Neurological Sciences (2022) 43:2699–2708
https://doi.org/10.1007/s10072-021-05693-2

ORIGINAL ARTICLE

Paradoxical manifestations during tuberculous meningitis treatment among HIV-negative patients: a retrospective descriptive study and literature review

Rogelio Domínguez-Moreno[1] · Miguel García-Grimshaw[1] · David Medina-Julio[1] · Carlos Cantú-Brito[1] · Alejandra González-Duarte[1]

Received: 29 June 2021 / Accepted: 27 September 2021 / Published online: 27 October 2021

Abstract

Background Tuberculous meningitis (TBM) is the most frequent, severe, and disabling form of central nervous system (CNS) tuberculosis (TB). TBM paradoxical manifestations are characterized by clinical or paraclinical worsening after 1 month of effective anti-TB treatment in patients who initially responded to treatment despite the use of adjunctive corticosteroids.

Methods Retrospective descriptive study of consecutive HIV-negative adult patients (≥ 18 years) with definitive TBM who developed a paradoxical manifestation following anti-TB in a tertiary-care hospital in Mexico from 2009 to 2019; we also conducted a literature review of published cases/series of paradoxical manifestations in HIV-negative patients from 1980 to 2020.

Results We detected 84 cases of definitive TBM; 55 (68.7%) HIV-negative patients and 29 (36.3%) HIV-infected patients. Among HIV-negative patients, four (7.3%), three female and one male (19–49 years old), developed a paradoxical manifestation within 4–14 weeks following treatment initiation despite receiving adequate corticosteroid doses; *Mycobacterium bovis* was isolated from the cerebrospinal fluid of three cases and *Mycobacterium tuberculosis* in one more. Two patients developed vasculopathy-related cerebral infarctions, one severe basilar meningitis, and hydrocephalus, one more a tuberculoma. Two were treated with intravenous cyclophosphamide, and two with steroids. One of the patients treated with steroids died; patients who received cyclophosphamide had a good clinical response.

Conclusions This case series illustrates the diverse clinical/radiologic paradoxical manifestations of TBM in HIV-negative patients. Cyclophosphamide may be safe and effective in treating TBM-associated paradoxical manifestations. Specific diagnostic and care protocols for these patients are needed.

Keywords Tuberculous meningitis · Paradoxical manifestation · Cyclophosphamide · Mycobacterial infection · Central nervous system tuberculosis

Introduction

Tuberculous meningitis (TBM) is the most frequent, severe, and disabling form of central nervous system (CNS) tuberculosis (TB) [1, 2]. The World Health Organization estimates that 8.9–11 million persons will develop TB each year [3]. With approximately 100,000 new cases each year, TBM accounts for roughly 1% of all TB cases and ~ 5% of extrapulmonary TB cases [1, 2]. Despite adequate anti-TB treatment, its mortality ranges from 20 to 50%, being significantly higher for human immunodeficiency virus (HIV)–infected patients [4–6]. Paradoxical manifestations in TBM are characterized by clinical or paraclinical worsening after 1 month of effective anti-TB treatment in patients who

Rogelio Domínguez-Moreno and Miguel García-Grimshaw contributed equally to this work as co-first authors. Carlos Cantú-Brito and Alejandra González-Duarte are senior co-authors

✉ Rogelio Domínguez-Moreno
rogelio_dm@hotmail.com

✉ Miguel García-Grimshaw
miguelgrimshaw@gmail.com

[1] Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas Y Nutrición Salvador Zubirán, Vasco de Quiroga #15, Col. Sección XVI Belisario Domínguez, 14080 Tlalpan, Mexico City, Mexico

initially responded to treatment despite the use of adjunctive corticosteroids [7–9]. Its diagnosis requires excluding other causes of deterioration, mainly poor treatment compliance, treatment failure due to microbiological resistance to first-line anti-tuberculosis drugs, and co-existence of another CNS infection [7, 8].

In HIV co-infected patients, a paradoxical manifestation may develop following antiretroviral treatment initiation, mostly in treatment-naïve patients with high viral load and low CD4 + cell counts who simultaneously receive antiretroviral and anti-TB treatment [10, 11]. The frequency of CNS paradoxical manifestations among HIV-negative patients with TBM can be up to 56% [12], with a mortality as high as 35% [13]; however, most of the evidence derives from a few case reports and small case series. Here we report a series of HIV-negative patients with definitive TBM who developed clinical and radiographical CNS paradoxical manifestations despite being treated with high doses of corticosteroids and an updated literature review on paradoxical manifestations among HIV-negative patients.

Methods

This retrospective descriptive study was conducted at the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*, a tertiary-care reference hospital in Mexico. The study was revised and approved by our institutional Ethics and Research Committees (Reference: NER-2706–18-18–1). Due to the nature of the study, both Committees waived the need for signed informed consent. We reviewed electronic medical records of consecutive adult patients aged ≥ 18 years with definitive TBM diagnosed and treated at our center from January 2009 to December 2019. This case series only included HIV-negative patients who developed a paradoxical manifestation following anti-TB treatment for TBM. One of the reported cases (case 1) was diagnosed and treated at our center by two of the authors (C.C-B and A.G-D) and previously published elsewhere [14].

TBM was diagnosed according to the uniform case definition for clinical research in TBM [15]. In all cases, the presence of *Mycobacterium tuberculosis complex* (MTBC) in the CSF was confirmed by either cartridge-based nucleic acid amplification test (CB-NAAT) (Xpert MTB/RIF assay; Cepheid Inc., Sunnyvale, CA, USA) or liquid culture media (Bactec MGIT 960; Becton Dickinson, Sparks, MD, USA) or solid Löwenstein-Jensen medium. The GenoType *Mycobacterium* CM/AS (common mycobacteria/additional species) probe assay (Hain Lifescience, GmbH, Nehren, Germany) was used for mycobacteria typification. Disease severity at admission was graded according to the British Medical Research Council (BMRC) criteria as follows: grade I, patient with a Glasgow Coma Scale (GCS) of 15 points without focal neurological signs; grade II, patient with a GCS of 11–14 points or with 15 points and focal neurological signs; and grade III, patient with a GCS of ≤ 10 points with or without focal neurological signs [15, 16].

