# Disseminated central nervous system tuberculoma in a patient with scrub typhus: A case report

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**Abstract.** Central nervous system (CNS) tuberculosis mainly manifests as tuberculous meningitis and intracranial tuberculosis; intramedullary tuberculosis is uncommon. Scrub typhus is an acute naturally occurring infectious disease caused by *Orientia tsutsugamushi*. CNS tuberculoma following typhus is rare. The present study described a 60-year-old man with high fever, muscle soreness, yellowish skin and sclera and hepatosplenomegaly. At first, the patient was diagnosed with scrub typhus, after treatment with doxycycline he recovered completely. However, half a month after discharge, the patient experienced headache, night sweats and anorexia. Tuberculosis-specific enzyme-linked immunospot assay showed positive Mycobacterium tuberculosis antibody in cerebrospinal fluid (CSF). Metagenomic next-generation sequencing detected the presence of *Mycobacterium tuberculosis* in CSF. Magnetic resonance imaging of the brain and spinal cord showed multiple rings enhancing lesions in the cerebral hemispheres, cerebellum, brainstem and spinal cords. After the diagnosis of CNS tuberculoma, the patient was started on conventional anti-tuberculosis therapy resulting in a good prognosis.

## Introduction

Scrub typhus is an acute naturally occurring infectious disease caused by *Orientia tsutsugamushi*. The majority of patients have a history of field activities and the clinical manifestations are mainly characterized by fever, eschar, swollen lymph nodes and rash (1). It involves all the organ systems of the body, ranging from gastrointestinal symptoms to fatal illnesses such as acute respiratory distress, meningoencephalitis, acute renal failure and coagulation disorders (2,3).

Tuberculosis is a fatal infectious disease that poses a serious threat to global public health. The presence of central nervous system (CNS) tuberculosis is rare, accounting for ~0.5-2% of tuberculosis cases (4). CNS tuberculosis mainly manifests as tuberculous meningitis and intracranial tuberculosis; intramedullary tuberculosis is uncommon. To the best of our knowledge, disseminated central nervous system tuberculoma after typhus has rarely been reported (5,6).

The present study described a 60-year-old male patient with intracranial and intramedullary tuberculoma following recovery from scrub typhus.

## Case presentation

A 60-year-old male patient was admitted to the Affiliated Changsha Central Hospital (Hunan, China) in January 2021, due to recurrent fevers for three weeks and headache for one week. Three weeks before, after working in the mountains, the patient experienced recurrent fevers (up to 39.4˚C), muscle soreness, yellowish skin and sclera, oliguria and hepatosplenomegaly. The blood laboratory results showed leukocytosis, thrombocytopenia and elevated levels of direct bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine and calcitoninogen. No abnormality was found in the cranial computed tomography (CT) and magnetic resonance imaging (MRI; Fig. 1). The chest CT showed infection in the right lung (Fig. 2). Subsequently, the patient developed multiple organ failures and after receiving antibiotics, methylprednisolone pulse therapy (500 mg/day for 3 days) and intravenous immunoglobulins, did not improve significantly. Subsequently, scrub typhus was suspected with based on field activities, positive Weil-Felix reaction (Oxk value=1:160), positive PCR nucleic acid test, hepatosplenomegaly and blood routine/biochemistry. As a result, the patient was treated with doxycycline and made a full recovery.

Half a month after discharge from the hospital, the patient had persistent severe headache without obvious cause, accompanied by night sweats, anorexia and significant weight loss. The patient had a history of tuberculosis exposure. Lumbar puncture revealed intracranial hypotension (50 mm$H_2O$ after mannitol administration), elevation leukocyte count and protein (1,204 mg/l), as well as a decrease in glucose (0.76 mmol/l) and chloride (112.8 mmol/l). CSF for

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*Abbreviations:* CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CT, computed tomography; mNGS, metagenomics next generation sequencing

