Author’s response to reviews

Title: ACTH-independent Cushing's syndrome with bilateral cortisol-secreting adrenal adenomas: a case report and review of literatures

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Author’s response to reviews:

Dear Margaret Keil,

We thank the reviewers for their valuable suggestions on our manuscript entitled “ACTH-independent Cushing's syndrome with bilateral cortisol-secreting adrenal adenomas: a case report and review of literatures”. We have carefully revised the manuscript according to the comments. The point-to-point response is listed below:

Reviewer 1:
In their manuscript titled "ACTH-independent Cushing's syndrome with bilateral cortisol-secreting adrenal adenomas: a case report and review of literatures" Wei et al. describe a Chinese female patient with Cushing's syndrome caused by bilateral functional adrenal adenomas. However, there are still some important issues that should be declared. Quality of written English: needs some language corrections before being published.

[Response] We appreciate your comments. The language has been strictly reviewed and corrected.

1. In table 1, when did this patient receive plasma ACTH sampling?

[Response] Blood samples were collected at 8 a.m. for measurement of plasma ACTH.

[Changes] The Table 2 has been supplemented with this information (page 23).

2. In page 5 line 97, the authors should mention which site of bone for DEXA.

[Response] Bone mineral density in the lumbar spine, femoral neck and total hip were measured by DEXA.

[Changes] In the Case presentation section, page 5, line 98, the “Bone mineral density measured by dual-energy X-ray absorptiometry scans showed osteoporosis” has been changed to “Bone mineral density measured by dual-energy X-ray absorptiometry scans showed that the T score of lumbar spine, femoral neck and the total hip was -3.0, -3.2 and -3.3, respectively, which indicated osteoporosis”.

3. In page 7 line 125, why did this patient receive hydrocortisone replacement only? Most of patients receiving bilateral total adrenalectomy were prescribed Florinef too.

[Response] Mineralocorticoid deficiency could be only observed in a proportion of patients underwent bilateral total adrenalectomy present. As florinef is not available in mainland China, we usually prescribe glycyrhriza preparations for the affected patients. Fortunately, there is no evidence of mineral corticoid deficiency in the presented patient.

4. Recently, the morning plasma cortisol after 1-2 days of removing adrenal adenoma for adrenal Cushing's syndrome could be valuable marker to predict the success of surgery. Could the authors provide the plasma cortisol level after bilateral adrenalectomy?

[Response] The 8 a.m. plasma cortisol after 3 days of two-step bilateral laparoscopic adrenalectomy was 37.30nmol/L.
[Changes] In the Treatment and follow-up section, page 7, line 126, the “The 8 a.m. plasma cortisol after 3 days of bilateral adrenalectomy was 37.30nmol/L” has been added.

5. Finally, I think this manuscript should be shortened in text and Table 3 could be omitted.

[Response] We agree with the reviewer that the manuscript should be shortened. We have removed Table 3 and made some adjustments in our manuscript.

[Changes] 1) In the Abstract section, page 2, line 21, the “rarely reported in the literature” has been changed to “rarely reported in the literatures”.

2) In the Abstract section, page 2, line 28, the “adrenal venous sampling (AVS) adjusted by plasma aldosterone revealed the hypersecretion of cortisol from both adrenal glands” has been changed to “adrenal venous sampling (AVS) adjusted by plasma aldosterone revealed hypersecretion of cortisol from both adrenal glands”.

3) In the Background section, page 3, line 43, the “Endogenous CS can be divided into ACTH-dependent and ACTH-independent etiologies” has been changed to “Endogenous CS includes ACTH-dependent and ACTH-independent etiologies”.

4) In the Background section, page 3, line 44, the “the latter accounts for 15~20% of the cases and usually induced by unilateral adrenal adenomas or adrenal carcinomas accompanied by autonomous adrenal cortisol production” has been changed to “the latter accounts for 15~20% of the cases and is usually induced by unilateral adrenal adenomas or adrenal carcinomas accompanied by autonomous adrenal cortisol secretion”.

5) In the Background section, page 3, line 54, the “which was diagnosed by adrenal venous sampling” has been changed to “which was diagnosed through adrenal venous sampling”.

6) In the Background section, page 3, line 56, the “In addition, previous similar cases appearing in the literatures were briefly summarized to investigate the diagnosis and treatment of this disorder” has been changed to “In addition, similar cases in the literatures were briefly summarized for discussion”.

7) In the Case presentation section, page 4, line 59, the “A Chinese female aged 55 was admitted to our hospital” has been changed to “A 55-year-old Chinese female was admitted to our hospital”.

