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Paraganglioma in a young female. Are we missing a possible inherited aetiology? A case report

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Abstract

Background:

Pheochromocytomas and paragangliomas are commonly associated with underlying inherited syndromes. Association is stronger at a younger age and with paragangliomas. Recognition of an inherited syndrome enables an individualised management approach.

Case presentation:

An-18-year-old female presented with episodic headache, palpitations, sweating and recurrent episodes of fainting associated with hypertension for two years. Hypertension persisted even between paroxysms. Her parents are first cousins. There was no family history of tumours. She had marfanoid body habitus; otherwise, her physical examination was normal. Urine metanephrines were elevated, and CT-abdomen showed an avidly enhancing 3.2×2.7×4.3 cm mass with smooth margins in the left para-aortic area below the renal vessels suggesting paraganglioma. The whole-body MRI did not show other lesions. She underwent laparoscopic resection of the tumour. Histology confirmed paraganglioma. There was complete resolution of hypertension and paroxysms following surgery. Whole-exome sequencing from blood could not detect any mutations associated with paraganglioma. Post-operative urinary metanephrines after one year were normal.

Conclusions:

This patient's presentation strongly suggests a possible underlying inherited syndrome despite the lack of recognition of an underlying genetic mutation previously reported to be associated with paraganglioma. While the search for similar patients would help recognise such associations, close surveillance for additional tumours and recurrence would be warranted for the patient as of a patient with inherited endocrine tumour syndrome.

Keywords: Paraganglioma, Genetic, Narfanoid, Consanguinity

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Background

Catecholamine secreting tumours arising from the chromaffin cells of the adrenal medulla are called pheochromocytomas (PCC). Paragangliomas (PGL) represent extra-adrenal tumours, either derived from chromaffin cells of paravertebral sympathetic ganglia of thorax, abdomen and pelvis or arising in the head and neck region from parasympathetic ganglia of the Vagus and Glossopharyngeal nerve [1].

Altogether these are denoted PPGLs & are rare, with a 0.4 to 2 per million person-years reported in several national registries. Sympathetic PGLs are rarer since more than 80% of catecholamine secreting tumours have been PPC [2]. Due to their rarity, knowledge on clinical presentation, underlying genetic

mutations and genotype-phenotype associations were scarce. Recent advances in genetics and functional imaging have filled this gap, allowing individualised management. This has paved the way for precision medicine in patients with sympathetic PGLs [3].

Of all the endocrine tumour types, PPGLs have the highest degree of heritability. Multiple genetic syndromes are associated with an inherited predisposition to PPGLs with varying clinical, biochemical, and imaging characteristics [3]. The number of potential genetic mutations is rising with the recognition of new genetic mutations [4]. The possibility of having an underlying inherited syndrome goes up to 80% in the paediatric population [5].

The possibility of an underlying inherited syndrome is higher among patients with PGL compared to patients with PCC.

We report a female presented with PGL during the second decade of life with marfanoid body habitus and consanguinity warranting strong suspicion of an inherited syndrome. Negative screening for known genes of inherited syndromes would warrant vigilant assessment and close follow up considering the possibility of an unidentified mutation.

Case Presentation

An 18-year-old previously well female presented with episodes of palpitations, headache, dizziness, excessive sweating, shortness of breath, nausea and vomiting for 2 years. These used to occur spontaneously without an identifiable provocative factor. Symptoms lasted for about an hour and resolved spontaneously. The frequency of episodes gradually increased. During few episodes, blood pressure was found to be high. In between these episodes, she noticed fatigue and exercise intolerance. There was no postural dizziness.

She had a history of migraine with aura since seven years of age. This was initially treated medically for a short period, subsequently controlled well without any medicines. There were no other long-standing illnesses before. Mother has had hypertension from 40 years of age, well-controlled with a single agent. Father has had hypertension from 63 years of age. There was no significant family history of young hypertension or tumour syndromes. Her parents are first cousins. She has no siblings. She attained menarche at 12 years and has had regular menstruation since then. She had not undergone any surgeries.

