

Dear Editor and Reviewers:

We are truly grateful to your critical comments and thoughtful suggestions on our manuscript entitled 'Concurrent tuberculous transverse myelitis and asymptomatic neurosyphilis: a case report' (Manuscript NO.: 68373, Case Report). Based on these comments and suggestions, we have made appropriate modifications on the original manuscript, which we hope meet with approval.

Revised portion are marked in color in the paper, the main correction in the manuscript and the responses to the reviewers' comments are as following:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. Please be consistent in writing some terms. Which term is correct with this patient's diagnosis? neurosyphilis or syphilitic myelitis? because neurosyphilis is a clinical spectrum that can manifest as other symptoms like meningitis, stroke, etc. (according to your text in introduction section).

Response: Thank you for your correction. We think the diagnosis of asymptomatic neurosyphilis is better and we have made corrections in the manuscript. As the patient didn't have typical symptoms like headache and dementia. Both of the meningeal irritation sign and brain MRI are negative. The spinal MRI manifestation of the current patient is not consistent with typical MRI appearance of syphilitic myelitis, and the clinical symptom still progressed after anti-syphilis therapy.

2. In the case presentation section, please provide a detailed history of TB therapy of the patient to give more information about the previous TB status. Is it re-infection/treatment failure/drop out case? so you can analyze the patient's problem comprehensively.

Response: Thank you for your questions. After confirming with the patient and his wife again, the patient previously TB lesions was found by chest CT 7 years ago, but the patient had no symptoms and no standardized treatment was added. The symptoms may be due to reactivated tuberculosis. When the blood-CSF barrier was destructed after infecting syphilis, tuberculous myelitis appeared. We completed the information about the previous TB in the case presentation section.

3. Please specify this statement "Some of the patient's clinical symptoms gradually improved" in the follow up and outcome section. Which clinical symptoms were gradually improved?

Response: Thank you so much for your correction. Some of the patient's clinical symptoms gradually improved, including the temperature returned to normal, the pain of the lower limbs relieved significantly and the patient's muscle strength recovered (grade 4) after four months of anti-tuberculous treatment. But dysuria, fecal incontinence and numbness of lower limbs were not significantly improved. We supplement the information in the follow up and outcome section.

4. There is no further explanation about the possible immunocompromised state of this patient. Please add this in discussion section.

Response: Thank you so much for your comments. However, it was showed that neurosyphilis can stimulate immune response and delayed-type hypersensitivity participated in the immunopathobiology of syphilis[1]. In the animal model, opsonization, activated macrophages and pathogen-specific immunoglobulin G were proved to be involved in the immune process of infecting *T. pallidum*[2]. Thus, we hypothesized that the patient was in the possible hypersensitivity state after infecting syphilis, leading to generation of chronic inflammation and destruction of the blood-CSF barrier. Thus, the activated mycobacterium tuberculosis is more likely to invade the spinal cord or meninges in patients with neurosyphilis.

5. There are some grammatical errors in the manuscript. Please correct.

Response: Thank you so much for your advise. We have corrected some grammatical errors in the manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

Rarity is no criteria for acceptance of manuscript There is need of English language improvement. Manuscript has too long sentences at many places Title should have ..Tubercular transverse myelitis... Abstract Tunerculous myelitis is not extremely rare, is relatively rare Case summmary is too long What is logic of writing " Anti-syphilis treatment did not relieve the patient's symptoms at first; however, his neurological symptoms improved when anti-tuberculous treatment was added. "in case summary Conclusion is confusing Introduction is too long , need to be concise Case history Need to extract more from " History of past illness ,The patient

previously had TB, but the details were unknown. You had dysuria, any urine exam done Any abdominal usg done ? What was dose given , ceftriaxone 3 g or 2g Any Jarix Hexhemier reaction ? How long was ATT (DOTS) PRESCRIBED ? TOTAL FOLLOW UP You are "Anti-syphilis therapy (ceftriaxone 3 g q.d.) was added, but the patient complained that there was no improvement in his condition. "need to give details in which sense you are trying to convey, which objective symptoms improved What is message to take home

Response: Thank you so much for your detailed comments. We solved all the issues one by one.

