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Urinary Bladder Paraganglioma presenting as Micturition-Induced Palpitations, Dyspnea, and Angina

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 45
Final Diagnosis: Urinary bladder paraganglioma
Symptoms: Angina pectoris • dyspnea • palpitations
Medication: Phenoxybenzamine • Propanolol
Clinical Procedure: Open partial cystectomy
Specialty: Endocrinology and Metabolic

Objective: Rare disease

Background: Sympathetic urinary bladder paragangliomas are rare catecholamine-secreting neuroendocrine tumors arising from neural crest cells. They are uncommon urinary bladder neoplasms. Symptoms classically include micturition-related or unrelated palpitations and syncope with hypertension, headaches, diaphoresis, and hematuria. Other than being attributable to vasovagal reactions, micturition-induced cardiovascular symptoms should prompt a search for catecholamine-secreting tumors such as a urinary bladder paraganglioma, as in this case.

Case Report: A 45-year-old asthmatic African-American female presented with episodic hematuria that began 4 years ago and episodes of micturition-induced palpitations, dyspnea, substernal tightness, sweating, and throbbing headaches. Computed tomography with contrast revealed an enhancing mass along the anterior urinary bladder wall, measuring 2.4×3.5 cm. On Positron emission Tomography with [18F] fluorodeoxyglucose integrated with computed tomography (18F-FDG PET/CT), the urinary bladder mass was 18F-FDG avid. Serum normetanephrine and supine plasma norepinephrine were significantly elevated and there was mild elevation of supine plasma epinephrine.

Transurethral resection of the bladder mass revealed a neoplasm with microscopic features and immunohistochemical profile positive for synaptophysin and chromogranin, with negative screening cytokeratin AE1/AE3, suggesting a paraganglioma. Following resection of the paraganglioma, there was complete resolution of micturition-induced cardiovascular symptoms on long-term follow-up.

Conclusions: Micturition-related cardiovascular symptoms are commonly attributed to vasovagal reactions. However, urinary bladder pathologies must be ruled out as a cause, as in this rare case of a urinary bladder paraganglioma exhibiting catecholaminergic symptoms.

MeSH Keywords: Palpitations • Paraganglioma, Extra-Adrenal • Urinary Bladder Neoplasms

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/891388

Background

Micturition-induced cardiovascular symptoms should prompt a search for vasovagal reactions or catecholamine secreting tumors. Urinary bladder paragangliomas are rare neuroendocrine tumors and represent an uncommon variety of urinary bladder neoplasms. These tumors secrete catecholamines either spontaneously or in response to urinary bladder contractions upon micturition, thereby producing micturition-related symptoms.

We present the case of a woman with urinary bladder paraganglioma, which is a rare urinary bladder neoplasm, presenting with micturition induced palpitations, dyspnea, and angina.

Case Report

A 45-year-old African-American female presented with episodic hematuria that began 4 years ago and intermittent episodes of micturition-induced palpitations, dyspnea, substernal tightness, sweating, and throbbing headaches. The palpitations were of gradual onset and offset, fast, regular, and lasting a few minutes. There was a history of dyspnea, palpitations, and substernal tightness on climbing 5 steps and a normal stress test myocardial perfusion imaging. Her medical history was significant for mild-intermittent asthma, which was well controlled with an as-needed albuterol inhaler. Her mother had hypertension. She was a non-smoker and was a social alcohol drinker.

Examination revealed a loud first heart sound, a grade 2/6 midsystolic murmur in the second right intercostal space. The pulse and blood pressure were within normal limits, with an episodic highest recorded pulse of 118 beats per minute and blood pressure of 145/82 mm Hg.

Telemetry showed runs of sinus tachycardia during micturition. Hemoglobin was 8.9 gm/dl with microcytosis and hypochromia. Basic metabolic panel, routine urine, and chest radiograph results were normal. Electrocardiography revealed sinus rhythm, left ventricular hypertrophy, and fixed 1-mm sagging ST-segment depressions in anterior and lateral leads. Echocardiography revealed a hyperdynamic left ventricle with an ejection fraction of 80%.

