Paraganglioma in The Urinary Bladder: A Pitfall in Histopathologic Diagnosis

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ABSTRACT

Paraganglioma of the urinary bladder is a rare neuroendocrine tumor which originates from the chromaffin tissue of the sympathetic nervous system. It only accounts for about 0.05% of all vesical tumors. Bladder paraganglioma may also present with non-specific symptoms which could easily lead to misdiagnosis. In this report, emphasis on the histomorphology and immunohistochemical profile of the tumor is stressed as the morphological findings could overlap with relatively more common urothelial neoplasms. Distinction from other tumors is of utter importance because of different therapeutic options. Here, we present a case of a 52 year-old, filipino, male, previously diagnosed with colonic tubulovillous adenoma, presenting with dysuria and hematuria who, after undergoing CT Stonogram revealed an incidental finding of a lobulated mass measuring 5.7 cm located at the anteroinferior portion of the urinary bladder wall.

Keywords: *Paraganglioma, pitfall, urinary bladder, diagnosis.*

INTRODUCTION

Paraganglioma of the bladder, also called an extra-adrenal pheochromocytoma, originates from the chromaffin tissues of the sympathetic nervous system located in the detrusor muscle of the urinary bladder.[1-3] The first case was reported by Zimmerman in 1953.[2] Of the 10% of the extra-adrenal paragangliomas', 10% are localized within the bladder which accounts for only 0.05 % of all bladder tumors.[1]

Being a rare entity, it has a propensity to be misdiagnosed because of 1) its frequent involvement of the muscularis propia[1,4-6] 2) its non-specific symptoms which also occur in other tumors[3-6] 3) its morphology and immunohistochemistry that can mimic other tumors[5,7], and 4) its rare occurrence in the bladder.[1,3-6]

CASE ILLUSTRATION

A 52-year-old, filipino man, presented with a 7-month history of intermittent dysuria and hematuria. He had no other irritative lower urinary tract symptoms. The patient had no history of headache, palpitations, and dizziness. His medical history consisted of a history of hypertension and colonic tubulovillous adenoma diagnosed last 2018. There was no significant family history of similar disease. Physical examination was unremarkable and vital signs were stable. A non-contrast axial 256-multislice CT stonogram was done which revealed an intravesical, slightly irregular to lobulated mildly hyperdense mass approximately measuring 4.7x4.4x5.7 cm. This is located at the anteroinferior portion of the urinary bladder wall, near the neck. Cystoscopy revealed a large, irregularly shaped mass located at the

left anterolateral wall of the bladder and adjacent to the bladder neck. Transurethral resection of the bladder tumor was subsequently done. His intra- and post-operative course remained uneventful. The specimen was then submitted to the Histopathology Department. Description of the gross specimen consisted of several cream-tan to brown-tan, irregular soft tissue fragments with an aggregate measurement of 2.0 x 2.0 x 0.7 cm. The entire specimen was submitted for processing.

Microscopic evaluation showed nests of oval to polygonal cells underlying an unremarkable urothelium. These cells are arranged in nested, zellballen pattern, separated by prominent fibrovascular stroma. These cells also have abundant granular, clear to amphophilic cytoplasm, uniform round to oval nuclei with regular nuclear contour. Mitosis was inconspicuous and no necrosis was seen. **(Figure 1 and Figure 2)**.

Histological differential diagnosis at this time were Urothelial Carcinoma, Colorectal Carcinoma, Malignant Melanoma, and Paraganglioma.

Immunohistochemistry showed tumor cells to be positive for Chromogranin, Synaptophysin, and GATA-3 **(Figure 3 to Figure 5)**.

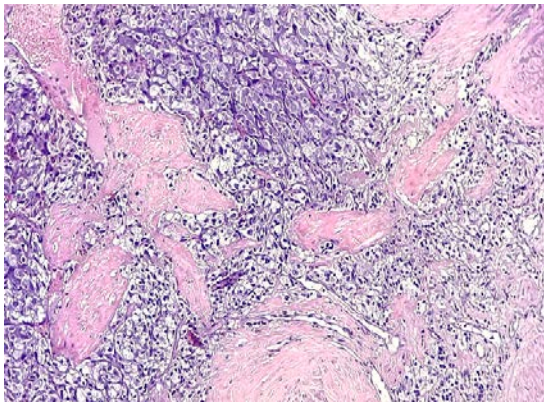

Figure 1. Low magnification of the urinary bladder paraganglioma.

