Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(3):258-263. doi: 10.33719/yud.2023;18-3-1287231**

Olgu Sunumu / Case Report

Paraganglioma of Urinary Bladder: A Case Report

Mesane Paragangliomu: Olgu sunumu

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Geliş tarihi (Submitted): 2023-04-24
Kabul tarihi (Accepted): 2023-08-13

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Özet

Mesane lezyonlarının büyük çoğunluğu, papiller ve/veya düz görünümlü ürotelyal neoplazilerdir. Ürotelyal tümör dışındaki neoplaziler oldukça nadirdir. Paragangliomalar, sempatik gangliyon veya kromafin hücre kaynaklı katekolamin salınımı yapan nadir görülen tümörlerdir. Paragangliomaların yaklaşık %10'u adrenal dışı bölgede görülür, bunun %10'u mesanede izlenir ve tüm mesane tümörlerinin %0.05'ini oluşturur.

42 yaşında kadın olguda, mesane sol anterolateralinde, lümene protrüde 50x43 mm boyutlarında santrali nekrotik, periferinde vaskülarite artışı olan solid kitle görüldü. Dış merkez ve hastanemizde yapılan mesane tümörünün transüretral rezeksiyon materyeline ait örnekler patolojide incelendi ve paraganglioma tanısı aldı. Nadir görülmesi ve ürotelyal karsinom ile karışabilmesi nedeniyle mesanede tümörlerinde paraganglioma her zaman akılda tutulmalıdır.

Anahtar Kelimeler: mesane, paraganglioma, ekstra adrenal

Abstract

Objective: The majority of bladder lesions are papillary and/or flat-appearing urothelial neoplasms. Neoplasms other than urothelial tumors are extremely rare. Paragangliomas are rare catecholamine-releasing tumors of sympathetic ganglion or chromaffin cell origin. Approximately 10% of paragangliomas occur in the non-adrenal region, of which 10% are seen in the bladder and constitute 0.05% of all bladder tumors. About 10% of paraganglioma occur in extra-adrenal sites, of which, 10% are located in bladder wall accounting for 0.05% of all bladder tumors.

In a 42-year-old female patient, a mass on the anterolateral wall of the bladder, measuring 50x43 mm solid mass protruding into the lumen with necrotic center and increased vascularity on the periphery was reported. The specimens of the, transurethral resection bladder material obtained from an external center and our hospital were examined by pathology and diagnosed as paraganglioma. Because of its rarity and confusion with urothelial carcinoma, paraganglioma should always be recognized when dealing with bladder tumors.

Keywords: bladder -paraganglioma -extra adrenal

How to Cite; Bıçak T, Özekinci S, Bıçak Y, Dağgülli M. Paraganglioma of Urinary Bladder: A Case Report. New J Urol. 2023;18(3):258-263. doi: 10.33719/yud.2023-18-3-1287231

INTRODUCTION

The majority of bladder lesions are papillary and/or flat-appearing urothelial neoplasms. Neoplasms other than urothelial tumors are extremely rare (1). Rare tumors may be misdiagnosed because they morphologically resemble urothelial neoplasia. Bladder paraganglioma is an example. Paragangliomas are catecholamine-releasing tumors originating from sympathetic ganglia or chromaffin cells. They are more common in women and in the 3rd-4th decade (2). About 10% of paraganglioma occur in extra-adrenal sites, of which, 10% are located in bladder wall accounting for 0.05% of all bladder tumors (3,4). Approximately 200 bladder paragangliomas are reported in the English literature by 2017 (5).

Nearly half of paraganglioma cases are associated with hereditary conditions. Among bladder tumors, hereditary tumors have a very high incidence. Hypoxia (SDH, VHL, EGLN1, EGLN2), WNT pathway (SCSDE1, MAML3), kinase signaling pathways (RET, TNEM127, HRAS, NF1) and MAX mutation-related genes are involved in hereditary cases (4, 6). Histopathologic examination is essential for clinical diagnosis. Although prognosis for bladder paragangliomas is excellent, about 15% of these cases are capacity to metastasize. The World Health Organization recommends the use of the term "potential to metastasize" instead of "malignant" in paraganglioma in the initial diagnosis as in other neuroendocrine tumors. Indicators for potential metastatic disease includes young age, bulky tumor, and a micturition-induced sympathomimetic attacks, vascular invasion or SDHB mutation (4). Paraganglioma may show muscle infiltration in the bladder and is not a criterion for malignancy.