*Key words:* central nervous system, tuberculoma, scrub typhus

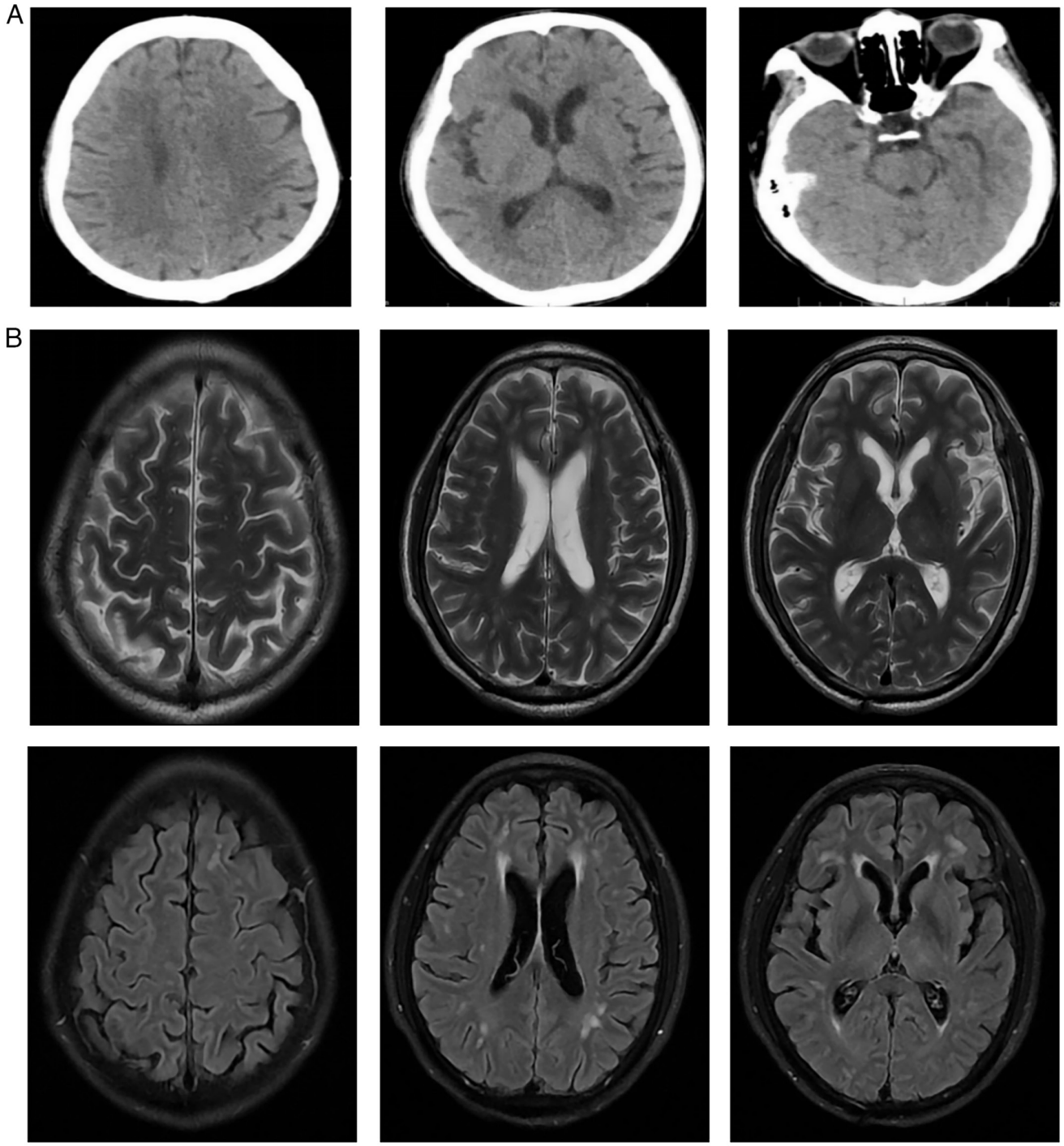


Figure 1. Cranial imaging examination. The initial normal cranial (A) CT and (B) MRI. CT, computed tomography; MRI, magnetic resonance imaging.

antibodies to *Mycobacterium tuberculosis* (December 2020) and T-SPOT four days later (December 2020) were positive. At the time of admission in January 2021, the patient had memory loss, inability to walk independently, weak limb muscle strength (4/5) and meningeal irritation. There were no abnormalities in blood routine test, liver or renal function, erythrocyte sedimentation rate, C-reactive protein. Ultrasounds of the liver, pancreas, spleen, renal and bladder were normal (Fig. 3). The skin tuberculin test was negative. The changes in the CSF are shown in Table 1. Xpert MTB/RIF was negative in the CSF in January 2021. Metagenomic next-generation sequencing detected the presence of *Mycobacterium tuberculosis* complex with 17 sequence copies in the CSF on the same day. Fibreoptic bronchoscopy showed severe purulent secretion in the trachea and the left and right main bronchi. The absence of *Mycobacterium tuberculosis* in bronchoalveolar lavage and blood was detected by macrogenomics next generation sequencing (mNGS). Repeated CT of the chest revealed infection in both lungs and multiple small calcifications in the hilar and mediastinum (Fig. 4). MRI of the brain and spinal cord (December 2020) showed multiple rings enhancing lesions in cerebral hemispheres, the cerebellum, the brain stem and spinal cords (at the C2, C4, C5 and T3 levels) with perilesional edema (Fig. 5). The patient

