



Acute bladder retention secondary to bladder paraganglioma in an 86-year-old female: case report

Retención urinaria aguda secundaria a paraganglioma vesical en femenino de 86 años: reporte de caso

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Abstract

Clinical case: an 86-year-old female comes for medical evaluation during an episode of acute urinary retention, upon medical questioning she only refers previous events of nonspecific chills and malaise; after an urotomography is ordered, an exophytic lesion was identified in the bladder wall. Cystoscopy was performed with resection of the lesion, further immunohistochemical analysis helped make the diagnosis of sympathetic bladder paraganglioma. Absent catecholamines were found at follow-up.

Relevance: bladder paragangliomas are extraordinarily rare, with an estimated incidence of 0.6-0.8 cases per 100,000 person-years. When located in the abdomen, it affects the organ of Zuckerkandl in 70 % of cases; the bladder is involved in only 10 % of cases of intra-abdominal paraganglioma.

Clinical implications: the cyclic secretion of catecholamines, originated by the neoplastic cells that compose the paraganglioma, causes systemic symptoms related to their activity in other organs. The clinical presentation of sympathetic bladder paragangliomas can be highly insidious, due to the wide range of local and systemic symptoms that can be observed.

Conclusions: due to the local effect of the neoplasm or its catecholamine-secreting activity, the index of suspicion for this type of neoplasm should be high and coupled with a detailed anamnesis to identify the catecholamine-related signs and/or symptoms.

Keywords:

Bladder paraganglioma,
catecholamines,
neoplasm, sympathetic,
bladder

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Resumen

Caso clínico: femenino de 86 años acude a valoración por episodio de retención urinaria aguda, al interrogatorio sólo refiere episodios previos de escalofríos inespecíficos y malestar general; tras la realización de una urotomografía se identifica una lesión exofítica en la pared vesical. Se realizó cistoscopia con resección de la lesión, el análisis inmunohistoquímico estableció el diagnóstico de paraganglioma simpático vesical. Al seguimiento se observó ausencia de catecolaminas.

Relevancia: los paragangliomas vesicales son extraordinariamente raros, con una incidencia estimada de 0.6-0.8 casos por 100 000 personas-año. Dentro del abdomen, se ubican al órgano de Zuckerkandl en 70 % de los casos; la vejiga sólo está afectada en el 10 % de los casos de paraganglioma intraabdominal

Implicaciones clínicas: la secreción cíclica de catecolaminas, originada en las células neoplásicas que componen el paraganglioma, provocan síntomas sistémicos relacionados con su actividad en otros órganos. La presentación clínica de los paragangliomas simpáticos vesicales puede ser muy insidiosa, debido a la amplia gama de síntomas locales y sistémicos que pueden observarse.

Conclusiones: debido al efecto local o a su actividad secretora de catecolaminas, el índice de sospecha de este tipo de neoplasia debe ser alto y aunado a una anamnesis detallada, para identificar los signos y síntomas relacionados.

Palabras clave:

Paraganglioma
vesical, catecolaminas,
neoplasia, simpático,
vejiga

Introduction

Paragangliomas are extra-adrenal neuroendocrine tumors that originate from the autonomic paraganglionic chains. They are classified as sympathetic or parasympathetic, according to their capacity to secrete catecholamines, the latter being those that lack catecholamine secretion capacity.^(1,2) On the other hand, most sympathetic paragangliomas are functional and secrete catecholamines into the systemic circulation; they can be located at any point of the sympathetic chain, from the head and neck to the bladder and prostate, with the organ of

“Zuckerkandl” being the most common site of localization within the abdomen.⁽¹⁻³⁾

The incidence of both paragangliomas and pheochromocytomas is estimated to be 0.6-0.8 cases per 100,000 person-years.^(4,5) Most cases occur between the 3rd and 5th decade of life, with a median age at diagnosis of 40-47 years and higher prevalence in women.^(2,3,6,7) According to a 2016 meta-analysis, the mean age at diagnosis was 43.3 years, with a female-male ratio of 1.07:1, preferentially affecting the Caucasian race.⁽⁸⁾

The present work aims to present the case of a sympathetic bladder paraganglioma with an atypical clinical presentation, consisting of isolated acute urinary retention and a vague non-specific history of symptoms related to the secretion of catecholamines. We intend to review the pathophysiology, clinical picture, and treatment to help the reader become familiar with this uncommon type of neoplasm. We hope that this work serves as feedback both to our team, which had a low index of suspicion due to the non-classical presentation, and to the readers.