Initially computed tomography with contrast revealed an enhancing mass along the anterior urinary bladder wall, measuring 2.4×3.5 cm, which was 18F-FDG avid on PET scan. Serum metanephrine was <25 pg/ml (normal <57 pg/ml) with an elevated serum normetanephrine of 248 pg/ml (normal <149 pg/ml). The 24-hour urinary metanephrine was 69 mcg/g creatinine (normal 33–192 mcg/g creatinine) with elevated 24-hour urinary normetanephrine of 515 mcg/g creatinine (normal 107–436 mcg/g creatinine). Supine plasma epinephrine of 53 pg/ml (normal <50 pg/ml) was mildly elevated, supine plasma norepinephrine of 1893 pg/ml (normal 112–658 pg/ml) was significantly elevated. The 24-hour vanillylmandelic acid of 3.3 mg/g creatinine (normal 1.1–4.1 mg/g creatinine) was normal (Table 1).

Table 1. Laboratory values.

	Patient's values	Reference range
Serum metanephrines	<25 pg/ml	<57 pg/ml
Serum normetanephrine	248 pg/ml	<149 pg/ml
24-h urine Metanephrines	69 mcg/gm creatinine	33–192 mcg/gm creatinine
Supine plasma epinephrine	53 pg/ml	<50 pg/ml
Supine plasma norepinephrine	1893 pg/ml	112–658 pg/ml
24-h urinary VMA	3.3 mg/gm cr.	1.1–4.1 mg/gm cr.

Immunohistochemical analysis of the urinary bladder tumor obtained by diagnostic transurethral resection revealed positive staining for synaptophysin and chromogranin, equivocal S-100 staining, and negative cytokeratin AE1/AE3 staining, suggestive of paraganglioma (Figures 1–4). She was started on alpha-receptor antagonist phenoxybenzamine with intravenous fluids for volume resuscitation prior to undergoing surgical removal of the mass. Propranolol was later added because she had persistent micturition-related palpitations while on phenoxybenzamine prior to her surgery. Pathological analysis of the bladder tumor resected by open partial cystectomy confirmed a paraganglioma. Following resection of the paraganglioma, there was complete resolution of micturition-induced cardiovascular symptoms on long-term follow-up.

Discussion

Sympathetic urinary bladder paragangliomas are rare catecholamine-secreting neuroendocrine tumors arising from neural crest cells. They represent an uncommon variety of the urinary bladder neoplasms. However, when present, the most common site of the paraganglioma is the trigone of the urinary bladder [1].

In contrast to predominant epinephrine secretion by adrenal pheochromocytoma, urinary sympathetic paragangliomas secrete mainly norepinephrine, spontaneously or in response to urinary bladder contraction [2–5]. Elevated serum and/or urine norepinephrine and normetanephrine are characteristic. The basic molecular biology of this phenomenon is explained by the presence of phenylethanolamine N-methyltransferase (PNMT) in the adrenal cells, an enzyme which converts norepinephrine

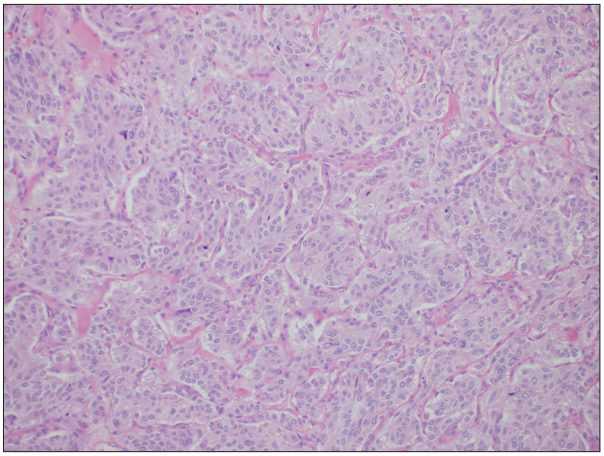

Figure 1. High power view (H & E stain) of the bladder paraganglioma.