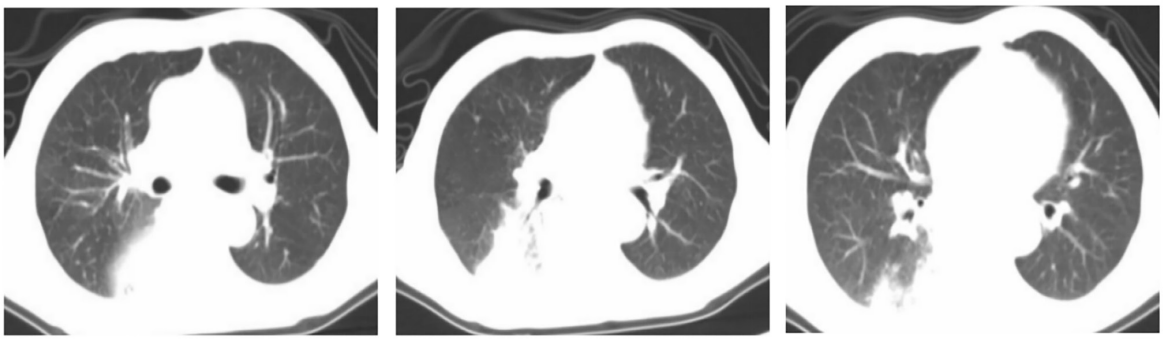

Figure 2. The initial chest CT showed infection in the right lung. CT, computed tomography.

