Author's response to reviews

Title: Paroxysmal hypertension secondary to a periprostatic pheochromocytoma: case report and review of the literature.

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Author's response to reviews: see over
Dear section editors of *BMC Endocrine Disorders*,

please find enclosed our revised version of the case presentation entitled: “Hypertension secondary to a periprostatic paraganglioma: case report and review of the literature”, which we would like to resubmit to *BMC Endocrine Disorders*.

We would like to thank the reviewers for their great expertise and we were fortunate to be able to extensively edit our manuscript in order to improve its quality. In this rebuttal letter, we provide a point-by-point response to the reviewer’s criticism. We hope that you and the reviewers can reconsider our manuscript for publication.

Yours sincerely,

Jesper Kers, corresponding author
1. Comments by Andre Faria

1. Please note that the correct nomenclature for extra-adrenal pheochromocytomas is paragangliomas. Therefore, anywhere in the text referred as “pheochromocytomas” should be changed to “paragangliomas”, including the title.

The text including the title has been edited.

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2. Line 5: change “het” to “he”.

The text has been edited.

3. Line 8: please specify which drugs and what doses was the patient on.

The full antihypertensive regimen plus other medicaments with their doses have been added to the text.

4. Line 9: better to write “...which was presumed initially to be due to white coat phenomenon.”.

The text has been edited.

5. Line 9-10: better to write “Figure 1A illustrates...at that time which did not confirm this hypothesis, showing a sustained hypertension pattern.” (this is what the chart shows and, therefore, the title of the article should also be corrected).

The text plus the title have been edited.

6. Line 12: change “non-insulin dependent” for “type 2” and “macula degenerative disease” for “macular degeneration”.

The text has been edited.

7. The authors affirm that the patient suffers from iron-deficiency anemia but do not present any biochemical iron studies. Please note that anemia is not a common presentation of pheochromocytoma/paraganglioma (and this should be mentioned in the text). Rarely, erythrocytosis may occur. In the described setting, other underlying causes of anemia should be seeked (anemia of other chronic underlying disease?). This part should be much more detailed since the anemia probably has nothing to do with the main diagnosis. It would be interesting to add a table with general blood tests including the complete blood count (including MCV and MCH indexes) as well as other tests such as renal and liver function studies, electrolytes, etc.
We added table 1 to the manuscript, which shows the full work-up of the patient at time of presentation at the medical and urological outpatient clinic. We do not consider the anaemia with reticulocytosis to be caused by the paraganglioma, since a second episode at time of revision of this manuscript took place, one year after preperitoneal resection of the tumour. The provisional diagnosis to date is occult gastrointestinal blood loss (in combination with ferriprive anaemia), for which re-evaluation by panscopy and videcapsule endoscopy is planned. We have added this new finding to the case presentation as well.

8. Line 18: please correct “reason FOR referral”.

The text has been edited.

9. The authors also describe that the patient did not experience LUTS (e.g. dysuria, nocturia, frequency, etc) but did he report any symptoms while voiding (e.g. headaches)? If not, deny in the text.

The text has been edited. The patient did not experience other complaints while voiding. Interestingly, this phenomenon mostly occurs in patients with an intraprostatic paraganglioma (table 3).

10. Line 21: What complaints have changed?

Complaint have not changed, which was the reason for performing CT thorax-abdomen with contrast. The text has been edited.

11. Line 24: please add description of the tumour enhancement pattern following contrast.

Unfortunately, this was not a 4-phase CT, therefore tumour enhancement has not been described by the radiologist. Therefore Hounsfield units have no additional value in this case as well since there is no blank CT abdomen.


Postcontrast has been added to the text, Hounsfield units did not contribute to the differential diagnosis in this patient. This is explained in the text.

1. Line 7: figures should be described in the sequence they appear in the text. Therefore, this should be Figure 2D.

The figures plus text have been edited.

2. Line 15: Add calcium metabolism (PTH, 25OH Vitamin D, etc) to previously suggested
Full work-up of the patient has been added as table 1 to the manuscript, including indices for calcium metabolism.

3. Line 16: Please note that primary hyperparathyroidism is a component of MEN2A but not of MEN2B. Also add to discussion if there are criteria for indications of surgery for this disease (osteoporosis, decrease in renal function, etc) using current guidelines and if further surgery was planned.

After discussion with the internist, the hyperparathyroidism is considered secondary, which does not need surgical intervention. The patient’s corrected serum calcium improved by vitamin D supplementation. This was added to the text.

4. Line 20: Octreotide scintigraphy (Octreoscan) is not a commonly performed test while searching for paragangliomas and did not give any further clue (since MIBG was positive) in this case. This should be excluded from the discussion.

Data on the Octreoscan have been deleted from the text, because it does not have any value in the description of the case.

