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CASE REPORT

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Thalidomide as an adjunctive therapy in complex childhood neuro-tuberculosis: a case report

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Abstract

Background Tuberculosis remains a global health challenge, with central nervous system tuberculosis (CNSTB) affecting 5–10% of extrapulmonary tuberculosis cases, leading to severe complications in children aged 2 to 4 years. Despite timely diagnosis and intervention, management of CNSTB is a challenge. Thalidomide, a TNF-α inhibitor, is a potential therapeutic option in cases resistant to adjuvant corticosteroid therapy. This case report describes the management of complicated CNSTB utilising thalidomide, a less commonly used drug, with a favourable outcome.

Clinical presentation A 3-year-old boy diagnosed with CNSTB and having a ventriculoperitoneal shunt presented with left-sided hemiparesis. He was previously diagnosed with tubercular meningitis at 2.5 years of age. On anti-tubercular treatment and corticosteroid, he had a complicated course with drug-induced liver injury (DILI) and paradoxical reaction. Despite a year of anti-tubercular therapy, there was a deterioration in neurological symptoms, accompanied by an increase in the number of tuberculomas observed on MRI. Adjuvant treatment with thalidomide proved effective in suppressing immunological activation, leading to a reduction in tuberculomas.

Conclusion This case highlights the intricacies of CNSTB, including complications and refractory tuberculomas. Thalidomide was effective in managing these challenges, offering a potential therapeutic option in challenging CNSTB cases. Positive clinical and radiological responses underscore the need to further explore thalidomide as an adjunctive therapy in similar paediatric cases.

Keywords Neuro-tuberculosis, Drug-induced liver injury, Paradoxical reaction, Tuberculoma, Thalidomide

Background

Mycobacterium tuberculosis (MTB) remains a significant contributor to morbidity and mortality (Varshney et al. 2023). Among the diverse manifestations of TB, central nervous system tuberculosis (CNSTB) is particularly severe, encompassing tuberculous meningitis (TBM), tuberculoma without meningitis, and spinal tuberculosis. CNSTB represents 5–10% of all extrapulmonary TB cases and 1% of total TB cases, with increased prevalence in children aged 2 to 4 years (Caraffa et al. 2018). The diagnosis of CNSTB relies on clinical assessment, detection of MTB in cerebrospinal fluid (CSF), characteristic CSF parameters, and neuroimaging (Liu et al. 2022). Early diagnosis is crucial for favourable outcomes; however, delayed identification, leading to brain injury, is associated with death and disability despite a microbiological cure (Toorn et al. 2021a). Therapeutic strategies primarily target MTB eradication, complemented by adjunctive therapies to prevent and address disease complications (Toorn et al. 2021b).

The cytokine tumour necrosis factor-alpha (TNF-α) plays a pivotal role in the neuropathogenesis of MTB,

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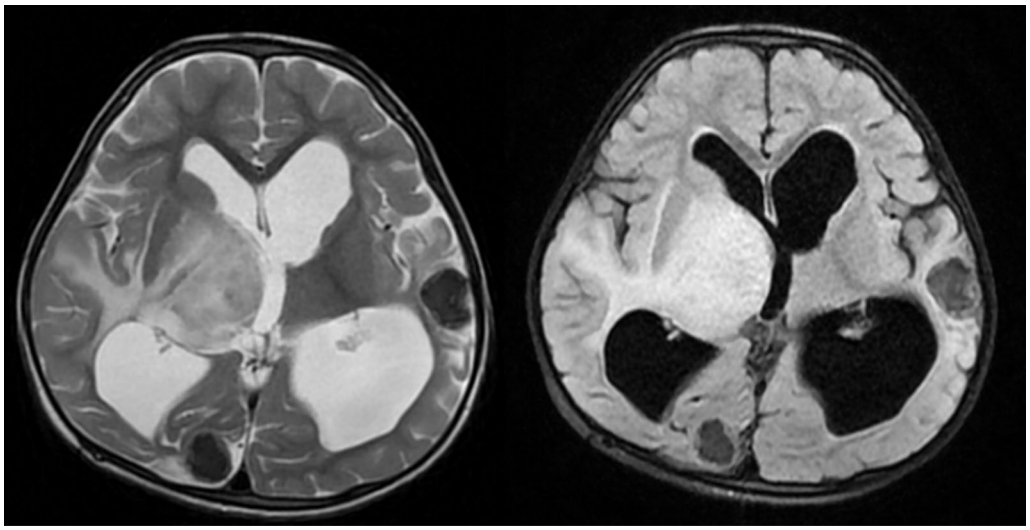

