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CASE REPORT
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# A Giant Urinary Bladder Paraganglioma

**ABSTRACT**

Paragangliomas are catecholamine-secreting neuroendocrine tumors originating from extra-adrenal neural crest cells. Urinary bladder paragangliomas are extremely rare and usually present with micturition-related hypertension, palpitations, headaches, dizziness, and sweating. We report a middle-aged female with a giant urinary bladder paraganglioma that was symptomatic for 6 years but unfortunately remained undiagnosed for more than half a decade. The patient exhibited the typical noradrenergic biochemical phenotype that characterizes paragangliomas. The patient was successfully managed with subtotal cystectomy and augmentation cystoplasty. Ours is the patient with largest reported case of urinary bladder paraganglioma and the only one managed with augmentation cystoplasty.

**Keywords:** Metanephrines, paraganglioma, urinary bladder

## Introduction

Paragangliomas (PGLs) are neuroendocrine tumors originating from extra-adrenal neural crest cells that secrete catecholamines. Urinary bladder PGLs account for 6% of all PGLs and are usually functional and symptomatic.[1] However, urinary bladder PGLs may remain undiagnosed for many years. We are reporting a urinary bladder PGL that was symptomatic for 6 years.

## Case Presentation

A 52-years-old female presented with a history of palpitations, headache, dizziness, and facial pallor for 6 years. These symptoms were episodic and associated with the act of micturition. Initially, the episodes used to occur every 2-3 weeks, but for the past 1 year, the episodes used to occur 3-5 times per week. The patient denied any history of diaphoresis, weight loss, or hematuria. Family history was unremarkable. For the previous 6 years, she had consulted at least 6 general practitioners and was given non-specific treatment. Routine urine examination done on multiple occasions was normal. A routine ultrasonography (USG) of the abdomen done for vague abdominal pain 4 weeks before referral to our center revealed a 6.7 × 7.2 × 7.1 cm mass lesion with vascularity in relation to the right lateral wall of the urinary bladder. For further evaluation and management, she was admitted to the endocrinology unit of our center. Initial clinical assessment at our center revealed a well-built, anxious female with a heart rate of 102 beats/min and blood pressure (BP) of 140/90 mm Hg without a significant postural drop. Systemic examination was unremarkable. On the basis of symptomatology, hypertension and USG documented bladder mass, and the possibility of urinary bladder PGL was strongly considered. Laboratory evaluation revealed normal complete blood counts and serum electrolytes, creatinine, calcium, blood glucose, and liver functions. The 24-hour urinary excretion of metanephrines was normal at 66.24 µg (normal <400 µg) while that of normetanephrines was strikingly elevated at > 10 000 µg (normal <900 µg). Twenty-four-hour urinary vanillylmandelic acid excretion was also markedly elevated at 62.44 mg (normal range 4-11 mg). Magnetic resonance imaging (MRI) revealed a well-circumscribed huge lobulated well-enhancing mass measuring 7.3 × 9.3 × 6.9 cm in relation to the right anterolateral aspect of the urinary bladder (Figure 1). On the basis of clinical profile, biochemical evaluation, and MRI characteristics a diagnosis of urinary bladder PGL was made. Before surgery, adequate alpha and beta (β)-adrenergic blockade was achieved with prazosin and metoprolol. During hospitalization, the patient developed 1 episode of atrial flutter with variable conduction which reverted to sinus rhythm spontaneously.

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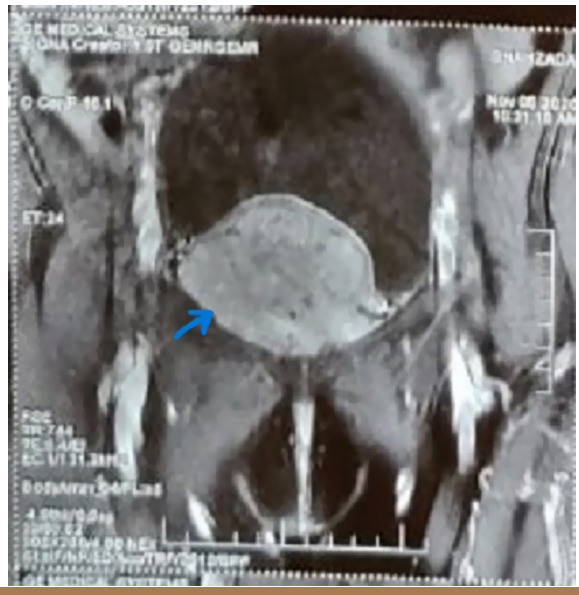

Figure 1. T2 magnetic resonance imaging shows well-circumscribed, lobulated homogenously enhancing urinary bladder mass.

The patient was successfully subjected to subtotal cystectomy with augmentation cystoplasty of the urinary bladder by placing a patch of ileum over the urinary bladder. Intraoperative findings revealed a huge, highly vascular mass occupying the right anterolateral wall of the urinary bladder (Figure 2). Postoperatively, the patient developed hypotension that responded to intravenous fluids and noradrenaline. On histopathology, tumor cells were round to oval with vesicular chromatin and eosinophilic granular cytoplasm. The cells were arranged in nests "Zellballen" pattern (Figure 3). On follow-up after 12 months, she had no episodes of palpitations/diaphor esis and her BP and urinary metanephrines/normetanephrines are normal.

