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Case Report

Paraganglioma of urinary bladder – A rare case report

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A B S T R A C T

Background: Extra-adrenal chromaffin related tumors are called Paraganglioma. These tumors constitute 18% of extra-adrenal pheochromocytomas and are exceptionally rare in the bladder accounting for $< 0.06\%$ of bladder tumors.

Case Report: A 45-year-old female came with history of painless hematuria of 3 days duration. On MRI scan, she was found to have a bladder tumor arising from the posterior wall. Transurethral resection of the bladder tumor (TUR-BT) was done. During the procedure, the patient had a sudden increase in blood pressure with acute left ventricular failure and pulmonary edema. Multiple grey brown TUR-BT specimen bits on microscopy showed tumor cells in "Zellballen" pattern. These cells were round to polygonal with abundant granular cytoplasm, round, regular nuclei with stippled chromatin. Mitotic figures were seen occasionally. Immunohistochemistry for Chromogranin A showed strong positivity confirming the diagnosis to be paraganglioma of the bladder. Follow-up cystoscopy of the patient didn't show any evidence of the tumor, also her urinary and plasma vanillylmandelic acid (VMA) levels were within normal range post-operatively.

Conclusion: Paraganglioma of the bladder is extremely rare. Our case presenting with only painless gross hematuria was a close mimicker of urothelial carcinoma. It has a benign coarse but has a very high recurrence rate. It is essential to differentiate it from its histological differentials for proper management and follow-up.

1. Introduction

Paragangliomas are chromaffin cell related tumors arising from sympathetic paraganglia accounting for 10% of the cases of extra-adrenal pheochromocytoma. The bladder is one of the rare sites for paraganglioma, constitutes to less than 0.06% of the bladder tumors.[1–4]

A 45 years old female presented to the surgeon with painless hematuria of 3 days duration with no history of hypertensive episodes. On MRI, she was found to have a tumor of size 3x2x2cm arising from the posterior wall of the bladder and projecting into bladder cavity. Transurethral Resection of Bladder Tumor (TUR-BT) was done. During surgery, there was profuse bleeding from the tumor site and sharp increase in her blood pressure. Also, the patient developed acute left ventricular failure and pulmonary edema intraoperatively requiring intensive care support for 3 days post-operatively.

Grossly, multiple grey brown bits altogether measuring 3x2x2cms was received. Microscopically, the tumor cells were arranged in a nested pattern characteristically known as "Zellballen" pattern, separated by fibrovascular septa. These cells were round to polygonal with abundant granular cytoplasm and round, regular nuclei with stippled chromatin. Focal infiltration into the underlying detrusor muscle was noted. Immunohistochemical study revealed strong positive staining for Chromogranin A confirming the diagnosis of urinary bladder paraganglioma.

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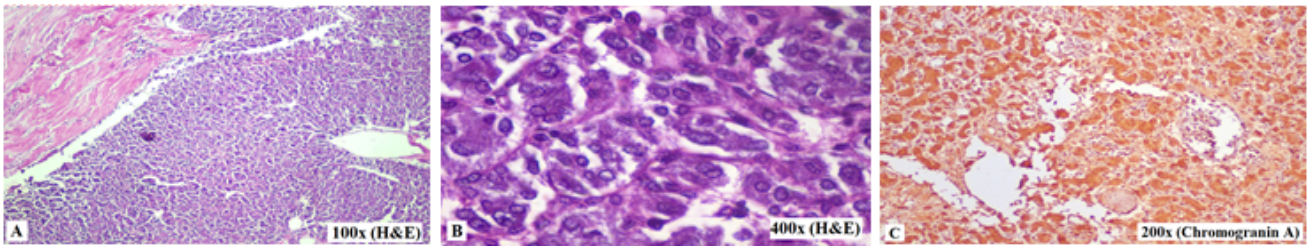

Fig. 1: A). Photomicrograph of paraganglioma in TURBT specimen showing well encapsulated lesion composed of tumor cells arranged in "Zellbalen" pattern with delicate blood vessels in between the tumor nests. (100x H&E). B). High power image showing tumor cells having abundant amount of eosinophilic granular cytoplasm with round regular nuclei and stippled chromatin. (400x H&E). C). Tumor cells showing strong positivity for Chromogranin A IHC marker. (200x).

2. Discussion

Paragangliomas are extra-adrenal catecholamine secreting tumors. In 1953, Zimmerman et al. reported the first case of bladder paraganglioma.[1] It is one of the rare tumors which presents with varied clinical features and usually mimics most of the other medical conditions associated with increased catecholamines.

