A rare and challenging pediatric case of drug toxicity and immune reconstitution inflammatory syndrome during the treatment of intracranial tuberculoma: A case report

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Abstract. Intracranial tuberculoma represents one of the most severe complications of central nervous system tuberculosis (TB), with an incidence that is relatively low. In cases of intracranial tuberculoma, patients may develop drug toxicity and/or immune reconstitution inflammatory syndrome (IRIS) while receiving anti-TB treatment. The current study presented the case of a seven-year-old female patient with intracranial tuberculoma who developed drug-induced hepatotoxicity and IRIS during the course of treatment. During the follow-up of the patient, anti-TB drug-induced hepatitis developed, which led to the discontinuation of the drug twice. In the seventh month of treatment, cranial MRI showed the progression of tuberculoma lesions. The possibility of IRIS or treatment failure was considered and the treatment was restarted with steroids and non-hepatotoxic anti-TB drugs. With steroid and anti-TB treatment, the lesions regressed almost completely and the neurological deficit regressed. Patients receiving treatment should be followed up closely due to the possible side effects of anti-TB drugs, especially IRIS, which develops as an immune restructuring response during the recovery of the immune system.

Introduction

One of the most severe complications of tuberculosis (TB) is intracranial tuberculomas. While tuberculoma is observed in 1.8% of patients with TB, ~25% of these cases present as isolated central nervous system (CNS) tuberculoma (1,2). Tuberculomas can be easily confused with diseases such as lymphoma, glioblastoma, metastatic masses, fungal infections, toxoplasmosis and neurocysticercosis (3,4). Contrast-enhanced computed tomography and magnetic resonance imaging (MRI) are instrumental in the diagnosis of tuberculoma. However, the optimal diagnostic imaging tool is MRI (2,5).

Patients receiving anti-TB drugs should be monitored for side effects, including nausea, vomiting, abdominal pain and hepatotoxicity (6,7). Isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) are all hepatotoxic. RIF can discolor urine and cause thrombocytopenia. Ethambutol (E) can produce dose-dependent optic neuritis and peripheral neuropathy. PZA can cause various cutaneous reactions, asymptomatic hyperuricemia and gouty arthritis. Streptomycin can cause ototoxicity and vertigo (8,9). INH can also cause peripheral neuropathy, but this reaction can be prevented by pyridoxine supplementation (10,11). Another important point is that paradoxical deterioration in the clinical status of patients with CNS tuberculoma may be observed after an increased inflammatory response during the return of the immune system in patients whose steroid treatment is reduced or discontinued. Immune reconstitution inflammatory syndrome (IRIS) is a life-threatening condition with a poor prognosis (6,12).

This case report presents a rare case of CNS tuberculoma in a pediatric patient who developed hepatotoxicity twice, followed by IRIS, and whose disease was controlled with different regimens of anti-TB drugs and prolonged steroid treatment.

Case report

A 7-year-old female patient who had no underlying disease was started on oral antibiotic treatment with a preliminary diagnosis of sinusitis at another medical center where the patient had presented 3 weeks previously with complaints of headache, loss of appetite, nausea and vomiting. During follow-up, the patient complained of difficulty stepping on the right foot

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and walking with a dragging right foot. Contrast-enhanced brain MRI performed for these symptoms revealed multiple lesions in the left frontoparietal region, the largest of which was 13x7 mm, covering an area of ~7x5 cm, with massive vasogenic edema extending to the corpus callosum. Most lesions demonstrated prominent peripheral ring-like contrast enhancement, with certain lesions displaying a nodular, closely juxtaposed appearance. In addition, a 7-mm shift to the right in the midline was observed (Fig. 1). No contrast enhancement was observed on diffusion MRI (Fig. 2A and B). In April 2022, the patient was admitted to the Department of Pediatric Infection of Balcalı Hospital (Sarıçam, Turkey) with a preliminary diagnosis of brain tuberculosis and a mass. On initial examination, the patient's general condition was moderate and consciousness was clear. In the neurological examination of the patient based on the data of the Turkish Neurological Association, the Babinski sign was positive on the left, gaze limitation was positive on the left and muscle strength in the lower extremities was 4/5 (13). No other pathological findings were noted. Empiric INH, RIF, PZA, E and steroid at 2 mg/kg were started with a prediagnosis of tuberculoma.

