Author’s response to reviews

Title: Pheochromocytoma as a rare cause of hypertension in a 46 X, i(X)(q10) Turner syndrome: a case report and literature review

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Manuscript ID BEND-D-2018-00027 entitled "Pheochromocytoma as a rare cause of hypertension in a 46 X, i(X)(q10) Turner syndrome: a case report and literature review"

== [Technical Comments] ==

1. Please change the heading 'Disclosure Statements' to "Competing Interests".

2. Please remove the duplicate copy of 'Availability of data and materials'.

→ I corrected and removed these points according to editor's comments

Reviewers’ comments:

Reviewer 1:
Comment 1

Interesting case presentation that highlights a rare but potentially lethal cause of hypertension in Turner syndrome. Although a causative relationship cannot be established due to scarcity of relative reports, and hence a proposition for regular screening of patients would be superfluous, this case reports alert us not to miss the diagnosis of pheochromocytoma in patients with additional symptoms or adrenal incidentalomas, who would have otherwise been subjected to biochemical testing according to current guidelines.

Reply 1)

Thank you for your kind review and comments.

Reviewer 2:

Comment 1

This is a unique case of Pheochromocytoma occurring in a patient with Turner's syndrome, which is worthwhile to report. The novelty of this case, is that in patients with Turner's syndrome developing hypertension, we classically are taught to consider differentials like cardiovascular abnormalities (aortic stenosis / coarcatation), however, physicians may not consider other important secondary causes like pheochromocytoma. This point should be emphasized, and appropriately expressed, in the abstract and discussion. Failure to consider can lead to mortality (as in the other reported case)

Reply 1)

Thank you for your kind comments.

I added this point in abstract and discussion section (page 3, line 61, page 8, line 167, 181).

Comment 2

Pheochromocytomas is now known to be hereditary in 30-40% of cases, and it is even more likely in young patients. Hence, it will strengthen the case report if appropriate genetic screening could be done for this index case before submission. Are patients with chromosomal abnormalities (Turners) at even greater risk? This will be something important to add to the current knowledge.

Reply 2)

Thank you for your kind comments.
As you well known, genetic testing should at least be considered in all patients and is strongly indicated in specific patients such as those with a positive family history of pheochromocytoma and paraganglioma or carriers of tumor susceptibility gene mutations, and those with syndromic features or metastatic disease. However, unfortunately, our patient had no family history of pheochromocytoma and refused a genetic testing due to expensive cost. In addition, we cannot perform a targeted gene panel test or next generation sequencing (NGS) at our hospital, yet.

Comment 3

1. the presentation of the case report.

- In the initial presentation, authors may want to mention absence of radio-femoral delay (important feature of coarctation of the aorta)

Reply 3: Thank you for your kind comments.

I added this point in presentation section (page 6, line 122).

There was no radio-femoral delay which meant delay between the radial pulse and femoral pulse suggesting coarctation of aorta.

Comment 4

- should ideally mention the laboratory workup of pheochromocytoma, Before the abdominal CT results, as abdominal CT should not be used as a first line investigation to workup 'sudden onset hypertension' (this was mentioned in the abstract, but should be mentioned first in the case presentation, before the CT)

Reply 4: I corrected this point in presentation section (page 6, line 125).

Comment 5

- discuss about the high washout of the pheo, which is often quoted as a marker of benign adenomas, but is not 100% when used to rule out a pheo (pheos can mimic many lesions). more importantly, the lesion on CT appears very heterogenous and vascular, which should be used to determine the type of lesion more than the washout.

- MIBG - reason for doing this? Not routinely recommended in the latest endocrine society guidelines, but in view of her young age, and possibly other paragangliomas this would be warranted.

Reply 5: Thank you for your comments.
Actually, radiologist of our hospital initially interpreted CT image as a lipid poor-adrenal adenoma in this case. As you well-known, pheochromocytomas are usually large tumors with high vascularity, and they are usually round or oval masses with an attenuation similar to that of the liver. Larger lesions frequently demonstrate necrosis, hemorrhage, and fluid-fluid levels. As a result, they often appear inhomogeneous. In our case, CT scan had a limited ability for diagnosis for typical pheochromocytoma due to relative small size of tumor (1.9cm). Therefore, we performed MIBG scan which had a high specificity for diagnosis of pheochromocytoma and for detection of extra-adrenal pheochromocytoma in view of young age.

Considering these point, I added words and corrected sentences in presentation section (page 6, line 130).

Comment 6

- line 51 you may want to clarify "no recurrence developed at 24 months of follow-up" via biochemical tests or CT imaging?

Reply 6: Thank you for your comments. I added this point in case presentation section (page 7, line 143).

Comment 7

- biochemical results. This pheo was predominantly secreting noradrenaline / normetanephrine, and you may want to comment on that (and also compare with the other cases in literature)

- Was there a reason the urinary normetanephrine was normal? This is unusual as normetanephrine is more sensitive to norepinephrine. What was the urine volume and renal function?

Reply 7: Thank you for your comments. I added this point in discussion section and Table 1 (page 8, line 181, page 14, table 1).

In case of clinical suspicion of pheochromocytoma, biochemical testing including plasma free or urinary metanephrines should be measured. In our case, serum norepinephrine, serum normetanephrine, and urinary norepinephrine were increased. However, urinary normetanephrine was within normal reference value. We simultaneously measured urinary creatinine excretion to verify complete 24-hour urine collection. In our case, renal function was normal, and 24 hours urine volume was 1650 mL and urinary creatinine was 1171.9mg/24 hr. It is well known that the very high diagnostic sensitivity of metanephrines is due to the continuous diffusion of intratumorally-produced metanephrines into the circulation, which contrasts with the episodic secretion of the parent catecholamines [19]. However, it is not clear why the value of urinary normetanephrine was normal in this case. Previous two studies also reported increased metanephrine and normetanephrine [12,13], however, levels of catecholamines and their catabolic products in serum or urine had not been determined in Knisely et al. study [11].
Comment 8

AS this is a literature review, there should be greater discussion about the other cases in the literature and how they compare to the current index case, and if the authors feel that Turner's may predispose to Pheo, or is it just two unusual diseases occurring in the same patient by chance. Again the genetic tests will be very relevant.

Reply 8: Thank you for your important comments. I added this point in discussion section (page 9, line 192).

Although cancer risks in Turner syndrome except having an increased gonadoblastoma have not been clearly established, high incidence of extragonadal neoplasms with a preponderance of neurogenic tumors has been reported [20-22]. Although the overall risk of cancer was not increased in a population-based study, women with Turner syndrome had an increase of site-specific risk for gonadoblastoma, meningioma, childhood brain tumors, bladder, and uterine cancer when compared with the general population [23]. However, the clinical importance of this result is unclear due to very small number of cases. Like this population-based study, the related mechanisms between Turner syndrome and pheochromocytoma remain unclear, and it is also uncertain whether pheochromocytoma is over-represented in Turner syndrome because coexistence of these two diseases is extremely rare. Therefore, further studies including genetic tests are necessary to define the mechanisms underlying this association.

Again, unfortunately, our patient refused a genetic testing due to expensive cost and we cannot perform a targeted gene panel test or next generation sequencing (NGS) at our hospital, yet.

Comment 9

- Figure 3 is not adequately labelled (A-B-C-D)

Reply 9: Thank you for your comments. I added labels in figure legend and figure 3.