

Case Report

Asian Pacific Journal of Tropical Medicine

doi:10.4103/1995–7645.356995

Impact Factor: 3.041

Neurological paradox during treatment in a non-HIV patient with pulmonary tuberculosis: A case report

Thanyalak Amornpojnimman, Song Srisilpa, Pornchai Sathirapanya ✉

Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand

ABSTRACT

Rationale: To report neurological paradox in a non-HIV patient with pulmonary tuberculosis.

Patient concerns: A 26-year-old non-human immunodeficiency virus immunosuppressed female patient presented with diffused headache, diplopia, ascending paraparesis with loss of bowel and bladder control.

Diagnosis: Disseminated neurological paradoxical reaction developed during tuberculosis treatment in a non-human immunodeficiency virus patient.

Intervention: High-dose intravenous corticosteroid was added to the anti-tuberculous drugs, followed by tapered dose of oral prednisolone in 3 months.

Outcome: A favorable neurological outcome was obtained 6 months later.

Lessons: Neurological paradoxical reaction cannot be overlooked among the tuberculosis-treated cases who present with newly emerged neurological disorders.

KEYWORDS: *Mycobacterium tuberculosis*; Paradoxical reaction; Nervous system; HIV

1. Introduction

Tuberculosis (TB) is among the top ten infectious causes of death worldwide even though it is curable and preventable[1]. A paradoxical reaction (PR) during anti-tuberculosis treatment is defined as a clinical or radiological deterioration of pre-existing tuberculous lesions, or emergence of new lesions in the patients whose TB symptoms initially responded to anti-tuberculosis treatment[2,3]. Neurological PR has been well-described in HIV patients, but it is rarely reported in non-HIV patients. It was reported to have 6%-30% incidence and the prevalence is greater in Asian and African population and can occur in various parts of the body[2–4]. The definite pathogenesis of neurological PR is undetermined. Immune reconstitution or over-reaction to the dead mycobacterium during anti-tuberculosis treatment was proposed. Risk factors of PR

in non-HIV patients included extrapulmonary involvement, lower baseline lymphocyte counts and higher surge in lymphocyte counts during treatment[2]. Although there is no strong supporting evidence, corticosteroid is suggested for treatment of neurological PR. Here, we presented a rare case of extensive neurological PR in a non-HIV patient during anti-tuberculosis treatment.

2. Case report

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

A 26-year-old Thai female presented with low-grade fever that does not exceed 38 °C, dry cough, and significant weight loss (6 kg) 4 months prior to the presentation. Pulmonary TB was diagnosed by an abnormal chest film and a positive sputum smear for acid fast bacilli. A regimen of anti-tuberculous drugs consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol was given and her symptoms of respiratory infection improved in a couple of weeks post treatment. However, one month after the treatment initiation, she developed diffuse headache and binocular diplopia. Two weeks later, she had numbness and weakness of both feet. Later on, the motor weakness worsened to wheelchair-bound status. At the same time, constipation and urinary retention occurred. She confirmed strict adherence to the anti-tuberculous medication.

On physical examination, she was afebrile and had an unremarkable systemic evaluation. Her neurological examination reported full consciousness, normal size and light reaction of both

✉To whom correspondence may be addressed. E-mail: sporncha@medicine.psu.ac.th
This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

©2022 Asian Pacific Journal of Tropical Medicine Produced by Wolters Kluwer-Medknow.

How to cite this article: Amornpojnimman T, Srisilpa S, Sathirapanya P. Neurological paradox during treatment in a non-HIV patient with pulmonary tuberculosis: A case report. Asian Pac J Trop Med 2022; 15(10): 474–476.

Article history: Received 21 May 2022 Revision 15 September 2022
Accepted 21 September 2022 Available online 31 October 2022

pupils, but partially limited right lateral rectus muscle power. Motor power assessment revealed proximal muscles as grade 3 and the distal muscles as grade 2 symmetrically on lower extremities, as per Medical Research Council. Pinprick sensation decreased below the 8th thoracic spinal (T8) level and vibration sensation also decreased below the T4 level. Hyporeflexia was detected in both lower limbs. Digital rectal examination showed loose anal sphincter tone. Impaired perianal sensation and bulbocavernosus reflex were associated.

