Author’s response to reviews

Title: Intracranial actinomycosis of odontogenic origin masquerading as auto-immune orbital myositis: a fatal case and review of the literature

Authors:

Gijsbert Hötte (g.hotte@oogziekenhuis.nl)
Maarten Koudstaal (maarten.koudstaal@sll.se)
Robert Verdijk (r.verdijk@erasmusmc.nl)
Maarten Titulaer (m.titulaer@erasmusmc.nl)
Franka Claes (j.claes@franciscus.nl)
Elske Strabbing (e.strabbing@erasmusmc.nl)
Aad Van der Lugt (a.vanderlugt@erasmusmc.nl)
Dion Paridaens (d.Paridaens@oogziekenhuis.nl)

Version: 1 Date: 28 Jul 2019

Author’s response to reviews:

L.S.

Thank you for your meticulous comments and suggestions on the manuscript “Intracranial actinomycosis of odontogenic origin masquerading as auto-immune orbital myositis: a fatal case and review of the literature”. I have made an effort to address the points raised by the team of reviewers and provide a point-by-point description of the changes made to the manuscript. Please find this description attached below.

Please be advised that the lines indicated by the reviewers may not be accurate anymore, because of the changes made to the text.

Yours sincerely,

Gijsbert J. Hötte
Reviewer 1:

General comments:
- This manuscript presents an interesting case where things went really bad. Actinomyces is likely but not definitely the cause. The time sequence is not very clear. The authors might add a schema presenting the timeline of the events as this case is indeed of educative merit. I also feel like congratulating the authors for publishing this case rather than simply using it for internal audit. The discussion is overly lengthy. My suggestion is to truncate. Further, there are three important issues to be discussed:
  ***The timeline has been changed from a table format to a more visual format, providing a better overview of the presentation, diagnostic assessment, presumed diagnosis and therapeutic interventions during the clinical course. Please see the additional material provided with this manuscript.
  - Overall I believe this case merits attention, to inform readership so as to reduce any future similar incidents. But the timeline needs to be very clear, especially with regard to steroid use and antimicrobial agents prescribed. What is more the three issues above need very emphatically be discussed as they convey educational value. Then the discussion of similar published cases adds nothing, so it should be better be truncated.
  ***See above, the timeline has been altered. Some of the published cases have been removed from the discussion (lines 170-172, 191-194, 200-203, 205-206, 212-213, 231-233).

Detailed comments:
1. Steroid administration: How often, how much time? Mention that in the timeline proposed please.
  ***We have mentioned the doses used for the steroids in the text (lines 83, 95, 104, 112). We feel that it would make the timeline less clear if too many details are mentioned.
2. The PDS sheet used. PDS is resorbable but in an infectious enviroment, it could well serve as a foreign body that aggravated the infectious inflammation.
  ***This is certainly an interesting question and have adopted it into our discussion section (lines 237-239).
3. The radiological findings which have not been noted on time; rather they were only noticed after the coroner report.
  ***The importance of the radiological findings has been discussed in the case report section and in the discussion.

(Reviewer 2):

General comments:
- As I understood the manuscript, the microbiological diagnosis is based on the histopathological findings typical for actinomycosis only, or have I understood this wrong? The authors write on several occasions that 16S rRNA PCR was positive but it is not defined what they mean by this. Positive for a certain Actinomyces species? If it is not yet done, the manuscript would benefit of microbiological verification of actinomycosis diagnosis, for example, by having 16S rRNA sequencing done from the formalin embedded autopsy sample with typical histopathological findings. The Discussion could be condensed a bit.
The 16 rRNA PCR that was used in the initial diagnostic process was a broad range PCR that confirms presence of bacteria but does not further determine. After the histopathological findings of actinomycosis, 16s rRNA PCR for further determination was not possible as these samples were formalin fixated paraffin embedded. We have further clarified this in the manuscript (lines 146-147, 248-249, 251-254)

Detailed comments:
1. Lines 58-59. It is mostly only the periodontal infections that drain through the gingival area. Periapical dental pathoses usually develop because of the root canal infection. In these cases, chronic forms are rather asymptomatic, still usually bone resorption can be seen around the apex of the tooth. Acute periapical infections on the other hand cause abscess formation and infection can spread to medullary bone and perforate the cortical bone and thereafter spread into submucous or subcutaneous tissues and possibly drain through these, but typically not via gingival area. So please correct the first sentence as most odontogenic abscesses do not resolve by spontaneous drainage through the gingival tissues. The authors could simply state that most odontologic infections are self-limiting and localized (as opposed to the rare cases of dissemination).

2. Line 63 and line 145. Please update the bacterial classification.

3. Throughout the manuscript: The first letter of antibiotics should not be capitalized.

4. Line 86. Please specify: Borrelia type tested. Borrelia burgdorferi? Instead of writing lues, I suggest writing which antibodies were tested for Treponema pallidum.

5. Line 111. Cerebro?

6. Line 112. Which species of staphylococci? Coagulase negative? I assume not Staph. aureus. Please specify. Was the finding considered to be a contamination?

7. Line 118. What was the CSF finding suggestive of tuberculous meningitis? Was this based only on inflammatory findings in the CSF or was for example TB PCR or serology done from CSF?

8. Lines 124-125. Was PCR for Mycobacterium tuberculosis done from both the CSF and sputum?

9. Lines 125-126. What was the sample type for bacterial, mycobacterial and fungal cultures?

10. Although IgG was positive for Toxoplasmosis, IgM was not. These findings were interpreted as an earlier exposure but no current infection (lines 135-137). Lymphoma was ruled out by the absence of
monoclonal B-cell or abnormal T-cell populations in the CSF (137-18).

13. Line 130-131. Was no sequencing done? From which sample type the 16S rRNA was positive?
***The 16S rRNA was positive for the CSF sample (line 142). Further sequencing was uninterpretable (line 142).

14. Line 134. Why was there no 16S rRNA PCR and sequencing done from the sample with typical findings?
***The paraffin embedded samples allowed no further genetic determination by sequencing (lines 146-147).

15. Line 148. Not all Actinomyces species are strict anaerobes. Some of them are microaerophilic. Please add this.
***This is a valid point and have added it to the text (161).

16. Line 156. Nerve > nervous
***To better truncate the discussion, this paragraph has been deleted (lines 170-172).

17. Line 208. Please clarify BSE and add to the list of abbreviations. Could not find it.
***This has been a mistake, we meant ESR. “BSE” has been replaced by “ESR” (line 224).

18. Line 230. Please clarify what does it mean that 16S rRNA PCR was positive? Sample type? See also above.
***Please see the discussion above. The tests have been further clarified in the text (lines 248-249 and 251-254).

19. Line 253. Tetracyclines should rather be mentioned as a reasonable alternative because there is less resistance for it. See also reference number 27.
***This is a valid point. “Tetracyclines” has been added (line 274).

20. Because there were a great many tests done, a table summing up the tests done would be useful for the reader. Some of my above suggestions for changes could be clarified in the table as well and then there would not be need for opening e.g. different serological tests in the text itself. Indeed many tests have been done.
***The timeline has been altered, providing a better overview of the diagnostic assessment. To keep the timeline clear, we do feel however, that a more detailed description is better suited in the main text.

21. Figure text 4. Add sample type/ location where was taken.
***“Autopsy” has been replaced by “Autopsy samples from the brain” (line 436).

22. Figure text 5. Please add appropriate letters indicating each finding and figure as you have done through a-c. Currently it is a bit unclear.
***In our opinion, the letters do refer to the correct findings in the corresponding figures. For now, no changes have been made to the text.