

# Paraganglioma of the urinary bladder

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## ABSTRACT

Since paragangliomas of the urinary bladder are rare and not easily recognised, histological examination is often the only leading key to diagnosis. We report on a patient with a paraganglioma of the urinary bladder. Although the patient presented with classical signs and symptoms, these were only appreciated after histological examination of a transurethral resection specimen had elucidated the correct diagnosis.

## KEYWORDS

Micturition-induced palpitations, paraganglioma, urinary bladder

## INTRODUCTION

Pheochromocytomas are catecholamine-producing tumours usually localised in the adrenal medulla. However, 9 to 23% may arise extra-adrenally and are referred to as paragangliomas.<sup>1</sup> Since paragangliomas of the urinary bladder are rare and not easily recognised, histological examination is often the only key leading to diagnosis. We report on a patient with a paraganglioma of the urinary bladder. Although the patient presented with classical signs and symptoms these were only appreciated after histological examination of a transurethral resection specimen had elucidated the correct diagnosis. In presenting this case and a supplementary review of previously published cases and literature, we bring attention to the specific signs and symptoms and management of paraganglioma of the urinary bladder.

## CASE REPORT

A 47-year-old man presented to the urologist with headache, palpitations, sweating and pallor immediately following

micturition. Ultrasonography revealed an abnormal mass in the urinary bladder wall. This was confirmed by cystoscopy demonstrating a smooth tumour in the wall of the bladder with normal mucosa (*figure 1*). Additional computed tomography of the abdomen showed a solitary tumour limited to the bladder wall (*figure 2*). Subsequently, transurethral resection was performed to obtain tissue material for histological examination. During this procedure, a transient elevation of blood pressure with a concomitant decrease in heart rate occurred (*figure 3*). Histological examination revealed positive immunostaining for anti-S100, anti-CD 56, antichromogranin and antisynaptophysin, compatible with a paraganglioma. After referral to the department of internal medicine, additional testing showed that the plasma concentration of norepinephrine was already substantially elevated before micturition with a threefold increase directly following micturition (*table 1*). Urinary excretion of

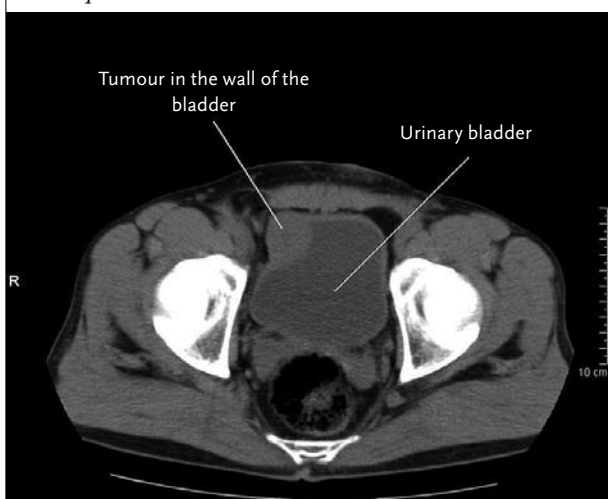
**Figure 1.** Cystoscopy showing a smooth tumour located in the urinary bladder wall with normal mucosa



Figure 1

The impression in the middle of the tumour is due to the transurethral resection performed during a previous cystoscopy.

**Figure 2.** Computer tomography scan of the abdomen showing a tumour with a diameter of 35 mm in the urinary bladder wall



metanephrine in 24-hour urine samples remained within the normal range. However, urinary concentrations of normetanephrine were elevated up to 8.70  $\mu\text{mol}/24\text{ h}$  (reference value:  $<5.1\ \mu\text{mol}/24\text{ h}$ ). Metaiodobenzylguanidine scintigraphy (iodine-131-MIBG) showed no uptake. Following treatment with  $\alpha$ - and  $\beta$ -adrenergic blocking agents, a partial cystectomy was performed without complications. In the postoperative phase, the plasma norepinephrine level returned to normal and the patient's symptoms disappeared. Because of the extra-adrenal localisation of the pheochromocytoma occurring at an age of 47 years, genetic testing was performed to identify the risk of inheritance. We searched for germ-line mutations of genes encoding for succinate dehydrogenase (SDH) subunits B and D. However, no such mutations were found. Up until now, there are no signs of recurrence.

