Peer Review File

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Reviewer Comments

Comment 1: This is an interesting case report that may however have been overtaken by the time interval between management and case reporting. The issue is that it is now abundantly clear that a single spot PAC is an extremely poor index of a patient's aldosterone status, with two consequences. The first is that the prevalence of PA is 3-5 times higher than previously thought to be the case, when aldosterone status is estimated on the basis of 24 hour urinary excretion of aldosterone; the second is that many of those who get to be screened for PA are termed negative on the basis of the single spot blood draw. A useful indicator might be the Annals of Internal Medicine paper (Martin J et al 2020), and the accompanying editorial commentary; a paper 40 years earlier (Helber et al Klin Wochenschr 1980) shows the superiority of UEA over a single PAC, so this is not just breaking news.

What this means for the patient being reported is that her polydipsia/polyuria status may be causally related to the aberrant ARR, or may not. Much of the difference between PAC and UEA reflects the role of episodic ACTH release, as a very powerful short term secretagogue of aldosterone (Gouli et al 2011), and similarly renin release on orthostasis. It is thus not inconceivable that such a patient may be more than normally subject to stress and repeated orthostasis; I presume that no 24 hour urinary collection was made.

Reply 1: Thank you very much for these valuable comments. I agree with you that false-negative ARR frequently occurred when it derived from a single spot blood draw, which had been reported by many studies. And, some studies even show that ARR derived from different spot of blood samples of one patient varied significantly (Hypertension. 2021 Mar 3;77(3):891-899). Abundant evidence shows that UEA show superiority over ARR, but its accuracy could be affected by daily urine output volume. What is regrettable is that we had not tested the patient's UAE because it cannot be tested in our hospital and 24-hour urinary collection of this patient was difficult (up to 18L per day).

Accordingly, in a revised version, in addition to the above I would suggest follows:

Comment 2: Lines 40-43. What damages the CVS etc is not just elevated aldosterone; it is inappropriately elevated aldosterone for sodium status. Aldosterone levels even higher than those commonly seen in PA do not cause damage in protracted sodium deficiency.

Reply 2: Thank you for these comments. We deleted the sentence 2 in Page 3, Line 41-43.

Comment 3: The current Endocrine Society Guideline is unfortunately out of date, as in fact are all the guidelines and consensus statements.

Reply 3: Thank you for this comment. We changed the expression into "According to the published Endocrine Society clinical guidelines and consensus statements" in page

3 line 42.

Comment 4: Reference 4-12 in many cases report concurrence of PA and the condition addressed, and not causation; this might be made very clear by so saying, in the Discussion rather than the Introduction.
Reply 4: It is a good suggestion. We deleted the corresponding sentences in Page 3 line 47-51.

Comment 5: The Intro should be very brief – the first sentence up to (1), then a rewritten the third to last (In the present study we report a PA patient with polydipsia, polyuria, hypokalemia and hypertension with false negative ARR results), and the final two sentences.
Reply 5: Thank you for this suggestion, we modified the introduction section according to you suggestion.

Comment 6: Given her age and BP – and the subsequent finding of a KCNJ5 somatic mutation – were levels of 18-oxocortsisol to assist in choosing not to undergo AVS?
Reply 6: This comment is very important. More and more evidences indicate that 18-oxocortsisol is useful for PA subtyping. However, our hospital and other hospital or commercial laboratory agency in China have no techniques to measure it right now. we stored the patient's plasma sample before surgery, expecting to test is in the near future.

Comment 7: Line 85 - Bartter, not Batter.
Reply 7: I am sorry for this typo. I have corrected it.

Comment 8: Line 102 – 140/90 is a high BP for a young woman; 130/80 would be preferable. The authors might detail her BP throughout her time with them.
Reply 8: Thank you for your carefully reviewing our manuscript. The patients BP fluctuated between 110-130/70-90mmHg post adrenal surgery. We changed this data in Page5-6, line 102-103.

Comment 9: The discussion needs to be shortened and radically refocused. The distinct possibility that her aberrant ARR reflects a single spot PAC, and has nothing to do with her PP, needs to be aired. If the authors have a additional suggestion for there being an alternative possibility advance the rationale but leave out all refs 4-12, even where they have some currency (eg OSA) – they are not relevant to her case.
Reply 9: Thank you for this comment. We have revised our manuscript per your advice, please seem more detail in the text.

Comment 10: Finally, although the timelines are not given in detail, why didn't the authors just go in post-imaging and remove the APA?
Reply 10: The patient was with a younger age (27-year-old), had hypertension, spontaneous hypokalemia, a right adrenal nodule, and a normal contralateral adrenal gland. All these clinical clues suggesting APA. While, her condition was complicated

with aberrant ARR, primary polydipsia, a notable family history (both her parent's had hypertension, her father had hypokalemic periodic paralysis, her mother had a history of polydipsia and polyuria), so we have done what we can do, including changing anti-hypertension agent that influencing ARR, water intake control, desmopressin application to see if her ARR could turn positive, and next general sequencing to exclude other clinical conditions, tried to find a uniform mechanism to explain all her manifestations before suggesting adrenalectomy.