

CASE REPORT**PARADOXICAL EXPANSION OF CEREBRAL TUBERCULOMAS DURING TREATMENT OF TUBERCULOUS MENINGITIS**

Mehdi Mohamadnejad MD*, Ali Bidari MD**, Mehdi Moghaddasi MD***, Seyed-Reza Mirpour MD****

Department of Internal Medicine, Tehran University of Medical Sciences, **Department of Emergency Medicine, *Department of Neurology, ****Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran*

Cerebral tuberculomas account for a large proportion of space occupying brain lesions, especially in the developing countries. The authors describe a patient with paradoxical progression of intracranial tuberculomas four months after successful treatment of tuberculous meningitis, and the possible immunological mechanisms of this phenomenon are discussed.

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Keywords • seizure • tuberculoma • tuberculosis

Introduction

Cerebral tuberculoma is a well-known feature of the central nervous system tuberculosis. It develops when intracranial tubercles enlarge without rupturing into the subarachnoid space, walled off from the brain parenchyma by a thick fibrous capsule. Tuberculoma may occur simultaneously with tuberculous meningitis or independently.¹ Although it is now thought to be rare in the western world, it accounts for a large proportion of space occupying brain lesions in the developing countries.¹

We report an unusual case with intracranial tuberculomas which paradoxically expanded during treatment for tuberculous meningitis.

Case Report

A 42-year-old woman was admitted to the Rasool-e-Akram Hospital on October 1999 because of tonic-clonic seizure and hemiparesis.

The patient had been well until four months before admission when she experienced severe

headache and vomiting, and was admitted to another hospital. At that time, meningeal signs were detected but the physical examination including neurological examination was otherwise unremarkable. In addition, brain CT scan was normal.

Cerebrospinal fluid examination revealed a white blood cell count of 200 per mL (80% lymphocytes and 20% neutrophils), a protein content of 180 mg/dL, and a glucose level of 33 mg/dL (serum glucose level 90 mg/dL). No acid fast bacilli (AFB) were seen in the direct smear and the microbiological culture was negative for *Mycobacterium tuberculosis*. Antituberculous treatment (isoniazid, rifampin, pyrazinamide, and ethambutol) were given with good compliance. She gradually improved with this treatment. After three months, pyrazinamide and ethambutol were stopped, and the treatment with isoniazid and rifampin continued. Four months after the onset of the therapy, she experienced several episodes of tonic-clonic seizures on the left side with unconsciousness during attacks. She was then referred to our hospital.

She was a native of Afghanistan who had immigrated to Iran 8 months before her recent admission. Her mother had died 20 years ago because of tuberculosis. On physical examination,

•Correspondence: M. Mohamadnejad MD, Department of Internal Medicine, Shariati Hospital, North Karegar Ave, Tehran, Iran. Fax: 98-21-8012992, E-mail: mohamadnejad@hotmail.com.

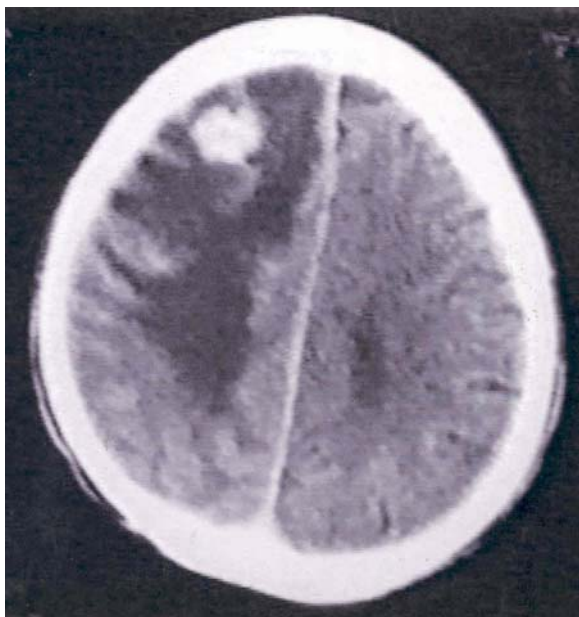


Figure 1. A CT scan of the brain after administration of intravenous contrast material showing one of the contrast enhanced lesions in the right frontal lobe, with surrounding vasogenic edema.

she had no fever. Suppurative cervical lymphadenopathy was present on the left side of the neck. On neurological examination, she was alert and oriented though her speech was dysarthric. There was central paresis of the left facial nerve; muscle strength was 3/5 in the left and 5/5 in the right extremities. Deep tendon reflexes were 3⁺ on the left side and 2⁺ on the right side. Babinski response was present on the left.

Brain CT scan with intravenous contrast material revealed multiple areas of contrast enhancement in the right frontoparietal region with surrounding vasogenic edema. A slight mass effect effaced the left frontal horn of the lateral ventricle (Figure 1). A tuberculin skin test (5TU) was positive. Antinuclear antibody, antibodies to HIV, and HTLV1 were negative. The results of other laboratory tests were normal.

Excisional brain biopsy from the right frontal lobe lesion revealed granulomatous inflammation with caseous necrosis compatible with tuberculoma (Figure 2). Acid fast bacilli were not detected and culture for mycobacteria was negative. Consequently, the cervical lymph node was aspirated and thick pus was obtained that was positive for acid fast bacilli on direct smear, but culture for mycobacteria was negative.

