

Paraganglioma Non-Functional of Urinary Bladder: A Rare Differential Diagnosis of Urothelial Carcinoma not to be misdiagnosed - Case Report

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Abstract

Paraganglioma are rare type of neuroendocrine tumors that arise from embryonic neural crest. Paraganglioma of adrenal medulla is known as Pheochromocytoma. Extra-adrenal localization is observed in 5-10% of all paragangliomas, which can extend from upper cervical region to pelvis related to autonomic nervous system in a functional, secreting catecholamines, or non-functional phenotypes. Bladder paraganglioma is outside the usual distribution of paraganglionic tissue accounting for <0.05% of all bladder tumors. Nonfunctional paraganglioma of the bladder (NPB) and urothelial carcinoma of the bladder (UCB) are subtypes of bladder tumors, but which are entirely different entities with distinct tissue origins and anatomical locations. However due to the similarities in their clinical features and cystoscopic features NPB is often misdiagnosed as UCB whose therapeutic approach and prognosis are completely different. We present a case of paraganglioma in a 45-year-old male presenting with haematuria. Clinical provisional diagnosis rendered based on cystoscopic findings and radiology was urothelial carcinoma; however, was confirmed to be a case of paraganglioma of bladder on histopathological and immunohistochemical evaluation. Cystoscopic biopsy is of high diagnostic value, which should be considered in the preoperative diagnosis of NPB.

Keywords: Paraganglioma • Urothelial • Carcinoma-bladder • Pathology • Surgery

Introduction

Paraganglioma are rare type of neuroendocrine tumor that arises from embryonic neural crest [1]. Paragangliomas are tumors originating from the neuroendocrine elements of the Para ganglia. The most common localization of paragangliomas is the adrenal medulla and they are usually pheochromocytomas. Extra-adrenal localization is observed in 5-10% of all paragangliomas [2]. The most common extra adrenal paragangliomas occur as carotid, orbit, nose, ear, mediastinum or duodenum bodies. Bladder paraganglioma is exceedingly infrequent originating from the autonomic Para ganglion tissues embedded in the muscular layer or the lamina propriety [3]. Instead of the epithelial layer. They are divided into functional, secreting catecholamines and nonfunctional phenotypes. The latter, nonfunctional paragangliomas of the bladder (NPBs), lack typical manifestations of catecholamine syndrome [4]. And account for approximately 38.7% of all paragangliomas of the urinary bladder [5]. NPBs frequently present with nonspecific painless hematuria or no symptom. Urothelial carcinomas of the bladder (UCBs) are the most common malignant bladder tumors. As opposed to NPBs, UCBs arise from the epithelial layer of the bladder wall, frequently presenting with painless hematuria or occasionally without any symptoms. Thus, symptomatically NPBs extremely mimic UCBs.

Although both NPB and UCB are subtypes of bladder tumors, they are independent entities with distinct tissue origins and anatomical locations. More importantly, they are distinct in surgical approaches, adjuvant therapies, follow up protocols, and expected prognoses. Due to the rarity and similar symptoms of NPB to UCB, it is frequently preoperatively [6] misdiagnosed as UCB, potentially leading to severe consequences. However, an identification of characteristic histopathology feature, which coupled with immunohistochemistry often, establishes the correct diagnosis.