The white blood cell count was 13.300/μl (normal range, 4.500-15.500/μl), hemoglobin was 13 g/dl (normal range, 11.5-15.5 g/dl), platelets were 494.000/μl (normal range, 150.000-450.000/μl), liver and renal function tests were normal, the erythrocyte sedimentation rate was 43/h (normal range, 0-20/h) and C-reactive protein was 1.82 mg/l (normal range, 0-0.8 mg/l). According to standard laboratory tests, anti-human immunodeficiency virus, as well as toxoplasma IgM and IgG were negative. An ophthalmic examination revealed papillary congestion. A contrast-enhanced MRI of the spine, chest and abdomen was normal. There was no known history of TB in the family. Interferon-γ release assay (IGRA) was positive in the study conducted with the QuantiFERON®-TB Gold Plus ELISA kit (cat no. 0590-0301) according to the manufacturer's instructions (14). A tuberculin skin test performed with PPD Tuberculin 5 TU/0.1 ml solution revealed a result of 0x0 mm (15). A Bacille Calmette-Guérin (BCG) scar was present (16). For a definitive diagnosis, the patient's intracranial mass was removed as much as possible. According to standard laboratory tests, cerebrospinal fluid (CSF) obtained during surgery showed no growth in TB culture. In this CSF sampling, no microorganisms were seen in the Acid-fast stain and the cell count showed 80/mm^3 erythrocytes. However, CSF biochemistry could not be performed due to insufficient sample size. While necrotizing granulomatous inflammation was detected in the patient's intracranial pathology samples (Fig. 3A and B), IgG4-related disease, *Aspergillus*, *Bartonella*, Tularemia, Epstein-Barr virus, *Cytomegalovirus*, *Brucella* and *Toxoplasma gondii* tests performed in the Public Health Laboratory and private external laboratories found negative results. The results of the analyses indicated that the samples were negative for the presence of parasites and viruses. The evaluations were made as standard hospital microbiology tests and by the Public Health Laboratory. In the pathology sample, the TB PCR test gave a positive result (Fig. 4; the materials were run on the same gel strip). The patient result was compared to positive and negative control DNA samples maintained at the laboratory and the 123 bp alignment was detected as positive. For the PCR method, mycobacterial DNA

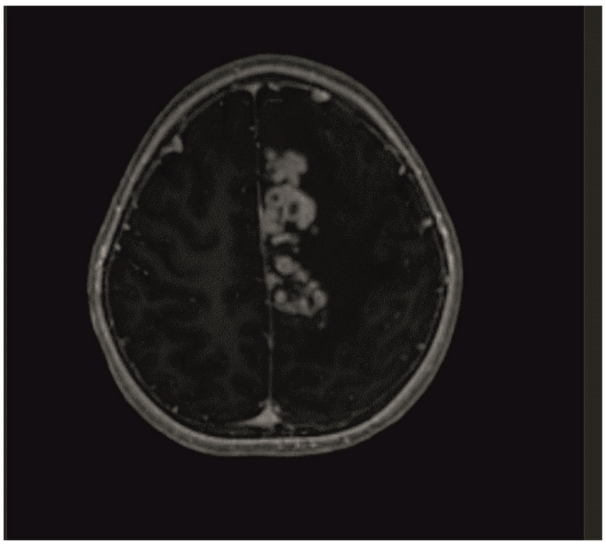

Figure 1. Contrast-enhanced brain MRI was performed in April 2022. Axial contrast-enhanced section, at the level of the centrum semi-oval in the left frontoparietal, showing numerous lesions, most of which have peripheral ring-shaped contrast enhancement, are located close to each other and have widespread edema around them. Some are nodular.

was isolated first solation of *Mycobacterium* DNA Using Chelex-100 Solution (10%)/DNA Extraction from BACTEC 12 B Bottle, and purified. The PCR product of the 65-kDa heat shock protein region specific to all mycobacteria was cut with restriction enzymes and mycobacterial species were identified. Mycobacterial DNA was detected using *Mycobacterium tuberculosis* Complex Specific IS6110 PCR. The primers TB4 (sequence, 5'-CCT-GCG-AGC-GTA-GGC-GTC-GG-3') and TB5 (sequence, 5'-CTC-GTC-CAG-CGC-CGC-TTC-GG-3') were used for the detection of *Mycobacterium tuberculosis* by PCR. Samples were run on a 7.5% polyacrylamide gel containing 2% ethidium bromide for electrophoresis and then examined by UV analysis. The observation of an amplification compound of 123 bp was considered to indicate a positive result (17). The patient's standard immunodeficiency and rheumatological test results performed in the standard serology and biochemistry laboratory were found to be normal. The diagnosis of malignancy was excluded.

