



Adjuvant immunosuppression for paradoxical deterioration in tuberculous meningitis including one case responsive to cyclosporine. A tertiary referral hospital experience

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ABSTRACT

Background: Tuberculous meningitis (TBM) accounts for 1–4% of all tuberculosis (TB) presentations. Paradoxical deterioration in non-HIV patients is a common manifestation of anti-tuberculosis therapy, characterised by clinico-radiological deterioration. We report a case series of TBM admissions to our institution including one case with paradoxical deterioration refractory to corticosteroids who responded to adjuvant cyclosporine.

Methods: Retrospective review of 12 HIV-negative patients admitted to Liverpool Hospital, Sydney (2005–2016) with laboratory and/or radiologically confirmed TBM.

Results: Median patient age was 40 (range 22–81 years), M:F = 7:5. Eleven patients (92%) were of Asia-Pacific origin. Eleven initially presented with central nervous system manifestations and one had preceding miliary TB. Nine patients had extra-cranial TB involvement including eight with past or current pulmonary disease. Cerebrospinal fluid (CSF) TB PCR/culture was positive in 10 patients. Paradoxical deterioration developed in three patients despite concomitant corticosteroids in two. One patient with paradoxical deterioration was refractory to corticosteroids: A 22-year-old Vietnamese male with TBM developed worsening headaches and altered mentation after seven weeks concomitant anti-TB and corticosteroid treatment. Interval MRI brain demonstrated increased size and number of tuberculomas as well as hydrocephalus. Cyclosporine was added with gradual improvement and ultimately good outcome.

Conclusion: Our case series highlights the seriousness of paradoxical deterioration in TBM and the potential role of adjuvant cyclosporine in patients refractory to corticosteroids.

1. Introduction

The incidence of tuberculosis (TB) in Australia has been relatively constant since the mid-1980s ranging from 4 to 7/100,000/year [1,2]. Patients born in Asia, in particular India, Vietnam, the Phillipines and China, are at significantly higher risk than those born in Australia [1,2]. The most commonly affected site of infection is pulmonary although extrapulmonary involvement is not uncommon [3,4], and more likely to occur in patients with coexisting Human Immunodeficiency Virus (HIV) infection [5].

Tuberculosis meningitis (TBM), a severe form of extrapulmonary TB that is associated with over 20% morbidity and mortality [6,7],

accounts for 1–4% of all TB presentations [3,8]. Pathogenic mechanisms for death and disability include intracranial hypertension and/or hydrocephalus from a highly proteinaceous and hypercellular basal meningitic exudate and cerebral vasculitis with infarction [9,10].

Paradoxical deterioration, postulated to be caused by immune reconstitution of T helper 1 CD4+ immune responses during the course of treatment [11,12] and/or a delayed-type immune reaction against *Mycobacterium tuberculosis* antigens [8,13–15], may contribute to potentially life-threatening clinical deterioration in both HIV-positive and negative patients with TBM. Paradoxical deterioration typically develops > 4 weeks after commencement of anti-TB therapy [8] and may manifest clinically, radiologically or on cerebrospinal fluid (CSF)

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analysis [8,13–15]. Neuroimaging abnormalities include new or enlarging tuberculomas, new infarcts and worsening leptomeningeal enhancement [8,13–15]. Paradoxical deterioration can be picked up incidentally on follow-up MRIs and depending on the extent of the deterioration may not necessarily have a clinical correlate or a significant impact on overall patient outcome.

Corticosteroid therapy, used concomitantly with anti-TB treatment in the first 4–8 weeks following clinical diagnosis, has been shown to reduce mortality [9,16]. Thwaites et al. reported a tapering regimen of dexamethasone for treatment of TBM in adolescents and adults, according to disease severity, in which patients with mild disease received two weeks of intravenous therapy followed by four weeks of reducing dexamethasone dosage [16]. Unfortunately, patients may experience paradoxical deterioration whilst on stable or weaning corticosteroid therapy, or after steroids have been withdrawn [8,13,14]. Recommencement or increased dose of corticosteroids is currently recommended for symptomatic paradoxical deterioration although there have been no randomised control trials [8,13,14]. Other immunomodulatory therapies reported in the literature as potential treatments for paradoxical deterioration of TBM include the tissue necrosis factor (TNF)-alpha antagonists infliximab [17,18] and adalimumab [19], thalidomide [14,20,21] and γ -interferon [14].

