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# *A Case of Multiple Brain Tuberculomas in the Subarachnoid Cisterns: Recognition of Radiological Characteristics Regarding the Development of Paradoxical Response during Antituberculosis Treatment*

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## Abstract

**Brain tuberculoma and its occurrence within the subarachnoid cisterns is rare in Japan. Serological and cerebrospinal fluid (CSF) examinations and imaging findings lack specificity; thus, preoperative diagnosis is often challenging. This report presents the case of a 70-year-old woman admitted to our hospital with a one-month history of low-grade fever and altered mental status. Based on the CSF analysis and her history of latent tuberculosis infection seven years ago, she was strongly suspected of suffering from tuberculous meningitis (TBM). Consequently, the patient was enrolled in a clinical trial for antituberculosis treatment (ATT). CSF soluble interleukin-2 receptor level decreased from 2,926 U/mL on day 1 to 225 U/mL 42 days after initiating ATT. Her condition improved after five weeks; however, contrast-enhanced T1-weighted magnetic resonance imaging (MRI) revealed multiple enhanced lesions within the basal subarachnoid cisterns 25 days after admission. As the number and size of these lesions increased, a biopsy confirmed brain tuberculoma diagnosis, and the treatment was continued. In conclusion, when intracisternal scattered mass lesions are identified during TBM treatment, we should consider the possibility of tuberculoma developments arising from a paradoxical response (PR) during the treatment. Serial MRIs are crucial in monitoring PR development in cisternal tuberculomas, an extension of severe TBM. Finally, a PR can be effectively managed by continuing ATT with adjunctive corticosteroids.**

Keywords: tuberculoma, Mycobacterium tuberculosis, antitubercular agents, subarachnoid space, meningeal tuberculosis

## Introduction

Japan was previously considered a moderately endemic country for tuberculosis (TB). However, according to the 2022 TB Registry Information Survey, the number of newly registered TB cases in 2021 was 11,519, with a notification rate of 9.2 per 100,000 population, classifying Japan as a low-endemic country for TB.[1)] In addition, the number of newly notified meningeal TB was only 100 (0.87%) in 2021.[1)] Iihara et al. recently reported that the total number of brain TB cases comprised only 37 of 1,094,706 TB cases (0.0034%/2 years) for 2018 and 2019, according to the Japan Neurosurgical Database.[2)] Brain tuberculoma is often difficult to diagnose preoperatively because serological tests, cerebrospinal fluid (CSF) examinations, and intracranial imaging findings lack specificity.

This report highlights a rare case of multiple brain tuberculomas confined in the subarachnoid cisterns, which developed during the treatment course for tuberculous meningitis (TBM). Despite the treatment, the number and size of these lesions still increased, rendering it challenging to distinguish brain tuberculomas from other inflammatory lesions or neoplasms. In this case, the definitive diagnosis of brain tuberculoma was only established through

