

Malignant Paraganglioma of the Urinary Bladder in a 45-Year-Old Woman

Amruth R. Palla, MD, MPH¹
 Thomas Hogan, MD²
 Sindhu Singh, MD²

¹*Department of Internal Medicine, Danbury Hospital, Danbury, CT;*

²*Department of Internal Medicine, Section of Hematology and Oncology, Mary Babb Randolph Cancer Hospital, West Virginia University, West Virginia*

Introduction

Paragangliomas are neuroendocrine tumors arising from the extra-adrenal sympathetic or parasympathetic nervous system,¹ either from the chromaffin-positive paraganglionic tissue or the chromaffin-negative glomus cells² derived from the embryonic neural crest. They are localized in either the head and neck, thorax, or abdominal area, and they are usually benign but can occasionally show malignant behavior.³ Although all paragangliomas contain neurosecretory granules, a few secrete clinically significant levels of catecholamines (functional paragangliomas)⁴ and can cause symptoms of sympathetic surge, including hypertension, anxiety, headaches, diaphoresis, and palpitations. Many paragangliomas are sporadic, but a few cases of familial disease—associated with mutations in the succinyl dehydrogenase genes and multiple endocrine neoplasia 2 syndromes—have been reported.⁵ Paraganglioma of the urinary bladder is rare, accounting for approximately 0.06% of all bladder tumors.⁶

Case Presentation

A 45-year-old woman with a history of rheumatoid arthritis, secondary hypertension, and anxiety was referred by her urologist for further evaluation and management of paraganglioma of the urinary bladder, which had been recently diagnosed through a recent transurethral resection for bladder tumor (TURBT) performed for severe hematuria. The patient had experienced symptoms of urinary urgency and back/flank pain since the age of 10 and episodes of hypertension and anxiety since

her second decade. She recently had experienced suprapubic discomfort and severe hematuria necessitating the TURBT. Initial positron-emission tomography (PET) and computed tomography (CT) scans performed at our hospital showed a bladder tumor and involvement of a single pelvic lymph node (Figure 1).

The patient underwent partial cystectomy with pelvic lymphadenectomy. Follow-up PET/CT scans remained negative 14 months after the surgery (Figure 2). Urine catecholamine levels at 2 and 6 months postoperatively were within the normal range. Chromogranin levels were mildly elevated 2 months after the surgery, but were normal on a repeat check 6 months postoperatively and have remained normal since. The patient's symptoms of back/flank pain and urinary urgency resolved after the surgery. However, the patient continued to experience hypertension and anxiety, which are therefore considered unrelated to the paraganglioma.

Discussion

Malignant paraganglioma of the urinary bladder constitutes 10–15% of all the bladder paragangliomas.⁷ Malignant paraganglioma cannot essentially be differentiated from benign bladder paragangliomas based on gross anatomy or histology, and the malignant behavior is determined based on deep local invasion, lymph node involvement, or metastasis either locally or to distant organs.⁸

Grossly, these tumors are well-circumscribed nodules or nodular aggregates that can be found anywhere on the bladder wall. On microscopy, the tumor cells are arranged in a Zellballen pattern⁸ and are surrounded by a fibrous network rich in blood vessels (Figure 3). On immunohistochemical analysis, the chief cells of the tumors are positive for neuroendocrine markers, such as chromogranin and synaptophysin (Figure 4).

Address correspondence to:
 Amruth R. Palla, MD, 5212 Avalon Valley Drive, Danbury, CT 06810; Phone:
 646-775-1985; Fax: 304-293-2519; E-mail: dr_amruth@yahoo.com.

