Sporadic Noradrenergic Adrenal Pheochromocytoma in an Adolescent Patient

Sasi K. Penukonda 1, Craig B. Chu 2

1. Pediatric Endocrinology, Willis-Knighton Health System, Shreveport, USA 2. Pediatrics, Willis-Knighton Health System, Shreveport, USA

Corresponding author: Sasi K. Penukonda, psasikiran@yahoo.com

Abstract

Pheochromocytoma and paraganglioma are neuroendocrine tumors that occur less commonly among children compared to adults. The excess catecholamines secreted by the tumor cells result in hypertension, tachycardia, excess sweating, and headache. Other symptoms include abdominal pain or distension caused by the adrenal mass. Here, we report a case of pheochromocytoma arising from the left adrenal medulla in a 14-year-old boy, which was exclusively secreting norepinephrine, as suggested by elevated plasma and 24-hour urinary norepinephrine and its metabolite normetanephrine. The epinephrine and its metabolite metanephrine were within normal limits. He presented with abdominal pain, recurrent vomiting, and headache and was noted to have elevated blood pressure. He underwent adrenalectomy after controlling his blood pressure with an alpha-blocker Prazosin. His blood pressure remained stable after surgery, and his plasma-free metanephrines returned to normal limits. He tested negative for hereditary paraganglioma-pheochromocytoma gene panel.

Introduction

Pheochromocytoma and paraganglioma are rare neuroendocrine tumors arising from the catecholamine-producing chromaffin cells of the adrenal medulla or paraganglia with an estimated incidence of 0.11 per million children [1]. Hypertension is the most consistent manifestation of these tumors, and it is more likely seen in children with or without paroxysmal crisis superimposed [2]. The excess catecholamines produced are mostly metabolized to metanephrines within the tumor cells by membrane-bound catecholamine O-methyltransferase [3]. Hence, the Endocrine Society guidelines recommend the measurement of plasma-free metanephrines or urinary fractionated metanephrines to diagnose pheochromocytoma and paraganglioma [4]. The catecholamine phenotype varies in pheochromocytoma and paraganglioma, with most paragangliomas presenting with lower epinephrine and metanephrine plasma concentrations compared to pheochromocytoma [5]. Here, we report a case of pheochromocytoma in a 14-year-old adolescent male patient with excess norepinephrine and normetanephrine but normal epinephrine and metanephrine levels.

Case Presentation

A 14-year-old adolescent male patient presented with incidentally discovered left adrenal mass measuring 6 × 6 × 7.4 cm on a computed tomography (CT) scan (Figure 1) while being investigated for vague left upper abdominal pain and recurrent vomiting. On further questioning, he reported frequent headaches. There was no history of palpitations or excess sweating. His blood pressure was elevated around 140/78 mmHg, and his heart rate was 103 beats per minute.
Further investigations revealed elevated plasma-free normetanephrine and 24-hour urine normetanephrine and norepinephrine. Plasma-free metanephrine and 24-hour urine metanephrine and epinephrine were within normal limits (Table 1).

![Coronal MPR CT image with contrast demonstrating heterogeneously enhancing left adrenal mass (black arrow).](image)

**FIGURE 1: Coronal MPR CT image with contrast demonstrating heterogeneously enhancing left adrenal mass (black arrow).**

MPR: multiplanar reformation; CT: computed tomography

| Plasma-free metanephrines | 24-hour urinary fractionated metanephrines | 24-hour urinary fractionated catecholamines |
|---------------------------|------------------------------------------|------------------------------------------|
| Free normetanephrine      | Free metanephrine                         | Normetanephrine                          |
| 30 nmol/L                 | <0.2 nmol/L                               | 8,887 µg/24 hour                         |
| Reference range           |                                          |                                          |
| <0.9 nmol/L               | <0.5 nmol/L                               | 91–456 µg/24 hour                        |

**TABLE 1: Laboratory findings at initial presentation.**
Iodine-123 meta-iodobenzylguanidine scan revealed intense uptake in the region of mass in the left adrenal gland. No other abnormal areas of uptake were noted throughout the chest, abdomen, pelvis, extremities, head, and neck (Figure 2).