Her height was 165 cm, weight 40 kg, BMI- 14.7 kg/m^2. Arm span was 174 cm. She had thoracic scoliosis, a high arched palate, and features of joint laxity. There were no cutaneous or mucosal lesions. There were no corneal abnormalities, lens dislocation or glaucoma.

Heart rate was 92/min, and blood pressure was 140/80 mmHg when asymptomatic. The rest of the systems were normal.

Electrocardiogram was normal, and an echocardiogram revealed myxomatous mitral valve, the billowing of the anterior mitral valve leaflet and trivial mitral regurgitation. Twenty-four-hour ambulatory electrocardiogram was normal. Twenty-four-hour ambulatory blood pressure monitoring confirmed persistent hypertension. Blood investigations are summarised in table 1.

Due to elevated urinary metanephrines with the characteristic clinical presentation, a provisional diagnosis of PPGL was made. Contrast-enhanced CT chest, abdomen and pelvis showed an avidly enhancing 3.2×2.7×4.3 cm round mass with smooth margins in the left para-aortic area below the renal vessels. Suprarenal glands were normal. This was in favour of a PGL (Figure 1).

MRI sympathetic trunk to look for synchronous lesions did not reveal additional lesions.

USS neck and serum calcitonin levels performed to look for medullary thyroid carcinoma, and serum calcium and phosphate to detect primary hyperparathyroidism were normal.

Whole exome sequencing was performed using patient's blood by SureSelect ® Human All Exon V6 kit on an Illumina ® HiSeq ®4000 Next Generation Sequencer. The DNA sequence was compared with the USCS hg19 reference sequence. The study did not yield any variant of clinical significance, including mutations in the following genes: *FH, MAX, VHL, NF1, TMEM 127, SDHA, SDHAF2, SDHB, SDHC, SDHD* and *RET*.

She was started on extended-release prazosin followed by bisoprolol. After starting medications, she did not develop further paroxysms. She underwent laparoscopic excision of the tumour under general anaesthesia one month after the presentation. A well-circumscribed single tumour measuring 5.5×3.8×3 cm was removed

Table 1 : Summary of blood investigations of the patient on presentation

Investigation	Result	Reference range
Haemoglobin (g/dL)	14.9	11-16
White Cell Count ($\times 10^9$/L)	10.2	4-11
Platelet Count ($\times 10^9$/L)	370	150-450
Serum Creatinine (mg/dL)	0.7	0.5-1.1
Sodium (mmol/L)	142	135-145
Potassium (mmol/L)	3.9	3.5-5.1
Aspartate transaminase (U/L)	21	<40
Alanine transaminase (U/L)	29	<40
Bilirubin (mg/dL)	0.6	0.5-1.1
Albumin (g/L)	44	45-55
Globulin (g/L)	37	20-30
Calcium (mg/dL)	8.2	8.4-10.2
Phosphate (mg/dL)	3.2	2.6-4.7
Fasting plasma glucose (mg/dL)	96	<100
Twenty-four-hour urinary metanephrines (mg)	2.2	<1
Thyroid Stimulating Hormone (mIU/L)	1.1	0.5-4.7
Serum calcitonin (pg/mL)	1	1-4.8

