Reviewer's report

Title: Case report of long-term follow-up after denosumab treatment for osteoporosis: rebound associated with hypercalcaemia, parathyroid hyperplasia, severe bone mineral density loss and multiple fractures

Version: 0 Date: 25 Jul 2019

Reviewer: Akira Onishi

Reviewer's report:

1. Do you believe the case report is authentic? Yes
2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments: No, written informed consent was obtained from the patient in this manuscript.

3. Does the Introduction explain the relevance of the case to the medical literature? Yes
4. Does the article report the following information? Where information is missing, please specify.
   a. The relevant patient information, including:
      - De-identified demographic information (age, gender, ethnicity)
      - Main symptoms of the patient
      - Medical, family and psychosocial history
      - Relevant past interventions and their outcomes
   b. The relevant physical examination findings
   c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month.
   d. Diagnostic assessments, including:
      - Diagnostic methods
      - Challenges (e.g., financial, language/cultural)
      - Reasoning and prognostic characteristics (e.g., staging), where applicable
   e. Types and mechanism of intervention
   f. A summary of the clinical course of all follow-up visits

Comments: The comments are included in 9. additional comments.

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented? Comments: The comments are included in 9. additional comments.

6. Is the anonymity of the patient protected? Yes
   Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

7. Is the Abstract representative of the case presented? Comments: Yes

8. Does the case represent a useful contribution to the medical literature? Comments: Yes

9. Additional comments for the author(s)? Thank you for inviting me to review this manuscript. The authors mainly emphasized the misleading diagnostic management of this case, especially several explorations to eliminate neoplasia in the setting of rebound effect after denosumab cessation. Although the concept of rebound effect after discontinuation of denosumab is not widely recognized, these explorations could be avoided in this case with careful consideration based on serum PTH, calcium, phosphate, vitamin D and urine calcium level and therefore the novelty of this case is limited in this point. Hypercalcemia associated with malignancy is caused by PTH-related protein production, osteolytic metastasis, increased production of 1,25-dihydroxyvitamin D or rarely ectopic PTH production. The first three disorders suppress serum intact PTH level, while only ectopic PTH production elevates serum intact PTH level. Hypercalcemia with mid-upper normal to minimally elevated PTH level in this case suggests ectopic PTH or primary/tertiary hyperparathyroidism, and therefore neck exploration
would be conducted at first to identify parathyroid adenoma, hyperplasia, or carcinoma. Based on these considerations, the etiology of hypercalcemia with mid-upper normal to minimally elevated PTH level in this case seems to be more interesting and novel because previous study showed hypercalcemia with low PTH levels due to the bone resorption. The authors should clearly mention the probable etiology and relevant differential diagnosis of hypercalcemia and their reasons in this case with mid-upper normal to minimally elevated PTH level and hypercalcinuria. The authors also discuss the association of the probable diseases with denosumab discontinuation. I also have the following several comments.

Major comments.
1. Medication history, such as calcium and vitamin D supplementation or medication before, on and after denosumab treatment should be provided.
2. The reference range values of the PTH assay the authors used should be provided.
3. Plasma PTH concentration a few months after surgery and after 2 infusions of zoledronate should be provided.
4. The authors should clearly state why several explorations to eliminate a neoplasm could be avoided and in what situation these explorations are essential.
5. The authors emphasized T3 fracture was atypical location. Although it is true that a solitary vertebral fracture in vertebrae higher than T4 is unusual, these fractures are more common when there are also multiple vertebral fractures at lower levels (De Smet AA. Radiology. 1988;166(2):497). The authors should modify the discussion.
6. Although the authors stated only the possibility of tertiary hyperparathyroidism, coexistence of primary hyperparathyroidism with denosumab use is also probable. The authors should discuss it.
7. In addition, tertiary hyperparathyroidism commonly refers to autonomous secretion of PTH probably resulting from prolonged stimulation of parathyroid cell growth in CKD patients due to high phosphate, low calcitriol, and hypocalcemia results in nodular hyperplasia. By contrast, this case has normal phosphate, mid-upper normal calcium, and normal creatinine. The authors should state why the concept of tertiary hyperparathyroidism is applicable to this case.
8. Although the authors stated "PTH and 1,25 OH vitamin D3 levels increase by about 30% during the first few weeks after denosumab injection, but they tend to return to normal values thereafter [6]," the citation seems to be wrong and should be corrected.
9. Although the authors stated "although most cases of tertiary hyperparathyroidism in kidney transplant recipients resolve within a few months [15]," the reference [15] suggested "Serum parathyroid hormone (PTH) concentrations decrease progressively during the first 3 to 6 mo after grafting. However, 1 yr after transplantation, resolution of hyperparathyroidism is incomplete in 50% of recipients" and "Posttransplantation hypercalcemia is a common problem that results from the effect of increased PTH concentrations on different target tissues." The authors should correct their logic of discussion.
10. Although the authors stated "the hyperparathyroidism described occurred rapidly after a single injection of denosumab, with a 22-fold increase in PTH levels at three months and normal calcemia throughout," the reference should be cited. The authors discuss the link between hyperparathyroidism and denosumab without distinguishing primary from secondary hyperparathyroidism. The reference [16] the authors cited was secondary hyperparathyroidism due to hypocalcemia with denosumab treatment. The authors should cite and discuss the reference associated with the etiology of this case.
11. In the third paragraph of the discussion section, the authors discussed the eight cases of hypercalcemia without distinguishing ones on denosumab from ones after denosumab discontinuation. The authors should cite only the relevant references.
12. In addition, although the authors mentioned the mechanisms of hypercalcemia after cessation of denosumab in the third paragraph, this mechanism is likely to be true for patients with low PTH. However, this mechanism is not applicable to this case with mid-upper normal to minimally elevated PTH level and hypercalcinuria. The authors should discuss the specific mechanisms for this case.
14. The authors used capital letter of denosumab and zoledronate (p3, p5) even when they are generic names. They should be corrected to small letter. 15. The authors used the abbreviations without defining them in the text at first use, such as L2, T5, SD, CRP, PTH, MRI, MIBI etc. They should be defined. 16. The authors used T1 and T2 for MRI while T3, T5, T9 etc. were used for thoracic spine. These abbreviations are confusing and therefore should be clearly specified.

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An article of importance in its field

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