Treatment, with isoniazid and rifampin, was continued and dexamethasone and phenytoin sodium were also administered.

In the following month, the patient's condition

gradually improved in the hospital. Subsequently, dexamethasone was tapered off and the patient was discharged without any neurological deficits. Isoniazid and rifampin were continued for another 4 months. A brain CT scan with intravenous contrast, one month after completion of treatment, showed right frontal lobe hypodensity without enhancement.

Discussion

Neurological deterioration in patients with tuberculosis who are receiving antituberculous treatment should alert clinicians to the possibility of paradoxical expansion of intracranial tuberculomas. Few cases of cerebral tuberculomas with such presentation have been documented.²⁻⁴ It is interesting that these tuberculomas enlarged after initial favorable response to antituberculous treatment. Eventually, most of these cases responded to the original antituberculous drug regimen.^{3, 4} None of the aforementioned reports demonstrated drug resistant strains in the isolated microorganisms from these lesions.

Tuberculous involvement of the central nervous system in our case (clinical meningitis) was evident at the initial presentation. It was not until the fourth month of antituberculous treatment when the brain parenchymal abnormality was

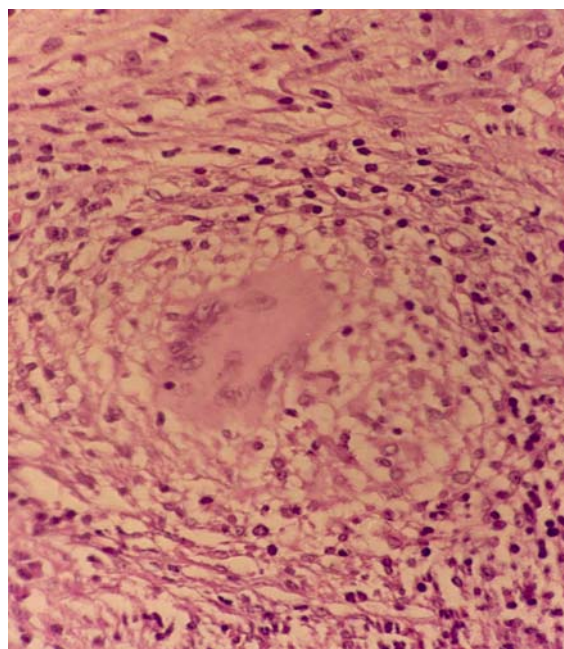


Figure 2. A microscopic view of brain tissue indicating a Langhans type giant cell surrounded by epithelioid histiocytes and numerous lymphocytes, compatible with granulomatous inflammation. The caseous necrosis which was present elsewhere is not demonstrated in this view.

initially noted. In contrast to the initial presentation which was due to active tuberculosis, the secondary presentation most probably reflected an immunologic reaction. The complete clinical response to the initial antituberculous regimen excluded the possibility of drug resistance and strongly suggested a reactive phenomenon.

T-cell suppression and anergy during active tuberculosis have been well recognized.⁵ This phenomenon is related in part to the production of interleukin-10 by peripheral blood T-lymphocytes during active tuberculosis.⁶ After completion of tuberculosis therapy, T-lymphocytes no longer produce interleukin-10.⁶ It is known that interleukin-10 down-regulates T-helper cell activity.⁵ Therefore, it is not surprising that successful treatment may reinstitute T-cell activity. It means that, over the course of tuberculosis treatment, a heightened immune response may occur despite the vanishing pool of viable mycobacteria. This reversal of anergy state can explain the paradox of expansion of cerebral tuberculomas despite institution of effective antituberculous drug therapy in our case.

Lymph node enlargement during treatment of tuberculous lymphadenitis has been reported.⁷ Interestingly, in our case, suppurative cervical lymphadenopathy developed at the time of detecting cerebral tuberculomas. It is notable that the lymph node aspirate proved to be positive for acid fast bacilli on direct smear but no viable mycobacteria was recovered by culture. It has been suggested that there is specific trapping of antigen-reactive lymphocytes in lymph nodes in some patients with tuberculosis.⁸ More recent studies indicate that there may be a compartmentalization of the cellular immune response in patients with active tuberculosis.⁹ We hypothesize that massive antigen release from dead mycobacteria, precipitated by effective anti-tuberculous chemotherapy, provoked a rebound immunologic response and led to the paradoxical enlargement of the cervical lymph node.

We believe that the concurrency of the two paradoxes (i.e. enlargement of the cervical lymph

node and development of cerebral tuberculomas, despite effective antituberculous chemotherapy) in our case, is quite impressive and points to a common pathogenic mechanism.

Why does such phenomenon occur only in few patients with tuberculosis? This may be attributed to the differences in the immune responses of patients. There is compelling evidence that the host response to *Mycobacterium tuberculosis* plays a major role in determining the clinical manifestations and ultimate outcome of persons who encounter this pathogen.⁹

Regardless of the mechanism, it is worth emphasizing that expanding central nervous system tuberculomas do not mandate alteration of antituberculous chemotherapy.² In such circumstances, adding systemic corticosteroids may be effective.³

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