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CASE REPORT

Adalimumab treatment may replace or enhance the activity of steroids in steroid-refractory tuberculous meningitis

Ho-Su Lee · Yumi Lee · Sang-Oh Lee · Sang-Ho Choi · Yang Soo Kim · Jun Hee Woo · Sung-Han Kim

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Abstract We describe a paradoxical response involving the central nervous system in a patient with steroid-refractory tuberculous meningitis that was unresponsive to systemic corticosteroids but was improved with adalimumab. The immunomodulatory effect of tumor necrosis factor inhibitors may have a role in replacing or enhancing the activity of steroids in the management of steroid-refractory tuberculous meningitis.

Keywords Tuberculosis · Paradoxical reaction · Steroid-refractory · Tumor necrosis factor inhibitor · Adalimumab

Introduction

Central nervous system (CNS) tuberculosis (TB) is observed in approximately 1% of all TB patients. Paradoxical reaction (PR) is defined as the clinical or radiologic deterioration of TB during appropriate anti-TB therapy. PRs involving the CNS can be life threatening [1]. However, there are no consensus guidelines for the management of PRs. Adjunctive corticosteroids and surgical intervention are widely advocated but can occasionally be ineffectual [2]. A few reports have documented success with thalidomide as an adjuvant in PRs refractory to corticosteroids [3, 4]. However, there is controversy concerning the effectiveness of adjunctive thalidomide. A randomized controlled trial of thalidomide for the treatment of tuberculous meningitis in children was stopped early because of an increase of adverse events in the thalidomide arm [5]. Hence, there is a urgent need for an immunomodulatory agent in patients with PRs refractory to corticosteroids.

PRs are thought to be the result of exaggerated cellular immune responses to the antigens released from tubercle bacilli killed or damaged by anti-TB therapy [1]. Affected tissues have usually contained granulomas, but cultures have been negative [2]. Tumor necrosis factor (TNF) plays an essential role in the granulomatous immune response to *Mycobacterium tuberculosis* [6]. Recently, two case reports have described successful treatment of refractory PRs with TNF inhibitors [1, 7]. Here, we present a case of severe PR that was unresponsive to corticosteroids but was successfully treated with the TNF inhibitor adalimumab acting as an immunomodulatory agent replacing or enhancing steroid activity.

Case report

A 63-year-old man was admitted to hospital with fever, personality change, and drowsiness, which progressively worsened over 3 weeks. Two days before admission, he presented with urinary incontinence and ataxia, which led to admission to the emergency department. His temperature was 38.2°C, and other vital signs were normal. Brain magnetic resonance imaging (MRI) failed because of lack of cooperation, and computed tomography (CT) of the head revealed mild hydrocephalus (Fig. 1). Lumbar puncture was performed, and analysis revealed lymphocytic pleocytosis [white blood cell (WBC) count, 112/mm^3; 78% lymphocytes and 12% polymorphonuclear cells], elevated protein (568 mg/dl), normal glucose [89 mg/dl; ratio of glucose concentration in cerebrospinal fluid (CSF) to that in serum,

H.-S. Lee · Y. Lee · S.-O. Lee · S.-H. Choi · Y. S. Kim · J. H. Woo · S.-H. Kim (✉)
Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Poonganp dong, Songpa-gu, Seoul 138-736, Republic of Korea
e-mail: kimsunghanmd@hotmail.com

