Intracranial Multifocal Lesions Associated with Phthisis Miliaris: Tuberculoma or Inflammatory Granuloma?

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Abstract

Background Miliary cerebral tuberculosis, a rare variant of intracranial tuberculoma secondary to hematogenous spread of tubercle bacillus, was reported mostly concomitant with or secondary to phthisis miliaris and usually associated with tuberculous meningitis or meningoencephalitis. In this study, we described two cases of central nervous system tuberculosis supported by clinical symptoms and cranial MRI while a biopsy confirmed the granulomas consisting of inflammatory cells instead of Langhans giant cells and caseous necrosis. To our knowledge, this is the first report of this kind in the literature.

Case presentation Two Han’s patients were admitted to Jinling hospital between 2002 and 2010. One was a 17-year-old well-developed female complaining of progressive headache, vomiting and lethargy; and another was a 30 years old female presenting with violent headache, intermittent vomit and transient blurred vision. Both patients were diagnosed with phthisis miliaris and received anti-tuberculosis therapy before their admission. On admission, their physical examinations only showed elevated blood pressure, mild neck stiffness and bilateral papilloedema. Their blood evaluations were normal except for elevated erythrocyte sedimentation rate and positivity of tuberculosis antibody. Their cerebrospinal fluid evaluations were absolutely normal except for the increased intracranial pressure. Their cranial MRI revealed numerous parenchymal granulomas with ring enhancement and surrounding edema widespread in bilateral cerebral and cerebellar hemispheres and brain stem. The first patient had a biopsy of brain lesion, and the histologic
examination revealed a clear margin between the brain tissue and the nodule and no marked inflammatory changes with the surrounding brain tissue and found neither Langhans giant cells nor caseous necrosis. There were no pathological results supporting the diagnosis of miliary cerebral tuberculosis or other infections. Both them received continuously anti-tuberculosis therapy with supplement of prolonged corticosteroids treatment. On follow-up, their clinical symptoms remitted rapidly and their lesions of cranial MRI completely disappeared.

**Conclusion** Based on our observation, the inflammatory granuloma may be another pattern of central nervous system tuberculosis but not miliary cerebral tuberculosis, and prolonged administration of corticosteroids were helpful to clinical and imaging remission. This may create new awareness about tuberculosis-associated central nervous system changes, especially its clinical forms and pathological features.

**Key words:**

Central nervous system tuberculosis; Phthisis miliaris; Granuloma; Paradoxical response; Corticosteroid
Background

Although over the past decades there has been a constant decline in the incidence of tuberculosis (TB), it is still a major global health problem with 8.8 million incident cases and 1.45 million deaths in 2010, of which the majority (59%) are in Asia \[1\].

Central nervous system tuberculosis (CNS-TB) is the most devastating type of TB with high rates of mortality (up to 60%) and neurological sequel (25% of the survivors) \[2\]. Despite the new diagnostic techniques, CNS-TB continues to be a tremendous challenge for clinicians with respect of its diagnosis, therapeutic strategies, and even the pathogenesis and pathological classification \[3, 4\]. With this report, we aimed to create new awareness about CNS-TB or maybe TB-associated CNS changes, especially its clinical forms and pathological features.

Case presentation

Case 1

A 17-year-old well-developed female was admitted to our hospital in December 2002 with complaints of progressive headache, vomiting and lethargy for 8 days. About 4 months earlier she was diagnosed with phthisis miliaris on account of clinical symptoms (midrange fever, non-productive cough and night sweats), positive sputum smears for Acid Fast Bacillus (AFB), the chest radiograph and CT scanning (Fig.1 A). She received a four drug combination of Isoniazid (INH) 600mg, Rifampicin (RFP) 450mg, Pyrazinamide (PZA) 1000mg and Ethambutol (EMB) as daily doses. She left the hospital for the marked improvement of clinical symptoms and the negative
sputum examinations 4 weeks later, and continued with the same antibiotic regimen strictly.

