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CASE REPORT

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Epistaxis, paroxysmal anxiety episodes, and hypertension in a child with *SDHB*-associated paraganglioma: A case report

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Abstract

A child presented with anxiety and weight gain which were overlooked until she had epistaxis. She was found to have hypertension secondary to paraganglioma. She was managed with curative surgery involving multidisciplinary care. The tumor removal led to the amelioration of symptoms and marked control of hypertension.

KEYWORDS

68Ga-DOTANOC, catecholamines, neuroendocrine tumor, paraganglioma, *SDH* mutation, secondary hypertension

1 | INTRODUCTION

Pheochromocytomas and paragangliomas are known as "the great masquerader" as the symptoms are non-specific, occurring in paroxysmal spells and remaining asymptomatic. The sensitivity in the diagnosis of pheochromocytoma and paraganglioma using the classical triad of palpitations, headache, and diaphoresis is only 58%.[1] Pheochromocytoma and paraganglioma often present as secondary hypertension in childhood and adolescence and contribute to significant premature atherosclerosis and cardiovascular disease.[2] In children between 1 and 13 years, hypertension is diagnosed when blood pressure values on three separate visits are >95th percentile for the age, sex, and height of the patient (Table 1).[2]

The atypical presentations of pheochromocytomas and paragangliomas include paroxysms of syncope, abdominal pain, diarrhea, pallor, tremor, weight loss, nausea, fever, and flushing.[3] Neuropsychiatric presentations include anxiety or panic attacks and depression which are easily missed when occurring in adolescents.[4,5] Here, we present a case of paraganglioma in a female child who presented with anxiety and weight gain which were overlooked as a part of adolescence. She gained medical attention when she developed recurrent epistaxis and was found to have endocrine hypertension. She had *SDHB* (succinate dehydrogenase complex iron sulfur subunit B) mutation that has helped guide evaluation for similar disease in family members.

2 | CASE PRESENTATION

A 10-year-old female child had paroxysmal episodes of anxiety and increase in appetite with weight gain for 12 months. She was brought to medical attention with recurrent episodes of spontaneous bleeding from the nose, palpitations, and headache. The nose bleeds were precipitated by cough or sneezing, relieved within minutes by putting pressure on the nose. She had multiple episodes of palpitations, not associated with chest pain and loss of consciousness. She also had global headache with no specific aggravating or relieving factors, not associated with nausea, vomiting or visual disturbances. There were no mucocutaneous bleeds, fever, neck pain, altered sensorium, trauma, or features of hyperthyroidism.

Blood pressure categories	For children aged 1 to <13 years	For children aged ≥13 years
Normal	<90th percentile	<120/<80 mmHg
Elevated blood pressure	≥90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	120/<80 to 129/<80 mmHg
Stage 1 hypertension	≥95th percentile to <95th percentile +12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	130/80 to 139/89 mmHg
Stage 2 hypertension	≥95th percentile +12 mmHg, or ≥140/90 mmHg (whichever is lower)	≥140/90 mmHg

TABLE 1 Definitions of blood pressure categories and stages as per the clinical practice guideline for screening and management of high blood pressure in children and adolescents, American Academy of Pediatrics, 2019[2]

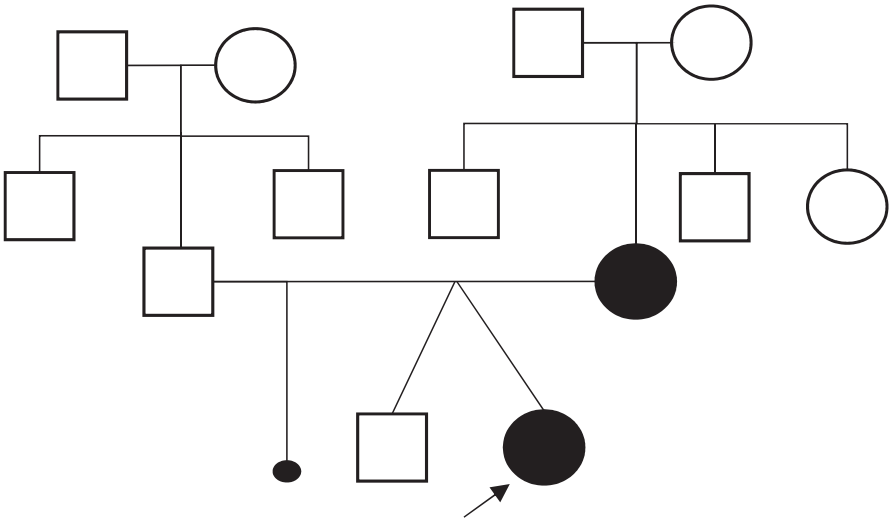

FIGURE 1 Pedigree chart of the 10-year-old female subject with multicentric paraganglioma (indicated with arrow head) with history of similar illness in the mother.

