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Case of Bilateral Pheochromocytoma in a Young Female with VHL Mutation - A Glance into Novel Insights on Genetics of Pheochromocytoma

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ABSTRACT

Pheochromocytoma is a tumour of chromaffin cells arising in the adrenal medulla, for which genetic susceptibility is the only known causative factor. Here we describe a case of a 15-year-old girl who presented with hypertension and associated symptoms like headache and chest tightness lasting for nearly one month. On evaluation, she was found to have bilateral Pheochromocytoma, following which she underwent bilateral adrenalectomy and the diagnosis was confirmed by histopathology. Being a bilateral tumor we proceeded with further genetic studies. Clinical exome sequencing revealed a VHL gene mutation. Management of Pheochromocytoma Paraganglioma (PPGL) has now taken new turns which is based on molecular classification that groups them into three specific gene clusters based on underlying gene mutations, which have definite clinical, biochemical, imaging and prognostic significances. Molecular characterization of Pheochromocytoma hence becomes of utmost importance in the era of personalized patient management plans.

Keywords: Pheochromocytoma, VHL, Gene Clusters

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BACKGROUND

Pheochromocytoma is a tumour of chromaffin cells that arises in the adrenal medulla. It is important to recognize these tumours as they are rare causes of hypertension that can be surgically corrected. Genetic susceptibility is the only known causative factor for the development of this tumor[1] and nearly 70% of these have underlying gene mutations.[2] Many familial syndromes are also associated with the development of the same. Recent updates on molecular classification cluster these tumours into 3 groups which aid personalized patient management plans.[2–11]

CASE PRESENTATION

A 15-year-old girl presented with complaints of episodes of palpitations, breathlessness, chest tightness, and headache, followed by diaphoresis and a feeling of impending doom, altogether lasting for around 10 to 15 minutes. These symptoms would then resolve spontaneously. She had 8 to 10 such episodes each day, for nearly one month, by the time she was brought to the clinician. She also had a history of giddiness while getting up from bed. She didn't have any such symptoms in the past. She also didn't have any family history of young hypertension, premature CAD or CVA.

On evaluation, she was found to have hypertension, 180/100 mm of Hg and postural fall in BP. Her pulse rate was normal with regular rhythm. She did not have pallor/ plethora/ thyroid nodule/ galactorrhea/ or virilizing features. There were no lesions suggestive of neurofibromatosis or tuberous sclerosis. She had BMI of 24kg/m^2. All other systems were within normal limits. So, a clinical suspicion of Pheochromocytoma was made.

Routine blood investigations showed Hb-12.1gm/dl, a total count of 9600 cells/mm^3, N75L25. Renal function tests, liver function tests and serum electrolytes revealed normal study. Further, ECG, chest X-ray, and USG neck were done, which all turned out to be unremarkable. A CECT abdomen was done, which

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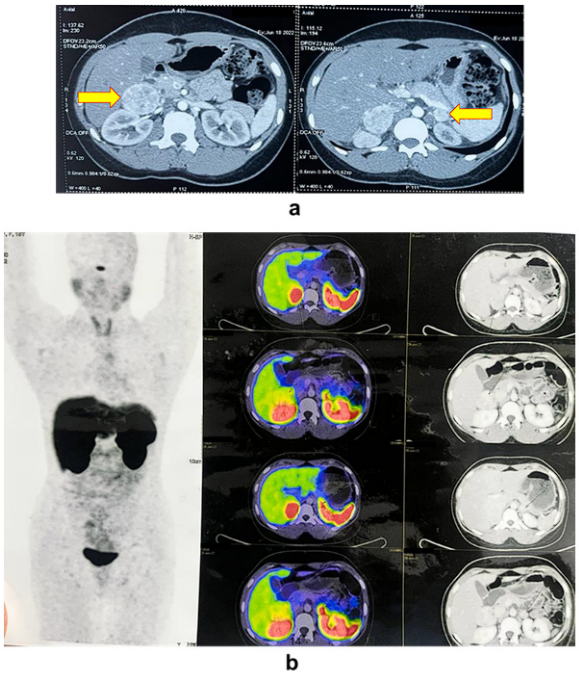