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Case Report

A 45-year-old male, presented to the urology department of our university hospital with a complaint of intermittent hematuria for two months. There was no other significant history like fever, dysuria, abdominal pain, etc. No tabetic and medical/surgical history was insignificant. He was not known to be diabetic, hypertensive, hypothyroid, or hyperlipidemia. The patient had no history of headaches, palpitations, or dizziness associated with micturition or postural changes. There was no significant family history of similar disease. The rest of the hematological and biochemical tests were within normal range. No abnormalities were noted on physical exam. Both ultrasound examination and computed tomography (CT) scan demonstrated a mass on the dome of the bladder, measuring 4.5 × 3 x3 cm our patient underwent cystoscopy examination showed a solitary sub mucosal/ intramural and non-papillary broad-base tumor surrounded by smooth bladder mucosa arising from the dome of the urinary bladder (Figure 1). No sign of any metastatic disease was found on ultrasound examination or CT scan of other abdominal organ systems. Doppler scan showed arterial vascular lesion. A possibility of soft tissue/mesenchyme lesion was considered along with a possibility of other variant of urothelial carcinoma. On the basis of the first diagnosis of bladder tumor a transurethral resection of bladder tumor (TURBT) was done and the procedure was uneventful with no hypertension or occurrence of massive bleeding. (Figure 2) The surgical specimen was sent to us for histopathological examination. (Figure 2)The specimen was in multiple fragmented bits, gray tan in color. Microscopic evaluation showed a tumor disposed in nesting pattern (Zell Baleen Pattern), separated by thin walled blood vessels. Individual cells were polygonal, with finely granular eosinophilia to basophilic cytoplasm, uniform round to oval nuclei, regular nuclear outline, evenly dispersed granular chromatin, and inconspicuous nucleoli (Figure 3). Focal clear cell changes were seen. The tumor was seen to invade the muscular is prairie/detrusor muscle. Significant mitotic activity is not seen. High cellularity and diffuse growth pattern is not seen. Necrosis is not seen. No intraepithelial neoplastic (CIS) or papillary lesion was seen. At places, nests of bland urothelium (von Brunn nest). Phenotyping immunohistochemistry showed tumor cells to be positive for synaptophysin, chromogranin as neuroendocrine markers, and negative for pan cytokeratin AE1/AE3 allows eliminating a carcinoma of bladder (Figure 4). Ki-67 staining revealed a proliferation index of <2%, and as a radiological extension assessment is negative, the diagnosis of a benign paraganglioma is retained. Succinate deshydrogenase (SDHB, SDHD or SDHC) immunohistochemistry was suggested as a predictive

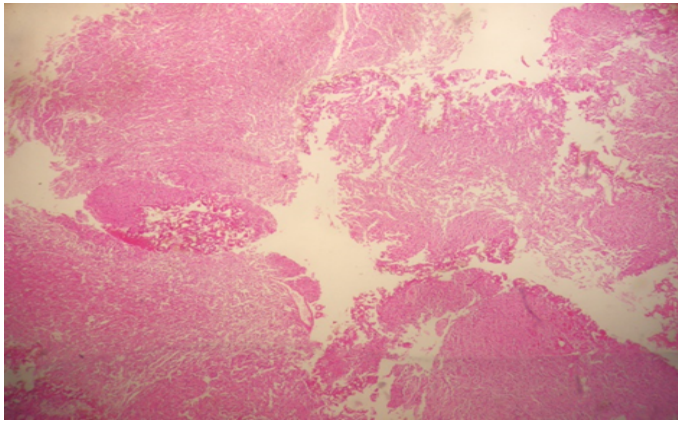


Figure 1. CT showing a nodular mass with hyper intensive enhancement on dome of the bladder

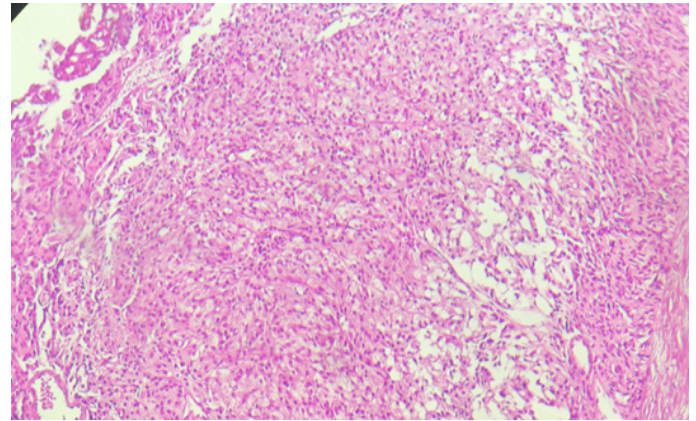


Figure 2. Cystoscopy of submucosal/intramural NGB with broad base tumor.

