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# A case report on Phaeochromocytoma in a young girl; A great masquerader hidden among many clinical clues

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## Abstract

**Introduction :**

Phaeochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that can be lethal if left undiagnosed. But the variability in the clinical presentation can make the diagnosis challenging even to the most experienced clinician.

**Case Description:**

We describe a case of a phaeochromocytoma in an 18-year-old girl who had had a multitude of non-specific symptoms over 3 years without apparent hypertension but with persistent tachycardia. Despite having had classic symptoms of PPGLs at times (episodic flushing, palpitations, and headaches), a phaeochromocytoma was not suspected as she was labeled with panic attacks due to her social circumstances at the time of presentation. A large adrenal mass was detected incidentally and further evaluation revealed elevated metanephrine levels. She underwent curative surgery successfully and remains symptoms free to date. She will be under lifelong surveillance for a recurrence as the possibility of an underlying genetic defect is high considering her young age.

**Conclusion:**

PPGLs can have a very diverse presentation, evading early detection. A high degree of suspicion is needed to diagnose during the early course of illness.

**Keywords:** Phaeochromocytoma and paraganglioma, adrenal incidentaloma, metanephrines

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## Introduction

PPGLs are rare neuroendocrine tumors derived from chromaffin cells of either the adrenal medulla or the extra-adrenal sympathetic or parasympathetic ganglia with a reported incidence of about 0.6 cases per 100,000 person-years[1]. But recent studies found an increased incidence due to the investigations of adrenal incidentalomas who are clinically asymptomatic. 4.8 fold increase in incidence was noted in one nationwide study from 1.4 in 1977 to 6.6 in 2015 per million person-years which was mainly attributed to this large proportion of incidentalomas[2]. Currently, the PPGLs are known as one of the most inherited endocrine tumors with at least 12 associated genetic syndromes and 15 driver genes in contrast to the past teaching [3]. Identification of these responsible genes has paved a pathway for more personalized management of PPGLs.

PPGLs are known as the great mimicker in medicine since the symptoms and signs of it can mimic more than 30 medical disorders[4,5].

Clinical symptoms are caused by the catecholamines secreted by the tumors and their action on various types of sympathetic receptors. Thus, the type of catecholamine will determine the clinical features: for an example the persistent or paroxysmal hypertension

or whether it is orthostatic hypotension will be determined depending on whether the tumor is secreting noradrenalin/adrenalin or dopamine respectively.

Biochemical confirmation of PPGL is done by measuring the catecholamine metabolites in blood and urine. Plasma metanephrines and normetanephrine and urine fractionated metanephrines and normetanephrine will be elevated in epinephrine & norepinephrine-secreting tumors. Dopamine-secreting tumors will have elevated 3 -methoxytyramine(3-MT) levels in the serum. Plasma-fractionated metanephrines have a sensitivity of 96–100 %, with a specificity of 85–89 %[4]. Thus, in high-risk patients' plasma fractionated metanephrines are the investigation of choice. Urine measurement of fractionated metanephrines has a 97% specificity with 91% sensitivity, making it the ideal investigation in the low-risk population[6]. Catecholamine metabolite measurements, especially serum 3MT measurement can be affected by posture and several food and beverages. Additionally the metanephrine measurement also can be affected by several drugs giving rise to false positive tests[7].

Even though the principal in endocrinology is to perform imaging after the biochemical confirmation of the underlying diagnosis, the ever-increasing detection of adrenal incidentalomas has reversed the pathway of diagnosis for phaeochromocytomas. CT and MRI are used for differentiation between benign and malignant adrenal tumors which are detected as incidentalomas. Non-enhanced Hounsfield unit (HU) of less than 10 in CT indicates a benign tumor whereas a value of more than 10 is seen in lipid poor possibly malignant lesions[8]. Further differentiation between malignant and benign tumors can be done with contrast washout studies. 30% of benign adrenal adenomas can be lipid poor and have higher Hu values. In those cases, absolute and relative washout values of <60% and 40% respectively in CT indicate the possibility of a malignant lesion[8]. But a recent retrospective study on a large cohort of diagnosed patients with phaeochromocytoma determined that the contrast washout studies are unreliable in ruling out phaeochromocytomas[9]. On imaging, phaeochromocytomas can mimic the characteristics of adrenocortical carcinomas as both have a rich vascular supply and a high chance of necrosis and calcifications. Phaeochromocytomas enhance avidly but can be heterogeneous with areas of absent