Fig. 1 MRI T2 and FLAIR sequences showing multiple tuberculomas with hydrocephalus

contributing significantly to granuloma formation and containment of mycobacterial infections (Rock et al. 2008). Thalidomide stimulates natural killer T cells, prevents lymphocyte apoptosis, and improves the interplay between T cells and dendritic cells. Additionally, it modulates monocyte cytokine levels, promoting Th2 cytokine production (interleukin-4 and interleukin-5) while simultaneously inhibiting Th1 cytokine production (interferon-γ), leading to a shift in the immune response from Th1 to Th2 type (Toorn et al. 2015).

However, in experimental bacterial meningitis, local production of TNF-α within the central nervous system (CNS) is implicated in altered blood–brain barrier (BBB) permeability and CSF leukocytosis (Rock et al. 2008). Thalidomide, a TNF-α inhibitor, is a potential therapeutic option, particularly when traditional high-dose corticosteroid therapy fails to manage chronic inflammation and neurological complications associated with CNSTB (Liu et al. 2022).

We describe a child with severe CNSTB exhibiting a paradoxical reaction (PR) and drug-induced liver injury (DILI) in response to anti-tubercular therapy (ATT). The patient had a good outcome with adjunctive use of thalidomide.

Case presentation

A 3-year-old boy presented with left hemiparesis for eleven months. His history revealed that the child was healthy until the age of 1.5 years, when he had an episode of status epilepticus, following which he had recurrent fever-triggered seizures. The complete documentation for his treatment was untraceable.

Around 2.5 years of age, he was evaluated at a different centre for the above complaints. The CSF and brain magnetic resonance imaging (MRI) were suggestive of tubercular meningitis, and he was started on ATT and steroids. Around one month into his treatment, the child exhibited clinical jaundice with deranged liver function tests suggestive of DILI. As a result, isoniazid, rifampicin, and pyrazinamide were discontinued, while ethambutol and steroids were continued with the addition of levofloxacin. He developed hydrocephalus for which ventriculoperitoneal shunting was performed. The child's liver function tests normalised after a month, and ATT was gradually reintroduced along with steroids. Despite ongoing treatment, the child worsened with seizures. A PR was considered, for which second-line ATT, amikacin, and ciprofloxacin were initiated. In consideration of PR, thalidomide was administered. Following clinical improvement marked by the cessation of seizures, thalidomide was discontinued after a month, and the initial first-line treatment was reinstated. These events occurred before the child's admission to our hospital.

He subsequently presented to our hospital with left-sided hemiparesis with upper motor neuron signs and was bound to the bed.

MRI scans revealed multiple hyperintense lesions in the right thalamus, cerebral peduncle, and hemipons indicative of tuberculomas Figure 1. Despite one year of ATT, the child's tuberculomas worsened with clinical deterioration for which a possibility of alternative diagnosis was sought; however, the workup again pointed towards tuberculosis. Considering worsening tuberculomas with active arachnoiditis, thalidomide was restarted with gradual up-titration of the dose. As the

child had tolerated the drug earlier, the same was started at 1.7 mg/kg/day with gradual up-titration to 3.4 mg/kg/day and was given for two months. The child showed clinical improvement, and LFT was monitored, considering the potential effects of thalidomide on the liver. The liver function remained in normal ranges (total bilirubin:0.6 mg/dl, SGOT-40.8 IU/L & SGPT-23.8 IU/L), and a follow-up MRI showed a significant decrease in tuberculomas in size and number. The patient's progress was closely monitored over the next few months; around two months into treatment, the child, who was bed-bound, had improvement in power and reduced tone of left upper and lower limbs and started to walk without assistance. His liver functions on follow-up are in the normal range.

