Author’s response to reviews

Title: Hypercortisolism and primary aldosteronism caused by bilateral adrenocortical adenomas: a case report

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Author’s response to reviews:

Dear editors and reviewers,

We are very glad to receive these valuable suggestions on our manuscript entitled “Hypercortisolism and primary aldosteronism caused by bilateral adrenocortical adenomas: a case report” (BEND-D-19-00019). After careful consideration and discussion within our team, we tried to answer all the comments and questions as following.
Editor's comments

1. Please revise the title of the manuscript to remove the reference to a literature review (e.g. Hypercortisolism and primary aldosteronism caused by bilateral adrenocortical adenomas: a case report).

[Response] We agree with this comment. In page 1, line 1, the title of the manuscript has been changed to “Hypercortisolism and primary aldosteronism caused by bilateral adrenocortical adenomas: a case report”.

2. In the Declarations, please include a section for Ethics approval and consent to participate.

[Response] Thanks for this suggestion. In the Declarations, page 11, line 217, a section for Ethics approval and consent to participate has been added. This case study was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee and the consent to participate was waived. The ethics approval number is 2019-158. The ethical approval can be provided if needed.

Reviewer 1's comment

1. Abstract, the sentence "Elevated aldosterone to renin ratio and negative saline infusion test suggested primary aldosteronism" is somehow confusing: a negative saline infusion test do not suggest primary aldosteronism, please modify.

[Response] We appreciate this comment. In the Abstract section, page 2, line 22, “Elevated aldosterone to renin ratio and negative saline infusion test suggested primary aldosteronism” has been changed to “Elevated aldosterone to renin ratio and unsuppressed plasma aldosterone concentration after saline infusion test suggested primary aldosteronism”.

Reviewer 2's comments

1. Can the authors clarify if there was any suppression of plasma cortisol following the first partial adrenalectomy? The column headings in Table 3 need some explanation - does PTC-24 mean the day 1 (24h) cortisol and PTC-8 mean Day 8?? Were any peri-operative glucocorticoids used? It appears that if interpreted correctly the post-op day 1 cortisol was 63 nmol/L so low but recovered quickly over the first week.

[Response] Thank you for helping us improve the messages to convey. In Table 3, “PTC-24” was a plasma total cortisol measured at 24:00, and “PTC-8” was a plasma total cortisol measured
at 08:00. We also added these clarifications as footnotes for Table 3. Peri-operative glucocorticoids had been used in this case. Hydrocortisone was given intravenously to the patient during the left partial adrenalectomy, and was maintained at a daily dose of 150-75 mg for 5 days after the operation. On the day after the hydrocortisone supplementation discontinued, the plasma total cortisol was 154 nmol/L at 08:00 with ACTH of 18.85 ng/L. But the patient did not have any symptoms associated with adrenal insufficiency. The patient’s cortisol concentrations recovered quickly and retained normal circadian variations without supplementation 10 days after the operation as shown in Table 3. The rapid recovery of cortisol circadian might be explained by his Cushing’s syndrome being mild and subclinical. The changes are listed as following.

1) In the Treatment and follow-up section, page 5, line 95, “One week after left partial adrenalectomy, the patient’s cortisol concentrations retained normal circadian variations and 0.5 mg dexamethasone suppressed endogenous cortisol secretion” has been changed to “Hydrocortisone was given intravenously during the left partial adrenalectomy, and was maintained at a daily dose of 150-75 mg for 5 days after the operation. The patient did not have any symptoms associated with adrenal insufficiency after the hydrocortisone supplementation discontinued. Ten days after left partial adrenalectomy, the patient’s cortisol concentrations retained normal circadian variations and 0.5 mg dexamethasone suppressed endogenous cortisol secretion”. And in the Treatment and follow-up section, page 5, line 102, “The rapid recovery of cortisol circadian might be explained by his Cushing’s syndrome being mild and subclinical.” has been added.

2) In the Table headings section, page 16, line 320, “ACTH, adrenocorticotropic hormone; ODMST, overnight dexamethasone suppression test; PTC, plasma total cortisol” has been changed to “ODMST, overnight dexamethasone suppression test; DMST, dexamethasone suppression test; PTC-24, plasma total cortisol at 24:00; PTC-8, plasma total cortisol at 08:00; PTC-N8, plasma total cortisol at next 08:00 after DMST; ACTH, adrenocorticotropic hormone”.

3) In table 3, the “Low-dose ODMST” has been changed to “Standard low-dose DMST” and the table footnotes have been changed to “ODMST, overnight dexamethasone suppression test; DMST, dexamethasone suppression test; PTC-24, plasma total cortisol at 24:00; PTC-8, plasma total cortisol at 08:00; PTC-N8, plasma total cortisol at next 08:00 after DMST; ACTH, adrenocorticotropic hormone”.

2. Please round up or down the plasma cortisol to whole numbers - 62.77 nmol/L should read 63 nmol/L.

[Response] Thank you for your comments. We revised the presentation of plasma cortisol throughout our work. Detailed changes are listed as followings.
1) In the Case presentation section, page 5, line 88, the “Additionally, 7701.00 nmol/L, the cortisol concentration in LAV” has been changed to “Additionally, 7701 nmol/L, the cortisol concentration in LAV”.

2) In the Treatment and follow-up section, page 5, line 100, the “plasma total cortisol was 32.49 nmol/L at 08:00 the next day” has been changed to “plasma total cortisol was 32 nmol/L at 08:00 the next day after 0.5 mg overnight dexamethasone suppression test”.

3) In table 3, plasma total cortisol concentration “146.30” has been changed to “146”, “346.00” has been changed to “346”, “272.70” has been changed to “273”, “274.40” has been changed to “274”, “62.77” has been changed to “63”, “304.80” has been changed to “305”, “29.17” has been changed to “29”, “32.49” has been changed to “32”, and “389.40” has been changed to “389”.