We defined paradoxical manifestations as clinical deterioration or the development of any new neurological signs or symptoms with either worsening of preexisting central nervous system (CNS) lesions or the appearance of lesions on follow-up neuroimaging studies with an increase in cerebrospinal fluid (CSF) protein levels in patients who initially responded to anti-TB drugs and had been receiving them for ≥ 4 weeks, after excluding other potential causes [7, 8]. Functional outcome was assessed using the modified Rankin scale (mRS) [17]. Using a standardized case report format, we collected demographic characteristics, comorbidities, the interval between TBM symptoms onset to hospital presentation. The clinical/radiologic characteristics, CSF analysis, and microbiological approach result at the time of TBM diagnosis and when the paradoxical manifestation was diagnosed, the interval between treatment initiation and paradoxical manifestation onset, clinical manifestations, treatments, and outcomes.

We also conducted a systematic literature review of all peer-reviewed case reports and case series describing paradoxical manifestations in adult (age ≥ 18 years) HIV-negative patients with TBM, published from January 1980 to December 2020. We searched on PubMed/National Library of Medicine, MEDLINE, SCOPUS, Web of Science, Lilacs, and SciELO, using the MEsH terms: "tuberculous meningitis" OR "tubercular meningitis" OR "central nervous system tuberculosis" OR "tuberculomas" AND "paradoxical reaction" OR "paradoxical response" OR "paradoxical deterioration OR "paradoxical manifestation." Papers were selected in the first screening if they described paradoxical manifestations in patients with TBM. We abstracted papers published in English or Spanish that reported age, sex, time from anti-TB treatment initiation to paradoxical manifestation onset, clinical findings, treatments, and mortality.

Results

During the studied period, 84 cases of definitive TBM were diagnosed and treated at our center; 55 (68.7%) HIV-negative patients and 29 (36.3%) HIV-infected patients. Among HIV-negative patients, we found four (7.3%) who developed paradoxical a manifestation. Demographics, time from symptoms onset to TBM diagnosis, type of mycobacteria, type of corticosteroid and doses before the paradoxical manifestation onset, CSF characteristics at baseline and at the time of paradoxical manifestation diagnosis, manifestations, treatment, and outcome of these cases are summarized in Table 1.

Table 1 Findings of our reported cases of paradoxical manifestations among HIV-negative patients with definitive tuberculous meningitis

	Case 1	Case 2	Case 3	Case 4
Sex / age, years	F / 19	M / 30	F / 46	F / 49
Time from symptoms onset to TBM diagnosis	1 week	3 weeks	2 weeks	4 weeks
BMRC grade	II	II	I	II
Baseline CSF findings	Proteins: 189 mg/dL Leukocytes: 47 cells/mm^3 Glucose: 14 mg/dL	Proteins: 290 mg/dL Leukocytes: 585 cells/mm^3 Glucose: 43 mg/dL	Proteins: 290 mg/dL Leukocytes: 585 cells/mm^3 Glucose: 43 mg/dL	Proteins: 183 mg/dL Leukocytes: 35 cells/mm^3 Glucose: 40 mg/dL
Type of mycobacteria	*Mycobacterium bovis*	*Mycobacterium tuberculosis*	*Mycobacterium bovis*	*Mycobacterium bovis*
Type of steroid and dose before PM	PDN 100 mg/day	DXM 34 mg/day	PDN 10 mg/day	DXM 20 mg/day
Time from treatment to PM	4 weeks	12 weeks	14 weeks	7 weeks
Paradoxical manifestations	Seizures, CNS vasculopathy, and ischemic stroke	Headache, altered mental status, CNS vasculopathy, and ischemic stroke	Headache, altered mental status, and hydrocephalus	Headache and fever
CSF findings at PM diagnosis	Proteins: 502 mg/dL Leukocytes: 7 cells/mm^3 Glucose: 57 mg/dL	Proteins: 524 mg/dL Leukocytes: 20 cells/mm^3 Glucose: 65 mg/dL	Proteins: 486 mg/dL Leukocytes: 14 cells/mm^3 Glucose: 46 mg/dL	Proteins: 608 mg/dL Leukocytes: 52 cells/mm^3 Glucose: 23 mg/dL
PM immunosuppressive treatment	PDN 100 mg/day CFM 750 mg/m^2; 2 doses	DXM 36 mg/day CFM 750 mg/m^2; 3 doses	PDN 0.6 mg/kg/day	DXM 0.6 mg/kg/day
Functional outcome	mRS 4	mRS 4	mRS 6	mRS 0

Abbreviations: *F*, female; *M*, male, *TBM*, tuberculous meningitis; *BMRC*, British medical research council; *CSF*, cerebrospinal fluid; *PDN*, prednisone; *DXM*, dexamethasone; *PM*, paradoxical manifestation; *CNS*, central nervous system; *CFM*, cyclophosphamide; *mRS*, modified Rankin score

Case 1 A 19-year-old woman presented to the emergency department (ED) with fever (39 °C), headache, ataxia, altered mental status, and tachycardia. Neurologic examination showed papilledema, bilateral sixth nerve palsy, and neck stiffness (BMRC grade II). Magnetic resonance imaging (MRI) of the brain showed meningeal enhancement without parenchymal lesions. CSF examination revealed proteins of 189 mg/dL, glucose of 14 mg/dL, and leukocytes of 47 cells/mm^3. With a diagnosis of possible TBM, she was started on dexamethasone, isoniazid, rifampicin, pyrazinamide, and ethambutol. Two weeks later, *Mycobacterium bovis* grew from the CSF culture, resistant to pyrazinamide, isoniazid, and streptomycin; hence, treatment was modified to rifampicin, ethambutol, and levofloxacin. Dexamethasone was tapered and was discharged home. Three weeks later, she returned with seizures; a new MRI revealed an acute left cerebral infarct with basal ganglia involvement. CSF proteins (276 mg/dL) and leukocytes count (60 cells/mm^3) had increased. At this time, cultures were negative, and dexamethasone was increased to 4 mg/kg/day. A transcranial Doppler ultrasound (TCD) showed bilaterally increased velocities of the middle cerebral arteries, and MRI angiography showed severe vasospasm. During the next months, control MRIs showed new ischemic lesions, and in two subsequent spinal taps, protein levels continued rising (maximum 502 mg/dL), despite high doses of oral steroids (100 mg/day) for approximately 6 months and multiple negative cultures. Due to persistent CNS inflammation, two doses of cyclophosphamide (1 g, 750 mg/m^2) were administered over 5 weeks showing clinical, CSF, and TCD velocities improvement, without further recurrences.

