More Common than You Would Think: A Case of Catecholamine-Secreting Paraganglioma in the Urinary Bladder

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Abstract
A 57-year-old woman presented with headache, palpitations and hypertension associated with micturition and was found to have a bladder tumour on imaging. During cystoscopy, with manipulation of the mass, the patient became symptomatic and hypertensive, and a catecholamine-secreting paraganglioma was suspected. Biochemical testing confirmed the diagnosis of paraganglioma of the urinary bladder and she underwent successful resection after preoperative treatment with alpha- and beta-adrenergic blockade and volume expansion. In this article, we outline the prevalence of extra-adrenal paragangliomas and their possible genetic basis. We also overview the diagnosis, perioperative management, follow-up testing and prognosis of these tumours.

Résumé
Une femme de 57 ans présente des maux de tête, des palpitations et de l'hypertension associée à des mictions. L'imagerie médicale révèle la présence d'une tumeur à la vessie. Au cours d'une cystoscopie avec manipulation de la masse, la patiente devient symptomatique et hypertendue et on soupçonne la présence d'un paragangliome secrétant des catécholamines. Des tests biochimiques confirment le diagnostic de paragangliome de la vessie. Après une expansion volumique et l'administration préopératoire d'inhibiteurs adrénergiques alpha et bêta, la patiente subit une résection avec succès. Dans le présent article, nous soulignons la prévalence des paragangliomes extrasurrénaux et la possibilité de leur base génétique. Nous discutons aussi du diagnostic, de la prise en charge périopératoire, des examens de suivi et du pronostic de ces tumeurs.
**Key Points**

- Pheochromocytomas and paragangliomas (PPGLs) are tumours derived from chromaffin cells that often produce catecholamines. About one third of PPGLs are caused by inherited mutations.

- Paragangliomas of the urinary bladder can cause micturition attacks consisting of hypertension, headaches, diaphoresis and palpitations during urination.

- Diagnosis is established by biochemical testing for plasma free metanephrines or 24-hour urinary fractionated metanephrines followed by imaging with computed tomography (CT) or magnetic resonance imaging (MRI) to localize the tumour.

- The mainstay of treatment is surgical resection of the tumour with preoperative correction of volume contraction and administration of alpha-adrenergic receptor blockers to prevent severe intraoperative hypertension.

**Case Presentation**

A 57-year-old woman presented to the emergency department with headache, palpitations and hypertension associated with micturition. She reported a two-year history of similar paroxysmal symptoms with increasing frequency. She had been recently diagnosed with hypertension by her family physician and was taking perindopril. Past medical history included asthma (on salbutamol as needed) and hypothyroidism (on levo-thyroxine). There was no significant family history of illness. Initial investigations including computed tomography (CT) scan of her head were normal and she was diagnosed with migraine headaches in the emergency department.

Several months later she developed left lower quadrant abdominal pain and microscopic hematuria. A CT of her abdomen showed a 6 cm hypervascular mass involving the left anterior and superior aspects of the urinary bladder (Figure 1). Cystoscopy showed an intramural bladder mass covered with irritated mucosa. She became hypertensive during the procedure. Based on previous experience with a similar case, her urologist decided not to biopsy the bladder mass at this time. Given her constellation of symptoms and their association with micturition, a diagnosis of paraganglioma of the urinary bladder was considered and biochemical testing was pursued. A 24-hour urine collection showed elevated metanephrines (14.1 umol/day, normal < 5.5 umol/day) and norepinephrine (5242 nmol/day, normal < 600 nmol/day).

I-metaiodobenzylguanidine (MIBG) scintigraphy showed focal activity of the left anterosuperior aspect of the urinary bladder. There was no evidence of metastatic disease.

She was diagnosed with a likely catecholamine-secreting paraganglioma arising from the urinary bladder. She was referred to internal medicine and anesthesiology for management prior to resection. In our internal medicine clinic, her blood pressure prior to voiding was 115/90 mmHg with a heart rate of 115 beats per minute. After voiding, her blood pressure was 172/79 mmHg with a heart rate of 130 beats per minute. She was treated with prazosin for alpha-adrenergic blockade. This was chosen over phenoxybenzamine as it was more readily available and had already been initiated with good effect in this patient. She also started sodium chloride tablets and was instructed to increase her fluid and salt intake as an outpatient. She was admitted to hospital three days prior to surgery for intravenous fluid administration, titration of her prazosin and initiation of a beta-adrenergic blocker as she remained tachycardic.

When her blood pressure and heart rate were adequately controlled she underwent a partial cystectomy. Pathology on the resected bladder lesion was consistent with paraganglioma without malignant features. The resection margins and resected lymph nodes were negative for paraganglioma. Intra- and post-operatively, she developed hypotension requiring vasopressor medications and volume resuscitation. This resolved within 24 hours. She did not develop hypoglycemia. Her anti-hypertensive medications were stopped and she did not develop recurrent hypertension. Her voiding symptoms also resolved. A 24-hour urine collection was repeated and metanephrines were within the normal range (1.9 umol/day, normal < 5.5 umol/day). She was referred to a geneticist for
consideration of testing for inherited mutations associated with this type of tumour. Unfortunately, she chose not to pursue genetic testing.

