Reviewer’s report

Title: A rare case of watery diarrhea, hypokalemia and achlorhydria syndrome caused by pheochromocytoma

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Reviewer: Jacques Lenders

Reviewer’s report:

This is a case report of a patient with a vasoactive polypeptide (VIP) secreting pheochromocytoma. This is a rare syndrome with only 10 other documented cases in the literature. This case report is nicely written although I am not completely convinced yet that this patient had a pheochromocytoma. Indeed, the patient had a retroperitoneal tumor that must have secreted VIP since the clinical syndrome of diarrhea and hypokalemia disappeared after tumor removal. The other peculiar finding is the complete reversal of terminal renal failure after tumor removal. I have however the following comments and questions:

1. The main issue why I am not completely convinced that this is indeed a pheochromocytoma is based on the following arguments:
   a. Pathology: only immunohistochemistry with chromogranin A was done. This and the elevated plasma chromogranin A argue of course for a pheochromocytoma but why couldn’t this be an other neuroendocrine tumor such as a carcinoid instead of a pheochromocytoma? The authors do also not describe the typical ‘Zellballen’ structure in the HE staining and I can not see this in the figure 2. Therefore I would like to see some other immunohistochemical marker such as synaptophysin or tyrosine-hydroxylase, showing that this is indeed a chromaffin cell tumor; b. now the authors might bring in the argument that the plasma NMN was hugely elevated in the presence of an only marginally elevated MN. My explanation for this very high plasma NMN level is the extreme sympathetic activation due to severe dehydration and prerenal failure. (when was the plasma sample for NMN taken?). In addition, it is very unusual, although not impossible, to have such a large pheochromocytoma with such a marginally elevated plasma MN since one would expect also an increased epinephrine secretion; c. a last argument of the authors might be the positive PET/CT scan but this is not specific for pheochromocytoma.

2. Did the patients have any spells or other typical signs and symptoms indicating pheochromocytoma?

3. Line 71, page 4: What is Smecta? Please use the generic name of this drug.

4. Please provide the normal ranges of all laboratory measurements to table 1. In addition, the serum albumin should be added in view of the abnormal calcium level.

5. If the authors can provide more evidence that this indeed was a pheochromocytoma, I would suggest to add a table summarizing the most
relevant features of all published cases.

6. Although the abnormal bone markers, suggesting more osteoclastic activity than osteoblastic activity, is interesting in the context of the increased VIP, the absence of a bone biopsy limits the interpretation of these data. It is also not essential for this case. However I would use these data in the Discussion only to explain the hypercalcemia. Is there any relation between this disturbed bone formation versus resorption with the increased unexplained calcitonin levels?

7. Was the thyroid nodule examined for calcitonin staining?

8. The length of the Abstract should be rigourously reduced from 2 pages to maximally 1 page.

9. Figure 2: panels B, C and E can be omitted since they are not essential here.

**Level of interest:** An article of importance in its field

**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 that I have no competing interests