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1. A stepwise approach based on the clinical scenario, rather than screening for every disease-causing gene, is generally recommended since it is more cost-effective. This should be added to the discussion. In this case of an abdominal paraganglioma, for example, a more rational approach would be to screen initially for RET (because of the associated PHP, although extra-adrenal pheochromocytomas are rare in this syndrome) followed by SDHB, SDHD and VHL (see Welander et al. Endocr Relat Cancer. 2011 Dec;18(6):R253-76).

We fully agree, a suited genetic workup should have been performed as described by Erlic et al. 2009 Clin Cancer Res or Welander et al. 2011 Endocr Relat Cancer. By mistake, the full panel of genes related to any type of pheochromocytoma was performed at the genetic department of the University of Nijmegen. We describe in the text that a stepwise approach is more suitable.

2. Line 6: “Figure 2F” should read “Figure 2E”.

The text has been edited.

3. Ideally, patients should be started on alpha-blockade at least 10-14 days before surgery is planned – this should be discussed (see Pacak. J Clin Endocrinol Metab. 2007 Nov;92(11):4069-79). Please also specify the doses of each medication. What formulation of nifedipine was used (Slow release? Short acting?)? Why was metoprolol added to the regimen?
The patient received an increasing dose of alpha blockade starting 4 weeks prior to surgery. Beta blockade was initially halted and reintroduced as metropolol retard. Finally nifedipine was added to the regimen and preoperative fluid resuscitation was performed according to the scheme by Pacak. The text was edited.

4. Line 18: Was drug treatment optimized after the 1-month visit since it was above target BP recommendations?

Hydrochlorothiazide+valsartan was added to metoprolol, which resulted in a blood pressure of 149/91. This was added to the text.

5. Line 19: “Figure 2E” should read “Figure 2F” and it should be specified that this picture represents the macroscopic specimen.

The text was edited.

Page 8

The conclusions section is poorly written. It should be much improved with the previously discussed points. Additional points:

We have edited the discussion section.

1. Line 5: change “by incidence” for “incidentally”.

This has been edited in the text.

2. Lines 21-23: change for “In the case presented in the current manuscript, the patient had been diagnosed with hypertensive cardiomyopathy two years before the diagnosis of the paraganglioma.”

This has been edited in the text.

3. Line 25: “…in the context of a GENETIC syndrome…”

This has been edited in the text.
2. Comments by Urs D. Lichtenauer

Major Compulsory Revisions

- line 8 Abstract page: the authors describe a coincidental discovery of the tumor upon rectal examination. However, in line 6 auf the conclusion page and line 23 of the case presentation page, the tumor seems to be discovered upon a screening CT scan. Please clarify.

The tumour was discovered upon screening CT thorax/abdomen with contrast, digital rectal examination affirmed the findings of the CT scan. This was edited in the text.

- line 4 case presentation: The patient suffers from iron-deficiency anemia since 2010. Line 20 same page: cause of anemia still unclear. Line 4 conclusion: unexplained microcytic anemia. Please clarify. What turned out to be the cause for the anemia in the end?

The microcytic hypochromic anaemia with reticulocytis led to the provisional diagnosis of occult gastrointestinal blood loss (with ferriprive anaemia). One year after resection of the tumour, the patient was readmitted with similar complaints (hemoglobin 3.3M, reticulocytosis). We have planned an panscopy including videocapsule endoscopy. This was added to the text. We consider the anaemia not to be related to the paraganglioma.

- line 15 case presentation page 6: the diagnosis of primary hyperparathyroidism is not comprehensible for the reader: What were the calcium and phosphate serum und urine concentration? What were the intact PTH and the vitamin D levels? Secondary hyperparathyroidism due to vitamin D deficiency must be excluded as it is a common finding in the elderly. If the diagnosis of primary hyperparathyroidism is correct, the authors should include in the text, how they want to control hypercalcemia and osteoporosis of this Patient in the future and if exploratory parathyroidectomy is planned.

After discussion with the internist, the hyperparathyroidism is considered secondary, which does not need surgical intervention. The patient’s corrected serum calcium improved by vitamin D supplementation. This was added to the text. We added table 1, which includes calcium metabolism.

- line 17 case presentation page 6: MEN2B is not associated with primary hyperparathyroidism and should be excluded from the text.

The text was edited.

- line 17 conclusion: This is not the classical triad. Please see also comment under Discretionary Revisions

Indeed, none of the symptoms of the classical triad were present in the current case, we have edited the text.

- what were the postoperative/follow-up metanephrine levels as a proof that the
catecholamine excess was attributed to the tumor?

> *Table 2 shows the fractionated urinary metanephrine levels 2 weeks and 5 months post-surgery. This shows clear improvement of catecholamine excess.*

Minor Essential Revisions

- line 8 case presentation page 6: The authors should mention the percentage of Ki-67 positive cells, as this figure is discussed as a marker to improve the staging/grading system. What was the PASS-score?

