

Infliximab for paradoxical reactions in pediatric central nervous system tuberculosis.

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Abstract

Paradoxical reactions in central nervous system tuberculosis (TB) are associated with significant morbidity and mortality. We describe four HIV-uninfected children treated for TB meningitis with severe paradoxical reactions unresponsive to corticosteroids. All made a full recovery after treatment with infliximab, highlighting the safety and effectiveness of infliximab for this complication.

Introduction

Children are at high risk of disseminated tuberculosis (TB) after infection with *Mycobacterium tuberculosis*. TB infection of the central nervous system (CNS-TB), including TB meningitis (TBM), is associated with significant long-term disability and mortality^{1,2}. There have been few trials of immunomodulatory agents, such as steroids³ and cyclophosphamide⁴, to address the damaging inflammatory responses in TBM^{3,4}. Paradoxical reactions occur in up to one-quarter of TBM cases, and are characterized by clinical deterioration after initial improvement despite appropriate anti-tuberculous therapy, usually coinciding with cessation or weaning of corticosteroid therapy⁵. Paradoxical inflammatory lesions may affect vital brainstem and spinal cord structures, causing permanent neurological sequelae or death⁶.

Corticosteroids are the mainstay of treatment but only marginally reduce cerebrospinal fluid (CSF) tumor necrosis factor alpha (TNF α), the key cytokine implicated in the underlying exaggerated inflammatory response^{7 8}. Anti-TNF α monoclonal antibodies, including infliximab, have shown encouraging results in adult case series^{9,10}. We report the largest case series of infliximab treatment for paradoxical reactions in children with CNS TB. Table 1 provides an overview of the cases.

Case 1. An 11-month old girl presented with 4 weeks of fever, lethargy, and generalized seizures, one month after return from a 8-week visit to India. She received Bacille Calmette-Guérin (BCG) vaccine in the first week of travel. Chest X-ray (CXR) was consistent with disseminated/miliary TB and brain magnetic resonance imaging (MRI) showed widespread enhancing nodules (largest in left thalamus

measuring 5.6 x 4.1 mm) with left temporal leptomeningeal enhancement.

CSF acid-fast bacilli (AFB) smear and Xpert MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA) were positive, and *Mycobacterium tuberculosis*, was cultured, susceptible to all first-line drugs. She received isoniazid (H), rifampicin (R), pyrazinamide (Z) and moxifloxacin with 8 weeks of oral dexamethasone starting at 0.6 mg/kg/day.

One week after steroids and pyrazinamide were ceased, she developed intermittent vomiting. Her neurological examination was normal but an MRI brain showed an increase in the size and number of tuberculomas, including a new enhancing left suprasellar lesion adjacent to the optic chiasm and left optic nerve (figure 1, supplement). There was no papilloedema and she had normal visual acuity. Dexamethasone 0.6 mg/kg/day was restarted and infliximab given with prompt resolution in vomiting.

Two weeks later, her MRI brain showed marked reduction in the number of tuberculomas and size of the suprasellar lesion (figure 1, supplement). Steroids were weaned over 6 weeks and two further doses of infliximab given. Repeat MRI at 6 weeks showed ongoing improvement. Developmental milestones, including vision, were normal 9 months after treatment commencement.

Case 2. A 9-month old girl presented with fever, seizures, and right hemiparesis. MRI brain revealed widespread enhancing nodules and communicating hydrocephalus. Her CSF cultured a fully-susceptible *M. tuberculosis* complex species (*M. africanum*) (table 1). Treatment with HRZ, ethambutol (E), moxifloxacin and dexamethasone was started. Her clinical condition improved and moxifloxacin ceased after 2 weeks, dexamethasone weaned over 8 weeks, and ZE ceased after 2 months. She had

persistent right hemiparesis but remained well.

Eleven months after starting treatment, she developed vomiting, lethargy and ataxia. CT brain showed worsening hydrocephalus, requiring ventriculoperitoneal shunt insertion. Repeat CSF culture and PCR were positive for *M. africanum*. Treatment was broadened (table 1) whilst awaiting repeat drug susceptibility testing, which showed isoniazid resistance. Treatment was continued with RZ, moxifloxacin, and linezolid, and dexamethasone was weaned over 4 weeks.

