CASE REPORT

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Paradoxical Deterioration of Intramedullary Spinal Tuberculomas during Antituberculous Therapy

Keum Jun Jang, M.D., Cheol Su Jwa, M.D., Kang Hyun Kim, M.D., Jae Kyu Kang, M.D., Ph.D.

Department of Neurosurgery, National Medical Center, Seoul, Korea

"Paradoxical deterioration" during antituberculous therapy is generally defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves. The phenomenon of paradoxical deterioration in intramedullary tuberculoma of the spinal cord is rare and is a less established entity. The authors present an unusual case of paraparesis as a result of paradoxical deterioration of intramedullary tuberculoma despite adequate antituberculous therapy. Here, we review the relevant literatures and discuss its possible pathogenic mechanisms.

KEY WORDS : Tuberculoma · Spinal cord · Antituberculous therapy.

Introduction

Tuberculosis of the central nervous system is still an important cause of morbidity and mortality worldwide. It occurs in 0.5 to 2% of patients with systemic tuberculosis[5]. It is a potentially curable disease, but delayed diagnosis or inappropriate treatment often result in permanent neurological deficits. The final outcome was mainly determined by patient's compliance and tolerance and drug sensitivity.

"Paradoxical deterioration" during antituberculous therapy is generally defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves[3]. The paradoxical deterioration may complicate the course of the disease. This is an extremely rare case of a patient who developed paraparesis as a result of paradoxical deterioration of intramedullary spinal tuberculomas during antituberculous treatment. To our knowledge, two similar cases were reported by Lin et al.[8] and Skendros et al.[13] to date.

Here, we describe this case and discuss its pathogenesis with a review of the relevant literatures.

Case Report

A 31-year-old male patient was transferred to our department because of progressive paraparesis of 2-month history despite appropriate antituberculous therapy of intramedullary tuberculomas for 12 months. On past history, he presented with fever, drowsy mental change and walking

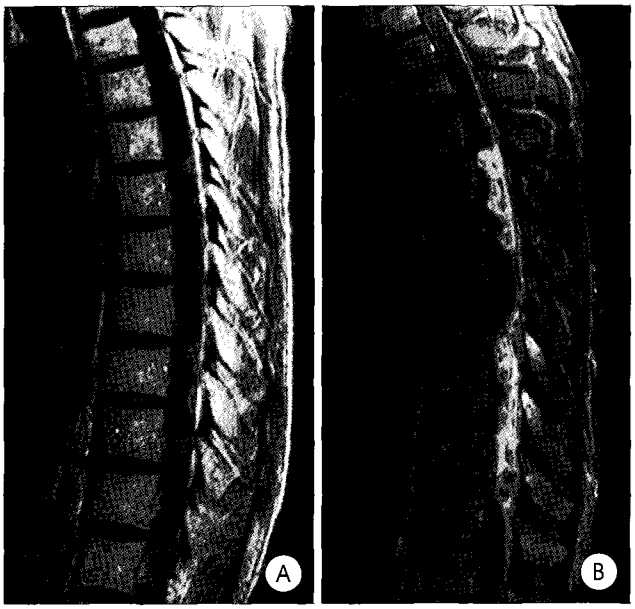

Fig. 1. Preoperative magnetic resonance images. A : Sagittal T1-weighted image with gadolinium injection after 12-month antituberculous therapy shows multiple, small intramedullary tuberculomas in the thoracic cord. B : Follow-up gadolinium-enhanced, sagittal T1-weighted image after 24-month treatment depicts diffuse intramedullary and leptomeningeal granulomas, abscesses, and severe cord swelling through the entire thoracic cord.

• Received : December 29, 2006 • Accepted : May 21, 2007
• Address for reprints : Cheol Su Jwa, M.D., Department of Neurosurgery, National Medical Center, 243 Eulji-ro, Jung-gu, Seoul 100-799, Korea
Tel : +82-2-2260-7279, Fax : +82-2-2271-2708, E-mail : chsjwa@hanmail.net