She was conceived through in vitro fertilization, was the second of twins, and born at term (Figure 1). Her mother had history of micturition syncope and palpitations at 18 years of age, was diagnosed with hypertension secondary to bladder paraganglioma, and was operated at age 19 years; no genetic testing was available.

On examination, her height was 151 cm (97th centile), weight 50 kg (>97th centile) and body mass index 21.9 kg/m^2 (>97th centile). Her pulse rate was 78/min, regular rhythm, blood pressure (BP) 142/92 mmHg in right arm, 140/90 mmHg in left arm, and 144/82 mmHg in lower limb (>95th centile). Twenty four-hour ambulatory blood pressure readings were >95th centile. There were no dysmorphic features, skin rash, pigmentation, mucosal neuroma, hirsutism or features of neurofibromatosis, Cushing syndrome, Marfan syndrome, or acromegaly. Her Tanner stage was B2P2. Examination of the cardiovascular, respiratory abdominal and neurological systems was essentially normal.

Her hemoglobin, blood counts, liver and renal profiles, fasting and 2-h postprandial blood glucose, urine analysis, ultrasonography of the abdomen, electrocardiogram, and 2D echocardiography had normal findings (Table 2).

The evaluation for causes of secondary hypertension were as follows: 24-h urinary metanephrines: 29.3 μg/24 h (normal: 25–312 μg), 24-h urinary nor-metanephrines: **1861** μg/24 h (normal 51–275 μg), overnight dexamethasone suppression test serum cortisol: 0.55 μg/dl (normal <2.01 μg/dl), plasma aldosterone/renin ratio: 0.639 ng/dl/μIU/ml (normal), serum intact parathyroid hormone: 30 pg/ml (normal 10–55 pg/ml) and 25 (OH) Vitamin D: 45 μg/dl (normal 30–50 μg/dl).

Imaging of the chest and abdomen with contrast enhanced computer tomography (CECT) showed brightly enhancing lesions in the retrocaval (Figure 2A,B) and left para-aortic (Figure 2C,D) regions in the abdomen and right paravertebral region in the thorax (Figure 2E,F) suggestive of extra-adrenal paraganglioma; bilateral adrenal glands were normal. Doppler renal ultrasonography and computed tomography angiogram of the renal vessels showed normal flow and structure. She underwent a Ga^{68} DOTANOC (dodecane tetraacetic acid-NaI3-Octreotide) scan that revealed soft tissue masses in the abdomen (Figure 3A,B) and right paravertebral region in the thorax (Figure 3C) with somatostatin receptor activity which were consistent with multicentric extra-adrenal paraganglioma, no skull base or neck

TABLE 2 Baseline laboratory parameters of a 10-year-old female child with *SDHB*-associated multicentric paraganglioma.

Parameter	Value	Normal Range
Hemoglobin (g/dl)	12.3	12–15
White blood cell count (/mm^3)	8400	4000–11,000
Platelets (/mm^3)	407,000	150,000–450,000
Urea/creatinine (mg/dl)	19/0.6	10–50/0.7–1.3
Na/K (mEq/L)	139/3.8	136–145/3.5–5.1
Calcium/phosphorus (mg/dl)	8.9/4	8.5–10.1/2.6–4.7
Fasting/postprandial plasma glucose (mg/dl)	82/105	<100/<140
Total protein/albumin (g/dl)	7.8/4.5	6.4–8.2/3.4–5
Bilirubin (mg/dl)	0.5	0.5–1.0
Aspartate transaminase (IU/L)	19	16–63
Alanine transaminase (IU/L)	20	15–37
HBsAg/Anti-HCV/Anti-HIV	Negative	
Urine analysis	No protein, sugar, blood or leukocytes; no red blood cells, casts, epithelial cells	
X-ray left wrist	Bone age =chronological age	

involvement. Therefore, with a history of paraganglioma in her mother and biochemical and imaging reports of paraganglioma, she was tested for succinate dehydrogenase-related *SDHx* genetic panel that was positive for heterozygous 14 base pair deletion in exon 4 of *SDHB* gene.