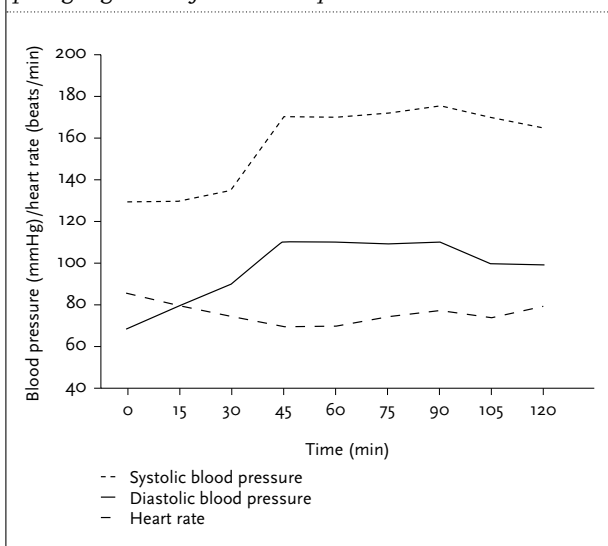
### DISCUSSION

In 1953 Zimmerman *et al.* reported the first case of bladder paraganglioma.<sup>2</sup> Paragangliomas of the urinary bladder are rare and represent 6% of all paragangliomas and constitute less than 1% of all bladder tumours.<sup>3,4</sup> They occur more frequently in women than in men, primarily during the second and third decades.<sup>3,5</sup> The embryonal origin of these tumours is uncertain. Small nests of paraganglionic tissue may persist along the aortic axis and in the pelvic regions and migrate into the urinary bladder wall during development.<sup>5</sup> Most paragangliomas of the urinary bladder are solitary and localised submucosally on the dome or the trigone of the bladder.<sup>4,5</sup> Histopathological examination shows a typical Zellballen pattern of growth and positive staining with S-100, chromogranin, NSE and synaptophysin. Between 5 to 15% of the paragangliomas of the urinary bladder are said to be malignant; however, no reliable histological criteria exist to distinguish malignant from benign neoplasms. Malignancy is suspected in case of local invasion or distant metastases.<sup>4,5</sup>

Contraction of the bladder musculature and changes in bladder pressure during micturition lead to systemic release of catecholamines and eventually to intermittent hypertension during or directly after micturition;<sup>3</sup> 55 to 60% of patients have haematuria. Furthermore, headache, palpitations, diaphoresis, dysuria, anxiety and recurrent cystitis may occur.<sup>3,5</sup> Hypertensive crises may be triggered by micturition, defecation, sexual activity, ejaculation or bladder instrumentation.<sup>3</sup>

The diagnosis of pheochromocytomas in general is established by measurement of catecholamines and catecholamine metabolites (metanephrine and normetanephrine) in plasma and 24-hour urine samples. The majority (83%) of paragangliomas of the urinary bladder are hormonally active. However, preoperative

**Figure 3.** Haemodynamic parameters during transurethral resection in a patient with a paraganglioma of the urinary bladder



**Table 1.** Norepinephrine, epinephrine and dopamine plasma concentrations in a patient with a paraganglioma of the urinary bladder

	Supine position		
	Before micturition (preoperative)	Post-micturition (preoperative)	Post-micturition (postoperative)
Norepinephrine (100-600 pg/ml)*	2130	6116	173
Epinephrine (20-100 pg/ml)*	16	7	22
Dopamine (0-60 pg/ml)*	10	86	6

\* Normal, reference values are given in parenthesis.

diagnosis of paraganglioma of the urinary bladder may be difficult since levels of catecholamines and their metabolites in plasma and urine can be normal.<sup>5</sup> A rise in plasma catecholamines is to be expected directly following micturition and attempts should be made to obtain plasma samples at that moment.<sup>3</sup> After biochemical confirmation, additional radiological imaging should be performed to locate the tumour. The most useful imaging techniques to localise primary and metastatic paragangliomas of the urinary bladder are cystoscopy and computed tomography or magnetic resonance imaging. Although all functional imaging methods are hampered by the excretion of radioisotopes in the urine, thus lowering their ability to localise a paraganglioma close to the kidneys or urinary bladder, iodine-131-MIBG scanning is essential to search for multifocal tumours or metastases. If the MIBG scan is negative, positron emission tomography (PET) imaging should be performed with specific ligands, preferably 6-[18F]-fluorodopamine ([18F]-DA) or [18F]-dihydroxyphenylalanine ([18F]-DOPA) whenever available.<sup>1</sup> About 80% of the paragangliomas can be seen on cystoscopy, revealing a submucous tumour with intact or superficially ulcerated overlying mucosa.<sup>4,5</sup>