Four months later, she deteriorated again, with vomiting, ataxia and torticollis. CSF was normal, including negative culture and PCR, but an MRI brain showed multi-loculated collections in the cerebellum, medulla oblongata and spinal cord (C6 to T4) (figure 2, supplement). High-dose dexamethasone was restarted for presumed paradoxical reaction however, a repeat MRI after 7 weeks of dexamethasone showed increased collections. Three doses of infliximab were given and dexamethasone ceased with the second dose. Her clinical condition improved after the first dose, with reduced vomiting and improved interaction, and her ataxia eventually resolved. The collections were smaller on an MRI 5 months after the final infliximab dose (figure 2). She completed 13 months of RZ with moxifloxacin and linezolid. Two months after stopping treatment, she had residual hemiparesis and mild intellectual disability; no further deterioration occurred.

Case 3. A 15-year old girl presented with fever, night sweats, weight loss, headache, dry cough and encephalopathy. She had migrated to Australia 2 years earlier from South Africa, where she received BCG at birth. CXR was consistent with miliary TB. MRI showed innumerable enhancing lesions throughout both cerebral and cerebellar

hemispheres, brain stem, basal ganglia and deep grey matter nuclei and diffuse dural and nerve root enhancement of the spinal cord with multiple enhancing intramedullary and dural-based nodules.

CSF Xpert MTB/RIF Ultra result was positive and *M. tuberculosis* was cultured; susceptible to all first line drugs. RHZ , moxifloxacin, and oral dexamethasone 0.4 mg/kg/day was started. Two attempts to wean dexamethasone to 0.3 mg/kg/day resulted in recrudescence of fever. The second attempt after 5 weeks led to confusion, headache and vomiting. Repeat MRI brain showed new enhancing nodules and increased perilesional oedema around pre-existing tuberculomas despite steroid treatment (Figure 3, supplement). She was treated with infliximab and dexamethasone 1 mg/kg/day for 48 hours then 0.4 mg/kg/day. Headaches and fever settled within 48 hours and infliximab doses were repeated at 2 and 6 weeks. A repeat MRI prior to her third infliximab dose showed smaller or stable lesions with reduced enhancement, although there was increased edema surrounding frontal subcortical and right thalamic lesions. Dexamethasone was weaned over 12 weeks after the last infliximab dose, with ongoing intermittent fevers, but no recurrence of neurological symptoms 4 months into her TB treatment.

Case 4 (previously reported¹¹). A 7-year old girl presented with subacute headache, vomiting and raised intracranial pressure causing bilateral 6th nerve palsy and requiring extra-ventricular drain insertion. She was not BCG vaccinated, and had traveled to Vietnam at the age of 2 months for 2 weeks. MRI brain showed 3 tuberculomas in the right frontal lobe and parenchymal abnormalities in the right frontal operculum, Broca area and splenium.

CSF Xpert MTB/RIF Ultra result was positive and she was treated with HRZ plus

moxifloxacin with dexamethasone 0.6 mg/kg/day weaned over 8 weeks, with good clinical response. In the final week of dexamethasone she developed “eye pain”, headache and reduced visual acuity. MRI showed a new mass lesion consistent with optochiasmatic arachnoiditis. Dexamethasone 0.45 mg/kg/day was restarted and infliximab given. MRI after one week showed significant reduction in the size of the mass. She received 2 further infliximab doses and continued prednisolone 2 mg/kg/day weaning over 8 weeks. She remained well and her visual acuity returned to baseline over 12 months follow-up.

Discussion

This case series highlights the safety and effectiveness of infliximab for treating paradoxical reactions unresponsive to conventional treatment with corticosteroids in children with CNS-TB. This is similar to the experience documented in a recent adult TBM case series¹⁰.

Corticosteroids are the mainstay of management for paradoxical reactions in TBM, although the optimal dosing and weaning schedule is unknown and evidence of benefit is limited¹². Tuberculomas affecting vital structures are difficult to treat and respond poorly to TB treatment and adjunctive corticosteroids^{1,13}. There are multiple case reports of TBM with protracted steroid-resistant paradoxical reactions¹⁴, and one case series of optochiasmatic arachnoiditis finding only 4 of 23 patients treated with steroids and appropriate TB treatment had improved vision after 6-months¹⁵. Of note, the two children in our series with optochiasmatic arachnoiditis had good outcomes¹⁵. A Cochrane review found that adjunctive steroids for TBM do not significantly reduce the risk of disabling neurological deficit at 2 to 24 months follow-up (RR 0.92, 95% CI 0.71 to 1.20; eight trials, 1314 participants)¹⁶.