The diagnosis of malignancy in paraganglioma is finalised when it metastasizes to the lymph node and other organs (3).

Paragangliomas of the urinary bladder can mimic urothelial carcinomas and misdiagnose. In this article, we will discuss the important morphological, clinical, and immunohistochemical studies in differential diagnosis.

CASE REPORT

A 42-year-old woman's bladder biopsy with two paraffin blocks and H&E stained slides were sent to our laboratory for consultation. Since the diagnosis of invasive urothelial carcinoma in the first center was not compatible with her clinical presentation, a second opinion was requested. It was diagnosed paraganglioma by histopathologic and immunohistochemical examination. The patient presented to the urology outpatient clinic with paraganglioma report. It was learned that she had painless coagulated hematuria which started 2 months ago, thyroidectomy 2 years ago and 30 pack years of smoking. Physical examination and system examination were unremarkable. Ultrasound scan demonstrated a mass on the anterolateral wall of the bladder, measuring 50x43 mm solid mass protruding into the lumen with necrotic center and increased vascularity on the periphery was reported. Intravenous pyelography showed bilateral orifices with natural appearance. A solid tumoral formation was seen adjacent to the left orifice extending to the left side wall and bladder neck. Enhanced computed tomography with contrast (CT) (Figure 1) revealed a solitary, low-density lesion located on the left wall of bladder, with a size of 50x43 mm. In laboratory tests, plasma normetanephrine was also significantly elevated (520.9 pg/mL, reference < 200 pg/mL). Other laboratory findings were unremarkable. Since the tumor was observed, transurethral resection bladder (TUR-B) was planned. During trans-urethral resection, the patient became severely hypertensive. Therefore, TUR-B could not be completed effectively. After 2 months, the control TUR-B was planned. The second TUR-B could not be full completed either because of the tumor size.

Microscopic Findings

15 cc curetted tissues were followed up on 8 cassettes. In the sections examined, a tumor was observed separated into islets with thin fibrous septae, containing thin-walled vascular structures, consisting of large polygonal, central nucleus, salt-pepper pattern,

thin chromatin, amphibolic cytoplasm, and cells with marked pleomorphism. Mitosis and atypical mitosis were not observed. The tumor was seen to be nested in the muscle tissue and invaded in a nodular pattern.

The tumour cells stained strongly positive for chromogranin a (Ventana,mouse antibody, Clone: LK2H10), synaptaphysin (Ventana,rabbit antibody, Clone: MRQ-40), gata3 (Ventana, mouse antibody, Clone: L50-823), S100 (Ventana, mouse antibody, Clone: 4C4.9) protein high lights sustentacular cells and negative for, cd10(Ventana,rabbit antibody, Clone: SP67), inhibin (Ventana, mouse antibody, Clone: R1), panck (Ventana, mouse antibody, Clone: AE1/AE3/PCK26), p63 (Ventana, mouse antibody, Clone: 4A4). Ki67 (Ventana,rabbit antibody, Clone: 30-9) stained approximately 1% positive. Further there was loss in succinate dehydrogenase A (SDHA) (Dako,mouse antibody, Clone: F2) immunohistochemically.

Control TUR-B material sent two months after these biopsies showed nodular tumor infiltration in the muscularis propria and dysplasia was not observed in the surface epithelium. In immunohistochemistry, tumor cells stained diffusely positive with chromogranin a, synaptaphysin, gata3. The patient was contacted later. It was learned that she underwent partial cystectomy in an external center and the diagnosis was confirmed in the material of that operation. The patient is alive and healthy for 5 years.

