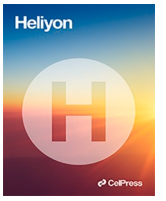
Heliyon 10 (2024) e32462

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Intracranial tuberculomas diagnosed with Xpert MTB/RIF Ultra assay of formalin-fixed paraffin-embedded brain tissues and treated with an optimized antituberculosis regimen: A case report

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ARTICLE INFO

Keywords:
Intracranial tuberculoma
Brain biopsy
Xpert MTB/RIF Ultra assay
Case report

ABSTRACT

Diagnosis of intracranial tuberculoma remains a challenge due to its rarity, non-specific clinical presentation, and radiological findings. Herein, we describe a case of intracranial tuberculomas in a male diabetic patient who presented headache and vomiting on admission. Neuroimaging findings indicated multiple ring contrast-enhanced lesions with extensive perilesional edema. However, a cerebrospinal fluid (CSF) examination was normal. When a biopsy of brain lesions was performed, pathological characteristics of tuberculosis were absent and acid-fast staining was negative. A tuberculosis diagnosis was subsequently obtained from an Xpert MTB/RIF Ultra assay of formalin-fixed paraffin-embedded brain tissue. The patient was treated with an optimized anti-tuberculosis regimen which included high-dose intravenous administration of rifampicin and isoniazid, and oral administration of linezolid. The patient recovered well and exhibited marked clinical improvement. This case report demonstrates that when CSF analysis does not indicate the presence of intracranial tuberculomas, analysis of formalin-fixed paraffin-embedded brain tissue specimens with the Xpert MTB/RIF Ultra assay may be able to confirm a diagnosis. Furthermore, a high dose of rifampicin and isoniazid plus linezolid may improve patient outcome.

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https://doi.org/10.1016/j.heliyon.2024.e32462
Received 29 December 2023; Received in revised form 7 May 2024; Accepted 4 June 2024
Available online 5 June 2024

1. Introduction

Intracranial tuberculoma is a rare manifestation of central nervous system tuberculosis (CNS-TB) which may be coincident with meningitis, or may emerge independently as solitary or multiple tuberculomas without meningeal involvement [1]. When intracranial tuberculoma occurs without meningitis, normal results can be obtained from cerebrospinal fluid (CSF) examinations [2]. Consequently, a biopsy of brain lesions for pathological and molecular examination is necessary to obtain a quick and accurate diagnosis.

The present case report describes a patient with multiple intracranial tuberculomas that were diagnosed by subjecting formalin-fixed paraffin-embedded brain tissue to an Xpert MTB/RIF Ultra assay. After receiving an optimized anti-tuberculosis treatment regimen which included a high dose of intravenous rifampicin (RIF) and isoniazid (INH), as well as oral linezolid (Lzd), the patient exhibited substantial clinical improvement.

2. Case report

A 46-year-old diabetic male was admitted to The Third People's Hospital of Shenzhen, China on July 19, 2023. The patient had developed a paroxysmal dry cough one month prior which was followed by a fever (maximum body temperature, 39 °C), headache, vomiting and weakness. A chest computed tomography (CT) scan at a local hospital detected diffuse miliary nodules in both lungs and thickening of the right pleura. The blood T-SPOT. TB test, a T cell-based interferon-gamma release assay for the detection of previous infection with *Mycobacterium tuberculosis*, was positive. The patient was overweight (bodyweight, 90 kg; BMI, 30.4 kg/m^2) and had lost 20 kg over the previous three months. Physical examination revealed nonspecific neurological symptomatology.

On admission, the patient was febrile. Biological examination showed an accelerated sedimentation rate, microcytic hypochromic anemia, and neutrophilic leukocytosis. Elevated levels of serum C-reaction protein (34.1 mg/L) and procalcitonin (0.1377 ng/mL) were also detected. Serum tumor markers were normal, including carcinoembryonic antigen, carbohydrate antigen 19-9, cancer antigen 125, squamous cell carcinoma antigen, cytokeratin 19 fragment antigen, and neuron-specific enolase. The patient underwent testing for fungal antigens, glucan, galactomannan, and cryptococcal antigen, and all the results obtained were negative. The hepatitis