> *The pathologist described hardly any Ki-67 positive cells, indicating low proliferation index of the tumor. The PASS score has not been performed, since it has been shown to not be able to reliably indicate metastatic or aggressive types of pheochromocytomas (not described for paragangliomas). [Agarwal et al. 2010 World J Surg]. We therefore consider this score of no additional value for the current manuscript.*

- line 14 case presentation page 6: Were plasma-metanephrines measured, as this measurement is the most sensitive and specific method available today?

> *To the best of our knowledge, urine fractionated metanephrins have equal sensitivity to detect catecholamine-producing tumour as compared to plasma fractionated metanephrins (>95%), however plasma metanephrins have lower specificity as compared to urinary metanephrins [Lenders et al. 2002 JAMA, Sawka et al. 2003 J Clin Endocr Metab, Sawka et al. 2004 BMC Endocr Disord]. We have not measured plasma fractionated metanephrine levels in the current case.*

- case presentation page 6: Although the elevated urine normetanephrines in this case seem clearly related to the tumor, the authors should discuss the exclusion of factors that are known to lead to false positive results such as a history of psychiatric disease and psychiatric drugs, smoking, etc. See also postoperative metanephrine Levels in the Major Compulsory Revisions section.

> *The text was edited.*

- line 5 case presentatin: ‘he’ instead of ‘het’ as just one example. Please re-read the manuscript carefully to eradicate misspellings. Although the manuscript is clearly written and a pleasure to read, some sentences are sloppily expressed, so to enhance the overall impression, I would recommend improve some of the wording .

> *The text was re-evaluated for typos and misspelled sentences were reconsidered*

Discretionary Revisions - Line 8 Abstract page: it would be nice if the tumor size could be integrated

- Line 6 background: the classic clinical triad of pheos includes: headaches, sweating, and
palpitations in a hypertensive patient. Paroxysms of hypertension are present in less than 40 - 50% of cases only. Paleness as a symptom is present in 30 - 60 % of cases. Maybe the authors could differentiate between the well accepted triad and the symptoms they found in their patient.

This was further explained in the text. The current case did not have a classical triad of symptoms.

- line 3 case presentation: ‘medicine department’ instead of ‘medicine ward’?

The text was edited.

- an extra-adrenal pheochromocytoma manifestation of a hereditary paraganglioma syndrome in a 76 year old is highly unlikely. Maybe the authors should point out, that such an extensive and expensive genetic evaluation is not recommended routinely in such a patient.

We agree that a hereditary syndrome is highly unlikely in this patient. In this case, we considered the advice by Erlic et al. to screen for RET, SDHx and VHL in extra-adrenal localization. By mistake, the genetics department of the Radboud University Medical Center sequenced all pheochromocytoma-related genes to date. We discuss this in the text.

- line 8 case presentation page 7: 7 days of pretreatment is quite short in a Patient with ischemic heart disease, as in most medical centers, adrenergic blockade usually starts 7–14 d preoperatively. Since this is a controversial field, it would be interesting to learn, if the authors had particular reasons to use doxazosine and nifedipin, as phenoxbenzamine is more widely being used.

By mistake, 7 days of pretreatment was noted in the case report. This should be 4 weeks. We started by halting nebivolol and initiated alpha blockade by an increasing dose of doxazosine (this medicament is widely used in the Netherlands as there is no evidence for a better control with use of phenoxbenzamine to date). Next metoprolol retard was initiated and finally nifedipine was added to the regimen as well, which resulted in an acceptable pre-operative blood pressure. Prior to surgery, fluid resuscitation according the scheme by Pacak was initiated.
3. Comments by Antonio M. Lerario

- Major Compulsory Revisions

There are just minor points.

- Minor Essential Revisions

- Figure 1 does not contribute to illustrate the presented case in this context and in my opinion should be abolished.

*We agree that this image is not specific for the treatment of the current paraganglioma but rather to paragangliomas or pheochromocytomas in general. However, since the current type of surgery differs from the more widely described laparoscopic surgery and the tumour localization is very rare, we find it illustrative to remain the current image for full documentation.*

- The diagnosis of concomitant hyperparathyroidism is mentioned on the text. Authors should provide biochemical and hormonal data that corroborate the diagnosis.

*Table 1, showing the full workup including calcium metabolism is added to the manuscript. Secondly, we reconsidered the hyperparathyroidism to be secondary (improvement with vitamin d supplementation, no indication of resection of parathyroid glands). The text was edited.*

- More details about genetic screening should be given. Did the authors perform just sequencing of the candidate genes? Methods for detecting large deletions for the SDHx genes (e.g. MLPA) were also employed? Authors should also provide a rationale for performing genetic tests in the context of a single extra-adrenal paraganglioma in a 76 year-old male patient.

*We agree, as opposed by the other reviewers as well, that a hereditary syndrome is highly unlikely in this patient. In this case, we considered the advice by Erlic et al. to screen for RET, SDHx and VHL in extra-adrenal localization. By mistake, the genetics department of the Radboud University Medical Center sequenced all pheochromocytoma-related genes to date. We discuss this in the text. MLPA in order to find larger deletions was performed as well (MRC-Holland kit P226-B2).*