

## Case report

# Paradoxical Tuberculomas after Completion of Antituberculous Treatment

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**Abstract:** Paradoxical reactions in tuberculosis have been reported in patients with tuberculous meningitis and appear as intracranial tuberculomas within 14–270 days of starting antituberculous therapy (ATT). Paradoxical reactions are due to the immune response of the host to ATT. They are commonly seen in the intensive phase of chemotherapy. However, paradoxical reactions occurring after completion of ATT are rare. We report 2 patients with tuberculous meningitis who had already completed ATT and then developed tuberculomas.

**Key words:** paradoxical reactions, tuberculomas, children, tuberculous meningitis

## INTRODUCTION

Cerebral tuberculoma is the most common extrapulmonary lesion in tuberculosis (TB), presenting with symptoms of intracranial space-occupying lesion [1, 2]. For unknown reasons, these tuberculomas sometimes become manifest, or expand, during successful treatment of tuberculosis and present as paradoxical reactions [3–6]. The explanation is not irregular medicines, drug resistance, or failure of drugs to penetrate the blood brain barrier. It has been proposed that paradoxical reaction is the result of an excessive inflammatory response in the context of immune reconstitution and increased antigen exposure after administration of antituberculous therapy (ATT) [1, 7]. Tuberculomas usually emerge after about 3 months of treatment, though the interval has been as short as 30 days and as long as 12 months [1, 2]. However, a paradoxical reaction occurring after completion of ATT is rare. We present 2 children who developed intracranial tuberculomas after completion of ATT.

## RESULTS

**Case 1:** -A 2 and half year-old boy presented with 2 episodes of seizures followed by right-sided hemiparesis. He was diagnosed as tuberculous meningitis (TBM) at 9 months of age and was given antituberculous therapy (ATT) for 1 and half years which was stopped just 2 months earlier. He also had undergone ventriculo-peritoneal shunt (VP shunt) 1 year earlier for hydrocephalus. He had delayed milestones and could only speak bisyllables and sit without

support prior to current hemiparesis following which he lost these milestones. On examination, the patient was 81 cm tall, weighed 14 kg, had right upper and lower limb weakness (power 3/5) with brisk reflexes and extensor planters. There was no cranial nerve weakness and other systems were normal. CT brain showed acute infarct in the left anterior cerebral and middle cerebral artery region with small granulomas in prepontine cisterns suggestive of TB. CSF examination was normal. EEG showed epileptic focus in the left hemispheric region. The child was started on 6 drug-ATT consisting of Isoniazid (H), Rifampicin (R), Ethambutol (E), Streptomycin (S), Ofloxacin (O) and Streptomycin (S) along with steroids and phenytoin. A repeat CT brain scan after 2 months of ATT showed multiple round disc and ring-enhancing lesions in the right CP angle, right cerebellar hemisphere, left frontal parafalcine region in the interhemispheric fissure, with perilesional edema and mild mass effect on 4th ventricle and dilated lateral and 3rd ventricle suggestive of progression of the disease, though clinically there was improvement in the right-sided weakness. In view of the deterioration noted on neuroimaging, a CSF TB PCR was done. This was negative, and CSF routine microscopy was normal. ATT was stopped after 1 year. The child again developed seizures after 6 months of stopping ATT and MRI brain scan showed multiple T<sub>2</sub> hypointense thick walled ring-enhancing lesions in the pons, upper medulla, right middle cerebellar peduncle, right CP angle and cisternal area suggestive of TB granulomas with compression of 4th ventricle and obstructive hydrocephalus. There was extensive enhancement along meninges and cisterns sug-

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gestive of meningitis with bilateral frontal and left parietal areas of gliosis and encephalomalacia. The child was then started on 2nd line ATT consisting of Amikacin, PAS, Moxifloxacin, Ethionamide. However, the child was lost to follow up.

**Case 2:** -A boy of 4 years and 4 months of age was referred to the TB clinic in December 2007 for further management. He had received a diagnosis of TB meningitis (TBM) in August 2004 at the age of 1 year, for which he had undergone anti TB treatment (ATT) for 13 months. [One month of streptomycin (S), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), Isoniazid (H) and Ciprofloxacin along with steroids, 2 months of HRZE and 10 months of HR]. He also underwent VP shunt insertion. He was fine until 3 years of age in May 2006 when he presented with polyuria and polydipsia. He received a diagnosis of central diabetes insipidus (DI) in view of higher serum osmolality (290 mosm/kg) as compared to urine osmolality (103 mosm/kg) and serum anti diuretic hormone (ADH) of 1.7 pg/ml. (Normal = 1–14 pg/ml). At that time he also was noticed to have visual impairment, and both eyes showed optic atrophy. He was started on vasopressin spray. MRI showed enhancing hypothalamic, infundibular stalk and pituitary granulomas and enhancing nodules over the quadrigeminal plate cisterna with vasogenic edema and mild hydrocephalus. Thus, he was restarted on ATT (2HRZE + 16 HR) which was continued. A repeat MRI brain scan in November 2007 showed significant shrinkage of the chiasmatic-hypothalamic granulomatous mass. Thus the child was continued on same ATT and steroids were added. However, the child was subsequently lost to follow-up.

## DISCUSSION

Central nervous system tuberculomas (CNST) are rare in developed countries. Approximately 1% of tuberculosis patients develop CNST. But in developing countries they still constitute one third of intracranial masses [3–5]. The expansion of tuberculomas during treatment is thought to be due to a disturbance in the immunity of the patient while responding to the treatment [3]. Infected hosts develop hypersensitivity to an array of mycobacterial proteins. Tuberculostatic drugs cause the destruction of mycobacterial structures and emit bacillar mycobacterial proteins, leading to the presence of inflammation and swelling of the focus [1, 7]. These provoke a delayed hypersensitivity reaction. The intracranial microtuberculomas grow slowly and become encapsulated after a latent period, resulting in paradoxical progression of existing lesions, supported by an immunological accompanying phenomenon, namely the local per-

lesionally secondary granulomatous vasculitis associated with intimal proliferation and degeneration of the vessel wall with occlusion of the vessel lumen, which worsens the penetration of the tuberculostatic drugs into the lesions [8].

These lesions are usually discovered accidentally when follow-up CT scanning is performed routinely or when new neurologic signs develop during the course of antituberculous therapy. In our first case, though deterioration was noted on neuroimaging, CSF TB PCR was negative and CSF routine microscopy was normal, suggesting that chemotherapy had been effective. In our second case, the child had extended granulomas with further worsening of the symptoms. Thus it may be worthwhile doing imaging studies prior to stopping ATT as extending the duration of antituberculous drugs in cases of paradoxical reactions can be effective [9]. In a study on adults by Anuradha et al., the only predictor of raised cerebrospinal fluid (CSF) protein (>3 g/l) [10]. Neither age nor immunosuppression have been shown to have any correlation with appearance of paradoxical tuberculomas, though it is generally assumed that these occur in patients with immune reconstitution.

No change in or discontinuation of antituberculous treatment is necessary when paradoxical reaction occurs. These patients should probably be kept under observation for years. Some studies suggest that early recognition and treatment with systemic corticosteroids might result in a more favorable outcome [3]. However, in some patients whose lesions fail to respond to the medical management and in patients with superficial lesions or spinal tuberculomas, surgical excision of the lesion may be needed [9, 11, 12].

## CONCLUSION

Attention should be paid to paradoxical reactions in patients with TBM, and these patients should be kept under observation even after completion of ATT.

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