Infliximab is a monoclonal antibody targeting TNF α . While it is thought not to cross the blood-brain-barrier, it is reported to reduce neuro-inflammation in case series of TBM paradoxical reactions, in Alzheimer's disease¹⁷, and traumatic brain injury¹⁸. It is administered intravenously over approximately two hours and requires monitoring for infusion-related reactions. The regimen of three doses at 0, 2 and 6 weeks in this series was extrapolated from rheumatoid arthritis and inflammatory bowel disease and has not been specifically studied for tuberculous paradoxical reactions. All cases in our series demonstrated clinical improvement after one dose.

Infliximab can be detected in serum for at least 8 weeks after a single dose of 5 mg/kg in adults. However, in children aged 2 to 6 years, the median steady-state infliximab exposure may be 40% lower¹⁹. TNF α antagonists are listed on the World Health Organization model list of essential medicines, but access may be limited in TB endemic regions due to resource constraints such as staffing and their high cost. Another possible disadvantage is the need to defer live-vaccines by 6 months after infliximab. These disadvantages may be outweighed by reduced steroid side effects and potential efficacy in reducing long-term neurological sequelae.

Thalidomide is an alternative therapy for paradoxical reactions, with encouraging observational data in children with complicated CNS-TB²⁰. However, high doses are associated with adverse events (hepatitis, rash, cytopenias)²¹ and thalidomide is not readily available in all settings.

This case series reports favourable treatment outcomes with infliximab for CNS-TB complicated by severe or refractory paradoxical reactions in children. Infliximab should be evaluated for this indication in prospective clinical trials.

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Table 1. Overview of four paediatric CNS TB cases treated with infliximab for paradoxical reactions

Country	Age/Sex /HIV status	Initial CSF results	TST, IGRA	TB site	Definitive TB treatment	Site/timing of paradoxical reaction	Infliximab/steroi d dosing regimen	Outcome
1 Australia	11 m F HIV negative	PMN 27x10 ⁶ /L L 51x10 ⁶ /L RBC 3x10 ⁶ /L Prot 0.59 g/L Gluc 3.0 mmol/L Culture <i>M. tuberculosis</i> , <i>rpoB</i> mutation -ve	TST and IGRA not performed	Disseminated /miliary TB, TBM/CNS TB, TB dactylitis	R 30 mg/kg/d, H 20 mg/kg/d Z10 mg/kg/d (2m) moxifloxacin 10 mg/kg/d (2m)	Opto-chiasmatic arachnoiditis, pituitary gland mass lesion; 9w into TB treatment	5 mg/kg x3 doses 0, 2w, 6w + dexamethasone 0.6 mg/kg/d (weaned over 6w)	Rapid resolution of vomiting and improvement in imaging (2w) Long term: normal development at 6m
2 Belgium	9 m F HIV negative	PMN 0 x 10 ⁶ /L L 2 x 10 ⁶ /L RBC 1 x 10 ⁶ /L, Prot 0.11 g/L Gluc 1.9 mmol/L Culture <i>M. africanum</i>	TST 11 mm	TBM/Spinal TB	R 18 mg/kg/d Z 30 mg/kg/d Moxifloxacin 15 mg/kg/d (changed to levofloxacin) Linezolid 10 mg/kg/d (13m) H 20 mg/kg/d and prothionamide 20 mg/kg/d (3m)	Cerebellar, brainstem, medulla oblongata and spinal cord mass lesions; 14m into TB treatment	5 mg/kg x 3 doses 0, 2w, 6w + dexamethasone 0.6 mg/kg/d (weaned over 9w)	Rapid clinical and radiological improvement Long-term: Mild, improving right hemiparesis and mild intellectual disability at 2y
3 Australia	15 y F HIV negative	PMN 10 x10 ⁶ /L L 116 x10 ⁶ /L RBC 6 x10 ⁶ /L Prot 3.38 g/L Glu 1.5 mmol/L Culture <i>M. tuberculosis</i> <i>rpoB</i> mutation -ve	IGRA positive	Disseminated /miliary TB, TBM/spinal TB	R 1500 mg/d (30 mg/kg/d) H 450 mg/d moxifloxacin 400 mg/d (2m) Z 2000 mg/d (2m)	Increase in tuberculomas throughout brain with increase in perilesional edema; 5w into TB treatment	5 mg/kg x 3 doses 0, 2w, 6w + dexamethasone 0.4 mg/kg/d (weaned over 23w, ongoing)	Rapid improvement of headache and neurological symptoms Long-term: Prolonged fever, no neurological sequelae at 3m
4 Australia	7 y F HIV negative	PMN 7x10 ⁶ /L L122x10 ⁶ /L RBC 15 x 10 ⁶ /L Prot 1.10 g/L Gluc 2.0 mmol/L PCR positive Culture <i>M. tuberculosis</i> <i>rpoB</i> mutation -ve	IGRA indeterminate	TBM	R 15mg/kg/d H 15mg/ kg d, moxifloxacin 10 mg/kg d (12m) Z 35mg/kg/d (2m) dexamethasone 0.6 mg/kg/d (weaned 8 w)	Opto-chiasmatic arachnoiditis with reduced visual acuity, 8 weeks after TB treatment	5 mg/kg x3 doses 0, 2, 6 weeks + dexamethasone 0.6 mg/kg/d (weaned 8 wks)	Rapid resolution of vomiting, radiological reduction in OCA Long-term: Full neurological recovery at 12m