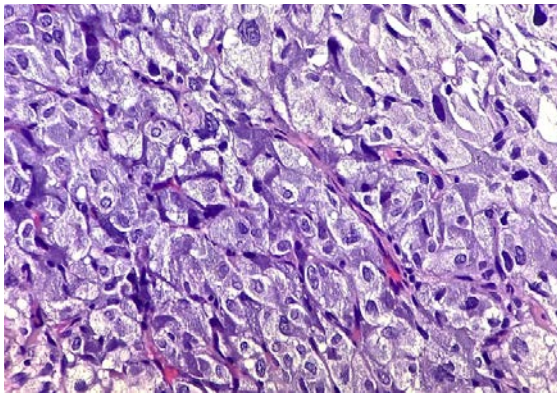

Figure 2. High magnification of the urinary bladder paraganglioma.

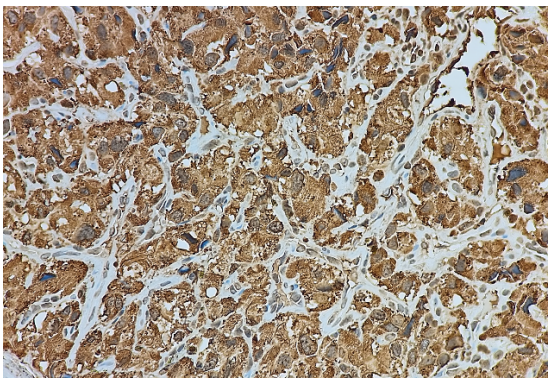

Figure 3. High magnification of positive cytoplasmic staining for Chromogranin.

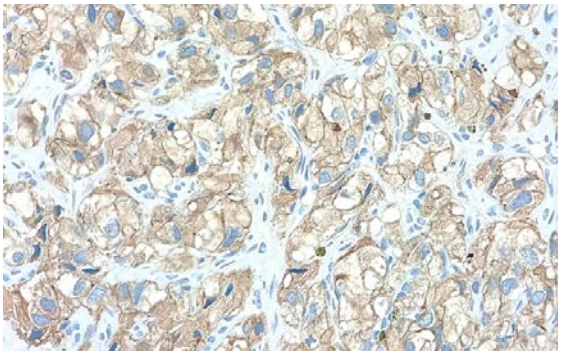

Figure 4. High magnification of positive cytoplasmic staining for Synaptophysin.

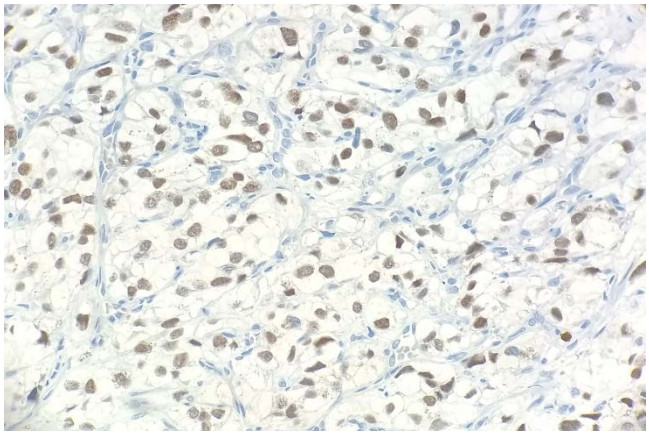

Figure 5. High magnification of positive nuclear staining for GATA-3.

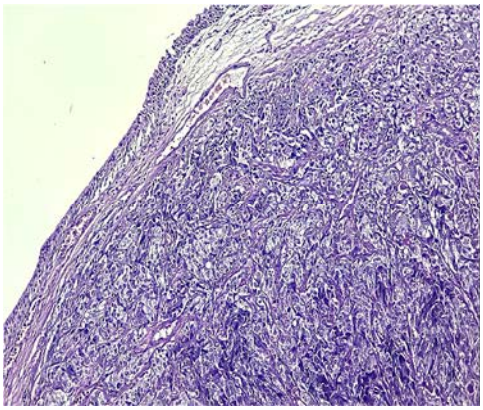

Figure 6. Low magnification of the Bladder Paraganglioma focally extending to the urothelium.

