Author’s response to reviews

Title: A pitfall of bilateral inferior petrosal sinus sampling in cyclic Cushing’s syndrome

Authors:
Adriana Albani (albaniadriana@gmail.com; Adriana.Albani@med.uni-muenchen.de)
Christina Maria Berr (berr.christina@gmx.de)
Felix Beuschlein (Felix.Beuschlein@usz.ch)
Marcus Treitl (marcus.treitl@med.uni-muenchen.de)
Klaus Hallfeldt (klaus.hallfeldt@med.uni-muenchen.de)
Jürgen Honegger (juergen.honegger@med.uni-tuebingen.de)
Günter Schnauder (guenter.schnauder@med.uni-tuebingen.de)
Martin Reincke (martin.reincke@med.uni-muenchen.de)

Version: 1 Date: 17 Jul 2019

Author’s response to reviews:

Munich, July 17, 2019
RE: BMC Endocrine Disorders - BEND-D-19-00040

Dear Prof. Byrne

Thank you very much for giving us the opportunity to address the excellent comments of the Reviewers and submit a revised version of the manuscript for consideration. Please find our replies to the helpful and insightful points raised by the Reviewers at the end of this letter. The resulting changes have been highlighted in yellow in the revised manuscript. We hope that the revised manuscript may be suitable for publication in the BMC Endocrine disorders

Sincerely yours,

Martin Reincke

Medizinische Klinik und Poliklinik IV
Ludwig Maximilian University Munich
Ziemssenstr. 1, 80336 Munich
Germany

Martin.Reincke@med.uni-muenchen.de

Replies to the Reviewers’ comments
Editor Comments:

In the Declaration, please clarify whether written or verbal informed consent for publication was obtained. Please refer to our guidelines for information regarding consent for publication.

We thank the editor. We clarified in the declaration in line 246 that a written consent for publication was obtained.

Reviewer: 1

Comment to the Author

A well-written manuscript from an extremely well-known group. Difficult case. The main issue for the editorial board is whether this nicely written case (a very good one for teaching and for presentation/discussion at a regional or national meeting for junior and senior colleagues alike) could be said to ADD anything to the literature as it already stands sufficient to merit publication. That's a matter of editorial judgement. There are some very minor points to make, none of which are major barriers to publication.

1. Reference is made in the case description on a number of occasions to results without details e.g. 'lack of suppression (line 106). It would be better to include the actual values for completeness. There are a number of examples through the case. E.g. line 127 ('slightly abnormal' is probably not really sufficient description).

We thank the Reviewer for the praise and favourable comments. We thank the Reviewer for pointing this out. We are happy to provide the numeric values for midnight salivary cortisol 121 nmol/L (normal range: < 41); 24hUFC 1051 nmol/24 h; serum cortisol after 1 mg dexamethasone 215 nmol/L (normal range: <50) (lines 129-131) and for serum cortisol after 8 mg dexamethasone 513 nmol/L (normal: < 50) (line 108).

2. Line 133. Subcutaneous pasireotide was administered and hypercortisolism disappeared shortly thereafter because of spontaneous remission. I didn't quite understand this. How would one know if it was the drug or spontaneous?

We thank the Reviewer for this intriguing question. First, we have been considering a therapeutic effect of pasireotide, however it was administered short–term for 4 days, and termination did not result in a recurrence. Based on the ectopic source of ACTH hypersecretion later confirmed, the most likely explanation is spontaneous cycling of ACTH excess. In the literature, there is only one case report of a pasireotide response in a case of a medullary carcinoma and ectopic Cushing syndrome (Verburg FA, Anlauf M, Mottaghy FM, Karges W. Somatostatin receptor imaging-guided pasireotide therapy in medullary thyroid cancer with ectopic adrenocorticotropin production. Clin Nucl Med. 2015 Jan;40(1):e83-4). In that patient, DOTATATE pet was positive and localized the tumor. However, our patients did not have a positive DOTATATE pet scan, making a pasireotide response unlikely. In the revised manuscript we clarified in lines 136-139 “Subcutaneous pasireotide was administered for four days with immediate normalization of cortisol levels, which remained normal thereafter suggesting a spontaneous remission rather than a therapeutic effect”
3. Hypokalaemia is referred to more than once, but no values are given (or bicarbonate). It does lack a degree of specificity, but profound hypokalaemia and alkalosis does alert the physician to the possibility of ectopic ACTH; what was the lowest one recorded (for interest).

We thank the Reviewer for the suggestion. Accordingly, in the revised manuscript we added the actual k+ values in lines 97 and 102. The lowest value recorded was 2.4 mmol/l (reported in line 40). Furthermore, in the figure n.2 we report potassium levels over the time (weeks).

Reviewer: 2

Comments to the Author
GENERAL COMMENTS: This case report describes a patient with cyclic ectopic cushing syndrome secondary to a neuroendocrine tumor. A BIPSS was done during an inactive phase of the disease leading to incorrect localization and surgery.
REQUESTED REVISIONS:
This is a very tough and interesting case. It demonstrate that Cushing syndrome is always challenging. I have some question regarding the cases.
It is not clear to me how retroduodenal NET was diagnosed? it was sampled during the whipple’s procedure? How you conclude that site was the primary?

We thank the Reviewer for the kind assessment.
We apologize for being confusing at this point. The primary tumor has not been identified so far. In the revised manuscript we clarified in lines 148-153 “Together with the clinical data (no further primary suspect focus detectable in the DOPA and DOTATATE PET/CT and MRI), the findings were suggestive for an occult, possibly pancreatic, NET WHO grade II with accompanying loco-region lymph node metastasis, located in the retro-duodenal tissue close to the pancreatic head. The tumor infiltrates reached the broken surface of the specimen, indicating an incomplete tumor resection.”

In the case report is not stated that the pancreatic met was a lymph node. This should be written more clearly.

We thank the Reviewer for the suggestion. Accordingly, we stated this in the revised manuscript lines 45-47 “Surprisingly, the histopathology was conclusive for ACTH-positive lymph node metastasis located in the retro-duodenal tissue of an occult neuroendocrine tumor WHO grade II”. In lines 143-144 we stated “histopathology did not confirm the pancreatic lesion but identified several ACTH-positive lymph node metastases”.

Additionally, how was the Ki67 of the initial biopsy (the met of the pancreas). It is very rare that a NET grade II transforms to a NET grade III.

We thank the Reviewer for the astute observation. In the revised manuscript in lines 145-148 we reported “The Ki67 staining was limited due to the strong fragmentation of the tissue and the presence of numerous intratumoral lymphocytes. On average, Ki67-positive tumor cell nuclei were less than 20%. Only in single hot spot region, areas with up to 25 to 30% positive tumor cell nuclei were identified.”
The bone biopsy showed a well differentiated tumor or a poor differentiated tumor?

We thank the Reviewer for this question. The bone biopsy described a bone marrow with infiltration of the ACTH expressing neuroendocrine carcinoma and a high proliferation rate: Ki67 was about 80%. The text states “Pathology report documented an ACTH-, synaptophysin- and chromogranin A-positive metastasis of the NET tumor with a proliferation rate of 80%” (Lines 161-163). The examination was unfortunately not reviewed according to the tumor grading system.

How was the RECIST response to chemo???

We thank the Reviewer for drawing attention to this important point. According with the RECIST criteria the disease was stable during chemotherapy. In the revised manuscript in lines 165-166 we added “Imaging studies documented unchanged number and size of target lesions, reflecting stable disease”.