Her hypertension was managed with sequential alpha- and beta-adrenergic blockade (Tab Prazosin 1.25 mg twice daily, gradually increased to 7.5 mg twice daily, followed by Tab Propranolol 20 mg twice daily), replenishment of intravascular volume with fluids and increased salt intake to prevent post-operative hypotension.

She underwent video-assisted thoracoscopic surgical excision of right thoracic tumor and laparotomy for excision of para-aortic and aortocaval tumors under general anesthesia and one lung-ventilation with invasive blood pressure monitoring. She had a stormy intra-operative course with persistent hypotension post-induction of general anesthesia, the lowest BP 90/60 mmHg requiring noradrenaline infusion, and hypertension during tumor manipulation, the highest BP 200/120 mmHg requiring nitroglycerin infusion.

The histopathological study showed a well-encapsulated tumor (Figure 4A), surrounded by sustentacular cells, arranged in a nested pattern giving a typical Zellballen appearance and the nests interspersed by numerous thin-walled capillaries (Figure 4B). The tumor contained polygonal cells with moderate amphophilic cytoplasm and vesicular nucleus with prominent nucleoli (Figure 4C). The tumor cells were positive for synaptophysin (Figure 4D) and chromogranin (Figure 4E); sustentacular cells were positive for S100 (Figure 4F). Lymphovascular emboli, necrosis or breach of surface were not seen; section from the lymph node showed reactive cells.

Post-operatively, she was managed in the intensive care unit with close monitoring of her vital parameters and supportive care. Her plasma fractionated metanephrines and nor-metanephrines were within normal limits suggestive of no residual tumor. The family has been counseled for genetic testing of the twin sibling and the mother. Presently, she is on outpatient follow-up and her BP is controlled with Amlodipine 5 mg once daily.

3 | DISCUSSION

The clinical features of pheochromocytomas and paragangliomas are due to catecholamines derived from the sympathetic or the parasympathetic nervous systems. The neuropsychiatric manifestations are due to predominant secretion of dopamine when tumor cells lack dopamine β-hydroxylase, required for the conversion of dopamine to noradrenaline.[6] These manifestations are often missed especially in children until they present with a hypertensive crisis. Hypertension resulting from hormonal excess accounts for 0.05%–5% of children with secondary hypertension in the west and 3.2% in a sample reported from India.[2,3] The combined prevalence of pheochromocytoma/paraganglioma in patients with hypertension in general outpatient clinics among adult population varies between 0.2 and 0.6%[7] and often is diagnosed in autopsy studies.[8] Although endocrine hypertension is rare, timely diagnosis and appropriate treatment results in dramatic response and overall benefit in terms of cardiovascular outcomes in early adulthood.[2]

Urinary or plasma catecholamines and their metabolic products are the recommended biomarkers for the

