Author’s response to reviews

Title: Intracisternal tuberculoma: a refractory type of tuberculoma indicating surgical intervention

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Reviewer reports:

Tai Mei- Ling Sharon (Reviewer 1): Interesting article

Strengths:
1. Surgery was performed on all the tuberculoma.

2. Good neuroimages pre and post op.

3. Beautiful intraop pictures.

4. Description of paradoxical tuberculoma.

5. Two patients with spinal tuberculoma were recruited (including one rare intradural extramedullary).

6. Common location of paradoxical tuberculoma in the brain was described.

Needs improvement in:

1. Grammatical errors and spelling mistakes were present.

Thank you very much for your suggestion! We carefully checked the manuscript and sent it to professional language editing corporation for language revision. If there is any problem, please tell us. Thank you!

2. The manuscript was too long. Suggest to reduce the number of words in all the parts of the manuscript especially the introduction (background section).

Thank you very much for your suggestion! We deleted some sentence and paragraph especially in the introduction part which elaborated the information already stated (Page 6, line 6 to 14; page 7, line 21 to 22; page 8, line 1 to 2; page 8, line 8 to 15.). Thank you!

3. Suggest to categorist the sentences in methodology and results properly.

Thank you! We modified some sentences and hope it will be better. Sorry and thanks!

4. What was the exclusion criteria?

Thank you very much for your suggestion. Because only the patients with surgical indication were admitted in the neurosurgery department of the two hospitals (Guangzhou First People’s Hospital and Changzheng Hospital). If the patients responded well to the ATT, they were treated
in the infectious disease hospital. We added “requiring surgical intervention” at page 7, line 21 to 22. We hope it is proper to elaborate the situation. Thank you very much!

5. What was the sensitivity of the CSF mycobacterial culture (if present) to ATT?

Thank you very much for your professional question! Frankly saying it is a complicated problem with mycobacterial culture. Firstly, it took a long time for the growth of the mycobacteria and some patients were transferred to the infectious hospital again after successful surgeries before the result came out. Secondly, some of the patients did not have successful CSF mycobacterial culture. Most importantly, all the patients showed severe neurological deficits. Operation is an only choice under this situation.

When admitted, we did not purposely acquire related data of mycobacterial culture from the patients and the infectious hospital. But according to the previous effectiveness of the ATT (except case 6llk and case 10lhw), ATT is effective in these nine cases before surgeries. Actually, the ATT regimens were proved effective in all cases following operations. Accordingly, although no data of CSF mycobacterial culture were acquired, the effectiveness of ATT regimen is definite. The clinical situation is in accordance with the definition of the paradoxical reaction.

6. Did all the tuberculoma show granuloma on HPE?

Thank you for your information! Our original description may be misleading (page 14, line 2 to 3) and thank you very much for your reminds! Actually not all the pathology of the patients showed granuloma (case 6llk is not). We modified the expression (page 14, line 2 to 3) and thank you again!

7. Suggest add the following literature:


Thank you for your suggestion! Actually reference 8 is the literature. Thank you!
nan zhou (Reviewer 2): Thank you very much for submitting your article to our journal. After carefully reviewing the letter, we think The paper is attractive it reported the refractory type of tuberculoma indicating surgical intervention. But the manuscript need some revision before accepted. The detailed comments are as follows:

1. In the article need mentioned more details about the outcome of patients after surgery not only KPS.

Thank you for your question! Because all these patients were in a poor economically condition. It was very difficult to do more examination or even ask them back to hospital although they are very gratitude to us. Most of the follow up was done by telephone or sometimes they will send us their recent photos. The information we obtained was about their daily activity. That’s why we used KPS to evaluate the status of the patients. We hope you will be so kind to agree to us. Sorry and thanks!

2. The paragraph of conclusion need some revise to fit the title.

Thank you so much for your suggestion! We modified the paragraph of the conclusion and hope it will fit the title. If there is any problem please tell us (page 18 to19). Thanks!

Mohammad Wasay (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Intracisternal tuberculoma

Interesting case series. Many questions need answers:

How paradoxical reaction is defined?
Thank you for your question! In 1974, Thrush and Barwick, for the first time, documented paradoxical reaction in a patient with central nervous system TB, who had multiple tuberculomas and developed a new tuberculoma during treatment with anti-tuberculosis drugs (Thrush DC, Barwick DD. Three patients with intracranial tuberculomas with unusual features. J Neurol Neurosurg Psychiatry 1974;37:566–9).