8) In the Case presentation section, page 4, line 61, the “but without evidence of acne, hirsutism or wide purple striae” has been changed to “without evidence of acne, hirsutism or wide purple striae”.

9) In the Case presentation section, page 4, line 66, the “no history of steroid usage” has been changed to “no history of steroid use”.
10) In the Case presentation section, page 4, line 75, the “hepatorenal functions” has been changed to “hepatorenal parameters”.

11) In the Case presentation section, page 4, line 76, the “Her serum level of cardiac troponin-T, creatine kinase-MB and brain natriuretic peptide (BNP) elevated slightly” has been deleted.

12) In the Case presentation section, page 5, line 81, the “The next morning serum cortisol level” has been changed to “The next morning (8 a.m.) serum cortisol level”.

13) In the Case presentation section, page 5, line 92, the “Steroid-induced diabetes was diagnosed according to the result of oral glucose tolerance test (Table 3)” has been deleted.

14) In the Case presentation section, page 5, line 100, the “In order to locate the functional lesions in this patient who suffered from ACTH-independent Cushing’s syndrome due to bilateral adrenal masses, AVS was performed through percutaneous femoral vein approach. The concentrations of plasma aldosterone and cortisol were then measured from both adrenal veins (AV) and inferior vena cava (IVC)” has been changed to “In order to locate the functional lesions in this patient, AVS was performed and the concentrations of plasma aldosterone and cortisol were measured from both adrenal veins (AV) and inferior vena cava (IVC)”.

15) In the Case presentation section, page 6, line 109, the “Table 4” has been changed to “Table 3”.

16) In the Case presentation section, page 6, line 110, the “this patient was diagnosed as CS” has been changed to “this patient was diagnosed with CS”.

17) In the Treatment and follow-up section, page 6, line 115, the “Laparoscopic right adrenalectomy via transperitoneal approach was performed, followed by left adrenalectomy after a two months recovery period” has been changed to “Laparoscopic right adrenalectomy was performed, followed by left adrenalectomy after a two-month interval”.

18) In the Treatment and follow-up section, page 6, line 119, the “Insulin was withdrawn following the first operation, and her blood glucose was well controlled with only lifestyle intervention” has been deleted.

19) In the Treatment and follow-up section, page 7, line 129, the “waist circumference was 71cm” has been changed to “waist circumference reduced to 71cm”.

20) In the Literature review section, page 7, line 144, the “with a later age of onset” has been changed to “with an adult onset”.

21) In the Literature review section, page 8, line 151, the “Table 5” has been changed to “Table 4”.
22) In the Literature review section, page 8, line 161, the “All patients received glucocorticoid replacement therapy postoperatively, and it is noteworthy that” has been changed to “All patients received glucocorticoid replacement therapy postoperatively. It is noteworthy that”.

23) In the Discussion section, page 9, line 181, the “Accurate diagnosis of bilateral adrenocortical lesions is challenged by the difficulty in defining the hormone-secreting status of each mass, which determines the surgical strategy” has been deleted.

24) In the Discussion section, page 9, line 184, the “The diagnostic value of AVS and 131I-6β-iodomethyl-19-norcholesterol (131I-NP-59) scintigraphy in adrenocortical diseases was well established” has been changed to “The diagnostic value of AVS and 131I-6β-iodomethyl-19-norcholesterol (131I-NP-59) scintigraphy for defining the hormone-secreting status in adrenocortical diseases was well established”.

25) In the Discussion section, page 11, line 216, the “Two similar cases have been reported that applied aldosterone to correct for side-to-side dilution differences previously, but there is still controversy” has been deleted.

26) In the Discussion section, page 11, line 218, the “Since this patient was by no means regarded as PA” has been changed to “Since PA was ruled out in this patient”.

27) In the Discussion section, page 11, line 222, the “AVS is generally safe, with a very low rate of adverse events” has been changed to “AVS is generally safe, with a very low risk of adverse events”.

28) In the Discussion section, page 11, line 228, the “In this case, no adverse event was reported throughout the treatment” has been changed to “In this case, no adverse event was observed throughout the duration of treatment and follow-up”.

29) In the Discussion section, page 11, line 229, the “Unlike CS induced by unilateral adrenal mass, for which unilateral resection was recommended, the optimal treatment for patients with bilateral cortisol-secreting adenomas was less clear” has been changed to “The optimal treatment for patients with bilateral cortisol-secreting adenomas remains uncertain”.