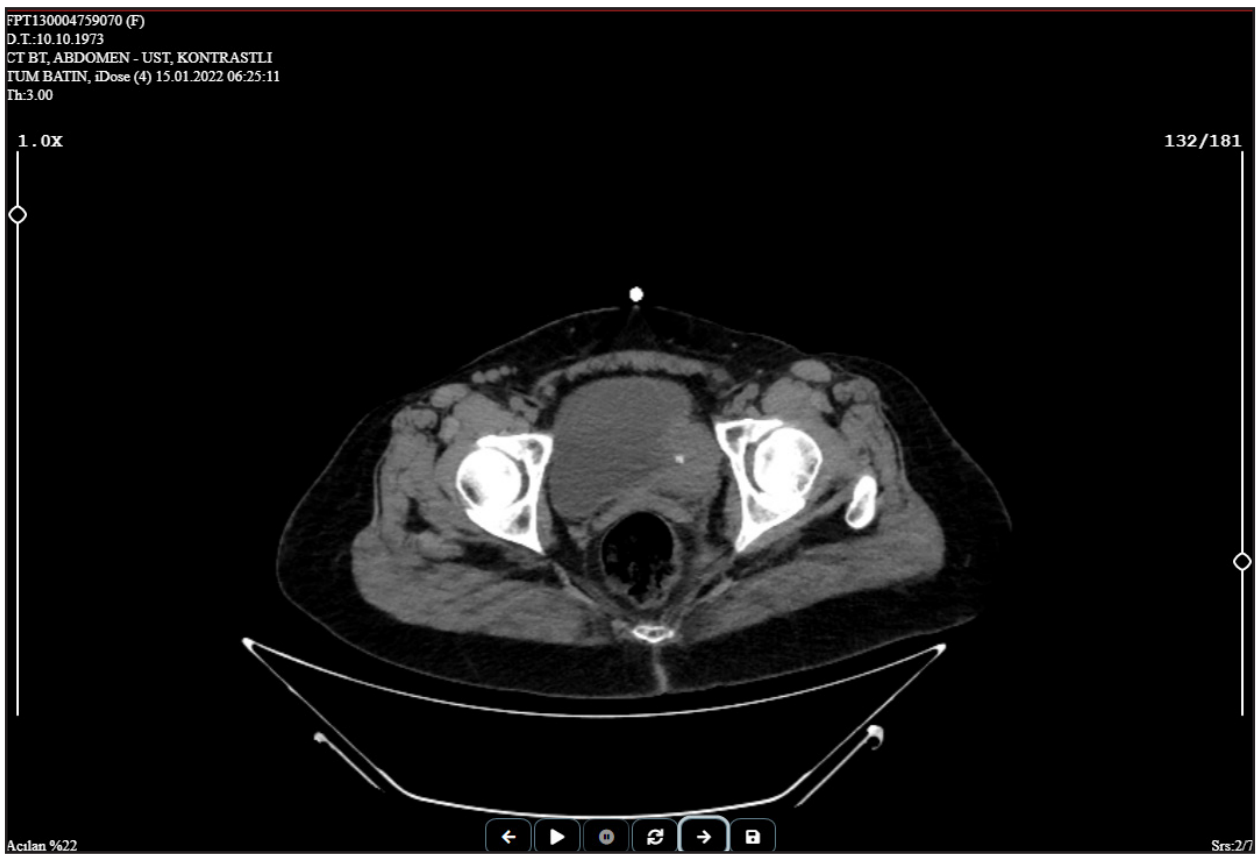

Figure 1. CT. This images showed 50 mm × 43 mm low-density mass on the left side of the bladder with clear edges, and Calcium density shadow was seen inside