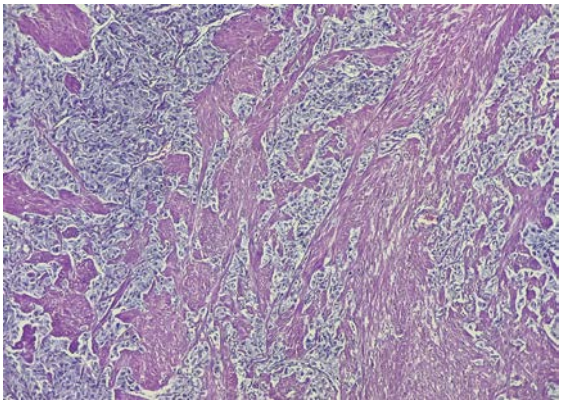

Figure 7. Low magnification of the Bladder Paraganglioma located within the muscularis propria.

The tumor cells are negative for CK, CK20, CDX2, Melan-A, Beta-catenin, and SATB2**.** Given the morphology of the tumor and the immunohistochemical profile, a diagnosis of Paraganglioma was rendered.

Two months after the initial procedure, the patient was admitted for a partial cystectomy. Consent and clearance were secured and on the 2nd hospital day, the patient underwent the planned procedure. Intraoperative finding revealed a 4.0 x 4.0 cm pedunculated tumor extruding from the left posterolateral bladder diverticulum. Specimen was then submitted to the Pathology Department for histopathologic processing. The patient's postoperative course was uneventful and he was then later discharged on the 6th hospital day.

Description of the gross specimen consisted of a tan brown to orange tan, pedunculated, firm tissue measuring 6.0 x 5.8 x 3.5 cm. Cut sections show a fairly circumscribed, pink tan, soft to solid mass measuring 5.5x3x2.7 cm. Representative sections were taken.

Microscopic evaluation showed cells showing the same histomorphology as those seen in the previous biopsy specimen. These tumor cells extend from the urothelium and eventually involve the muscularis propria (detrusor muscle). **(Figure 6 and Figure 7)**

The case was signed out as Paraganglioma with the Tumor involving the Muscularis Propria (detrusor muscle) and focally extending to the Urothelium.

DISCUSSION

About 98% of the paragangliomas are located in the abdomen, 90% of these are in the adrenal

medulla and 10% of them in extra-adrenal sites.[3,8]

Paragangliomas can occur in patients of any age, with a mean age at 43.3 years old.[1] Although more common in females[1,9], there are studies that show that paraganglioma can also occur in males. As shown by four studies where males are affected with ages ranging from 39 to 78-years-old, two of which are Japanese.[4,10-12] In a study done in Japan last 2020, it was found out that both males and females are equally affected. Out of 162 patients diagnosed with the tumor, 50% consisted of males.[11] Molecular studies of said tumor show frequent losses at 1p, 3q, and 22q and germline mutations in SDHA and SDHB genes.[1]

Paraganglioma occurs in any part of the bladder wall but has a predilection for the detrusor muscle with the most common locations being the dome and trigone of the bladder.[1] The tumor can be functional (catecholamine secreting) or non-functional.[1,13] Clinical symptoms are related to catecholamine release. These include hypertension, headache, blurred vision, intermittent gross hematuria, and hypertensive crisis during micturition.[1,4] Only a minority presented with catecholamine-associated symptoms accounting to about only 13% of the total cases.[4,5] While most of the cases presented with nonspecific symptoms such as painless hematuria or no symptoms at all.[4,5,15] Laboratory findings show elevated urine and serum catecholamine levels.[13]

Imaging findings are important for the diagnosis as it assesses the shape, size, and location of the tumor[14] which shows the bladder paraganglioma as a well-defined, solid, ovoid vascular mass located within the urinary bladder wall.[13] According to P. Humphrey, et al (2016), the tumor usually consists of a well circumscribed, exophytic lesion with an average size of 3.9 cm but tumor size can increase to up to of 9 cm.