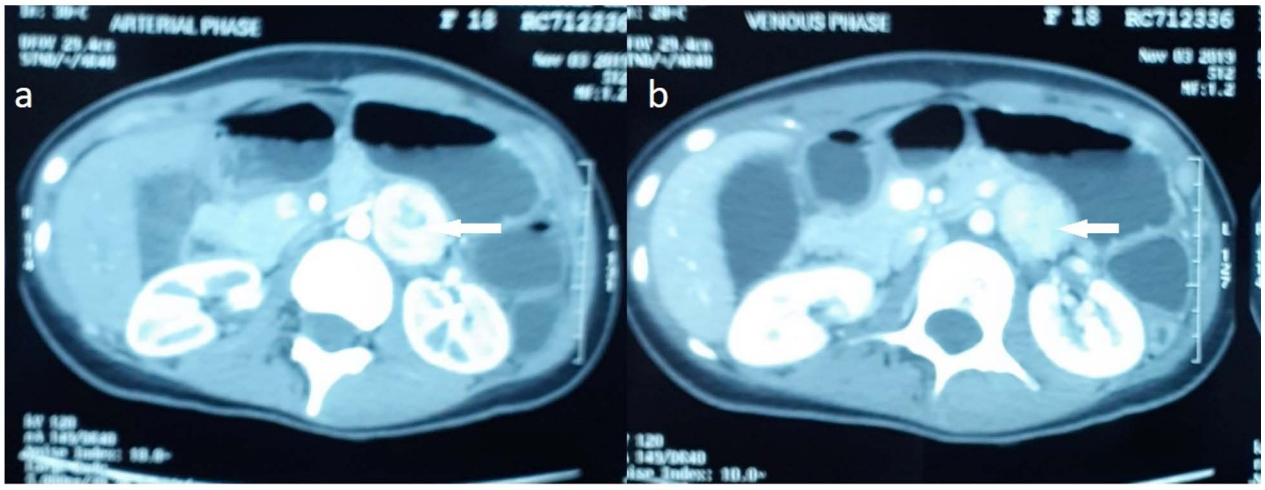

Figure 1 : Arterial and venous phase images of the Contrast-enhanced CT of the abdomen showing avidly enhancing 3.2×2.7×4.3 cm round mass with smooth margins in the left para-aortic area below the renal vessels.

One year after surgery, she remains asymptomatic and normotensive. Twenty-four-hour urinary metanephrine and contrast-enhanced CT abdomen are normal.

Discussion

One of the key clinical questions that the clinician must answer in evaluating a patient with a

genetic syndrome. There is a strong need for genetic testing in this patient due to young-onset disease and the presence of PGL rather than PCC [6]. There is a recent trend towards genetic testing in all patients with PPGL [3]. Knowing underlying genetic syndrome is useful for predicting the risk of recurrence and metastasis in paraganglioma, genetic counselling of family members, and looking for other organs' tumours. A negative screening test in this patient does not completely rule out the possibility of previously undiagnosed inherited tumour syndrome with low prevalence.

Using knowledge from research on the genetics of these tumours, they have been classified into three main clusters and subgroups [3]. They are the pseudohypoxia group, Wnt- signalling group and kinase signalling group. The Pseudohypoxia group has two subgroups. The first is Tricarboxylic acid (TCA) cycle-related mutations, including succinate dehydrogenase (SDH) subunit gene mutations. The second one is VHL/EPAS1 related gene mutations. Key syndrome associated with this mutation includes Von Hippel-Lindau (VHL) syndrome. Mutations in the kinase signalling pathway are responsible for tumours associated with Multiple Endocrine Neoplasia (MEN) 2, Neurofibromatosis and several other syndromes. Out of all, SDH mutations are mostly associated with PGL, and particularly, SDHB mutation is associated with abdominal paraganglioma [7].

Our patient had some marfanoid features seen in patients with MEN2B. However, medullary thyroid cancer usually precedes the onset of catecholamine secreting tumours in MEN2. On the other hand, most patients develop PCC rather than PGL in MEN2. extra-adrenal lesions are seen in less than 1% of patients with MEN2 [6]. Neurofibromatosis and VHL are also commonly associated with adrenal PGL, and they have distinct clinical features which were not observed in our patient. Genetic screening specifically looked for SDH mutations, MEN2, VHL and Neurofibromatosis. Therefore, we could be reasonably confident that any of those syndromes are unlikely to be present in our patient.

All the genetic syndromes described are inherited in an autosomal dominant pattern. Due to consanguinity, special interest would be placed on any syndromes with autosomal recessive inheritance. Though she has marfanoid skeletal characteristics and mitral valve changes, she has no ocular or other cardiac manifestations. Whole-exome sequencing did not find any mutation in the FBN1 gene, which is usually transmitted in an autosomal dominant manner. However, there are reports of conditions producing marfanoid features with autosomal recessive inheritance in other genes [8].