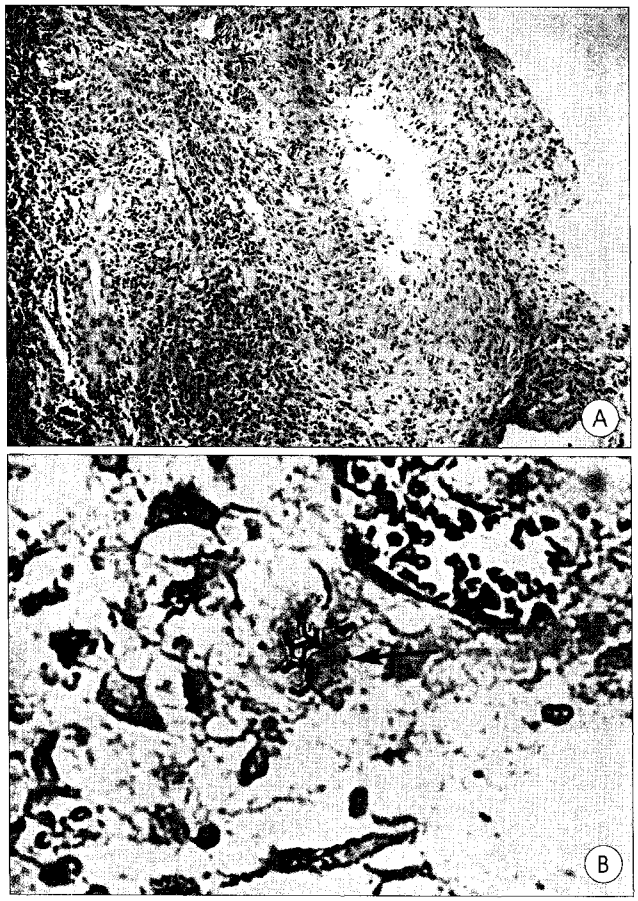

Fig. 2. Photomicrographs of the surgical specimens. A : The section of the spinal cord demonstrates typical chronic granulomatous inflammation with central necrosis. B : The pus smear from the lesion confirms the existence of acid-fast bacilli (arrow) (A : H&E ×100, B : AFB stain ×1000).

difficulty two years ago and had been diagnosed as miliary tuberculosis and acute hydrocephalus complicated by tuberculous meningitis. After extraventricular drainage, his neurological status was improved. Magnetic resonance (MR) imaging evaluation of the spine revealed diffuse meningeal irregularity and thickening with enhancement in the thoracic cord. He was discharged 2 months after operation and antituberculous medications with prednisolone 1 mg/kg. He was monitored regularly at outpatient department of neurology and has taken isoniazid 600 mg, rifampin 600 mg, pyrazinamide 1500 mg, ethambutol 1200 mg with a tapering course of prednisolone. He had good compliance and tolerance for the antituberculous regimens. However, follow-up MR images after 12 months showed the development of new lesions, small, multiple intramedullary tuberculomas in the thoracic cord (Fig. 1A). Therefore, the same treatment regimens continued through the additional 12-month period.

On admission to our department, neurological examinations showed severe motor weakness of both lower legs (grade I/I), hypesthesia below T4 level and sphincter disturbances. His medical history including acquired immuno-deficiency syndrome, malignancies, chronic alcoholics were unremarkable. The serological test for human immuno-deficiency virus was negative. The lymphocyte count was 1890 cells/μl. Cerebrospinal fluid studies revealed no inflammatory cells, protein 483 mg/dl and glucose 44 mg/dl. Other laboratory findings were within normal limit. Acid-fast bacilli stain and culture of *Mycobacterium tuberculosis (M. tuberculosis)* were negative. On MR studies, the previous small lesions were strikingly aggravated into diffuse intramedullary and leptomeningeal granulomas, abscesses, and severe cord swelling through the entire thoracic cord (Fig. 1B).

Surgery was performed for the definitive diagnosis and decompression. Laminectomy was made in the T5-T11 levels. Abnormal dural thickening and severe meningeal adhesions were observed. Gross operative findings of the lesions also showed severe cord swelling with inflammatory tissues, abscesses, and ongoing multifocal hemorrhages. A biopsy of the lesion was performed followed by duroplasty with artificial dura. Histopathological studies confirmed chronic granulomatous inflammations with caseous necroses and the presence of acid-fast bacilli in the lesions (Fig. 2). Also, the polymerase chain reaction for *M. tuberculosis* showed a positive finding. However, acid-fast bacilli culture was negative. Postoperatively, the patient was scheduled for second-line antituberculous drugs for 12 months. However, the patient showed no neurological improvement.

Discussion

Paradoxical deterioration during treatment of systemic tuberculosis is not uncommon, occurring in approximately 10% of patients with a clinical diagnosis of tuberculosis[1,3]. This paradoxical phenomenon has most frequently been reported in lymph node tuberculosis[1] and may involve cerebral tuberculomas, pulmonary infiltrates, or pleural disease[1,3]. Since Thrush and Barwick[15] first described the involvement of the central nervous system of this phenomenon, 41 cases have been reported in the literature[7]. The largest series was 10 cases reported by Teoh et al.[14]. Until the present time, there has been no rapid and reliable diagnostic test to substitute a clinical diagnosis of this phenomenon. But, a surge in the lymphocyte count, accompanied by an exaggerated tuberculin skin test can be observed[3]. Even biopsy of affected lesions usually show only granulomatous inflammation with negative acid-fast bacilli stains and cultures[4]. This phenomenon most frequently occurs during the first few months of treatment and tends to resolve with continued therapy because it is usually self-limited[4].

