CASE REPORT
Urooncology

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Renal Paraganglioma: A Rare Case of Secondary Hypertension in a Young Patient

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Abstract

Paragangliomas are catecholamine-secreting neuroendocrine tumors that form outside of the adrenal gland. A 19-year-old woman with a history of hypertension was found to have an incidental mass on the inferior right kidney on imaging after presenting to the emergency department with acute abdominal pain. The mass was removed via right robotic-assisted laparoscopic partial nephrectomy; histopathological findings supported the diagnosis of paraganglioma. The hypertension resolved following removal and genetic syndrome tests were negative. This case emphasizes the importance of a broad differential diagnosis in young patients presenting with hypertension, reviews genetic and histological associations with paragangliomas, and discusses treatment of these catecholamine-secreting tumors.

Keywords: Hypertension, paraganglioma, pathology, urooncology

Introduction

Sympathetic paraganglioma are extra-adrenal neuroendocrine tumors that produce catecholamines and can lead to a myriad of symptoms including hypertension, tachycardia, and sweating (1). Paragangliomas and their intra-adrenal counterpart, pheochromocytomas, are exceptionally rare and have a reported incidence of approximately 2-8 cases per million, with roughly 20% of these cases occurring among the pediatric cohort (2). Paragangliomas/pheochromocytomas can be a sign of genetic syndromes, as up to 40% of individuals presenting with these tumors have germline mutations that leave them susceptible to syndromes such as Von-Hippel Lindau syndrome (*VHL* gene), multiple endocrine neoplasia type 2 (MEN2) (*RET* gene), and SDHx-associated Hereditary Paraganglioma-Pheochromocytoma Syndrome (*SDHB* gene) (3,4). We present a rare case of a 19-year-old female with hypertension and renal paraganglioma.

Case Presentation

A 19-year-old woman with a medical history of hypertension, hypomagnesemia, hypokalemia, and lower extremity edema presented with chronic abdominal pain and an incidental right renal mass. An informed consent patient consent was obtained. Following a cholecystectomy in May 2023, an abdominal ultrasound ordered for acute abdominal pain revealed a faint oval isoechoic right lower pole renal mass measuring 2.8x2.7 - 3 cm with minimal internal color flow. The patient was admitted to the emergency department in July 2023 after developing abdominal pain and vomiting. The patient was found to have elevated troponin I levels and nonspecific ST and T wave abnormalities on electrocardiography; the patient was discharged the following day after acute myocardial infarction was ruled out. The patient was subsequently referred to the cardiology department and was found to have mild concentric left ventricular hypertrophy and mild mitral valve regurgitation on echocardiogram. Due to concerns of her hypertension, the patient was to continue following up with cardiology in the outpatient setting.

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The patient was ultimately referred to urology for management of her right renal mass, and a computed tomography (CT) scan performed at that time demonstrated an oval-shaped, ill-defined, hypodense mass measuring 3x2.7 cm in the lower pole of the right kidney (Figure 1A, Figure 1B). The patient underwent an uncomplicated right robotic-assisted laparoscopic partial nephrectomy, which revealed a pT1NxMx renal paraganglioma. Immunohistochemical stains of the specimen included tumor cells positive for GATA3, synaptophysin, and CD56 and negative for AE1/3, PAX8, chromogranin, and isthmin-1 (ISM-1) (Figure 2C, Figure 2D, Figure 2E). S100 staining indicated sustentacular cells and a Ki-67 index of 10% in hotspot areas, findings consistent with paraganglioma (Figure 2F). Her severe hypertension normalized postoperatively.

Given the concern for hereditary paraganglioma-pheochromocytoma syndrome, the patient was referred for genetic counseling and testing. The patient tested negative for disease-causing mutations in genes associated with paraganglioma development, including *EGLN1*, *FH*, KIF1B, *MAX*, MEN1, *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *VHL*.

