Oncology

Pheochromocytoma with Negative Metanephrines: A Rarity and the Significance of Dopamine Secreting Tumors

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Abstract

We describe a case of a 25-year-old female with a dopamine secreting PPGL diagnosed retrospectively with biochemical analysis. This finding resulted in change in approach to investigation and management, given their important clinical implications. There are important differences in management of dopamine secreting PPGL compared to classical noradrenaline and adrenaline-secreting PPGL. This includes the risk of peri-operative cardiovascular collapse peri-operatively with alpha/beta blockade, risk of malignancy/recurrence, and associated genetic abnormalities.

Introduction

Pheochromocytomas, otherwise known as paragangliomas (PPGLs), are rare tumors of catecholamine-producing chromaffin cells. The sensitivity of plasma and urine metanephrines is close to 100% according to Van Berkel et al. Metanephrine-negative PPGL is rare. Dopamine-secreting PPGL are even rarer entities and can evade this strongly reassuring test. To date, their incidence is limited to case reports and only 53 have been described in the literature.

Eisenhofer et al defines dopamine secreting PPGL as tumors that produce dopamine (or its metabolite 3-methoxytyramine) greater than the combined concentrations of noradrenaline and adrenaline (or their metabolites), and corresponds to the biochemical findings in this case. We describe a case of a dopamine secreting PPGL, the resulting change in our approach to suspected PPGL, and the important implications of dopamine secreting tumors.

Case presentation

A 25-year-old female presented to our Urology department with an incidental finding of a right 5 cm para-caval lesion was noted on ultrasound of the urinary tract (Fig. 1). She denied any symptoms suggestive of a secretory PPGL (headache, tremor, palpitations, diaphoresis, constipation and abdominal pain). There was no other significant personal or family medical history, including any relevant familial cancer syndromes such as Multiple Endocrine Neoplasia type 2 (MEN2), Von-Hippel Lindau (VHL) and Neurofibromatosis (NF1).

On examination she was mildly hypertensive with a blood pressure of 145/80 mmHg. A Computed Tomography (CT) scan of the abdomen and pelvis demonstrated the 5 cm lesion positioned along the medial aspect of the right kidney, between the right renal artery and renal vein, which was highly suggestive of a PPGL given anatomical location, morphology, being low attenuation on non-contrast study and showing marked contrast enhancement with rapid washout as compared to the renal parenchyma (Fig. 2).

Plasma metanephrines were within the normal reference range. Twenty-four hour urinary catecholamines demonstrated urine noradrenaline (NAd) was within normal limits at 466 nmol/day (normal range <780 nmol/day). Urine dopamine was at the higher end of normal limits at 2907 nmol/day (<3200 nmol/day). Urine adrenaline was minimally elevated above the reference range at 93 nmol/day and, when repeated, was normal.

Based on the presence of normal metanephrines and catecholamines, the impression was that the para-caval mass was non-functioning. Resection was warranted due to the patient and clinician concern of malignancy based on location and size. The patient proceeded to operation without peri-operative alpha or beta blockade.

Laparotomy revealed a well circumscribed, encapsulated tumor densely adherent to the right renal vein and inferior vena cava. Due to the dense adherence to these structures and unknown pathology of the tumor, a right-sided nephrectomy and partial Inferior Vena
Cava (IVC) resection was performed to achieve complete excision (Fig. 3). The patient had an unremarkable post-operative recovery and had no further episodes of hypertension during her admission and post-operative follow up.

Histologically, the microscopic appearance of the tumor revealed cell morphology and arrangement in a typical pattern of a non-invasive, benign extra-adrenal PPGL.

Retrospective analysis of 3-methoxytyramine (a type of meta-nephrine and the metabolite of dopamine) on tandem mass-spectrometry from pre-operative metanephrine measurements indicated probable elevation.

In this case given the surprising histological findings above, we concluded that this type of tumor was likely to represent a dopamine-secreting PPGL. This is supported by the concentration of urinary dopamine being proportionally higher than that of noradrenaline and adrenaline combined; and by a probable elevation of 3-methoxytyramine on mass spectrometry.

Discussion

The clinical presentation of most documented dopamine secreting PPGLs is commonly incidental, with patients being asymptomatic and normotensive. Because they are identified incidentally and with a delayed presentation, they are commonly larger tumors than noradrenaline and adrenaline secreting PPGLs. Patients may present with symptoms of flushing, vomiting and dizziness secondary to orthostatic hypotension from direct effects of excess dopamine.4

Not all patients may be appropriate for alpha and beta adrenergic receptor blockade. Because dopamine-secreting paragangliomas may not secrete noradrenaline or adrenaline, the vasodilatation effects of dopamine may predominate and result in cardiovascular collapse. This was evident in one case in the literature where this cardiovascular collapse occurred post-operatively and the patient died 6 days later.5

The reported malignancy rate of dopamine secreting tumors has been reported to be as high as 66—90% compared to only 21—29% of noradrenaline and adrenaline secreting tumors.4,5 Decreased dopamine beta-hydroxylase in dopamine secreting PPGL may be reflective of more de-differentiated tumors, and may explain their higher recurrence rates and malignant potential.

Post-surgical follow up and genetic testing has an important role in patients with dopamine secreting tumors.1 Long term follow up should include routine investigation with plasma metanephrines (including methoxytyramine) and imaging. Combined anatomical and functional imaging such as positron emission tomography coupled with computed tomography (PET-CT), provides almost 100% diagnostic sensitivity.5

We acknowledge there are limitations associated with this case report. Unfortunately given that we are reporting on a case that has already undergone treatment, reporting intra-tumoral levels of catecholamines to confirm the diagnosis of a dopamine secreting PPGL was not possible, nor is the test available at our health care facility. We concede that this test would have also provided additional support of this case reflecting a dopamine secreting tumor if dopamine...
beta-hydroxylase was found to be deficient. Also it would have been preferable to report a precise value of 3-methoxytyramine rather than a qualitative result. However, the specialist laboratory was unable to perform retrospective analysis on pre-operative blood test.

**Conclusion**

Dopamine secreting PPGL are rare entities. This case has changed our approach to the long term follow-up and observation of this patient, which consists of more regular clinical review and imaging with PET/CT as opposed to follow up of a benign tumor and earlier discharge into the community.

**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this paper. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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