Since the biopsy was positive for necrotizing granulomatous inflammation and IGRA and the TB PCR test was positive, other causes were ruled out and the patient was diagnosed with isolated CNS tuberculoma. The patient's family was questioned again for TB and it was revealed that a relative of the uncle had TB. There was no close contact with this distant relative. The entire family was screened for TB (tuberculin skin test and lung X-ray). At the first examination, the classical 4-drug regimen (INH, RIF, PZA and E) antituberculosis treatment was started and continued for 2 months. Thereafter, maintenance treatment was initiated. Steroid treatment was continued at a dose of 2 mg/kg for ~2 months and was tapered and discontinued at the follow-up visit. During the fifth month of treatment, the patient developed vomiting and abdominal pain. The aspartate aminotransferase (AST) level was 914 U/l (normal range, 15-42 U/l) and the alanine transaminase (ALT) level was 900 U/l (normal range, 8-38 U/l), and the treatment was

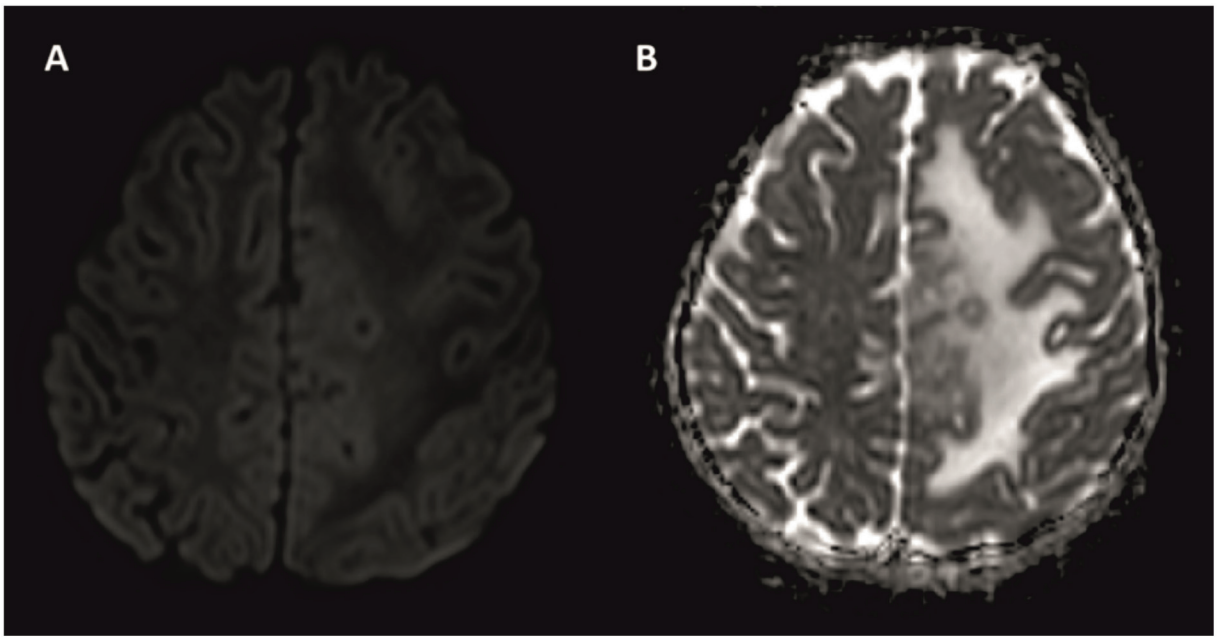

Figure 2. Restricted diffusion was not observed on (A) diffusion weight imaging, and (B) the apparent diffusion coefficient map.