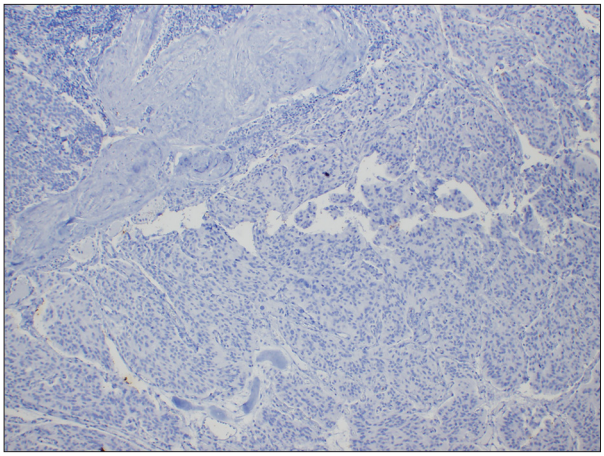

Figure 3. Negative AE1/AE3 staining.

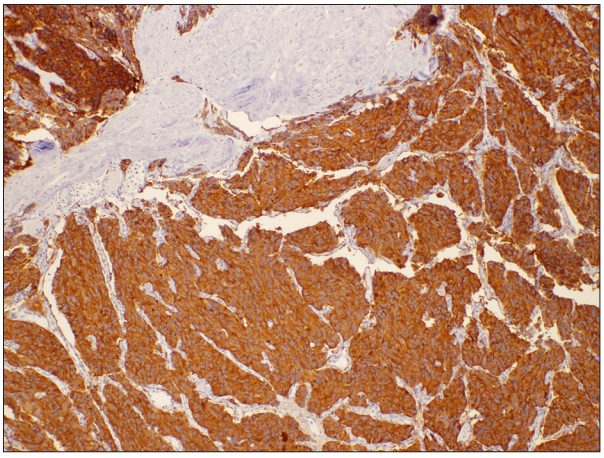

Figure 2. Positive staining for Synaptophysin (in brown) with negative staining in light blue in the left upper portion of the picture.

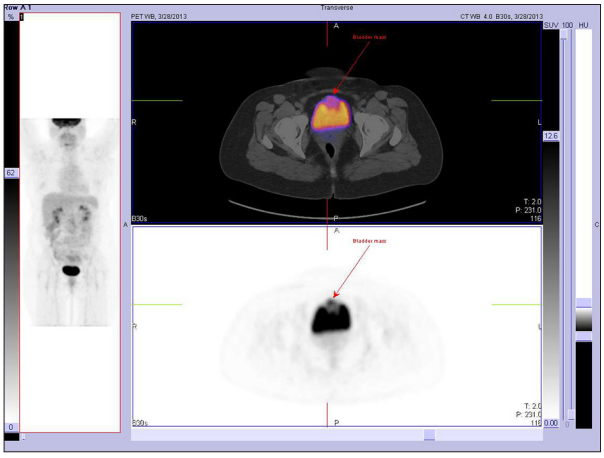

Figure 4. ^{18F}fluorodeoxyglucose uptake by the urinary bladder paraganglioma in the PET scan image.

to epinephrine [6]. Sympathetic neurons and extra-adrenal paraganglia, although closely related to the adrenal medulla developmentally, show little or no PNMT expression.

Symptoms of urinary bladder paraganglioma include micturition related or unrelated palpitations, hypertension, headaches, diaphoresis, syncope, and hematuria [7]. Immediate symptomatic treatment can be performed by addition of alpha-blockers like phenoxybenzamine. Beta-blockers can also be used and should be added only after addition of alpha-blocking agents, as was done in our patient [8]. Our patient was not on alpha-blockers at the time of the initial diagnostic biopsy because at that time, bladder carcinoma was considered more likely to be the working diagnosis given the patient had a history of chronic hematuria with a bladder mass on imaging studies. However, after a pathological diagnosis of paraganglioma was established, she was started on the alpha-blocker phenoxybenzamine and subsequently propranolol perioperatively. Resection generally ensures radical and effective treatment of urinary bladder paraganglioma in the long term.

The patient was followed up in the out-patient clinics and, based on the Endocrine Society guidelines [9], she was involved in shared decision-making for genetic testing for paraganglioma, which consists of testing for succinate dehydrogenase (SDH) gene mutation. However, the patient deferred genetic testing. She was subsequently lost to follow up.

Conclusions

Micturition-related cardiovascular symptoms are commonly attributed to vasovagal reactions. However, urinary bladder pathologies must be ruled out as a cause, as in this case of a urinary bladder paraganglioma.

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