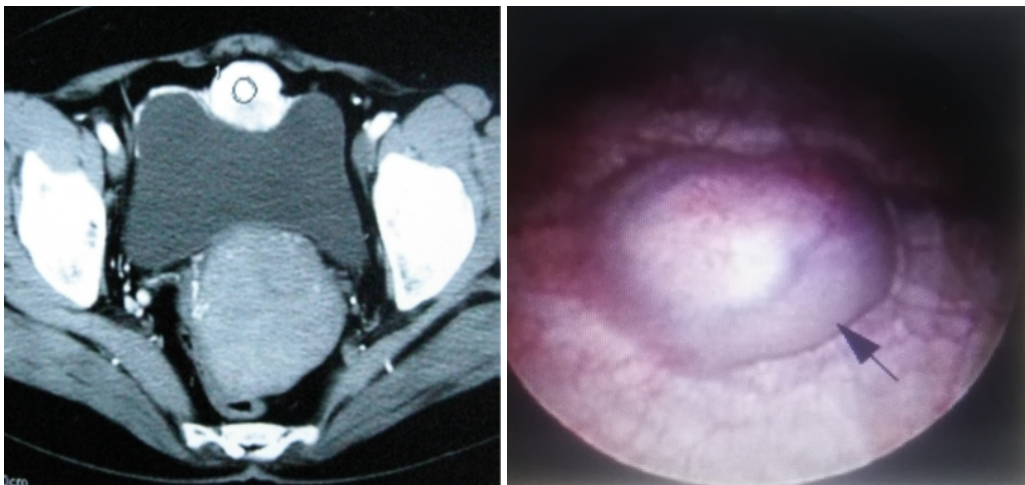


Figure 3. Histological examination (a) H&E staining (40x) (b) H&E staining (200x) showing zellablen pattern and large nuclei with dark color.

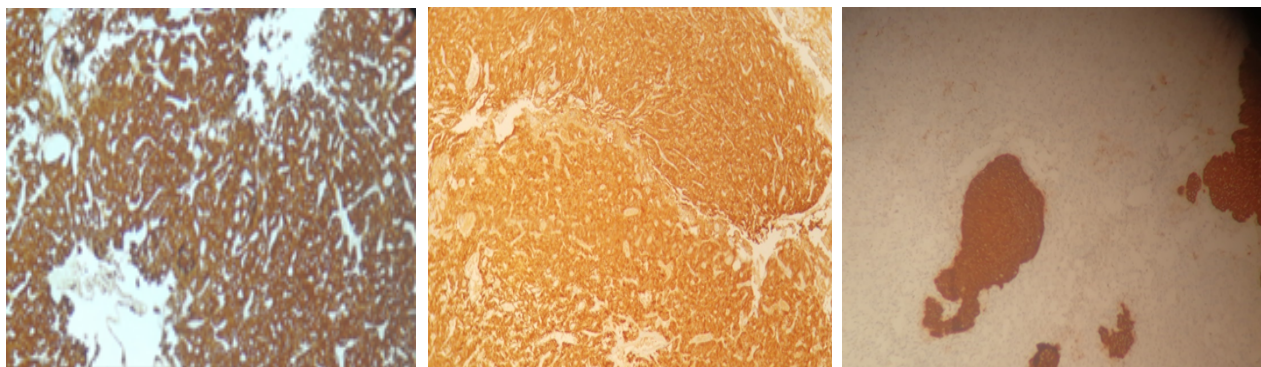


Figure 4. Immunohistochemical staining shows positive expression of Chromogranin (a), and Synaptophysin (b), negative expression of AE1/AE3 with positive bland urothelium as internal control (c).

marker of paraganglioma syndrome, but the patient couldn't afford it. As the possibility of paraganglioma was not considered on a prior basis, plasma and urinary Metanephrine/ normetanephrine have not been done. The patient was in follow-up with regular cystoscopy, urinary and plasma metanephrines/ normetanephrine estimation for 8 months without any recurrence.

Discussion

Paragangliomas (PG) are extra-adrenal forms of pheochromocytomas arising from embryonic nests of chromaffin cells from the sympathetic plexus. In the urinary bladder, they arise from the chromaffin cells embedded in the muscular layer or the lamina prairie instead of the mucosal layer [7]. Ten percent of the PGs occur in the extra-adrenal site and the urinary bladder is a rare site of

PG accounting for 10% of all extra adrenal PGs. Also, PG in the bladder is extremely rare bladder tumor accounting for less than 0.05% of all bladder tumors and was first described by Zimmerman in 1953 [8, 9].

As being a rare entity, it has propensity to be misdiagnosed as urothelial carcinoma; however, characteristic histomorphological and immunohistochemical features aid in the correct diagnosis. The reasons behind its misdiagnosis being frequent involvement of the muscularis propriety (detrusor muscle) layer morphology mimics urothelial carcinoma particularly in transurethral resection specimens, especially, if there are artifactual changes induced by surgical cautery or by a defective fixing ; failure to include it in histological differential diagnosis while evaluating a bladder tumor; and only a minority of patient present with catecholamine associated symptoms that might prompt consideration of the diagnosis [10].

