Reviewer's report

Title: Hypercalcemia in metastatic GIST caused by systemic elevated calcitriol: A case report and review of the literature.

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Reviewer: Gregory Kline

Reviewer's report:

In this case report, the authors present a rare cause of a common problem, hypercalcemia of malignancy. The report is succinct and clear and provides reasonable evidence to suggest that the patient’s hypercalcemia was indeed mediated by calcitriol. As they point out, this is very rare in GIST tumours and is thus deserving of reporting.

There are a few areas for discussion that the authors could address (Discretionary Revisions):

1. It is probably worth pointing out that there are many tumours, not just myeloma, that induce bone disease/hypercalcemia via the RANK/RANKL system. This is important for recognizing situations where hypercalcemia is due to excessive osteoclast activity that will likely respond best to potent inhibitors of osteoclast function. Along those lines, it is interesting that the present patient’s hypercalcemia didn’t really respond to the zoledronic acid treatment. There are no pre-treatment markers of bone resorption such as C or N telo-peptide to help know whether bone resorption played a major role in the patient’s presentation but the non-response to zoledronic acid would support a non-bone related mechanism for the hypercalcemia. Thus, the message might be that non-bone mechanisms of cancer-related hypercalcemia should always be considered if there is failure to respond to bisphsophonate or denosumab.

2. It is perhaps similarly surprising that the hypercalcemia failed to respond to glucocorticoid therapy which traditionally is thought to be highly effective in calcitriol mediated hypercalcemia. The literature supporting and reporting this is not of especially high quality and so perhaps the non-response was due to a dose that was too low or perhaps the response rate is just less than traditionally thought. Either way, it is probably worth mentioning this somewhat atypical observation.

3. The definitive treatment of the hypercalcemia was the tyrosine kinase inhibitor and it therefore bears mentioning that this therapy should perhaps be considered for control of severe tumoural hypercalcemia even in cases where it is not otherwise being used for anti-cancer purposes and bisphosphonate therapy has failed.

4. I agree with your point that high tissue 1-alpha-hydroxylase activity would need to be demonstrated for the most convincing clinical evidence of mechanism.
5. Minor note – in abstract, should probably specify the enzyme you mean.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**
I declare I have no competing interests.