Author’s response to reviews

Title: Corticosteroid dose increase is a risk factor for nonalcoholic fatty liver disease and contralateral osteonecrosis of the femoral head: A case report

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Response to Reviewers

We deeply appreciate the Editors and the Reviewers for their logical comments. We can try to give another quality to this paper. Responses to comments or suggestions are shown as following.

Changes of the manuscript are written in red.

Reviewer reports:

Lynne Jones, PhD (Reviewer 3): This manuscript presents a case report of the development of osteonecrosis in the contralateral femoral following an original diagnosis of unilateral disease. Although several studies have reported the rate of bilateral disease, there is a paucity of studies which report the development of osteonecrosis in the contralateral side after only one side had been diagnosed. Furthermore, no studies have evaluated why certain patients do not develop bilateral disease. This report describes a case in which osteonecrosis developed after the corticosteroid dose for a patient with Sjögren's syndrome had been increased.
The primary concern with this manuscript is that correlation is not causation. The two primary findings: osteonecrosis in the contralateral femoral head and increased level of liver enzymes may have each occurred following increasing the level of corticosteroid therapy without being causally related. Koo et al. (Clin Rheumatol (2002) 21:299-303) in patients up to 16 months after initiation of corticosteroid therapy, although most were notably shorter time periods. Of interest is the fact that in these patients, corticosteroid therapy was increased - indicating reaching a new threshold.

It would be of interest to study how many of the unilateral osteonecrosis patients that have their corticosteroid therapy continued and/or increased due to treatment for co-morbidities and then what number of patients then develop bilateral disease. As a case report, the findings provide evidence that this can happen although we do not know the relative risk.

Authors response and action: Thank you for your important comments. We agreed with the reviewer’s pointing out that correlation between the contralateral ONFH occurrence and increased level of liver enzymes was not causation. To clarify the correlation directly, we should investigate the cytochrome P450 3A activity, liver enzyme and occurrence of the ONFH in the patients receiving increase of corticosteroid in the future observational study. Additionally, we also agreed with the reviewer’s pointing out that increasing glucocorticoid might cause reaching a new threshold of the ONFH occurrence. However, because it is not fully understood if increasing glucocorticoid could be a risk for the contralateral ONFH occurrence, the future observational study should address this concern. We revised the discussion section. (Page 5 Line 99-106, Page 6 Line 127-130)

Page 5 Line 99-106

Koo et al. reported that ONFH occurred in patients received corticosteroid up to 16 months after initiation of corticosteroid therapy [13] and Piyakunmala et al. reported the high incidence rate and high extension area of asymptomatic osteonecrosis of the contralateral femoral head of the hip in high-risk patients in a cross-sectional study [14]. Therefore, increase of corticosteroid in this case might cause reaching a new threshold of the ONFH occurrence. Because it is not fully understood if increasing glucocorticoid could be a risk for the contralateral ONFH occurrence, the future observational study should address this concern.

Page 6 Line 127-130
Additionally, the future observational study of increase the corticosteroid dose should monitor the cytochrome P450 3A activity and address the correlation with ONFH occurrence and liver enzymes abnormalities.

The authors have addressed most of the items outlined in the previous critiques. There are a few queries that should be addressed.

Specifically,

Lines 71 and 78  Please indicate the stage of disease using an established classification system (ARCO, Japanese, e.g.).

Authors response and action: Thank you for your valuable comments. We usually used the Japanese Investigation Committee classification, we added the stage of disease. Left side was type C2 and stage 1, and right side was type C1 and stage 1. We revised the case presentation section. (Page 4 Lines 73-74, Page 4 Line 80)

Page 4 line 73-74

Based on the Japanese Investigation Committee (JIC) classification[11, 12], we diagnosed the ONFH (type C-2, stage 1).

Page 4 line 80

Then, she was diagnosed with right ONFH (type C-1, stage 1)

Line 91  'in each of the femoral heads'

Authors response and action: Thank you for your careful reading. We revised the discussion section. (Page 5 line 90-91)

Page 5 line 90-91

We present a case of bilateral corticosteroid-induced ONFH in which the timing of the development of ONFH in each of the femoral heads and corticosteroid-induced NAFLD differed.

Line 115 'not examined then'
Authors response and action: Thank you for your careful reading. We changed from them to then. (Page 6 line 122)

Page 6 line 122

Unfortunately, our patient was not examined then.

Line 121 While there is no issue to monitoring patients with abnormal hepatic metabolism and hepatic steatosis, the following statement is the author's opinion and additional studies with higher levels of evidence is needed.

Authors response and action: Thank you for your careful reading. As the reviewer pointed out, we agreed that this sentence would be too speculative. We deleted this sentence from manuscript.

Other:

Please include the call for the need for studies of higher level of evidence that confirm or refute the findings of these case reports.

I suggest including the following reference:


Authors response and action: Thank you for your important comment. We agreed with the reviewer’s comment that the future study should address the correlation and confirm this finding. We also appreciate for letting us know Piyakunmala’s study. Although we thought that it might be difficult to distinguish between the bilateral occurrence and the contralateral occurrence in cross-sectional study using different modality, we should also address it in the future longitudinal observational study. We revised the discussion section. (Page 5 Line 99-106, Page 6 Line 127-130)

Page 5 Line 99-106

Koo et al. reported that ONFH occurred in patients received corticosteroid up to 16 months after initiation of corticosteroid therapy [13] and Piyakunmala et al. reported the high incidence rate and high extension area of asymptomatic osteonecrosis of the contralateral femoral head of the hip in high-risk patients in a cross-sectional study [14]. Therefore, increase of corticosteroid in this case might cause reaching a new threshold of the ONFH occurrence. Because it is not fully
understood if increasing glucocorticoid could be a risk for the contralateral ONFH occurrence, the future observational study should address this concern.

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Additionally, the future observational study of increase the corticosteroid dose should monitor the cytochrome P450 3A activity and address the correlation with ONFH occurrence and liver enzymes abnormalities.