Case 2 A 31-year-old man with a 5-year history of systemic lupus erythematosus presented with fever, headache, and progressive altered mental status for the past 3 weeks; on examination, there were no focal neurological signs (BMRC grade II), and his initial MRI was unremarkable (Fig. 1A). CSF analysis revealed proteins of 290 mg/dL, glucose of 43 mg/dL, and leukocytes of 585 cells/mm^3; CB-NAAT for MTC in the CSF was positive. We started him on rifampicin, isoniazid, ethambutol, pyrazinamide, and IV dexamethasone (36 mg/day). He was asymptomatically discharged a few weeks later. *Mycobacterium tuberculosis* was isolated from CSF. He returned 3 months after discharge with headache, altered mental status, and right-sided hemiplegia. An MRI revealed a left internal ischemic lesion (Fig. 1B); TCD showed severe vasospasm of the left middle and right posterior cerebral arteries. CSF analysis showed an increase in proteins (524 mg/dL), leucocytes of 20 cells/mm^3, and normal glucose levels (65 mg/dL); at this time, CB-NAAT and cultures were negative, with those finding, IV dexamethasone was restored (34 mg/day) without clinical

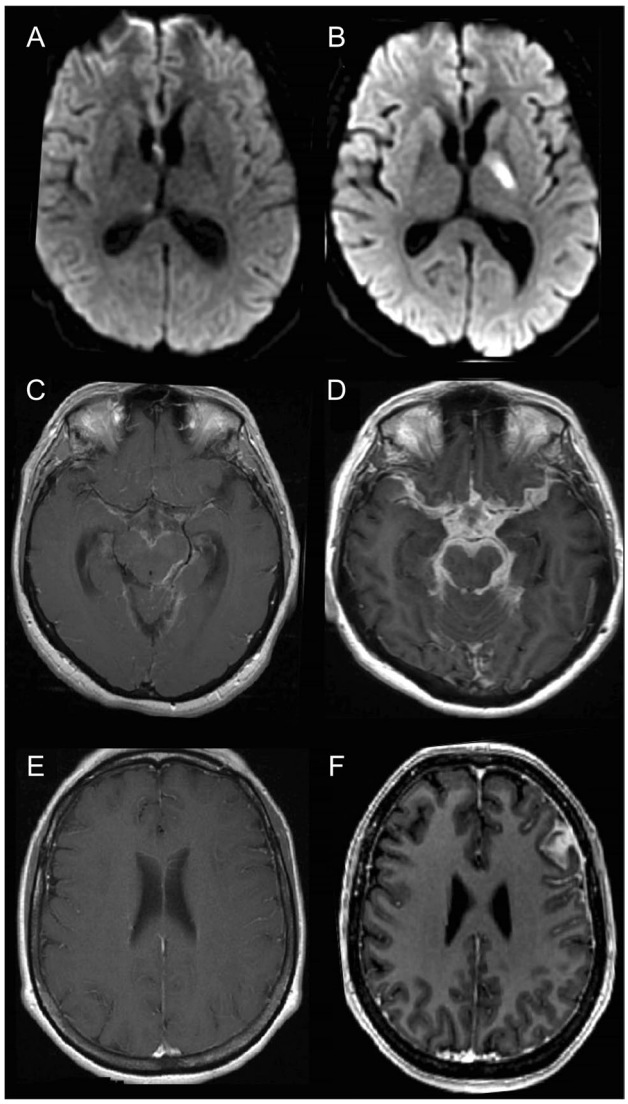

Fig. 1 Findings on magnetic resonance imaging (MRI) of the brain among HIV-negative patients with tuberculous meningitis who developed a paradoxical manifestation. Case 2. **A** normal diffusion-weighted imaging (DWI) at baseline, **B** follow-up imaging 12 weeks after anti-tuberculous treatment initiation revealed an internal capsule infarct. Case 3. **C** gadolinium-enhanced T1-weighted image (T1WI) showing mild/moderate basal meningeal enhancement at the time of tuberculous meningitis diagnosis, **D** follow-up MRI 14 weeks after treatment initiation showed severe pachymeningeal enhancement and hydrocephalus. Case 4. **E** baseline gadolinium-enhanced T1WI shows minimal leptomeningeal enhancement, **F** follow-up imaging seven weeks after treatment revealed a left frontal tuberculoma

improvement. Therefore, three doses of cyclophosphamide were administrated (750 mg/m^2) 3 weeks apart. His symptoms subsided after the first bolus; during follow-up, 1 year later, he remains without further recurrences (mRS 4).

Case 3 A previously healthy 46-year-old woman presented to the ED with a 2-week history of fever, night sweats, and headache; her neurological examination was unremarkable (BMRC grade I). Brain MRI revealed mild/moderate post-contrast basal meningeal enhancement (Fig. 1C). CSF analysis revealed proteins of 85 mg/dL, glucose of 35 mg/dL, and leukocytes of 97 cells/mm^3; CB-NAAT for MTC in the CSF was positive. She also was diagnosed with lymph node TB. We started treatment first-line anti-TB drugs and IV dexamethasone (0.4 mg/kg/day), and we discharged her asymptomatically 4 weeks after admission on anti-TB drugs and prednisone 10 mg/day. During the forthcoming weeks, a positive CSF culture for *Mycobacterium bovis* was reported. Ten weeks after discharge, she developed altered mental status, fever, and seizures, despite adequate treatment adherence. A contrast-enhanced brain MRI showed severe pachymeningeal enhancement and hydrocephalus (Fig. 1D). CSF analysis revealed increased proteins in 486 mg/dL, leukocytes of 14 cells/mm^3, and glucose levels of 46 mg/dL; CB-NAAT and cultures were negative. Hydrocephalus was treated with an external ventricular drain; however, due to severe clinical deterioration and aspiration pneumonia for which the patient required invasive mechanical ventilation, we were unable to add intensive immunosuppressive therapies. She developed brain death and died two weeks after admission.

Case 4 A previously healthy 49-year-old woman presented with fever, aphasia, and altered mental status; on examination, there were no other neurological signs (BMRC grade II). Contrast-enhanced MRI showed mild leptomeningeal enhancement (Fig. 1E). CSF analysis revealed proteins of 183 mg/dL, glucose of 40 mg/dL, and leukocytes of 35 cells/mm^3; CB-NAAT was negative. However, a sputum smear was positive for acid-fast bacilli. Two weeks later, *Mycobacterium bovis* grew from the CSF culture. We started treatment with rifampicin, isoniazid, ethambutol, pyrazinamide, moxifloxacin, imipenem, amoxicillin-clavulanate, and IV dexamethasone (0.4 mg/kg/day). Lastly, she was diagnosed with disseminated TB (meningeal, pulmonary, and peritoneal). Her mental status gradually improved, and the aphasia resolved; we discharged her 5 weeks after admission on anti-TB treatment and oral dexamethasone (10 mg/day). Seven weeks later, she was readmitted due to new episodes of fever and headache. An MRI showed that she had developed meningeal and parenchymal tuberculomas (Fig. 1F). CSF analysis revealed an increase in proteins to 608 mg/dL, leukocytes of 52 cells/mm^3, and glucose of 23 mg/dL; CB-NAAT and cultures were negative. After ruling out other CNS infections, dexamethasone was increased to 0.6 mg/kg/day; her symptoms resolved, and we discharged her without neurological sequelae. On follow-up, she remains asymptomatic.

