Received 28 August 2022 | Accepted 12 December 2022
DOI: http://doi.org/10.4038/sljon.v9i1.127

SLJoN

CASE REPORT

Paradoxical reaction in the treatment of tuberculous meningitis – pitfalls and challenges

Thevarajah Rameshkumar[1,2], **Thashi Chang**[1,3]

[1]University Medical Unit,
National Hospital of Sri Lanka.

[2]Department of Pharmacology,
University of Colombo,
Sri Lanka.

[3]Department of Clinical Medicine,
University of Colombo,
Sri Lanka.

Correspondence

Thevarajah Rameshkumar

University Medical Unit,
National Hospital of Sri Lanka,
Colombo 10,
Sri Lanka.

Email: thevarajah@pharm.cmb.ac.lk

Abstract

Paradoxical reaction during the treatment of tuberculous meningitis (TBM) poses both diagnostic and therapeutic challenges. We report a patient with miliary tuberculosis and TBM who developed an enhanced paradoxical reaction and discuss the challenges of its management.

A 22-year-old woman presented with fever and headache for two weeks with features of meningism on examination. Miliary tuberculosis with TBM was diagnosed based on positive cerebrospinal fluid (CSF) and sputum Gene-Xpert MTB/RIF. The chest radiograph showed a miliary pattern. Six weeks after starting antituberculosis treatment (ATT), she presented with worsening headache and repeat magnetic resonance imaging (MRI) showed increase in the number and size of tuberculomas. Prednisolone dose was increased. At 10 weeks after starting ATT, her symptoms persisted, and MRI showed further worsening of lesions. Intravenous dexamethasone was administered and gradually tapered with oral prednisolone. This resulted in resolution of symptoms and radiological lesions. Paradoxical reaction in TBM is a recognized phenomenon during the treatment of tuberculosis. Awareness of this complication and its treatment can prevent the morbidity associated with this reaction.

KEYWORDS
Tuberculosis, paradoxical reaction, miliary tuberculosis

INTRODUCTION

Tuberculosis is a major public health challenge and a target addressed in the sustainable development goals of the United Nations.[1, 2] In the year 2019, 7.1 million people were newly diagnosed with the disease worldwide; 95% being from developing countries. It is one of the top ten causes of death worldwide and the leading cause of death from a single infectious agent.[3] Tuberculous meningitis (TBM) is the most lethal form of tuberculosis and represents 5% of extra-pulmonary tuberculosis. Early recognition of the disease and prompt initiation of treatment has a favourable outcome with better neurological recovery.[4] Paradoxical clinical deterioration is characterised by headache, vomiting, meningeal signs, focal neurological deficits, vision loss, raised intracranial pressure or cranial nerve palsies. It is seen in 31% of patients treated with anti-tuberculous treatment.[5,6] Paradoxical reactions during the treatment of tuberculosis is a form of immune reconstitution inflammatory syndrome.[7]

We report a patient with miliary tuberculosis and TBM who developed an enhanced paradoxical reaction and discuss the challenges of its management.

CASE DESCRIPTION

A 22-year-old woman presented with loss of appetite and nausea for one month, daily persistent headache for two weeks and low-grade fever for one week. There were no respiratory symptoms or a contact history of tuberculosis. On the initial physical examination, her body mass index (BMI) was 17.2 kg/m^2. She appeared lethargic, with heart rate of 98 beats/min. Her blood pressure was 110/70 mmHg. Her Glasgow coma scale (GCS) score was 15/15. There was neck stiffness, right abducens nerve palsy, without papilloedema or other neurological signs. The rest of the examination was normal.

Her investigations on admission are shown in Table 1.

Renal and liver profiles were within normal limits except for a hyponatraemia of 122 mmol/L. Osmolality studies were suggestive of syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Gadolinium-enhanced cranial magnetic resonance imaging (MRI) showed multiple ring enhancing lesions in bilateral cerebral hemispheres, pons and cerebellum with peripheral T2 hyperintensity and basal meningeal enhancement suggestive of TBM and multiple tuberculomas (Figure 1A). Her cerebrospinal fluid (CSF) showed a lymphocytic pleocytosis with a lymphocyte count of 40 per µL (reference range <5), elevated protein of 112 mg/dL (reference range 15-45), and reduced sugar of 16 mg/dL (blood sugar - 99 mg/dL). Chest radiograph showed diffuse nodular infiltrates suggestive of miliary tuberculosis (Figure 2A). Gene-Xpert MTB/RIF (Cepheid Sunnyvale, CA, United States) in both CSF and sputum were positive and rifampicin resistance was not detected.