We present a case series of 12 HIV-negative TBM admissions to our institution including a case with paradoxical deterioration refractory to corticosteroids who responded to adjuvant cyclosporine.

2. Materials and methods

A retrospective study of patients admitted to Liverpool hospital, Sydney, Australia with TBM between January 2005 and December 2016 was conducted. A diagnosis of TBM required identification of *Mycobacterium tuberculosis* on CSF direct smear, culture, nucleic acid amplification test such as polymerase chain reaction (PCR) or histopathological analysis and clinical and/or radiological features of intracranial involvement. Patients with TB isolated to the spine were excluded. Health Information Exchange and medical record data of patients hospitalised between January 2005 and December 2016 with a diagnosis of central nervous system TB and/or TBM were reviewed by co-authors DL, SE, CCS and DC to identify patients fulfilling diagnostic criteria. Data was also extracted from New South Wales (NSW) Health Pathology Liverpool laboratory records of patients with microbiologically proven TB admitted to Liverpool hospital during the same time period. Co-authors DL and SE reviewed the SWS Pathology patient files to identify patients not captured by the HIE or medical record databases. The study was approved by the local Human Research Ethics Committee.

3. Results

Twelve patients were identified (Supplementary Table 1), median age 40 years (range 22–81 years). All patients were HIV-negative. Eleven patients (92%) were of Asia-Pacific origin. Eleven patients (92%) presented with central nervous system manifestations and one patient (8%) had prior diagnosis of military TB. Nine patients (75%) had evidence of extracranial TB involvement including 8 with past or current pulmonary disease (Supplementary Table 2). CSF TB PCR/culture was positive in 10 patients (83%). One patient had TB resistance to pyrazinamide. The rest of the patients with positive TB culture were fully sensitive to first line antibiotics. All patients were commenced quadruple anti-TB therapy (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol). Doses as recommended by WHO: Treatment of Tuberculosis guidelines 2010. Patients 9–12 presented prior to the publication of these guidelines but were treated with the same medications at similar doses. Eleven patients (92%) were started on concomitant corticosteroid therapy at the time of clinical diagnosis. Corticosteroid therapy was continued for a minimum of six weeks in all

patients (excluding case three who died at day 21). The exact duration and dosage of corticosteroids varied between patients, depending on the patients' clinical status and the preferences of the responsible clinician. We have detailed the exact doses and duration for individual patients in Supplementary Tables 2 and 3. Five of our cohort made a complete recovery, whilst two of our cohort died within the subsequent year (Supplementary Table 3), One as a result of progressive disease whereby TB was only recognised post-mortem and the second where poor compliance with anti-TB therapy played a significant role. Paradoxical deterioration of TBM developed in three patients despite concomitant corticosteroids in two. The paradoxical deterioration in case one was treated with adjuvant cyclosporine. Cyclosporine was also added to patient 10 (Supplementary Table 3) at day 14 due to neurological deterioration despite quadruple anti-TB therapy and concomitant high dose corticosteroids.

4. Case 1

A 22-year-old Vietnamese male presented with a 6-week history of progressive headache and neck stiffness. On admission, he was febrile to 38 °C, mildly confused and had a Glasgow Coma Score (GCS) of 14 out of 15. CSF analysis demonstrated 61 white cells (75% neutrophils, 25% lymphocytes), raised protein 2.67 g/L ($N < 0.45$ g/L) and low glucose 2.1 mmol/L. He was commenced quadruple anti-TB therapy with rifampicin, isoniazid, pyrazinamide and ethambutol and prednisolone 60 mg once daily 4 days after he was admitted following a positive CSF TB PCR result. A second lumbar puncture performed 3 days later due to worsening headache showed increasing CSF white cells;690 (80% neutrophils) and protein 3.92 g/L. He was changed to oral dexamethasone 4 mg three times daily. This was reduced after 1 week to 2 mg three times daily and after a further week to 5 mg once daily. Due to initial significant clinical improvement his dexamethasone dosing was tapered by 1 mg per week.