Discussion

In this study, 7.3% of HIV-negative patients with definitive TBM developed a clinical and radiologic paradoxical manifestation, a lower frequency than the 8–56% reported in other series [12, 18]. Interestingly, in three out of four patients, *Mycobacterium bovis* was the etiological agent, a mycobacterium associated with higher mortality in patients with TBM [19]. In 1974, Thrush and Barwick documented the first case of a CNS paradoxical manifestation in a patient who developed a new tuberculoma while receiving anti-TB treatment [20]. Since that initial description, a broad spectrum of CNS manifestations has been reported [21]. Clinical manifestations in three of our patients included new-onset headaches, two presented with altered mental status, and one with new-onset seizures. On neuroimaging during the paradoxical phase, all patients developed diffuse pachymeningitis (not shown for cases one and two), one with severe basal enhancement suggesting the presence of thick basal exudates, causing severe hydrocephalus; also, two patients developed vasculopathy-related cerebral infarcts. As in most series describing HIV-negative patients, timing from treatment initiation to paradoxical manifestation onset was highly variable (Table 2).

Brain tuberculomas which are conglomerate caseous foci containing mycobacteria in a dormant state [30] represent the most frequent CNS paradoxical manifestation [7, 8]. When the host cellular immunity wanes, replication of these resting bacilli may resume, leading to reactivation of the disease [30]. Dysregulation of the tumor necrosis factor (TNF)-α and other cytokines plays a crucial role in the pathogenesis of tuberculomas and other paradoxical manifestations [31]. A series of 34 patients found that females are more susceptible to develop tuberculomas as a paradoxical manifestation [26]. However, as of this day, no other predictors have been found. Paradoxical tuberculomas may appear within the second week and up to the twenty-seventh month after treatment initiation, more frequently around the sixth week [13, 24].

Multiple manifestations can simultaneously co-exist or share common mechanisms. For example, basal exudates surrounding the circle of Willis might result in compressive or inflammatory vasculopathy [32], manifested as acute infarcts within the main arteries perforating branches territory; ischemic lesions are usually located within the *so-called* TB zone, which includes the periventricular regions, internal capsule, thalamus, and basal nuclei [32, 33]. Exudates may also develop in the Sylvian fissure, posterior fossa, and the optochiasmatic region, the latter causing vision impairment/loss. Additionally, exudative material allocated in the basal cisterns may lead to communicating hydrocephalus [34, 35], a complication significantly associated with mortality and poor outcome [36], which is more frequent when CSF proteins are ≥ 250–500 mg/dL [37].

Clinically, some patients may only present with mild and sometimes misleading symptoms, such as an isolated new-onset headache. Also, enlarged lymph nodes can be seen mainly in the cervical and supraclavicular regions. [38]. Some findings on ancillary tests that may help make the diagnosis include the presence of new or progressive subclinical lesions on neuroimaging studies [8, 39], a steady increase of intracranial vessels mean flow velocities (vasculopathy), or pulsatility indexes (elevated intracranial pressure) by TCD, an increase of the CSF protein levels or a cellular shift in its components [14, 40]. However, CSF changes occur in some patients even before clinical or radiological manifestations develop [35, 41].

The pathophysiological mechanisms involved in the development of these paradoxical manifestations among HIV-negative patients remain incompletely understood. It has been hypothesized that it may result from an exaggerated inflammatory reaction following anti-TB treatment initiation triggered by antigens directed to the mycobacterial cell wall, which are also present in the infected brain tissues [7, 8]. In line with this hypothesis, it has been reported that a combination of low CSF interferon (IFN)-γ and TNF-α levels at the time of TBM diagnosis may predict clinical deterioration related to a severe inflammatory reaction; however, this has only been observed in a small series of HIV-infected patients [42]. Also, increased CSF neutrophil count, interleukin (IL)-6, and IL-10 levels have been associated with tuberculomas' paradoxical development or progression [43]. The paradoxical shift of the CSF cellular components from a lymphocytic to a neutrophilic predominance early during treatment suggests that neutrophils also play a role in its pathogenesis [8, 41]. Furthermore, polymorphisms of the gene encoding leukotriene A4 hydrolase (LTA4H), an enzyme that regulates the balance between pro-inflammatory and anti-inflammatory response and influences TNF-α expression, which is also related to corticosteroid response, has been associated with higher mortality in patients with TBM [44–46]. These polymorphisms may explain why some patients develop paradoxical manifestations despite corticosteroid treatment.

Paradoxical manifestations should be distinguished from poor treatment compliance, treatment failure, drug toxicity, microbiological resistance to first-line anti-tuberculosis drugs, co-existence of another CNS infection, or other non-infectious causes [8]. Therefore, it is imperative to obtain drug susceptibility patterns in cases of culture-positive TBM or by other molecular methods such as the Xpert MTB/RIF or Xpert MTB/RIF Ultra, both of which detect the presence of MTBC and rifampicin resistance simultaneously in less than 2 h [2, 47]. Differential diagnosis includes less frequent

Table 2 Summary of series including more than ten cases with central nervous system tuberculosis describing paradoxical manifestations in HIV-negative patients