4) In table 4, cortisol concentration “7701.00” has been changed to “7701”, “601.10” has been changed to “601”, “280.90” has been changed to “281”.

3. The authors have not really explained why the plasma renin activity was not suppressed initially when the patient clearly did have primary aldosteronism. In line 151-2, high plasma cortisol can indeed bind the MR if the inactivating enzyme 11 beta hydroxysteroid dehydrogenase 2 is overwhelmed, but this also suppresses renin. The answer may lie in an old paper by Krakoff J Clin Endocrinol Metab. 1973 Jul; 37(1):110-7 - glucocorticoids increase "renin substrate" - angiotensinogen - and this may be enough to elevate plasma renin activity above the expected level.

[Response] Thank you for suggesting this valuable paper and we added it to our discussion (cited as reference 15). The changes are listed as following.

1) In the Discussion section, page 8, line 155, the “The failure of aldosterone to suppress renin, presented as a normal ARR that excluded our patient from further PA screening upon admission, might caused by the interference from high plasma cortisol which may inhibit the binding of aldosterone to renal mineralocorticoid receptors” has been changed to “Since PRA was measured by radioimmunoassay of generated angiotensin I, the failure of aldosterone to suppress renin, presented as a normal ARR that excluded our patient from further PA screening upon admission, might be caused by the interference from high plasma cortisol which could significantly increase plasma angiotensinogen level and consequently increase generated angiotensin I, leading to falsely increased PRA15”.

2) In the References section, page 15, line 286, the reference “Omura M, Sasano H, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Clinical characteristics of aldosterone-producing microadenoma, macroadenoma, and idiopathic hyperaldosteronism in 93 patients with primary aldosteronism. Hypertens Res. 2006 Nov; 29(11): 883-9” has been changed to “KRAKOFF,

4. Overall the English is good, but the manuscript could do with another proof read, eg line 168 - gold standard rather than golden standard and line 170-1 the aldosterone to cortisol ratio is the most widely used measure rather than wildly.

[Response] We have carefully checked our manuscript. And some spelling and grammar mistakes were found and have been corrected, as shown below.

1) In the Abstract section, page 2, line 20, the “who complained of intermittent muscular weakness for over 3 years” has been changed to “who complained of intermittent muscle weakness for over 3 years”.

2) In the Case presentation section, page 4, line 71, the “Routine laboratory tests revealed an extremely low serum potassium (2.12 mmol/L) with relatively high urinary potassium (38.66 mmol/24 h). Twenty-four hour urinary free cortisol was 140.7 ug and 137.7 ug on two separate occasions” has been changed to “Routine laboratory tests revealed an extremely low serum potassium (2.12 mmol/L) with relatively high urinary potassium (38.66 mmol/24h). Twenty-four-hour urinary free cortisol was 140.7 ug and 137.7 ug on two separate occasions”.

3) In the Case presentation section, in page 4, line 74, the “His aldosterone-to-renin ratio (ARR) was within normal range after discontinuing nifedipine for more than 2 weeks, when drug-induced false-negative results were likely eliminated. Thus, further PA work-up was not performed (Table 2) 9” has been changed to “His aldosterone-to-renin ratio (ARR) was within normal range after discontinuation of nifedipine for more than 2 weeks, when drug-induced false-negative results were likely eliminated. Thus, further screening for PA was not performed (Table 2)9”.

4) In the Case presentation section, page 4, line 77, “In overnight and low-dose dexamethasone suppression tests, dexamethasone failed to suppress endogenous cortisol secretion, indicating CS (Table 3)” has been changed to “In overnight and standard low-dose dexamethasone suppression tests, dexamethasone failed to suppress endogenous cortisol secretion, indicating CS (Table 3)”.

5) In the Case presentation section, in page 4, line 80, the “The mass on the right was 19×14 mm while the one on the left 25×15 mm” has been changed to “The mass on the right was 19×14 mm while the one on the left was 25×15 mm”.

6) In the Treatment and follow-up section, page 6, line 103, the “However, the patient remained hypertensive (165/118 mmHg) and and hypokalemia (serum potassium was 1.98 mmol/L, table
has been changed to “However, the patient remained hypertensive (165/118 mmHg) and hypokalemia (serum potassium was 1.98 mmol/L, Table 1).”

7) In the Discussion section, page 8, line 149, the “The presented patient did not have typical Cushingoid features or PA, which promoted a challenge in clinical practice to establish the accurate diagnosis” has been changed to “The presented patient did not have typical Cushingoid features or PA, which promoted a challenge in clinical practice to establish accurate diagnosis”.

8) In the Discussion section, page 9, line 176, the “AVS should be the golden standard for making a definitive diagnosis and for lateralizing functioning adrenocortical adenomas” has been changed to “AVS should be the gold standard for making a definitive diagnosis and for lateralizing functioning adrenocortical adenomas”.

9) In the Discussion section, page 9, line 178, the “because the aldosterone to cortisol ratio, which was the most wildly used measurement in clinical practice” has been changed to “because the aldosterone to cortisol ratio, which was the most widely used measurement in clinical practice”.

5. The authors should cite the original work of Young et al. World J Surg. 2008; 32:856-62 regarding the interpretation of the AVS (controlled for epinephrine) in the setting of cortisol excess.

[Response] We added this helpful paper to the Discussion section (cited as reference 20), page 9, line 182, “To minimize misinterpretation, we also measured the concentrations of plasma epinephrine in both adrenal veins and inferior vena cava to enable adjustment in the present patient.”


Thanks for your attention and patience.

Yours sincerely,

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