She was commenced on antituberculosis treatment (ATT) with daily three tablets of fixed dose combination (FDC4) with intramuscular streptomycin 0.75 g daily, pyridoxine 12.5 mg daily and intravenous dexamethasone. Hyponatraemia was corrected with fluid restriction. Clinical improvement was noted and she was discharged on day 10 after admission with FDC4 and prednisolone 1 mg/kg daily (45 mg).

The patient presented six weeks into the ATT with progressive intermittent headache with loss of appetite. She was on prednisolone 15 mg daily at the time of re-presentation. Her clinical, biochemical, and haematological parameters were within normal ranges (Table 1). MRI brain showed an increase in the number of tuberculomas and irregularities in the intracranial arteries suggestive of tuberculous arteritis. There was no venous sinus thrombosis. Paradoxical reaction to ATT was diagnosed, and the prednisolone dose was increased to 30 mg daily. The ATT was converted to individual drugs instead of the combined pill and she was given rifampicin 450 mg, isoniazid 200 mg, pyrazinamide 1000 mg, and ethambutol 600 mg; all given daily.

TABLE 1 Laboratory data on admission and on subsequent follow up at six and 10 weeks

	On admission	Six weeks of treatment	10 weeks of treatment	Reference range, adults
White cell count (per µL)	10370	5700	5400	4000-10000
Differential count (per µL)				
Neutrophils	9260 (89%)	4190 (73%)	3500 (64%)	2000-7000
Lymphocytes	670 (6.5%)	680 (12%)	1200 (22%)	800-4000
Monocytes	430 (4%)	830 (15%)	700 (13%)	120-1200
Eosinophils	0	0	0	20-500
Haemoglobin (g/dL)	10.6	11.4	11.6	11-16
Haematocrit (%)	32.8	33.8	34.4	37-54
Platelets (per µL)	260,000	349,000	262,000	150,000-400,000
Erythrocyte sedimentation rate (mm 1st hour)	22	Not done	20	<20
C-reactive protein (mg/L)	<6	<6	<6	<6

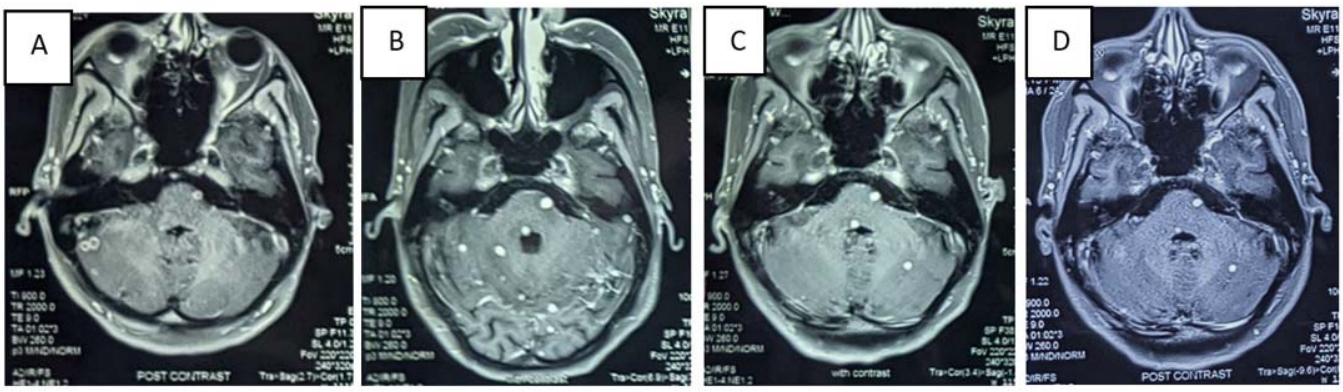

FIGURE 1 **Contrast T1 MRI brain (A) at diagnosis; (B) at six weeks; (C) at 10 weeks; (D) at 18 weeks of antituberculosis treatment.**