Author (year)	Total cases, *N*	PM cases, *n* (%)	Sex (%)	Age (years)	Interval between treatment and PM	Main PM findings	PM treatment	Mortality
Watson et al. [22]. (1993)*	22	7 (31.8)	M (57.1)	Range 17–68 y	Tuberculoma, mean 2.3 months Meningitis, mean 17 days	Headache, fever, cognitive decline, visual loss, and cranial nerve palsy	Steroids	14.3%
Sütlaş et al. [23]. (2003)**	61	20 (32.7)	M (56.5)	Mean 34.5 y, range 16–74	≥ 1 week	CSF shift from lymphocytic to neutrophilic pleocitosis and tuberculomas	Steroids	27.8%
Unal and Sütlaş [24]. (2005)***	22	14 (64)	M (64.3)	Range 19–52 y	Range 7 days to 7 months	Tuberculoma	Steroids	14.3%
Carvalho et al. [18]. (2006)*	137	11 (8)	M (73)	Median 37 y, range 26–68	Median 107 days, range 31–443 days	Tuberculomas (6 cases) Lymph node enlargement (5 cases)	Steroids	NR
Anuradha et al. [13]. (2011)**	110	7 (6.3)	M (68.7)	Median 31 y, range 14–85	Mean 9 months	Tuberculoma	Steroids	35%
Misra et al. [25]. (2013)**	40	20 (50)	M (55)	Median 26.5 y	Mean 3 months	Tuberculoma, infarction, hydrocephalus	NR	12.5%
Kalita et al. [26]. (2014)***	34	Neuroimaging, 22 (64.7) Clinical, 12 (35)	M (61.7)	Mean 34.1 y, SD ± 13.2	Mean 3 months	Tuberculoma, focal neurological deficit, and AMS	Steroids	9.1%
Lu et al. [27]. (2015) ****	101	27 (27.8)	M (58.4)	Median 36.7 y, range 14–81	Range 18 to 30 days	Angiographic changes	Steroids	NR
Tai et al. [12]. (2016) *	41	23 (56)	M (50)	Median 32.3 y, SD ± 11.7	Range 28 days to 9 months	Fever, headache, AMS, new ischemic lesions, hydrocephalus, and tuberculomas	Steroids	15%
Kalita et al. [28]. (2017)**	51	Neuroimaging, 25 (49) Clinical, 14 (27)	M (58.8)	Median 35 y	Mean follow-up 3 months	Hemiplegia-infarct, tuberculoma, and hydrocephalus	Steroids Aspirin	15.7%
Ledingham et al. [29]. (2019)**	12	3 (25)	M (58.3)	Median 40 y, range 22–81	Mean 7 weeks	Worsening headaches and AMS	Cyclosporine	16.7%
Liu et al. [9]. (2019)*	50	26 (52)	M (54)	Mean 34.9 y, SD ± 18.1	Mean 30 days, range 15–330	Fever, headache, AMS, and spinal meningeal involvement	Steroids	NR

Abbreviations: *F*, female; *M*, male; *PM*, paradoxical manifestation; *SD*, standard deviation; *AMS*, altered mental status; *NR*, not reported

*Data for cases with paradoxical manifestations. **Age, gender, and mortality for cases with paradoxical manifestations not reported ***Data for cases with paradoxical manifestations, defined as development of tuberculomas. ****Age, gender, and mortality for cases with paradoxical manifestations not reported; only angiographic changes were studied

entities, such as neurosarcoidosis, meningeal carcinomatosis, CNS mycoses, and CNS other granulomatous diseases [7, 8]. After excluding other causes, performing a brain biopsy may be considered if there is no clinical improvement or if the patient continues deteriorating [8].

Ideally, CNS tuberculosis treatment should be guided according to antimicrobial sensitivity patterns [37]. Nevertheless, if clinical suspicion is high, empirical treatment must be started while waiting for confirmation. Most cases often respond to first-line anti-TB drugs. Duration of anti-TB treatment in TBM is 9–12 months with adjunctive corticosteroids, tapered over 6–8 weeks [48, 49]. Corticosteroids have a benefit in short-term mortality but not in long-term disability or HIV-infected patients [50]. A trial re-evaluating the role of adjunctive dexamethasone patients with HIV has been recently registered (ClinicalTrials.gov Identifier: NCT03092817). A recent meta-analysis has shown that 81–150 mg/day of aspirin significantly reduces the risk of infarctions but not survival [51]. However, due to small sample sizes, these results must be taken with caution. Surgery is only recommended to treat hydrocephalus or large tuberculomas with significant mass effects and a high risk of herniation [52].

As for paradoxical manifestations, there are no protocols or consensus regarding surveillance, diagnosis, and treatments [8]. Case reports and case series have used different corticosteroid doses, most of them according to the Thwaites protocol [53], designed for TBM and not for treating paradoxical manifestations. When corticosteroids at TBM doses fail to control the immunological response, increasing the dosage or extending its use for longer periods is feasible; optimal duration and doses are still unknown [1, 37]. Even so, up to 47% of cases may not respond to those strategies [42, 54], and doses over 0.6 mg/kg/day probably will not provide any further benefit, increasing the risk for developing adverse events [55, 56].

In these scenarios, the empirical use of other immunosuppressants and immunomodulatory drugs is imperative (Table 3). With the rationale that TNF-α plays a crucial role in regulating the inflammatory response in CNS TB, anti-TNF-α drugs such as infliximab and adalimumab have been successfully used [57–59]. A possible disadvantage of these monoclonal antibodies could be the cost, given that low-middle-income countries account for most TB cases worldwide [3]. Thalidomide, also a TNF-α inhibitor with anti-inflammatory and immunomodulatory activity, could be considered to treat tuberculomas that are not responding to standard treatment or high-dose corticosteroids [49]; however, its use remains controversial. A randomized trial assessing the effects of adjunctive thalidomide in conjunction with standard anti-TB drugs and corticosteroids in children with TBM was terminated early due to increased mortality, although apparently, the groups

Table 3 Potential immunosuppressant and immunomodulatory drugs previously reported in the treatment of paradoxical manifestations in patients with central nervous system tuberculosis

Agent	Rationale	Disadvantage	Dose
Ruxolitinib [63]	Inhibition of pathways such as JAK1/JAK2-dependent IFN-γ and IL-6 signaling, JAK2-dependent GM-CSF and IL-12 signaling, and JAK3-dependent IL-2 signaling	Cost and cytopenias due to inhibitory effects of hematopoietic cytokines	20 mg twice daily (effects have been seen at 2 and 5 months, used for up to 20 months)
Infliximab [59] Adalimumab [57]	Anti-TNF-α	Cost, risk of tuberculosis reactivation, or other intracellular infections	Infliximab (5 mg/kg, 3 doses) Adalimumab (40 mg, 3 doses)
Interferon-γ [61, 62]	Macrophage activation	Cost, flulike symptoms, and headache	50–100 mcg/m^2 (up to 19 months)
Cyclophosphamide [14, 64, 65]	Depletion of B-cells and T-cells (cytostatic)	Nausea, vomiting, hemorrhagic cystitis, infertility, and cytopenias	750 mg/m^2 (2–3 monthly doses)
Cyclosporine [29]	Calcineurin activity inhibitor and nuclear factor of activated T-cells, inhibiting T-cells activation and shifts cytokine expression from Th1 to Th2	Co-occurrence of infections, skin changes, and tremor	150 mg twice daily (4 mg/kg/day) for up to 2 years
Thalidomide [49, 60]	TNF-α inhibition	One pediatric clinical trial showed increased mortality, peripheral neuropathy, and seizures	1–1.2 mg/kg/day or 50, 100, 150, 200 mg twice a day (5–7 months)
NSAID [66, 67]	Modulation of immune responses by reducing fraction of T-cells and specific cytokine responses	No human data, gastric and renal injury	Doses and timing are not well stablished

Abbreviations: *NSAID*, non-steroidal anti-inflammatory drugs; *JAK*, Janus kinase; *INF-γ*, interferon-γ; *IL*, interleukin; *TNF-α*, tumor necrosis factor alpha

were unbalanced [60]. Interferon (IFN)-γ, an immunoregulatory cytokine that plays a crucial role in controlling mycobacterial infections through macrophage activation, has shown good results [61, 62].

