Use of Adjunctive Treatment with Interferon-γ in an Immunocompromised Patient Who Had Refractory Multidrug-Resistant Tuberculosis of the Brain

Issam Raad, Ray Hachem, Norman Leeds, Raymond Sawaya, Ziad Salem, and Samir Atweh

We describe a patient with acute lymphocytic leukemia and multidrug-resistant tuberculosis of the brain and spinal cord. Despite treatment with six antituberculous drugs and a steroid medication for 11 months, there was no appreciable clinical or radiological improvement in the patient's condition. Within 5 months of initiating adjunctive therapy with IFN-γ and granulocyte colony stimulating factor (GCSF) were used successfully as adjunctive therapy for refractory MDRTB infection of the brain and spinal cord.

Case Report

A 26-year-old woman presented to our center in April 1993 with a 2-month history of headaches, neck pain, and bilateral numbness in the upper extremities. Acute lymphocytic leukemia (ALL) had been diagnosed in 1991, at which time she was treated with high-dose cyclophosphamide plus vincristine, doxorubicin, and dexamethasone. A neurological examination showed left-sided motor weakness, paresthesia of the upper extremities, and cerebellar dysfunction with a bilateral positive Babinski's sign. Laboratory test results, except for a lymphocytic leukocytosis of 308/mm³ and a CD4 cell count of 17/mm³, were normal. Analysis of the CSF showed a WBC count of 500 mg/dL and a glucose concentration of 64 mg/dL. Serology for cryptococcal antigen and an acid-fast stain were negative, as was serology for antibodies to HIV-I. Findings on a chest radiograph were normal. However, an MRI scan revealed multiple ring-enhancing lesions within the brain and spinal cord.

An increase in the incidence of tuberculosis has accompanied the AIDS epidemic in the United States [1]. Recently, multidrug-resistant tuberculosis (MDRTB) has emerged and is associated with a high mortality among immunocompromised patients [2]. IFN-γ has been shown to activate monocytes and macrophages against Mycobacterium tuberculosis in vitro [3-5]. In addition, IFN-γ has been used successfully with conventional antimycobacterial therapy in the treatment of refractory atypical mycobacterial infections such as those due to Mycobacterium avium complex [6-8]. We describe a patient with leukemia in whom IFN-γ and granulocyte colony stimulating factor (GCSF) were used successfully as adjunctive therapy for refractory MDRTB infection of the brain and spine.

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Reprints or correspondence: Dr. Issam Raad, Section of Infectious Diseases—Box 47, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030.
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1994 revealed complete resolution of the brain lesions and a marked decrease in the size of the spinal cord lesion. By March 1995 the dose of dexamethasone had been lowered to 3 mg/d; the patient’s CD4 cell count had increased to 322/mm³, and another MRI scan had confirmed the complete resolution of the lesions in the brain and spinal cord (figure 1b). At that time, treatment with ethionamide and cycloserine was discontinued; treatment with pyrazinamide, ethambutol, ciprofloxacin, dexamethazone, and IFN-γ was continued until April 1995. In June 1995 the patient had another relapse of ALL and presented to the American University of Beirut Hospital with neutropenic colitis, which resulted in her death. Postmortem examination revealed a normal brain and spinal cord on gross evaluation. Microscopically, there was moderate thickening of the leptomeninges with subependymal gliosis. Acid-fast smears and cultures of specimens from the brain and spinal cord were negative.

Discussion

To our knowledge, this is the first reported case of refractory MDRTB of the brain in an immunocompromised patient, which was successfully treated with adjunctive IFN-γ therapy. MDRTB is a serious infection in the immunocompromised patient: a case fatality rate of 91% has been reported among patients with AIDS [2]. On presentation, our patient had a profound cell-mediated immunodeficiency (CD4 cell count of 17/mm³); hence, like the prognosis for AIDS patients with MDRTB, the prognosis for our patient was poor.

Several investigators have reported the successful treatment of tuberculomas in immunocompetent patients with use of antituberculous agents and high-dose steroids [9]. Despite the use of six active antituberculous agents and high-dose steroids over an 11-month period, no appreciable progress in the treatment of our patient was noted until IFN-γ and GCSF were administered. Adjunctive treatment with IFN-γ and GCSF resulted in total resolution of the brain lesions (figure 1). Several in vitro studies have shown that IFN-γ can augment the bactericidal activity of monocytes and macrophages against *M. tuberculosis* [3–5]. In addition, recent clinical studies have demonstrated the immunoenhancing role of IFN-γ as adjunctive treatment for refractory disseminated infection due to atypical mycobacteria [6–8]. IFN-γ does not penetrate well through the blood-brain barrier. However, the resolution of the brain lesions could

![Figure 1. A: MRI scan (axial T1-weighted image at the ventricular level after injection of contrast medium) of the brain of a patient with acute lymphocytic leukemia and tuberculosis. The MRI scan was obtained in March 1994 after 11 months of antituberculous chemotherapy and before treatment with IFN-γ and revealed several large and small nodules (open arrows). Focal subcortical enhancement is observed at the biopsy site in the right frontal regions (closed arrows). B: Axial T1-weighted image (after injection of contrast medium) at the ventricular level reveals resolution of nodules. The MRI scan was obtained in March 1995 after 12 months of IFN-γ adjunctive therapy.](https://academic.oup.com/cid/article-abstract/22/3/572/278894/18January2019)
be attributed to activation of peripheral blood monocytes that are known to penetrate this barrier. In addition, IFN-γ is not known to increase the CD4 cell count. Use of this agent resulted in the successful tapering of steroid treatment which, in our opinion, contributed to the abatement of the lymphocytopenia and the reversal of this refractory process.

Brown et al. [10] have shown that neutrophils as well as monocytes and macrophages are able to kill *M. tuberculosis* [10]. Although our patient was not neutropenic, GCSF was given to enhance her neutrophilic activity against *M. tuberculosis*, [8, 10], while IFN-γ was given to enhance her macrophage activity against the organism [3–5]. Hence, GCSF, in addition to IFN-γ, could have played an important role in the resolution of this refractory case of MDRTB. The distinctive role of IFN-γ in the adjunctive treatment of MDRTB infection should be further investigated in a prospective randomized clinical study.

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References