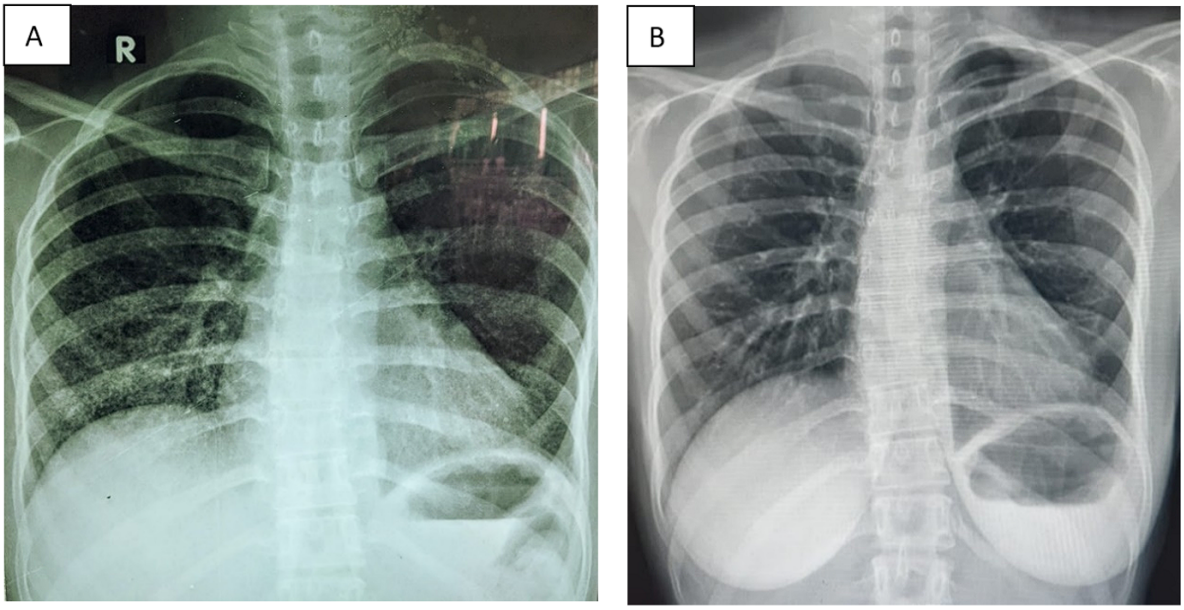

FIGURE 2 **Chest radiograph (A) at admission; (B) at 10 weeks of antituberculosis treatment.**

She was reviewed at 10 weeks with a repeat MRI brain and chest radiograph. There was no improvement in her symptoms despite the biochemical and haematological parameters being normal (Table 1). The repeated MRI brain showed increase in the number and enhancement of the tuberculomas with interval increase in basal meningeal enhancement but the irregularities in the intracranial arteries had resolved (Figure 1C). However, chest radiograph showed resolution of the miliary tuberculosis (Figure 2B). She was started on intravenous dexamethasone and converted to oral prednisolone 45 mg daily.

Human immunodeficiency virus (HIV) screening was negative and immunoglobulin levels (IgG, IgA, and IgM), complement levels (C3 and C4) and flow cytometric analysis of lymphocyte subsets were within normal limits. Nitroblue-tetrazolium assay showed normal activity in >95% of neutrophils. Lymphocyte function test using lymphocyte proliferation following stimulation with concanavalin A showed normal proliferation after 72 hours of stimulation. Anti-nuclear antibody (ANA) and rheumatoid factor were negative. She was reviewed at 18 weeks of treatment; her symptoms had resolved and the repeated MRI at 18 weeks of treatment (Figure 1D) showed reduction in the number and enhancement of the tuberculomas. ATT was continued for one year while prednisolone was gradually tapered.

DISCUSSION

Our patient had bacteriologically confirmed miliary tuberculosis with TBM. However, her inflammatory markers were normal, thus response to treatment could be monitored only with clinical and radiological parameters. Worsening clinical status coupled with new lesions and increased enhancement in the cranial MRI despite ATT suggested a paradoxical reaction.