Discussion

Sympathetic paraganglioma are norepinephrine-secreting neuroendocrine tumors that can be found along the sympathetic chain from the skull base to the pelvic region (5). The incidence of paraganglioma is exceedingly rare, occurring in approximately 2-8 per million individuals; genitourinary paraganglioma are reported to make up roughly 7% of these cases in the United States (2,6). A previous systematic literature review revealed only 13 reported cases of intrarenal paraganglioma, with a mean patient age at presentation of 42.6 years (7). The mean age for diagnosis of paraganglioma and pheochromocytoma is approximately 40 years, which can often make this diagnosis difficult in younger adults, as seen in our case (8). The initial disease presentation of sympathetic paraganglioma often includes hypertension with associated symptoms such as palpitations, sweating, and headache (9). The hypertension is often refractory to medical management and may require multidrug regimens to obtain adequate blood pressure control. Misattribution of classic pheochromocytoma symptoms to anxiety can further exacerbate diagnostic delays (10). This emphasizes the importance of documenting an extensive patient history and maintaining a broad differential diagnosis for causes of both primary and secondary hypertension. Secondary hypertension comprises approximately 5-10% of hypertension cases in adults, with renal parenchymal disease being the most common cause (11,12). In addition to paraganglioma, the differential diagnosis of secondary hypertension in a young adult should include renal artery stenosis caused by fibromuscular dysplasia, primary hyperaldosteronism, and oral contraceptive use (11,13).

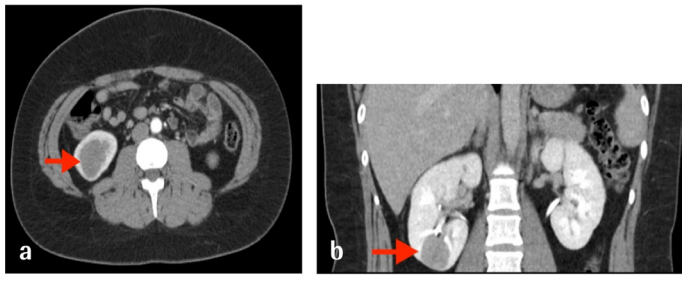

Figure 1. Computed tomography visualization of paraganglioma. Coronal view measuring 2.7 cm (a). Axial view measuring 3.0 cm (b)

Following an extensive review of patient history, the diagnosis of paraganglioma includes biochemical testing, imaging, and genetic testing. Initial biochemical testing of suspected paraganglioma often involves the measurement of urinary and plasma catecholamines, urinary fractionated metanephrines, plasma free metanephrines, and urinary vanillylmandelic acid (14). CT imaging of a paraganglioma typically reveals a mass with an unenhanced density greater than 10 Hounsfield units with a dense capillary network, delayed washout, and possible