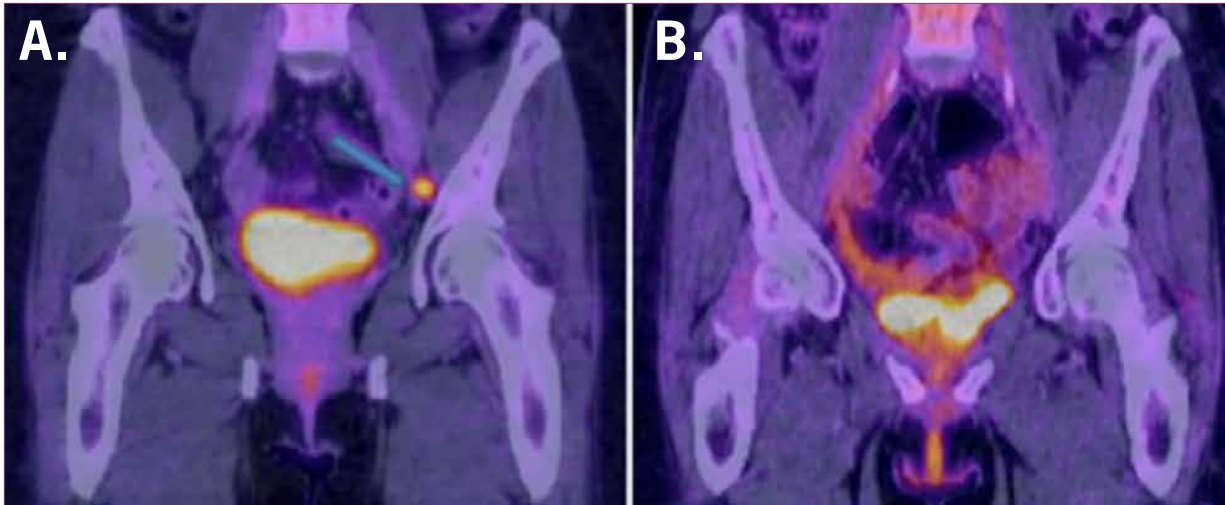


Figure 1. Preoperative and postoperative positron-emission tomography scans showing involvement of a single left pelvic lymph node (A), which was successfully resected (B).

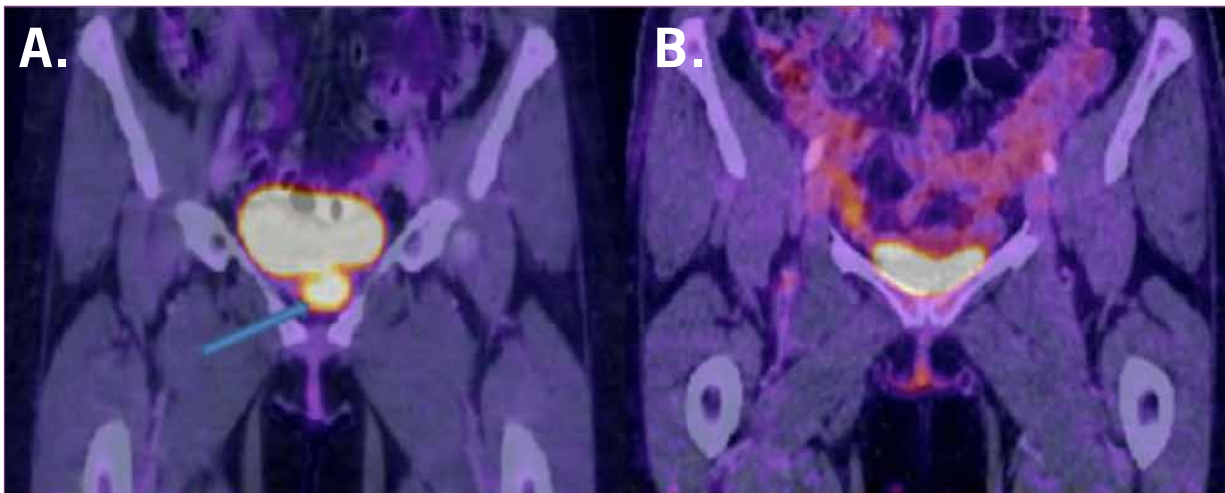


Figure 2. Preoperative and postoperative positron-emission tomography scans showing a bladder paraganglioma close to the neck of the bladder (A), which was successfully resected (B).