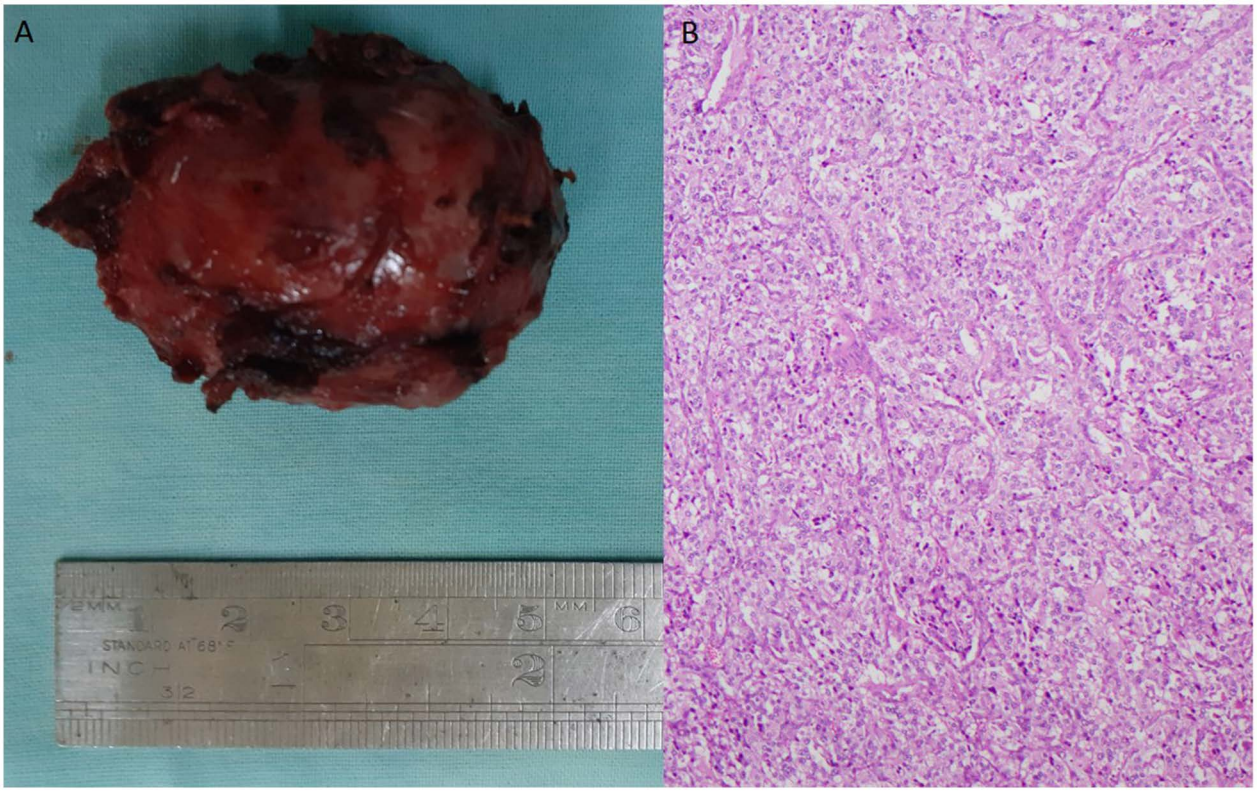

Figure 2 : Macroscopic and microscopic appearance of the tumour. Laparoscopically resected tumour showing a well-circumscribed tumour measuring 5.5×3.8×3 cm **(A)**. H&E sections of the tumour **(B)**.

Considering all these characteristics, we believe that the possibility of a rare inherited tumour syndrome is high in this patient. Close clinical follow up for tumour recurrence and other tumours as of a patient with inherited tumour syndrome would be the safest approach until we succeed in recognising such an association. Reporting of such patients would assist in recognition of similar patients in the future so that possible inherited syndromes can be identified.

Conclusions

This case report describes an atypical presentation of a young-onset PGL in a patient with marfanoid body habitus and consanguinity. The possibility of unidentified genetic mutation should be considered due to the constellation of these atypical features.

Abbreviations:

MEN2 - Multiple endocrine neoplasia type 2
PGL - paraganglioma
PCC - pheochromocytoma
PPGL - phaeochromocytoma and paraganglioma
SDH - succinate dehydrogenase
TCA - Tricarboxylic acid
VHL - Von Hippel-Lindau

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