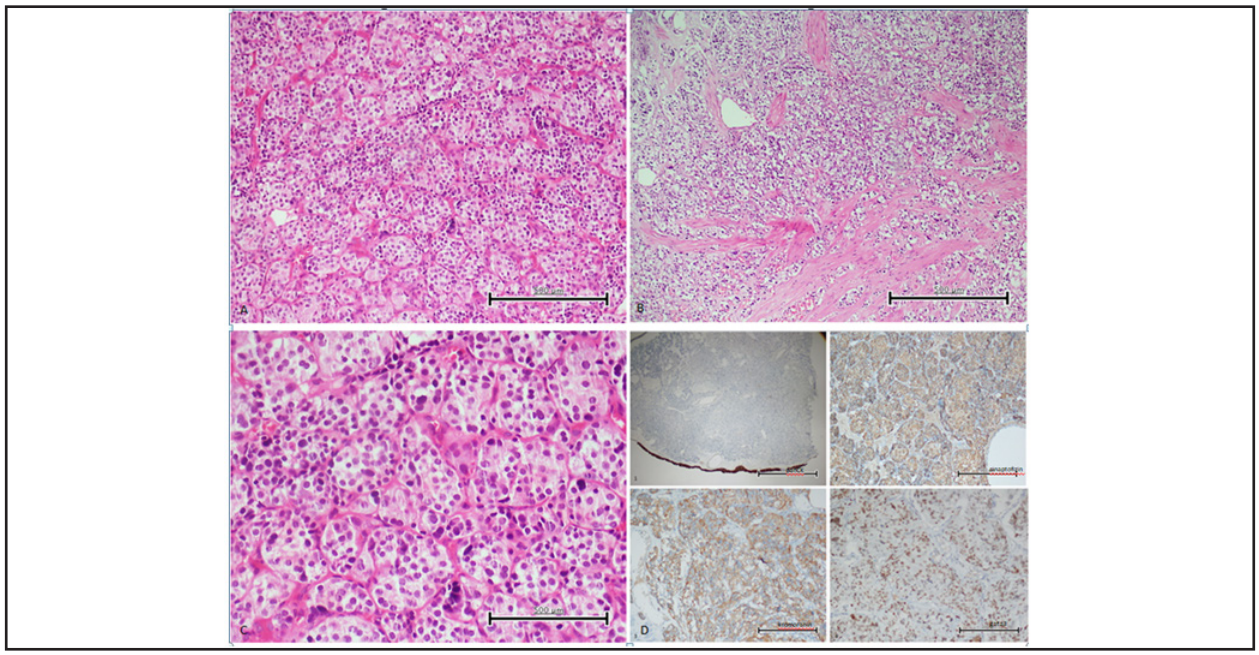

Figure 2. A-H&E 40x, "zelballen" islets. B-H&E, 40x, Tumor cells between detrusor muscle bundles. C-H&E, 400x, Tumor cells with thin chromatin and amphibolic cytoplasm D -1-4: 40x, panck, synaptophysin, chromogranin a, gata 3

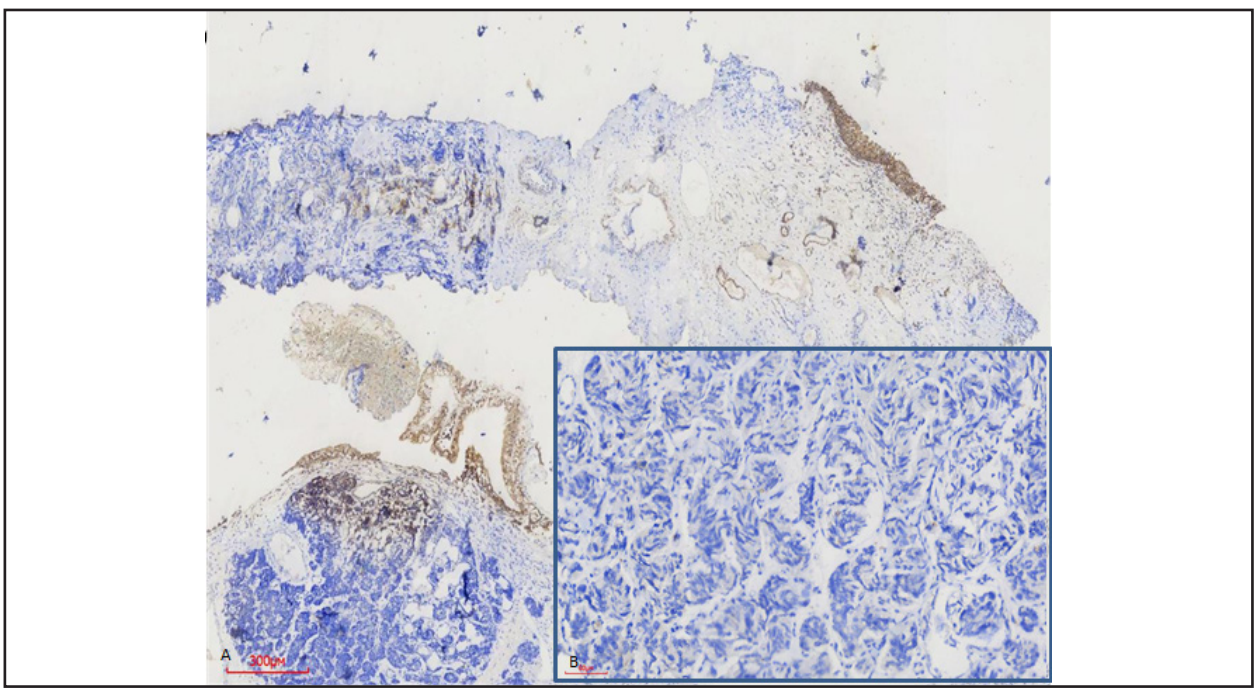

Figure 3. SDHA immunohistochemistry. A- x40 immunostaining for SDHA showing absent cytoplasmic labelling but retained granular cytoplasmic labelling in normal urothelial epitelium and endothelial cells (internal positive control) B- x400 The tumor negative for SDHA

DISCUSSION

The histopathologic differential diagnosis of bladder paraganglioma is quite broad; first of all, it is critical to exclude urothelial carcinoma.