The sustentacular cells are positive for S100 protein but negative for epithelial markers, such as cytokeratin. This characteristic differentiates paraganglioma from urothelial cancers and carcinoid tumors, which are positive for cytokeratin and melanomas on HMB-45 and melanin A stains.⁹

Functional tumors can lead to symptoms of catecholamine surge (eg, hypertension, anxiety, paroxysmal headaches, diaphoresis, and palpitations),¹⁰ especially during micturition. Nonfunctional tumors can be asymptomatic. Painless hematuria is another commonly reported symptom. Rarely, the tumors can also cause urinary obstruction, depending on their location.¹¹

Surgery is the most common mode of treatment, and patients generally undergo partial cystectomy with lymphadenectomy. Radiation¹² and chemotherapy, either

in the neoadjuvant¹³ or adjuvant^{14,15} setting, has been used in a few cases. There are infrequent reports of hypertensive urgency, due to release of excess catecholamines during surgery, and appropriate perioperative preparation for this possibility must be included in the management plan. Because bladder paragangliomas are likely to recur and to metastasize, lifelong follow-up with annual measurement of catecholamine levels is essential.¹⁰

A Medline/PubMed search of the term *malignant paraganglioma* of the urinary bladder yielded a total of 76 articles in many languages; 44 were pertinent to our study. Sixty cases of bladder paragangliomas were described in these 44 articles, with 30 malignant cases being reported thus far in the literature. The ages of the patients ranged from 12–77 years (irrespective of benign or malignant status). Surgery was the most commonly applied treat-

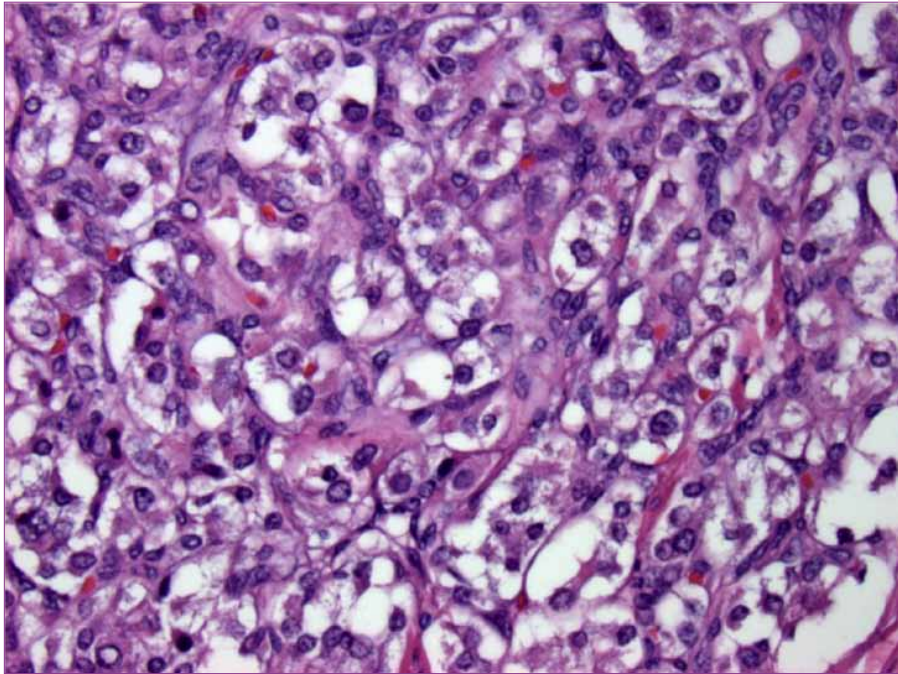


Figure 3. Paraganglioma of the urinary bladder showing the typical Zellballen pattern.