At week 7 post-initiation of treatment, he deteriorated with a recurrence of fever, headache, reduced GCS and reduced oral intake. His dexamethasone dose was 2 mg daily and he remained on quadruple anti-TB therapy. Magnetic resonance imaging (MRI) brain demonstrated significant interval changes (Fig. 1(a)–(d)) including progressive hydrocephalus, an increase in size and number of tuberculomas, right anterior thalamic and right medial temporal lobe infarcts and worsening basal meningitis. This was recognised to reflect paradoxical deterioration. An extraventricular drain was inserted and he was given 3 days of intravenous methylprednisolone, followed by dexamethasone 4 mg QDS. There was minimal change in his clinical condition and hence a week after increasing corticosteroids cyclosporine was started at 150 mg twice daily (4 mg/kg/day). Cyclosporine was selected due to local experience in using this induction dosing to manage TB meningitis and other neurological conditions within the department.

He was felt to make a good clinical improvement over the following 1–2 weeks with return to normal alertness and resolution of fever. At this point there were signs of a mild cognitive impairment with a Rowland Universal Dementia Assessment Scale score of 27/30 and clinical signs of a mild spastic paraparesis attributed to his TBM-related basal meningitis and cerebral infarcts. Following commencement of cyclosporine, dexamethasone was tapered by 2 mg per fortnight over 2 months and then weaned until cessation over another 4 weeks due to the development of bilateral avascular necrosis of the hips at this time which was managed conservatively. Between 7 weeks to 12 months he reported ongoing cognitive slowing and a global, persistent daily headache of dull quality and fluctuating severity which gradually subsided. Concomitant cyclosporine was continued for 2 years, primarily due to headache recurrence and persistence of MRI brain abnormalities on cyclosporine dosing reduction at 12 months. The cause of headache recurrence at 12 months was unclear but suspected to reflect raised intracranial pressure inter-related to his TBM and paradoxical reaction. At 18 months, cyclosporine dose was tapered to 50 mg