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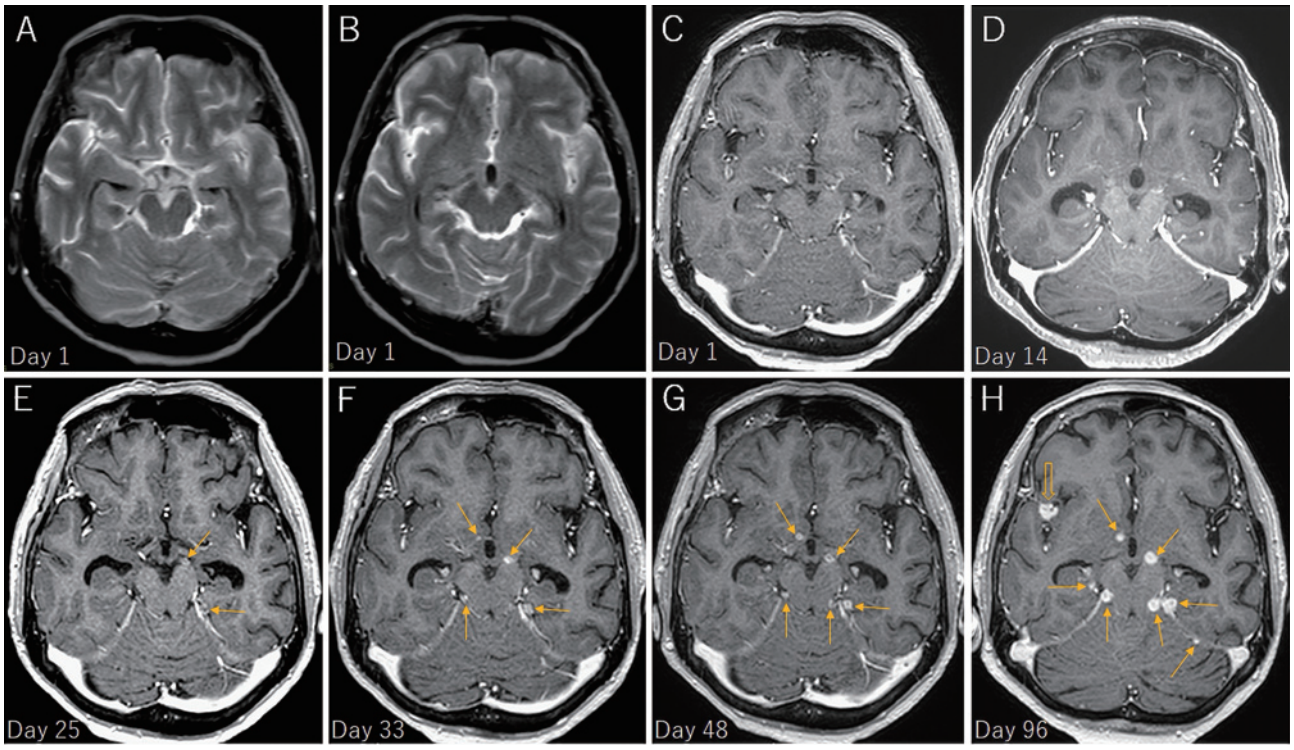


**Fig. 1 CE FLAIR and CE T1-weighted MRI showing extensive leptomeningitis and brain lesions increasing over time. CE FLAIR MRIs on day 1 (A and B) after admission show dense and diffuse leptomeningeal enhancement of the entire subarachnoid space. CE T1-weighted MRIs performed on days 1 (C) and 14 (D) after admission show no mass lesion around the midbrain but progression of hydrocephalus. Multiple round enhanced lesions with a gradual increase over time are observed on days 25 (E), 33 (F), 48 (G), and 96 (H) after admission (arrows). A new lesion appears in the right insular cistern on day 96 (H) after admission (open arrow). Hydrocephalus is spontaneously improving over time (E-H). CE, contrast-enhanced; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging**

biopsy. It is known that paradoxical response (PR) sometimes occurs during the TBM treatment.[3] However, the radiological characteristics of PR development remain vague. We visualized the occurrence of PR in a patient with TBM using serial magnetic resonance imaging (MRI) monitoring.

## Case Report

A 70-year-old woman presented with a one-month history of low-grade fever and was admitted to our hospital owing to altered mental status. She had a prior history of latent TB infection seven years ago. Initial blood tests were normal. Chest computed tomography displayed hilar and supraclavicular lymphadenopathy. T-SPOT assay showed a positive result. Meanwhile, sputum smears for acid-fast bacilli (AFB) and *Mycobacterium tuberculosis* (MTB) cultures were negative. Serological examination yielded a nonreactive result for human immunodeficiency virus. CSF examination revealed total cell counts of 331 cells/μL, with lymphocytes comprising 93%, glucose level of 21 mg/dL, protein level of 462 mg/dL, adenosine deaminase level of 12 U/L, and soluble interleukin-2-receptor (sIL-2R) level of 2,926 U/mL. No AFB was detected in the CSF smear, and the CSF culture was negative for MTB. The fungal antigen and DNA polymerase chain reaction of MTB in the CSF were negative.

On day 1, the contrast-enhanced (CE) fluid-attenuated inversion recovery MRI of the brain revealed dense and diffuse enhancement of the entire subarachnoid space, suggesting extensive leptomeningitis (Fig. 1A and B). The patient was enrolled in a clinical trial for antituberculosis treatment (ATT) (isoniazid, rifampicin, pyrazinamide, and ethambutol) on day 5 based on her symptoms, CSF analysis, MRI findings, and prior latent TB infection. Seventeen mg of intravenous dexamethasone was also administered and continued with gradual tapering. Consequently, the CSF level of sIL-2R was reduced from 2,926 U/mL on day 1 to 1,368 U/mL on day 11, then 380 U/mL on day 32, and 225 U/mL on day 47. Meanwhile, leptomenigitis gradually ameliorated. Head CE MRI revealed no mass lesion until 14 days after admission (Fig. 1C and D).

