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’s comments:

Wing-Hoi Cheung (Reviewer 1): This is a simple case report on the phenomenon that increasing corticosteroid increases the potential risk for nonalcoholic fatty liver disease and development of contralateral osteonecrosis, which reported one case only.

Nowadays, publishing a case report should report those very rare disease or very new technology. The phenomenon reported in this article is not very rare and the association is well known. The author should accumulate more similar case and find proper control cases for a fair comparison. Based on one clinical case only, there is very limited scientific value to publish as a case report.
Response and Actions:

Thank you for your precious review. We agreed with the reviewer suggestion that a case report should be published if it is considered as an appropriate value in terms of science. To our best knowledge, the development of contralateral ONFH which is induced by steroid have been reported in three cases until now. The two cases (Zhao., et al., C Orhop Surgery. 2015, Sonoda K., et al., Springer Plus. 2016) of three cases reported different intervals from the initial development of lateral ONFH to the contralateral development. These reports evaluated the timing of the occurrence with only initial steroid administration and the intervals were very short period (approximately 6 weeks). Considered that there is a possibility that these two cases might have reflected the results of radiological examinations with short periods for so-called bilateral ONFH which have been considered as occurring, there might be only one case that developed new ONFH in the contralateral hip (Sonoda K. et al. J Orthop Sci. 2015).

Additionally, as you already know, the mechanism of occurrence of ONFH has still been unclear. Although previous studies reported the association between occurrences of ONFH and liver enzyme, there was no clinical report to observe liver histology. This current case report was actually diagnosed as non-alcoholic fatty liver disease (NAFLD) by the liver histology and ONFH mostly in the same period. It can indicate the clinical reinforcement of the association between NAFLD and ONFH, which is induced by steroid. Therefore, we believed that the current case report was not rare but scientifically valuable case that could have potential to reaffirm the significance of the association between the occurrence of ONFH and the abnormality of hepatic metabolism.

Satoshi Ikemura (Reviewer 2): Thank you for letting me read and review this case report entitled, "Increasing corticosteroid dose is a potential risk for nonalcoholic fatty liver disease and contralateral osteonecrosis of the femoral head". The manuscript is well written regarding the patient’s clinical course and presented images are appropriate.

Page 6, Line 113

As authors mentioned, I agree that individual variability in the level of cytochrome P450 3A activity play an important role for the development of osteonecrosis of the femoral head. Masada et al. reported that cytochrome P450 3A activity inversely correlated with the incidence of osteonecrosis and extent of the necrotic area. Ikemura et al. (Cytochrome P4503A activity affects the gender difference in the development of steroid-induced osteonecrosis in rabbits. Int J Exp Pathol. 2014;95:147-52) suggested that gender difference in the rate of incidence of osteonecrosis (male > female rabbits) is caused by the gender difference in the cytochrome P450
3A activity (female > male rabbits). Please expand the final paragraph of the Discussion section using above two animal studies.

(e.g.) Several animal studies focused on the correlation between cytochrome P450 3A activity and the incidence of osteonecrosis. Unfortunately, our patient was not examined cytochrome P450 3A activity. Therefore, whether the abnormality of hepatic metabolism could directly play an important role in ONFH occurrence remains unclear. However, recent reports showed the association between cytochrome P450 3A activity and expression in NAFLD as well as between corticosteroid use and NAFLD.

Response and Actions

Thank you for your favorable and valuable comments. We added the references and revised the Discussion section as the reviewer suggested. (Line 112-115)

Line 112-115: Several animal studies focused on the correlation between cytochrome P450 3A activity and the incidence of osteonecrosis [8] [11]. Additionally, clinical reports showed that low hepatic cytochrome P450 3A activity is a risk for corticosteroid-induced osteonecrosis [7] [12]. Unfortunately, our patient was not examined them.

Lynne Jones, PhD (Reviewer 3):

1. Line 29 Bilateral corticosteroid-induced ONFH does not always develop concurrently.

Asynchronous lesions often occur. Are you trying to say that there is a high incidence of bilateral disease? Does ref #1 discuss bilateral disease?

Response and Actions

Thank you for your careful reading and sorry for your confusing. We would like to say that there is a high incidence of bilateral disease. As the reviewer pointed out, ref #1 showed the national-wide epidemiologic data and didn’t discuss bilateral disease. Min et al. reported that idiopathic ONFH can be bilateral in up to 60% of cases at initial diagnosis. Therefore, we revised the
Abstract (line 28-29) and the Introduction section (line 49-50), and added the reference as the reviewer suggested.

Line 28-29 There is a high incidence of bilateral corticosteroid-induced osteonecrosis of the femoral head (ONFH).

Line 49-50 ONFH can be bilateral in up to 60% of cases at initial diagnosis [3].

2. Line 35 Does this mean that she received continuous corticosteroids for 25 years?

Response and Actions

Thank you for your careful reading. Yes, she received continuous corticosteroids for 25 years. To avoid confusing, we revised the Abstract section (line 34-36).

Line 34-36; A 32-year-old woman had been treated with continuous corticosteroids of up to 10 mg/day for Sjögren’s syndrome for 25 years and corticosteroid-induced ONFH in the left side.

3. Line 43 Suggest rephrasing "might be". This does not appear to be a strong conclusion. Perhaps a sentence stating to watch individual carefully that have hepatic enzyme abnormality to screen for ON.

Response and Actions

Thank you for your valuable comment. We agreed with the reviewer’s suggestion. We revised the Abstract (Line 42-43).

Line 42-43: Therefore, it would be useful and important for screening of ONFH to watch individual carefully that have hepatic enzyme abnormality.
4. Line 59 There are other manuscripts that have looked at this. Please see: Goker B, Block JA. Risk of contralateral avascular necrosis (AVN) after total hip arthroplasty (THA) for non-traumatic AVN. Rheumatol Int. 2006 Jan;26(3):215-9.

Response and Actions

Thank you for your valuable comment. We carefully reading this article. However, Goker stated that “None of the 13 patients who were free of radiographic evidence of contralateral AVN at study entry developed evidence of AVN during the follow-up”.

5. Line 114 Also reported in patients:

Response and Actions

Thank you for your careful reading. We revised the Discussion section (Line 113-114) and added the reference (ref12).

Line 113-114: Additionally, clinical reports showed that low hepatic cytochrome P450 3A activity is a risk for corticosteroid-induced osteonecrosis [7] [12].

6. Please mention here are in line 117 that the association is with reduced levels of P450 3A activity.

Response and Actions

Thank you for your valuable comment. We agreed with the reviewer’s pointing out. It is the important point. We revised the Discussion section (Line 117-118).
Line 117-118: However, recent reports showed the association between reduced level of cytochrome P450 3A activity and expression in NAFLD [13] as well as between corticosteroid use and NAFLD [14].

7. Figure 2 Please make sure that both figures are displayed in the same way with the R side on the left side of the figure. Please confirm that comment made in line 71 is true for the right hip.

Response and Actions

Thank you for your careful reading and sorry for confusing. Line 71 “right” was “left”. We revised the Case presentation section (Line 71-72).

Line 71-72: T1-weighted magnetic resonance imaging (MRI) at 3 months after the onset of pain clearly showed a low-intensity band within the left femoral head (Fig. 2b).