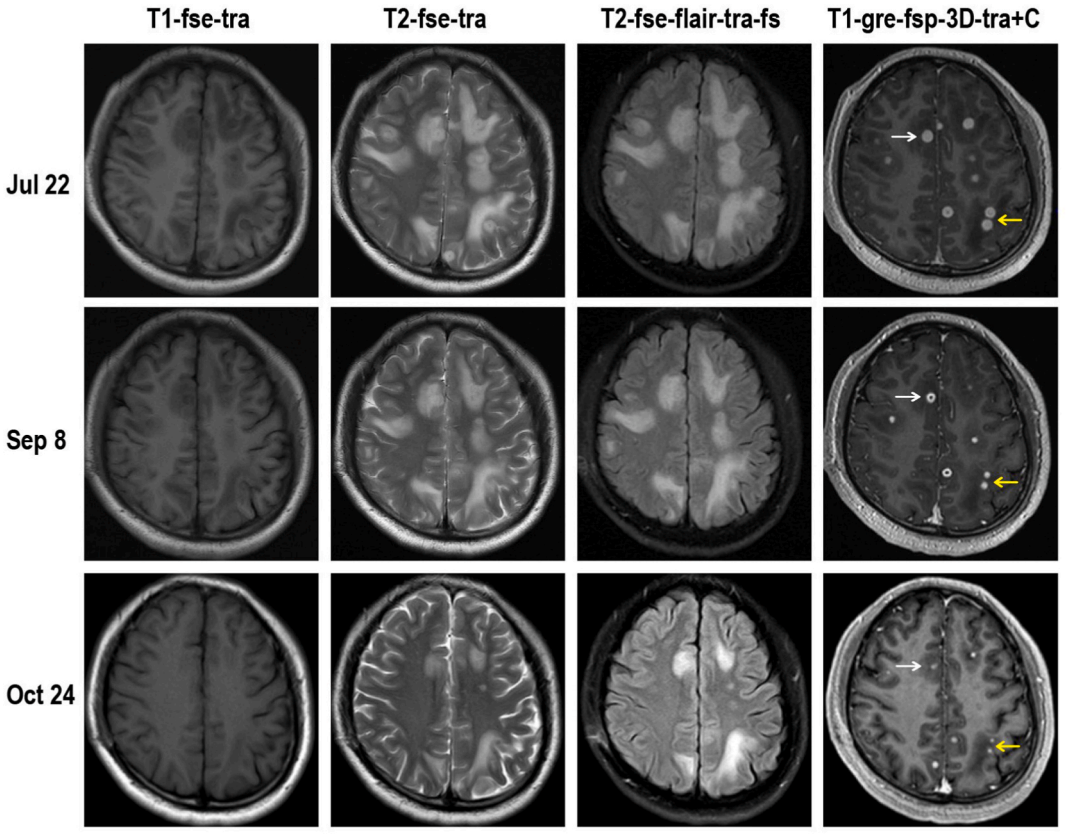

Fig. 1. MRI images. A MRI scan performed on July 22 showed multiple lesions in both frontal and parietal lobes of the patient. In addition, perilesional edema, high signal intensity on T2-weighted image (T2WI), low signal intensity on T1-weighted image (T1WI), and circular or nodular enhancement following administration of contrast agent were observed. After 3 months of treatment (Oct 24), MRI re-examination showed significant absorption of the lesions (white and yellow arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

B surface antigen (HBsAg) and antibodies for anti-hepatitis C virus, anti-human immunodeficiency virus and syphilis were routinely tested, and all were negative. Serological tests were performed to exclude parasitic infections, including *Schistosoma japonicum, Angiostrongylus cantonensis, Paragonimus westermani, Echinococcus granulosus, Cysticercus cellulosae*). Three sputum specimens for acid-fast bacilli smear and another sputum Xpert MTB/RIF assay were conducted and the results were negative. Lumbar puncture revealed rising intracranial pressure exceeding 360 mmH_2O. However, white blood cell counts and levels of adenosine deaminase, protein, glucose, and chloride in CSF were normal. GeneXpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) and Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid Inc., Sunnyvale, CA, USA) assays of the CSF also did not detect MTB. Metagenomic next-generation sequencing (mNGS) of CSF did not detect any pathogens, except for herpes simplex virus type 2 (HSV2) with a sequence count of 3. However, a real-time PCR test for HSV2-DNA in CSF was negative. Both CSF fungal and mycobacterial cultures were negative. Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed multiple circular enhanced nodules with extensive perilesional edema (Fig. 1). Abnormal signals within the spinal cord at the 3rd and 4th thoracic vertebrae (T3-T4) were also detected.