FIGURE 2: MIBG scan images showing intense uptake of iodine-123 in the region of the left adrenal mass (yellow arrow).

MIBG: meta-iodobenzylguanidine

He was treated with an alpha-blocker prazosin for two weeks prior to adrenalectomy to control his blood pressure. He was also advised a high-salt diet and increased fluid intake to expand blood volume and prevent hypotension after removal of the tumor. The patient underwent robot-assisted left adrenalectomy, and his postoperative period was uneventful. Prazosin was discontinued as his blood pressure remained stable after surgery. Biopsy confirmed the diagnosis of pheochromocytoma. His plasma-free metanephrine levels two weeks after surgery were normal (Table 2).

| Plasma-free metanephrines | Before surgery | Two weeks after surgery | Reference range |
|---------------------------|---------------|------------------------|----------------|
| Free normetanephrine      | 30 nmol/L     | 0.59 nmol/L            | <0.9 nmol/L    |
| Free metanephrine         | <0.2 nmol/L   | <0.2 nmol/L            | <0.5 nmol/L    |

TABLE 2: Plasma-free metanephrine levels before and after surgery.

He tested negative for hereditary paraganglioma-pheochromocytoma gene panel, including Von Hippel-Lindau (VHL), succinate dehydrogenase complex subunit B (SDHB), succinate dehydrogenase complex subunit D (SDHD), and RET genes.
Discussion

Pheochromocytomas and paragangliomas are heterogeneous tumors with diverse phenotypes. Paragangliomas predominantly or exclusively secrete norepinephrine, whereas epinephrine secretion is usually confined to pheochromocytomas arising from the adrenal medulla [6]. The excess production of epinephrine limited to tumors arising from the adrenal medulla is thought to be due to the proximity of these tumors to adrenal cortical steroids, which induce the production of phenylethanolamine-N-methyltransferase (PNMT), the enzyme that converts norepinephrine to epinephrine [7]. However, it was later demonstrated that neither in vivo (direct contact between pheochromocytes and cortical cells) nor in vitro (pheochromocytes treated with dexamethasone) is sufficient to ensure PNMT transcription [5].

Approximately one-half of adrenal tumors produce nearly exclusively norepinephrine, and the other half produce a variable mixture of epinephrine and norepinephrine [8,9]. Our patient had adrenal pheochromocytoma exclusively producing norepinephrine. One study revealed that noradrenergic tumors usually present with sustained hypertension, as seen in our patient, and the tumors producing high levels of epinephrine cause paroxysmal hypertension [10]. More than 50% of patients aged less than 20 who present with pheochromocytoma/paraganglioma were found to have identifiable germline mutations, and the most common genes involved were VHL, RET, SDHD, and SDHB [11]. The catecholamine phenotype in hereditary pheochromocytomas can vary with underlying gene mutation, with those from Von Hippel-Lindau syndrome (VHL gene mutation) producing predominantly norepinephrine, and the tumors from multiple endocrine neoplasia type 2 (RET gene mutation) producing a mixture of epinephrine and norepinephrine [12]. Our patient tested negative for all common genetic mutations associated with pheochromocytoma, suggesting sporadic type.

Surgical excision is the treatment of choice. Hormonally functional pheochromocytomas need treatment with alpha-blockers such as phenoxybenzamine or prazosin to prevent perioperative cardiovascular complications. Another option is the administration of calcium channel blockers. Beta-blockers can be added to control tachycardia after administration of alpha-blockers. Other supportive care includes a high-sodium diet and increased fluid intake to reverse catecholamine-induced blood volume contraction preoperatively, and thereby prevent severe hypotension after tumor removal [4,15].

