

Case report

Pediatric hypertensive emergency: a rare case report of metanephrines negative pheochromocytoma

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Received: 08 February 2025

Accepted: 10 March 2025

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ABSTRACT

Pheochromocytomas are catecholamine-secreting paragangliomas (PPGL) arising from chromaffin cells in the body. It is a rare cause of secondary hypertension in adults but is even rarer in children. Ten percent occur in children, in whom they present most frequently in the age group 6-14 years. The annual incidence among children is approximately 0.8/1000000 person-years. A 7-years-old child presented with hypertensive emergency and differences in blood pressure between the upper and lower limbs > 10 mmHg. Contrast-enhanced computed tomography of the abdomen suggested the diagnosis of right-sided pheochromocytoma. Urine and plasma metanephrines were within normal limits. The hypertensive emergency was managed with anti-hypertensives and the mass was surgically resected which was confirmed as malignant Pheochromocytoma on histopathology. Pheochromocytoma can be diagnosed by measurement of 24-hour urinary or plasma metanephrines which has sensitivity and specificity of nearly 95% and 85%. However, in our case these levels were normal. It could be because of rarest dopamine-producing PPGL which produces more dopamine than the combined concentration of epinephrine and nor-epinephrine. 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 positron emission tomography – computed tomography (PET/CT) as opposed to follow up of a benign tumor and earlier discharge into the community.

Keywords: Pheochromocytoma, Metanephrine-negative, Dopamine, Catecholamine, Paraganglioma

INTRODUCTION

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare neuroendocrine tumors that account for 0.5–2% of the causes of hypertension in the pediatric age group. PCC accounts for 80–85%, while PGL accounts for 15–20% of the catecholamine-secreting tumors.¹ PCC originates from the adrenal medulla, whereas PGLs are extra-adrenal in location. PGLs are sympathetic PGL, which arises from sympathetic ganglion chains in the chest, abdomen, and pelvis, and parasympathetic PGL, which arises from parasympathetic tissue from the head and neck.² These tumors can occur sporadically or in association with few hereditary disorders, such as

multiple endocrine neoplasia (MEN) type 2, Von Hippel-Lindau (VHL) type 2, neurofibromatosis (NF) type 1, and the Paraganglioma-Pheochromocytoma syndromes (SDHx).³ The child, commonly boys (M: F: 2:1), presents at 11–13 years of age, most commonly sustained hypertension in 60–90% of the pediatric population, in contrast 50% of adults presents with paroxysmal hypertension.⁴ Symptoms may differ based on which type of hormone is being secreted; e.g., a child with a catecholamine-secreting tumor may present with hypoglycemia and hypotensive shock due to excessive catecholamine secretion, whereas a dopamine-secreting tumor have a delayed diagnosis as these patients are usually asymptomatic until presents due to the mass

effect of the tumor.⁵ The gold standard for diagnosing the PCC and PGL includes measuring plasma-free metanephrines (metanephrine and normetanephrine) and 24-hour urinary fractionated metanephrines. Their production is independent of the release of catecholamine that is secreted episodically.⁶

Berkel et al, reported an almost 100% sensitivity of plasma and urine metanephrines for diagnosing PCC and PGL.⁷ Dopamine-secreting PCC/PGL is rarer, which shows normal metanephrine levels, thus making the diagnosis of PCC/PGL difficult. Only 53 cases have been described in the literature.^{7,8} We hereby describe a case of pediatric patient with stage II hypertension with normal urinary metanephrine levels, ultimately diagnosed as pheochromocytoma on imaging and histopathology.

CASE REPORT

A 7-year-old girl child presented to our pediatric emergency department with complaints of intermittent headaches for last 15 days. There was no history of vomiting, visual blurring, abnormal movements, nasal congestion, fever, tremors, palpitations, excessive sweating, constipation, abdominal pain. Past history revealed multiple episodes of intermittent headaches for which the child was prescribed analgesics and refraction testing to which the child showed no improvement. The family medical history was unremarkable. The girl was first child of parents, born out of non-consanguineous marriage, at term, with a birth weight of 3200 grams, with an uneventful antenatal, natal and postnatal period. The child had achieved her developmental milestones at appropriate ages, was immunized as per age, and was on average Indian diet receiving adequate proteins and calories as per age.

On examination, the child was conscious but irritable. She had a weight of 33 Kg (Z-score 1.87 as per age), height 129 cm (Z-score 1.38 as per age) and body mass index of 19.83.

