Therapeutic Use of Infliximab in Tuberculosis to Control Severe Paradoxical Reaction of the Brain and Lymph Nodes

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Paradoxical reactions are immune-mediated exacerbations of disease triggered by tuberculosis treatment. Paradoxical reactions involving the central nervous system may be life threatening. Infliximab (tumor necrosis factor antibody) profoundly inhibits cellular immune responses to *Mycobacterium tuberculosis*. We describe a case in which infliximab was used to control steroid-resistant tuberculosis paradoxical reaction involving the central nervous system.

The term paradoxical reaction (PR) refers to disease exacerbation after initiation of antituberculous therapy. Its typical manifestations include fever, pulmonary infiltrates, hypoxia, and lymphadenopathy [1]. New lesions may appear in previously uninvolved organs, particularly in patients with miliary or disseminated disease at tuberculosis (TB) diagnosis [2]. PRs may be severe or life-threatening if they involve the CNS; such cases require treatment with high-dose corticosteroids and neurosurgical intervention. Clinical outcomes may be poor, even when CNS involvement is promptly recognized and treated.

The clinical manifestations of TB PR are thought to reflect the recovery of exaggerated but otherwise normal cellular antimycobacterial immune responses. They appear to be triggered by chemotherapy, through the release of antigens by dying cells, and by the interruption of disease-related immunosuppressive mechanisms. TNF plays a central role in the granulomatous immune response to *Mycobacterium tuberculosis*. In this article, we describe a case of severe TB PR that was unresponsive to high-dose corticosteroids and cyclophosphamide but was successfully treated with the anti-TNF antibody infliximab.

Case report. A 42-year-old female nurse of Indian birth who was residing in New Zealand presented with symptoms of fever, cough, and night sweats that were unresponsive to treatment with routine antibiotics. Chest radiograph findings included small nodules throughout both lungs that were compatible with miliary TB. The patient was hospitalized, and treatment was begun with isoniazid, rifampin, ethambutol, and pyrazinamide. Drowsiness was noted on the day of hospitalization, followed by focal neurological signs, including bilateral third and left sixth cranial nerve palsies, bulbar palsy, and right arm pyramidal weakness. CT of the head revealed a single nonenhancing lesion in the left parietal lobe. Examination of CSF samples revealed a WBC count of 216×10^6 cells/L; 78% of the WBCs were mononuclear. The patient's protein level was elevated (1.93 g/L), and the patient's glucose level was normal. Microscopy findings were unremarkable. Treatment with dexamethasone (16 mg/day) was started; calcitriol (0.25 μg/day) was administered because of vitamin D deficiency. MRI revealed small lesions in the brain stem that were consistent with the findings of the neurologic examination (figure 1). Drug-susceptible *M. tuberculosis* was cultured from respiratory samples; cultures of CSF samples were negative for *M. tuberculosis*. After initial improvement, the cranial nerve palsies worsened, and the patient's level of consciousness decreased, accompanied by

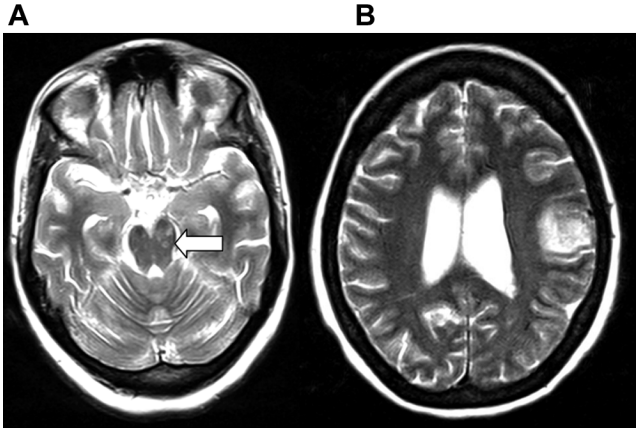

Figure 1. T2-weighted MRI, obtained shortly after hospital admission, showing lesions in the brain stem *(A; arrow)* and in the left parietal lobe *(B)* that are consistent with cerebritis.