Table 1: Frequency of common signs and symptoms in phaeochromocytoma[4]

| Symptom | | Frequency (%) |
|---|---|---|
| Hypertension/Hypotension | Sustained Hypertension | 50 |
| | Paroxysmal Hypertension | 30 |
| | Orthostatic Hypotension | 12 |
| Headache | | 60-90 |
| Palpitations | | 50–70 |
| Sweating | | 55–75 |
| Pallor | | 40 |
| Weight loss | | 20-40 |
| Fatigue | | 25-40 |
| Anxiety and panic | | 20-40 |
| Hyperglycemia | | 40 |
| Fever | | 6 |

enhancement due to cystic changes and necrosis[4]. In a magnetic field proton in water and lipid oscillate at different frequencies. MRI chemical shift imaging uses this to differentiate between lipid-rich benign adenomas and lipid-poor adrenal lesions. Adrenal adenomas usually lose signal intensity on out-of-phase images compared with in-phase images, whereas malignant lesions and pheochromocytomas that lack intracellular lipids remain unchanged in both phases [8]. This MRI feature is useful in evaluating adrenal masses to determine the possibility of a malignant lesion.

Once a phaeochromocytoma is diagnosed surgery is the treatment of choice. In phaeochromocytomas, special perioperative measures should be taken to prevent a crisis intraoperatively which includes alpha blockade followed by beta-blockade and intravascular volume expansion by increasing fluid intake and salt intake before surgery to prevent postoperative hypotension. Patients should be monitored postoperatively for rebound hypoglycemia caused by hyperinsulinemia in addition to the hypotension[7,10].

As PPGLs are having a strong genetic background patient should be kept under lifelong surveillance for recurrences. Even though PPGLs are most of the time benign there can be PPGLs with high malignant potential. Genetics and biochemical characteristics along with histology characteristics can give clues to the malignant potential of the tumor but only the presence of metastases of chromaffin tissue at sites where no chromaffin tissue should be expected will confirm the malignant nature of PPGLs[4,5].

## Case Presentation

An 18-year-old school girl presented with a history of severe lethargy, non-specific ill health persisting for 3 years with a fluctuating course. Initial evaluation revealed a vitamin D deficiency; despite the correction, her symptoms persisted. Six months before the current presentation she had developed episodic flushing, palpitations, and headaches with persistent tachycardia (100-110bpm) while maintaining a normal Blood Pressure (BP) throughout. She was started on Sertraline with a probable diagnosis of panic attacks, with that symptoms neither improved nor worsened. Further evaluation pursuing a cause for her symptoms revealed a large right adrenal mass in the abdominal ultrasound scan. A Contrast enhanced computer tomography (CECT) of the abdomen was planned and the patient was given methylprednisolone considering her allergic history precipitating a hypertensive crisis. A clinical diagnosis of 'Phaeochromocytoma' was made with high probability at this instance.

She was underweighted with a Body Mass Index (BMI) of 17.3kg/m$^2$. There was no goiter or sweating or tremors, nor there were any cutaneous stigmata of neurofibromatosis. BP at the time of examination was 90/50mmHg with persistent tachycardia in the range of 100-110bpm. Apical impulse was un-displaced and in normal character. The rest of the systemic examination was unremarkable and fundoscopy did not reveal any hypertensive retinopathy changes.

Her 24-hour fractionated urinary metanephrines were elevated 15.22mg/24 hours in a urine volume of 3.46 L (<1mg/24 hours is considered normal) along with a normal adrenal hormonal profile (Table 2). Her serum calcium levels, thyroid functions and rest of the basic biochemical investigations were within normal limits.

CECT adrenal protocol revealed a well-defined right adrenal mass measuring 4cm x 4.5cm x 5cm with a pre-contrast HU of 31 and an absolute washout of 52% and a relative washout of 26% (Figure 1). Following confirmation of the clinical diagnosis of Phaeochromocytoma, she was started on Prazosin 0.5mg twice daily followed by Propranolol 40mg twice daily targeting a seated BP of <130/80mmHg while maintaining a standing BP of >90mmHg. A resting heart rate target of 60-70bpm was achieved. Preoperatively she was started on a high salt diet and hydrated to expand the intravascular volume aiming towards a hematocrit of 30%.

A laparoscopic right adrenalectomy was performed and intra-operatively, she had maximum blood pressure fluctuation between 70-190mmHg. It was managed with IV fluid boluses and IV MgSO4. Post-operative course was uneventful. At 6 months postoperatively she is clinically well and off all medication and was confirmed biochemically to be cured as well. However routine surveillance for paragangliomas and other adrenal phaeochromocytomas is planned considering her young age at presentation. Currently, we are awaiting genetic study results.