The use of cyclophosphamide, an alkylating agent that reduces the number of circulating B cells and T cells widely used in rheumatological and hemato-oncological diseases with relatively safe profile [64], has been reported in a few patients [14, 65]. This immunosuppressant has the advantage of being a low-cost and widely available drug. A randomized placebo-controlled clinical trial has been registered to evaluate its efficacy and safety in the treatment of refractory proliferative arachnoiditis in CNS TB (ClinicalTrials.gov Identifier: NCT04620772). In a recent report, ruxolitinib, a Janus kinase inhibitor, was used with favorable clinical/radiologic outcomes in a woman with disseminated TB and multiple tuberculomas that progressed despite adequate anti-TB treatment, adjunctive corticosteroids, and two surgical resections [63].

In murine models of pulmonary TB, ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), significantly reduced the percentage of affected lung area and increased the survival of these animals treated with ibuprofen alone [66]. Besides ibuprofen, other NSAIDs such as oxyphenbutazone, carprofen, celecoxib, and indomethacin, have demonstrated inhibitory properties towards *Mycobacterium tuberculosis* cells [68, 69]. In vitro, indomethacin significantly reduced the fraction of T regulatory cells with a concomitant reduction of specific cytokine responses (TNF-α, IFN-γ, IL-2) and T cell proliferation in the serum of patients with active TB compared to the serum of patients with latent TB [67]. Still, the exact mechanisms on how NSAIDs may modulate the inflammatory immune response in TB and their potential benefits as adjuvants to anti-TB treatments remains to be elucidated. Although mortality for patients with TBM who develop CNS paradox manifestations can be up to 35% (range 5.8–35%) [13, 26], the prognosis may be favorable if symptoms are detected early before structural damage occurs. Additionally, in a recent series including 141 HIV-infected and HIV-negative patients, paradoxical manifestations do not adversely affect these patients' functional outcomes or survival [7]. However, we consider that those findings must be taken with caution, as methodologically, the study was not designed to answer that question.

This study has limitations, including our retrospective design with data collection from electronic medical records and the small sample size limited to a few cases reports. Also, the fact that in our center, these patients were not systematically screened for the development of paradoxical manifestations during follow-up; hence, subclinical and asymptomatic radiologic manifestations may not have been detected, which may explain the low frequency we report when compared to other series.

In conclusion, this case series illustrates the diverse clinical/radiologic paradoxical manifestations that HIV-negative patients with definitive TBM can develop. Two of the cases hereby reported expand the evidence of cyclophosphamide's safety and efficacy in treating paradoxical manifestations. The use of adjuvant aspirin may reduce the risk of cerebral infarctions in TBM. Due to its anti-inflammatory effects, low cost, and safety profiles, the repurposing of NSAIDs as adjuvants in TBM treatment seems feasible. Randomized clinical trials evaluating the safety and benefits of the different immunosuppressants and immunomodulatory drugs used in treating TBM paradoxical manifestations are needed to establish treatment and care protocols for these patients.

Data availability All the data supporting our findings are contained within the manuscript.

Code availability Not applicable.

Declarations

Ethical approval The study was revised and approved by our institutional Ethics and Research Committees (Reference: NER-2706–18-18–1). Due to the nature of the study, both Committees waived the need for signed informed consent.

Conflict of interest The authors declare no competing interests.

References

1. Wilkinson RJ, Rohlwink U, Misra UK et al (2017) Tuberculous meningitis. Nat Rev Neurol 13:581–598. https://doi.org/10.1038/nrneurol.2017.120
2. Manyelo CM, Solomons RS, Walzl G, Chegou NN (2021) Tuberculous meningitis: pathogenesis, immune responses, diagnostic challenges, and the potential of biomarker-based approaches. J Clin Microbiol 59:e01771-e1820. https://doi.org/10.1128/JCM.01771-20
3. World Health Organization (2020) Global tuberculosis report 2020. https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf. Accessed 24 Feb 2021
4. Wen L, Li M, Xu T et al (2019) Clinical features, outcomes and prognostic factors of tuberculous meningitis in adults worldwide: systematic review and meta-analysis. J Neurol 266:3009–3021. https://doi.org/10.1007/s00415-019-09523-6
5. García-Grimshaw M, Gutiérrez-Manjarrez FA, Navarro-Álvarez S, González-Duarte A (2020) Clinical, imaging, and laboratory characteristics of adult Mexican patients with tuberculous meningitis: a retrospective cohort study. J Epidemiol Glob Health 10:59–64. https://doi.org/10.2991/jegh.k.191023.001
6. Thao LTP, Heemskerk AD, Geskus RB et al (2018) Prognostic models for 9-month mortality in tuberculous meningitis. Clin Infect Dis 66:523–532. https://doi.org/10.1093/cid/cix849
7. Singh AK, Malhotra HS, Garg RK et al (2016) Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. BMC Infect Dis 16:306. https://doi.org/10.1186/s12879-016-1625-9