1) Rarity is no criteria for acceptance of manuscript There is need of English language improvement. Manuscript has too long sentences at many places Title should have ..Tubercular transverse myelitis... Abstract Tuberculous myelitis is not extremely rare, is relatively rare Case summary is too long. Introduction is too long , need to be concise

We cut down some long sentences and simplified the case summary and introduction. What's more, we revised the title of the article as 'Concurrent tuberculous transverse myelitis and asymptomatic neurosyphilis: a case report' and tuberculous myelitis is relatively rare in the manuscript. Further, we improved the English language of the case.

2) What is logic of writing " Anti-syphilis treatment did not relieve the patient's symptoms at first; however, his neurological symptoms improved when anti-tuberculous treatment was added. "in case summary

At first, neurosyphilis was diagnosed due to the positive results of syphilis serology and CSF and anti-syphilis therapy was added, but the patient's symptoms still progressed, like fever, pain and weakness of lower limbs. What's more, fecal incontinence also appeared. Meanwhile, numbness and pain in both lower limbs, dysuria and fever still exist. After one week, the results of MRI, NGS and CSF successively came out and tuberculous myelitis was considered eventually. Subsequently anti-TB drug therapy was initiated empirically and the patient symptom gradually improved. We Organized the history in the case summary.

3) Conclusion is confusing

We rewrote the summary and clarified our meaning.

4) Case history Need to extract more from " History of past illness ,The patient previously had TB, but the details were unknown.

The patient's previous tuberculosis was asymptomatic and didn't get treatment. We completed the information about the previous TB in the case presentation section.

5) Youi had dysuria, any urine exam done Any abdominal usg done ?

The urine exam like routine urine test and urinary ultrasound were normal.

6) What was dose given , ceftriaxone 3 g or 2g Any Jarix Hexhemier reaction ?

Before coming to our hospital, the patient received two days of anti-syphilis therapy (ceftriaxone 2 g b.i.d and dexamethasone 5 mg b.i.d, combined with long-acting penicillin 2.4 million units, intramuscular injection) and no Jarix Hexhemier reaction was found. Then in our hospital, we gave ceftriaxone 3 g q.d for treatment.

7) How long was ATT (DOTS) PRESCRIBED ?

Quadruple anti-TB drug therapy was initiated at the first 2 months (isoniazid 600 mg, pyrazinamide 20 mg/kg, rifampin 600 mg, and ethambutol 15 mg/kg daily), then duplex anti-TB treatment (isoniazid 300 mg and pyrazinamide 500mg tid) were used from last September till now.

8) TOTAL FOLLOW UP

We totally followed up for about 1 year. Some of the patient's clinical symptoms gradually improved, including the temperature returned to normal, the pain of the lower limbs relieved significantly and the muscle strength recovered (grade 4) after four months of anti-tuberculous treatment. But dysuria, fecal incontinence and numbness of lower limbs were not significantly improved. Meanwhile, the CSF results at that time (October 30, 2020) were better than before: CSF pressure, 160 mmH₂O; protein, 72.1 mg/dL; glucose, 2.41 mmol/L; leukocyte count, 6 cells/mm³; TPPA+ and TRUST-. During the 1-year follow-up, the patient still had dysuria, fecal incontinence and numbness below the waist. And the latest results of cerebrospinal fluid (March 26, 2021) were indicated that: CSF protein, 59.8 mg/dL; glucose, 2.04 mmol/L; leukocyte count, 4.0 /uL, suggesting the disease still fluctuates and not completely cured.

9) You are "Anti-syphilis therapy (ceftriaxone 3 g q.d.) was added, but the patient complained that there was no improvement in his condition. "need to give details in which sense you are trying to convey, which objective symptoms improved What is message to take home

Anti-syphilis therapy (ceftriaxone 3 g q.d.) was added at first because the patient was initially diagnosed as syphilitic myelitis, but the patient complained the progression of symptoms as fecal incontinence appearing. Meanwhile numbness and pain in both lower limbs still exist , dysuria and fever did not improve as well. We detailed the information in the treatment section.

REFERENCES

1. Carlson, J., G. Dabiri, B. Cribier, and S. Sell, The immunopathobiology of syphilis: the manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. *The American Journal of dermatopathology* 2011; 33, 433-60 [PMID:21694502 DOI:10.1097/DAD.0b013e3181e8b587].
2. Gonzalez, H., I. Koralnik, and C. Marra, Neurosyphilis. *Seminars in neurology* 2019; 39, 448-455 [PMID:31533185 DOI:10.1055/s-0039-1688942].