Case presentation

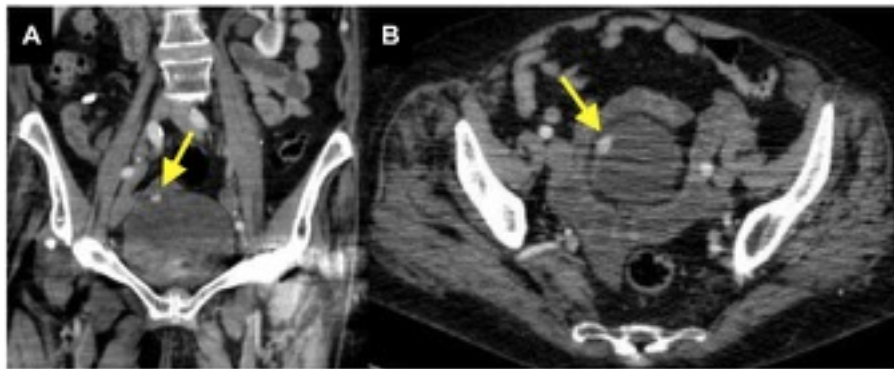
The patient is an 86-year-old female patient, originally from and resident of Chihuahua, Chihuahua, Mexico. She denies alcohol consumption and smoking. During medical interview, she only comments on a history of uncomplicated diverticulosis, and hiatal hernia that required surgical management. Upon family health history questionnaire, she comments about a sister who was diagnosed with malignant pheochromocytoma four years ago at 72 years of age. The patient's relatives report approximately four previous episodes of general malaise and chills 8-10 months apart, which resolved spontaneously without requiring any management or determined origin.

Her condition began 3 days before her admission, with intense abdominal pain located in the left flank and hypogastrium, abdominal

distension, difficulty urinating, and deterioration of her general condition. Hours prior on the same day of evaluation, she developed diaphoresis, chills and worsening pain that prompted medical consultation. On admission vital signs showed a blood pressure of 161/83, heart rate of 77 bpm, O₂ saturation of 97 %, and respiratory rate of 17 rpm.

Physical examination of the abdomen revealed a distended hypogastrium, with pain on both light and deep palpation, attributed to acute urinary retention. Contrast-enhanced computed tomography (CT) of the abdomen was ordered (Figure 1); a large bladder distended by urine, and an exophytic lesion with positive intrinsic reinforcement of approximately 10 mm in the inner apical region of the bladder were identified. Afterward, a Foley catheter was placed to relieve pain from acute urinary retention, resulting in normalization of the patient's blood pressure without the need for antihypertensive therapy. Urology was consulted, and the patient was admitted for surgical management. Cystoscopy with transurethral resection and biopsy of the bladder lesion was performed two days after admission. Under regional anesthesia via subarachnoid block, a nodular, highly vascular lesion, approximately 1 cm in diameter was identified and completely resected. The specimen was submitted for pathological evaluation. Intraoperatively, the patient's blood pressure remained within normal limits, and no antihypertensive agents were required.

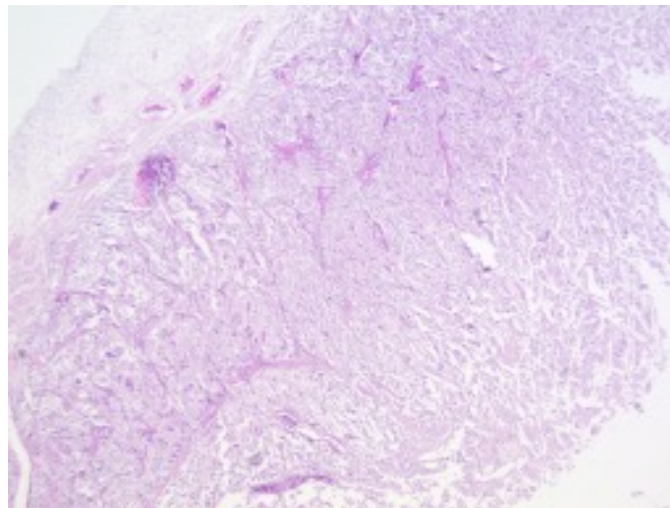
Figure 1. Contrast-enhanced computed axial tomography of the abdomen



A. Coronal section. B. Axial section. Distended urinary bladder, showing an exophytic lesion of approximately 10 mm in the inner apical region of the bladder, with positive intrinsic and pedicle contrast enhancement (arrows); considered a primary infiltrative lesion due to contrast medium uptake in an area in the anterior part of the bladder wall.

The initial pathology report described an invasive poorly differentiated carcinoma of probable urothelial origin, but a need to further identify the origin of tumor cells (Figure 2).

