Author’s response to reviews

Title: A case of pleural effusion caused by Mycobacterium fortuitum and Mycobacterium mageritense coinfection

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David Kateete MSc, Ph.D

Editor-in-chief

BMC Infectious Diseases

Dear Editor

Thank you for inviting us to submit a revised draft of our manuscript entitled, “A case of pleural effusion caused by Mycobacterium fortuitum and Mycobacterium mageritense coinfection” to BMC Infectious Diseases. We also appreciate the time and effort you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

To facilitate your review of our revisions, the following is a point-by-point response to the questions and comments delivered in your letter dated 1 July 2019.
Reference to the Reviewer 1’s comments:

Comment: The authors report a rare combination of two nontuberculous mycobacteriosis produced by the rapidly growing mycobacteria, M. fortuitum and M. mageritense in pleural effusions (extrapulmonary) and BAL (pulmonary). The patient is affected by several risk factors, including advanced age, an autoimmune disease (rheumatoid arthritis) or immunosuppression therapy.

Response: Dr. Rivero-Lezcano, we really appreciate for your comments and suggestion about our paper. You will find our responses to your suggestive comments. We are grateful for the time and energy you expended on our behalf.

Major points

Comment: 1. How many times were the microorganisms isolated from BAL or pleural effusions? Just once? May the authors rule out the possibility of cross-contamination?

Response: Thank you for the important question. We obtained the positive culture from BAL and pleural effusions just once. But we consider the possibility of cross-contamination to be extremely low because these samples were obtained in different room at one week apart.

Comment: 2. Did the authors obtained negative cultures from BAL and pleural effusions after treatment?

Response: Thank you for the question about her treatment. We could not obtain the negative cultures from BAL and pleural effusions, because the patient refused the bronchoscopy and the pleural effusions are diminished after the treatment. As an alternative, now we check her negative cultures from sputum and chest X ray repeatedly.

Comment: 3. Mycobacteriosis require prolonged treatments with drugs that may have adverse effects. Did the patient suffer any of these effects? How was the tolerance of the drug regime?

Response: Thank you for the question about her maintenance therapy. Fortunately, the patient did not suffer any of side effects.
Minor points:

Comment: 1. In keywords and throughout the text, Non-tuberculosis mycobacteria is Nontuberculous mycobacteria.
Response: Thank you for your advice. We corrected the manuscript (at the keywords section).

Comment: 2. Name of species always in italics (see keywords).
Response: Thank you for your advice. We corrected the manuscript (at the keywords section).

Comment: 3. In the abstract, it should be added in the Discussion paragraph that there are no previous reports of coinfection with nontuberculous mycobacteria in pleural effusions.
Response: Thank you for your kindness suggestion. We added the paragraph to the manuscript (at the discussion section, Line 9-10).

Response: Thank you for your kindness advice. We modified the paragraph in the manuscript (at the Background section, Line 3).

Comment: 5. Do the authors have a hypothesis to explain the low proportion of lymphocytes in leukocytes (22.7%).
Response: Thank you for the important indication about the clinical laboratory data. Unfortunately, we do not have any hypothesis about this laboratory data. We consider the complication of bacterial pneumonia, but the causative agent of pneumonia has not been proven.

Comment: 6. Some fragments in the discussion has already been described in the results section. Consider avoiding repetitions.
Response: Thank you for your kindness advice. We corrected the manuscript and deleted the repetition point.
Again, we appreciate all of your insightful comments. We worked hard to be responsive to them. Thank you for taking the time and energy to help us improve the paper.

Reference to the Reviewer 2’s comments:

Comment: Hirabayashi and coauthors from the respected Kobe City Medical Center have written a case report on the successful management of a parapneumonic effusion from Mycobacterium fortuitum and Mycobacterium mageritense. The case will interest readers particularly NTM clinicians and microbiologists and it is important that these cases be published in order for NTM management experiences to be shared. The microbiological methods employed are sound and the manuscript is concise. It would benefit from a little English language editing, but is generally well-written. The chosen radiological images are good. There are however some major and minor issues that need to be addressed.

Response: Dr. Qvist, we are very grateful to your comments and suggestions. We found them quite useful as we approached our revision.

Major comments:

Comment: 1. It is important to report if the patient was resampled from any sites, whether she became sputum or BAL negative (or was simply unable to produce). And how fast did her infection resolve. In the image texts it is simply written "after the treatment" - this should be specified - how many weeks into treatment? The length and content of the maintenance therapy is very important, and what was the status at the time of manuscript writing. Was she still on treatment? Is she considered cured? She clearly fulfilled the ATS/IDSA criteria for NTM pulmonary disease when she presented and this should be mentioned. But did she also fulfill the criteria for being cured or is she still in treatment and is it in fact too early to say (which is okay - the timeline should just be clear).