On histomorphology, the majority of cases consist of the cells arranged in nests, called Zellballen pattern, while the remaining 20% are arranged in a diffuse pattern. They are separated by vascular network or fibrous septa.[1,15] These cells are large and polygonal with abundant clear, granular, amphophilic or acidophilic cytoplasm and uniform round to ovoid nuclei. Mitosis, focal hemorrhage, and necrosis are rare.[1,4,16] The tumor cells can be seen located within the muscle bundles of the muscularis propria (detrusor muscle) with absence of desmoplasia.[1,4,5] Paragangliomas can be confirmed with positive immunostaining for neuroendocrine markers such as chromogranin and synaptophysin[1,4,9], with a majority also staining for GATA3[1,7], and S100 in sustentacular cells.[1] They are negative for epithelial markers.[1,4,9]

Because of the frequent involvement of the muscularis propria and positive staining for GATA-3, a misdiagnosis of Urothelial Carcinoma can be given.[1,4,5,7] Records of fifteen patients diagnosed with paraganglioma of the urinary bladder were reviewed back in 2004. Twelve of which were transurethral resection specimens while the remaining three were partial cystectomies. Tumors showing nested, zellballen pattern consisted of 12 out of the 15 cases while diffuse growth pattern were seen in the remaining 3 cases. Ten cases showed the tumor nests located between the muscularis propria. Eleven of these cases were misdiagnosed as urothelial carcinoma and the remaining four were diagnosed as bladder tumor.[5] In our case, the senior author's previous experience as well as his paper on paragangliomas, helped in including is a differential diagnosis. As well as not readily diagnosing this as a urothelial neoplasm.

Urothelial Carcinoma is the most common malignant neoplasm of the urinary tract with higher pathologic staging indicating the presence of muscularis propria invasion.[1]Majority (67-90%) of the tumor cells express GATA3 and cytokeratin markers.[1] On histomorphology, urothelial carcinoma may exhibit a nesting pattern which could mimic the nesting, zellballen pattern of the Paraganglioma. However, cytologic atypia of urothelial carcinoma is usually more pronounced and there are no vascular networks surrounding the tumor cells. The tumor nests invading the muscularis propria should also exhibit a desmoplastic response.[5]

Malignant Melanoma is a neoplasm of melanocytic origin.[1] As of 2021, there are only a total of 40 cases of Malignant Melanoma of the bladder[17] reported whereas compared to Paraganglioma of the urinary bladder, wherein

there were already a total of 69 reported cases just from the year 2010 to 2021 alone.[18] Extracutaneous melanoma is rare and consists of only 4-5% of all diagnosed melanoma with primary malignant melanoma only accounting for less than 0.2% of all melanomas.[19,20] Classic microscopic feature consists of large epithelioid or spindle cells containing melanin pigments. Melanoma cells show positivity for S100, HMB45, and Melan A.[1] Based from the rarity of the cases as well as the histomorphology and immunohistochemical profile of the index case, we favor a diagnosis of a Paraganglioma rather than a Malignant Melanoma.

For metastatic tumors of the bladder, majority originates from the colorectum[1] with the genitourinary tract infiltrated by 3-10% of the total cases of advanced colorectal tumors.[21-24] Tumors that originate from this location expresses CK20, SATB2, and CDX2.[1,9,25] Due to the presence of APC or CTNNB1 mutation, the tumor also exhibits nuclear expression of β-Catenin.[9] Histomorphology and immunohistochemical findings of the index case does not support these findings. However, due to the patient's aforementioned history of colonic tubulovillous adenoma, a colorectal lesion was still ruled out via immunohistochemistry.

Surgical resection is the common treatment modality for bladder paraganglioma.[10,15,18] This includes: (1) Transurethral resection of the bladder tumor (TURBT) (2) Partial Cystectomy and (3) Total Cystectomy.[15,18] Transurethral resection of the bladder tumor (TURBT) is the treatment of choice for non-functional, non-invasive lesion measuring less than 3 cm in size while partial cystectomy is done when the tumors extend into the deep layers of the detrusor muscles. The last option consists of a total cystectomy if the lesion is too large that preservation of the bladder could not be considered or if there is metastasis to the lymph nodes. Long term follow up with annual measurement of catecholamine is recommended because of the increase chance of recurrence and metastasis.[10,15,18]

CONCLUSION

Although this tumor is rare, having its own histologic and immunohistochemical features should prompt the Pathologists to include it in their differential diagnosis. However, misidentification of the tumor still occurs because of its rare entity, as well as its histological features mimicking other more common urothelial neoplasms. Identification and accurate diagnosis necessitate complete knowledge of the morphological, histochemical, and molecular features of this tumor in order to better differentiate it from other neoplasms.

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We have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest.

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