Discussion
A pheochromocytoma is a tumour of chromaffin cells in the adrenal medulla that often produces catecholamines including epinephrine, norepinephrine and dopamine. Chromaffin cells are neuroendocrine cells that are similar to sympathetic neurons and often found closely associated with the sympathetic nervous system. These cells originate from the embryonic neural crest and most migrate to the adrenal medulla during development.2 Additional chromaffin cells are found at extradural sites near sympathetic ganglia as well as in the sympathetic plexus within the bladder wall. A paraganglioma is a tumour derived from these extra-adrenal chromaffin cells. Paragangliomas make up 15–20% of all chromaffin-cell tumours (higher than the often-taught “rule of 10”).3 They can be found almost anywhere in the body but are often located in the head, neck, and abdomen. Paraganglioma of the urinary bladder comprises less than 1% of all chromaffin-cell tumours and about 10% of all paragangliomas.5 Both pheochromocytomas and paragangliomas (PPGLs) can be sporadic or hereditary. About 30% of patients have a disease-causing inherited mutation.6 Paragangliomas are four times more likely to be caused by an inherited mutation than pheochromocytomas.7 In addition, some mutations are associated with more malignant tumours.3 Given the prevalence of disease-causing mutations, genetic testing should be considered for all patients with PPGLs. The specific genetic tests done should be based on clinical features and decisional algorithms to guide testing.3

Clinical Presentation
PPGLs often present with symptoms due to the actions of secreted catecholamines, though about 15% of cases are asymptomatic.7 Typical symptoms include hypertension, tachycardia, diaphoresis, headache, and anxiety.7 Pheochromocytoma should be suspected in anyone with these symptoms, especially if paroxysmal or provoked by typical medications (e.g., dopamine antagonists, beta-adrenergic receptor blockers, and sympathomimetics), anyone with an adrenal incidentaloma, and anyone with a family history or features of a syndrome associated with pheochromocytoma.1 Bladder paragangliomas are typically catecholamine-secreting.8 Common symptoms include hematuria, hypertension, and micturition attacks consisting of syncope, headaches, anxiety, diaphoresis, and palpitations due to catecholamine release with urination.8

Diagnosis
Biochemical testing is the first step in diagnosis and the preferred initial tests include plasma free metanephrines or 24-hour urinary fractionated metanephrines because of their superior operating characteristics.3,4 These tests have higher sensitivity than urine catecholamines and vanillylmandelic acid (VMA). The plasma test may have a higher specificity; however, more evidence is required to definitively recommend this over urinary fractionated metanephrines.3 Blood should be collected after 30 minutes supine to avoid false-positives tests.3 Certain medications including acetaminophen and tricyclic antidepressants, as well as physiologic stress and extreme illness can also cause false positive tests.3 The presence of PPGL is extremely likely when plasma metanephrines are three-fold or more above the upper limits of normal.7 For borderline results, repeat sampling or the clonidine suppression test can be considered.

Once a biochemical diagnosis is made, imaging should be performed to locate the tumour. As most PPGLs are located in the abdomen, CT of the abdomen and pelvis with contrast is the best initial imaging test because of its excellent sensitivity.3 Alternatively, magnetic resonance imaging (MRI) can be performed and may have a higher sensitivity in detecting metastatic disease, extra-adrenal and recurrent tumours.3 Functional imaging with I-MIBG scintigraphy is most useful when metastatic disease has been detected by another imaging modality and radiation therapy using I-MIBG is planned.1,3 It can also be used to detect metastatic or recurrent disease in patients at increased risk, for example, those with extra-adrenal or very large tumours.2 In these situations, however, guidelines state that F-fluorodeoxyglucose (F-FDG) positron emission tomography (PET)/CT scanning is the preferred imaging modality, though it is less widely available.3

Management
The mainstay of treatment for PPGLs is surgical resection. Adequate preoperative preparation is crucial to prevent intra- and post-operative complications. Goals of management include alpha- and beta-adrenergic blockade to prevent a catecholamine surge during surgery and correction of volume contraction caused by catecholamine excess. Retrospective studies support α-adrenergic receptor blockers as the first line agents.7 Phenoxybenzamine is the most commonly recommended medication. If phenoxybenzamine is unavailable or not tolerated, other agents including prazosin and terazosin can be used. These agents should be started 7–21 days prior to surgery and titrated to a blood pressure less than 130/80 mmHg sitting and systolic blood pressure greater than 90
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mmHg standing. An orthostatic decrease in blood pressure is expected with adequate treatment. Several days after initiating α-adrenergic blockade, a high sodium diet (greater than 5 g daily) and high fluid intake should be instituted to counteract catecholamine-induced volume contraction and orthostasis. Beta-blockers should never be used alone but can be added after adequate α-adrenergic blockade to control tachycardia targeting a heart rate of 60–70 beats per minute (BPM) seated and 70–80 BPM standing. Finally, metyrosine is a newer agent that inhibits catecholamine synthesis and can be used in combination with α-adrenergic blockade to improve perioperative hemodynamic stability.

All patients undergoing surgical resection of PPGLs require intraoperative monitoring for both hypertensive crisis as the tumour is manipulated and hypotension can occur after tumour removal. Hypertension can be treated with phentolamine, sodium nitroprusside or nicardipine intraoperatively. The most common postoperative complications include hypotension and hypoglycemia requiring close monitoring for 24–48 hours. Hypoglycemia is due to the rebound hyperinsulinemia that occurs with reduction of insulin-suppressing catecholamines after tumour removal.

Prognosis
Approximately 17% of PPGLs are malignant, defined as the presence of metastases in non-chromaffin tissue. It is not possible to definitively rule out malignancy based on pathology. Because of this, follow-up is important and biochemical testing should be performed one to four weeks after surgery to document successful tumour removal and then annually lifelong to detect recurrent or metastatic disease. If postoperative biochemical testing is negative, antihypertensive medications should be weaned, though about 20% of patients will remain hypertensive lifelong.

Competing Interests
None

Contributors
All authors contributed to the literature review and to writing and revising the article. All authors approved the version submitted for publication.

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