Response: Thank you for your suggestive comments about the patient’s treatment. We treated the patient for 6 months, by 8 weeks of Imipenem/Cilastatin, Minocycline and Levofloxacin followed by 4 months therapy using Minocycline and Levofloxacin. After the initial 2 months therapy, her pleural effusion diminished, and her sputum culture was negative. We could not retry the bronchoscopy because she refused the re-examination. Now we follow her for 2 years by antibiotics free, but her sputum culture is still negative and chest x-ray is clear. We expect she is cured, but it is too early to say because she continues the immunosuppression therapy. We added this point to the manuscript (at the Case section, Line 33, the last paragraph).
Comment: We would like to know the rationale behind the chosen therapy (which seems like reasonable choices and doses). But was it local guidelines or a multidisciplinary team decision based on clinical experience.

Response: thank you for your point about her therapy. Our therapy was on a multidisciplinary team decision. We referred the ATS guideline (Am J Respir Crit Care Med Vol 175. pp 367–416, 2007) and the letter about M. mageritense (Emerging Infectious Diseases Vol. 17, pp 556-558, 2011)

Comment: I'm not sure the concluding remark about "If the species cannot be identified, mycobacterial coinfection should be considered" is validated or backed up in guidelines.

Response: Thank you for the comment about our concluding remark. As you pointed out, there are no validation or back up in guidelines. In this sentence, we intended to suggest that "If the species cannot be identified, the possibility of mycobacterial coinfection should be considered" and we changed the sentence.

Comments: In general the case needs to be placed better within the context of the existing literature. ATS/IDSA guidelines are correctly mentioned, but they predate some methods and I think the manuscript would benefit from referring to the new British Thoracic Society NTM guidelines by Haworth and Floto published in Thorax. It's section 8 contains evidence graded statements on diagnostics including MALDI-TOF (that are generally positive).

Response: Thank you for your significant suggestion to our manuscript. We referred the guideline and cited to the manuscript (Discussion section, Line 14).

Minor comments:

Comment: Abstract Line 19: Grammar - remove the word "who" after "pegol".

Response: Thank you for the advice. We corrected the grammar.
Comment: Abstract line 42: "There are no previous report about the coinfection with two different mycobacterial species."

This sentence is not precise and contextually confusing. Pulmonary coninfection with NTM has been observed, for example in cystic fibrosis, although not that commonly. This point is correctly made later in the manuscript, but this sentence is too reductive. I agree that pleural effusion/infection with two rapid-growers is unreported. So the sentence should be reformulated with the words pleural effusion and "mycobacterial" should be changed to "non-tuberculous mycobacterial".

Response: Thank you for the important advice about the discussion. We corrected the word.

Comment: Concerning keywords: remember non-tuberculous is often spelled nontuberculous, "NTM" is relevant keyword too

Response: Thank you for the comment about the key word. We corrected the sentence.

Comment: Background page 4 line 15: "As a group of NTM, rapid-growing mycobacteria (RGM) contain Mycobacterium abscessus, M. chelonae, and M. fortuitum group species which include M. mageritense.

This sentence structure is too convoluted and uses passive voice - should be reworded.

Response: Thank you for the comment. We changed the sentence.

Comment: Background page 4 line 18: Mycobacterium abscessus is a complex of 3 subspecies. Should be written as "Mycobacterium abscessus complex"

Response: Thank you for the suggestion. However, we modified the sentence because of the suggestion from the other reviewer and the term M. abscessus complex is deleted.

Comment: Case report page 4 line 56: 9 years ago should be changed to "9 years prior" or "earlier"

Response: Thank you for the comment. We changed the word.
Comment: Page 5 line 18: A sentence on occupational exposure could be included after smoking.
Response: thank you for the suggestion. This patient worked as a pharmacist and we added the occupational history on the manuscript.

Comment: Page 5 line 40: Was the thoracentesis performed as a diagnostic or therapeutic procedure (or both?) Was the 150 ml the entire effusion? Later on in the discussion, the importance of thoracentesis should probably be repeated - how important was this procedure therapeutically? Was it pus or clear fluid?
Response: thank you for the question about the thoracentesis. The thoracentesis performed only as a diagnostic procedure. The 150ml was not the entire effusion, it was the amount of sample submitted for laboratory and microbiological testing. The pleural effusion was clear fluid, so we decided it is not pus and did not drainage whole fluid.