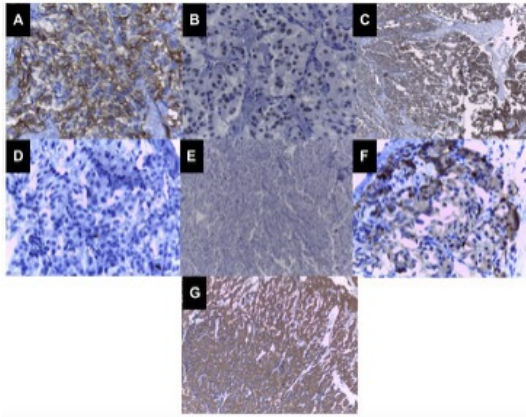
Figure 2.



The neoplasm is composed of loose solid nests of cells with abundant granular eosinophilic cytoplasm, with mild nuclear pleomorphism; neoplastic invasion of the lamina propria was observed.

Immunohistochemical analysis was subsequently requested (GATA-3, PAX-8, CD-56, synaptophysin, chromogranin, protein S-100, & Ki-67) to help determine the cellular lineage (Figure 3); afterward the diagnosis of infiltrating sympathetic paraganglioma on the bladder wall was established.

Figure 3. Pathology microphotographs of immunohistochemistry analysis of the resected bladder tumor



A. CD-56 (+). B. GATA-3 (+). C. Chromogranin (+). D. Ki67 (+, in 2 % of cells). E. PAX 8 (-). F. S-100 (+, in sustentacular cells). G. Synaptophysin (+).

Urine culture taken on admission was negative; the patient was discharged 48 hours later with a Foley catheter, which was removed ten days later. At nine months follow-up, plasma metanephrines (free metanephrine, plasma normetanephrine, and total metanephrines) and vanillylmandelic acid in 24-hour urine were requested for control, both with results below reference values (<25 pg/ml and 1.2 mg/24 hr, respectively). No additional imaging studies were ordered, given the complete resection of the tumor and negative plasma metanephrine and vanillylmandelic acid levels.

Literature review

Pheochromocytomas and paragangliomas cannot be differentiated by histopathologic features, so their distinction is based purely on their anatomic location; the former being adrenal and the latter extra-adrenal.⁽⁴⁾ This led to the creation of the term “extraadrenal paraganglio-

ma” by the World Health Organization in 2017, encompassing all extraadrenal tumors originating from ganglionic tissue, regardless of their catecholamine-secreting status or anatomic location.⁽³⁾ As previously stated, paragangliomas can be further divided into sympathetic and parasympathetic, based on their ability to produce and secrete catecholamines, with the former being the secretory type (as in our case).^(1,2)

It is estimated that roughly 75 % of these tumors are found within the abdomen; of these 10 % are anticipated to be located in the urinary bladder or prostate, and comprise less than 0.6 % of all types of bladder tumors.^(2,3,8) Within the bladder, they are found primarily on its posterior wall or the bladder trigone.^(2,8)

The clinical picture seen in sympathetic paragangliomas is primarily secondary to the systemic effects of catecholamine hypersecretion by the chromaffin cells.^(4,6) There is a wide range of signs and symptoms that may be observed, such as headache, palpitations, sweating, fever, weight loss, panic attacks, or hyperglycemia; however, hypertension, either continuous or paroxysmal, is considered to be the most common finding.^(1,2,8) The classic triad of diaphoresis, palpitations/tachycardia, and headache could be seen during a hypertensive crisis, having a specificity of 90 % and a prevalence of 40 % according to some case series.^(3,4,9) It is noteworthy, that there is no previous reference to a presentation consisting mainly of acute urinary retention as the present case, which could reflect the local effect of catecholamine activity in the bladder. During the medical interview, symptoms may be precipitated by postural changes, anxiety, exercise, or any action that increases intra-abdominal pressure and induces the release of catecholamine into the bloodstream.⁽¹⁾ In the

case of bladder paragangliomas, they are characteristically preceded by sexual intercourse or urinary urination; on the same note, voiding syncope is considered the characteristic finding of condition.^(3,10) Furthermore, a triad of symptoms triggered by urination or intercourse, hypertension, and intermittent hematuria is considered almost diagnostic of this type of cancer, but exists in approximately 50 % of cases.^(2,10)

Diagnosis is usually established between the third and fourth decade of life, highlighting that the younger the age at diagnosis, the greater the probability of a disorder with familial inheritance;^(2,11) these observations contrast significantly with the present case, with an age of 86 years at diagnosis, and family history of pheochromocytoma in a sister, suggestive of a possible hereditary syndrome. Although needing a high index of suspicion due to the wildly variable presentation paragangliomas can have, early recognition so proper management can be initiated is vital, because they carry a high risk of causing potentially lethal paroxysms.^(2,4)

