Author's response to reviews

Title: Pituitary and adrenal involvement in diffuse large B-cell lymphoma, with recovery of their function after chemotherapy

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Author's response to reviews: see over
March 18, 2013

Dear Editor-in-Chief,

BMC endocrine disorders

Attached please find our revised manuscript, “Pituitary and adrenal involvement in diffuse large B-cell lymphoma, with recovery of their function after chemotherapy” by Nakashima Y et al., which we would like to submit for publication as a case report in BMC endocrine disorders.

We read the reviewers’ comments and revised our manuscript according to their recommendations. The details of the revisions are listed below.

We would appreciate it if you consider our manuscript for the publication in BMC endocrine disorders.

Sincerely yours,

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**Comments for Reviewer:** Brian Layden

Minor Essential Revisions

In section “case presentation”

1) The sentence that starts with “the had polydipsia” is missing a word.
Answer: The authors corrected this sentence. (P.6, line 2)

In figure 3,

2) I think this is an important figure, but its presentation is confusing. I would try to simplify.
Answer: According to the reviewer’s comment, Figure 3 has been revised as provided.

In Figure 4, A-F.

3) Is the loading test done with CRH, TRH, and LHRH at the same time? It is not clear to me.
Answer: These tests were performed at the same time. To make it being clear, the description has been added in the result part (P.7, lines 11-12).

4) In table 2, it would be helpful to report the results of the stimulation test after treatment, relative to the baseline level.
Answer: The authors would like to keep the table 2 as it is. Since the comparison of the stimulation tests before and after treatment are shown in Figure 4.
Comments for Reviewer: Urs D Lichtenauer

Major Compulsory Revisions

1) Diagnosis of central Diabetes insipidus is questionable: Values of serum and urine osmolality as well as urine sodium, urine volume and total fluid intake are not provided. Plasma sodium levels were normal and signs of dehydration, or results of a deprivation test were not described.

Answer: According to the reviewer’s comment, these important data have been added in Table 1 and case presentation part (P.6, line 2-5). In addition, the description of clinical sign of dehydration has been also added in the case presentation part (P.6, line 2-5). The deprivation test was not performed.

2) Diagnosis of tumor associated primary adrenal insufficiency in addition to the secondary insufficiency unlikely: the blunted adrenal response to exogenous ACTH administration can be most likely explained as secondary to the prolonged ACTH deficiency. Along the same line, a significant adrenal tumor burden would have impaired the renin-angiotensin-aldosterone-axis. As serum potassium is normal, this is unlikely. Nevertheless, the authors should provide more adrenal parameters such as aldosterone, renin, DHEA.

Answer: The authors agree with the reviewer’s comment on the etiology of the adrenal insufficiency. The adrenal insufficiency mainly resulted from hypopituitarism. However, in this clinical setting, the authors cannot exclude the possibility of primary adrenal insufficiency. The corresponding sentences in the result part have been revised (P.8, lines 8-11).

Additional parameters including DHEA, plasma renin activity and aldosterone have been added (Table 1 and P.5, lines 17-18).

3) Why was LHRH- and CRH-loading test chosen, as the results are difficult to interpret and the insulin-hypoglycemia test represents the 'gold standard' for the evaluation of the adrenal and somatic axis? Furthermore, besides that administration of TRH could have become dangerous for the patient, the TSH results were not provided. However, interpreting the test is extremely problematic and displaying low basal thyroid levels (including fT3) is sufficient to convince the reader of the impairment of the thyroid axis. Was the impairment of the thyroid axis so mild, that 25 µg levothyroxine was an adequate substitution dose?

Answer: LHRH and CRH test were necessary for the evaluation of the anterior pituitary gonadotroph function as well as corticotroph function. Indeed, quantitative
evaluation of the pituitary function could be done in the present case as shown in Fig.4. In case of adrenal insufficiency, insulin tolerance test that induce hypoglycemia might be dangerous. Therefore, the authors have chosen CRH loading test instead of ITT. As the reviewer pointed out, TRH test may cause pituitary apoplexy in case of pituitary tumor. However, this is not the case. The diagnosis of DLBCL had been already made when the test was carried out. Collectively, well-planned examinations were carried out. Consequently, interpretations of those results can be justified.