Figure 1. **a) CECT findings: Well circumscribed enhancing lesions in the right and left suprarenal regions. b) GA DOTATATE scan shows multiple somatostatin receptor expressing lesions in bilateral suprarenal regions**

showed two well-circumscribed lesions showing significant arterial phase enhancement in the suprarenal regions on both sides. On right side, lesions measured 4x3.9x3.9 cm and 4.2x4x2.9cm. On the left side, the lesions measured 2.4x2.5x1.7cm and 2.2x1.9x1.4cm. With the strong clinical suspicion of Pheochromocytoma, plasma metanephrine, normetanephrine, and 3 methoxy tyramine levels were assessed. She was found to have elevated plasma normetanephrine - 3720 ng/dl (normal-20-135 ng/dl) and 3 methoxy tyramine-272ng/dl (normal <18.4ng/dl), and normal metanephrine level. So further, a GA DOTATATE scan was done, which showed the Somatostatin receptor expressing multiple intensely enhancing lesions involving bilateral adrenal glands (R>L), see **Figure 4**. No similar foci were detected elsewhere in the body.

Considering bilateral Pheochromocytoma of adrenal location, producing normetanephrine, VHL mutation was the most likely possibility. Clinical exome sequencing was hence done, which confirmed VHL gene mutation. Our patient was also screened for other lesions coming under the spectrum of VHL mutation, all of which turned out to be negative. Any additional gene mutations was ruled out.

Our patient was planned for bilateral adrenalectomy. Preoperatively, she was started on alpha-blocker Prazosin and was also advised liberal salt intake.

Figure 2. **Adrenalectomy specimen: a) Right and b) Left.**

Metoprolol was added after 5 days. Preoperatively, pulse rate was 70/min and blood pressure was 120/80mm of Hg. Though laparoscopic adrenalectomy was planned since the patient had intraoperative bleeding and hypotension, right open adrenalectomy was done on 22/10/2022. Following adrenalectomy, she had intraoperative hypertension, which was managed with NTG (Nitroglycerin) injection. Blood pressure was controlled and left adrenalectomy was planned a few months later. On post-operative day 1, the patient had hypotension which was managed with IV fluids. The rest of the post-operative period was uneventful and she had partial remission of symptoms. A left adrenalectomy was done on 13/2/2023, following which the patient recovered nearly well.

Bilateral adrenalectomy specimens were received in the Department of Pathology at an interval of 3 and half months. We received two brown nodular masses from each side, lesions on the right side measuring 4x4x2.5 cm and 4x4x3 cm, and on the left side measuring 3.2x2.5x1.5cm and 2x1x1.5cm see **Figure 2.**

Microscopy from right side showed **(Figure 3)** a compressed adrenal cortex with a circumscribed

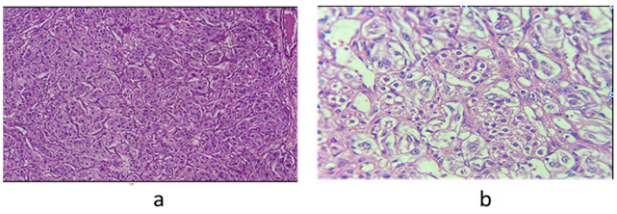

Figure 3. **a) Right adrenalectomy shows neoplasm arranged in zellballen pattern (100X) and b) Cells are round to oval with moderate amount of clear cytoplasm and vesicular nuclei (400X).**

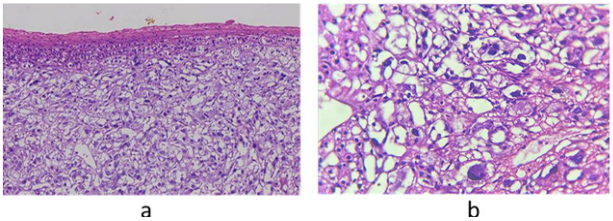

Figure 4. **a) Left adrenalectomy shows neoplasm arranged in diffuse sheets and b) Cells are pleomorphic with moderate to abundant clear cytoplasm and hyperchromatic nuclei, with occasional bizarre forms.**

