, as a result of enlargement or development of intracranial tuberculoma and hydrocephalus.¹⁻⁴ Paradoxical tuberculomas are observed in approximately 1% of all active tuberculosis cases.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

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

Learning points

- ▶ An initial improvement during antitubercular therapy (ATT) followed by deterioration despite a definitive diagnosis, treatment and compliance to treatment, should be suspected as a paradoxical reaction to ATT even in an immunocompetent person.
- ▶ Discontinuation of 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.

Contributors BP, KP and BB participated in the management of the patient. BP, KP, MS and BB participated in design of the report, collection of the data and writing of the manuscript. All the authors have read and approved the final version of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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