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fever and diaphoresis. An additional MRI revealed multiple new lesions with surrounding vasogenic edema throughout the brain, particularly in the middle cranial fossa, that were consistent with tuberculomas. Methylprednisolone (1 g/day) was given for 5 days without clinical or radiological response. There was no clinical response to therapeutic lumbar puncture; CSF samples revealed a slight reduction in WBC count and protein level. Recurring high fever and tachycardia, cranial nerve palsies, and decreased consciousness persisted. Dexamethasone therapy (16 mg/day) was continued. After >2 months without clinical improvement, cyclophosphamide (100 mg/day) was added to the treatment regimen. A frontal brain lesion biopsy specimen obtained 1 month later revealed granulomatous inflammation with rare bacilli on examination with auramine fluorescent microscopy, but it showed no growth on prolonged culture. Cervical and axillary lymph nodes increased in size. Fine-needle aspiration revealed granular necrotic debris, occasional lymphocytes, and occasional auramine-positive bacilli. Cultures were again negative for *M. tuberculosis*.

Four months after the initiation of therapy, the patient's overall status remained poor; she was obtunded for all but 4 h per day (figure 2) and required feeding via a percutaneous enteral tube. T2-weighted MRI of the head revealed multiple thick-walled cavities consistent with tuberculomas, with extensive surrounding vasogenic edema and mass effect (figure 3*A*). Cyclophosphamide therapy was stopped. After extensive discussion with the patient's family, informed consent was obtained for treatment with infliximab. Three 10-mg/kg doses of infliximab were administered to the patient at monthly intervals. Standard TB therapy was continued. Within days after administration of the first dose, the patient became more responsive. In the month after the first infliximab infusion, the patient's mean waking hours increased from 4.7 to 6.1 h per day (figure 2). The cranial nerve palsies improved, as did speech and mobility. An additional MRI, performed 1 month after the first infusion, revealed a reduction in the size of the lesions and in the extent of the surrounding edema (visible in the right panel of figure 3*B*). A reduction in lymphadenopathy was also apparent on physical examination and CT scan. Treatment with infliximab was continued until no further radiologic improvement was seen. The patient was discharged from hospital rehabilitation services 10 months after diagnosis. Twelve months of anti-TB chemotherapy were completed. The patient's fever, resting tachycardia, and drowsiness slowly improved. The feeding tube was removed. At present, 17 months after the original diagnosis, the cranial nerve palsies have resolved, and the patient has regained fluent speech and the ability to walk, although significant spasticity persists in the lower limbs.

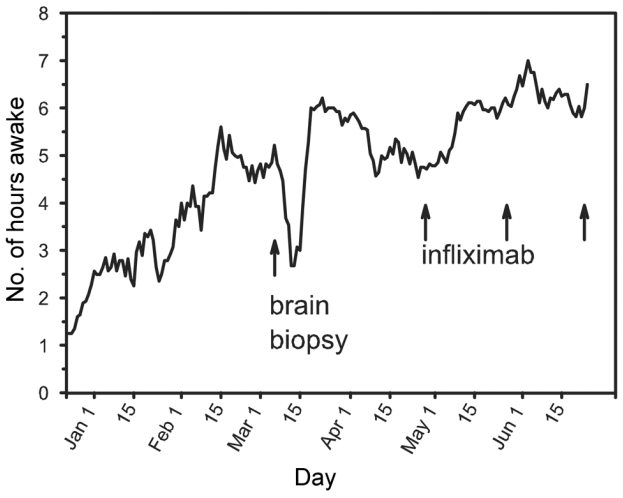

Figure 2. Summary of daily hours of wakefulness after diagnosis and treatment of tuberculosis paradoxical reaction involving the brain and lymph nodes, as recorded by the patient's family during the early part of her treatment. Data indicate the rolling mean values for each day of 7-day intervals. Mean waking hours increased from 4.7 to 6.1 h per day after the first infusion of infliximab.