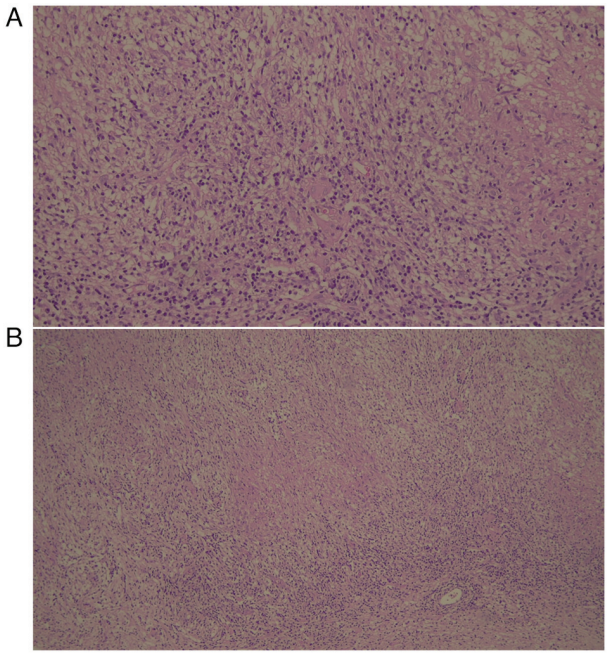

Figure 3. In the histological sections prepared with hematoxylin and eosin staining, necrotizing granulomatous inflammation consisting of multinucleated giant cells, epithelioid histiocytes and lymphocytes accompanied by necrosis are present at (A) x20 and (B) x4 magnification.

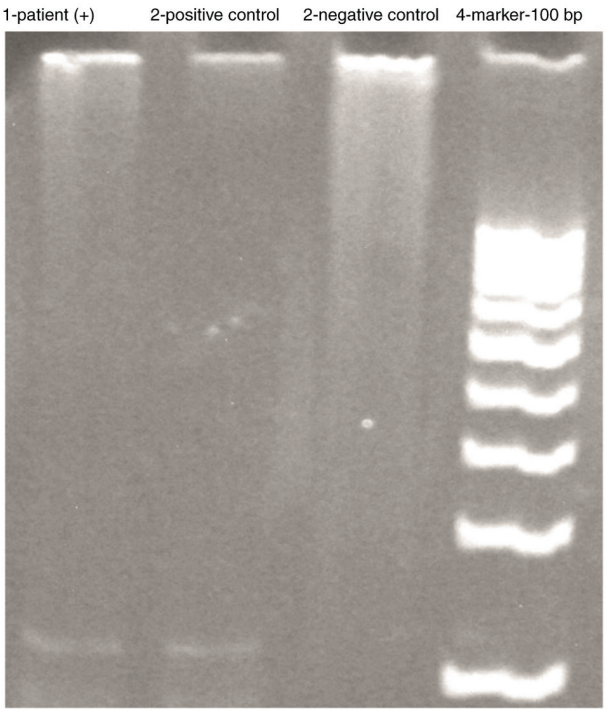

Figure 4. Tuberculosis PCR test, run on page gel.

discontinued. This condition was considered drug-induced hepatotoxicity. After a 15-day interruption, anti-TB treatment was resumed because AST/ALT levels had returned to normal. In the seventh month of treatment, the patient again had nausea, vomiting and abdominal pain, and the AST/ALT level was 912/128 U/l, so the anti-TB treatment was interrupted for the second time. Treatment failure and IRIS were considered due to edema and lesion progression found on the MRI taken at the 7th month of anti-TB treatment (Fig. 5). The patient was started on a non-hepatotoxic regimen and 3% saline for cerebral edema. Hypertonic saline was given as a 20-min infusion at 2-5 ml/kg. Oral levofloxacin, ethambutol, linezolid, cycloserine and intramuscular amikacin were started. Steroid was restarted at 2 mg/kg. When the AST/ALT levels had reached normal levels, RIF and then INH were gradually added to the anti-TB regimen. The treatment regimen is presented in Fig. 6. During the hospital stay, the patient received treatment in an isolated room. During the follow-up, the patient could not go to

