Author’s response to reviews

Title: Atypical or typical ACTH-producing pulmonary carcinoids and the usefulness of 11C-5-hydroxytryptophan positron emission tomography: a case series

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Version: 2 Date: 6 February 2013

Author’s response to reviews:

The Editor in Chief,
Professor Michael Kidd
Journal of Medical Case Reports

Dear Sir,

Thank you for the constructive comments on our manuscript “MS: 1332711640881854, Atypical or typical ACTH-producing pulmonary carcinoids: report of two cases and the usefulness of 11C-5-hydroxytryptophan positron emission tomography.”

We have now revised the manuscript according to the comments of the reviewers. Our response to the points raised by the reviewers is given in detail below. The title of the manuscript is changed to “Atypical or typical ACTH-producing pulmonary carcinoids and the usefulness of 11C-5-hydroxytryptophan positron emission tomography: a case series.”

We hope the changes we have made to the manuscript, in accordance with the comments by the referees, make the paper suitable for publication in The Journal of Medical Case Reports

February 6, 2013

Yours sincerely

Bertil Ekman, MD, PhD
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Reviewer’s report
Title: Atypical or typical ACTH-producing pulmonary carcinoids: report of two cases and the usefulness of 11C-5-hydroxytryptophan positron emission
Wo case reports report straight forward garden-variety cases of ectopic ACTH-producing neuroendocrine tumors.
Especially case 2 is very common.
Case 2 is interesting for the use of 11C-5HTP Pet. However, as noted by the authors the added value of this imaging modality has previously been described.

Answer: We agree that pulmonary carcinoid tumours are quite common, however an ACTH producing pulmonary carcinoid is a novelty. Reports of the use of 11C-5HTP PET exist, but it is an examination restricted to a highly specialized endocrine tumour units. Case 1 underline the need of collaboration with such centres, bilateral adrenal ectomy was avoided and the carcinoid was successfully removed.

Reviewer's report
Title: Atypical or typical ACTH-producing pulmonary carcinoids: report of two cases and the usefulness of 11C-5-hydroxytryptophan positron emission tomography
Version: 1 Date: 22 January 2013
Reviewer: Christian Koch
Which of the following following best describes what type of case report this is?: Unexpected or unusual presentations of a disease
Has the case been reported coherently?: Yes
Is the case report authentic?: Yes
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: Yes
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: Yes
Does the case report have diagnostic value?: Yes
Will the case report make a difference to clinical practice?: Yes
Is the anonymity of the patient protected?: Yes
Comments to authors:
The authors report a well written case series of 2 patients with ectopic ACTH syndrome which is rare.

There are some typographical and minor errors in Grammar in addition to omissions of certain laboratory and/or imaging and treatment modalities that should be mentioned/addressed.

Abstract:
first sentence: say "have" instead of has

Answer: Thanks, we have now corrected the grammar.

specify ethnic group or race of woman and man reported here
Answer: The ethnic group has been added to the report (both patients are Caucasians).

add follow up time period before conclusion
Answer: The follow up time has been added to the report (both patients has a follow up time of 24 months)

Introduction:
add additional references mentioning pancreatic and ileal ectopic ACTH-secreting tumors –

Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production upon second recurrence.

Ectopic Cushing's syndrome caused by a well differentiated ACTH-secreting neuroendocrine carcinoma of the ileum.

Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome?
Uwaifo GI, Koch CA, Hirshberg B, Chen CC, Hartzband P, Nieman LK, Pacak K.

Answer: Thanks for suggesting these references. We have added Miehle et al and Singer et al to the introduction.
Case 1:
specify ethnic group or race of the woman
Answer: The woman is Caucasian. This information is added to the case presentation.

was plasma chromogranin A and/or neuron specific enolase measured?
Answer: Chromogranin A was slightly elevated to 8.2 nmol/L (reference <6) The patient did not have any proton-pump inhibitor. Information is added to the case presentation.

instead of "achieved" say received
Answer: Achieved is changed to received as suggested.

what were the side effects of ketoconazole for this woman?
Answer: Ketokonazole was discontinued due to increased liver specimens.

what were the side effects of cabergoline and why was it added anyway, as it is known to be not very efficacious in patients with Cushing's syndrome?
Answer: The rationale for using cabergoline stems previous reports suggesting moderate decreasing levels of ACTH/Cortisol in pituitary adenomas. Cabergoline was added as an ex juvantibus treatment before we had received the results from the sinus petrosus sampling. We have rewritten the section of medications as it was wrongly stated that cabergoline was added after the other medications and we have also described the side effects of cabergoline.

This text is added to the case presentation:
“Before we had the results from the sinus petrosus sampling, treatment with cabergoline was added, but it was quickly withdrawn due to side effects of dizziness, nausea, and uncontrollable shakings. The reason to start with cabergoline and not with ketokonazole was moderately elevated liver specimens.”