Although the patient's condition improved, the head CE MRI on day 25 revealed small, round, ring-enhanced lesions in contiguity with midbrain and left tentorium cerebelli (Fig. 1E). Furthermore, follow-up head CE MRI

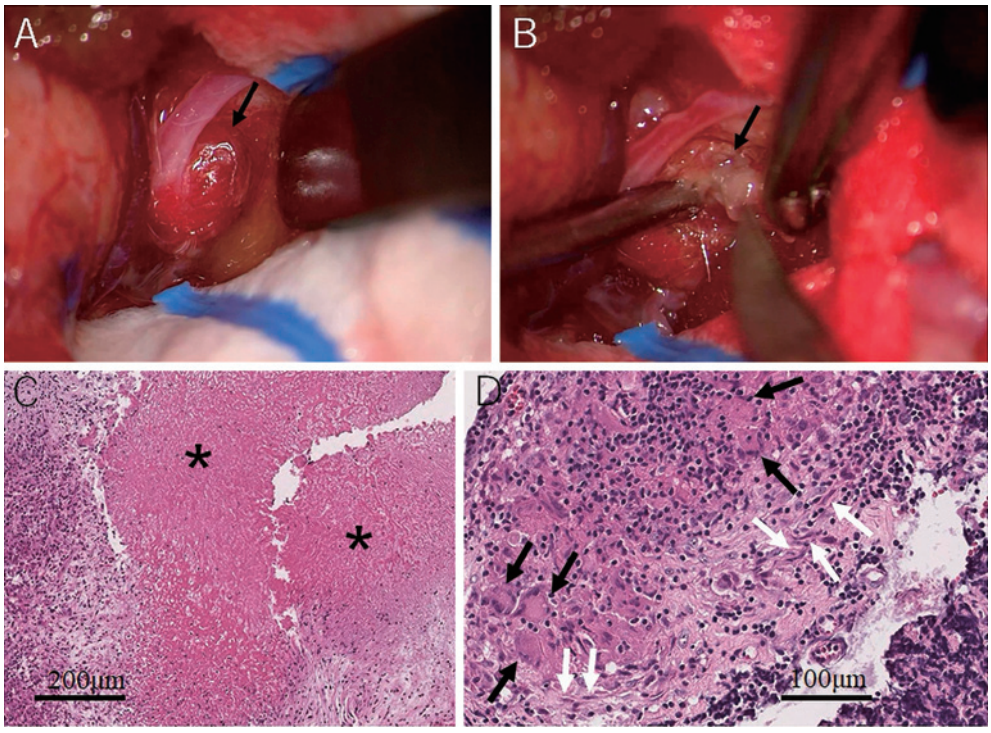


**Fig. 2 Upper row: Intraoperative photographs showing brain tuberculoma in the shallow insular cistern of the right Sylvian fissure. The tumor is a reddish solid mass adhering to the surrounding arachnoid and middle cerebral artery (A: black arrow) and comprises yellowish, firm, and tenacious components inside (B: black arrow). Lower row: Histopathological findings of the lesion at the insular cistern of the right Sylvian fissure. Necrosis (C: asterisks, HE × 100), multinucleated giant cells (D: black arrows, HE × 200), and epithelioid macrophages (D: white arrows, HE × 200) are shown. HE: hematoxylin and eosin staining**

showed an increased number of nodular lesions in the suprasellar and ambient cisterns (Fig. 1F and G). Considering the depth of these lesions, a biopsy was not feasible. As the patient showed high fever and impaired consciousness due to the reduction of dexamethasone, 7 mg of daily oral dexamethasone was finally required as maintenance treatment until the radiological amelioration of the lesions would be achieved. During hospitalization, CSF specimens were cultured six times, all resulting negative for MTB. As the patient regained alertness and independence without any symptoms and neurological deficits, she was discharged on day 71 and followed up at the outpatient service. Although ATT with 7 mg of oral dexamethasone persisted, CE MRI on day 96 revealed an increase in the number, size, and enhancement of the lesions, along with a new lesion in the right insular cistern (Fig. 1H). Consequently, the patient was readmitted for a definitive diagnosis.