Pheochromocytomas generally occur sporadically, but may also be inherited as part of several distinct syndromes such as multiple endocrine neoplasia type 2A and type 2B, von Hippel-Lindau's syndrome and von Recklinghausen's neurofibromatosis type 1 or paraganglioma syndromes associated with germ-line mutations of genes encoding for SDH subunits B, C and D (SDHB, SDHC, SDHD).<sup>6,7</sup> Carriers of SDHB mutations are at increased risk of extra-adrenal or metastatic pheochromocytomas as well as recurrence.<sup>8-10</sup> Therefore, it has been suggested that all patients younger than 50 years of age, patients with either bilateral pheochromocytoma, extra-adrenal or multifocal pheochromocytoma or with a family history of pheochromocytoma or paraganglioma should undergo genetic testing.<sup>6,7,9,11</sup>

Surgical resection is the treatment of choice after preoperative treatment with  $\alpha$ - and  $\beta$ -blocking agents. Due to the multilayer involvement of the bladder wall, open surgery to perform a partial cystectomy is recommended.<sup>12,13</sup> Transurethral resection is believed to be feasible in tumours <2 to 3 cm without deep parietal infiltration.<sup>3</sup> In the presence of proven metastasis, radical cystectomy with pelvic lymphadenectomy is

recommended.<sup>4</sup> Radiotherapy and chemotherapy have limited effectiveness. Since MIBG is specifically taken up by chromaffin tumours, treatment with MIBG radiotherapy has also been reported. Long-term annual follow-up is recommended in all paragangliomas.<sup>4,5</sup>

## CONCLUSION

Paragangliomas of the urinary bladder are rare. Although, as in our case, patients might present with typical signs and symptoms, they are not easily recognised and diagnosis is sometimes achieved only after excision and histological examination of the tumour.

## REFERENCES

1. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* 2004;89:479-91.
2. Zimmerman IJ, Biron RE, MacMahan HE. Pheochromocytoma of the urinary bladder. *N Engl J Med* 1953;249:25-6.
3. Pastor-Guzmán JM, López-García S, Giménez-Bachs JM, et al. Paraganglioma of the bladder: controversy regarding treatment. *Urol Int* 2004;73:270-5.
4. Ansari MS, Goel A, Goel S, Durairajan LN, Seth A. Malignant paraganglioma of the urinary bladder. A case report. *Int Urol Nephrol* 2001;33:343-5.
5. Doran F, Varinli S, Bayazit Y, Bal N, Özdemir S. Pheochromocytoma of the urinary bladder. *APMIS* 2002;110:733-6.
6. Neumann HPH, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459-66.
7. Dluhy RG. Pheochromocytoma – death of an axiom. *N Engl J Med* 2002;346:1486-8.
8. Gimenez-Roqueplo A, Favier J, Rustin P, et al. Mutations in the SDHB gene are associated with extra-adrenal and/or malignant pheochromocytomas. *Cancer Res* 2003;63:5615-21.
9. Lenders JWM, Eisenhofer G, Mannelli M, Pacak K. Pheochromocytoma. *Lancet* 2005;366:665-75.
10. Dahia PLM. Evolving concepts in pheochromocytoma and paraganglioma. *Curr Opin Oncol* 2006;18:1-8.
11. Gimm O, Armanios M, Dziema H, Neumann HPH, Eng C. Somatic and occult germ-line mutations in SDHD, a mitochondrial complex II gene, in nonfamilial pheochromocytoma. *Cancer Res* 2000;60:6822-5.
12. Naqiyah I, Rohaizak M, Meah FA, Nazri MJ, Sundram M, Amram AR. Pheochromocytoma of the urinary bladder. *Singapore Med J* 2005;46:344-6.
13. Lamarre-Cliche M, Hernigou A, Boutouyrie P, Plouin P, Azizi M. Pheochromocytoma of the urinary bladder. *Circulation* 2002;106:2143-4.