Ideally, and when there is a high index of suspicion, the diagnosis is established by prior measurement of plasma and urine metanephrines, followed by anatomical documentation of the tumor by a imaging, preferably by CT.^(11,12) However, due to ambiguity of some cases, another route (as in this case) commonly followed is the imaging localization of the tumor without prior measurement of catecholamines.^(4,13,14) Because intratumoral metabolism of catecholamines occurs independently of the secretory state of the tumors, their measurement is effective for diagnosis in both types of paragangliomas.^(3,12) It is worth mentioning that the increasing use of sectional imaging methods has led to an increase in the num-

ber of incidental adrenal masses found by these means.⁽²⁻⁴⁾ In our case, neither plasma nor urine metanephrines were measured due to a low index of suspicion for bladder paraganglioma, and CT imaging revealed only an exophytic bladder lesion. This scenario can be hazardous, as patients may undergo surgical intervention without appropriate preoperative alpha-adrenergic blockade. Given this potential risk, thorough clinical history taking and a high index of suspicion are essential in evaluating atypical bladder masses.

Regardless of site or catecholamine-secreting capability of paragangliomas, the definitive diagnosis is confirmed by histopathologic analysis.⁽³⁾ As previously stated, pheochromocytoma and paraganglioma are indistinguishable at the cellular level, since both present the same histological and morphological characteristics; namely, a "Zellballen" type pattern, formed by a thin capsule and trabeculae of stromal tissue separating nests of well-differentiated round or polygonal cells.^(3,4) In cases where the initial histopathological diagnosis is inconclusive, immunohistochemistry may be used to help conclusively determine the chromaffin cell lineage.⁽¹¹⁾

Although 90 % of cases are benign, evidence of metastasis is the only evidence of malignant disease.^(4,8) For paraganglioma, the main site for metastasis is the liver, differing from pheochromocytomas, which usually invades lymph nodes and bone.⁽⁴⁾

The treatment of choice, and the only one considered curative, continues to be complete surgical resection of the localized tumor, which can be performed open or endoscopically.^(2-4,8) In the case of bladder paragangliomas, the surgical approach can be through cystoscopy with tumor resection, or either partial or radical cystectomy, depending on the degree of inva-

sion and the surgeon's preferred technique;⁽³⁾ emphasis on the special care of adjacent structures, such as the ureters, during resection should be noted, due to their proximity to the bladder trigone.⁽²⁾

Current recommendations state that all patients should receive standard preoperative beta and alpha-adrenergic blockade, achieve blood pressure control, and avoid the intraoperative risk of hypertensive crisis secondary to catecholamine release with tumor manipulation.^(2,4,11,12) Because there is an estimated 20 % chance of recurrence within the first 5 years, the NCCN recommends close follow-up with blood pressure and biochemical profile monitoring every 6-12 months for the first 3 years and then annually for 10 years.^(3,15) In turn, protocols state that all patients should receive a genetic panel analysis since up to 40-50 % of patients have an inherited mutation.⁽²⁻⁴⁾ In this case, although preoperative alpha-adrenergic blockade was not administered, the patient's elevated blood pressure normalized following pain relief from acute urinary retention. However, similar cases should not rely on such a benign course, as appropriate preoperative management remains critically important to prevent potentially life-threatening complications. Follow-up biochemical testing in our patient yielded negative results, and no further episodes of acute urinary retention have been reported.

Conclusion

Sympathetic paragangliomas of the bladder have a low incidence, both in the general population and as bladder tumors overall. Their clinical presentation can be broad and complex

due to the wide range of signs and symptoms that can be developed, both locally (i.e. local activity of catecholamines and mass effect) and systemically (involving multiple systems secondary to the activity of secreted catecholamines). Although young and middle-aged adults are the expected group to be involved, this case in an elderly woman is a reminder not to let our guard down in this population. Ideally, the diagnosis should be established early to avoid the risk of developing cardiac alterations or potentially lethal paroxysms. In this case report, our patient presented mainly with local manifestations in the bladder, probably due to the local activity of the catecholamines secreted by the neoplastic cells; this atypical presentation made the initial suspicion of this type of tumor as the cause of the acute urinary symptoms difficult. Clinicians should have a high index of suspicion for tumors such as paragangliomas, especially when the clinical picture of sympathomimetic activity is related to inducing actions; the medical approach is also complex, being staged and multidisciplinary. Cases like this one help provide a reference for feedback to serve as valuable learning experiences, especially for urologists in Mexico, who must incorporate a broad medical team in similar cases.

CRediT Taxonomy

- **Raymundo Alfonso Muñoz Cabello:** Conceptualization, Investigation, Writing – Original Draft & Writing – Review & Editing.
- **Gaspar Iglesias Miramontes:** Conceptualization, Methodology & Validation.
- **Gaspar Iglesias Palacios:** Conceptualization, Project Administration & Visualization.
- **Fernando Aguilera Almazán:** Formal Analysis, Investigation, Resources & Supervision.

- **Arturo Luévano González:** Formal Analysis, Resources & Validation.

Conflict of interests

The authors declare that they have no conflicts of interest.

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