Author's response to reviews

Title: Paradoxical response to disseminated non-tuberculosis mycobacteriosis treatment in a patient receiving tumor necrosis factor-alpha inhibitor: a case report

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Version: 3
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Author's response to reviews: see over
Dear Editor

We thank referees for careful reading our manuscript and for giving useful comments. In response to the Referees’ comments, we have revised the manuscript.

We look forward to a publication of our manuscript in BMC Infectious Diseases

Sincerely yours, Shigeki Nakamura, M.D., Ph.D.

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Our responses to the referees’ reports are as follows:

Reply to reviewer: David Cohn.

Reviewer's report

Title: aradoxical response to disseminated non-tuberculosis mycobacteriosis treatment in a patient receiving tumor necrosis factor-alpha inhibitor: a case report

Version: 2
Date: 30 January 2014
Reviewer: David Cohn

Reviewer's report:

General Comments
This is an interesting and unique case report of a patient with relapsing polychondritis treated with a TNF# inhibitor (adalimumab) who developed disseminated MAC infection, and then significantly worsened after initiation of appropriate antimycobacterial therapy and discontinuation of the anti-TNF# inhibitor, presumed to be due to a paradoxical reaction. The case is well documented by the description of clinical course, microbiological and radiographic findings. There are numerous structural or grammatical changes which should be made as suggested below.

Major Compulsory Revision (Recommendation)
A thorough literature search should be re-done to ensure there are no prior case reports of NTM with paradoxical reactions in HIV-uninfected patients (as there are with tuberculosis), including those that may be embedded in series of opportunistic infections in patients treated with TNF# inhibitors.
Thank you for your suggestion. We have done literature search again, however we couldn’t find any prior case reports of NTM with paradoxical reaction in non-HIV patients.

Minor Essential Revisions

We appreciate your kind comments. We corrected the word or grammatical changes, and modified the sentences, according to each of your following suggestions. All changed points were written in red-colored characters in the manuscript. And we had the manuscript checked by the editorial staff again.

1. P3 p1 Abstract Add …revealed “new” granular…
2. You use the term M. intracellulare and M. avium complex (MAC) interchangeably throughout the manuscript. I would suggest using one or the other. Was the isolate definitely speciated as M. intracellulare, as opposed to MAC, or not? If yes, perhaps state that it was M. intracellulare when you first report the culture results, and use MAC in the rest of the manuscript. If not, use MAC throughout.
3. P3 p2, P4 p1, P7 p1 Change “mediastinum” to “mediastinal”
4. P4 p1 Delete …in “the” tuberculosis…
5. P4 p1, P8 p1 Change “reduce’ to “decrease”
6. P4 p2 Delete “The” clinicians…
7. P4 p2 Change “got” to “get”
8. P4 p2, P10 p3 Change “adequate treatment” to “optimal management”
9. P5 p1 After …”fungal infections.” add additional references from the literature on opportunistic infections with biological agents
   →Thank you for your comment, we added a following reference.
10. P5 p1 Add ..with” known” NTM…
11. P5 p2 Delete …tuberculosis ”infection” after…
12. P6 p1 What was the dose (or dose range) of prednisolone used?
   →Thank you for your comment. We added the sentence “at a dose of 30 mg/day”.
13. P6 p1 For IGRA and anti-MAC antibody assays, add in parentheses the manufacturers of tests that were used
   →We added the manufacturers of each tests.
14. P6 p1 Change “manifestation” to “manifestations”
15. P6 p2 For CRP, give normal range or upper limit of normal for your lab after 13.81 mg/dl
16. P6 p2 For “almost”, do you mean “all”? 
   →We meant all, so we deleted “almost”.
17. P7 p1 Change “…the” to “this” NTM…
18. P7 p1 If you are going to use abbreviations, for rifampicin, I would use “RIF” instead of “RFP” and for ethambutol, “EMB” instead of “EB”
   →Thank you for your comment, we changed these abbreviations.
19. P7 p1 Change the “4-month treatment” to “4 months of treatment”
20. P7 p1 Move “increased” to after “lymphadenopathy”
21. P7 p1 Paragraph break at “Because…”
22. P7 p1 Before “We then changed..”, add “After ? months of antimycobacterial therapy with CAM, RIF and EMB…”. It appears this change in therapy occurred later than the 4 months referred to above (looks like about 6 or 7 months in Figure 2 ??)
   →We added the following sentence “after 5 months of antimycobacterial therapy with CAM, RIF, and EMB.”.
23. P7 p1 Change …abscesses “still enlarged.” to “continued to enlarge.”
24. P7 p1 Change …nodes “were enlarged” to “enlarged more” with…
25. P8 1 Delete ..in “the” tuberculosis…
26. P8 p1 Change “…has now been” to “was” increased…
27. P8 p1 Change …continued to “reduce” to “decrease in size”.
28. P8p1 Change sentence to read “The clinical course, culture results, treatment regimens and CT scan images are shown serially in Figure 2”
29. P8 p2 Change “Conclusion” to “Discussion”
30. P8 p2 Change “…about RP case complicating with NTM” to “of a RP case with NTM as a complication”.
31. P8 p2 Change “…is” to “has been” reported “in Thailand and Taiwan”…”MAC” to “NTM”, and IFN- # “antibody” to “autoantibodies” (as described in ref 5)
32. P8 p2 Change …was “not positive” to “negative” for…
33. P8 p2 Change …cases “were” to “have been” reported.
34. P8 p2 Change …relation ”to the use of a” TNF# inhibitor.
35. P9 p1 Add …including “the use of” infliximab…
36. P9 p1 Change to “…average “ time from the initiation of biological agents to the development of NTM was 10 months”…”similar to” our case…
37. P9 p1 Change “included” to “reported”. “the adequate” to “to appropriate”
38. P9 p1 Change “indicated” to “had a” …paradoxical “effect” to “reaction”
39. P9 p2 Add references after sentences on definition of IRIS (e.g., Meintjes et al) and IRIS in HIV-infected patients (e.g., Shelburne et al, Burman et al, Lawn et al, Narita et al)

Thank you for your kind comments. We added the following references.