In addition, cautery artifact, which is frequently encountered in cases of transurethral resection, may obscure the structural and cytologic features of paraganglioma.

Cases misdiagnosed as urothelial carcinoma have been reported in the literature because paraganglioma also shows features such as diffuse growth, necrosis, and infiltration of muscle bundles (7).

It may be confused with nested variant urothelial carcinoma because of their nest structures; therefore, zellballen structures are very helpful in diagnosis.

Tumor cells with large cytoplasm in paraganglioma may also be confused with urothelial carcinoma, clear cell variant (8, 9). Paraganglioma have muscularis propria invasion without a desmoplastic reaction. In urothelial carcinomas, a stromal reaction is expected to accompany muscle invasion. Sometimes pleomorphic or bizarre cells that are considered neuroendocrine atypia can be observed in paraganglioma. These cells can be confusing for urothelial carcinoma, but the absence of mitosis supports the diagnosis of paraganglioma.

The distinction between paraganglioma and urothelial carcinoma is extremely important because of the different treatments. Nowadays, for non-muscle invasive urothelial carcinomas, intravesical chemotherapy using with epirubicin, mitomycin C, adriamycin, and gemcitabine, intravesical bacillus Calmette-Guerin (BCG) immunotherapy, re-TUR-B, and cystoscopic follow-up are commonly performed, whereas for localized muscle-invasive urothelial carcinoma requires more aggressive treatment in form of radical cystectomy or chemotherapy and radiotherapy. TUR-B/partial cystectomy with complete removal of tumor is treatment of choice in paraganglioma, even if the muscles are infiltrated. Chemotherapy and radiotherapy may be required in rare metastatic paraganglioma on the other hand treatment modalities for urothelial carcinoma are dependent on the stage of the disease (2, 5).

The differential diagnosis includes metastatic renal cell carcinoma (RCC), prostate cancer, malignant melanoma, carcinoid or other neuroendocrine tumors and granular cell tumor (2, 7).

RCCs are usually morphologically distinct from paraganglioma, although they show an intertwined growth pattern, thin vascular septa and sometimes granular cytoplasm.

In men, prostate adenocarcinoma may exhibit a nested, island tumor appearance, especially in pattern 4. It may contain nuclei with a uniform, monotonous appearance. However, nuclei with prominent nucleoli are typical. Melanoma can mimic many tumors, including paragangliomas. Paragangliomas may be confused with S100 positivity and melanin pigment. Carcinoid and other neuroendocrine tumors typically have a zellballen-like insular pattern. It is differentiated from paraganglioma by nuclear morphologic features and Panck negativity.

Granular cell tumor may morphologically resemble paraganglioma. However, it is positive for S-100 and negative for neuroendocrine markers.

Our patient also had a history of thyroidectomy, whose diagnosis we could not reach. Metastatic disease of the bladder accounts for less than 1% of all bladder neoplasms. Follicular thyroid carcinoma metastases to the lung and rarely to the liver and kidneys. Lymph node metastasis is common in papillary carcinomas of the thyroid. Differentiation from thyroid carcinoma metastasis is not difficult with the help of morphologic features and immunohistochemistry (10).

The age and gender of the present case are consistent with the mean age and female predominant gender reported in the literature (2, 9). Extra-adrenal paragangliomas are most commonly found in the head and neck region and are nonfunctional. When located in the bladder, it is observed on the lateral wall and frequently in the trigone region with a mean diameter of 2 cm. In our case, the tumor was localized on the lateral wall, but the largest tumor diameter was 5 cm (5). Frequently reported symptoms are painless hematuria and flank pain, which were also observed

in our case (3). Histomorphologically, the zelballen pattern, which is most commonly observed, and the absence of atypical mitosis are compatible with the histomorphologic findings in our case (7).

In cases with paraganglioma, genetic examination is recommended for patients under the age of 50 years, with a family history, bilateral, multifocal and extra-adrenal localization, since the hereditary incidence in tumors is quite high (4). There was no family history in our patient. Because of his age and the location of the tumor in the bladder, he was referred to an external center for genetic examination.

CONCLUSION

Urinary bladder paraganglioma is a rare entity. Although it has characteristic histologic and immunohistochemical features, it is often mistakenly diagnosed as urothelial cancer because of its morphology overlapping with urothelial cancer and pathologists' failure to include paraganglioma in the differential diagnosis of bladder tumors.

In summary, treatment approaches for paraganglioma and urothelial carcinoma are very different from each other; therefore differential diagnoses should be made carefully.

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