The reviewer’s comment that ‘TSH results were not provided’ comes from misreading. The results of TRH loading test have been explicitly shown in Table 2.

Minor Essential Revisions
1) Diabetes insipidus: 24 hour urine volume and amount of fluid intake must be provided. Did the Patient suffer from nocturia?
   Answer: According to the reviewer’s suggestion, the data for making a diagnosis of diabetes insipidus such as urine volume and fluid intake have been provided in the case presentation part (P.6, lines 2-3). In addition, Table 1 has been revised.

2) MRI-imaging: was there a mass distinct different from the pituitary, or was the entire pituitary gland diffusely enlarged. If the latter, take out the word ‘mass’. Please give the size of the pituitary before and after therapy.
   Answer: According to the reviewer’s suggestion, the authors corrected the words ‘mass’ or ‘tumor’ to ‘lesion’, and the size of the pituitary before and after therapy have been added (P.5, line 4 and P.7, lines 2-3).

3) Figure 3:
   - time scale is truncated and cannot be read.
     Answer: The incomplete figure 3 was accidentally provided. The figure 3 has been corrected.
   - figure legend, except for the abbreviations, does not describe what is depicted.
   - explain the abbreviation sIL-2R in the figure legend.
     Answer: According to the reviewer’s comment, figure legend of Figure 3 has been revised (P.16, lines 8-10).
   - are those ACTH levels depicted stimulated (e.g. after CRH administration) or basal? If basal, they appear very high. Please clarify.
Answer: Those ACTH data are basal values. To make it being clear, the figure legend of Figure 3 has been revised and the following sentence has been added in the results.

The ACTH levels are within reference range of our institution. According to the reduction of hydrocortisone, the basal ACTH levels gradually improved to the upper limit of the reference range (P.7, lines 14-16).

Discretionary Revisions
4) Page 6, line 1: word 'patient' is lacking
Answer: The authors corrected this sentence (P.6, line 2).
5) Page 8, 3rd line from below: better: 'similar to a pancoast tumor'
Answer: According to the reviewer’s comment, this sentence has been revised. (P.9, line 12)
6) Dosage of replacement Regimen and the dose reductions possible after treatment should not only be displayed in the figures, but also mentioned in the text.
Answer: According to the reviewer’s comment, the authors provide the dosage of replacement therapy in the text (P. 6, lines 9-10).

7) Post-therapeutic basal thyroid, cortisol, and testosterone concentrations should be provided.
Answer: According to the reviewer’s suggestion, the post-therapeutic basal concentrations of thyroid, cortisol and testosterone have been provided in the text (P. 8, line 15 - P.9, line 1).

8) Figure 1: it would be nice to have a post-treatment Image of the pituitary
Answer: According to the reviewer’s suggestion, the post-treatment Images have been provided in Figures 1I and J.

9) Figure 3: it would be nice if the authors could present IL-2R concentrations in the text and how they changed over time. Why do they remain elevated after successful therapy. Please discuss.
Answer: The level of sIL-2R had been within reference range during the chemotherapy, so the authors consider that the transition of the data is not significant. To make it being clear, the authors revised the text (P. 7, lines 6-7).

10) Table 1: reference range for each value should be given, and pathologic
Parameters could be highlighted.
Answer: According to the reviewer's comment, Table 1 has been revised as provided.

11) It would be nice, if the dosage of the chemotherapy regimen was provided.
Answer: According to the reviewer's suggestion, the dosage of the chemotherapy have been added (P. 6, line 12 - P. 7, line 1) and figure legend of Figure 3 (P. 16, lines 13-18).

12) Table 2: FSH Response could be judged as normal as there are no valid cut off criteria established. However, there is no doubt that the adrenal axis is severely affected. What was the reason, not to replace testosterone? Please discuss. Was the bone mineral density measured?
   Answer: Because the basal LH level is extremely low as shown in Table 1, the existence of the hypogonadotropic hypogonadism is clear. As the reviewer pointed out, there is no valid cut off criteria of FSH level and FSH is sometimes hypo-responsive even in healthy subjects. In our case, the response of FSH was kept to some extent. The detailed mechanisms underlying this discrepancy between LH and FSH remain unknown. Although the secretion of both LH and FSH is under the control of GnRH, each response to GnRH has been shown to be quite different.
   The bone mineral density was not measured.