Peer Review File

Article information: http://dx.doi.org/10.21037/gs-20-475.

REVIEWER A:

We aim to publish case reports that are not just rare but fill a knowledge gap. Though this case is rare, quite a few previous literatures have reported similar cases. I fail to see what this case report adds to present knowledge. How it's different from other similar ones.

Some similar cases (also as 9 cases listed in the manuscript):
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008857/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031973/
https://bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-7-791
https://www.elsevier.es/en-revista-endocrinologia-nutricion-english-edition--412-articulo-ganglioneuroma-as-an-uncommon-cause-S2173509311000146
http://www.ijcem.com/files/ijcem0074905.pdf
https://academic.oup.com/jcem/article/95/7/3118/2596226
https://www.jstage.jst.go.jp/article/internalmedicine/51/17/51_51.7726/_pdf
https://medcraveonline.com/UNOAJ/adrenal-ganglioneuroma-a-rare-case-report-and-literature-review.html
http://www.ijcasereportsandimages.com/archive/2016/008-2016-ijcri/CR-10679-08-2016-tungenwar/ijcri-1067908201679-tungenwar-full-text.php
https://cyberleninka.org/article/n/940672
https://www.spandidos-publications.com/10.3892/ol.2015.3021
https://www.wjon.org/index.php/wjon/article/view/783/535
http://jde.endokrin.com/tam-metin/17/eng

Thank you for your comments. While it is established that ganglioneuromas cannot be diagnosed pre-operatively, the majority of ganglioneuromas described in the literature are non-functional tumors. Our case report describes a functional ganglioneuroma in the absence of a composite tumor with emphasis on the fact that ganglioneuroma should be included on the differential diagnosis for functional dopamine secreting adrenal tumors especially during histopathologic analysis as the benign nature of ganglioneuroma alters the clinical management. We also include examples of the pre-operative cross sectional imaging of the tumor for this specific tumor, further illustrating the diagnostic difficult preoperatively.

REVIEWER B:

Dear authors,
I congratulate you on this very well written manuscript. This is an interesting case and should be a differential diagnosis during work up for pheochromocytoma.

Thank you. We appreciate your review.

REVIEWER C:

The authors describe a rare case of dopamine-secreting GN. My suggestions:

1. Introduction: add plasma renin activity, and plasma aldosterone concentration to "Thorough assessment includes evaluation of aldosterone, metanephrine, and cortisol levels." Metanephrines in plural. Remove cortisol, and instead add 'cortisol excess', as cortisol levels alone are not used in the evaluation of adrenal masses, but rather in the context of UFC, salivary cortisol or 1mg ODST (as in this case).

We agree with the reviewer and revised the sentence to: "Thorough assessment includes evaluation of metanephrine levels, screening for cortisol excess, and measurement of plasma renin activity and aldosterone concentration." (lines 57-59).

2. Based on this aldosterone/renin ratio, the patient appears to have low renin hypertension, with mild primary aldosteronism. Did the patient have repeat aldosterone/renin post op? Although the endocrine society uses a cutoff of 15 for aldosterone and ARR, milder cases exist, and it has been postulated that a lower cutoff of aldosterone of atleast 7 (with suppressed renin) represents the milder end of the spectrum:

https://academic.oup.com/edrv/article/39/6/1057/5074252

It would be important to obtain a post op aldo/renin. If aldo falls, renin rises, then perhaps aldo co-secretion was also possible. If so, tumor CYP11B2 IHC would be an important addition.

We agree with the reviewer that this is an important consideration in a select patient population. The patient did not have a post-operative aldosterone or renin measured. Given the absence of preoperative or postoperative diagnosis of hypertension, the diagnosis of hyperaldosteronism was not considered, nor indicated from the histopathologic findings of normal adrenal cortex.

3. Can the authors add a sentence on medications, supplements or food that the patient was not consuming, that could have accounted for the elevations in dopamine, such "dopamine diets".

Thank you for this suggestion- we have added the sentence "The patient denied use of supplements, medications, or a dopamine diet that could account for elevations in dopamine." (lines 85-87).

4. Dopamine secreting PPGL are typically head and neck tumors, not adrenals. Please add this info in the sentence on differential diagnosis.

We agree with the reviewer that paragangliomas are often located in the head and neck. However, our differential diagnoses for this case are limited to etiologies of adrenal tumors rather than extra-adrenal tumors, like a paraganglioma.

5. Was methoxytyramine measured? Please modify accordingly.

Pre-operative methoxytyramine measurement was considered, however, the markedly elevated urine dopamine was determined to be a sufficient tumor marker.

6. Since ACC was on the differential, was DHEAS or other hormones including testosterone measured? Please add and modify accordingly.

We agree with the reviewer that this is an important consideration in the workup of ACC. DHEAS and testosterone were not measured pre-operatively based on the lack of symptomatology suggestive of virilizing tumor. In the absence of demonstration of excess medullary hormones, further cortical hormone excess workup would have been performed.

7. Did the patient have any symptoms of dopamine excess? Please list and modify accordingly.

We agree with the reviewer and added the sentences: "She reported possible symptoms of hypomania but denied other major symptoms of dopamine excess such as agitation, anxiety, nausea, or vomiting. (line 84-85).