A piece-by-piece biopsy of the lesion was conducted through right frontotemporal craniotomy. During surgery, a reddish solid tumor was identified in the shallow insular cistern of the right Sylvian fissure (Fig. 2A), strongly adhering to the surrounding arachnoid membrane and middle cerebral artery (Fig. 2A). The interior of the tumor comprised yellowish, firm, and tenacious components (Fig. 2B). Histopathological examination of the lesion revealed necrosis, multinucleated giant cells, and epithelioid macrophages (Fig. 2C and D). The patient received a diagnosis of brain tuberculoma. While ATT with gradual tapering of dexamethasone continued, a head CE MRI performed 17 weeks after the second discharge showed a size reduction in each lesion. However, because a few small lesions were still recognized one year after the biopsy, we decided to continue ATT for three months until the radiological resolution of the lesions was confirmed. We also considered discontinuing the ATT within 18 months even if small residual tuberculomas were confirmed. The patient currently remains in good health without any disabilities.

## Discussion

### Development of tuberculomas in subarachnoid cistern

A definitive diagnosis of TBM is only achieved when AFB is detected or MTB is cultured or identified from the CSF through a reliable molecular method.[3] TB mainly affects the lungs and spreads through lymphatic or hematogenous dissemination.[4] Subsequently, MTB spreads to the brain parenchyma or meninges. Focal MTB accumulation changes over time, developing from a caseous tuberculoma to a fluid-filled tuberculous abscess.[4] Rupturing this abscess into the subarachnoid space may cause TBM.[4] TBM affects the basal structures, such as the suprasellar, ambi-

**Table 1 The summary of reported cases of multiple brain tuberculoma limited to the subarachnoid cisterns**

| First author Pub. Year | Age | Sex | Involved subarachnoid cisterns | Symptom | Past history | LME | Surgery | ATT (duration) | PR (latency) | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Nozaki H[9] (Case 2) 1992 | 3 | M | Suprasellar Ambient | Fever, Nausia, Vomiting, Impaired cons. | Family history of pulm. TB | + | - | + (NM) | + (6 mos) | Mental retard. Severely disabled |
| Gücüyener K[10] 1993 | 7 | M | Suprasellar Ambient Sylvian | Headache, Fever, Vertigo, Impaired cons. | NM | + | - | + (1 year) | + (3 mos) | Asymptom. |
| Sharma K[12] 2003 | 14 | F | Suprasellar Ambient | Headache, Fever, Vomiting, Visual loss | No contact with TB | + | Removal | + (NM) | NM | Blindness |
| Garg K[12] 2014 | 22 | M | Sellar Suprasellar Superior cerebellar | Fever, Headache, Visual dist. | NM | + | - | + (NM) | NM | Asymptom. |
| Pinto DS[13] 2016 | 26 | F | Suprasellar Ambient | Ptosis / outward deviation of the left eye | TB-Peri | + | - | + (25 mos) | + (13 mos) | Asymptom. |
| Fujii T[14] 2016 | 61 | M | Suprasellar Ambient Sylvian | Dist. of the visual field | Neonatal TB | - | Decomp | - | - | Dist. of the visual field, Independent |

Pub., publication; LME, leptomeingeal enhancement; ATT, antituberculosis therapy; PR, paradoxical response; cons., consciousness; pulm., pulmonary; NM, not mentioned; mos, months; retard., retardation; dist., disturbance; Asymptom., asymptomatic; TB-Peri, tuberculous peritonitis; TB, tuberculosis; Decomp., decompression

ent, and pontine cisterns.[4,5] Subsequently to the TBM, we hypothesize that small MTB foci form and grow on the surface of the leptomeninges facing the subarachnoid cisterns, resulting in multiple cisternal tuberculomas. Our case's serial CE MRIs strongly supported this hypothesis (Fig. 1A-H).