CNS-TB, central nervous system tuberculosis; d, day; F, female; Glu, glucose; H, isoniazid; HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; L, lymphocytes; m, months; PMN, polymorphs; Prot, protein; R, rifampicin; RBC, red blood cells; TB, tuberculosis; TBM, tuberculous meningitis; TST, tuberculin skin test; wks, weeks; y, years; Z, pyrazinamide; -ve, negative. Protein normal range: 0.20–0.40 g/L, glucose normal range 2.8–4.0 mmol/L) *rpoB* mutation: rifampicin resistance gene mutation.

Figures

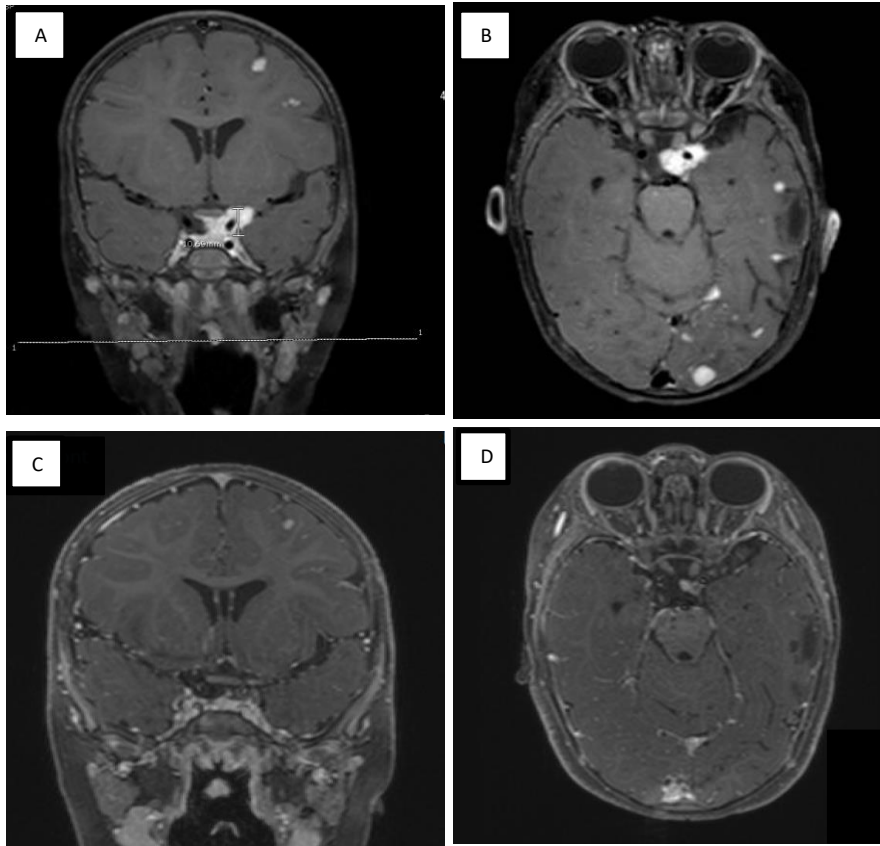


Figure 1. Contrast enhanced T1 images for case 1. A. coronal and B. axial views demonstrating an enhancing extra-axial left suprasellar lesion (11 x 20 x 11 mm) adjacent to the optic chiasm, left optic nerve, and encasing the distal left internal carotid artery (ICA), left middle cerebral artery (MCA) and pituitary gland and stalk, and multiple new contrast-enhancing cortico-subcortical nodules in the left temporal and occipital lobes noted 9 weeks after initial TB treatment, with marked improvement after two doses of infliximab (C, D).

