January 8, 2017

Re: Manuscript No 30965

Dear Dr. Wong,

Thank you for the constructive feedback from the reviewers regarding our manuscript entitled, "Tuberculosis in Kidney Transplant Recipients: Case Series and Review of the Literature".

Please see our point-by-point response to the questions and comments on the following page. We have revised the manuscript, as indicated in the responses, and have uploaded a clean copy with marked version to highlight the changes from the original manuscript. We feel that manuscript has been significantly improved with the revisions and appreciate the opportunity to submit a revised version for consideration. We look forward to hearing from you again.

Kind Regards,

Manish Anand, MD
Assistant Professor of Medicine
Division of Nephrology and Hypertension
University of Cincinnati Medical Center
Cincinnati, OH 45267

Reviewer: ***00721262***

Author: *Thank you for your input and decision to accept our manuscript.*

Reviewer: ***00504802***

1. Ethical approval of the study.

   Since this was a retrospective chart review of the cases, ethical approval was not required by Institutional Review Board at Vanderbilt University in Nashville.

2. Case #4: avid “quantiferon gold” (a brand name) listing first – identify test as IGRA, with brand name in parentheses

   We have modified this in the manuscript as advised.

3. Case #4: not entirely clear course – what was the dose of ethambutol? What was the subjects renal function – was ethambutol adjusted for renal failure?

   Patient developed acute kidney injury with serum creatinine of 3 mg/dl. Dose of Ethambutol was changed from 1600 mg daily to 1600 mg every 36 hours. This information has been added to the revised manuscript.

4. What is the Authors’ opinion on IGRA, to separate BCG vaccinated persons form true latent TB patients?

   We feel that IGRA is more specific due to utility of MTB specific antigens with no cross reactivity with BCG, thus distinguishing true latent TB from BCG vaccinated individuals. This has been incorporated in the manuscript.

5. What would have the course of action (in hindsight) for macrophage activation syndrome? Any role for intensified immunosuppression, e.g. glucocorticoids?

   Macrophage Activation Syndrome is a life threatening complication with poor prognosis. Treatment of the triggering factor is of paramount importance. Optimal therapy remains debatable but immune modulatory agents such as high-dose steroids, Interleukin-1 receptor blocker Anakinra, Etoposide, Cyclosporine, intravenous immunoglobulin all have been tried with varied success, in the absence of controlled trials. Our patient did not receive any intravenous steroids or chemotherapy. This has been added to the case history in the manuscript.

Reviewer: ***00504802***
A retrospective reflection on missing the diagnosis at the first place should be made and a way of improvement should be suggested.

In our manuscript in the diagnosis section of discussion, we acknowledge missing the diagnosis of latent TB in Case 1 and 3 who had positive PPD testing but were not treated for latent TB prior to transplantation. Case 2 had prior granulomatous disease on chest x ray with exposure to endemic area by history as well. This patient did not get tested or treated for latent TB. Case 4 had negative IGRA but had calcified lung nodules on chest x ray. In retrospect, case 3, though received INH post transplantation for presumed latent TB, did not have active TB excluded by AFB smears, cultures or molecular testing. This patient later developed active TB. Other possibilities in this patient have been described in the management section of discussion, related to inadequate INH levels and host immune response.

Above illustrates the importance of diagnosis of latent TB and exclusion of active TB so that appropriate treatment can be given prior to transplantation to minimize development of active TB. In the diagnosis and pre-transplant section of discussion, we recommend thorough history taking and comprehensive physical examination with a special focus on the medical and social risk factors for TB. History of TB exposure with inquiry about residence and travel history to endemic areas, contact with a known active TB case, and prior TST testing results is important to elicit.

In the management section, we provide indications of LTBI treatment in recipient candidates to include a positive TST/IGRA as well as those with a negative TST/IGRA or indeterminate IGRA with risk factors: radiographic evidence of prior TB in the absence of treatment, donor with recent TB exposure, positive TST or radiographic signs, or close prolonged contact with an active TB case. Active TB needs to be ruled out by appropriate smears, cultures and molecular testing before treatment for latent TB is initiated. In high-risk patients, urine for AFB and renal imaging should also be performed to rule out genitourinary TB.

In our conclusions section, we further discuss the need for better diagnostics for LTBI and again emphasize on exclusion of active TB prior to LBTI therapy. More widespread use of rapid NAA assays and line probe assays is recommended to screen high-risk TB donors, and for diagnosis of TB in recipients. Also we mention that given disseminated and extra-pulmonary disease are more common in transplant recipients, studies are needed to assess the performance of NAA assays in body fluids, other than sputum, in this population. Given limitations of diagnostic testing for latent and active TB, and diverse presentation in transplant recipients, clinical acumen remains essential for early diagnosis and treatment to decrease mortality in this population.