Author’s response to reviews

Title: Natural history of Mycobacterium fortuitum pulmonary infection presenting with migratory infiltrates: A case report with microbiological analysis

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Response to reviewer’s comments

INFD-D-17-00627 ‘Natural history of Mycobacterium fortuitum pulmonary infection presenting with migratory infiltrates: A case report with microbiological analysis’

13 November 2017

Christopher Vinnard
Dear Dr. Vinnard,

I, along with my coauthors, thank you for the recent review of our manuscript and would herewith like to re-submit it, with revisions based on the reviewers’ comments, which we found to be very helpful in improving the manuscript.

Responses to the reviewers’ comments have been prepared, on a point-by-point basis, with explanations of how we addressed the suggestions or critique. We hope that the revised manuscript is now suitable for publication in your journal.

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Replies to the reviewers’ comments

Dr. Taskar (Reviewer 1):

We thank Reviewer 1 for the insightful and valuable comments that helped us improve our manuscript. Our responses to the specific points raised by Reviewer 1 are provided here.

1. Please consider revising the clinical history of the patient (tabulation/figure) to describe each episode of the infection in more detail including duration of therapy and drugs. This may help the reader understand why the patient remained relapse free after treatment for the last episode (I suspect longer duration of therapy)
Reply: Thank you for your suggestion. We added the following text in the Case presentation section on page 6, which describes the treatment regimen before the referral. In addition, we have created a new Table 1, showing the clinical course of the treatment in the Case presentation section.

“Eight months before the referral, treatment with isoniazid, rifampicin, ethambutol, and clarithromycin was reinstituted for the relapse; however, pulmonary involvement did not resolve.” (Page 6, Lines 109-111)

“The clinical course of the treatment is shown in the Table 1.” (Page 7, Lines 147-148)

2. Were culture sensitivities performed during each episode, was there any evidence of development of resistance.

Reply: We agree that this is an important point. We performed tests for additional drug sensitivities, and there was no evidence of development of resistance during the course. We added this information to the manuscript and Table 2 as follows:

“The drug sensitivity of these strains is shown in Table 2. There was no evidence of development of resistance during the course of the case.” (Page 8, Lines 152-153)

3. Did the patient continue to smoke? Could this have contributed to his failure to clear his infection.

Reply: Thank you for your suggestion; we added the information regarding smoking history in the Case presentation section as follows:

“He was a current smoker of 25 pack-years and then quit smoking after referral.” (Page 6, Line 105)

4. Any gastrointestinal studies or treatments to reduce reflux and any data if available on their association with persistent infection.

Reply: Thank you for your important suggestion. At the first admission to our hospital, he was treated with rabeprazole for his esophageal reflux symptoms. At the admission 38 months after his referral, he underwent an esophagastroduodenoscopy, which revealed a large amount of food residue, which made it difficult to observe the esophageal mucosa. Treatment with camostat and mosapride improved his reflux symptoms partially, but the migratory infiltrates did not resolve. These results support that the migratory infiltrates were probably caused by M.
fortuitum infection. We added this information in the Case presentation and Discussion section as follows:

“Treatment with rabeprazole for his esophageal reflux symptoms was administered, and he was followed up without treatment with antibiotics.” (Page 6, Lines 121-123)

“Esophagogastroduodenoscopy revealed a large amount of food residue, which made it difficult to observe the esophageal mucosa. Treatment with camostat and mosapride improved his reflux symptoms partially, but the migratory infiltrates did not resolve.” (Page 7, Lines 138-140)

“In our case, treatment for esophageal reflux with rabeprazole, camostat, and mosapride did not improve his migratory infiltrates.” (Page 9, Lines 193-194)

5. The primary focus has been the radiological, microbiology and pathology so I do not see much clinical data about the patient - functional status, weight changes. What happens with each episode - fever, cough, sputum. Any inter-current symptoms. This may be useful to add since clinicians may often consider therapy if the patient’s clinical status warrants.

Reply: Thank you for your suggestion. We added information regarding the patient’s symptoms in the Case presentation section as follows:

“At the time of referral to our hospital, he only had an intermittent cough and sputum.” (Page 6, Line 112)

“During the period following his referral, he occasionally had cough and sputum without fever and weight loss.” (Page 7, Lines 124-125)

3. Minor revision:

Good discussion about migratory pulmonary infiltrates, consider incorporating radiographic distribution to distinguish infiltrates from underlying disorder versus infective.

Reply: We appreciate your very important suggestion. However, because this is the first case report of M. fortuitum pulmonary infection with migratory infiltrates, it is difficult to propose a particular radiographic pattern which would successfully distinguish migratory infiltrates caused by M. fortuitum infection from that by other disorders. Therefore, in this paper, we would like to refrain from mentioning that point.
Dr. Griffith (Reviewer 2):

We also thank Reviewer 2 for the insightful and valuable comments that helped us improve our manuscript. Our responses to the specific points raised by Reviewer 2 are provided here.

Comment #2: In the case presentation, the authors note that the patient was treated with rifampicin, ethambutol, clarithromycin and levofloxacin, three years and eight months respectively before the referral. These are interesting antibiotic choices since rifampicin and ethambutol do not have activity against M. fortuitum and clarithromycin is ineffective because M. fortuitum has an active inducible macrolide resistance gene (erm gene) leaving only levofloxacin with expected activity against M. fortuitum. It is not surprising there was not resolution of M fortuitum disease with this regimen. It also raises the possibility of acquired mutational levaquin resistance. The authors should include the in vitro drug susceptibility results from the M fortuitum isolates.