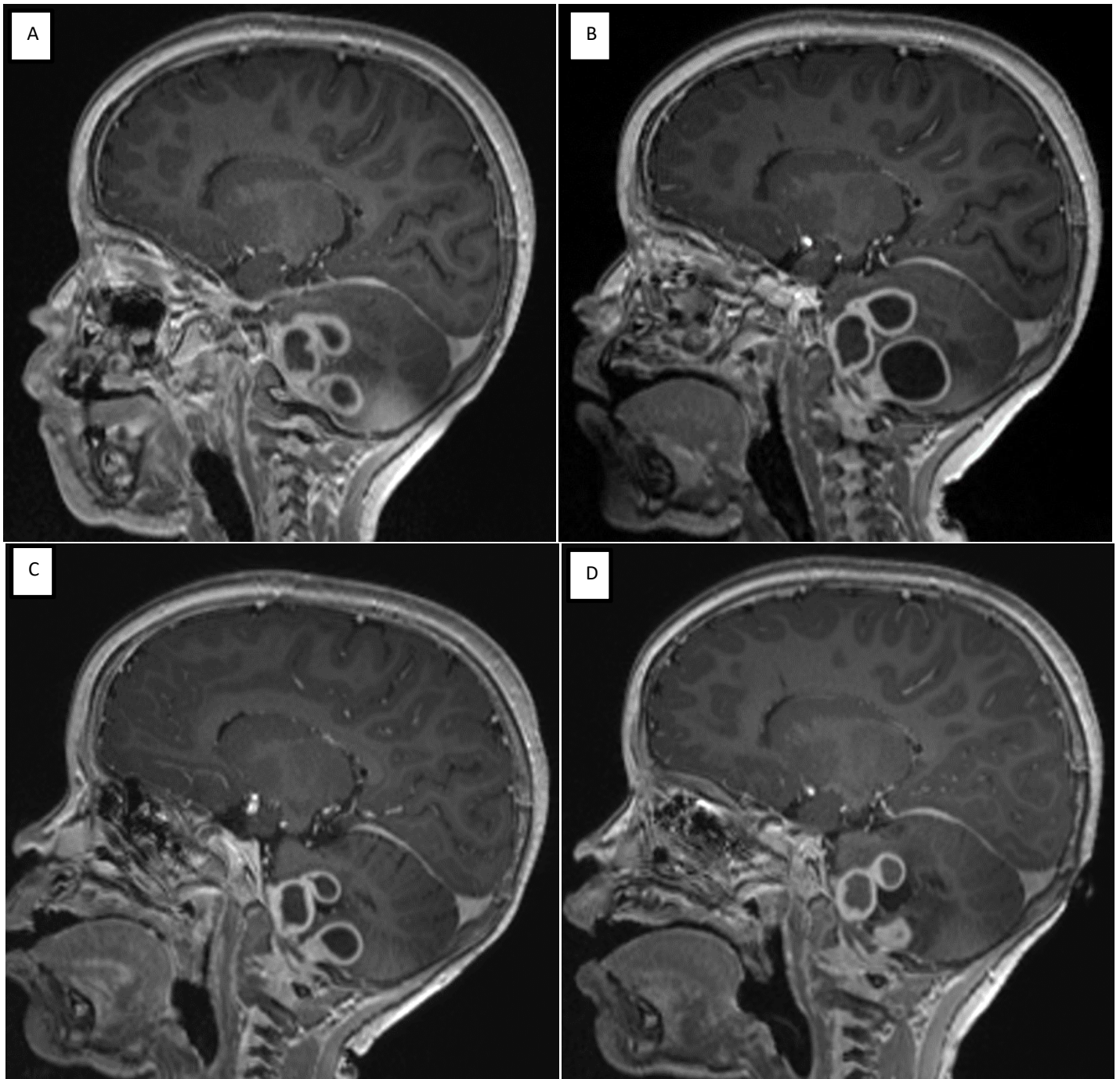


Figure 2 : Sagittal contrast-enhanced T1 images for case 2. **A.** 15 months after initial TB-treatment; before re-treatment with high-dose corticosteroids or infliximab, largest granuloma: 1.4 x 1.8 cm; **B.** 7 weeks later, after high-dose corticosteroids, before infliximab, largest granuloma: 2.3 x 3.0 cm; **C.** 3 months later, after 3 doses of infliximab, largest granuloma: 1.6 x 1.6 cm; **D.** 5 months after infliximab treatment, largest cyst: 1.6 x 0.7 cm. Baseline MRI shows multiple intra- and extra-axial thick-walled rim-enhancing lesions in the right-sided posterior fossa (involvement of brainstem, right cerebellar hemisphere and basal cisterns) (A). The lesions were progressive under high-dose corticosteroid treatment (B), but showed gradual regression after administration of infliximab (C, D).