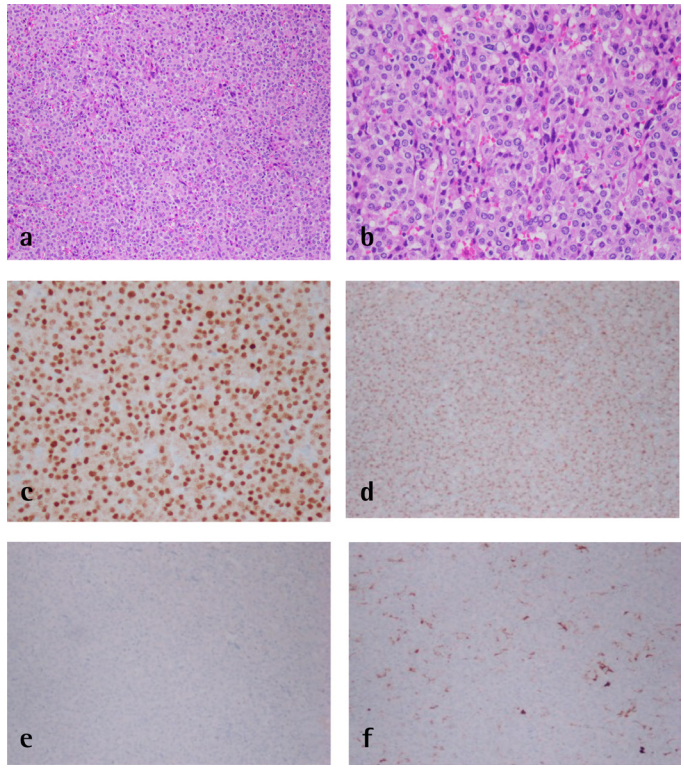

Figure 2. H&E and immunohistological staining of paraganglioma. H&E 100x (a) and H&E 200x (b) illuminate sheets of tumor cells arranged in vague nests or zellballen pattern with fibrovascular stroma. The cells have abundant finely granular cytoplasm and salt and pepper chromatin. IHC stain shop tumor cells positive for GATA3 (c) and a neuroendocrine marker, synaptophysin (d), while negative for pancytokeratin AE1/3 (e). Sustentacular cells are highlighted by S100 (f)

IHC: Immunohistochemistry, H&E: Hematoxylin and eosin

cystic changes; however, there is no method to differentiate between paraganglioma and renal cell carcinoma on imaging (15,16). 40% of paragangliomas and pheochromocytomas are associated with genetic syndromes, including von Hippel Lindau disease, MEN2, and neurofibromatosis type 1, which should prompt screening for germline mutations in *VHL*, *RET*, and *NF1* genes, respectively. Germline mutations in succinate dehydrogenase subunits (SDHX), Myc-associated *MAX*, hypoxia-inducible factor 2 alpha, and malate dehydrogenase 2 have also been associated with tumor development (17).

Primary management of non-metastatic paraganglioma involves surgical removal of the tumor, with radiotherapy/radiosurgery reserved for patients with surgical contraindications (18). Preoperative alpha-blockade is necessary to prevent perioperative hypertensive episodes caused by systemic tumor catecholamine release. However, as seen in our case, successful paraganglioma resection can be achieved without pre-operative alpha-blockade when the presence of paraganglioma is not suspected or diagnosed pre-operatively (19). Regardless of tumor location and preoperative alpha-blockade, careful intraoperative blood pressure monitoring and management are imperative to reduce the morbidity of surgical resection. This includes administration of an alpha blocker preoperatively and a reduction or cessation of other antihypertensive therapies (20). Medications such as dopamine D2 receptor antagonists, B-adrenergic receptor blockers, and tricyclic antidepressants are contraindicated prior to the administration of alpha blockade in order to prevent hypertensive crises due to unopposed a-adrenoreceptor stimulation during surgery (21).

The "gold standard" of paraganglioma diagnosis is lesional biopsy (5). These tumors can be diagnosed histologically by the presence of cells in well-circumscribed nests, known as the Zelballen pattern, surrounded by a stromal component along with cells in the periphery of the Zellballen, known as "sustentacular" cells (Figure 2A, Figure 2B) (22,23). Considering the neuroendocrine origin of these tumors, paragangliomas often stain positively for markers such as neuron specific enolase, S-100 protein, synaptophysin, and CD56 (22). As seen in our case, paragangliomas can also stain positively for GATA3, an essential zinc-finger transcription factor in neuronal embryogenesis (24).

In conclusion, we present a rare case of a 19-year-old female with hypertension and renal paraganglioma. The general rarity and abnormal location of this neuroendocrine tumor emphasizes the importance of creating a broad differential diagnosis for secondary causes of hypertension in young adults. A heightened index of suspicion for paraganglioma should be maintained in young patients presenting with renal mass and moderate to severe or uncontrolled hypertension.

Ethics

Informed Consent: Written consent has been given for patient data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., N.M., M.Z., A.G.A., J.T., Concept: M.J.F., A.S., N.M., M.Z., J.T., Design: M.J.F., A.S., N.M., M.Z., J.T., Data Collection or Processing: M.J.F., A.G.A., J.T., Analysis or Interpretation: M.J.F., A.G.A., J.T., Literature Search: M.J.F., Writing: M.J.F., A.S., M.Z., A.G.A., J.T.

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