Author’s response to reviews

Title: Disseminated cryptococcosis presenting initially as lower limb cellulitis in a renal transplant recipient - A Case Report

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Author’s response to reviews:

Dear Reviewers of BMC Nephrology,

It is with excitement that I resubmit to you a revised version of manuscript BNEP-D-16-00515 Disseminated cryptococcosis presenting initially as lower limb cellulitis in a renal transplant recipient - A Case Report. Thank you for giving us the opportunity to revise and improve our manuscript. We deeply appreciate the time and detail provided by each reviewer and have made a number of changes to our manuscript as recommended from review.

The following changes have been made to the manuscript in response to each reviewer:

Reviewer 1 (Pranatharthi H. Chandrasekar)

1. We have amended our manuscript to enhance emphasis on suspicion of systemic cryptococcosis on the discovery of a bilateral cellulitis.

2. CSF data has now been included.

3. Treatment was commenced on 19th August as soon as suspicion of disseminated cryptococcosis was identified on lumbar puncture (prior to confirmation with serum cryptococcal antigen result became available).

4. The dose of ambisome was 3mg/kg daily (200mg daily) and flucytosine 1500mg twice daily. There were no toxicity issues with ambisome and renal function remained stable,
although there was a transient decline in GFR at one stage which coincided with C.Difficile colitis and dehydration.

5. CSF remained positive for Cryptococci for some time (positive on 24/08, 25/08, 26/08 and 02/09. The final lumbar puncture performed on the 29/09 was india ink positive but culture was negative for Cryptococci.

6. A prolonged induction therapy was based on clinician reasoning due to CSF cultures remaining positive for longer than expected.

7. Our patient is planning to have lifelong fluconazole due to a risk of reactivation of cryptococcosis (if dormant) as the patient will remain on long term potent immunosuppression.

8. We have reduced the figures down to 3 and provided more descriptions for our histological pictures.

Reviewer 2 (Alexandre Alanio)

1. Unfortunately further sub specification of the organism was not carried out. We therefore do not have this information to include.

2. Indeed this case highlights uncertainty about whether the cryptococcal cellulitis was a manifestation of systemic cryptococcosis or primary cryptococcal cellulitis which later became disseminated. Each hypothesis is possible. Given our patient had no significant pulmonary involvement prior to identification of disseminated cryptococcosis we propose cutaneous entry as plausible. We have amended the manuscript to highlight that both hypotheses are possible in our patient.

3. We have included more information on opportunistic infections in transplant patients, with specific reference to when cryptococcosis is most likely to occur.

4. We have also included information on cryptococcosis and dormancy with reference to suggested literature – thank you for this invaluable addition / suggestion.

5. Our patient had been taking care of his bird for years. He had been regularly cleaning the bird cage (including bird droppings) until the time of presentation.

Reviewer 3 (Manuel Pestana)

Thank you for your review and we are pleased you found it informative and well written.

We hope that this new and improved manuscript is worthy of publication in BMC Nephrology and again thank the reviewers for their invaluable suggestions for improvement.
Warm regards,

Katrina Chakradeo