Paradoxical reaction in tuberculosis is defined by a clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions, in patients receiving ATT who initially improved on treatment.[8] The reported incidence of paradoxical reaction is 31% and majority of them were within 3 months of starting of ATT.[5]

The mechanism of paradoxical reaction is hypothesized to occur due to an exaggerated inflammatory response to mycobacterial antigens. The delicate balance between the pro-inflammatory and anti-inflammatory response to tuberculosis is important, especially in the treatment of central nervous system (CNS) tuberculosis. Regulatory T cells are important in reducing the inflammatory response and preventing tissue damage.[9]

Paradoxical reaction poses a challenge in the treatment of CNS tuberculosis since it is a diagnosis of exclusion. The presentation of paradoxical reaction can be misdiagnosed as treatment failure, drug resistance, tuberculosis relapse and alternative diagnosis or superimposed infection. Our patient did not have rifampicin resistance, immune deficiency or an alternate cause for progression.

There are no strong predictors for paradoxical reaction apart from the associations derived from the descriptive studies. Occurrence of paradoxical reaction was associated with female gender, concomitant HIV infection, shorter duration of illness, lower baseline lymphocyte counts and greater surge in lymphocyte counts during paradoxical response.[5,10] There are no randomized trials in the management of paradoxical reaction TBM and no consensus on the standard treatment. Based on hypothesized pathogenesis, it is treated with immuno-suppressive drugs. Drugs used are corticosteroids, tissue necrosis factor-α antagonists, thalidomide and cyclo-phosphamide.[6,11] Our patient responded to intravenous dexamethasone and did not require further immune-suppressive agents.

CONCLUSION

Paradoxical reaction in CNS tuberculosis is a well-recognized phenomenon during the treatment of tuberculosis. Awareness of this complication and use of immunosuppressive drugs can prevent the morbidity associated with this reaction.

Conflict of interest

No financial support was received from any party for the management of the patient or the preparation of this manuscript.

REFERENCES

1. United Nations. (2015). Transforming our world: the 2030 Agenda for Sustainable Development. https://wedocs.unep.org/20.500.11822/9814.
2. Osborn D, Cutter A, Ullah F. Universal sustainable development goals. Understanding the transformational challenge for developed countries. Report of a study by Stakeholder Forum. 1-25 May 2015. https://sustainabledevelopment.un.org/content/documents/1684SF_-_SDG_Universality_Report_-_May_2015.pdf
3. World Health Organization. (2020) Global tuberculosis report 2020: executive summary. World Health Organization; https://apps.who.int/iris/handle/10665/337538.
4. Kasper D, et al. Harrison's Principles of Internal Medicine, 19th ed. New York: McGraw-Hill, 2015.
5. Singh AK, Malhotra HS, Garg RK, et al. Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. *BMC Infect Dis*. 2016;16: 306-. doi: 10.1186/s12879-016-1625-9.
6. Garg RK, Malhotra HS, Kumar N. Paradoxical reaction in HIV negative tuberculous meningitis. *J Neurol Sci*.2014;340(1): 26-36. doi: 10.1186/s12879-016-1625-9.
7. Lanzafame M, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. *J Clin Tuberc Other Mycobact Dis*. 2016;3: 6-9. doi: 10.1016/j.jctube.2016.03.002.
8. Bloch S, Wickremasinghe M, Wright A, et al. Paradoxical reactions in non-HIV tuberculosis presenting as endobronchial obstruction. *Eur Respir Rev*. 2009;18(114):295-9. doi: 10.1183/09059180.00003709.
9. Saenz B, Hernandez-Pando R, Fragoso G, et al. The dual face of central nervous system tuberculosis: a new Janus Bifrons? *Tuberculosis* (Edinb). 2013;93(2):130-5. doi: 10.1016/j.tube.2012.11.011.
10. Cheng VC, Yam WC, Woo PC, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis*. 2003;22(10): 597-602. doi: 10.1007/s10096-003-0998-z.
11. Blackmore TK, Manning L, Taylor WJ, et al. Therapeutic Use of Infliximab in Tuberculosis to Control Severe Paradoxical Reaction of the Brain and Lymph Nodes. *Clinical Infectious Diseases*. 2008;47(10):e83-e5. doi: 10.1086/592695.