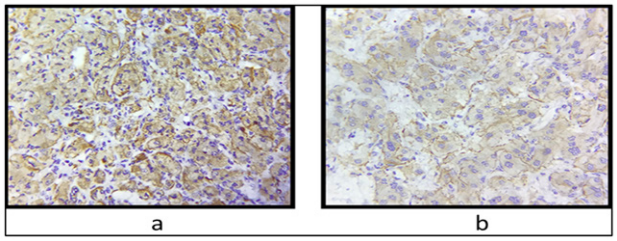

Figure 5. **Immunohistochemistry Synaptophysin : a) right and b) left**

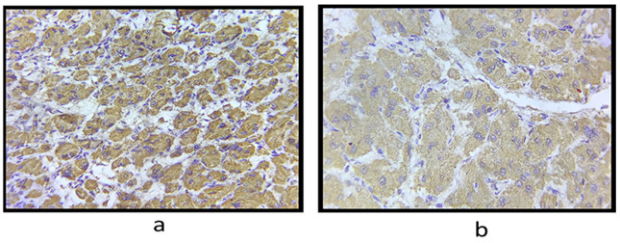

Figure 6. **Immunohistochemistry chromogranin: a) right and b) left.**

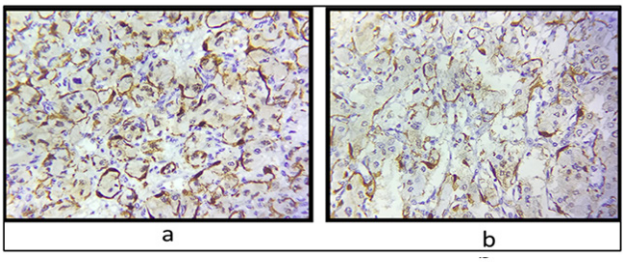

Figure 7. **Immunohistochemistry S100: a) right and b) left.**

neoplasm underneath, predominantly arranged in zellballen pattern. Individual cells were round to oval with a moderate amount of clear cytoplasm, and round vesicular nuclei. Microscopy from the left side showed **(Figure 4)** an encapsulated neoplasm arranged predominantly in sheets, with individual cells showing pleomorphism with moderate to abundant clear cytoplasm and pleomorphic hyperchromatic nuclei. Bizarre cells were also seen.

Immunohistochemistry was done in both lesions, which showed positivity for Synaptophysin and Chromogranin, and S100 highlighted the sustentacular cells. Ki67 was 5% on both sides **(Figures 5, 6 and 7)**. Diagnosis of bilateral Pheochromocytoma was hence confirmed.

DISCUSSION

Pheochromocytoma and Paraganglioma (PPGL) have the highest degree of heritability among all human tumors[11] and genetic susceptibility is the only known risk factor development of PPGL.[1] Nearly 70% of these have underlying genetic alterations and most frequent genes involved are RET, VHL, SDHB, SDHC, SDHD. Number of genetic syndromes have

Table 1. Tumors associated with subtypes of VHL (Von Hippel Lindau).

VHL subtypes	Tumors
TYPE 1	Hemangioblastoma, Renal cell Carcinoma
TYPE 2A	Hemangioblastoma, Pheochromocytoma
TYPE 2B	Hemangioblastoma, Renal Cell Carcinoma, Pheochromocytoma
TYPE 2C	Pheochromocytoma

Pheochromocytoma as its component, like MEN2, VHL, Neurofibromatosis-1 etc. Pheochromocytoma in the setting of VHL syndrome is normetanephrine producing and rarely dopamine producing.

VHL (Von Hippel Lindau) syndrome is an autosomal dominant cancer syndrome with many components, one of which is pheochromocytoma. It is divided into subtypes based on components present **(Table 1)**.[1] Our patient had only bilateral pheochromocytoma, so she falls to Type 2C. She neither had any other lesions nor a positive family history. In a study conducted by Kittah et al.,[12] out of the 1161 patients with Pheochromocytoma considered, 94 (8%) patients had bilateral disease. Family history was reported in 37% patients, and 18% patients had history of bilateral disease. Of the 75 patients with genetic disease, most had MEN2A (40.53%), followed by VHL (18.24%), MEN2B (9.12%) and NF1(8.11%).