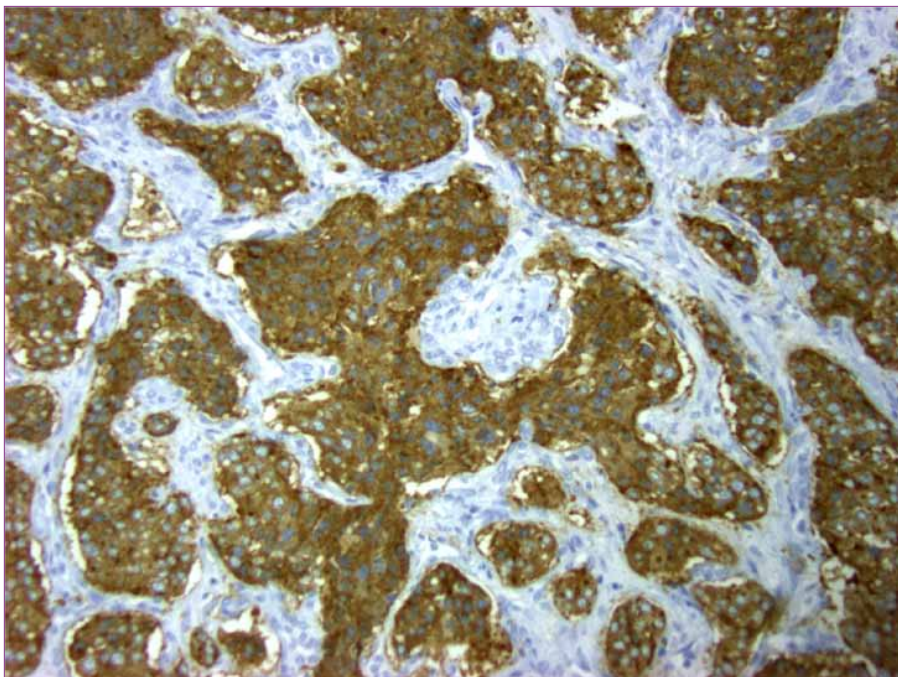


Figure 4. Paraganglioma of the bladder showing synaptophysin reaction on immunohistochemistry.

ment modality, with a few cases mentioning the use of radiation or chemotherapy. One report described the use of cisplatin and etoposide,¹⁶ and 2 other reports described the use of cyclophosphamide, vincristine, and dacarbazine.^{13,15} One case described a woman with hypertension that persisted for 30 years before she was diagnosed with

malignant bladder paraganglioma.¹⁶ Otherwise, diagnosis was usually made within 3–5 years after symptom onset.

Since our patient continued to have hypertension and anxiety despite the surgery, and also given the fact that her catecholamine levels were always within normal limits, it is opined that these comorbidities were unrelated to the

paraganglioma, which was most likely non-functional in nature. Her hypertension could be related to vasculitis from the underlying rheumatoid arthritis.

Conclusion

Urinary bladder paraganglioma, although rare, should be included in the differential diagnosis of patients presenting with nonspecific urinary symptoms along with symptoms of catecholamine excess. An early cystoscopy, if considered in such patients, may help diagnose this clinical entity prior to malignant transformation and will enable prompt treatment that can reduce morbidity and offer quicker symptom relief. It should be noted that patients can have hypertension (primary or secondary) from other causes coexisting with a non-functional paraganglioma, as in the case described.

Information regarding the natural history of this disease is available through case reports that followed patients prospectively for recurrence. Our case is one of very few that provide retrospective information on the presence of symptoms for a prolonged period of time prior to the diagnosis of the bladder paraganglioma.