The patient was primarily considered to have disseminated tuberculoma involving the brain and spine with miliary pulmonary tuberculosis. An anti-tuberculosis regimen was immediately prescribed which included intravenous INH (800 mg daily) and RIF (1000 mg daily), in combination with oral pyrazinamide (2000 mg daily), ethambutol (1000 mg daily), and Lzd (1200 mg daily). A short-course of low-dose corticosteroid therapy (dexamethasone, 0.2 mg/kg/d of initial dose) was also prescribed. The patient's temperature subsequently normalized, but he complained of recurrent headaches and dizziness. A re-examination of the lumbar puncture showed an elevated CSF pressure of 330 mm H_2O. On August 4, a biopsy of the right temporal lobe lesion was performed under general anesthesia (Fig. 2A). The histopathological results showed brain parenchyma modified by a polymorphic inflammatory infiltrate of epithelioid cells and poorly formed granulomas (Fig. 2B). Acid-fast staining and hexamine silver staining for the detection of mycobacteria and fungal organisms were both negative. The result from a formalin-fixed paraffin-embedded brain tissue performed by GeneXpert MTB/RIF assay was negative; yet an Xpert MTB/RIF Ultra assay was weakly positive (trace). RIF resistance was also inconclusive.

Postoperatively, the patient's headache continued to worsen and was accompanied by vomiting. The dose of RIF administered was subsequently increased to 1200 mg/d (13 mg/kg/d). His plasma RIF concentration was 6.3 mg/L and CSF concentration was 0.3 mg/L. After two weeks, the patient's headache was relieved. On August 18, a lumbar puncture result showed a decrease in CSF pressure. In addition, his cranial MRI lesions were reduced and a chest CT scan showed significant absorption of the lung lesions. On September 8, the patient was discharged from the hospital. Two months later, the patient recovered with further reduction of his intracranial lesions and he exhibited substantial clinical improvement.

3. Discussion

CNS-TB occurs in approximately 1 % of all TB cases and represents the most devastating form of TB. It can manifest as meningitis, tuberculoma, and/or spinal tuberculosis [1]. However, in most cases, CNS-TB causes an inflammatory reaction affecting the meninges [3]. Following the rupture of a meningeal tubercle, *Mycobacterium tuberculosis* and disintegration products are released into the CSF. A diffuse inflammatory reaction is then distributed to the cerebrospinal membrane [3]. Thus, MTB and its nucleic acid components, as well as biomarkers of inflammation, can be detected in CSF. However, when tuberculoma is present independent of meningitis, CSF may appear normal. In the present case report, highly sensitive methods such as CSF mNGS and Xpert MTB/RIF assays failed to detect MTB in the patient's CSF. The reason for the absence of meningitis despite multiple tuberculomas being present extensively in the brain parenchyma and spinal cord is still unknown.

Radiologically, intracranial tuberculomas classically appear isointense to gray matter with perilesional edema on T2-weighted MRI with ring enhancement after contrast administration [4]. However, MRI images of intracranial tuberculomas are nonspecific and can often lead to a delayed diagnosis [5]. In the present case, MRI imaging at admission showed multiple circular or nodular enhancements with a hypo-intense center, each surrounded by edema. These presentations detected with MRI are common in tuberculoma, but are not specific. Furthermore, it is difficult to differentiate these findings from other intracranial space-occupying lesions that are due to metastasis, lymphoma, parasitic diseases, etc [6,7]. Thus, it was necessary to obtain a biopsy of the patient's brain lesions in order to