8. Garg RK, Malhotra HS, Kumar N (2014) Paradoxical reaction in HIV negative tuberculous meningitis. J Neurol Sci 340:26–36. https://doi.org/10.1016/j.jns.2014.03.025
9. Liu Y, Wang Z, Yao G et al (2019) Paradoxical reaction in HIV-negative tuberculous meningitis patients with spinal involvement. Int J Infect Dis 79:104–108. https://doi.org/10.1016/j.ijid.2018.11.366
10. Lanzafame M, Vento S (2016) Tuberculosis-immune reconstitution inflammatory syndrome. J Clin Tuberc Mycobact Dis 3:6–9. https://doi.org/10.1016/j.jctube.2016.03.002
11. Thuong NTT, Thwaites GE (2017) Treatment-associated inflammatory deterioration in tuberculous meningitis: unpicking the paradox. J Infect Dis 215:665–667. https://doi.org/10.1093/infdis/jiw565
12. Tai M-LS, Nor HM, Kadir KAA et al (2016) Paradoxical manifestation is common in HIV-negative tuberculous meningitis. Medicine (Baltimore) 95:e1997. https://doi.org/10.1097/MD.0000000000001997
13. Anuradha HK, Garg RK, Sinha MK et al (2011) Intracranial tuberculomas in patients with tuberculous meningitis: predictors and prognostic significance. Int J Tuberc Lung Dis 15:234–239
14. Gonzalez-Duarte A, Higuera-Calleja J, Flores F et al (2012) Cyclophosphamide treatment for unrelenting CNS vasculitis secondary to tuberculous meningitis. Neurology 78:1277–1278. https://doi.org/10.1212/WNL.0b013e318250d84a
15. Marais S, Thwaites G, Schoeman JF et al (2010) Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 10:803–812. https://doi.org/10.1016/S1473-3099(10)70138-9
16. Rock RB, Olin M, Baker CA et al (2008) Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin Microbiol Rev 21:243–261. https://doi.org/10.1128/CMR.00042-07
17. Banks JL, Marotta CA (2007) Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 38:1091–1096. https://doi.org/10.1161/01.STR.0000258355.23810.c6
18. Carvalho ACC, De Iaco G, Saleri N et al (2006) Paradoxical reaction during tuberculosis treatment in HIV-seronegative patients. Clin Infect Dis 42:893–895. https://doi.org/10.1086/500459
19. González-Duarte A, Ponce de Leon A, Sifuentes Osornio J (2011) Importance of differentiating Mycobaterium bovis in tuberculous meningitis. Neurol Int 3:9. https://doi.org/10.4081/ni.2011.e9
20. Thrush DC, Barwick DD (1974) Three patients with intracranial tuberculomas with unusual features. J Neurol Neurosurg Psychiatry 37:566–569. https://doi.org/10.1136/jnnp.37.5.566
21. Cheng VCC, Ho PL, Lee RA et al (2002) Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 21:803–809. https://doi.org/10.1007/s10096-002-0821-2
22. Watson JD, Shnier RC, Seale JP (1993) Central nervous system tuberculosis in Australia: a report of 22 cases. Med J Aust 158:408–413. https://doi.org/10.5694/j.1326-5377.1993.tb121837.x
23. Sütlaş PN, Unal A, Forta H et al (2003) Tuberculous meningitis in adults: review of 61 cases. Infection 31:387–391. https://doi.org/10.1007/s15010-003-3179-1
24. Unal A, Sütlaş PN (2005) Clinical and radiological features of symptomatic central nervous system tuberculomas. Eur J Neurol 12:797–804. https://doi.org/10.1111/j.1468-1331.2005.01067.x
25. Misra UK, Kalita J, Singh AP, Prasad S (2013) Vascular endothelial growth factor in tuberculous meningitis. Int J Neurosci 123:128–132. https://doi.org/10.3109/00207454.2012.743127
26. Kalita J, Prasad S, Misra UK (2014) Predictors of paradoxical tuberculoma in tuberculous meningitis. Int J Tuberc Lung Dis 18:486–491. https://doi.org/10.5588/ijtld.13.0556
27. Lu T-T, Lin X-Q, Zhang L et al (2015) Magnetic resonance angiography manifestations and prognostic significance in HIV-negative tuberculosis meningitis. Int J Tuberc Lung Dis 19:1448–1454. https://doi.org/10.5588/ijtld.15.0113
28. Kalita J, Misra UK, Bhoi SK et al (2017) Possible role of transforming growth factor β in tuberculous meningitis. Cytokine 90:124–129. https://doi.org/10.1016/j.cyto.2016.11.004
29. Ledingham D, El-Wahsh S, Sebire D et al (2019) Adjuvant immunosuppression for paradoxical deterioration in tuberculous meningitis including one case responsive to cyclosporine. A tertiary referral hospital experience. J Neurol Sci 404:58–62. https://doi.org/10.1016/j.jns.2019.07.002
30. DeLance AR, Safaee M, Oh MC et al (2013) Tuberculoma of the central nervous system. J Clin Neurosci 20:1333–1341. https://doi.org/10.1016/j.jocn.2013.01.008
31. Bekker LG, Maartens G, Steyn L, Kaplan G (1998) Selective increase in plasma tumor necrosis factor-alpha and concomitant clinical deterioration after initiating therapy in patients with severe tuberculosis. J Infect Dis 178:580–584. https://doi.org/10.1086/517479
32. Lammie GA, Hewlett RH, Schoeman JF, Donald PR (2009) Tuberculous cerebrovascular disease: a review. J Infect 59:156–166. https://doi.org/10.1016/j.jinf.2009.07.012
33. Tai M-LS, Viswanathan S, Rahmat K et al (2016) Cerebral infarction pattern in tuberculous meningitis. Sci Rep 6:38802. https://doi.org/10.1038/srep38802
34. Davis AG, Rohlwink UK, Proust A et al (2019) The pathogenesis of tuberculous meningitis. J Leukoc Biol 105:267–280. https://doi.org/10.1002/JLB.MR0318-102R
35. Donovan J, Figaji A, Imran D et al (2019) The neurocritical care of tuberculous meningitis. Lancet Neurol 18:771–783. https://doi.org/10.1016/S1474-4422(19)30154-1
36. Raut T, Garg RK, Jain A et al (2013) Hydrocephalus in tuberculous meningitis: incidence, its predictive factors and impact on the prognosis. J Infect 66:330–337. https://doi.org/10.1016/j.jinf.2012.12.009
37. Zunt JR (2018) Tuberculosis of the central nervous system. Continuum (Minneap Minn) 24:1422–1438. https://doi.org/10.1212/con.0000000000000648
38. Obeid T, Mousali Y, Wali S et al (1999) Paradoxical enlargement of lymph nodes during therapy of central nervous system tuberculosis. Ann Saudi Med 19:530–532. https://doi.org/10.5144/0256-4947.1999.530
39. Gupta RK, Kumar S (2011) Central nervous system tuberculosis. Neuroimaging Clin N Am 21:795–814. https://doi.org/10.1016/j.nic.2011.07.004
40. Tai M-LS, Sharma VK (2016) Role of transcranial Doppler in the evaluation of vasculopathy in tuberculous meningitis. PLoS ONE 11:e0164266. https://doi.org/10.1371/journal.pone.0164266
41. Ramesh AK, Hagler S, Beal JC, Moshé SL (2014) Pearls & Oysters: CSF analysis and the therapeutic paradox in tuberculous meningitis. Neurology 83:e145-146. https://doi.org/10.1212/WNL.0000000000000859
42. Marais S, Meintjes G, Pepper DJ et al (2013) Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. Clin Infect Dis 56:450–460. https://doi.org/10.1093/cid/cis899
43. Thwaites GE, Macmullen-Price J, Tran THC et al (2007) Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. Lancet Neurol 6:230–236. https://doi.org/10.1016/S1474-4422(07)70034-0
44. Narendran G, Kavitha D, Karunaiananthan R et al (2016) Role of LTA4H polymorphism in tuberculosis-associated immune reconstitution inflammatory syndrome occurrence and clinical severity