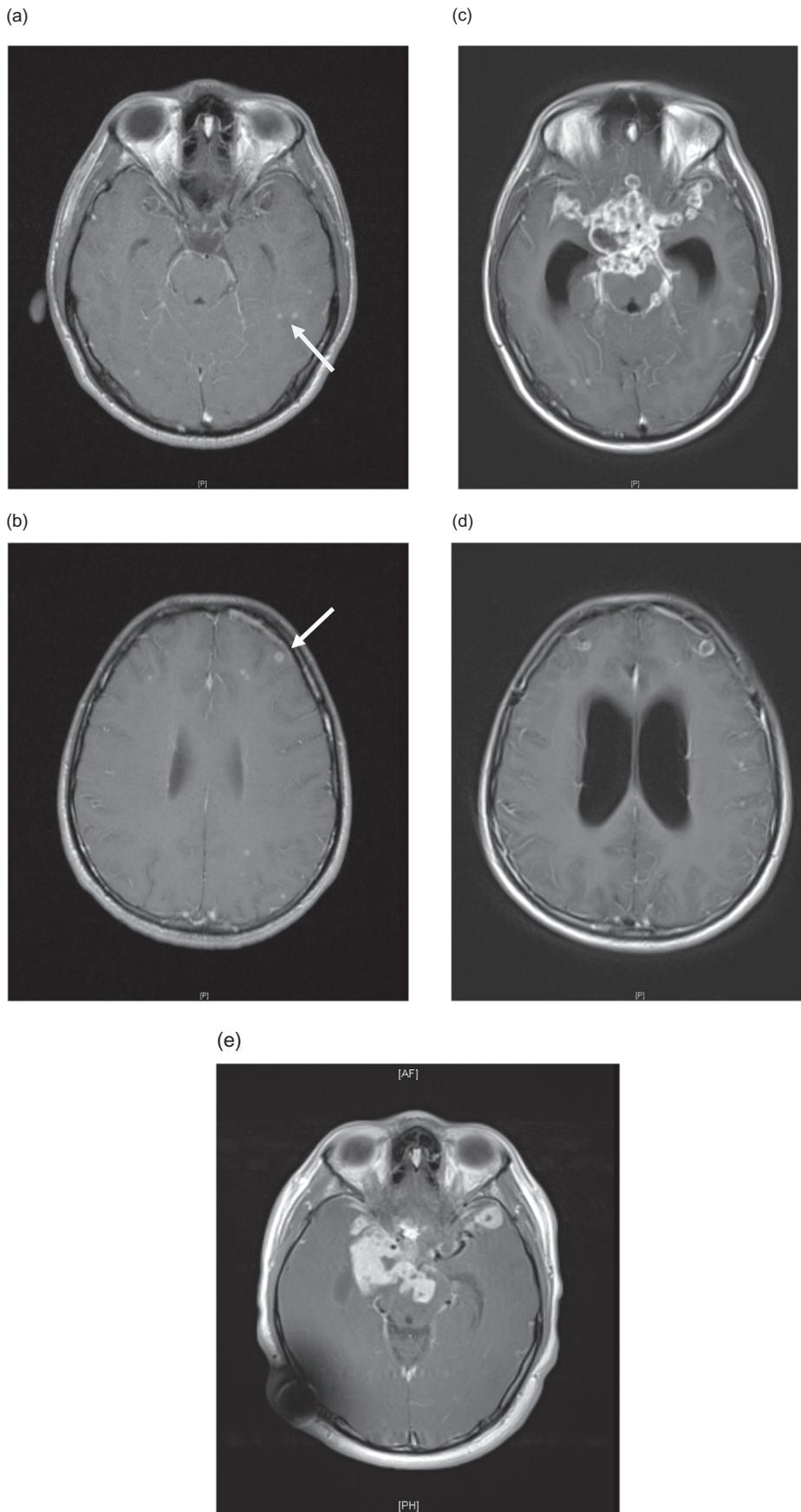


Fig. 1. 1. (a) and (b) Post-contrast cerebral MRI T1 axial images at the time of admission (pre-treatment) showing multiple contrast-enhancing lesions (white arrows). The lesions are seen within the cortex and deep white matter in the cerebrum and cerebellum bilaterally. The largest lesion (5 mm) is located in the left frontal cortex and is ring-enhancing; (c) Post-contrast cerebral MRI T1 axial images at day 52 (post-diagnosis and initiation of anti-TB therapy) showing multiple contrast-enhancing lesions of varying size in the pre-pontine, perimedullary and suprasellar cisterns extending into the Sylvian fissures bilaterally. There is associated ring enhancement, pial thickening and enhancement in the extra-axial sulcal spaces; (c) and (d) Progressive hydrocephalus is also noted. His repeat MRI at 2 and a half years following treatment (at this point he was 6 months off cyclosporine but remained on anti-TB therapy) demonstrated stable appearances of the supra-sellar and basal cistern meningeal enhancing lesions. Post contrast T1 axial images (e).

BD and successfully weaned over a further 6 months. At 3 years he had made an excellent recovery. He was married and working full time with no clear cognitive deficit detectable in a clinic setting. He unfortunately has a degree of mechanical gait impairment related to his previous bilateral hip necrosis. Lower limb neurological examination was normal at 3 years other than a mild degree of hyperreflexia.