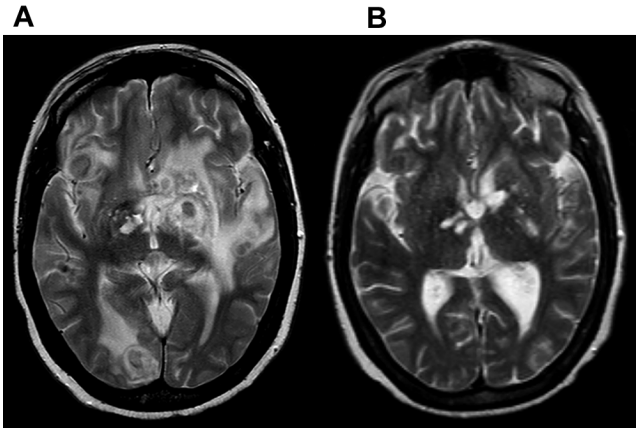

Figure 3. T2-weighted MRI of the head obtained shortly before *(A)* and 1 month after *(B)* administration of the first dose of infliximab. Multiple thick-walled cavities with extensive surrounding vasogenic edema and associated mass effect are seen on the initial MRI. The subsequent MRI shows these lesions to be smaller, with thinner walls, and with substantially reduced edema.

Discussion. This case illustrates the devastating effects of PRs in patients with neurotuberculosis. Physicians today may be more familiar with this phenomenon as immune reconstitution inflammatory syndrome in the context of TB and HIV coinfection. However, PRs occur often during the treatment of disseminated or extrapulmonary TB, regardless of HIV serostatus [1]. Immune reconstitution inflammatory syndrome is the result of an outpouring of cytokines produced by T cells that are activated by somatic mycobacterial antigens [3]. The pathogenesis of PR in persons who are not HIV infected is also

thought to reflect an exaggerated cell-mediated immune response against mycobacteria that are damaged or killed by chemotherapy.

The manifestations of TB often continue to evolve during the early period of treatment in patients with extrapulmonary disease, including the appearance and progression of tuberculomas in patients who present initially with meningitis [2]. The natural history of such lesions is highly variable. Some cases resolve spontaneously, whereas others require corticosteroids or surgical intervention. In the present case, multiple symptomatic lesions emerged despite early treatment with corticosteroids. Surgical intervention was deemed impractical because of the number, size, and locations of the lesions and the lack of response to therapeutic lumbar puncture, which left few satisfactory treatment alternatives [4, 5]. It was the consensus of the neurologist, the neurosurgeon, and the infectious disease physicians that the chance of a useful recovery in this case was remote with conservative management.

TNF is required for granuloma formation in TB [6]. The anti-TNF antibody infliximab is highly effective in treating other types of granulomatous inflammation, such as Crohn disease [7]. Indeed, infliximab withdrawal may precipitate PR in patients for whom infliximab therapy is discontinued after receipt of a TB diagnosis [8]. Clinical experience with adjunctive TNF blockade in TB is limited. One study of adjunctive etanercept (a soluble TNF receptor) in patients with HIV-associated pulmonary TB found trends toward superior responses with regard to several clinical parameters, including sputum culture conversion [9]. However, these responses were small compared with those associated with receipt of high-dose corticosteroids [10], a treatment that had already failed for our patient. The effects of soluble TNF receptor are also small when compared with the effects of TNF antibody, both in chronic murine experimental TB and in latent human TB infection [6, 11]. These factors were all weighed when making the selection of infliximab as therapy in the present case.

It may seem counterintuitive that a drug such as infliximab, which predisposes to TB, may be safely used to treat TB complications. However, several studies have observed that microbiologic responses to TB chemotherapy are accelerated, rather than delayed, when host immune responses are inhibited by adjuvant anti-TNF treatment [12]. This may indicate protection by granulomas of sequestered mycobacteria from the bactericidal effects of chemotherapy. The rapid clinical response to infliximab therapy in the present case was more likely to have been attributable to the direct anti-inflammatory effects of TNF blockade, however, because of the prior 4 months of chemotherapy and negative results of brain and lymph node cultures. In this case, earlier intervention with infliximab may have hastened recovery and reduced the extent of irreversible brain damage from ischemia and necrosis.

In summary, this case illustrates a prompt, beneficial effect of infliximab therapy on the clinical and radiographic manifestations of PR in a patient with neurotuberculosis. The safety profile of this therapy may be superior to that of long-term, high-dose corticosteroid therapy. Additional studies of adjunctive therapy with anti-TNF antibody in patients with TB are warranted.

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