0.5], and high adenosine deaminase levels (32 IU/l). Serological testing for human immunodeficiency virus (HIV) was negative. From the time of admission, treatment was begun with isoniazid, rifampin, ethambutol, and pyrazinamide, plus dexamethasone (12 mg/day). On day 2, nested polymerase chain reaction (PCR) for TB on a CSF specimen was positive. After initial improvement in consciousness, on the 6th day of hospitalization drowsiness was noted. Dexamethasone (20 mg/day) was increased for a presumed diagnosis of paradoxical reaction. Despite high-dose dexamethasone, the patient's awareness gradually deteriorated. On day 10, his mental status worsened and respiratory distress developed, requiring intubation and mechanical ventilation. An additional CT revealed progression of hydrocephalus (Fig. 1), and extraventricular drainage was performed. The patient was transferred to the intensive care unit. Ethambutol and pyrazinamide were switched to moxifloxacin and streptomycin owing to concern about poor gastrointestinal absorption. The patient regained consciousness and could be weaned off the ventilator. On day 19, extraventricular drainage was removed. Dexamethasone (20 mg/day) was given for 3 weeks. CSF culture yielded *M. tuberculosis* without any mutations to mutations resistant to isoniazid and rifampicin by PCR assay, and the isolate eventually was determined to be susceptible to all drugs tested. The dose of dexamethasone was slowly tapered, from 20 to 12 mg daily. Unfortunately, cognitive impairment increased considerably during the steroid tapering, and repeat lumbar puncture revealed increased protein levels (Fig. 1). We obtained informed consent and initiated adalimumab (40 mg) subcutaneously on day 47. The patient's cognitive status improved slightly, but memory impairment remained. However, dexamethasone dosage was reduced to 6 mg/day on day 48 and to 4 mg/day on day 55 without additional neurological dysfunction. The patient was transferred to a rehabilitation hospital on day 56, on anti-TB therapy and dexamethasone (4 mg/day).

However, a week after discharge, the patient was readmitted following recurrent episodes of ataxia and increasing somnolence. An enhanced T_1-weighted brain MRI revealed more prominent meningeal enhancement along the basal cistern and both middle cerebral artery trunks and around the brainstem (Fig. 1). CSF examination revealed a switch to a neutrophil-predominant situation in the differential cell count (76% polymorphonuclear cells and 16% lymphocytes), with an increase in total cell count to 116/mm^3. The next day, dexamethasone (8 mg/day) and a second dose of adalimumab (40 mg) ware administered, and over the next few days, we observed progressive clinical improvement, with a rise in Mini Mental State Examination score. Dexamethasone was gradually tapered from day 20, and on day 36 the patient again presented with drowsiness. A third dose of adalimumab (40 mg) was administered on day 37 without increasing the dexamethasone dose. The patient made a recovery and was eventually discharged on day 41. Before giving adalimumab for the second time, the patient's mini mental state examination score was 9 (of a total of 30), and it had risen to 17 by the time of discharge. Corticosteroid was slowly tapered off over 9 months, and anti-TB therapy was maintained for 12 months. Serial MRI scans during the follow-up period (6 and 10 months after first admission) showed progressive improvement of the leptomeningeal enhancement along the basal cistern (Fig. 1). The patient is currently being followed up at 2-month intervals and is in good health, with mild memory dysfunction and no other neurological deficits.