Comment: Page 5 line 50: Was a pH value obtained? The fluid cells counts are mentioned, but we lack some interpretation of the finding. In the discussion, the issue of (parapneumonic) effusion vs. empyema could be mentioned.
Response: 

Comment: Page 5 line 56: Sentence structure problem. Should probably say: "Acid-fast bacilli were detected by Ziehl-Neelsen staining, but the species could not be identified by DNA-DNA hybridization or MALDI-TOF." Then the bit about drug susceptibility.
Response: Thank you for the suggestive comment about the sentence. We modified the sentence, and you will find the modified sentence at Page 6 line 1 to 5.

Comment: Remember MALDI-TOF cannot suggest or determine drug susceptibility - that part of the sentence should be changed. MALDI-TOF under the score cut-off might point in the direction of rapid growing mycobacteria", but really no susceptibility conclusions should be drawn from this.
Response: thank you for the important point about the microbiological testing. We changed the sentence, which is the same to the previous comment (at Page 6 line 1 to 5).
Comment: Page 6 line 40: Was an initial loading dose of minocycline used?

Response: thank you for the question about treatment. We did not use an loading dose of minocycline.

Comment: Page 6 line 43: How long was maintenance therapy and with which compounds? How fast did it take for her fever / cough to resolve?

Response: thank you for the important suggestion. We were mentioned about the maintenance therapy at your major comment, and we modified the manuscript. All of her symptoms resolved within 2 weeks of starting treatment.

Comment: Page 7 line 1: "There are several reports of pulmonary infection or pleural effusion caused by NTM and MTC coinfection or M. avium and M. intracellulare coinfection."

This sentence is confusing for a number of reasons. It’s the first time tuberculosis is mentioned, so the abbreviation should be written out, the use of "or" (twice) is not easy to understand. Remember also that M. avium is a complex (MAC) of which intracellulare is a part - so the phylogeny should be clear here.

Response: Thank you for the beneficial suggestion about the phylogeny on our discussion. We modified the sentence here, Page 7 line 1 to 4.

Comment: Page 7 line 11: Yes, the mentioned contamination problem is relevant, although I wonder if the authors are thinking more about a airway "colonization" problem. If the patient's airways is infected with one NTM and simultaneously colonized by another, than the sputum culture might show both and not discriminate between the meaningful infection and the transient colonization. In this case report, certainly we are more likely to think that both rapid growers are significant. So I agree on that point, but I think the word "contamination" should be replaced with "colonization".

If the authors are in fact thinking about nosocomial or lab contamination, remember that even aseptic aspiration is subject to environmental exposure later in the lab as some procedures take place in the open and in vials that might have been exposed to tap water. The most common lab contaminant is a species such as M. gordonae, but others are also seen.

Response: thank you for the suggestion, this is very important for our case report. As you pointed out, we thought “the contamination of some bacteria in the respiratory tract”, which completely mean the word “colonization”. We changed the word.
Comment: Page 7 line 21: I would leave out the words "in a rare occurrence" as the point has been made quite a few times

Response: Thank you for the suggestion. We modified the sentence and leave out these words.

Comment: Page 7 line 34: Grammar: "MALDI-TOF MS is one of the developing methods for identifying the mycobacteria" I would rephrase "developing methods", use NTM instead of mycobacteria and remove "the" before NTM. I would refer to the BTS guidelines here also and mentioned the context.

Response: Thank you for the suggestion about the molecular diagnosis. As you pointed out, MALDI-TOF is one of the establishing method for identifying NTM. We modified the sentence and cited the BTS guideline.

At last, we authors really appreciate all of your meaningful comments. We worked hard to be responsive to them. Thank you for taking the time and energy to help us improve the paper.

Reference to the Reviewer 3’s comments:

Dr. Venketaraman, your comments and suggestions always helped us approach to our revision more meaningful. We appreciate you to spend your time and effort for our report.

Comment: Sentence 28: Myobacteria should be corrected to mycobacteria

Response: thank you for your suggestion. It is basic spelling mistake and we modified the word immediately.

Comment: Sentence 56: Acronym should be provided for RGM

Response: thank you for your suggestion. It is also a basic mistake and we modified the sentence.

Comment: Did the patient have type 2 diabetes?

Response: Thank you for the question about the patient. she don’t have type 2 diabetes.
Again, we thank to your suggestion. Thank you for taking the time and energy to help us improve the paper.

Sincerely,

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