Recent advances in laparoscopic surgery have increased the feasibility of laparoscopic adrenalectomy in pheochromocytoma [14,15]. Open surgery is recommended for tumors greater than 6 cm as it allows complete removal of the tumor and minimizes systemic catecholamine release [4]. Adrenal “cortical sparing” procedures have been advocated for patients with bilateral tumors to avoid the need for long-term steroid replacement and the risk of Addisonian crisis [15]. Our patient underwent robot-assisted adrenalectomy with one of the abdominal incisions widened to remove the intact adrenal mass.

Conclusions

Pheochromocytoma and paraganglioma are relatively rare in the pediatric population. Children presenting with adrenal mass or hypertension should be investigated for pheochromocytoma/paraganglioma. Measurement of catecholamine metabolites such as normetanephrine and metanephrine in plasma and 24-hour urine helps accurately diagnose these tumors. Children diagnosed with pheochromocytoma/paraganglioma need further evaluation to rule out germline mutations associated with these tumors.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Spoudeas H, Harrison B: Paediatric endocrine tumours. A multidisciplinary consensus statement of best practice from a working group convened under the auspices of the BSPED and UKCCSG. Novo Nordisk Ltd., Sussex, UK; 2005.
2. Barontini M, Levin G, Sanso G: Characteristics of pheochromocytoma in a 4- to 20-year-old population. Ann N Y Acad Sci. 2006, 1073:30-7. 10.1196/annals.1355.003
3. Eisenhofer G, Keiser H, Friberg P, et al.: Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. J Clin Endocrinol Metab. 1998, 83:2175-85. 10.1210/jcem.83.6.4870
4. Lenders JW, Duh QY, Eisenhofer G, et al.: Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014, 99:1915-42. 10.1210/jc.2014-1498
5. Grouzmann E, Tschohp O, Triponez F, et al.: Catecholamine metabolism in paraganglioma and
pheochromocytoma: similar tumors in different sites?. PLoS One. 2015, 10:e0125426. 10.1371/journal.pone.0125426

6. van der Harst E, de Herder WW, de Krijger RR, et al.: The value of plasma markers for the clinical behaviour of pheochromocytomas. Eur J Endocrinol. 2002, 147:85-94. 10.1530/eje.0.147085

7. Funahashi H, Imai T, Tanaka Y, et al.: Discrepancy between PNMT presence and relative lack of adrenaline production in extra-adrenal pheochromocytoma. J Surg Oncol. 1994, 57:196-200. 10.1002/jso.2930570312

8. Kimura N, Miura Y, Nagatsu I, Nagura H: Catecholamine synthesizing enzymes in 70 cases of functioning and non-functioning pheochromocytoma and extra-adrenal paraganglioma. Virchows Arch A Pathol Anat Histopathol. 1992, 421:25-32. 10.1007/BF01607135

9. Eisenhofer G, Lenders JW, Goldstein DS, et al.: Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. Clin Chem. 2005, 51:735-44. 10.1373/clinchem.2004.045484

10. Ito Y, Fujimoto Y, Ohara T: The role of epinephrine, norepinephrine, and dopamine in blood pressure disturbances in patients with pheochromocytoma. World J Surg. 1992, 16:759-63; discussion 763-4. 10.1007/BF02067379

11. Neumann HP, Bausch B, McWhinney SR, et al.: Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002, 346:1459-66. 10.1056/NEJMoa020152

12. Eisenhofer G, Walther MM, Huyhn TT, et al.: Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. J Clin Endocrinol Metab. 2001, 86:1999-2008. 10.1210/jcem.86.5.7496

13. Naranjo J, Dodd S, Martin YN: Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth. 2017, 31:1427-39. 10.1053/j.jvca.2017.02.023

14. Gagner M, Lacroix A, Bolté E: Laparoscopic adrenalectomy in Cushing’s syndrome and pheochromocytoma. N Engl J Med. 1992, 327:1033. 10.1056/NEJM199210013271417

15. Ludwig AD, Feig DI, Brandt MI, Hicks MJ, Fitch ME, Cass DL: Recent advances in the diagnosis and treatment of pheochromocytoma in children. Am J Surg. 2007, 194:792-6; discussion 796-7. 10.1016/j.amjsurg.2007.08.028