30) In the Discussion section, page 12, line 237, the “Recently, partial adrenalectomy (removed the adenomas only) was performed in some similar cases” has been changed to “Recently, partial adrenalectomy (removal of the adenomas only) was performed in some similar cases”.

31) In the Conclusion section, page 12, line 243, the “we reported a Chinese female patient with ACTH-independent CS caused by bilateral cortisol-secreting adenomas, who was diagnosed by aldosterone-adjusted AVS” has been changed to “we reported a Chinese female patient with ACTH-independent CS caused by bilateral cortisol-secreting adenomas. She was diagnosed through aldosterone-adjusted AVS”.


6. There are some written mistakes about "ICV" in the manuscript which would be "IVC" for inferior vena cava.

[Response] Thanks for your kind review. We have corrected these typos.

[Changes] 1) In the Case presentation section, page 6, line 106, the “ICV” has been changed to “IVC”.

2) In the Discussion section, page 10, line 194, the “ICV” has been changed to “IVC”.

Reviewer 2:

Jia Wei et al reported a patient with bilateral adrenal adenoma, reporting also a literature review describing all reported cases. The paper is well written, the case reported is interesting, the literature review is comprehensive.

[Response] Thanks for the positive comments.

There are some minor issues to be considered before publication.

1. Why medical treatment was not considered? At least to reduce cortisol levels shortly after diagnosis. It is recommended by Endocrine society and suggested by several reviews, authors and literature.

[Response] Medical therapy was recommended by Endocrine Society only for bilateral macronodular adrenal hyperplasia (BMAH). Instead, Endocrine Society recommended surgical resection for the rest types of bilateral adrenal disorders (J Clin Endocrinol Metab, 2015, 100(8):2807-2831). As BMAH had been excluded in the current patient, she underwent surgery shortly after diagnosis. Considering the potential safety issue and benefit from the medical therapy within a week, we did not prescribe the medical therapy to the patient.

2. In the discussion there could be a comparison with BMAH, as that described by Albiger st al (Clin Endo 2015), i.e. the use of medical treatment versus bilateral adrenalectomy.

[Response] This advice is very helpful in improving our manuscript. We have added the comparison with BMAH in the Discussion section, and cited the research of Albiger et al in References (No. 26).

[Changes] In the Discussion section, page 9, line 166, the “In addition to the low incidence, difficulties in differential diagnosis from PPNAD, AIMAH and unilateral functional adenoma with contralateral non-functional lesion might result in misdiagnosis of this disorder. AIMAH or PPNAD can be initially differentiated from adrenal adenomas by their typical radiographic and clinical features, while definite diagnosis depends on histo-pathology” has been changed to “This disorder should be differentiated from PPNAD, AIMAH and unilateral functional adenoma with
contralateral non-functional lesion for the determination of therapeutic regimen. PPNAD is characterized by multiple small pigmented nodules of hyperplastic adrenocortical cells and cortical atrophy with an early age of onset [25]. AIMAH, in which the bilateral enlarged adrenal glands with numerous nodules larger than 1 cm in diameter lead to an irregular contour on CT or MRI, is associated with aberrant expression of hormone receptors and can be treated by appropriate antagonist [26, 27]. The definite diagnosis of AIMAH or PPNAD depends on histopathology”.

3. Why adrenalectomy in 2 times and not in the same surgical procedure? Why do you choose to expose the patient twice to the increased thrombotic risk of surgery?

[Response] As stated in the manuscript (page 6, line 114), a two-step operation was planned due to her poor cardiac function. Prolonged operation duration may put the patient in an even serious condition.

4. Why authors performed 8mg DST? It is a test for ACTH dependent CS not for adrenal CS.
[Response] Thanks for your reasonable concern, 8mg DST is not necessary in this particular case. We thus removed the result to prevent potential misunderstandings.

[Changes] 1) In the Case presentation section, page 5, line 83, “High-dose dexamethasone overnight suppression test (8mg) was also failed to suppress serum cortisol either” has been deleted.

2) In the Treatment and follow-up section, page 6, line 121, “Overnight 1mg and 8mg dexamethasone suppression test were repeated two weeks after surgery” has been changed to “Overnight 1mg DMST was repeated two weeks after surgery”.

3) The relevant parts in Table 2 have also been deleted (page 23).

[Changes in References] There are also some changes in the Reference section due to the adjustments above. In page 17, line 355 and line 357, Number 25 and 26 have been cited in our manuscript.

[Changes in Table headings] The Table 3 heading has been deleted and the order of the remaining tables has been adjusted.

We greatly appreciate your assistance.

Sincerely,

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