Reply: We appreciate your educational comments. We agree that this is an important point. We performed tests for additional drug sensitivities, and there was no evidence of development of resistance during the course. We have added the results to the manuscript and Table 2 as follows:

“The drug sensitivity of these strains is shown in Table 2. There was no evidence of development of resistance during the course of the case.” (Page 8, Lines 152-153)

Comment #3: The authors do not detail the patient's therapy for GERD and aspiration. He apparently developed aspiration pneumonia 38 months after referral but no other symptoms are reported. It is important to know what interventions were made with regard to his GERD and recurrent aspiration, when they were made and if there was any indication of response to those measures.

Reply: Thank you for your suggestion. We treated the patient with rabeprazole after he was referred to our hospital. Moreover, before the multiple antimicrobial therapy was started, he received treatment with camostat and mosapride against reflux, which was confirmed via esophagogastroduodenoscopy. However, these treatments did not improve his migrating infiltrates. We added this information in the Case presentation section, as follows:

“Treatment with rabeprazole for his esophageal reflux symptoms was administered, and he was followed up without treatment with antibiotics.” (Page 6, Lines 121-123)

“Esophagogastroduodenoscopy revealed a large amount of food residue, which made it difficult to observe the esophageal mucosa. Treatment with camostat and mosapride improved his reflux symptoms partially, but the migratory infiltrates did not resolve.” (Page 7, Lines 138-140)
Comment #4: The major question I have about the radiographic findings in this study is how can the authors be sure that the migratory infiltrates were not due to recurrent aspiration events. The patient's sputum was AFB culture positive for M. fortuitum on several occasions, however the patient had 4 invasive diagnostic efforts (3 TBLB, 1 FNA) none of which were AFB culture positive. The authors note that "treatment [for M. fortuitum] resulted in clinical improvement, and pulmonary lesions had improved" but as noted in comment #3, there is no mention of treatment for his chronic GERD and aspiration.

Reply: We appreciate your important suggestion. As you point out, the possibility of the migratory infiltrates due to recurrent aspiration events cannot be denied. However, we believe that these infiltrates were caused by M. fortuitum pulmonary infection for two reasons. First, we treated reflux as we replied on your comment #3, but the infiltrates were not improved. Second, multiple antibiotic therapy against M. fortuitum resulted in dramatic improvement of infiltrates with no relapse. To clarify this, we have added this information to the manuscript in the Discussion section as follows:

“In our case, treatment for esophageal reflux with rabeprazole, camostat, and mosapride did not improve his migratory infiltrates. Moreover, multiple antimicrobial therapy for M. fortuitum resulted in improvement with no relapse. Based on these findings, we consider that migratory infiltrates were probably caused by M. fortuitum infection related to aspiration due to esophageal reflux.” (Page 9, Lines 193-197)

Comment #5: The significance of the positive M. fortuitum intestinal fluid culture is not clear. The authors suggest that the fluid could have been the source of the respiratory M. fortuitum isolates. It seems at least as likely that the positive intestinal fluid culture was due either to swallowed respiratory secretions containing M. fortuitum or from swallowed material from an environmental source (household water) that was the common source for the respiratory and intestinal M. fortuitum isolates. The common genotypes only point to a common source of the organism, they are not proof of a specific disease pathophysiology.

Reply: We agree that this is an important point. Although the exact pathogenesis is difficult to prove, we speculate that chronic exposure to gastrointestinal fluid may have caused the pathogenesis of M. fortuitum pulmonary infection, even though positive gastrointestinal fluid culture might simply be the result of swallowing respiratory secretions containing M. fortuitum. We have changed the relevant sentences in the Discussion and conclusions section as follows:

“Although the exact pathogenesis is difficult to prove, we speculate that chronic exposure to gastrointestinal fluid may have caused the pathogenesis of M. fortuitum pulmonary infection, even though positive gastrointestinal fluid culture might simply be the result of swallowing respiratory secretions containing M. fortuitum.” (Page 9, Lines 176-180)
Comment #6: The second treatment regimen included imipenem for 2 weeks, amikacin for 3 months, and clarithromycin, minocycline and levofloxacin for 5 years. There is a 2 year gap between the radiograph done at 38 months after referral and 5 years after referral. The authors note "pulmonary lesions had improved" during that time, but did he continue to have at least some migratory infiltrates during the 2 years between months 38 and 60? As an aside, it is certainly reasonable that 3 months of amikacin, minocycline and levofloxacin could have been adequate treatment for a pulmonary M. fortuitum infection.

Reply: Thank you for your suggestion. In Figure 2E, we present the chest radiograph at 38 months after referral, which is before the second treatment had started. Figure 2F is the chest radiograph 5 years after the second treatment had started. Therefore, there is an approximately 5-year gap between Figure 2E and 2F. During this period, the infiltrates improved and never recurred. We changed the expression of the sentence so that it is easy for readers to understand the course of the patient. As you point out, the treatment of M. fortuitum infection is generally considered to be sufficient in a shorter period of time. However, we considered that there was a risk of recurrence due to discontinuation of antimicrobial drugs because we already knew that treatment of reflux alone (rabeprazole, camostat, and mosapride) did not control the disease. To address this, we have revised the manuscript as follows:

“He continued the treatment for 5 years, during which the migratory infiltrates did not recur (Fig. 2F).” (Page 7, Lines 146-147)