On admission she was drowsy with elevated blood pressure (154/76mmHg), mild neck stiffness and bilateral papilloedema, but without other apparent abnormalities on physical examination. Cranial MRI with gadolinium indicated numerous small, round enhancing lesions with edema surrounded sprinkled throughout the parenchyma of cerebra, brain stem and cerebellum, and maybe the meninges. But no obvious basal meningeal enhancement was displayed (Fig.1 B-1E). The erythrocyte sedimentation rate (ESR) was 48mm/hour and the TB-antibody was positive, other hematological laboratory evaluations were normal. Lumbar puncture after intravenous injection of 150ml 20% mannitol revealed an elevated intracranial pressure (ICP, 250 mmH2O). But cytological examination and other laboratory evaluations of cerebrospinal fluid (CSF), including TB-PCR, bacterial and fungal culture, were absolutely normal.

According to the unitary theory, miliary cerebral tuberculosis was diagnosed even though without the bacteriological evidence and typical changes of CSF. We improved the daily dosage of INH to 900mg concerning to its rapid pharmacokinetics in Asian and adjunctive dexamethasone 10mg/day was prescribed. The clinical symptoms and the ICP ameliorated gradually. She was discharged from the hospital 5 weeks later and required to ambulatory follow-up per month with the same antiphthisic therapy and prednisone 45mg/day. But just 10 days later she was rehospitalized with recurrence of the primary symptoms and an abrupt episode of generalized convulsion. The intracranial lesions seemed expended to some extent on
MRI rescan (Figure.1F) and ICP posterior to the dehydration treatment as before increased to 370 mmH\textsubscript{2}O, but still no other abnormalities were discovered referred to the CSF. The previous diagnosis was suspected and biopsy of the lesion located in the right polus frontalis was accomplished under the consent of the patient and her families. The histologic examination revealed a clear margin between the brain tissue and the nodule and no marked inflammatory changes with the surrounding brain tissue. The granuloma was mainly composed of epithelioid cells with infiltration of lymphocytes, plasmacytes, eosinophils and neutrophils. Neither Langhans giant cells nor caseous necrosis were found. Acid-fast stain, PAS stain and TB-PCR were also negative (Fig.1I-1L). So there were no sufficient pathological evidences supporting the diagnosis of miliary cerebral tuberculosis or other infections. After a series of detailed inquiries about her out-hospital medication, finally she confessed that prednisone was omitted in fear of the side effect 5 days before the recrudescence. In such a case, dexamethasone 10mg per day was described again and the symptoms of intracranial hypertension remitted obviously one week later. After discharged from the hospital, she was requested to continue with INH 600mg, RFP 450mg, PZA 1000mg and also prednisone which was started from 1mg/kg daily for 7 days, then tapered off by 5 mg/week till 20mg/day, and maintained at 20mg/day for 2 months. Follow-up cranial MRI scan performed 6 months later showed almost complete regression of the lesion (Fig.1 G, 1H).

Case 2

A 30-year-old immunocompetent female was referred to our clinic for persistent
intracranial hypertension syndrome after more than 50 days anti-tuberculosis therapy. She began to feel fatigue, anorexia and mild headache concomitant with productive cough and night sweat from October 25, 2010. At first she just took Bufferin Cold and the symptoms seemed to be controlled. But 10 days later, she was admitted to Nanjing Chest Hospital for the aggravation of aforementioned complaints. On admission examination she was mildly febrile. There were crepitations and a few moist rales over both lungs without any neurological signs. Blood investigations indicated a high leukocyte count and elevated ESR. Sputum smears and cultures for AFB were positive, and the chest CT was consistent with the miliary pulmonary tuberculosis (Fig.2 A). She received anti-tuberculosis therapy with INH 600mg, RFP 450mg, PZA 1000mg and EMB 750mg as single daily doses since November 15. Two weeks later she complained of violent headache, intermittent vomit and transient blurred vision. Neurological examination showed papilledema and neck rigidity, but without Kernig's sign and other positive signs. Cranial MRI revealed numerous parenchymal granulomas with ring enhancement and surrounding edema widespread in bilateral cerebral and cerebellar hemispheres and brain stem (Fig.2 B-2E). Though the CSF evaluations were normal except for the increased ICP (up to 380 mmH$_2$O after dehydration with mannitol), the cerebral miliary tuberculosis was considered as a matter of course. Intrathecal administration with INH (100mg) and dexamethasone (2.5mg) twice a week and dehydration with 20% mannitol was introduced to the previous chemotherapy. 4 weeks later, the chest CT and the sputum examinations returned to normal. But there were new lesions on the cranial MRI rescanning and
ICP persistently fluctuated between 200~300 mmH\textsubscript{2}O. In view of the first case we met and the duration of former regimen, she was prescribed with oral prednisone (1mg/kg/day) without the intrathecal administration and EMB after she was transferred to our hospital on January 6, 2011. Her symptoms resolved rapidly and ICP returned to normal after 2 weeks. The parenchymal granulomas gradually decreased on follow-up and almost completely disappeared 3 months later (Fig.2 F-2H).