Majority of paragangliomas are sporadic in origin. Only a few are genetic, associated with various syndromes such as Multiple Endocrine Neoplasia type 2A and type 2B (MEN2A, MEN2B), Von Hipple-Lindau's (VHL) syndrome, Neurofibromatosis Type 1, paraganglioma syndromes associated with germ line mutation in SDH gene subunits B, C and D. Carriers of SDHB mutations are known for poorer prognosis because of increased risk of recurrence and metastatic potential. Therefore, patients with multifocal paragangliomas and a family history of paraganglioma should be evaluated by genetic testing.[5]

They are more common in women with majority occurring in second to fourth decade. The common sites of paraganglioma are along the parasympathetic plexus of head and neck which includes carotid body, jugulotympanic nerve, Vagus nerve and larynx, sympathetic chain of thoracoabdominal segment which comprise reteroperitoneum, thoracic paravertebral region, periadrenal, perirenal, Organ of Zukerlandl, abdominal aorta, heart and genitourinary system. In the genitourinary tract, the most common site is urinary bladder (79.2%), followed by urethra (12.7%), pelvis (4.9%) and ureter (3.2%). In the bladder, trigone and posterior wall are stated as the most common sites.[6]

Most of the bladder paraganglioma are solitary and are present submucosally in the dome or trigone of the bladder. They are further classified into functional and non-functional. Functional paraganglioma are characterized by the synthesis and release of catecholamines into circulation. As a result, patients present with hematuria, paroxysms of hypertension, syncopal attacks, tachycardia and palpitations which are aggravated by micturition, defecation, sexual activity, ejaculation and bladder instrumentation. Nonfunctional paragangliomas are asymptomatic or presents with just painless hematuria.[6,7]

Biochemical analysis of plasma and urine shows elevated VMA, epinephrine, norepinephrine and metanephrine levels. Twenty-four-hour urine and serum sample should be drawn during attack to avoid false negative results.[8] Assessment of plasma and urinary levels of catecholamines are essential even if the patients are asymptomatic so that patients can be treated with anti-adrenergics pre-operatively to prevent adverse intra-operative complications.

Radiological investigations which are helpful in the pre-operative diagnosis of paraganglioma are cystoscopy, computed tomography (CT) scan, magnetic resonance imaging (MRI) and MIBG (I-131 metaiodobenzylguanidine) scintigraphy scan. However, cystoscopy, CT and MRI imaging studies have poorer sensitivity and specificity compared to MIBG scintigraphy scan in the diagnosis of bladder paraganglioma. However, scintigraphy is unhelpful in the diagnosis of nonfunctional paraganglioma.[6]

Surgery is the mainstay of the treatment. If diagnosed preoperatively, partial cystectomy is preferred over trans-urethral resection as the majority of these tumors extend in to the deep layers of the detrusor muscle.[9–11] Total cystectomy should be done for large lesions when bladder preservation is not possible or in the presence of distant metastasis.[9–11] Patients should be treated pre-operatively with anti-adrenergic drugs in order to prevent intra-operative catecholamine related complications as occurred in our case. Bladder paraganglioma is chemo-resistant and radioresistant tumor, though radiation and chemotherapy, either in the neoadjuvant or adjuvant setting, has been used in a few cases.[12,13]

Histologically, these tumors are poorly circumscribed and the cells will be arranged in a characteristic nested pattern called Zellbalen pattern and diffuse pattern. These cells have eosinophilic granular cytoplasm with round, regular nuclei with stippled chromatin. However, there are no histologic criteria to differentiate between benign and malignant tumor. Malignancy is considered only when there is local invasion or distant spread of the tumor.[14]

Bladder paraganglioma resemble many tumors both on gross and histologically. The most common is the nested variant of urothelial carcinoma. The cells in this tumor will be seen infiltrating into underlying muscular fibers and is stated as an aggressive carcinoma. These two can be differentiated by immunohistochemical studies. Urothelial carcinomas show strong positivity to cytokeratin 7 and 20 and other epithelial markers. Whereas, paraganglioma is positive for neuroendocrine markers. The other differential diagnosis includes melanoma, metastatic renal cell carcinoma, granular cell tumor, carcinoid tumor, prostatic carcinoma in males. The mere presence of melanin pigment does not rule out paraganglioma, as a pigmented variant of it can have melanin pigment in the cytoplasm of tumor cells. Hence immunohistochemistry again plays an important role in differentiating melanoma from paraganglioma. Likewise, in prostatic carcinoma, elevated PSA levels, negative for CK7, CK20 and positive for AMACR markers will contribute when the morphology is confusing. Carcinoid tumor mimics paraganglioma morphologically and immunohistochemically by showing positive to neuroendocrine markers. In addition, carcinoid tumors also show positive to cytokeratin AE1/AE3, CAM5.2 and CK18.[5]

The prognosis of bladder paraganglioma is moderate. As it is known for its recurrence, patients should be followed-up closely with repeated cystoscopic, MIBG scintigraphy scan, urine and plasma VMA levels. The diagnosis is crucial when it is asymptomatic and when histologically resembles common tumors like urothelial carcinomas. Although, immunohistochemistry is useful in ruling out the mimickers of paraganglioma, the identification of salient features like "Zellballen" pattern and cell morphology should arouse the thought of such rare tumors in the bladder. Our case in a middle-aged female presented with only painless hematuria was suspected to be a urothelial carcinoma clinically, turned out to be a case of Paraganglioma on thorough histological and immunohistochemical evaluation.

3. Conclusion

Paragangliomas of the bladder are rare tumors and are commonly mistaken for urothelial carcinomas. Hence a thorough preoperative evaluation including urinary vanillyn mandelleic acid (VMA) should be done whenever there is clinical or radiological suspicion. These tumors are known for their recurrence. Also, the malignancy is only determined by the metastasis of the tumor. So, I-23-metaiodobenzylguanidine (MIBG) scintigraphy scan or at least urinary and serum levels of VMA should be advised to look out for recurrence and metastasis on every follow-up.
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5. Conflict of Interest

None.

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