Author's response to reviews

Title: Tuberculous Meningoencephalitis associated with Brain Tuberculomas during Pregnancy: Case report

Authors:

Sadije Namani (sadie_namani@yahoo.com)
Shemsedin Dreshaj (shemsedindreshaj@msm.com)
Arieta Berisha (arietazogaj@gmail.com)

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Response Reviewers

The title of article is changed from Intracerebral Tuberculomas during Pregnancy: Case report

To:

Tuberculous Meningoencephalitis associated with Brain Tuberculomas during Pregnancy: Case report

Reviewer reports:

Reviewer #1: This case report is of great interest for the clinicians dedicated to the care of patients with tuberculosis and specially to those focused on epidemiology of such disease. This is a good manuscript, however, I think it needs a review of the way in which it is written. For instance, the background in the abstract is not very informative about the epidemiology of tuberculous meningitis globally and the current state of the presentation of CNS tuberculosis in the context of gestation.

Answer: we have changed the background according to your recommendations and the aim of the study.

Instead of, the authors are stating that even when the incidence of this disease is declining over time, they could found a case in a pregnant woman thanks to the availability of MRI, so, if they did not have such technology they would not be able to diagnose tuberculosis?
Answer: Only last few years the MRI is available at our hospital center, so this patient was sent to a private clinic for brain MRI and this is the reason for the delay of doing it. With brain MRI we diagnosed for the first time a pregnant woman with brain tuberculomas.

In the case presentation of the abstract I suggest to describe the last part of it as follows:

Instead of: Brain magnetic resonance imaging showed multiple intracerebral tuberculomas, chest radiography normal finding, while Koch's bacillus was isolated only from urine cultures. On long-term follow up, she was cured with no sequelae and got two girls after two years of treatment.

Write it as: "Although findings on chest radiography were normal brain magnetic resonance imaging showed multiple intracerebral tuberculomas and Koch’s bacillus was isolated from urine cultures. On long-term follow up after delivery, she was cured with no sequelae and become pregnant again without any additional complication."

Answer: It is re written.

I suggest to use more specific key words, i.e.: tuberculous meningitis, pregnancy.

Answer: Key words: tuberculous meningitis, pregnancy, intracerebral tuberculomas, tuberculosis

L8: I suggest to add that some of the clinical signs of SNC tuberculosis are subacute and some of them might be confused with presentation of other diseases related with pregnancy such as pre-eclampsia, hyperemesis, brain tumors and even epilepsy during gestation. Also, authors should include a short introduction to the case.

Answer: The clinical signs of CNS tuberculosis are subacute and some of them might be confused with presentation of other diseases related with pregnancy such as pre-eclampsia, hyperemesis, brain tumors and even epilepsy during gestation.

L21: "unemployed" corrected

L5-8 of the 5th page: "The differential diagnosis….. is low", do not mention it, just simply describe the case, Corrected
which revealed no pathological findings, ultrasound of abdomen was normal, …Corrected

she got pregnant again by IVF… Corrected

last few years occurred around 900 cases annually… Corrected

I do not have comments regarding the discussion.

Conclusions are poor written and do not reflect the importance of the case findings to the management of pregnant women with neurological signs. Corrected

Images of brain MRI in figure 1 are of poor quality.

We added new brain MRI images

Although there is no an enhancement of the meninges at the base of the brain, it is clear that in addition to the parenchymal tuberculoma there is also certain degree of brain edema, augmented subarachnoid space and ischemia at left parietal lobe suggesting meningoencephalitis compared with brain MRI in figure 2. So, be careful with the form in which you are describing and classifying the patient, since along all the manuscript you are assuming tuberculoma and meningitis as the same clinical entity. I think that you should describe the case as a patient with tuberculoma accompanied with acute meningoencephalitis, or simply as a case of central nervous system tuberculosis. Therefore, even title of the case report must be reconsidered. We presented a case of Tuberculous Meningoencephalitis with Brain Tuberculomas

Table 1 is not mandatory to appear in the manuscript. Table 1 is removed

Reviewer #2: An extremely interesting and rare case of manifestation of CNS tuberculosis during pregnancy is here presented. However, regarding the content of the manuscript, the authors forgot in their introduction to cite the relevant literature, which would reveal the unique clinical aspects of the presented case. Reasoning explaining the necessity for the performed diagnostic procedures is sometimes missing. Corrected

For example it remains unclear why a brain - MRI was performed three weeks after starting an antimycobacterial therapy, when the patient presented with vaginal bleeding.