Discussion

The anti-TB treatment for CNSTB parallels that of pulmonary TB, emphasising the importance of first-line ATT in treating relatively dormant bacilli within the lesions (Rock et al. 2008). However, DILI, a dreaded complication of ATT, poses a severe challenge, which was seen in our child. Isoniazid, rifampicin, and pyrazinamide, the primary first-line drugs, exhibit hepatotoxic potential, contrasting with the safety profile of ethambutol and streptomycin. Discontinuation of treatment based on symptoms and investigations would prevent severe progression of hepatic failure at an earlier stage (Gafar et al. 2019).

Research has established the significance of TNF-α, IL-2, IL-6, and IFN-γ levels in the CSF in the pathogenesis and severity of TBM (Caraffa et al. 2018). PR is a clinical or radiological worsening of existing TB lesions or the development of new lesions in a patient who had initiated ATT at least two weeks before and in whom a clinical improvement had been observed. A change in the ATT used or in the duration of this therapy is not recommended during PR treatment (Rock et al. 2008). Since dysregulated immune response contributes significantly to the morbidity and mortality associated with PR, host-directed therapy (HDT) is crucial for improving survival and clinical outcomes, with corticosteroids being the only proven HDT to decrease mortality. Thalidomide, a TNF-α inhibitor used for PR, has recently gained attention for treating complicated CNSTB, with multiple reports supporting its benefit (Gafar et al. 2019).

Adjunctive thalidomide can be considered for children who develop life-threatening neurological complications. Typically, 3–5 mg/kg/day is prescribed, and the duration of therapy should be tailored based on clinical and radiological responses (Toorn et al. 2021a). However, adverse effects of thalidomide noted were maculopapular rash, peripheral neuropathy, elevation of liver transaminases without hepatic failure and excessive sleepiness (Panda et al. 2021). Our child had experienced excessive sleepiness when thalidomide was given for PR; hence, we scheduled the dose for the night when we gave it for the second time. Satisfactory responses on serial MRI involve a reduction in the size of the lesion, a decrease in peri-lesional oedema, calcification, and decreased T2 brightness (loss of T2 signal). Discontinuation of thalidomide, without relapse, is feasible when optimal clinical improvement is attained or reaches a plateau, irrespective of whether radiological resolution is achieved (Toorn et al. 2021a). There is evidence suggesting complete neurological recovery even in bedridden patients with significant neuro deficits (Toorn et al. 2021b; Toorn et al. 2015).

Conclusion

Our patient showed an excellent response to thalidomide, which was marked by clinical improvement and radiological resolution in the form of reduced tuberculomas.

This case emphasises the complexity of TBM with DILI, PR, and worsening tuberculomas despite prolonged ATT. Thalidomide effectively managed both paradoxical reactions and unresponsive tuberculomas, highlighting its potential as a therapeutic option in challenging TBM cases. This underscores the need to explore thalidomide as adjunctive therapy in paediatric CNSTB.

Abbreviations

ATT	Anti-Tubercular Treatment
BBB	Blood Brain Barrier
CNSTB	Central Nervous System Tuberculosis
CSF	Cerebrospinal Fluid
DILI	Drug-Induced Liver Injury
HDT	Host Directed Therapy
MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis
PR	Paradoxical Reaction
TB	Tuberculosis
TBM	Tuberculous Meningitis
TNF-α	Tumor Necrosis Factor Alpha

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Author contributions

AV analysed patient data and contributed to writing the manuscript. NK, DRR, and VSK analysed and interpreted the patient data, managed the case, and contributed to writing the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Data will be shared on request.

Declarations

Ethics approval and consent to participate
As per institutional policy, case reports do not need ethics approval; however, the committee was intimated regarding this submission.

Consent for publication
Written informed consent was obtained from the patient's parents/legal guardians for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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