Author’s response to reviews

Title: Dissemination of multidrug-resistant tuberculosis in a patient with acute HIV infection

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Author’s response to reviews: see over
Dear Professor Cherryl Lyn Raytos

Editor, BioMed Central

We would like to thank you and the reviewers for your review of our manuscript. We have addressed the critique, to the extent possible, and revised manuscript. Please see below our responses to these comments; revised portions are highlighted in the revised manuscript.

<Responses to the editor’s comment>

After the reviewers’ comments I suggest a few revisions describing the methods of drug resistance testing. I agree with the need to cite other diseases during primary HIV infection as well as the need to question the co-infection /TB and HIV, where HIV might have triggered a latent TB infection

1. Revisions describing the methods of drug resistance testing

- According to the editor’s comment, we have added the following sentences in the revised manuscript.

  Drug susceptibility test (DST) was performed using the conventional absolute concentration method with Löwenstein-Jensen medium at the Korean Institute of Tuberculosis, the supranational reference laboratory for mycobacterial culture and DSTs in Korea [2]. Antimicrobial susceptibility tests were performed by the recommendations of the Clinical and Laboratory Standards Institute [3]


2. The need to cite other diseases during primary HIV infection
- According to the editor`s comment, we have quoted the following literatures of other diseases during primary HIV infection


3. The need to question the co-infection of TB and HIV, where HIV might have triggered a latent TB infection

- We agree to the editor’s comment about questioning of reactivation of TB, rather than primary infection of TB. We have described both mechanisms of co-infection of primary TB and HIV and reactivation of latent TB in an acute HIV infection stage in the revised manuscript. Please see the revised manuscript.

In this case, however, it is difficult to distinguish whether dissemination of TB occurred as a result of primary infection or reactivation of latent infection during the acute HIV infection stage. The reactivation of latent TB could be suggested as another possible contributor to the development of TB [19]. Especially during acute HIV infection, regulatory T cells (Tregs) are upregulated, but HIV can target CD4+ Treg cells for infection, and Treg cells can suppress ant-HIV immunity, which may together promote an increase in acute viremia and infected cells [20]. High levels of Treg as well as numerical deficit of CD4+ T cells during acute phase of HIV infection imply immune dysregulation and this may have favoured the reactivation of latent TB [1]


<Responses to the referee #1’s major compulsory revision>

1. The authors should indicate: How drug susceptibility testing was done and how long it took to get the results
- According to the reviewer#1’s comment, we have added the description of the methods of drug resistance testing

  Please see the response to the editor’s comments.

- According to the reviewer#1’s comments, we have added how long it took to get the results by conventional DST methods in the revised manuscript.

  In this case, DST for TB in sputum revealed the patient was infected with an MDR pathogen 80 days after admission. DST was performed by conventional indirect proportional method in Löwenstein-Jensen media at the Korean Institute of Tuberculosis. The conventional DST method usually took longer than two months to execute [10], so it could prolong the diagnosis and treatment of MDR pathogen. Recently, rapid direct susceptibility tests such as Genotype MTBDRplus assay were found to be useful to detect MDR-TB earlier [11].

2. Why TB medications were re-modified 73 days after admission

- Initial results of DST for TB in sputum were reported 80 days after admission. Anti-TB medications were re-modified based on the results of DST in sputum (resistance to isoniazid, rifampicin and quinolone and sensitivity to rifabutin, ethambutol, pyrazinamide, amikacin, cycloserin, prothionamide and kanamycin). After 30 days of anti-TB treatment with re-modified regimens, the additional resistance to ethambutol and pyrazinamide for TB was reported in DST result in CSF. We subsequently added amoxicilllin-clavulanate and excluded ethambutol and pyrazinamide. Finally, 120 days after admission, 40 days since the re-modified TB medication was started according to DST results in sputum, the patient had recovered.

- According to the reviewer#1’s comments, anti-TB medication re-modified 80 days after admission, not 73 days. We have adjusted the date from 113 days to 120 days. Please see the revised manuscript.

  The results of susceptibility tests in sputum led us to re-modify the patient’s anti-TB medication regimen to rifabutin, ethambutol, pyrazinamide, PAS, cycloserin, prothionamide and kanamycin. After 30 days of anti-TB treatment with re-modified regimens, the additional resistance to ethambutol and pyrazinamide for TB was reported in the result of tuberculosis DST in CSF, compared to that in sputum. We subsequently added amoxicilllin-clavulanate and excluded ethambutol and pyrazinamide after DST result of CSF was identified.
Finally, 120 days after admission, 40 days since the re-modified TB medication was started according to DST results in sputum, the patient had recovered and exhibited no fever.

3. Why, in their opinion, additional resistance was detected in CSF vs sputum

- Additional resistance was detected in DST result from CSF, in this case, which was acquired after 30 days of anti-TB medication. The acquisition of additional resistance during the treatment of TB was frequently observed in cases with HIV/TB co-infection, baseline resistance to 1st-line drugs and young age in the study of Jenkins HE et al. According to the reviewer’s comments, we have added the following sentences in the revised manuscript.

Interestingly, additional resistance to ethambutol and pyrazinamide of TB was detected in DST result from CSF, which was acquired after 30 days of anti-TB medication. The acquisition of additional resistance during treatment might be associated with baseline resistance to 1st-line drugs, higher degree of lung pathology, and HIV co-infection [12].


<Responses to the referee #1’s discretionary revision>

1. The Authors could quote more literature on opportunistic infections described during primary, symptomatic HIV infection.

- Please see the response to the editor’s comments.

<Responses to the referee #2’s minor essential revision>

1. Line 81 correct “Tomography”
   - According to the reviewer#2’s comments, the correction was done.

2. Line 98 and Line 103 are not consistent. Please clarify if the growth of M. tuberculosis in sputum was observed or not.
   - According to the reviewer#2’s comments, we have clarified the results of microbiologic test in
the revised manuscript.

The growth of bacteria including *M. tuberculosis* was not observed in blood, sputum and urine cultures.

3. Line 158 Capital letters Western Blot
   - According to the reviewer#2's comments, the correction was done.

4. Line 193 correct “favored” with “favoured”
   - According to the reviewer#2’s comments, the correction was done.

5. Line 130 correct “augmentin” with “amoxicillin-clavulanate”
   - According to the reviewer#2’s comments, the correction was done.

<Responses to the referee #2’s discretionary revision>

1. Line 91: It might be interesting add the percentage of T cells CD4+ and the ratio CD4/CD8 if available.
   - According to the reviewer’s comment, we have added the percentage of CD4+ and CD4/CD8 ratio in the revised manuscript.

   The CD4 cells accounted for 33.5% of lymphocytes. The ratio of CD4/CD8 was 0.55

2. Line 101 Explain the choice and start time of antiretroviral regimen (according to national guidelines?)
   - When to start ART in patients with active TB has been a subject of debate. Although disseminated TB disease requires prompt initiation of anti-TB treatment, early initiation of ART could result in severe complications of high pill burden, toxicities, drug interaction and the potential for development of IRIS. According to guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents by the HHS panel, we started ART within 2 weeks of anti-TB treatment because he had CD4 T-cell counts around 50 cells/µL and severe organ dysfunction.

   On the 21st day after admission, we started ART with efavirenz, lamivudine, and abacavir within 2 weeks of anti-TB therapy, because he had CD4 T-cell counts around 50 cells/µL and severe organ dysfunction (http://aidsinfo.nih.gov/guidelines).
We hope that you find this revised manuscript considerably improved.

Sincerely yours
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