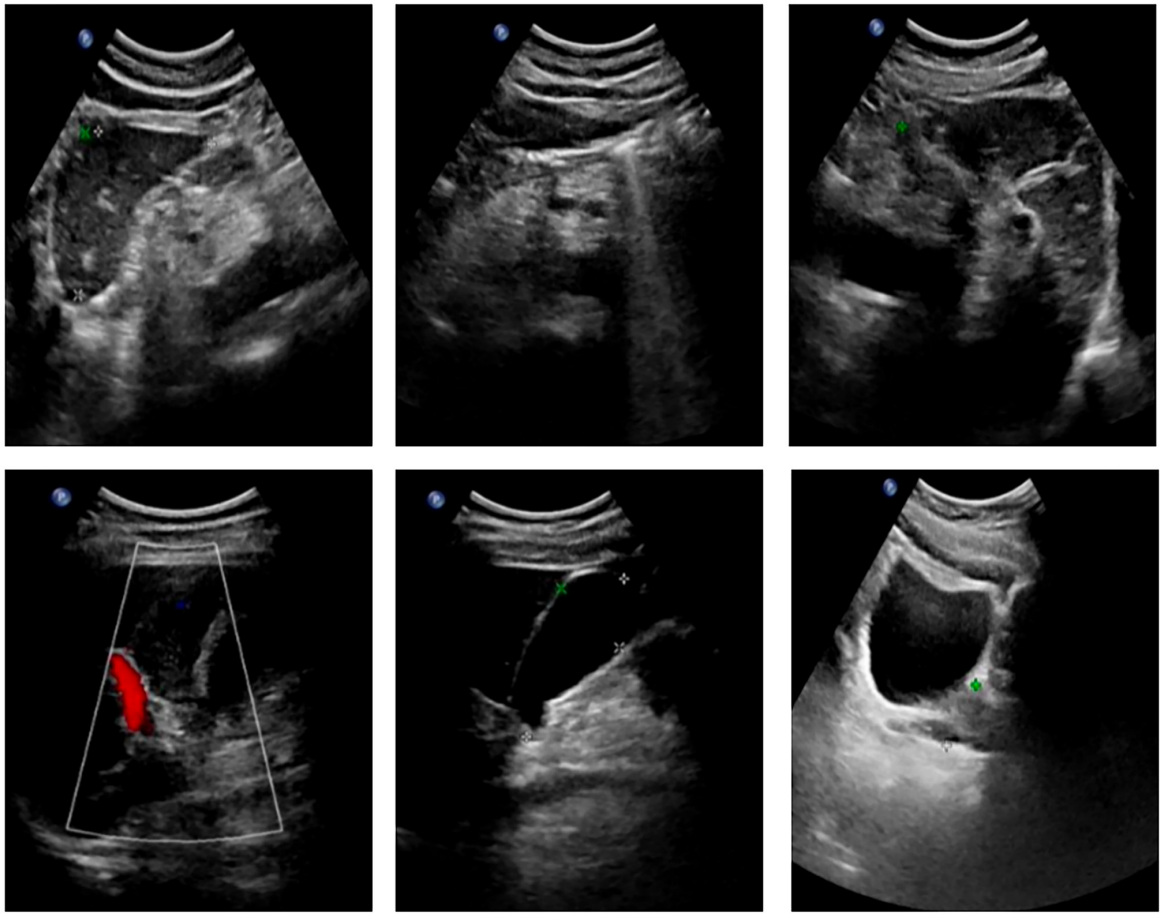

Figure 3. Abdominal ultrasound showed normal.

was diagnosed with disseminated CNS tuberculoma based on the typical MRI findings, medical history and CSF results. The patient was orally treated with rifampicin 450 mg qd, isoniazid 600 mg qd, pyrazinamide 1,250 mg qod, ethambutol 750 mg qd and moxifloxacin 400 mg qd. The patient had a good response to anti-tuberculosis treatment as shown in the CSF data (Table I).

The patient came for a follow-up visit in July 2021. Although the patient's reactions remained a bit slow, memory had improved and the patient could walk independently. The results of lumbar puncture are shown in Table I and the results of MRI of the brain and spinal cord shown in Fig. 6. TB-DNA in CSF (July 2021) was negative while T-SPOT on the same day was positive. The clinical manifestations and related examination results indicated that the patient had a good prognosis.

## Discussion

Scrub typhus is an acute febrile disease caused by *Orientia tsutsugamushi*. It spreads in the form of bites from mite larvae (7). Tuberculosis of the CNS is secondary to the blood transmission of distant lesions, such as tuberculosis infection of the lungs. Intracranial tuberculoma tend to be located in the areas of the brain with the richest blood flow, such as the brain parenchyma, subcortex and basal part of the brain. Few cases have been reported

Table I. The routine and biochemical changes of cerebrospinal fluid.

| Date | Appearance | Pressure (80-180 mm$H_2O$) | Cell counts (0-5x$10^6$/l) | Glucose (2.5-4.4 mmol/l) | Chloride (120-130 mmol/l) | Protein (0.15-0.45 g/l) |
|---|---|---|---|---|---|---|
| December 13, 2020 | Yellowish | 50 | 384 | 0.76 | 112.8 | 1.204 |
| December 2020 (8 days later) | Yellowish | 100 | 323 | 0.92 | 110.4 | 1.281 |
| January 2021 (25 days later) | Transparent | 82 | 34 | 2.08 | 120.5 | 1.05 |
| January 2021 (7 days later) | Transparent | 82 | 20 | 2.85 | 117.7 | 0.99 |
| January 2021 (6 days later) | Transparent | 105 | 34 | 2.64 | 121.2 | 0.88 |
| July 2021 (5 months later) | Transparent | 110 | 0 | 3.24 | 125.6 | 0.433 |

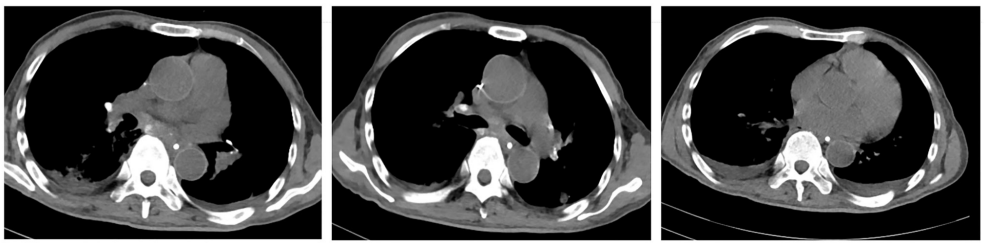

Figure 4. CT scan of chest showed bilateral pleural effusion, along with multiple small calcifications in the hilar and mediastinum. CT, computed tomography.