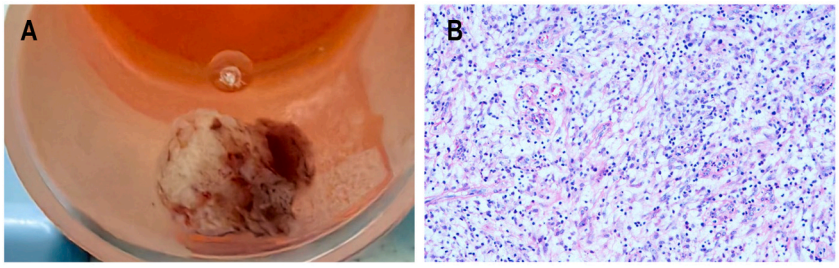

Fig. 2. Pathologic features of brain biopsy specimens from the patient. (A) A gross specimen of a biopsied brain lesion from the patient. (B) Histopathological analysis showed the brain parenchyma modified by fibroblasts and epithelioid cells infiltrated with polymorphic inflammatory cells (lymphocytes, monocytes, neutrophils, and a few plasma cells) and poorly formed granulomas. The sections were stained with hematoxylin-eosin (H&E) and examined by light microscopy (magnification, 200 ×).

perform pathological and pathogenic tests as soon as possible. The Xpert MTB/RIF Ultra assay is reported to exhibit higher sensitivity than its predecessor, GeneXpert MTB/RIF, for paucibacillary liquid specimens such as CSF [8]. Moreover, for tissue specimens, the Xpert MTB/RIF Ultra assay has exhibited excellent performance in diagnosis of tuberculous bone spondylodiscitis, lymphadenitis, and other extrapulmonary TB [9]. However, to the best of our knowledge, its reliability for analyzing paraffin-embedded brain tissue has not been reported. In the present case, the pathological presentation of the patient showed no characteristics consistent with TB, and acid-fast staining was negative. Meanwhile, the application of the Xpert MTB/RIF Ultra assay to paraffin-embedded brain tissue specimens showed trace positive results. Therefore, the Xpert MTB/RIF Ultra assay of paraffin-embedded brain tissue may be appropriate for patients suspected of intracranial tuberculosis, yet having a normal CSF test result. It is possible that formalin may damage the integrity of TB-DNA and lower the sensitivity of MTB detection [10,11]. As a result, sensitivity of the Xpert MTB/RIF Ultra assay may be higher with fresh brain tissue, which needs further investigation.

Rifampicin at standard dosing is undetectable in CSF in most TB meningitis patients. However, high-dose intravenous (20 mg/kg/day) or oral (35mg/kg/d) administrations of RIF have been shown to achieve ~6-fold higher dose exposure and CSF levels that exceed the minimal inhibitory concentration [12]. Isoniazid is metabolized primarily by the genetically polymorphic N-acetyltransferase 2 (NAT2) enzyme [13]. Among a Chinese population of TB patients, administration of INH at a high dose was generally considered helpful, as the majority of patients exhibited a fast or intermediate NAT2 metabolic genotype [14]. Meanwhile, Lzd has been reported to improve treatment outcome for severe TB meningitis due to its strong early bactericidal activity and excellent permeability of the blood-brain barrier [15]. In the present case report, a higher drug concentration was detected in both the patient's blood and CSF. The patient also recovered well following administration of the optimized anti-TB regimen and did not experience severe adverse effects such as hepatotoxicity.

4. Conclusion

Intracranial tuberculomas without involvement of the meninges may result in negative results on CSF analysis. For these patients, subjecting formalin-fixed paraffin-embedded brain tissue to an Xpert MTB/RIF Ultra assay is recommended. High doses of RIF and INH plus Lzd may also improve patient outcome if intracranial tuberculomas are present.

Consent for publication

Available.

Informed consent

Available on request from the author.

Data availability statement

All data are included in the article.

Ethical approval statement

Approval was obtained from the Ethics Committee of The Shenzhen Third People's Hospital (No. 2022-096-02). The patient provided written informed consent to publish this case and any related data.

Funding

This work is supported by the Project of Shenzhen Third People's Hospital (No. G2022058), Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (No. SZGSP010) and the Shenzhen High-level Hospital Construction Fund (No. G2022061).

CRediT authorship contribution statement

Wang Jin: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Chen Qifu:** Methodology, Investigation, Conceptualization. **Yu Hong:** Methodology, Investigation. **Huang Hua:** Methodology, Investigation. **Li Xuelin:** Methodology, Investigation. **Wang Xiaomin:** Resources, Data curation. **Lu Shuihua:** Resources, Funding acquisition, Formal analysis. **Fang Mutong:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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