As far as pathology of Pheochromocytoma is considered, a morphological diagnosis is not challenging and is often easily made. Pheochromocytoma in the setting of VHL mutation shows histopathological features like thick capsule, myxoid and hyalinized stroma, rich vascular network and clear cell change. They don't show medullary hyperplasia.[1]

Identification of specific underlying gene mutation becomes of utmost importance in current era because of the advent of precision medicine. An interesting advancement in this field is the characterization of the genetics of Pheochromocytoma and Paraganglioma (PPGL), which puts forward a potential molecular classification of PPGL based on the underlying gene mutations.[2–11] PPGL falls into 3 specific gene clusters, based on the gene mutations present. Cluster 1 involves genes of hypoxia signaling pathway and includes genes of Krebs citric acid cycle- mainly SDHB, SDHC, and SDHC in Cluster 1A and VHL and related genes in Cluster 1B. Cluster 2 involves genes of kinase signaling pathway like RET, MET, NF1. Cluster 3 involves genes of WNT signaling pathway. These three clusters have different clinical, biochemical and imaging signatures

Table 2. Gene clusters of Pheochromocytoma and Paraganglioma (PPGL)

	Cluster 1A	Cluster 1B	Cluster 2	Cluster 3
Gene	SDH x (SDHA, B, C, D, F2) FH, MDH2	VHL, EPAS1 (HIF2A), Sporadic noradrenergic	RET, NF1, MAX, TMEM127, HRAS, Sporadic noradrenergic	CSDE1, MAML3
Signalling pathways	Pseudo hypoxia (HIF-1a) & aberrant VEGF signaling		Kinase signaling: PI3 kinase/AKT, RAS/RAF/ERK, & mTorC1/p70S6K	Wnt signaling
Catecholamine type	Dopamine (DA), mixed DA & Noradrenaline	Noradrenaline	Adrenaline	Unknown
Tumour location	Extra-adrenal	Adrenal & Extra-adrenal	Adrenal	Adrenal
Age of presentation	Early (under 30 year-old)	Early	Late	Unknown
Imaging	[^{68}Ga]-DOTA-SSA PET/CT	[^{18}F]FDOPA PET/CT	[^{18}F]FDOPA PET/CT	Unknown
Metastatic risk by GAPP	Intermediate - High	Low - Intermediate	Low	High – intermediate

and also have different long-term prognosis. Features of three clusters are summarized in **Table 2.**

Clinical diagnosis in this case was not very challenging because of the classic spells and hypertension. Early age of onset in this case was as expected according to the cluster type. Further, Pheochromocytoma in this case was normetanephrine secreting which is in concordance with VHL mutation. GA DOTATATE scan was the imaging modality used, however, recent studies based on cluster identification advocates use of [^{18}F] FDOPA PET/CT scan superior to GA DOATATE scan. Cluster 1B shows both adrenal and extra adrenal locations of tumor, but in our case the patient had only bilateral adrenal tumor. Extra adrenal locations are associated most often with SDHB mutations. The patient needs long term close follow up as per the present consensus.[2]

Till date, she is symptomatically fine, except in stressful conditions like fever, where she takes more than normal time to recover to normalcy. Follow up MRI of brain and whole body showed no other lesions elsewhere. Considering the patient side, on comparing the advantages and disadvantages of partial against complete adrenalectomy, partial adrenalectomy was associated with higher risk of recurrence than total adrenalectomy. However, patients undergoing partial adrenalectomy had lower odds ratio of developing acute adrenal crisis as compared to the ones undergoing total adrenalectomy.[13] In a study that assessed the long-term outcome of surgical excision in children with pheochromocytoma, 26.7% patients recurred after the first operation. According to them, early diagnosis, surgical excision, and long term follow up are key to appropriate management of childhood Pheochromocytoma.[14]

However, considering the newer insights into the molecular signatures of morphologically similar Pheochromocytomas, development and availability of targeted drugs, which act at different levels of the genetic pathways involved in their tumorigenesis are much awaited, for a better and tailored patient management plan.

CONCLUSION

Our case was that of ya oung female who presented with hypertension and was found to have bilateral Pheochromocytoma. She was detected to have a VHL gene mutation (subtype 2C) and hence falls under Cluster 1B according to the new consensus of molecular classification based on underlying gene mutations. These molecular clusters are proven to have definite implications on the age of presentation, tumour location, catecholamine type, cell differentiation, malignant potential and genetic anticipation. Although targeted drugs are not yet available in our hospital settings, early identification, proper screening and molecular classification remain the cornerstone of future management strategy for Pheochromocytoma, which is precisely personalized.

END NOTE

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