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Review

Paraganglioma of the Bladder

Robert Jansen, MD, and
Stanley Zaslau, MD, MBA, FACS

West Virginia University, Division of Urology, Morgantown,
West Virginia

Palla and colleagues reported a case of a malignant bladder paraganglioma in a 45-year-old woman.¹ Paragangliomas are pheochromocytomas that arise outside of the adrenal medulla. According to the “rule of tens,” 10% of pheochromocytomas occur outside of the adrenals; however, the actual incidence of paragangliomas

has been reported to be as high as 23%.² These tumors may arise in the head/neck, thorax, and/or abdominopelvic regions. Bladder paragangliomas, in particular, represent 0.06% of all bladder tumors and less than 1% of all catecholamine-secreting tumors.³ Pheochromocytomas normally arise from chromaffin cells in the adrenal medulla. Chromaffin tissue is also located along the para-aortic sympathetic chain, the sympathetic chain in the neck and mediastinum, and within the wall of the urinary bladder.⁴ The source of the bladder chromaffin tissue is uncertain. Some researchers suspect that chromaffin tissue migrates to the bladder wall during embryonic development.⁵ Others have discovered small nests of paraganglionic tissue in the muscularis propria and deep submucosal layers of the trigone, posterior wall, and anterior wall of the bladder.⁶

Pheochromocytomas and paragangliomas may arise sporadically or as part of a familial pattern. Recent studies have shown a heritability of 27.4–51.7% for pheochromocytomas and paragangliomas, leading some to recommend genetic testing for affected individuals. Certain tumor syndromes, including Von Hippel–Lindau, multiple endocrine neoplasia type I, and neurofibro-

Address correspondence to:
Stanley Zaslau, MD, MBA, FACS, Professor and Chief, West Virginia University, Division of Urology, PO Box 9251, Morgantown, WV 26506

matosis type I, have associations with both tumor types, and multiple gene mutations, including *RET*, *NFI*, *VHL*, and *SDH*, have been discovered.⁷ Bladder paragangliomas show a slight female predominance, with patients usually presenting in the third, fourth, or fifth decades.^{8,9}

As pheochromocytomas and paragangliomas arise from neuroendocrine tissue, 80% of cases have the ability to produce catecholamines and are termed *functional* tumors.¹⁰ Presenting symptoms such as palpitations, pallor, headache, and diaphoresis occur due to a sympathetic surge from catecholamine release. Less common presentations may include hyperglycemia, panic attacks/anxiety, fever, weight loss, myocardial infarctions, and Raynaud's phenomenon.¹¹ Paragangliomas occurring in the bladder may cause gross hematuria in up to 60% of cases, although patients may also present with microhematuria or unremarkable urinalyses.³ The onset of the aforementioned symptoms, particularly with bladder tumors, is usually induced by micturition, bladder distention, or sexual activity.^{4,11}

Malignancy is present in approximately 10% of pheochromocytomas and 5–20% of paragangliomas.¹² Although definitions of malignancy vary, it is usually defined as the presence of distant metastases, as even tumors that locally invade adjacent organs may maintain an indolent course. Malignant tumors do not differ histologically or genetically from benign tumors, however, they tend to be larger and secrete more dopamine than benign lesions.^{13,14} Five-year survival rates of patients with malignant pheochromocytomas are between 36–60%.¹⁰

Diagnosis of bladder paragangliomas is accomplished using imaging, measurement of hormonal metabolites, and direct visualization via cystoscopy. On cystoscopy, the paraganglioma is a nondistinct entity, appearing as a homogenous submucosal mass with abundant vascularity.^{3,5,9} Immediate biopsy should be avoided due to the risk of precipitating massive catecholamine release and life-threatening complications. Whereas diagnosticians previously looked to serum/urine catecholamines to determine the presence of a functional tumor, researchers are now focusing on metanephrines. As such, recommendations from the 2005 International Symposium on Pheochromocytoma state that along with initial testing, evaluation should include measurements of plasma-free and urinary metanephrines, along with catecholamine levels.¹⁵ Sensitivity and specificity of 24-hour urine metanephrine measurement is 87–90% and greater than 99%, respectively, whereas serum metanephrine measurement carries a sensitivity of 85% and a specificity of 96%.¹¹ Compared to pheochromocytomas, bladder paragangliomas typically secrete a higher ratio of norepinephrine:epinephrine due to the lack of the *PNMT* conversion enzyme.³ Imaging studies, including computed tomography (CT) and