**Characteristics of tuberculomas in subarachnoid cistern**

Radiographic characteristics of brain tuberculoma depend on the lesion's nature. Caseous lesions with a solid center exhibit high iron and manganese levels, resulting in iso- to hypointensity on T1- and T2-weighted MRI and demonstrating ring enhancement on CE MRI.[4,6,7] Our findings agree with these characteristics. Brain tuberculomas may occur throughout the brain.[5] Multiple tuberculomas in the subarachnoid cisterns alone are rare, with only six detailed published cases identified (Table 1).[8-13] Three of these cases had a history of TB infection, and five exhibited leptomeningeal enhancement on CE MRI (Table 1). The differential diagnosis of multiple tumors mainly located in the suprasellar cistern should include inflammatory or nonneoplastic lesions, such as neurosarcoidosis, abscess, fungal granuloma, and neurocysticercosis,[4,6,7,12] and neoplasms, such as leptomeningeal lymphomatosis, gliomatosis, and metastasis.[4,7]

**Management of central nervous system (CNS) tuberculoma**

Administering first-line ATT comprising an initial 2-month induction therapy of isoniazid, rifampicin, pyrazinamide, and ethambutol is recommended for brain tuberculoma, followed by 7-10 additional months of isoniazid and rifampin as maintenance therapy for isolation if MTB is sensitive to these agents.[14] It has been reported that the consensus of the ATT duration ranges from 6-18 months.[15] Although the radiological resolution of tuberculoma is optimal, some experts suggest that a treatment exceeding 18 months may unnecessarily expose patients to potentially toxic drugs.[15] It may also lead to antimicrobial resistance. Several guidelines endorsed using adjunctive steroid therapy in central nervous system (CNS) TB.[14,16] Adjunctive corticosteroid treatment is empirically recommended in cases of neurological complications, such as rapid visual impairment, and for those whose symptoms remain uncontrolled by ATT.[16,17]

However, surgery is not the mainstay treatment, and biopsy for diagnosis should be considered if the definitive diagnosis is unclear.[14] In addition, resecting the lesion may be considered to relieve the symptomatic mass effect if the lesion is accessible.[15,17]

**Prognosis of CNS tuberculoma**

As the prognosis for CNS tuberculoma has significantly

improved over recent decades, the survival rate now exceeds 80% with timely treatment.[18] Meanwhile, the favorable outcome rate remains approximately 53% (121/230 cases) in the reported cases since 2000.[15] Nevertheless, the prognosis of multiple intracisternal tuberculomas is comparatively favorable (Table 1).

**Paradoxical response**

A PR is interpreted as the transient worsening of the disease at a preexisting site or the development of new tuberculous lesions in patients with TB who initially improved on ATT without relation to treatment failure or a secondary process.[3,15] The incidence of PR has been reported to range from 4.5% to 28%.[19] Marais et al. reported that PR occurred within the first 6 months after initiating ATT, potentially extending up to one year or beyond.[15] In addition, Chen et al.'s study reported that all six patients with tuberculomas in the subarachnoid cisterns developed a PR.[20] PR may indicate an aberrant immune response to TB antigens.[15] These responses can be effectively managed by continuing ATT.[3,15] Recognizing the clinically frustrating yet benign nature of PR, which usually does not require any changes in therapy, is crucial.[3,15] Acknowledging the significance of PR during TBM treatment with ATT is essential, even in cases where a biopsy is performed to confirm the diagnosis. Although Chen et al. reported the PR of the intracisternal tuberculomas using MRI,[20] our report pioneers the visualization of the developmental process of a PR resulting in multiple cisternal tuberculomas by MRI serial monitoring. Dense and extensive TBM is responsible for involving PR based on the development sites of tuberculomas.

## Conclusion

Brain tuberculomas should be considered in the differential diagnosis of multiple intracranial lesions during TBM treatment, even in cases where they are confined to the subarachnoid cisterns. Serial brain imaging is crucial after initiating ATT, and PR should be recognized, especially in cases of dense leptomeningeal enhancement. PR does not suddenly occur, but it is presumed to develop following as an extension of severe TBM. Finally, continuing ATT with adjunctive corticosteroids can effectively manage a PR.

## Informed Consent

The patient consented to the publication of her images and clinical description.

## Conflicts of Interest Disclosure

The authors have no conflicts of interest. All authors have registered online self-reported COI Disclosure Statement Forms through the Japan Neurosurgical Society website.

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