Author's response to reviews

Title: Hypercalcemia in a patient with disseminated Paracoccidioidomycosis (Case Report)

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Author's response to reviews: see over
Dear Editor,

We thank you for your attention and for the chance to revise the manuscript ID 2686950168229163 “Hypercalcemia in a patient with disseminated Paracoccidioidomycosis (Case Correspondence)”. The concerns of the reviewers are certainly of major importance and we have tried to answer them accordingly. The answers and modifications performed in the original text are detailed in the following pages. We hope the changes performed were able to improve the report and that the manuscript is now suitable for publication in *Journal of Medical Case Reports*.

We look forward to hearing from you.

Yours sincerely,

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Answer to Reviewer 1

The authors present an interesting observation of the occurrence of hypercalcemia in a patient with mycosis caused by Paracoccidioides brasiliensis. Observations eluding to possibly novel virulence mechanisms or host:pathogen interactions in this common and important fungal pathogen are to be welcomed. This reviewer has a few minor comments listed below:

We thank the reviewer for the comments.

1. Use correct microbiological taxonomy through-out (put Paracoccidioides brasiliensis in italics)

   We have corrected the microbiological taxonomy through-out the paper.

2. How was vitamin D intoxication ruled out? (Was the concentration of 25(OH)2D measured?)

   We have ruled out vitamin D intoxication by measuring 25(OH)D concentration. 25(OH)D levels were 42 ng/ml (normal range 10-80 ng/ml).

3. Comment on the occurrence of hypercalcemia in other mycoses (e.g. those caused by Coccidioides immitis and Cryptococcus neoformans). Is this a common observation and has it been linked to virulence or pathobiology of these infections previously? In this reviewers opinion, a short speculative statement on how elevated calcium levels could play a role in P. brasiliensis pathogenesis would add to the paper.

   Fungal diseases have rarely been implicated as causes of hypercalcemia [1-5]. In other cases of hypercalcemia, associated with Paracoccidioides brasiliensis, Coccidioides immitis or Cryptococcus neoformans, hypercalcemia was usually associated with disseminated or severe disease [2, 5-7].

   The association of Paracoccidioides brasiliensis and hypercalcemia is rare; to our knowledge, only two cases have been reported so far, neither of which with a clear documentation of the etiology of the hypercalcemia (6-7). However, further investigation is needed to clarify whether hypercalcemia may play a role in the pathogenesis of P. brasiliensis.

References

The case is well documented and written. The other potential causes of hypercalcemia have been evaluated. The association between hypercalcemia and elevated 1,25 dihydroxyvitamin D is most established in sarcoidosis. In TB the association has been more difficult to quantify and in coccidioidomycosis we found no evidence for it 7 cases. I feel the last sentence of the discussion section "Thus, 1,25(OH)2D might be the primary pathogenic mechanism of hypercalcemia in paracoccidioidomycosis" is overly strong due to the fact the test was still within the normal range and there were no repeat levels mentioned that exceeded the normal range. A response to prednisone and antifungals would be expected regardless if the etiology was vitamin D related or not. More cases with similar findings would be needed to justify the authors conclusion about etiology.

We thank the reviewer for the comments.

We agree that the last sentence of the discussion is overly strong and have modified it to: “Thus, 1,25(OH)2D might have a role in the pathogenic mechanism of hypercalcemia in paracoccidioidomycosis”.

The association of Paracoccidioides brasiliensis and hypercalcemia is rare; to our knowledge, only two cases have been reported so far, neither of which with a clear documentation of the etiology of the hypercalcemia [1, 2]. In the first case described, the serum 1,25(OH)2D levels were not measured; however, the calcium response to corticosteroids suggests that this may have been mediated by vitamin D excess [1]. In the second case, the patient had hypercalcemia and multiple bone lesions. Furthermore, paracoccidioidomycosis was associated with tuberculosis and the authors suggest that the bone involvement is the probable cause of hypercalcemia [2]. Thus, further investigation is needed in more cases with similar findings to clarify the mechanism of hypercalcemia in this disease.

References