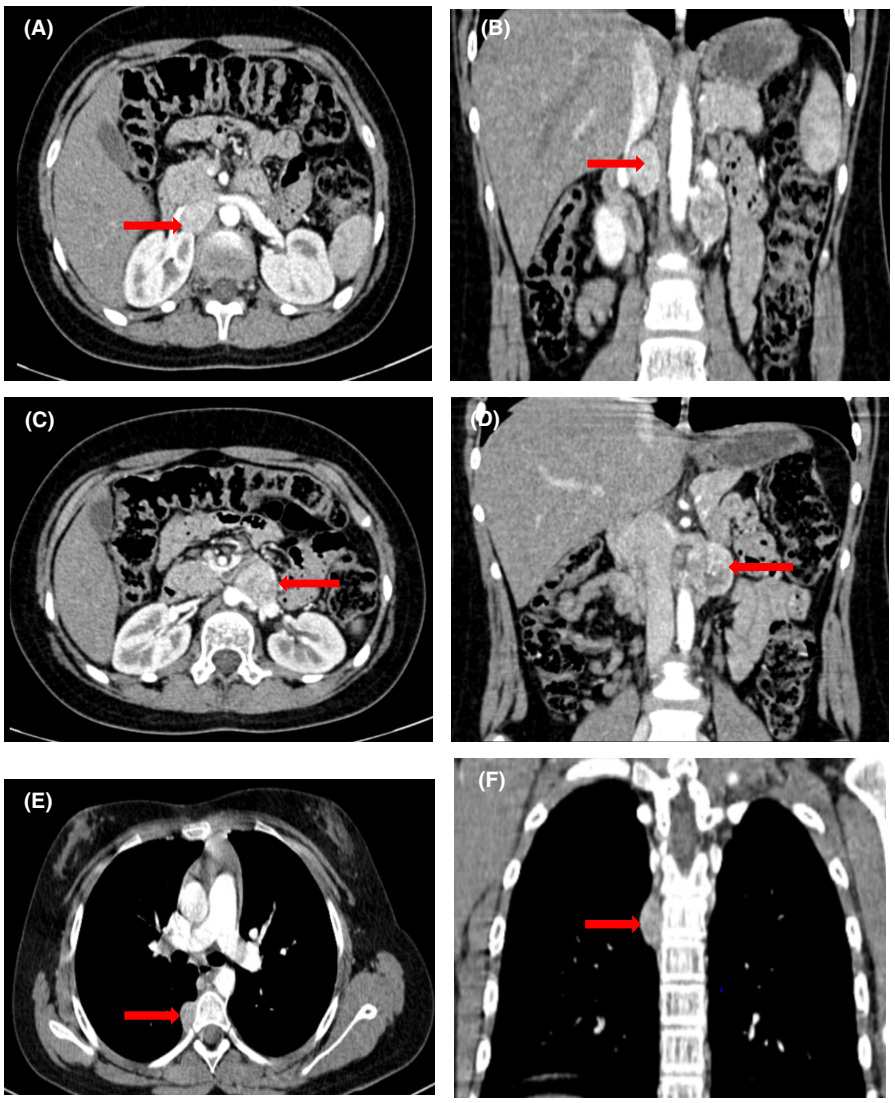

FIGURE 2 Contrast-enhanced computed tomography (CECT) imaging of a 10-year-old female child with hypertension secondary to paraganglioma. (A) and (B) CECT axial and coronal reformat of abdomen shows a well-defined, arterial phase avidly enhancing lesion in the retrocaval region. It measures 3.3 × 2.9× 3.5 cm. The angle of contact with the aorta at L1-L2 level is more than 90 degrees. The lesions appear to be abutting and displacing the IVC to right without obvious infiltration. (C) and (D) CECT axial and coronal reformat of abdomen showing a similar well-defined attenuating lesion on the left para-aortic region. (E, F) CECT axial and coronal reformat of thorax in mediastinal window shows a well-defined hypodense lesion in the right para vertebral region at the level of D5 vertebra.

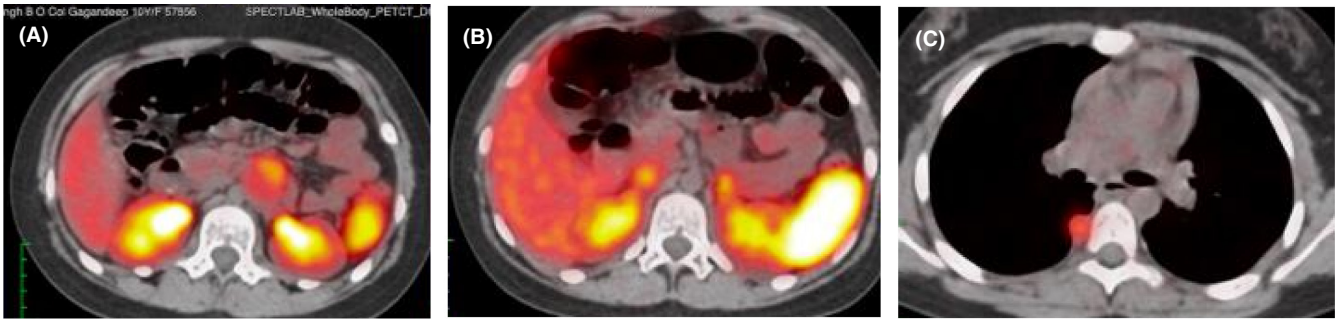

FIGURE 3 Ga^{68} DOTANOC axial scan with somatostatin receptor activity showing two soft tissue masses in the abdomen (A) and (B), and one mass in the right paravertebral region in the thorax (C).