She was afebrile, respiratory rate of 28/min, SpO₂ 99% in room air, pulse rate of 152/ minute and blood pressure (BP) of 182/154 mmHg in right upper arm, 180/152 mmHg in left upper limb and 188/160 mm Hg in lower limb. All peripheral pulses were equally palpable with no radio-femoral delay. The blood pressure values were repeated for confirmation and consistently fell in the category of stage 2 hypertension, according to American academy of pediatrics classification based on age, gender and height.⁹

There was no pallor, cyanosis, icterus, edema or lymphadenopathy, nor any neuro-cutaneous stigmata from head-to-toe examination. Systemic examination showed no abnormal respiratory findings or cardiac murmurs. The apical impulse was located at 4th intercostal space in the mid clavicular line and was heaving in nature. The abdomen was soft, non-tender

with no hepatomegaly or splenomegaly. Umbilicus was in centre and there was no lump, fluid or bruit on palpation. Neurological examination showed a Glasgow coma scale score of 11/15, power of 4/5 in all muscle groups, normal tone, cranial nerves examination with normal superficial and deep tendon reflexes and flexor planter response. Fundus examination revealed stage III hypertensive retinopathy, with no evidence of hemorrhage/ cotton-wool spots/ silver wiring. Based on history and examination, the child was diagnosed as a case of stage II hypertensive emergency, possible causes considered were renal parenchymal disease, renovascular or cardiac disease.

The child was admitted in pediatric intensive care unit, with continuous monitoring of vitals. She was started on maintenance fluids. The target mean arterial pressure (MAP) was planned at 86 mm Hg to be achieved in 48 hours with an aim to reduce 25% of the planned BP reduction over first 6 hours, followed by gradual reduction of BP to 95th centile for age, sex and height in next 24-48 hours. Labetalol infusion was started at 1mg/kg/hr which were gradually increased to 2.5 mg/kg/hr to achieve the MAP by 48 hours.

Oral Prazosin (alpha blocker) was added initially at 12th hour of labetalol infusion at a dose of 0.05 mg/kg/day which was gradually increased to 0.1 mg/kg/day to prevent first dose hypotension. Labetalol infusion was gradually tapered and omitted in next 12 hours of achieving of MAP and beta blocker-oral propranolol at dose of 2 mg/kg/day was added by 30 hours of initiation of labetalol infusion (24 hours post initiation of prazosin). Tablet amlodipine at dose of 0.3 mg/kg/day was added by day 6 of admission. Blood pressure was maintained at upper limit of 50-90th centile for age, sex and height. Serial BP recordings over hours spreading over days of admission are shown in Table 1. Investigations are shown in Table 2.



Figure 1 (a and b): A contrast- enhanced computed tomography (CT) scan of abdomen.

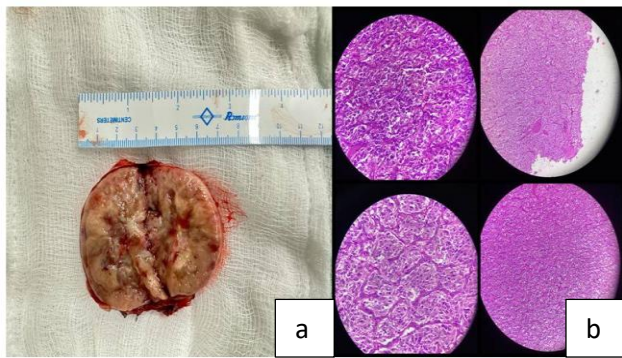


Figure 2 (a and b): Gross appearance of the tumor.

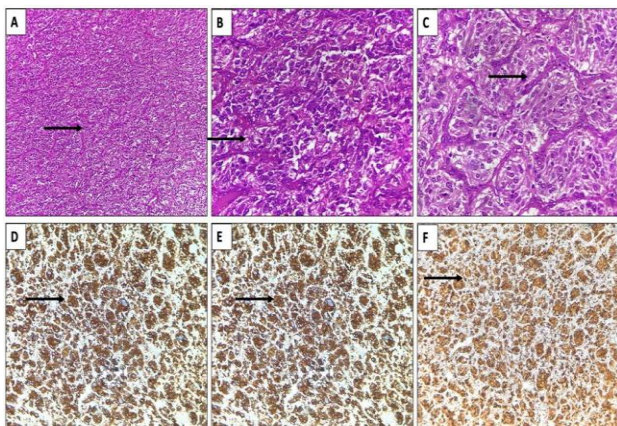


Figure 3 (A-F): Histopathology with immunochemistry of the specimen.