**Discussion**

Tuberculosis (TB) is still a major global health problem with 8.8 million incident cases and 1.45 million deaths in 2010, of which the majority (59%) are in Asia.\textsuperscript{[1]} CNS-TB is the most severe, life-threatening form of TB with high rates of mortality and neurological sequel\textsuperscript{[2]}. Based on the primary pathological changes, it could be mainly divided into three categories TBM (tuberculous meningitis or meningoencephalitis), intracranial tuberculoma and tuberculous brain abscess\textsuperscript{[3]}. More controversial and rare variant was tuberculous encephalopathy characterized by diffuse brain edema and firstly reported in Indian children with miliary tuberculosis\textsuperscript{[4]}. But accurately it may be a kind of post-infectious encephalomyelitis according to the post-mortem assessment\textsuperscript{[5]}. Secondary damages also are commonly encountered, such as hydrocephalus, infarct or hemorrhage due to angiopathy secondary to the tuberculosis.

The common cornerstones for TB diagnoses are the smear examination and culture
method. But as it is well known, the insensitivity of these tests and the polytropical clinical characteristics make the early diagnosis of CNS-TB a big problem \[6\]. Especially the development or worsening of intracranial lesions under therapy, which were reported and termed paradoxical response in many literatures \[7-9\], perplexes its diagnosis further. Paradoxical response was defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves. But until now the accurate mechanism about paradoxical response is unknown, most think it may be a kind of idiosyncratic reaction. Two cases here we reported shared some common features compatible with the paradoxical response. Both of them underwent CNS deterioration when their phthisis miliaris improved evidently after months of anti-tuberculosis chemotherapy. Subsequent expanding of intracranial nodules and newly-presented lesions were demonstrated on MRI during the hospitalization. Striking amelioration was achieved and these lesions approximately completely disappeared at last after the application of corticosteroids.

Intracranial tuberculoma may emerge solitarily or multiply with or without meningitis. The MRI presentation depends on the pathological changes. Tuberculomas without caseation are often homogeneous hyperintense on T2-weighted images. Caseating tuberculomas are isointense to markedly hypointense on T2-weighted images and exhibit rim enhancement \[10\]. Miliary cerebral tuberculosis, a rare variant of intracranial tuberculoma secondary to hematogenous spread of tubercle bacillus, was reported mostly concomitant with or secondary to phthisis miliaris and usually associated with
TBM\textsuperscript{[11, 12]}. Miliary tubercles appear as numerous round, homogeneously enhancing lesions less than 3 mm in diameter, mostly located at the paraventricular and gray white matter junction area. The MRI features of our patients were concomitant with miliary cerebral tuberculosis except no apparent meningeal involvement. In view of the definite history of phthisis miliaris and aforementioned characteristics, miliary cerebral tuberculosis with paradoxical response was taken for granted even through without the bacteriological evidence and typical changes of CSF. But what confused us mostly were the histopathological findings. Typically tuberculomas show a granulomatous reaction consisting of epithelioid cells, Langhans giant cells and infiltrating lymphocytes around a central area of caseating necrosis or sometimes without caseating core\textsuperscript{[13]}. In our first case, the pathology showed a granuloma with clear margin to the peripheral brain tissue, which was mainly composed of epithelioid cells with infiltration of lymphocytes, plasmacytes, eosinophils and neutrophils. No Langhans giant cells and caseous necrosis were found. AFB stain and TB-PCR were also negative. So it was difficult to make the diagnosis of tuberculosis in accordance with the histopathologic features.