Histology revealed cells with a Zell Ballen pattern with nests of polygonal cells. Diffuse growth, high cellularity, cellular monotony, spindle-shaped cells, marked nuclear hyperchromasia or pleomorphism, or mitoses were not seen. Capsular or vascular invasion was not evident. Immunohistochemistry- was strongly positive for chromogranin A and the PASS score was 0/20.

Table 2 : Adrenal hormonal profile

| Test | Patient's value | Reference range |
|---|---|---|
| ODST | 25 nmol/L | <50 nmol/L |
| DHEA | 0.648 mmol/L | 10-237 mmol/L |
| Total Testosterone | 0.13 ng/ml | <1 ng/ml |

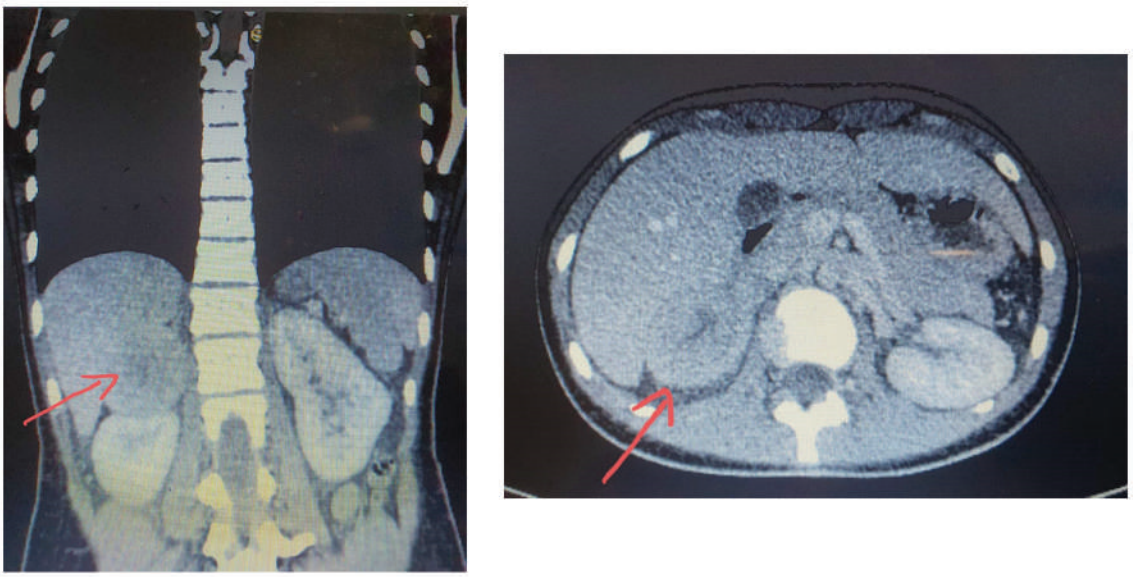

Figure 1: CECT adrenal protocol showing large right suprarenal lesion with a small area of central necrosis

## Discussion

We describe a case of a phaeochromocytoma in a young girl who had a delay of years before the diagnosis was made. Her presentation attests to the fact that PPGLs can be a great mimicker evading the diagnosis for years. Even though she had been symptomatic with palpitations and fatigue for a minimum of months, the diagnosis was only made when her tumor was more than 4 cm. In keeping up with the current trend it was also diagnosed as a phaeochromocytoma during the evaluation of an adrenal incidentaloma.

Our patient had a hypertensive crisis when prednisolone was given prophylactically. In addition to steroids, several other medications can precipitate a hypertensive crisis and it can be the first presentation of PPGLs or what hints at the possible PPGL diagnosis. The culprit drugs which can lead to a hypertensive crisis in a PPGL patient are listed in table 2.

Biochemically the tumor was secreting either epinephrine or norepinephrine or both as urinary fractionated metanephrines include metabolites of both. Exocytotic catecholamine release can be episodic and is largely responsible for the symptoms of phaeochromocytoma. However free metanephrines are produced within chromaffin tumor cells after leakage of catecholamines from storage vesicles into the cytoplasm, in the presence of membrane-bound catechol-O-methyltransferase (COMT). This process is continuous and occurs independently of exocytotic catecholamine release[11]. So, this explains how the biochemical investigations for phaeochromocytoma can be positive even without the typical symptoms of PPGLs.

