

Sunday, December 30, 2018

Xue-Jiao Wang

Science Editor, Editorial Office, Baishideng Publishing Group Inc.

Dear Ms. Wang,

Thank you for giving us the opportunity to revise our manuscript: "Non-Uremic Calciphylaxis Associated with Alcoholic Hepatitis - A Case Report and Review of Literature." for reconsideration of publication at the World Journal of Hepatology. We would like to thank the editors and the reviewers for their comments. Please find our response to the comments raised by the editor and reviewers, in our detailed response. We would like to thank the editorial board for their effort and timely response that reflects the importance of the current topic. We hope that following the modifications and improvements suggested by the reviewers would improve the quality of our manuscript and meet the publication standards of the *World Journal of Hepatology*.

We are looking forward to your positive response.

Sincerely,

Yasser Sammour, M.D. | Research Fellow

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Response to the reviewer #1:

Specific comments:

1. Calciphylaxis is a rare condition with high mortality. Most of the affected patients have advanced chronic renal failure and need dialysis. It is less well-known that calciphylaxis can also arise in patients with normal renal function. Obesity, diabetes mellitus, and mildly impaired renal function are risk factors for non-uremic calciphylaxis. Its pathogenesis is not yet well understood. This case had these risk factors. Because it is a rare disease, accumulation of cases is important for elucidation of the disease.

We thank the reviewer for his thoughtful comments and suggestions.

We agree with the reviewer that the rare nature of the case makes the publication of the case report necessary in order to accumulate literature to help better understand the disease etiology as well as the most appropriate medical management for such cases.

2. Major 1. Describe the patient history of treatment for obese. Was the operation effective?

We thank the reviewer for his comment and to further answer his questions the following section has been added to the case presentation:

"The patient was morbidly obese (BMI=56) status post Roux-en-Y gastric bypass done twelve years ago (pre-surgical BMI unknown), so we couldn't judge the effectiveness of the bariatric surgery. History was negative for

diabetes mellitus, kidney dysfunction, autoimmune diseases, hyperparathyroidism or Warfarin intake."

3. 2. Did the patient have a history of diabetes?

We thank the reviewer for highlighting this point. The patient did not have a history of diabetes mellitus despite being morbidly obese. A clarification of this point has been added to the case presentation.

Response to the reviewer #2:

1. The manuscript entitled "Non-Uremic Calciphylaxis Associated with Alcoholic Hepatitis-A Case Report" is well presented. This study represents a rare disease. In fact, presenting of such cases is important for better understanding the mechanism of calciphylaxis, which can help to develop an effective treatment regimen. This study represents valuable results.

The authors would like to thank the reviewer for the time and effort spent to review our case report and of his high regard of the importance of our current case.

2. However, the patient risk factors including history of diabetes mellitus and ... need to be clarified in detail.

We thank the reviewer for his suggestion, and accordingly, the following statements have been stated in the case report section:

"History was negative for diabetes mellitus, kidney dysfunction, autoimmune diseases, hyperparathyroidism or Warfarin intake."

3. The references are not according to the format of the journal. Reference section: PMID and DOI should be included. Text: The reference numbers should be superscripted in square brackets at the end of the sentence.

We thank the reviewer for highlighting this point. The references has been adjusted as recommended. The references are revised according to the format of the journal and the reference section included the PMID and DOI of the mentioned articles. In addition to, the reference numbers are superscripted in square brackets at the end of the sentence.

Response to the reviewer #3:

1. The authors present an interesting case report and it deserves to be published due to the rarity of the phenomenon in patients having liver disease.

The authors would like to thank the reviewer for the comments and suggestions.

2. I have 2 comments: 1- The level of proteins S should be detailed. The other factors are mentioned.

We would like to thank the reviewer for highlighting this point. The level of protein S was low normal and according to the comment, the following section has been added to our case presentation:

"The hypercoagulability panel showed low levels of Protein C 33 IU/dl (normal: 76-147), low normal levels of protein S 67 IU/dl (normal: 65-135)."

3. 2- In the discussion the authors mention MGP. The authors should mention why this was not determined. It is now recognized that cirrhosis is a pro-coagulant state as well with an increase in the incidence of DVT and PE. I think a sentence on this point would be useful/after addressing these minor comments I recommend the paper be accepted for publication.

We would like to thank the reviewer for his comment, the following two sections have been added to address the aforementioned comments:

“Total uncarboxylated MGP (t-ump) could reflect arterial calcification, with lower values being associated with more widespread calcium deposits^[8]. However, its level was not assessed in our patient; its measurement in future studies may be required.”

, and:

“Liver dysfunction can lead to low levels of coagulation inhibitors, specifically protein C and S, which can lead to vascular injury^[6] as well as thromboembolic manifestations such as deep venous thrombosis and pulmonary embolism.”