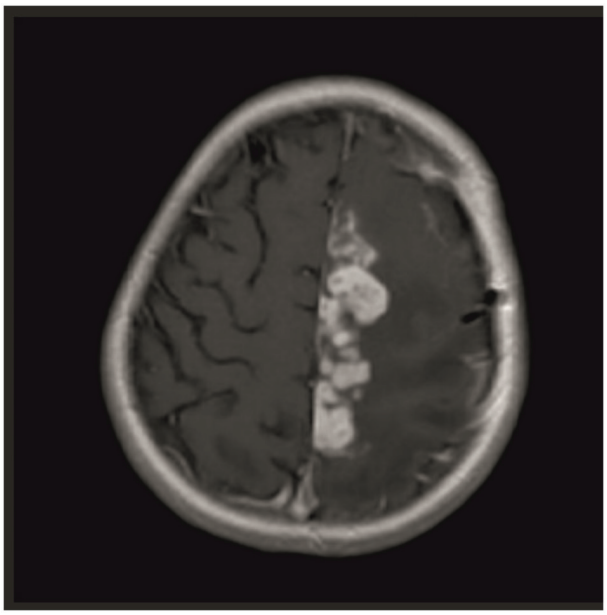

Figure 5. Imaging performed at the 7th month of anti-tuberculosis treatment showed progression, and intracranial tuberculomas were seen as large contrast-enhancing lesions similar to those on the initial imaging. Partially increased solidified contrast enhancement compared with the initial imaging was also noteworthy.

school and received education at home. Crowded places were also avoided.

Brain MRI (Fig. 7A and B) showed regression of the lesions in the fifth and 12th months of non-classical anti-TB regimen. Currently, the patient is in the 12th month of INH and RIF maintenance therapy, and steroid treatment has been tapered and discontinued. During the follow-up, the patient's neurological deficit regressed and radiological examinations showed improvement. The patient is being monitored and the planned duration of treatment is at least 18 months based on the clinical and MRI findings. There is currently no clear consensus on the usual treatment for this condition.

Discussion

TB continues to be one of the most common infectious causes of death (18). BCG vaccine, which has a historical importance in the prevention of TB, is known to have been administered to >4 billion individuals within its 100-year history (19). The prevention and reduction of pulmonary and systemic TB also reduces the incidence of CNS TB (20). CNS tuberculomas represent a distinct form of TB. Despite their rarity, they are of significant clinical importance due to their propensity to result in significant neurological complications in affected individuals (21).

Tuberculomas present as space-occupying lesions that vary in size and location, and clinical symptoms depend on these factors. Symptoms may include headache (50%), fever (14%), loss of consciousness (27%) and seizures (12-18%) (22). The diagnosis of cerebral tuberculoma is challenging due to the absence of distinctive clinical manifestations (23). Although histopathological analysis provides great advantages for definitive diagnosis, it is a difficult procedure (24). Early initiation of treatment in cerebral tuberculoma is associated with better treatment outcomes, and early diagnosis and complete treatment can reduce morbidity, mortality and the emergence of drug-resistant disease (20,25). Although there was no evidence of TB at the initial presentation of the case of the current study, anti-TB treatment was immediately initiated due to suspicion on brain imaging. The diagnosis was subsequently proven by both histopathological and molecular methods.

Studies are ongoing for the rapid and accurate diagnosis of TB, and Immuno-(I)-PCR, which is based on the detection of potential *Mycobacterium tuberculosis* antigens, has been shown to be useful (26,27). I-PCR, an ultrasensitive method, has been shown to provide a several-fold increase in sensitivity compared to ELISA by combining it with the amplification capacity of PCR with ELISA. Antigens/antibodies were detected in TB patients by I-PCR (28,29). Determination of moderately high choline/creatine ratios by magnetic resonance spectroscopy has been shown to be a useful method in the diagnosis of CNS tuberculoma (30). The aim is to provide early and correct diagnosis and treatment, following which the patient's response to treatment is good and sequelae can be reduced. It is also a protective factor against the development of drug resistance. Therefore, these studies are of high importance.

During treatment, it is necessary to be careful regarding drug side effects and conditions such as IRIS. The most common side effect of anti-TB drugs is hepatotoxicity. Hepatotoxicity continues to be an important problem because anti-TB treatment must be stopped or changed. If transaminase levels exceed 3 to 5 times the upper limit of normal or serum bilirubin exceeds 2.5 mg/l, it is recommended that hepatotoxic drugs should be changed to 2nd- or 3rd-line options (10,11). In the study conducted by Yurdakul *et al* (31), ALT enzyme elevation was found in 23.7% of patients receiving anti-TB treatment and complications requiring drug discontinuation were found in 11.3%.