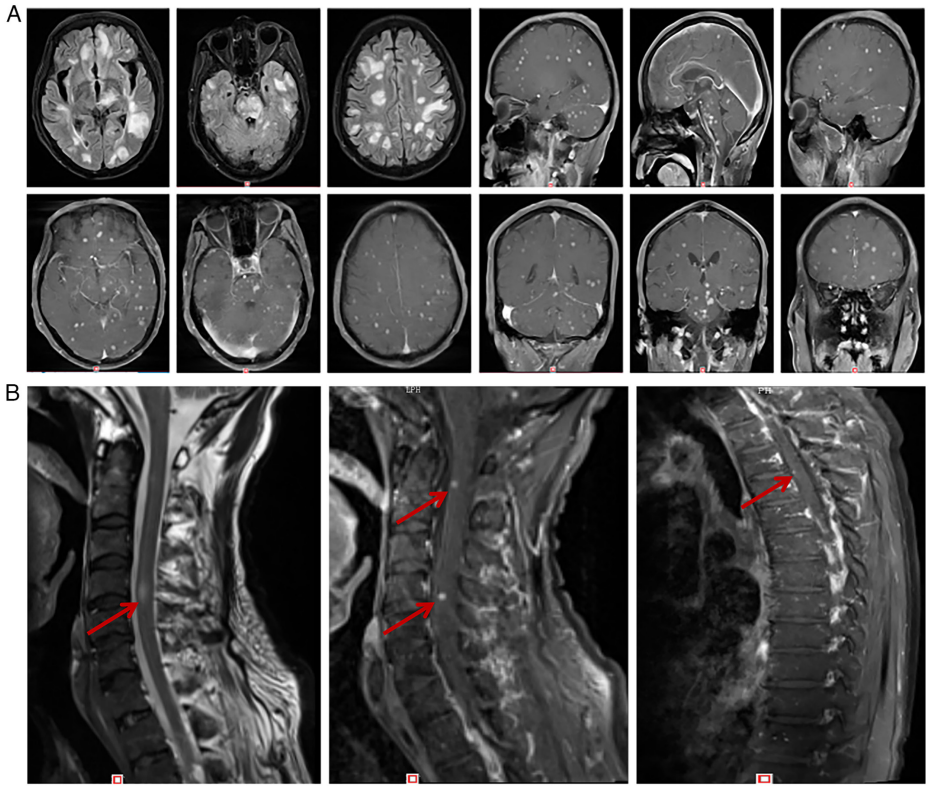


Figure 5. The changes of MRI T2-Flair MRI and T1 enhanced sequence of the brain (axial, sagittal and coronal) revealed (A) multiple round like abnormal signals of different sizes in both cerebral hemispheres, the cerebellum and brain stem. (B) Lesion showed ring-like or nodular enhancement with clear boundaries and patchy edema signals around. T2 and T1 enhanced MRI sequence of cervical and thoracic spine showed C2, C4-C5 and T3 level ring enhancing lesions with perilesional edema. MRI, magnetic resonance imaging; CT, computed tomography.

with combined intramedullary and intracranial tuberculomas (4,8). Active CNS tuberculosis is associated with immunodeficiency, malnutrition, malignant tumors and alcoholism.

In the present case, the patient's alveolar lavage fluid smear was negative. Although the chest CT revealed multiple small calcifications in the hilar and mediastinum, there was no clear