40. P9 p2 Change “during active” to “after the initiation of” antiretroviral…

41. P9 p3 Change …patients “who…infection”…to “with tuberculosis” after…

42. P10 p1 Add …evidence “to recommend a specific course of action” in…

43. P10 p2 Change …case “indicated paradoxical effect” to “had a paradoxical reaction” to…

44. P10 p2 Please double check that there are no case reports of NTM paradoxical reactions in HIV-negative patients

Although we have done literature search again, we couldn’t find such a case.

45. P10 p2 Delete …“unlike tuberculosis treatment.”

46. P14 Legend Figure 2 Add …clinical course, “microbiological results, treatment regimens” and computed…

According to the other reviewer’s comment, we changed the following point.

- We “Gaffky No.” to “Acid-fast stain” in figure 2.
- We added the following sentence on Discussion “The combination of adalimumab, tacrolimus and prednisolone therapy might have resulted in a high mycobacterial load that provoked an immune/inflammatory response when the adalimumab and tacrolimus were ceased.”
Reply to reviewer: Martyn French

We thank for your careful reading our manuscript and for giving useful comments. All changed points were written in red-colored characters in the manuscript.

Reviewer's report

Title: Paradoxical response to disseminated non-tuberculosis mycobacteriosis treatment in a patient receiving tumor necrosis factor-alpha inhibitor: a case report

Version: 2 Date: 18 January 2014

Reviewer: Martyn French

Reviewer's report:

The authors present data on a patient who appears to have experienced a paradoxical reaction to M. intracellulare infection after adalimumab and tacrolimus therapy were ceased as part of the management of disseminated M. intracellulare infection caused by a combination of adalimumab, tacrolimus and prednisolone therapy. The case report is of interest because such cases have not been reported before. However, it requires substantial change to make it suitable for publication.

1. The relationship between ceasing adalimumab and tacrolimus and the onset of the putative paradoxical reaction should be made clearer. The data in figure 2 indicates that it occurred after ceasing adalimumab and tacrolimus but on page, 7 discontinuation of adalimumab and tacrolimus is discussed after discussion of the use of anti-mycobacterial therapy. It is also unclear in the abstract that the paradoxical reaction followed cessation of adalimumab and tacrolimus.

→We appreciate your kind comments. The administration of tacrolimus was started when tapering the dose of prednisolone and discontinued on NTM diagnosis. We corrected the statement about timing of ceasing tacrolimus. And paradoxical reaction was first confirmed on chest CT from 1 month after initiation of anti-mycobacterium therapy. We corrected the statement as follows. “The size of the pulmonary nodules and mediastinal lymphadenopathy increased 1 month after the initiation of antimycobacterial therapy. The high fever and general fatigue worsened despite 4 months of treatment; paravertebral and subcutaneous abscesses also developed and the size of the mediastinal lymphadenopathy increased.”

2. In the first paragraph, the authors refer to IGRAs as “serological tests” and anti-MAC antibodies as a diagnostic test for MAC infection. These statements are incorrect. In addition, IGRAs are not used to demonstrate T cell responses against NTM.
Thank you for your comment. Our statements were confusing as you indicated, we corrected the sentence as follows “after a chest computed tomography (CT) scan indicated that he had no signs of tuberculosis or NTM. Interferon-γ (IFN-γ) release assays (T-SPOT. TB, Oxford Immunotec Ltd., Massachusetts, US) and anti-Mycobacterium avium complex (MAC) antibody assays (Capilia MAC, TAUNS laboratories, Inc., Shizuoka, Japan) indicated also negative results.”.

3. In the Discussion section, the authors indicate that they do not know why their case developed a paradoxical reaction. One possible explanation is that this case received a combination of TNF inhibitor and immunosuppressant therapies (adalimumab, tacrolimus and prednisolone). Did any other reported cases of NTM infection after TNF inhibitor therapy also receive immunosuppressant therapy? Could the combination of adalimumab, tacrolimus and prednisolone therapy have resulted in a high mycobacterial load that provoked an immune/inflammatory response when the adalimumab and tacrolimus were ceased?

Thank you for your comments, and we agree with your opinion. We have done literature search again, however we couldn’t find any prior case reports of NTM with paradoxical reaction in non-HIV patients. We added the following sentence as you mentioned “The combination of adalimumab, tacrolimus and prednisolone therapy might have resulted in a high mycobacterial load that provoked an immune/inflammatory response when the adalimumab and tacrolimus were ceased.”

4. In the footnote to table 2, what does “Gaffky No.” mean?

We appreciate your comment, we changed “Gaffky No.” to “Acid-fast stain”.

5. Finally and most importantly, there are many grammatical and spelling errors. The manuscript requires editing to improve the quality of the English language, either by the authors or by editorial staff.

Thank you for your suggestion. We had the manuscript checked by the editorial staff again.

According to the other reviewer’s comment, we corrected many grammatical changes, and added the reference #2, 12, 13.