To date, only 2 cases of this peculiar phenomenon in the

spinal cord are documented[8,13]. Lin et al.[8] reported a case of multiple intramedullary tuberculomas developing paradoxically during treatment of tuberculous meningitis. Skendros et al.[13] also reported an intradural, extramedullary tuberculoma despite adequate treatment of tuberculous meningitis. These reported cases have ultimately resolved by only prolongation of antituberculous therapy.

The pathogenesis of paradoxical deterioration in patient with the central nervous system tuberculosis is not well understood. However, its mechanism is likely to correspond with that of systemic tuberculosis. Chambers et al.[2] reported that in 4 cases with the paradoxical expansion of intracranial tuberculomas, the pathology may be somewhat similar to lymph node enlargement in treated glandular tuberculosis. A hypothesis, now generally believed, is interaction between the host immune response and direct effects of mycobacterial products[2,3,7,14]. It is related to hypersensitivity reactions to antigens released from dying tubercle bacilli.

Adjunctive corticosteroids may be effective in the management of paradoxical deterioration based on its immune-mediated reaction[3,7,10]. Recently, in the intractable intracranial lesions unresponsive to conventional antituberculosis treatment, corticosteroids, or surgery, adjuvant thalidomide, a potent inhibitor of tumor necrosis factor alpha has been advocated[11]. However, a randomized trial of thalidomide in children with tuberculous meningitis was discontinued because of severe adverse events.

This is an unusual case of the unexpected clinical and neuroradiological deterioration of intramedullary tuberculomas despite adequate antituberculous therapy. Initially, we preferentially presumed the possibility of multidrug-resistant *M. tuberculosis*, which tends to occur much more frequently in cases of re-treatment[9] and human immunodeficiency virus infection[6]. However, this was not a re-treatment case of tuberculosis and the patient has had a good compliance and tolerance for antituberculous therapy. He was also sereonegative for human immunodeficiency virus. Therefore, we believe that this is a peculiar case of "paradoxical deterioration" of intramedullary tuberculomas. However, we could not completely exclude multidrug-resistant *M. tuberculosis* because all mycobacterial cultures were negative through the course of treatment.

Conclusion

We experienced a rare case of paradoxical deterioration of intramedullary spinal tuberculomas despite adequate antituberculous therapy. Although it is rare, this phenomenon of paradoxical deterioration in the treatment of the central nervous system tuberculosis should be kept in mind.

References

1. Campbell IA, Dyson AJ : Lymph node tuberculosis : a comparison of various methods of treatment. **Tubercle 58** : 171-179, 1977
2. Chambers ST, Hendrickse WA, Record C, Rudge P, Smith H : Paradoxical expansion of intracranial tuberculomas during chemotherapy. **Lancet 28** : 181-184, 1984
3. Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al : Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. **Eur J Clin Microbiol Infect Dis 21** : 803-809, 2002
4. Chien JW, Johnson JL : Paradoxical reactions in HIV and pulmonary TB. **Chest 114** : 933-936, 1998
5. Citow JS, Ammirati M : Intramedullary tuberculoma of the spinal cord : case report. **Neurosurgery 35** : 327-330, 1994
6. Joseph P, Severe P, Ferdinand S, Goh KS, Sola C, Haas DW, et al : Multidrug-resistant tuberculosis at an HIV testing center in Haiti. **AIDS 20** : 415-418, 2006
7. Kumar R, Prakash M, Jha S : Paradoxical response to chemotherapy in neurotuberculosis. **Pediatr Neurosurg 42** : 214-222, 2006
8. Lin SK, Wu T, Wai YY : Intramedullary spinal tuberculomas during treatment of tuberculous meningitis. **Clin Neurol Neurosurg 96** : 71-78, 1994
9. Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al : Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. **N Engl J Med 338** : 1641-1649, 1998
10. Rao GP, Nadh BR, Hemaratnan A, Srinivas TV, Reddy PK : Paradoxical progression of tuberculous lesions during chemotherapy of central nervous system tuberculosis. Report of four cases. **J Neurosurg 83** : 359-362, 1995
11. Schoeman JF, Fieggen G, Seller N, Mendelson M, Hartzenberg B : Intractable intracranial tuberculous infection responsive to thalidomide : report of four cases. **J Child Neurol 21** : 301-308, 2006
12. Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, et al : Adjunctive thalidomide therapy for childhood tuberculous meningitis : results of a randomized study. **J Child Neurol 19** : 250-257, 2004
13. Skendros P, Kamaria F, Kontopoulos V, Tsitouridis I, Sidiropoulos L : Intradural, extramedullary tuberculoma of the spinal cord as a complication of tuberculous meningitis. **Infection 31** : 115-117, 2003
14. Teoh R, Humphries MJ, O'Mahony G : Symptomatic intracranial tuberculoma developing during treatment of tuberculosis: a report of 10 patients and review of the literature. **Q J Med 63** : 449-460, 1987
15. Thrush DC, Barwick DD : Three patients with intracranial tuberculomas with unusual features. **J Neurol Neurosurg Psychiatry 37** : 566-569, 1974