Chest X-ray and electrocardiogram (ECG) were normal. 2D echocardiography (ECHO) showed moderate left ventricular hypertrophy (LVH) with a posterior wall thickness of 14.2 mm. Ultrasonography (USG) of the abdomen, kidney, and urinary bladder (KUB) with Doppler revealed a suspicious hypoechoic lesion of size 3.5×5.2 cm over right kidney with no increase in vascular supply. Right kidney measured 8.2×3.4 cm, left kidney measured 8.0×3.5 cm, showed normal anatomy, echogenicity. Parenchymal thickness is normal with no obvious hydronephrosis.

A computed tomography (CT) scan of the abdomen done at day 5 of hospitalization revealed a well-defined, solid, retroperitoneal, heterogeneously enhanced mass lesion of size 5.4×4.1×4.3 cm (ap X tr X cc) in the right suprarenal (adrenal) location. On non contrast study, it appeared hypodense (34 HU) as compared to adjacent liver without any calcifications. On arterial phase it showed avid peripheral enhancement with vascular channels supplying the lesions originating from right renal artery and descending abdominal aorta. On porto- venous phase, it showed heterogeneous peripheral enhancement with central non- enhancing areas suggestive of necrosis, with an absolute percentage washout (APW) of 20%, indicating the possibility of pheochromocytoma

T2N0M0-stage II (Figure 2). Plasma free metanephrine levels were within normal limits (45.7 pg/ml) (biological references <100 pg/ml), and twenty-four urinary metanephrine levels were negative (111.51 µg/24 hrs) (Biological reference: <350 µg/24 hrs). Based on location and size and keeping a suspicion of pheochromocytoma, resection was planned due to the concern about malignancy. Pre operative control of BP was achieved with tablet prazosin, propranolol and amlodipine. The child received tablet prazosin and tablet propranolol in the morning of the surgery day. Laparotomy done at 14th day of admission revealed a well-encapsulated, circumscribed right adrenal mass of size 5×6 cm with no evidence of intra-abdominal metastasis or lymphadenopathy. Neovascularization was present around the adrenal gland, and dense adhesions were present medially in the inferior vena cava (IVC) with various collateral vessels.

A right adrenalectomy was performed, and the child was normotensive during the entire surgery. The patient developed hypotension, BP falling to 80/54 mmHg (below 5th centile for age, sex and height), 6 hours post-surgery, during the initial 24-hour postoperative period, which was managed with inotropic support. Injection nor-adrenaline was started at the rate of 0.2 µg/kg/minute for 24 hours and was tapered off and omitted in next 6 hours.

The child remained normotensive after that and required no further anti- hypertensives which were tapered off during hypotension. Serial blood pressures post-surgery is shown in Table 3. The gross specimen has been shown in Figure 2. The child was maintaining normal blood pressure between 50-90th centile for age, sex and height and required no further anti-hypertensives and discharged on post operative day 7.

Histologically, the microscopic appearance of the tumor revealed cells to be arranged in a Zellballen pattern. The individual cells are large, polygonal, with abundant cytoplasm with round to oval nuclei and prominent nucleoli, surrounded by sustentacular cells with focal areas of necrosis and atypical mitosis with no vascular or capsular invasion. On immunohistochemistry, the polygonal cells were positive for synaptophysin, and the sustentacular cells were positive for S100. A final diagnosis of malignant pheochromocytoma of the right adrenal mass was made.

Histopathology with immunochemistry has been shown in Figure 3. The patient was followed up monthly for a year till now and blood pressure was maintained between 50th to 90th centile for age, sex and height. Fluorodeoxyglucose-18 (FDG) positron emission tomography (PET) scan was planned to look for any evidence of metastasis and whole exome sequencing through next generation sequencing was planned to look for any genetic basis for the tumor, however, it could not be done due to monetary constraints.

Table 1: Serial BP recordings over hours spreading over days of admission.

Time from admission	Mean blood pressure (mm Hg)
0 hour	163
1 hour	155
6 hours	134
12 hours	129
18 hours	116
24 hours	109
36 hours	95
48 hours	87
60 hours	83
72 hours	78
84 hours	77
96 hours	75
108 hours	76
120 hours	77
1 st week	78
2 nd week	77
3 rd week	76
4 th week	75

Table 2: Investigations.