To our knowledge there were a few literatures on Medline referring to intracranial miliary lesions concomitant to phthisis miliaris with normal CSF \textsuperscript{[11, 12, 14]}, no of them with the pathological examination, but miliary cerebral tuberculosis was diagnosed without exception. According to Gupta’s study \textsuperscript{[12]}, patients with typical miliary pulmonary tuberculosis may more frequently have involvement of the CNS and most of them may be asymptomatic. Why most of them are asymptomatic? Considering
the widespread and more prolonged administration of corticosteroid in the treatment of CNS-TB, in conjunction with the pathologic and bacteriologic findings of our study, we suspected immune-mediated idiosyncratic reactions may play a key role in the pathogenesis of our patients. Tuberculoprotein was reported to be related to various pathological changes of different organs, such as Eales' disease\textsuperscript{[15]}, meningismus\textsuperscript{[16]} and acute respiratory distress\textsuperscript{[17]}. Tuberculous encephalopathy aforementioned may also be associated with the tuberculoprotein hypersensitivity\textsuperscript{[5]}. Chemotherapy of phthisis miliaris involves the destruction of M. tuberculosis and liberation of tuberculoprotein which spreads haematogeneously. It can also explain why the lesions of our patients spread over the grey/white matter interface, and why the CNS lesions emerged when their phthisis miliaris improved after anti-tuberculosis chemotherapy. So we conjecture the inflammatory granuloma caused by tuberculoprotein may be another pattern of CNS-TB. But of course, more evidences and investigations will be needed to identify this pattern of cerebral tuberculosis.

**Conclusion**

Our observation suggests that intracranial miliary lesions concomitant to phthisis miliaris with normal CSF do not always mean miliary cerebral tuberculosis but may be the inflammatory granuloma and another pattern of central nervous system tuberculosis. Although more evidences and investigations will be needed to identify this pattern of cerebral tuberculosis, however, when phthisis miliaris patients presented with worsening intracranial hypertension symptoms and without CBF cytological abnormalities during the course of regular anti-tuberculosis treatment,
supplement with corticosteroids for a prolonged duration may be helpful to clinical and neuroimaging improvement.

Consent

Written informed consents were obtained from the patients for publication of this Case report and any accompanying images.

Abbreviations

central nervous system tuberculosis (CNS-TB); central nervous system (CNS); Acid Fast Bacillus (AFB); tuberculosis (TB); intracranial pressure (ICP); Rifampicin (RIF); Isoniazid (INH); Pyrazinamide (PZA); Ethambutol (EMB); Cerebrospinal fluid (CSF); Magnetic Resonance Imaging (MRI); Computed tomography (CT)

Competing Interests

All the authors declare that there are no any competing interests.

Authors' contributions

LL and LW carried out clinical data collection and draft the manuscript. Wu B carried out the histopathological study. LZ, GL, YF and LX participated in its design and coordination and helped to draft the manuscript. LZ and ZR conceived of the study, participated in its design and helped to revise the manuscript. All authors read and approved the final manuscript.
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None
References


**Figure legend:**

**Figure 1A:** High-resolution chest CT before treatment indicated widespread hyperdense micronodules scattered throughout the bilateral lungs.

**Figure 1B-1E** (MRI before biopsy): Numerous small, homogeneous enhancing round lesions, some with apparent peripheral edema, sprinkled throughout the cerebra, brain stem, cerebellum, and maybe the meninges. Most of the lesions located at the cortex, subcortical white matter and paraventricular area. No obvious meningeal enhancement was displayed on post-contrast scans.

**Figure 1F** (MRI after biopsy): Subsequent expanding of intracranial nodules and newly-presented lesions were demonstrated on contrast-enhanced T1-weighted image.

**Figure 1G&1H** (MRI 6 months later): The lesions completely disappeared.

**Figure 1I** (HE ×40): A granuloma with clear border in brain parenchyma was revealed.

**Figure 1J** (HE ×100): There were some degenerated ganglion cells, but no apparent inflammatory response in the surrounding brain tissue.

**Figure 1K** (HE ×400): The granuloma mainly consisted of epithelioid cells with infiltration of inflammatory cells including lymphocytes, plasmocytes, Eosinophils and neutrophils. There were no evidences of caseous necrosis.

**Figure 1L** (×400): PAS staining for fungus was negative too.

**Figure 2A:** Chest CT before treatment showed uncountable miliary hyperdense nodules distributing in bilateral lung.
Figure 2B-2E: MRI Imaging showed multiple nodules with homogenous or ring enhancement spreading in both side of cerebra, cerebellum and brainstem.

Figure 2F-2H: MRI 6-month later demonstrated remarkable remission of the lesions.