diagnosis of pheochromocytoma/paraganglioma. Our patient had elevated nor-metanephrines in the 24-h urinary sample. Plasma free metanephrines has sensitivity 89.5%–100% and specificity 79.4%–97.6%; urine metanephrines has sensitivity 85.7%–97.1% and specificity 68.6%–95.1% in the diagnosis of paraganglioma.[8,9] Liquid chromatography with mass spectrometric or electrochemical detection methods are reported to have better diagnostic sensitivity.[8,9] False positive results are reported in patients on monoamine oxidase inhibitors, amphetamine, acetaminophen, ephedrine, phenylephrine, levodopa, and alpha-methyl dopa.[10]

After the establishment of biochemical evidence of paraganglioma, it is recommended to locate the

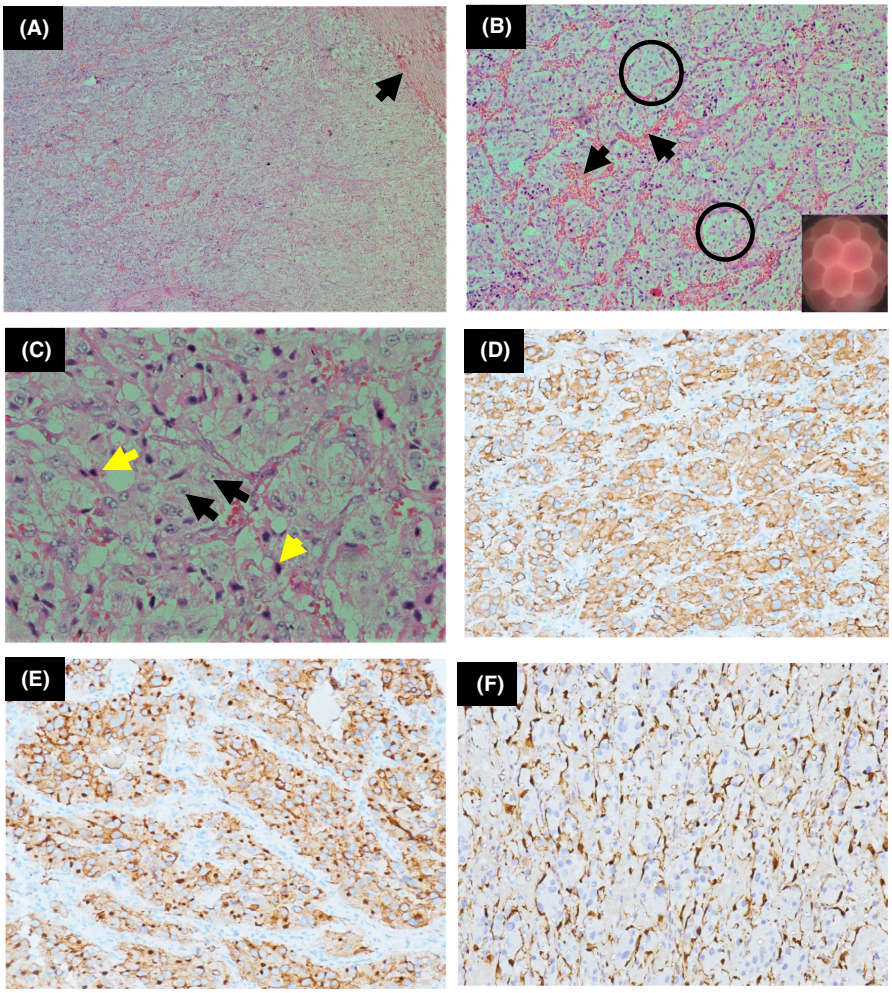

FIGURE 4 Specimen from the tumors from the thorax and abdomen of a 10-year-old female child with hypertension secondary to paraganglioma. (A) Hematoxylin and eosin stain at 40x shows well-encapsulated margins in black arrow-head (B) with cells arranged in zelballen nests (in black circles) with numerous thin-wall capillaries in between the nests (black arrow); inset shows zellballen pattern. (C) On hematoxylin and eosin staining at 400×, the tumor cells show cytoplasm abundant with eosinophilic granules (black arrow), vesicular nuclei and prominent nucleoli with supporting sustentacular cells (yellow arrow). On immunohistochemistry, the tumor cells are positive for (D) Synaptophysin and (E) Chromogranin. (F) The S100 stain highlights the sustentacular cells.