Investigations	Value	Reference
Hemoglobin (gm/dl)	11.3	11.2 – 14.5
Total leukocyte count (per cu.mm)	7500	4500 – 11000
Differential leukocyte count (%) (N/L/E/B/M)	58/39/5/4/4	
Platelet count (per cu.mm)	154000	150000 – 400000
Serum sodium (mEq/l)	141	135 – 145
Serum potassium (mEq/l)	4.3	3.6 – 5.2
Serum chloride (mEq/l)	103	96 - 106
Serum urea (mg/dl)	18	6 - 24
Serum creatinine (mg/dl)	0.5	0.3 – 0.7
Serum bilirubin (mg/dl) (total/conjugated)	0.3/0.1	0.2-1.3/<0.3
Alanine aminotransferase (U/l)	42	7-56
Aspartate aminotransferase (U/l)	39	10-50
Serum albumin (mg/dl)	4.1	3.4 – 5.4
Urine protein (mg/day)	85	<150
Dysmorphic red blood cells in urine	Negative	Negative
Total cholesterol (mg/dl)	155	<200
Total triglycerides (mg/dl)	112	<150

B-basophils; E-eosinophils; L-lymphocyte; M-monocyte; N-neutrophils.

Table 3: Serial blood pressures post-surgery.

Time (post-operative hours)	Blood pressure (mm Hg)	Mean blood pressure (mmHg)
0 hour	105/65	78
6 hours	80/54	63
12 hours	90/55	67
18 hours	95/57	70
24 hours	97/58	71
72 hours	100/60	73
96 hours	102/62	75
120 hours	107/65	79

DISCUSSION

Here, we present a rare case of malignant PCC, in which the imaging was suggestive of PCC but common catecholamines secreted by the tumor were negative, and the diagnosis was finally made on histopathology. The recommended initial biochemical test to diagnose PCC is plasma-free metanephrines or urinary fractionated metanephrine examination. It is highly sensitive as well as specific.¹⁰

However, there are certain cases of dopamine-secreting PCC wherein the tumor doesn't secrete epinephrine or norepinephrine but secrete dopamine. Produced at an earlier stage of catecholamine production, dopamine is a precursor of norepinephrine and requires dopamine beta-hydroxylase for its conversion. When there is a decreased expression of dopamine beta-hydroxylase, there is a decreased production of norepinephrine and overproduction of dopamine. This dopamine-secreting PCC doesn't show typical symptoms of PCC, instead shows symptoms based on plasma concentrations of dopamine. At low doses, it causes vasodilation, hypotension, and increased peripheral tissue perfusion. At high doses, it causes increased cardiac output by stimulating beta-1 adrenergic receptors. At even higher doses, it causes vasoconstriction, by stimulating alpha-1 receptors leading to hypertension.¹⁰⁻¹² Symptoms of adrenergic excess have been reported in 20% of patients and 13.3% of patients had hypertension at presentation in a study reported by Foo et al, but none of the patients had a hypertensive crisis at presentation.¹³ Due to financial constraints and the non-availability of a urinary dopamine level test at our center, we could not get the values done.

Surgical removal of the tumor is needed for PCC. For epinephrine and norepinephrine-secreting tumors, pre-operative control of blood pressure is required with alpha-blocker. However, most dopamine-secreting tumors are normotensive, and therefore, no alpha-blocker is usually needed, since there have been reports of hypotension following the use of alpha-blockers in patients with dopamine-secreting tumors. Since our patient presented in hypertensive crisis, preoperative control of blood pressure was achieved with combined alpha and beta blockers and once BP was controlled for a few days, the patient was taken up for surgery.^{8,11}

123I-meta-iodobenzylguanidine (MIBG) scintigraphy is the functional imaging modality of choice in patients with metastatic PPGLs. It has 90% sensitivity and specificity in diagnosing epinephrine and norepinephrine-secreting PCC. However, it could not diagnose the dopamine-secreting PCC, since MIBG is an analog of norepinephrine and dopamine-secreting tumors do not secrete epinephrine and norepinephrine. Thus, an 18F-FDOPA PET using a dopamine precursor could be used to diagnose them. In our case, MIBG was planned but could not be done since the patient was taken up for

surgery. PET was not performed due to non-availability in the hospital.

CONCLUSION

This study reports a case of a pediatric patient presenting in hypertensive crisis with normal metanephrines levels, to be finally diagnosed as Pheochromocytoma on immunohistochemistry. Furthermore, it highlights the need to test for urinary dopamine levels in patients with suspected Pheochromocytoma with normal metanephrines levels.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Goel N, Khatri H, Kumar S, Gupta R. Pediatric hypertensive emergency: a rare case report of metanephrines negative pheochromocytoma. *Int J Contemp Pediatr* 2025;12:690-5.