Increased immune response with steroid tapering or discontinuation is noteworthy with respect to IRIS. In general, the condition of IRIS is characterized by an improvement or reversal of the immune system, as well as a worsening of the pre-existing infection or the emergence of an acute symptomatic infection (10,32). In the case of the present study, the side effect of elevated liver enzymes developed in the fifth and seventh months of anti-TB treatment, and steroid treatment was discontinued in the fourth month of anti-TB treatment. The appearance of new tuberculomas in the MRI performed as a result of the second treatment interruption created a challenging situation. Treatment was resumed with both steroid and non-hepatotoxic regimens. To avoid confusion in these patients, follow-up brain imaging should not be delayed in cases where anti-TB drugs may need to be stopped. If necessary, non-classical anti-TB drug regimens should be considered earlier.

It is difficult to predict whether IRIS will occur during TB treatment and studies are ongoing on this subject. Detection of TB-lipoarabinomannan (LAM), a TB cell wall glycoprotein, in urine samples is helpful in risk stratification because LAM antigen positivity is associated with disseminated TB and low CD4+ T-cell counts. A positive association between LAM positivity and TB-IRIS has been reported (33). A recent study suggests that CD4+ T-cell

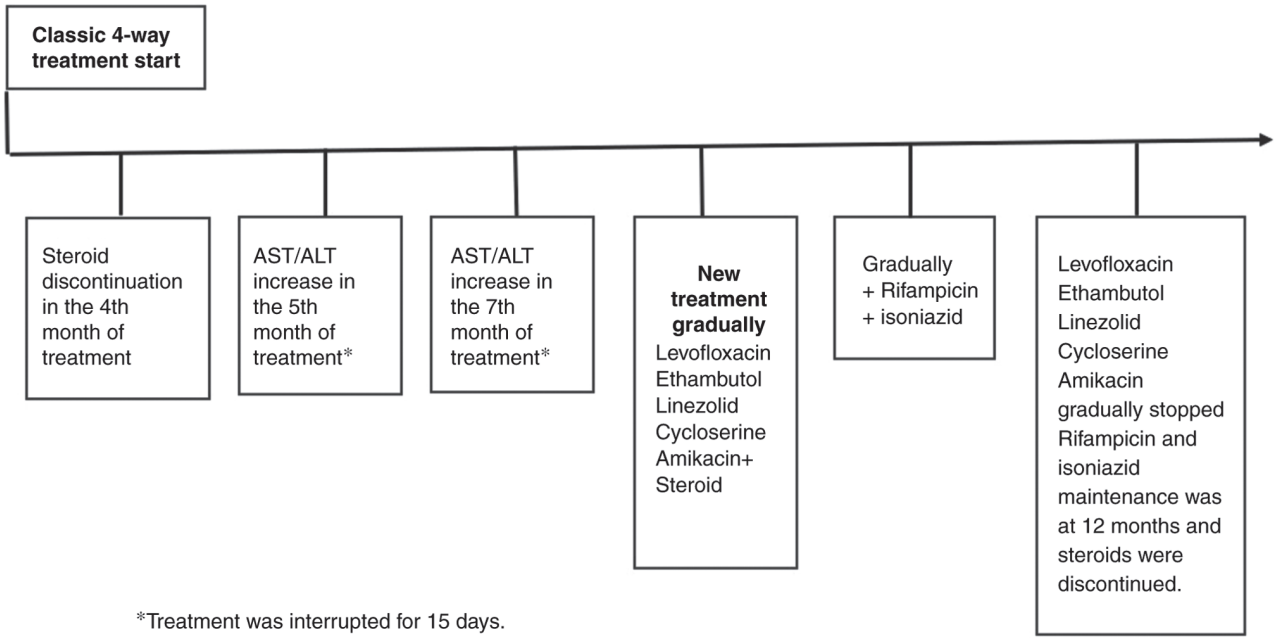

Figure 6. Initiation and continuation of the patient's anti-tuberculosis treatment regimen.