tumors through appropriate imaging modalities. Ultrasonography has the least diagnostic yield. CECT is recommended as the first-line diagnostic modality and has sensitivity 88%–100% and provides spatial resolution of the tumor location in the thorax, abdomen, and pelvis.[8] MRI has sensitivity of 93%–100% but specificity of only 50%.[8] Radioisotope imaging using MIBG (metaiodobenzylguanidine) scanning has sensitivity 56%–75% and specificity 84%–100%.[8] However, almost 50% of normal adrenal glands demonstrate physiological uptake of ^{123}I MIBG uptake and results in false positive tests. For *SDHx*-related paraganglioma, the overall sensitivity of ^{123}I MIBG scan is less than 50%.[8] Other options for imaging include ^{18}FDOPA (fluoro-3,4-dihydroxyphenylalnine) and ^{68}G-DOTANOC scans that are particularly useful in multicentric and metastatic tumors.[8] In our patient, CECT demonstrated multicentric extra-adrenal paraganglioma while Ga^{68} DOTANOC demonstrated somatostatin receptors within the tumor.

In the background of bladder paraganglioma in the mother and the patient having a twin-brother, we considered testing for common genetic mutations related to paraganglioma. There are six familial autosomal dominant disease syndromes associated with pheochromocytoma/paraganglioma—neurofibromatosis type 1, multiple endocrine neoplasia type 2, von Hippel–Lindau syndrome, renal cell carcinoma with *SDHB* mutation, Carney triad (paraganglioma, gastric stromal tumors, pulmonary chondroma), and Carney-Stratakis syndrome (paragangliomas and gastric stromal sarcomas). The identification of *SDHB* germline mutation is an important risk factor for malignancy in patients with paraganglioma, prevention or early detection of tumor and screening of asymptomatic family members.[11] Patients with mutations in *SDHA*, *TMEM127*, *MAX*, and *SDHAF2* genes may have tumors in any area where paraganglia are located and therefore need imaging from the skull base to the pelvis.[11,12] In our patient, we have advised genetic testing in the mother and the twin brother as *SDH* mutations predispose to multiple site and malignant forms of tumors.[13]

The definitive management of paraganglioma is surgical removal of the tumor.[10] Surgical removal is associated with catecholamine storm and hypertensive crisis. It is recommended that hormonally functional pheochromocytomas/paragangliomas should undergo pre-operative alpha- and beta-adrenergic blockade with maintenance of adequate intravascular volume through intravenous

hydration and increased salt intake.[8] Our patient had hormonally functional multifocal paraganglioma. As expected, she had a stormy intra- and post-operative course with hypotensive and hypertensive crises that required critical care monitoring.

Post-operatively, her plasma fractionated metanephrine and nor-metanephrine levels had returned to normal levels demonstrating no residual tumor. However, she had persistent hypertension that was controlled with Amlodipine. Persistent hypertension following surgery may be due to irreversible vascular alteration or structural changes in the kidney as a result of prolonged exposure to elevated levels of catecholamines.

Long-term follow-up of children with pheochromocytomas and paragangliomas is essential to detect the impact of hypertension-mediated organ damage and to monitor for evidence of recurrence of tumor through screening with plasma or urine metanephrines.[14] Our patient is being followed up with monthly BP assessment at the outpatient department. She is planned for follow-up with yearly plasma fractionated metanephrines and nor-metanephrines levels.

4 | CONCLUSION

Atypical presentations of pheochromocytomas and paragangliomas require keen clinical evaluation. Endocrine hypertension, though rare, is a potentially reversible cause of hypertension that can be diagnosed with biochemical profiling of tumor and imaging. In this individual, association with *SDHB* gene mutation was an important clinical guide for follow-up and testing in family members.

AUTHOR CONTRIBUTIONS

Thinley Dorji: Conceptualization; data curation; investigation; methodology; project administration; resources; validation; writing – original draft; writing – review and editing. **Vishesh Verma:** Conceptualization; data curation; investigation; methodology; project administration; resources; writing – review and editing. **Anil Menon:** Conceptualization; data curation; methodology; project administration; resources; writing – review and editing.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data sources are cited in this article.

ETHICAL APPROVAL

Informed written consent was taken from the parents of the subject. Institutional ethics review is not required for case reports.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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