Magnetic resonance imaging of the brain illustrated multiple nodules visualized in the bilateral cerebral hemispheres, brainstem, and cerebellar hemispheres (Figure 1). Extensive and thickened arachnoiditis with spinal cord compression from T3 to L1 was noted from the spinal magnetic resonance imaging (Figure 2). The cerebrospinal fluid (CSF) analysis showed a total white blood cell count of 12 cells/mm³ (reference range <5 cells/mm³) with all were mononuclear cells, protein 5.865 mg/dL (reference range <50 mg/dL) and glucose 65 mg/dL (serum glucose 114 mg/dL, ratio of CSF/blood glucose=0.57). The CSF polymerase chain reaction (PCR) test and culture for *Mycobacterium tuberculosis* (MTB) were both negative. A sputum smear to detect acid fast bacilli for 3 consecutive days and a real time PCR analysis for MTB in the sputum were both negative. The plain chest film showed a blunt right costophrenic angle with minimal reticular infiltration at the right lower lung zone. A serological test for human immunodeficiency virus (anti-HIV) was non-reactive. Consequently, she was diagnosed with neurological PR during treatment of pulmonary TB. Finally, a course of high-dose (15 mg/d for 7 days then 10 mg/d for 7 days) intravenous dexamethasone was promptly added to the anti-tuberculous drugs previously given followed by tapered dose oral prednisolone in 3 months, and combined intensive rehabilitation

program. All disabling neurological symptoms and signs dramatically improved to nearly complete recovery at 6 months post treatment.

3. Discussion

Neurological PR, or neurological paradox, is a form of immune reconstitution inflammatory syndrome (IRIS) which commonly occurs with treated cryptococcal infection in HIV patients. IRIS is rarely reported in non-HIV patients, especially during anti-tuberculosis treatment. Fundamentally, anti-tuberculous drug resistance, poor drug compliance, undesired effects of anti-tuberculosis therapy, and superimposed infection need to be excluded before neurological or non-neurological PR is diagnosed[3].

The pathogenesis of PR remains unclear. It was proposed that an activated immune response to MTB antigens or the dying bacteria after treatment was related[5]. Moreover, PR was attributed to tumor necrotic factor- α released from microglial cells. Bekker et al. reported that the rise in the plasma tumor necrotic factor- α level might be correlated with transient clinical deterioration after initiation of anti-tuberculosis agents in patients with severe TB[6]. In our patient, since the CSF and sputum real time PCR and culture for MTB were all negative, the markedly high CSF protein and low cell count could represent a robust immune reaction against the MTB antigen causing severe neurological inflammation during the development of neurological PR rather than TB re-infection.

The median time from initiation of TB treatment to non-neurological PR occurrence was reported to be 30-60 days[2,7]. Notably, another study reported a longer time in neurological PR

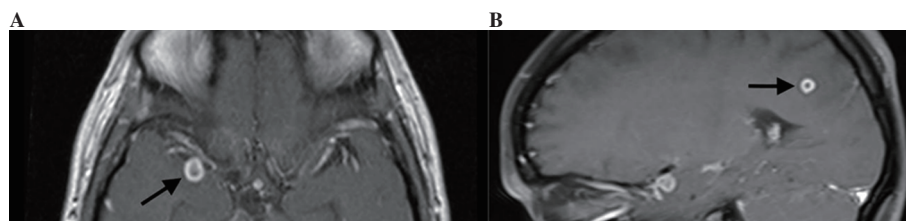


Figure 1. Magnetic resonance image of the brain of a 26-year-old woman with pulmonary tuberculosis, A) axial and B) sagittal view. The arrows revealed multiple enhancing small nodules in bilateral cerebral hemispheres, brainstem, and cerebellar hemispheres with diffuse pachymeningitis.

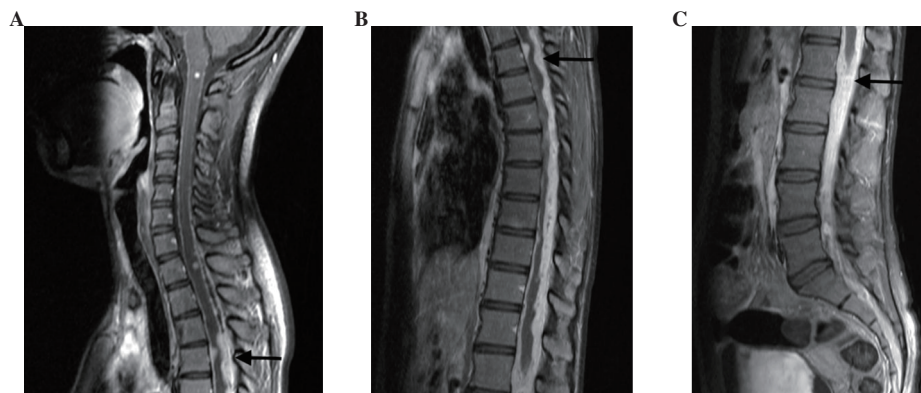


Figure 2. Magnetic resonance imaging of the spinal cord, A) Cervical spine, B) Thoracic spine and C) Lumbosacral spine. The arrows revealed spinal tuberculoma, extensive and thickened arachnoiditis with spinal cord compression from T3 to L1 level.