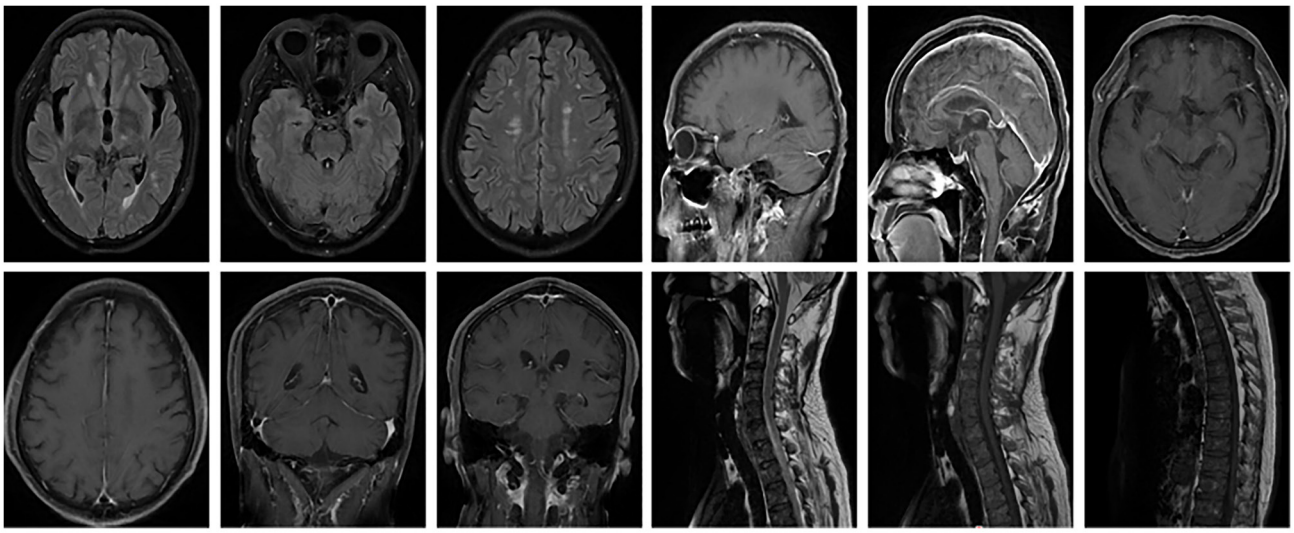

Figure 6. The changes of MRI T2-Flair MRI and T1 enhanced sequence of the brain (axial, sagittal and coronal) revealed significantly fewer abnormal signals than before. MRI of cervical and thoracic spinal cord showed no abnormalities. MRI, magnetic resonance imaging.

evidence of extra-neural tuberculosis or immunosuppression, which suggested primary neurotuberculosis in the patient. One-third of neurotuberculosis cases have been reported to have no evidence of extra-neural tuberculosis. In the present case, the diagnosis of CNS tuberculoma was based primarily on CSF biochemistry, MRI findings and mNGS. The MRI showed multiple round-like abnormal signal shadows of varying sizes in the brain. The lesions showed ring-like or nodular enhancement with clear boundaries surrounded by patchy edema signals. The imaging presentation were consistent with the characteristics of tuberculoma. T2 of Cervical thoracolumbar showed multiple patches of high signal in the spinal cord and the enhancement scan showed multiple nodules with obvious enhancement, which was consistent with the manifestations of spinal cord tuberculosis. Following anti-tuberculosis treatment, the patient's symptoms improved significantly.

The diagnosis of scrub typhus can be made based on the history of the patient, clinical features, serological tests and clinical efficacy. Doxycycline is the drug of choice for the treatment of scrub typhus. The rate of misdiagnosis has been rising due to an increase in atypical cases; most patients succumb to organ failure. In the present patient, there were no obvious manifestations of tuberculosis or MRI abnormalities during the period of scrub typhus. Previous literature found meningitis or meningoencephalitis in some patients during treatment with doxycycline (5,6), which may be related to the difficulty of doxycycline in crossing the blood-brain barrier and resistance to the drug (9). Valappil *et al* (10) reported diagnostic differences between tuberculous meningitis and typhus meningitis. However, this differs from reports of scrub typhus meningoencephalitis (11,12), in which our develops intracranial and intramedullary tuberculoma following a complete recovery from scrub typhus. The patient had a history of exposure to tuberculosis, but it was not until the patient was suspected of having scrub typhus signs of tuberculosis were observed. It was hypothesized that it may be related to high-dose hormone treatment (methylprednisolone pulse therapy 500 mg/day), decreased immunity and malnutrition. Under these conditions, patients are susceptible to tuberculosis (13). Studies have shown that *Orientia tsutsugamushi* can invade the CNS leading to vasculitis, meningitis and myelitis (14,15). Thus, tuberculous meningitis may accompany scrub typhus.

The differential diagnosis of CNS tuberculomas includes cerebral cysticercosis, cerebral abscesses and neoplastic lesions such as astrocytomas, metastases, or lymphoma. Sometimes, atypical CNS tuberculosis should be differentiated from scrub typhus. In this case, clinical and imaging features combined with the CSF findings were suggestive of tuberculous. The patient improved and was discharged on the basis of early, conventional and combination therapy.

Scrub typhus is not uncommon in patients with meningitis and encephalitis. However, few patients develop CNS tuberculoma after typhus treatment. It is rare for patients to have a concomitant presentation of intracranial and intramedullary tuberculosis. In the absence of typical clinical features, scrub typhus and tuberculoma are difficult to diagnose, but in our experience, it is very important to recognize them as quickly and effectively as possible and to treat them appropriately.

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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. The mNGS data from this study was deposited with the following link: https://www.ncbi.nlm.nih.gov/sra/PRJNA1073041.

## Authors' contributions

YY was a major contributor in writing the manuscript under the guidance of GH. YY and GH confirm the authenticity of all the raw data. Both authors read and approved the final manuscript.

## Ethics approval and consent to participate

Written informed consent was obtained from the patients or patient's children for publication of this paper and any accompanying images.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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