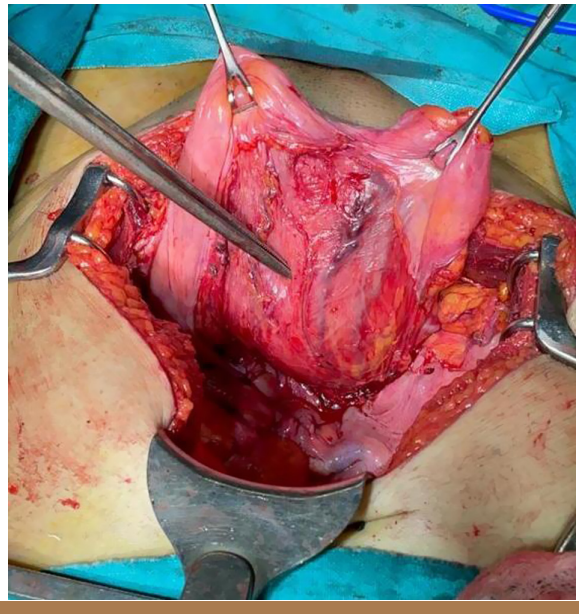

Figure 2. Intraoperative image shows a large and highly vascular mass occupying the right anterolateral wall of the urinary bladder.

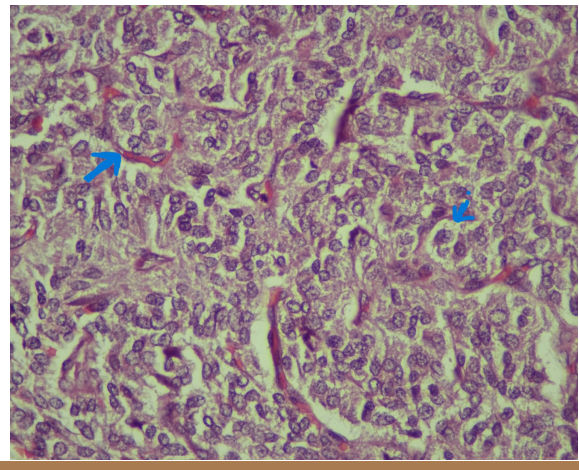

Figure 3. Photomicrograph shows round to oval tumor cells growing in a zellballen pattern with vesicular chromatin and eosinophilic granular cytoplasm (hematoxylin and eosin, 400×).

## Discussion

Paraganglioma of the urinary bladder originates from chromaffin tissue of the sympathetic nervous system associated with the urinary bladder wall and is usually present in the second to fourth decade of life with female predominance.[2] Majority of urinary bladder PGLs are usually functional and symptomatic.[3] The predominant symptoms include micturition-related hypertension, palpitations, headaches, dizziness, sweating, and syncope.[4] These symptoms may also be precipitated by defecation, sexual activity, ejaculation, or bladder instrumentation. Painless hematuria is a common presentation of bladder PGL reported in 55%-60% of patients.[5]

The diagnosis of PGL must be confirmed biochemically by the presence of increased concentrations of fractionated metanephrines (metanephrine and normetanephrine) and catecholamines (epinephrine and norepinephrine) in urine or plasma.[6] The patient had strikingly elevated urinary normetanephrines while metanephrines were normal which is typical of PGL. The basis for this distinctly noradrenergic biochemical phenotype is a negligible expression of phenylethanolamine *N*-methyltransferase in extra-adrenal neural crest cell tumors.

Computed tomography (CT) is frequently used for localizing PGL.[7] However on CT, bladder PGL often shows soft-tissue density and homogeneous enhancement which is non-specific. Magnetic resonance imaging is being increasingly used and homogeneous T1 hyperintensity is reported to be the key MR imaging characteristic for bladder PGL.[8] Additional localization studies are indicated with 68Ga-DOTATATE positron emission tomography/CT or scintigraphy with iodine-123 meta-iodobenzylguanidine ($^{125}$I-MIBG), if CT or MRI is inconclusive. In our patient, the size of PGL on MRI was 7.3 × 9.3 × 6.9 cm; to the best of our knowledge, this is the largest reported case of urinary bladder PGL.

Complete surgical removal of the tumor is the treatment of choice.[2] In the previously published cases, urinary bladder PGL was either removed by partial cystectomy or by transurethral resection.[9-11] In our patient as the tumor was huge, the whole of the anterolateral wall was excised and augmentation cystoplasty was undertaken to avoid small capacity urinary bladder and thus prevent

upper tract deterioration and protection of renal function. Our case is the only reported case of urinary bladder PGL managed with augmentation cystoplasty.

The classical histopathological features of PGLs include the "zellballen" pattern, that is, alveolar-patterned cell nests against well-vascularized stroma.[11] The tumor cells express neuroendocrine markers such as chromogranin A, synaptophysin, ISLET1, and INSM1 and are most often keratin-negative and GATA3-positive.[12] Pheochromo cytomas/PGLs are considered the most heritable of all tumors and more than 20 susceptibility genes with germline mutations have been reported till date.[13] In our patient, the location of PGL in the urinary bladder makes succinate dehydrogenase complex iron sulfur subunit B (SDHB) mutation a strong possibility, although due to lack of facilities we have not tested for it.

## Conclusion

Though the urinary bladder is an uncommon site for catecholam ine-secreting tumors, it should be part of differential diagnosis in an appropriate clinical setting in biochemically proven PGL, failure to localize tumor in the head, neck, and abdomen, or in any individual who presents with episodic symptoms related to catecholamine excess in temporal relation to micturition. This will minimize the delay in diagnosis and management of this potentially life-threatening but treatable disease.

**Informed Consent:** Written informed consent was obtained from the patient who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Declaration of Interests:** The authors declare that they have no competing interest.

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