In the perioperative management of our patient, we gave prazosin for alpha blockade even though the patient did not have persistent hypertension as it will prevent a hypertensive crisis at the time of surgery during tumor handling. Alternative to prazosin; a short-acting selective α1 blocker, phenoxybenzamine which is a nonselective α blocker can be used. But this can lead to prolonged hypotension following surgery due to a long half-life[10]. Because there was persistent tachycardia after 3 days from alpha blockade propranolol was added to control the heart rate to the target level of 60-80bpm before surgery[7]. Beta blockade before α blockade is not recommended as it

can precipitate a hypertensive crisis due to unopposed α action. The alpha blockade itself can lead to reflex tachycardia in a volume-contracted individual. Thus, to tackle this as well as to prevent postoperative hypotension after the removal of the tumor patients are advised to increase their fluid and salt intake once adequate α blockade had been achieved. Hematocrit value can inform the adequacy of volume resuscitation before surgery. Another drug useful in preoperative management is metyrosine which inhibits catecholamine synthesis and may be used in combination with α blockers for a short period before surgery to further stabilize blood pressure and to reduce blood loss and volume depletion during surgery[4,7,10].

Intraoperative blood pressure fluctuations are expected during surgery with hypertension before tumor removal and hypotension afterward. As in our patient, magnesium sulfate can be used to prevent hypertensive episodes as it inhibits adrenal catecholamine release. Further, it reduces α-adrenergic receptor sensitivity to catecholamines and dilates predominantly arteriolar vessels. Other drugs which can be used include sodium nitroprusside, phentolamine, and glyceryl trinitrate. Later two are nitric oxide donors, which cause venular and arteriolar vasodilatation. Esmolol, a short-acting selective β1 blocker with rapid onset of action can be used to control tachycardia[10].

As recommended in 2014 endocrine society guidelines since the tumor is less than 6cm in size patient underwent laparoscopic adrenalectomy and had an uneventful postoperative period. Typical histology of PPGL includes chief cells with abundant granular cytoplasm and large vesicular nuclei and basophilic to amphophilic cells a cell nesting pattern called the zellballen pattern. As mentioned earlier histopathological features can give clues to the possibility of the malignant potential of the PPGL. In 2002 a histopathological score called Pheochromocytoma of the Adrenal gland Scaled Score (PASS) was introduced to separate benign from malignant neoplasms[12]. Although metastatic behavior cannot be reliably predicted with a PASS score of 4 or higher, the "ruling-out criteria" for malignant behavior with a PASS score of <4 has been fairly consistent in several studies[13]. Thus, in our patient's case, the PASS score of 0 can reliably rule out the malignant potential of the tumor even though it occurred at a very young age.

In our patient's case, genetic diagnosis become very important for future follow-up decisions and family screening. And since she is very young, the possibility of a germline genetic defect is high compared to a sporadic mutation. And there has been a lot of evidence accumulating for the genotype-phenotype correlation of PPGLs so that underlying mutation can be predicted by distinct clinical presentations and biochemical characteristics and mode of transmission.

Our patient has an adrenal-origin tumor with high-fractionated urinary metanephrines which could include both adrenalin and noradrenalin metabolites. So the possibility of an underlying either VHL or RET mutation was high considering the origin and biochemical profile[4,14]. But as she is in her 2nd decade of life at the time of presentation likelihood of a VHL mutation is high compared to RET[5]. The SDHx mutations are the other group of mutations that should be tested in her considering her biochemical profile and age. In her case the possibility of MAX or TMEM127 gene defects are rare. These prediction models of underlying gene defects can be important for a country like ours with limited resources, so we can go for limited testing depending on the probability. Our patient should be on lifelong follow-up with both biochemical testing and imaging for a recurrence.

## Conclusions

Phaeochromocytomas and paragangliomas can have a very diverse presentation, evading early detection until they are big and secreting enough hormones to cause typical symptoms. So high degree of suspicion is needed to diagnose these early in the course of the illness.

### Consent

Consent was given by the patient for this case report.

### Conflicts of interests

The authors have no conflict of interest to declare.

### Abbreviations

| | |
|---|---|
| 3-MT | 3 methoxy tyramine |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CECT | Contrast Enhanced Computer Tomography |
| COMT | catechol-O-methyltransferase |
| DHEA | Dehydroepiandrosterone |
| HU | Hounsfield Unit |
| IV | Intravenous |
| ODST | Overnight Dexamethasone Suppression Test |

PASS Pheochromocytoma of the Adrenal gland Scaled Score

PPGLs Phaeochromocytomas and paragangliomas

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