Author's response to reviews

Title: Growing PET Positive Nodule in a Patient with Histoplasmosis

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Author's response to reviews: see over
To whom it may concern,

All the comments by the reviewers that needed to be revised were addressed and revised in our manuscript.

A point-by-point response to the concerns raised by the reviewers.

**Reviewer 1**

1- In the background section, second paragraph, our aim is not to mislead readers into believing that PET scan is a new modality for the detection of histoplasmosis. On the contrary, we do recognize that PET scan is a commonly used modality and that it is a cause of false-positive results. That is why we elude to the fact that this commonly used modality needs to be revised or perhaps modified in order to obtain more accurate results.

2- In the case presentation, in the second to last paragraph, I agree with the reviewer. Given the fact that the nodule enlarged from 1.7cm to 3cm there is no need for a PET scan. However, our PET scan was done prior to the enlargement of the nodule, when the nodule was still 1.7cm in size. There was no PET scan performed when the nodule enlarged. The F 18 FDG uptake mentioned in the paragraph refers to the only PET scan done when the nodule was 1.7cm in size.

3- This was revised in the first paragraph of the discussion section.

4- This was also revised in the first paragraph of the discussion section.

5- This was revised in the third paragraph of the discussion section.

6- Our aim is to educate the non informed reader specially in the non endemic areas for histoplasmosis with a basic review and background of this disease process while discussing in the last four paragraphs our experience and diagnostic dilemma we were faced with when dealing with this disease through our case presented here.

7- In our table we outline 7 patients with PET scan positive for histoplasmosis in the literature. The reviewer is correct, there are numerous reports about patients with PET scan and granulomatous disease. However, most of the data includes non specific granulomatous disease and when looking at histoplasmosis as a specific entity within these groups, our review outlines only 7 patients.

**Reviewer 2**

1- This was revised in the first paragraph of the case presentation section.

2- The reason for obtaining a PET scan, was the finding of pulmonary nodules on a prior CT scan in addition to the change in the patent’s presenting symptoms. It is true that the
patient had a recent fever, however, he had new complaints of weight loss in addition to a CT scan with positive nodules. This in our opinion warranted a PET scan.

3- There was an attempt to obtain a CT-guided needle biopsy that was non-diagnostic. Therefore, the patient was referred to us for a definitive diagnosis. Our approach to obtaining a tissue diagnosis was governed by the technically more feasible mass in order to obtain a working diagnosis since both masses probably represented the same disease process. However, our attention was later focused towards the PET positive left lower lobe mass as being a cancerous lesion (and as being different from the right sided mass) was only after this PET positive left mass had doubled in size despite adequate treatment for histoplasmosis.

4- The dose of itraconazole used was based on a multidisciplinary approach in consultation with both our pulmonary and infectious disease groups.

5- As mentioned earlier, the left lower lobe nodule was ultimately presenting as a cancerous lesion (PET positive, doubled in size, and couldn’t have been a histoplasmosis lesion as in the case of the right upper lobe mass since the patient was adequately treated for histoplasmosis). Therefore, a formal cancer operation through a formal thoracotomy incision for the removal of the entire lobe was performed.

6- As mentioned above, our aim was to educate the non informed reader specially in the non endemic areas for histoplasmosis with some background about this disease process while focusing in the last four paragraphs on our experience and diagnostic dilemma we were faced with when dealing with this disease through our case presented here.

**Reviewer 3**

1- The reviewer is correct in pointing out that there was a previous diagnosis of histoplasmosis in the right lung. However, to our knowledge, this infection was treated. Therefore, our suspicion that the left sided nodule was another histoplasmosis infection was very low, specially since the left nodule was PET positive and was growing.

2- A frozen section in this setting would have proved to be indeterminate with the pathologist not committing fully to one single true final diagnosis. This off course would not have changed our algorithm to treating a PET positive growing nodule, even if this patient had a known previous histoplasmosis infection, specially since he had been previously treated.

Sincerely,

Khaled F. Salhab M.D.