It is very critical to distinguish paraganglioma from urothelial carcinoma because of potential differences in therapy as well as prognosis. Treatment modalities for urothelial carcinoma are dependent on the stage of the disease. For non-muscle invasive carcinomas intravesical bacillus Calmette-Guerin (BCG), surveillance and TURBT are commonly done whereas for muscle-invasive urothelial carcinoma requires aggressive treatment in form of radical cystectomy. On the other hand, to avoid any recurrence, a partial cystectomy with complete removal of tumor is treatment of choice in PG, even if the muscles are invasive. Chemotherapy and radiotherapy may be required in rare metastatic settings [11, 12].

Clinical features suggesting the occurrence of PG are related to catecholamine secretion such as episodic or sustained hypertension, hypertensive crisis during micturition, headache, blurred vision, and also hematuria. Eighty-three percent of the paragangliomas in the bladder are hormonally active [7]. However, characteristic clinical features are present in minority of cases.

Intraoperative hypertensive crisis reported by Menno et al. may be catastrophic; hence urologists should pay attention to the differential diagnosis in patients with suggestive atypical cystoscopic finding for PGB [12]. Preoperative catecholamine level estimation may be helpful in such situations.

Our case presented with hematuria and no feature of catecholamine release was documented. Also, follow up in our case by radiology (CT) was done, which showed no tumor mass elsewhere in the body.

Age distribution of PG is one to two decades younger than the average age of urothelial carcinoma, median age being 43 years and 45 years. It can affect any part of the urinary bladder wall with predilection to the dome and trigon of the bladder, and in almost half the cases, muscularis propria is involved [8,13]. However, the index case was in an elderly male.

Histologically characteristic Zellballen pattern with nest delineated by thin fibrovascular septa should be present at least focally for diagnosis of PG. If not found in a first go, a diligent search is advocated. Tumor cells in PG are large epithelioid with abundant eosinophilia/amphophilic and granular cytoplasm, regular monomorphic nuclei. A rare bizarre nuclear atypia is acceptable however. Muscle involvement in PG is characterized by entrapped tumor cells within the muscle bundles without desmoplasia, the presence of later favor invasive urothelial carcinoma [10]. Rare mitosis, necrosis, and vascular invasion can be seen [8].

The main differential considered is urothelial carcinoma, a nested variant. The nested variant of urothelial carcinoma is characterized by confluent small nests and abortive tubular growth pattern. Individual tumor cells are mildly atypical with irregular infiltrating tumor-stromal interface and the epithelial layer of urothelial mucosa is often the seat of CIS. This variant is prognostically aggressive. Immunohistochemistry is useful in differentiating, urothelial carcinoma express cytokeratin and other epithelial markers while PG express neuroendocrine markers, e.g. synaptophysin, chromogranin [8-10]. Other differentials diagnosis considered are metastatic renal cell carcinoma, prostatic carcinoma involving bladder, metastatic melanoma, carcinoid, and granular cell tumor [10, 14]. A detailed discussion of differentials is out of scope of this report. However, characteristic histomorphology coupled with immunohistochemical profile helps in establishing the correct diagnosis.

Genetically, PG is heterogeneous with frequent loss of 1p, 3q, and 22q [8]. Thirty percent of paragangliomas are estimated to be familiar with germline mutations associated with von-Hippel Landau (VHL) syndrome, multiple endocrine neoplastic, type 2 (MEN2) syndrome, neurofibromatosis 1 (NF1) syndrome, and familial paraganglioma-pheochromocytoma syndromes (SDH gene). Genetic study for these germline mutations along with IHC for SDHB should ideally be undertaken in these tumors. Extra-adrenal paragangliomas with SDH mutation are more likely to have malignant potential [12]. No genetic syndromic study was done in our case; however, the patient did not have any family history of paraganglioma syndrome complex.

Conclusion

Urinary bladder paraganglioma is a rare entity. It is mostly unsuspected preoperatively and may be misdiagnosed as UCB when characteristic

symptoms are absent. Histopathological and immunohistochemical evaluation on cystoscopy biopsy is of high diagnostic value which should be considered in the preoperative diagnosis of NPB to have a proper diagnosis and treatment. A proper family screening and search for other neoplastic association to be followed.

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