Author's response to reviews

Title: A Case report of Severe osteomalacia caused by Tubulointerstitial nephritis with Fanconi syndrome in asymptomatic primary biliary cirrhosis

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Author's response to reviews: see over
Dear Dr. Hayley Henderson, Editor-in-Chief of *BMC nephrology*

Manuscript ID: 2045520586176283

“A Case of Severe osteomalacia caused by Tubulointerstitial nephritis with Fanconi syndrome in asymptomatic primary biliary cirrhosis”

By Shintaro Yamaguchi, Tatsuya Maruyama, Shu Wakino, Hirobumi Tokuyama, Akinori Hashiguchi, Shinichiro Tada, Koichiro Homma, Toshiaki Monkawa, James Thomas, Kazutoshi Miyashita, Isao Kurihara, Tadashi Yoshida, Konosuke Konishi, Koichi Hayashi, Matsuhiko Hayashi and Hiroshi Itoh

1st revision September 23th 2015

To the Editor

We are very glad to know that our paper is acceptable for publication in *BMC nephrology* after appropriate revision. We have revised the manuscript following the kind and constructive comments received from the reviewer. The revisions can be summarized as follows:

1. In compliance with the reviewer’s comments, we have taken out the description that is a mere repetition of the case presentation.
2. We have addressed the reviewer’s comments in the revised manuscript, in which changes and additions are shown in **bold and underlined font**.

We have prepared the new manuscript to take into account all of the reviewer’s comments. We have also formulated the replies to the reviewer. We hope that our revised manuscript will now be considered suitable for publication in *BMC nephrology*, and would like to thank you for your kind re-consideration of our paper.

Yours sincerely,

Tatsuya Maruyama, Hiroshi Itoh
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To Reviewer
We are most grateful for your helpful comments on our manuscript. We have addressed all of these comments and revised the paper accordingly. The changes to the manuscript are shown in **bold font and underlined**. We believe that all the points you raised have been clarified and cordially request your kind re-consideration of our manuscript.

Your comments and our replies are shown below:

**Major comments**

2. There are repetition of same content in the case summary section and discussion which need to be shortened.

Following your comment, we have taken out the description that is a mere repetition of the case presentation. Following parts are deleted from the original manuscript.

- The hormonally active form of vitamin D, 1,25 dihydroxyvitamin D₃, is generated in the proximal renal tubule by the 1α-hydroxylation of 25-hydroxvitamin D \(^{14}\). (line 148-149 of page 10 in the original manuscript)

- Tumor induced osteomalacia (TIO), a paraneoplastic syndrome, had to be considered as the important differential diagnosis of osteomalacia in this case because of the disorder of phosphorus reabsorption in the proximal renal tubule and abnormal regulation of 1α-hydroxylation of vitamin D \(^{21}\). A recent study indicated that the measurement of FGF23, the causal factor produced by tumors in TIO, is useful to
differentiate the diagnosis of hypophosphatemic diseases \(^{18,19}\). However, FGF23 levels are rather low and we could not detect any tumors with total body survey. Therefore, TIO does not seem to be included in the pathogenesis of osteomalacia in the present case. (line 156-164 of page 10-11 in the original manuscript)

-Main renal involvement of PBC is a distal type of RTA and TIN with Fanconi syndrome has rarely been documented \(^{7-9,11}\). Inappropriately alkaline urine in the presence of systemic metabolic acidemia in this patient indicated distal type of RTA. However, the bicarbonate loading test showed bicarbonate wasting and normal hydrogen excretion, suggesting proximal type of RTA. (line 165-169 of page 11 in the original manuscript)

Accordingly, we deleted the references 18 and 19 from the manuscript.

3. initial background section is too long (Need to be reduced)

In compliance with your comment, we have made the introduction concise. Following phrases are taken out because these explanations seem to be obvious and irrelevant to the present case.

-which predominantly affects middle-aged women, (line 76 of page 5 in the original manuscript)
-which are mainly caused by osteoblast dysfunction, (line 79 of page 5 in the original manuscript)
-an inflammatory disease characterized by lymphocyte infiltration in tubules and interstitium, (line 84-85 of page 5 in the original manuscript)

4. A correction is needed in line 193 as “lack of sun exposure” instead of “sun exposure”

Following your comment, we corrected the phrase in the conclusions “sun exposure” to “lack of sun exposure” (line 174 of page 11 in the revised manuscript)