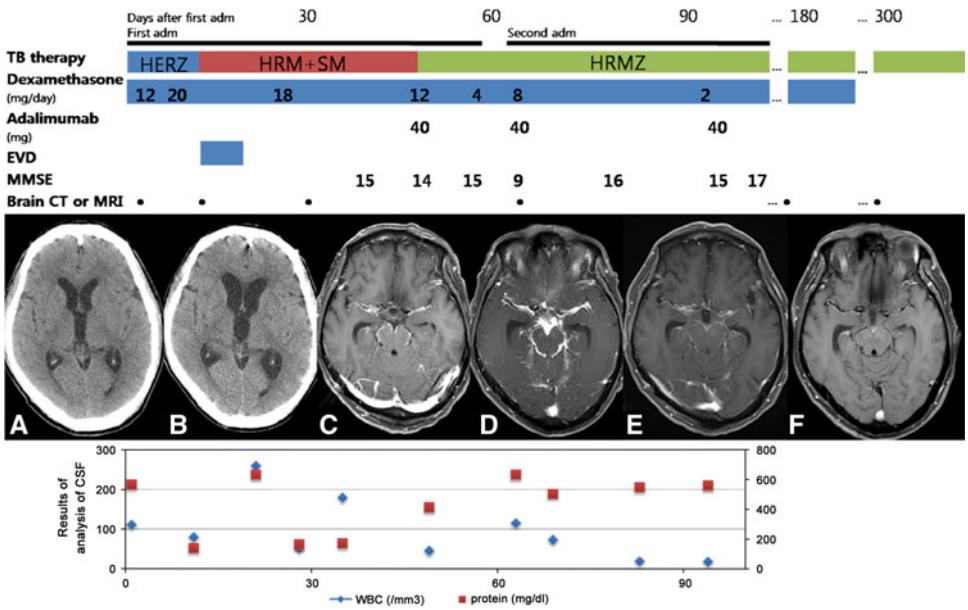

Fig. 1 Clinical course and laboratory data. Brain computed tomography and magnetic resonance images were obtained on initial hospital days 1 (*A*), 10 (*B*), and 30 (*C*), second hospital day 1 (*D*), and 6 months (*E*) and 10 months (*F*) after first admission. *Adm* admission, *TB* tuberculosis, *H* isoniazid, *E* ethambutol, *R* rifampin, *Z* pyrazinamide, *M* moxifloxacin, *SM* streptomycin, *EVD* external ventricular drainage, *MMSE* Mini Mental State Examination, *CT* computed tomography, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *WBC* white blood cell

Discussion

TNF inhibitors, notably anti-TNF monoclonal antibodies, increase the risk of reactivation of latent TB and other intracellular infections [7]. Paradoxically, the granulomatous host response to TB may protect the sequestered *M. tuberculosis* from the administered anti-TB therapy, suggesting that treatment might be improved by therapeutic disruption of the granulomas [2]. Hence, adjunctive immunotherapy could be a novel strategy in patients with active TB. Indeed, two prospective controlled studies involving patients with TB have indicated that TNF inhibition and steroid appears to accelerate, rather than compromise, tissue sterilization [8, 9].

This effect may be the result of enhanced penetration of TB drugs into granulomas, or enhanced bactericidal activity of the drugs [2]. Indeed, two randomized controlled trials of adjuvant use of immunomodulators (prednisolone [8] and etanercept [9]) in patients with pulmonary TB found that these interventions significantly accelerated negative conversion of sputum culture results. However, clinical experience with adjunctive TNF inhibitors in PRs is limited. To the best of our knowledge, only two cases, one involving steroid-refractory TB meningitis [1] and the other life-threatening pulmonary TB [7], have been reported, as well as one case of HIV-related immune reconstitution inflammatory syndrome caused by cerebral cryptococcosis [10].

In our case, the patient's neurological symptoms, such as memory dysfunction and gait disturbance, were unresponsive to corticosteroid and deteriorated rapidly as corticosteroids were reduced. Although a contributory effect of dexamethasone cannot be excluded (at the time of the second adalimumab infusion), we assume that the use of adalimumab played a key role in the clinical course by replacing or enhancing the activity of steroid in the management of his steroid-refractory TB meningitis. However, our single case study should be cautiously interpreted to apply anti-TNF therapy in TB meningitis patients with steroid-refractory paradoxical responses. So, anti-TNF therapy as a double-edged sword may not be applicable to all steroid-refractory TB meningitis cases. We thus suggest that systemic evaluation of the appropriate use and adequate dosing regimen of this class of immunomodulators for management of steroid-refractory TB meningitis should be performed to answer many questions.

In summary, this case illustrates the beneficial effect of adalimumab therapy in a PR that was unresponsive to high-dose corticosteroids because it replaced or enhanced the activity of steroid. Additional studies are needed of the role of anti-TNF monoclonal antibody as adjuvant therapy in patients with TB who have severe PRs.

Conflict of interest There is no conflict of interest for all authors.

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