in patients infected with HIV. PLoS ONE 11:e0163298. https://doi.org/10.1371/journal.pone.0163298
45. Tobin DM, Roca FJ, Oh SF et al (2012) Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. Cell 148:434–446. https://doi.org/10.1016/j.cell.2011.12.023
46. Thuong NTT, Heemskerk D, Tram TTB et al (2017) Leukotriene A4 hydrolase genotype and HIV infection influence intracerebral inflammation and survival from tuberculous meningitis. J Infect Dis 215:1020–1028. https://doi.org/10.1093/infdis/jix050
47. Chin JH (2014) Tuberculous meningitis: diagnostic and therapeutic challenges. Neurol Clin Pract 4:199–205. https://doi.org/10.1212/CPJ.0000000000000023
48. Lewinsohn DM, Leonard MK, LoBue PA et al (2017) Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis 64:e1–e33. https://doi.org/10.1093/cid/ciw694
49. Thwaites G, Fisher M, Hemingway C et al (2009) British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 59:167–187. https://doi.org/10.1016/j.jinf.2009.06.011
50. Prasad K, Singh MB, Ryan H (2016) Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 4:CD002244. https://doi.org/10.1002/14651858.CD002244.pub4
51. Rohilla R, Shafiq N, Malhotra S (2021) Efficacy and safety of aspirin as an adjunctive therapy in tubercular meningitis: a systematic review and meta-analysis. EClinicalMedicine 34:100819. https://doi.org/10.1016/j.eclinm.2021.100819
52. Davis A, Meintjes G, Wilkinson RJ (2018) Treatment of tuberculous meningitis and its complications in adults. Curr Treat Options Neurol 20:5. https://doi.org/10.1007/s11940-018-0490-9
53. Thwaites GE, Bang ND, Dung NH et al (2004) Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 351:1741–1751. https://doi.org/10.1056/NEJMoa040573
54. Marais S, Lai RPJ, Wilkinson KA et al (2017) Inflammasome ativation underlying central nervous system deterioration in HIV-associated tuberculosis. J Infect Dis 215:677–686. https://doi.org/10.1093/infdis/jiw561
55. Shah I, Meshram L (2014) High dose versus low dose steroids in children with tuberculous meningitis. J Clin Neurosci 21:761–764. https://doi.org/10.1016/j.jocn.2013.07.021
56. Schutz C, Davis AG, Sossen B et al (2018) Corticosteroids as an adjunct to tuberculosis therapy. Expert Rev Respir Med 12:881–891. https://doi.org/10.1080/17476348.2018.1515628
57. Lee H-S, Lee Y, Lee S-O et al (2012) Adalimumab treatment may replace or enhance the activity of steroids in steroid-refractory tuberculous meningitis. J Infect Chemother 18:555–557. https://doi.org/10.1007/s10156-011-0334-y
58. Santin M, Escrich C, Majòs C et al (2020) Tumor necrosis factor antagonists for paradoxical inflammatory reactions in the central nervous system tuberculosis: case report and review. Medicine (Baltimore) 99:e22626. https://doi.org/10.1097/MD.0000000000022626
59. Marais BJ, Cheong E, Fernando S et al (2021) Use of infliximab to treat paradoxical tuberculous meningitis reactions. Open Forum Infect Dis 8:ofaa604. https://doi.org/10.1093/ofid/ofaa604
60. Schoeman JF, Springer P, van Rensburg AJ et al (2004) Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. J Child Neurol 19:250–257. https://doi.org/10.1177/088307380401900402
61. Lee J-Y, Yim J-J, Yoon B-W (2012) Adjuvant interferon-γ treatment in two cases of refractory tuberculosis of the brain. Clin Neurol Neurosurg 114:732–734. https://doi.org/10.1016/j.clineuro.2011.12.013
62. Coulter JBS, Baretto RL, Mallucci CL et al (2007) Tuberculous meningitis: protracted course and clinical response to interferon-gamma. Lancet Infect Dis 7:225–232. https://doi.org/10.1016/S1473-3099(07)70054-3
63. Xie YL, Ita-Nagy F, Chen RY et al (2019) Neurotuberculosis: control of steroid-refractory paradoxical inflammatory reaction with ruxolitinib. Open Forum Infect Dis 6:ofz422. https://doi.org/10.1093/ofid/ofz422
64. de Jonge ME, Huitema ADR, Rodenhuis S, Beijnen JH (2005) Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet 44:1135–1164. https://doi.org/10.2165/00003088-200544110-00003
65. Celotti A, Vianello F, Sattin A et al (2018) Cyclophosphamide immunomodulation of TB-associated cerebral vasculitis. Infect Dis Lond Engl 50:779–782. https://doi.org/10.1080/23744235.2018.1467038
66. Vilaplana C, Marzo E, Tapia G et al (2013) Ibuprofen therapy resulted in significantly decreased tissue bacillary loads and increased survival in a new murine experimental model of active tuberculosis. J Infect Dis 208:199–202. https://doi.org/10.1093/infdis/jit152
67. Tonby K, Wergeland I, Lieske NV et al (2016) The COX- inhibitor indomethacin reduces Th1 effector and T regulatory cells in vitro in Mycobacterium tuberculosis infection. BMC Infect Dis 16:599. https://doi.org/10.1186/s12879-016-1938-8
68. Kroesen VM, Gröschel MI, Martinson N et al (2017) Non-steroidal anti-inflammatory drugs as host-directed therapy for tuberculosis: a systematic review. Front Immunol 8:772. https://doi.org/10.3389/fimmu.2017.00772
69. Maitra A, Bates S, Shaik M et al (2016) Repurposing drugs for treatment of tuberculosis: a role for non-steroidal anti-inflammatory drugs. Br Med Bull 118:138–148. https://doi.org/10.1093/bmb/ldw019