The brain MRI was done at the private clinic, while only last few years that the MRI is available at our hospital center.
Further, the authors conclude with recommending 'early screening for CNS tuberculosis during pregnancy', in countries with high prevalence of tuberculosis', but they do not discuss, or even mention the diagnostic modalities, which would be required for such a screening.

We added the diagnostic modalities for TB meningitis but for brain tuberculomas the neuroimaging is needed.

In my opinion, this case should underscore the necessity of prompt starting of an empirical antimicrobial therapy in such a case of meningitis (patient with meningitis, fitting CSF findings, fitting medical history, origin from a region of high prevalence of tuberculosis) which is crucial for patient outcome.

In conclusion is added: The necessity of prompt starting of an empirical anti-tuberculous therapy in such a case of meningoencephalitis (fitting clinical presentation, fitting CSF findings, fitting medical history, origin from a region of high prevalence of tuberculosis) is crucial for patient outcome.

Finally, the quality of English language is unsatisfactory.

The manuscript underwent native speaking evaluation.

Reviewer #3: General:

The authors state that meningitis in pregnancy might be caused by M. tuberculosis especially in high prevalence countries.

The course of the case is presented clearly but the chronological order seems to be inconclusive. when was brain MRI done? Please provide days after admission / diagnosis for more clarity.

Brain MRI was done 4 weeks after admission (one week after cesarean section) since she had to be sent to a private clinic to do it.

Information on the source of the disease and information on the reason for preterm delivery and the fatal outcome of the newborn twins is missing.

Answer: The preterm underweighted twins died: female baby 700 grams with Apgar scor 2 died within 24 and male baby 800 grams with Apgar score 4 who was transferred outside of country died within 72 hours. The female baby was sent to pathology Institute and I got informed that it
was not requested to do the autopsy. The male baby was sent outside of country (to Serbia) and the parents did not get the results of autopsy.

Please provide peripheral blood IGRA result, please provide TST result. Please provide more clinical information on the twins born in the 27th week of pregnancy.

It is written in the manuscript.

It is quite unusual to die within 72 hours having that gestational age. Signs of connatal tuberculosis? Was a histopathologic examination of the placenta(s) performed?

Apgar scores of twins were very low based on discharge paper and histopathological examination of placenta is not performed. Also gynecologists did not request the autopsy of female baby although they knew that the mother had tuberculous meningoencephalitis.

Is there information about a tuberculosis contact? Is / was a histopathology of the Fallopian tube available? No it was not done.

In our country the answer is always the same: no family member has tuberculosis, since they consider this disease ebbarysing. They did not show us previous resports of gynecologist as she was treated for salpingitis.

Is the conclusion to perform early MRI in altered mental state during pregnancy or are you advocating for early CSF QFT? Do you have modified recommendations for high and low prevalence countries?

Last few years we can perform both MRI and Xpert MTB/RIF at our hospital center while IGRA and QFT can be done in private clinics.

In the past, the diagnose of TB meningitis was made without availability of MRI, Xpert MTB/RIF, IGRA or QFT. Even for brain computed tomography scans we had to send our patients to other clinical centers outside of our town.

Please consider english proof-reading for better reading experience.

Answer: The manuscript was corrected by native language speaker.
page 2, line 26: prefer the term 'twin pregnancy' instead of 'gemelar' Corrected

page 2, line 33: elevated level instead of high level, please provide CSF fluid biochemical data, Corrected

page 3, line 6: initial treatment instead of early treatment Corrected

page 3, line 30: hematogenous instead of hematogenous, Corrected

page 3, line 50: reflects instead of is a reflection Corrected

page 3, line 53: like instead of similar to, Corrected

page 4, line 43: sub febrile instead of subfebrile Corrected

page 5, line 23: herpes simplex instead of herpes simples Corrected

page 5, line 49: mannitol instead of mannitol Corrected

page 6, line 18-23: check language 'which revealed without' Corrected

page 6, line 23: hyperintense instead of hiperintens, Corrected

page 6, line 31: mesencephalon instead of mesencephalon Corrected

page 10, line 23: tuberculomas instead of tubercolomas Corrected

page 10, line 50: minor risk instead of little risk Corrected


page 13, line 9: consider international abbreviation for Quantiferon test (QFT), Corrected

page 13, line 25: consider international abbreviation for toxoplasmosis (TOXO), Corrected

page 14, line 11: please provide approval id number, Added