because of difficult penetration of anti-tuberculous drugs through the blood-brain barrier[3]. However, Lui *et al.* reported a shorter onset time of PR development in younger and female patients[7], which was like the patient in our case who had neurological PR very early at one month after starting anti-tuberculosis treatment.

Typically, IRIS was more common, extensive, and severe in HIV patients[8,9]. In cases of TB, previous studies reported various sites of PR involvement including nervous system, respiratory system, lymph node, bone, and skin that were the common sites of tuberculosis infection[2–4,10]. The central nervous system was reported as the most common site of neurological PR in which meninges were the first and single site of involvement up to 50% of cases[2,3]. According to our reported case, we demonstrated a rare case with widespread neurological PR associated with pulmonary tuberculosis treatment in a non-HIV patient in whom brain tuberculoma, spinal tuberculoma, and thickened spinal arachnoiditis with spinal cord compression were found.

Based on the currently available evidence, corticosteroid remained the mainstay of treatment with different dosages and durations depending on the clinical severity and expert opinions[7,10]. In general, most neurological PR patients achieved favorable outcomes with immediate treatment with corticosteroid with exception of some cases with spinal cord involvement that residual neurological deficit might occur[7,9,10]. We believed that our reported case obtained a favorable outcome in 6 months due to immediate treatment with intravenous corticosteroid.

4. Conclusions

Although extensive neurological PR related to anti-tuberculous treatment in non-HIV patients is very uncommon, it should be a differential diagnosis among TB-treated cases who present with newly emerged neurological disorders. Prompt treatment with intravenous corticosteroids after exclusion of other possible causes usually yields a favorable neurological outcome. Timing for neurological response and outcome is possibly related to the severity of the neurological PR.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgements

The authors would like to thank Mr. Glenn Shingledecker for editing the English writing of the manuscript.

Funding

The authors received no funding or grant for the report.

Authors' contributions

TA and SS collected the clinical data, did the analysis and provided intellectual content. TA drafted the initial manuscript. PS did the conceptualization of intellectual content and revision of the manuscript. All authors read and approved the final manuscript before submission.

References

- [1] World Health Organization. *Global tuberculosis report 2014*. [Online]. Available from: http://www.who.int/tb/publications/global_report/gtbr14_main_text.pdf?ua=1. [Accessed on 13 September 2020].
- [2] Cheng VCC, Yam WC, Woo PCY, Lau SKP, Hung IFN, Wong SPY, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 597-602.
- [3] Cheng VCC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PCY, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 803-809.
- [4] Hawkey CR, Yap T, Pereira J, Moore DAJ, Davidson RN, Pasvol G, et al. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. *Clin Infect Dis* 2005; **40**: 1368-1371.
- [5] Garg RK, Malhotra HS, Kumar N. Paradoxical reaction in HIV negative tuberculous meningitis. *J Neurol Sci* 2014; **340**: 26-36.
- [6] Bekker LG, Maartens G, Steyn L, Kaplan G. Selective increase in plasma tumor necrosis factor- α and concomitant clinical deterioration after initiating therapy in patients with severe tuberculosis. *J Infect Dis* 1998; **178**: 580-584.
- [7] Liu Y, Wang Z, Yao G, Lu Y, Hu Z, Yao H, et al. Paradoxical reaction in HIV-negative tuberculous meningitis patients with spinal involvement. *Int J Infect Dis* 2019; **79**: 104-108.
- [8] Breen RAM, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004; **59**: 704-707.
- [9] Singh AK, Malhotra HS, Garg RK, Jain A, Kumar N, Kohli N, et al. Paradoxical reaction in tuberculous meningitis: Presentation, predictors and impact on prognosis. *BMC Infect Dis* 2016; **16**: 306.
- [10] Geri G, Passeron A, Heym B, Arlet JB, Pouchot J, Capron L, et al. Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. *Infection* 2013; **41**: 537-543.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.