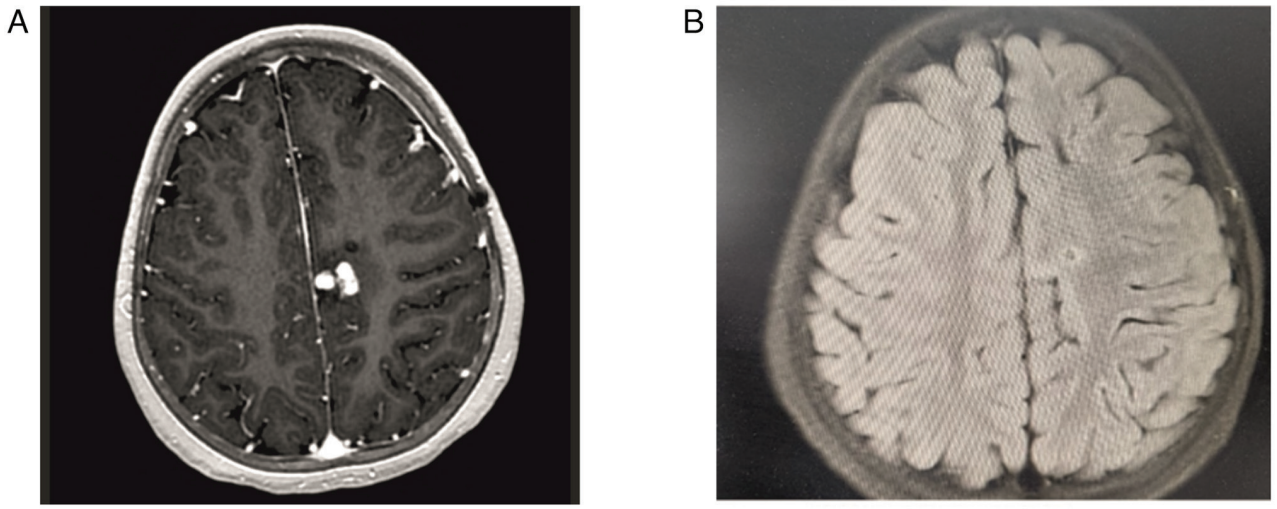

Figure 7. At the 5th and 12th months of non-classical anti-TB treatment, a millimetric lesion focus was observed in the left central semi-oval level on (A) magnetic resonance axial fluid-attenuated inversion recovery imaging, and no edema was observed. (B) In the magnetic resonance axial T1-weighted imaging, there were nodular areas of contrast medium uptake in the lesion area on the contrast medium-enhanced image, and a clearly regressed appearance was observed.

activation markers may predict TB-IRIS and that a combination of CD4+ and CD8+ T-cell markers may be helpful in diagnosing TB-IRIS (34).

The duration of treatment in intracranial tuberculoma is uncertain. The prevailing opinion is that the typical course of treatment should last between 12 and 18 months (35,36). In the study conducted by Li *et al* (36), patients with tuberculoma were given treatment for 18 months. Furthermore, in a study examining isolated brainstem tuberculomas, treatment was typically administered for a minimum of 18 months or until the tuberculoma regressed (37). Based on the clinical and brain MRI findings, the treatment duration for the present case was planned to be at least 18 months.

In conclusion, the prognosis of the disease is directly related to early diagnosis and the timing of initiation of anti-TB treatment. It should always be kept in mind that IRIS may occur in cases with tuberculoma and that anti-TB drug side effects may develop. In the present case of CNS tuberculoma, it was uncertain whether the progression of the patient's lesions was the result of IRIS or the interruption of anti-TB treatment due to drug side effects. Steroid treatment was started for IRIS and a different regimen was started for CNS tuberculoma. It is important to follow-up such patients clinically and at certain intervals with cranial MRI. We believe that there is no standardization in control MRI and that control imaging should be performed every 6 months for the slightest new neurological

complaint, transition to maintenance therapy or to evaluate the response to treatment. The current case is notable due to its rare and non-classical treatment regimen.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

FTC, UC, FK, OK, OOG and DA conceived the idea of the study. FTC, UC, FK, OK, NT, EB, AU and AD were involved in the study design. FTC, UC, FK, OK, NT, EB, AU, OOG, DA and AD collected and/or processed the data. FTC, UC, FK, OK, NT, EB, AU, OOG, DA and AD analysed and/or commented on the data. FTC, UC, FK, OK, NT, EB, AU, OOG, DA and AD performed the literature review. FTC, UC, FK and OK wrote the manuscript. FTC, UC, FK, OK, NT, EB, AU, OOG and DA critically reviewed the manuscript. All of the authors participated in the design and analysis of the study, and they have read and approved the final version. FTC, UC, FK, OK, NT, EB, AU, OOG, AD and DA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Verbal consent was obtained from the patient and written consent was obtained from the patient's mother for the publication of the present case report and accompanying associated images.

Competing interests

The authors declare that they have no competing interests.

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