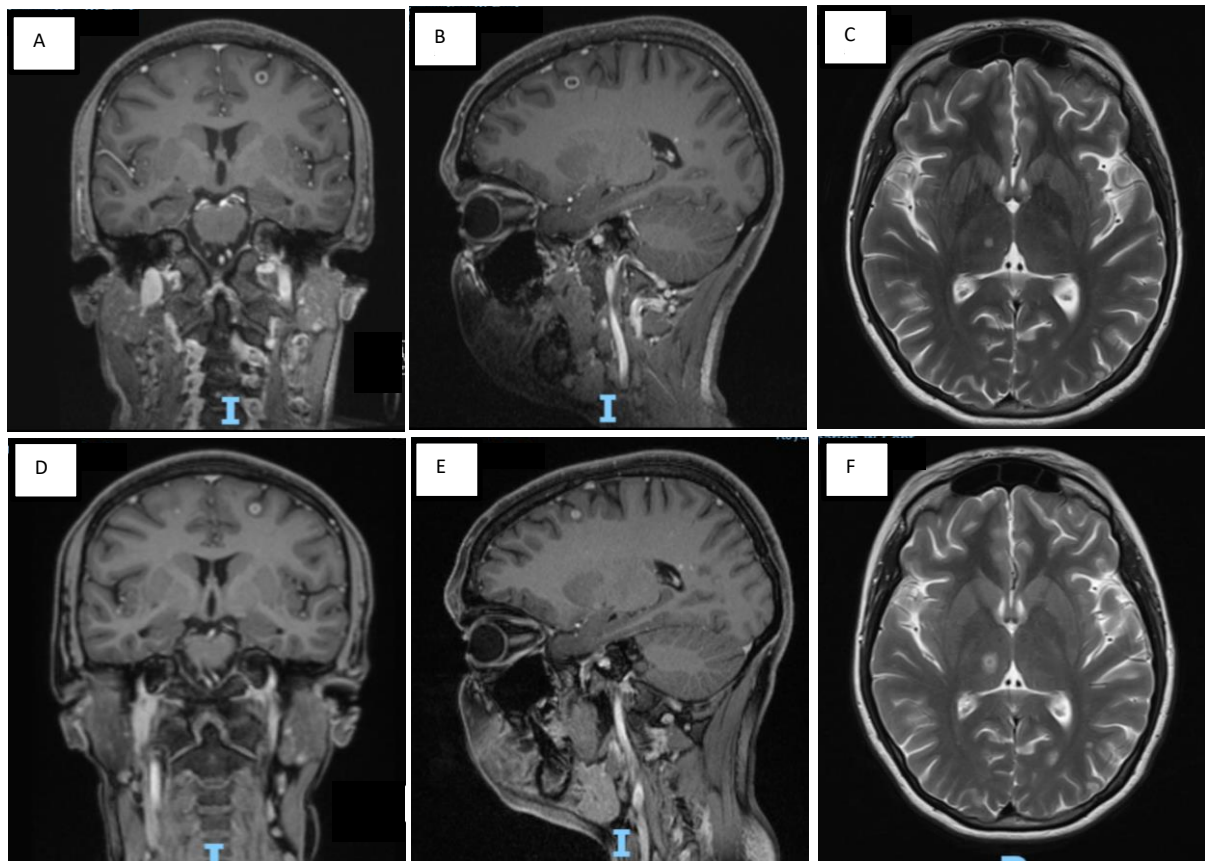


Figure 3. MRI brain images for case 3. Contrast-enhanced coronal and sagittal T1 images before (A, B) and 3 weeks after 2nd infliximab dose (D, E) showing reduction in size in the left frontal lobe lesion from 9 mm to 6 mm. T2 transverse images before (C) and 3 weeks after 2nd infliximab dose (F) with lesion in the right thalamus showing mild increase in degree of peripheral edema. Overall most lesions were either stable to reduced in size and degree of enhancement after infliximab.