Author's response to reviews

Title: Giant osteoclasts in patients under bisphosphonates

Authors:

  Fabrice Mac-Way (fabrice.mac-way@mail.chug.qc.ca)
  Andrea Trombetti (Andrea.Trombetti@unige.ch)
  Christian Noel (Christian.NOEL@CHRU-LILLE.FR)
  Marie-Hélène Lafage-Proust (Mmh.lafage.proust@univ-st-etienne.fr)

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Author's response to reviews: see over
Dear editorial board,

We are very thankful to the reviewers remarks concerning our article. We are convinced that reporting this case-report in "BMC Clinical Pathology" will allow to reach a high number of clinical pathologists and increase their awareness on this particular osteoclast morphology. The right recognition of these non-resorbing giant osteoclasts in bone tissues from patients treated with bisphosphonates is essential because giant osteoclasts are normally associated with active bone resorption and might be misinterpreted as markers of increased bone turnover as seen in Paget’s disease of bone, hyperparathyroidism or bone cancer. Please find hereby our answers point-by-point to the reviewers comments. The manuscript has been corrected as much as possible in agreement to the reviewers remarks although the "case report" nature of this article has not been changed.

**Point-by-point responses to reviewers**

**Reviewer 1**

The major issue with this paper is the case report nature, i.e. only two patients included.

We agree that the number of patients in this case report is not very high. However, our objective in publishing this article is to allow clinical pathologists to increase their awareness when faced to this particular OC morphology in bone tissue specimens. We have also seen these giant OC in other patients taking Bps, but we felt that focusing on 2 cases and describe the characteristics of these particular OC as a case-report is the best way to reach clinical pathologists. Our description, although limited to 2 patients, are in agreement with the description of other published papers that we report in the discussion section.

Otherwise it is sound

Thank you
Level of interest: An article of limited interest

The description of these giant OC in patients treated with bisphosphonates has rarely been reported in the literature. We feel that publishing this case-report is extremely important for every clinicians involved in the bone pathology field and particularly for a diagnosis purpose. The presence of these giant OC in a bone specimen from patients taking Bps should not be interpreted as an increased activity of OC or increased resorption that could lead to a false diagnosis of high bone turnover disease.

Quality of written English: Needs some language corrections before being published

All English errors have been corrected as much as possible. The article has been revised by an English professional.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer 2

Study on Giant osteoclasts in patients with bisphosphonates has been reported.

We agree with you but only very few published papers exist in the literature. Furthermore, we think that reporting this article to a “pathology” journal will specifically target the clinician pathologists working in the bone field and who are likely to see these giant OC in a daily basis. Bisphosphonates are widely used worldwide for osteoporosis treatment so bone specimens used for analysis are likely from patients treated with bisphosphonates.

This ms described two complicated cases of giant osteoclasts with the lack of sufficient evidence of so called "giant osteoclast". Authors will need to provide quantitative assessment of "giant osteoclasts" and TRACP staining.

In our paper, we carefully described the morphology of these giant OC and specifically mentioned their presence in each patient's bone biopsy. We have also put figures of these giant OC in the paper coming from **TRACP staining (OC are in purple color)** in standardized histomorphometry procedure. We specified in the figure title that these images were from TRACP staining. In the first part of the discussion section, we described in detail the characteristics of these OC (size, detachment from bone surface, apoptotic, not associated with resorption lacunae…). These characteristics are completely different from active, multinucleated OC that we could observe in other pathologies associated with high turnover bone disease. In addition, our specific description of these OC is in agreement with previously reported cases of giant OC as we mention in the discussion.
A control will need to be used to demonstrate bisphosphonate treatment did increase numbers of giant OC.

This article is a case report and was not intended to study the number of OC in patients with vs without bisphosphonates. We mentioned in the paper the increased number of OC in patient 2 only to point out the fact that increased OC number does not necessarily mean increased OC activity. We did not mean that Bps induced an increased number of OC in every patients, this statement would have been too affirmative based on the description of one patient. We have modified the manuscript accordingly to be more descriptive. Please note that OC number was normal in patient 1.

In addition, authors will need to report other abnormal pathology of bone in patients with Bis treatment, including abnormal mineralisation etc.

The focus of this paper was to report the presence of giant OC in patients treated with Bps and how the right recognition of these OC could help clinical pathologists in their interpretation of bone specimens. The 2 patients did not show any abnormalities of primary mineralization as shown by normal Mineralisation Lag Time (MLT) and Osteoid Volume (OV/BV) values (histomorphometry results in Table 2). The reviewer probably refers to secondary mineralisation that was not evaluated here. The standard way to evaluate bone secondary mineralisation is by imaging at high resolution scanner. This was not the purpose of this paper.

Level of interest: An article whose findings are important to those with closely related research interests

Thank you. We also agree that reporting these findings will expand scientific knowledge on the mechanisms of action of Bps and allow bone pathologists to better characterize these particular OC morphology. Our objective in publishing this article is to 1) increase pathologists awareness on these particular OC morphology for diagnosis purpose and 2) better understand the bisphosphonates mechanisms of action based on our description and what already published in the literature.

Quality of written English: Acceptable

A thorough language revision has been made to better improve the english quality of this article.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

There are no statistics involved in our paper.