A paradoxical reaction is defined as the worsening of pre-existing tuberculous lesions or the appearance of new tuberculous lesions in patients whose clinical symptoms initially improved with antituberculosis treatment (Afghani B, Lieberman JM. Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. Clin Infect Dis; Nicolls DJ, King M, Holland D, Bala J, del Rio C. Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis. Lancet Infect Dis)

We elaborated the definition of paradoxical reaction as above information at page 6, line 2 to 5.

Thank you!

Patients with HIV?

Thank you for your question. All the patients in this study without HIV as pre-operative examination of HIV was negative. Thanks!

Diagnosis was confirmed by histopathology/ microbiology in all patients?

Diagnosis was co-confirmed by specialist of the infectious hospital, histopathology of Guangzhou First People’s Hospital (7 cases) or Changzheng Hospital (4 cases) in all patients.

Indications for surgery? How long treated with ATT before surgical intervention

Thank you for your question! All the surgery of the patients were decided by the neurosurgeons of the two hospitals. All the patients showed severe neurological deficits including hemiplegia, cranial hypertension, paraplegia et al.. Actually, all the patients were transferred from other specialized infectious disease hospitals and medication was ineffective to rescue the neurological function.
As we listed in Table 1, the pre-operative ATT was 1 week to 12 months. Two patients with spinal tuberculoma underwent surgery 1 week after ATT as paraplegia fastly progressed. Both patients were not considered paradoxical response. The other patients were treated with ATT for 2 to 12 months and diagnosed as paradoxical reaction as the paradoxical reaction mainly occurred within 6 weeks (Coulter JB, et al. Tuberculous meningitis: protracted course and clinical response to interferongamma. Lancet Infect Dis; Unal A, Sutlas PN. Clinical and radiological features of symptomatic central nervous system tuberculomas. Eur J Neurol.).

Cisternal tuberculomas are refractory to ATT? need Reference

Thank you very much for your question! According to literatures, the subarachnoid space is a pathological and anatomical region where mycobacteria and their products frequently exist (Garg RK, Malhotra HS, Kumar N: Paradoxical reaction in HIV negative tuberculous meningitis. Journal of the neurological sciences). Actually, the exudates of TM and the arachnoiditis usually accumulate at the subarachnoid space. This kind of exudates in the cistern was considered one form of the paradoxical response which was an important pathological mechanism of tuberculoma (Schoeman JF, Donald PR: Tuberculous meningitis. Handbook of clinical neurology.). Based on these information, the intracisternal tuberculoma is usually a results of paradoxical reaction. Sinha et al. reported 8 patients with TBM mainly locating at the optochiasmatic cistern all developed paradoxical optochiasmatic tuberculoma (Sinha MK, et al., Paradoxical vision loss associated with optochiasmatic tuberculoma in tuberculous meningitis: a report of 8 patients. The Journal of infection). The immunological reaction based paradoxical reaction results in the progression of the lesion which calls for additional corticosteroids but no needs of change of ATT regimen (Dheda K, Barry CE, 3rd, Maartens G: Tuberculosis. Lancet.). Thus, prolonged therapeutic time is inevitable. This is why the intracisternal tuberculoma is refractory. Especially when rescuing neurological function is urgent.

MRS (spectroscopy) was done?

Thank you very much for you question! No MRS was done in this group of patients. This is because the diagnosis of tuberculosis was established by infectious hospital and Guangzhou First People’s Hospital or Changzheng Hospital. If the diagnosis is not definite, MRS is necessary. Thanks!

Discussion needs focus. How these results differ from previous information. Are these findings novel or confirmatory.
Thank you for your suggestion! We revised the discussion part adjusting the order of the 3 parts. The original third part “Intracisternal tuberculoma is refractory to ATT and an indication for surgical intervention.” and second part “Tuberculoma is frequently developed in subarachnoid space” was exchanged. And expression was modified. We think it is more proper to express our opinion.

Previous literatures mainly described the rarity of central nervous system and clinical situation including diagnosis, medications and outcomes of surgeries. The locations, possible pathogenesis and the relation between them were not mentioned in those reported cases. We found the cases in this study were closely related to the cistern or subarachnoid space. ATT was ineffective for fast elimination of the lesions while surgery was a cornerstone. This is the first time connect the site of the tuberculoma (intracisternal) and the choice of treatment. We hope it will be helpful for other doctor while encounter such a situation.

Thank you sincerely!