Throughout the 2 year period on cyclosporine no side effects thought primarily attributable to cyclosporine were detected. Blood pressure and renal function remained normal. He did not develop intercurrent infections, skin changes or tremor. The patient's headache improved whilst on cyclosporine and hence we do not think this medication contributed to the headache. His avascular necrosis was felt most likely to be related to high dose corticosteroid therapy although a contribution from cyclosporine cannot be excluded.

Anti-TB therapy was continued for 3 years due to the persistence of MRI brain abnormalities. His MRI brains were repeated on a regular basis. He developed no further infarcts or granulomas and the meningeal changes appeared stable on his last MRI performed two and a half years after his TBM diagnosis (Fig. 1(e)). Anti-TB therapy was ceased at 3 years due to the patient's clinical stability during the 24 to 36 month period post-treatment onset.

5. Discussion

We report a case series of 12 HIV-negative patients with TBM, three (25%) of whom developed clinical manifestations consistent with paradoxical deterioration following commencement of anti-TB therapy. In one of our patients, adjuvant corticosteroid therapy did not adequately prevent the development of new symptoms or signs necessitating use of a second immunomodulatory agent. A second patient with acute severe neurological deterioration despite quadruple anti-TB therapy and concomitant high dose corticosteroids was also administered cyclosporine (patient 10 – supplementary tables). His deterioration occurred prior to 4 weeks and hence could not be considered a true paradoxical deterioration. To the best of our knowledge, cyclosporine has not been previously reported as maintenance immunotherapy for paradoxical deterioration of TBM although there has been a case report of its use as bridging therapy for paradoxical deterioration in a patient treated with a combination of prednisolone and thalidomide [21]. A combination of anti-TB therapy, corticosteroids and cyclosporine was well tolerated and effective in stabilising the clinical course in both patients who received this treatment.

6. Paradoxical deterioration

Paradoxical deterioration has been reported in 31–56% of HIV-negative patients with TBM [8,15]. Although the majority make a good recovery, permanent neurological deficits or death occur in 30–40% of cases [8]. Paradoxical deterioration is a major challenge for resource limited low to middle income countries where HIV/TB co-infection are common [22]. Anti-retro viral therapy may precipitate [12] a TB-immune reconstitution inflammatory syndrome (TB-IRIS) in up to one-third of such patients [21]. In both HIV-positive and negative patients, the risk of a paradoxical deterioration is greater in those with extrapulmonary involvement [8,13–15]. In TBM, the time of onset of paradoxical worsening is longer than that seen in other sites [23]. In TBM, it develops after a median of 2 months from initiation of anti-TB treatment [8,23] but has been described to first manifest as late as 18 months post-treatment [13]. By definition, paradoxical deterioration cannot be attributed to the natural disease course and hence requires a period of clinical improvement following initiation of anti-TB therapy [8,13,23]. For this reason, a minimum of 4 weeks anti-TB therapy must have elapsed before making such a diagnosis [11,20]. The differential diagnosis includes progressive disease, multi drug resistance and treatment noncompliance all of which require exclusion [4]. In one series, paradoxical deterioration was found to last a mean of 82 days

(range 16–320 days) [15].

The frequency and timing of paradoxical deterioration may be influenced by concomitant corticosteroids which are a standard initial therapy, usually administered for between 4 and 8 weeks, when patients are first diagnosed with TBM [9]. Paradoxical deterioration, as seen in our study, may occur during stable concomitant corticosteroid therapy. There have been no randomised control trials but most published series of paradoxical deterioration have treated patients with corticosteroids, surgical intervention (most often ventricular-peritoneal shunting) and/or a change in anti-TB therapy [8,13,14]. In our case series, one patient deteriorated, after initial clinical improvement and despite concomitant corticosteroid therapy, necessitating a second immunomodulatory agent.