magnetic resonance imaging (MRI), have previously been used with good sensitivity in detecting the presence of tumors, although they lack specificity in identifying functional tumors. The standard functional imaging studies are 123I-metaiodobenzylguanidine (MIBG) scintigraphy and 131I-MIBG scintigraphy, which are useful in localizing metastatic deposits or multifocal tumors. Newer imaging modalities, such as 18F-fluorodopa positron-emission tomography (FDOPA-PET), have been evaluated in comparative studies; Fottner and colleagues report a sensitivity of 98% and specificity of 100% for FDOPA-PET, compared to 53% and 91% for 131I-MIBG.¹⁶

The treatment of choice for malignant pheochromocytomas and paragangliomas is surgical resection. Prior to surgery, blood pressure should be normalized, as preoperative blood pressure has been linked to perioperative complications.¹⁷ Patients also require preoperative alpha- and beta-adrenergic blockade to avoid intraoperative sympathetic surge from tumor manipulation.¹⁰ Partial cystectomy is mainly performed for resection of bladder paragangliomas, although radical cystectomy may be considered for trigonal tumors or tumors exhibiting local invasion or multifocality. It is interesting to note that in this patient, although partial cystectomy was performed, hypertension and anxiety have continued postoperatively. These conditions are likely not related to the paraganglioma. It is conceivable that the paraganglioma did not produce hypertension and was likely hormonally inactive in that regard.

In select cases, consideration for regional lymphadenectomy should be contemplated. Transurethral resection has been performed and may be useful for noninvasive tumors measuring less than 2–3 cm; however, due to the significant risk of hemorrhage, this modality is not preferred.^{6,18} Chemotherapy and radiation are generally considered palliative only, although some cases have shown effective treatment of metastatic disease.^{9,10,13}

Long-term follow-up should be pursued, as metastatic disease may present as long as 41 years after tumor resection.¹⁹ Some authors recommend clinical and biochemical (metanephrine measurement) assessment at 6 months and then annually thereafter in patients affected by a malignant tumor. Cystoscopy and imaging (CT, MIBG) may be considered as well, although there is no official algorithm or protocol defining the timing or necessity of these studies. Patients with suspected benign tumors (<5 cm, solitary, sporadic) may pursue follow-up with clinical and biochemical testing every 2 years.²⁰

Conclusion

Bladder paragangliomas are rare tumors with certain malignant potential. Functional tumors induce symptoms that are attributed to catecholamine release, although

these symptoms may overlap with other clinical entities, presenting an obstacle to prompt diagnosis and determination of true tumor functionality.

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should be avoided to minimize infectious complications during neutropenia. Our thinking about neutropenia has changed in recent years. Neutropenic precautions now depend on the degree of neutropenia and the type of cancer. Good hand hygiene is very important. In patients with prolonged neutropenia as experienced during hematologic malignancies and bone marrow transplantation, minimizing exposure to pets and live plants is recommended during periods of profound neutropenia. However, in solid tumor malignancies, most patients do not experience very long periods of neutropenia, and these precautions are more relaxed. A recently published Cochrane review on the benefit of a low-bacterial diet was not conclusive regarding evidence for or against recommending this approach. It is very important that each patient discuss these precautions with his or her doctor so that they can be tailored to specific needs.

It is very distressing for cancer patients to develop febrile neutropenia and end up in the hospital. This outcome tends to occur with the first cycle of chemotherapy, and it can be quite challenging because patients become frightened about what future cycles of chemotherapy will be like. Anything we can do to safely prevent febrile neutropenia is beneficial.

Suggested Readings

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