How would the authors define clinical improvement? Did glycemic control and/or blood pressure improve on ketoconazole and metyrapone? Usually the HPA axis overrides steroidogenesis blocker over time, i.e. ACTH and cortisol levels further rise. Why not here?
Answer: Unfortunately no symptoms related to her disease were relieved by the medication with ketoconazole and metyrapone, as stated in the case description. The patient was treated for a month and in that short period this treatment could show improvement regarding ACTH and cortisol levels (in her case stable, fortunately not further increase during medical treatment).

Say "investigations....are centralized...."
Answer: We agree and this is added to the case presentation.

Figure 1 does not show color, as it would be typical for this type of PET tracer and imaging method" - please explain.

Answer: We agree that colour picture is the typical and we have modified this and show the original colour picture instead = Fig 1.

How much hydrocortisone is the patient now taking - do not say "tablet" but hydrocortisone.

Answer: The patient is now taking 25 mg hydrocortisone per day. This information is added to the case presentation.

How many months of follow up does the patient now have after the tumor had been removed? Perhaps the patient was given too much HC thereby avoiding that the endogenous HPA axis recovers by its own.

Answer: The follow up time is now 24 months. Hydrocortisone doses of 25 mg per day usually not suppress the endogenous HPA axis. Attempts to further lower her hydrocortisone dose gives sign of severe hypocortisolism with low blood pressure, dizziness and stomach pain. In addition data on DXA scanning is added to the case presentation.

The text is changed as follows:

“DXA scan showed osteoporosis with T-scores of -3.0 both in L2-L4 lumbar spine and in total hip and she was prescribed annual Zoledrice acid infusions. At 24 months follow-up, she still has low morning cortisol levels below 100 nmol/L and plasma ACTH < 5 ng/L before hydrocortisone intake in the morning (25 mg total daily dose).”

Case 2:

- specify ethnic group/race

Answer: The male patient is Caucasian. This information is added to the case presentation.

- report normal range for total testosterone in parentheses

Answer: Reference levels for testosterone are added. We also comment on chromgranin A as suggested in case 1.

Added to the case presentation: “His chromgranin A levels and blood sugar levels were normal, while a very low serum testosterone of 2.6 nmol/l (7.6-31) was recorded”.

- did the patient have clinical features of osteoporosis or radiographic evidence for it?
Answer: A DXA scan showed normal bone mineral density. This information is added to the case presentation.

how was the 1 mg (and/or 8 mg) dex supp test BEFORE surgery?

Answer: He did not suppress his cortisol and ACTH levels at all on 1 mg dexamethasone suppression test. This information is added to the case presentation.

Was a pituitary MRI done? This should be stated here and why.

Answer: The first imaging investigation in an ACTH dependent Cushing syndrome is usually MRI of the sellar region.

The text is modified in the case presentation: “An MRI scan of his sella turcica did not visualise any pituitary tumour, while pulmonary chest radiograph and subsequent CT scan revealed a 12*9*14 mm cm diameter mass in the right lower pulmonary lobe, Figure 2.”

Discussion:

say "...have a better prognosis..."

Answer: This is changed as suggested.

Why would the authors state a normal pit MRI if here we deal with ectopic hypercortisolism and not Cushing's disease? suggest to delete this sentence.

say "for demonstrating an abnormal..."

Answer: We delete this sentence as suggested.

Would modify the statement before the conclusion: "if...a useful imaging modality in addition to laboratory follow-up parameters could have been set".

Answer: We have modified the statement as follows:

“Taken together, if the tumour can be visualized with somatostatin receptor scintigraphy or 11C-5-HTP-PET preoperatively in addition to laboratory specimens the post-surgery follow-up is facilitated.”

The authors cannot ignore the fact that the resolution of SSR is around 6 mm, i.e. tumors smaller than that may not be picked up by imaging even if these tumors carried receptors for SSR2,35.

The resolution for the mentioned specific PET tracer is around 4 mm to my knowledge and the authors should note these facts in a statement, ideally with respective literature cited.
Answer: We agree that the resolution of SSR around 6 mm is near the tumour size of 8 mm found in the case 1 and may be the reason to the negative result. We will add this additional information to the discussion:

“However, the tumour was not detected in our female patient and this could be due to possible lack of somatostatin receptors in the tumour or the size being only 8 mm, which is near the resolution limit of 6 mm for SRS methods [6].”

“Compared with CT and somatostatin receptor scintigraphy, 11C-5-HTP-PET has been shown to visualize more and smaller lesions down to 4-5 mm [5, 9].”

Conclusion:
The authors should modify their sentence by noting that such imaging can only be performed at highly specialized endocrine tumor centers and that selected patients should be considered to be referred to such centers.

Answer: We agree and one of the aims with this report is to highlight the possibility to send a patient for 11C-5-HTP-PET at a specialized center. We changed the last sentence in the conclusion to:

“We suggest that a referral to a specialized center for investigation with 11C-5-HTP-PET in selected cases is preferable when a CT/MRI examination fail to detect any ectopic ACTH-producing tumour.”

Quality of written English: Acceptable
Declaration of competing interests:
I declare that I have no competing interests