The pathophysiological mechanism of paradoxical deterioration in HIV-negative patients is not fully understood [12]. A possible mechanism is a localised immunosuppressive effect on T lymphocytes in surrounding tissue mediated by *Mycobacterium tuberculosis* organisms and reconstitution of T cells, in particular T helper 1 lymphocytes, following commencement of anti-TB treatment (a form of TB-IRIS) [11,12]. Another postulated mechanism is enhanced delayed type hypersensitivity mediated by T lymphocytes and macrophages at the sites of *Mycobacterium tuberculosis* antigen deposition [8,13,14]. High *Mycobacterium tuberculosis* virulence and antigen load may also contribute to an exaggerated response [14,15]. The importance of T lymphocytes in paradoxical deterioration may explain why cyclosporine, an inhibitor of T cell activation [24], was effective in stabilising the clinical course of our patient without compromising their microbiological response to anti-TB therapy.

7. Cyclosporine

Cyclosporine binds to an intracellular receptor, cyclophilin forming a complex which inhibits the activity of calcineurin, a phosphatase required to facilitate translocation of NF-AT (nuclear factor of activated T cells) across the nuclear membrane. NF-AT is critical for transcription of the interleukin-2 (IL-2) gene, which drives activation and proliferation of T cells via generation of γ -interferon, TNF-alpha and granulocyte-macrophage colony stimulating factor amongst other cytokines [25]. In this fashion cyclosporine inhibits T cell activation and shifts cytokine expression from a Th1 to Th2 type [26], potentially counteracting the change in cellular and cytokine profile that is believed to partially explain the basis of the paradoxical deterioration. This may explain why cyclosporine was effective in our patients. In the setting of TBM, use of rifampicin has the propensity to increase cytochrome P450 isoenzyme 3A4 activity which can reduce cyclosporine drug levels [21,27]. Our patient responded to a dose of cyclosporine < 5 mg/kg/day whilst on concomitant quadruple therapy that included rifampicin. A lower 'effective' dose of cyclosporine may have contributed to its safety and tolerability.

It is not possible to say whether the patient would have improved in the absence of adjuvant cyclosporine. The speed of recovery was rapid, which might be considered a factor against the improvement being a consequence of the immunomodulatory effect of cyclosporine, given most oral immunomodulatory agents are thought to require 1–2 months to have their maximum effect. On review of the literature the speed of immunomodulatory effect with cyclosporine is generally considered relatively rapid. At high intravenous doses it is used in the management of inflammatory bowel disease. A Cochrane analysis of two trials of cyclosporine used for the induction of remission in severe ulcerative colitis estimated that its effects were noticed in 5–7 days [28]. Systematic reviews of its use in other conditions have suggested that when used to treat psoriasis (at low dose, < 5 mg/kg) patients can expect a 25% clinical improvement in 2–3 weeks and a 50% improvement at 4–5 weeks [29]. Cyclosporine induction in auto-immune conditions is likely to be different from an infective disease like TBM. Hence, whether cyclosporine confers a similar early effect in paradoxical

deterioration of TBM is unknown. In our patient with paradoxical deterioration, discontinuation of cyclosporine after initiation of treatment was associated with worsening headaches, which was interpreted as an ongoing part of the paradoxical deterioration pathology.

TNF-alpha antagonists including infliximab and adalimumab, which inhibit TNF-alpha, a key inflammatory cytokine released from T lymphocytes to contain TB infection, have also been reported to safely control the inflammatory response associated with paradoxical deterioration of TBM [14,17–19]. Of note, one of our patients, case 6, was on the TNF-alpha antagonist certoluzimab (in addition to prednisolone and methotrexate) for treatment of psoriatic arthritis prior to diagnosis of TBM. This patient did not experience a paradoxical deterioration on therapy in spite of having miliary TB at diagnosis.

8. Conclusions

In conclusion, we report a case series of 12 HIV-negative patients with TBM of whom 25% developed paradoxical deterioration despite initial improvement including one with a severe reaction wherein adjunctive cyclosporine therapy was used to good effect. Our study suggests that cyclosporine could be considered a treatment option for patients with neurological deterioration refractory to corticosteroid therapy. Further studies of the treatment of paradoxical deterioration of TBM are warranted.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2019.07.002>.

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