

A rare case of malignant paraganglioma of urinary bladder

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Abstract

Paraganglioma are neuroendocrine tumors arising from extra adrenal sympathetic and Para-sympathetic nervous system,¹ either from the chromaffin positive paraganglion tissue or the chromaffin negative glomus cells² derived from the embryonic neural crest. Paraganglioma of urinary bladder is rare, accounting for approx. 0.06% of all bladder tumours.³ The majority of these tumors are benign but can occasionally show malignant behaviour.⁴ The only absolute criterion for malignancy is the presence of metastasis at sites where chromaffin tissue is not usually found. We report on a patient with a paraganglioma of urinary bladder. Although patient presented with asymptomatic hematuria and had a blood pressure of, these were appreciated after histological examination of total radical cystectomy specimen had elucidated the correct diagnosis.

Keywords: Paraganglioma, Urinary bladder, Neuroendocrine tumour.

Introduction

Paraganglioma are neuroendocrine tumors arising from extra adrenal sympathetic and Para-sympathetic nervous system,¹ either from the chromaffin positive paraganglion tissue or the chromaffin negative glomus cells² derived from the embryonic neural crest. Paraganglioma of urinary bladder is rare, accounting for approx. 0.06% of all bladder tumours.³ The majority of these tumors are benign but can occasionally show malignant behaviour.⁴ The only absolute criterion for malignancy is the presence of metastasis at sites where chromaffin tissue is not usually present. Although all paraganglioma contain neuro secretory granules, a few secrete clinically significant levels of catecholamine (functional paraganglioma)⁵ and cause symptoms of sympathetic surge including hypertension, anxiety, headache, diaphoresis and palpitation. Many paraganglioma are sporadic, but a few cases of familial disease have been reported.⁶

Case Report

A 45 year female presented with complain of asymptomatic hematuria. Patient had blood pressure of 160/100mmHg. Patient did not have complains like palpitations, sweating or headache. Ultra sonography of abdomen and pelvis showed large, irregular solid growth on left lateral wall. On CT scan, exophytic polypoidal masses measuring 8.5x3.5 cm² involving anterior and left lateral wall of urinary bladder suggested possibility of neoplastic lesion. Patient underwent for cystectomy of bladder tumor. During surgery, Intra operative imprint preparations of pelvic lymphnodes surrounding bladder showed evidence of metastasis from carcinoma. Therefore, total radical cystectomy had been performed with removal of surrounding pelvic lymphnodes and sent for histopathological examination.

We received whole urinary bladder specimen measuring approx. 11.5x8x5 cm³ in size. Outer surface

was irregular with polypoidal growth identified involving anterior and lateral wall of bladder which was 2 cm away from posterior wall.

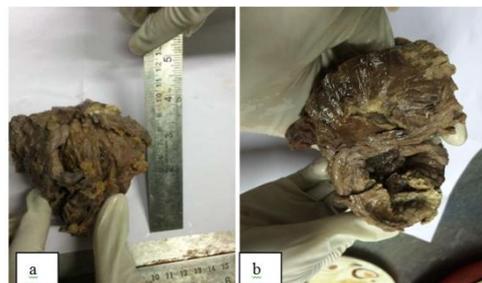


Fig. 1a,b: Gross view of urinary bladder 1

Histological examination of specimen showed tumor cells were arranged in nested pattern separated by delicate fibrovascular stroma. Tumor cells were round to oval in appearance with uniform vesicular nuclei at places showing salt and paper chromatin having prominent nucleoli at places with moderate amount of eosinophilic granular cytoplasm. There was invasion of muscle layer by tumor. Ureter was uninvolved by tumor. All of the pelvic lymph nodes were involved by tumor.

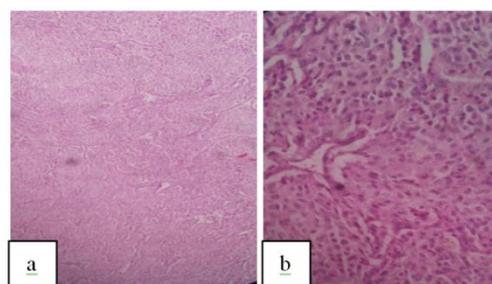


Fig. 2a: 10 X view of paraganglioma, (b). 40X view of paraganglioma

From the morphology and histology, main two differential diagnosis were: (1) Nested variant of urothelial carcinoma and (2) Paraganglioma. As growth was not involving overlying urothelium, diagnosis of paraganglioma of bladder was more in favoured. Immunohistochemistry was performed for confirmation of diagnosis. Tumor cells were immunonegative for CK-7 and CK-20. Tumor cells showed immunoreactivity for synaptophysin, chromogranin. S-100 focally highlighted elongated sustentacular cells surrounding the tumor nests.

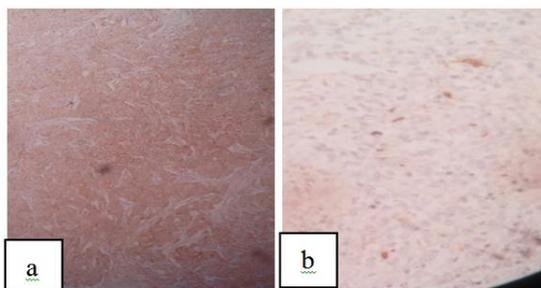


Fig. 3a: Synaptophysin positivity (b). S-100 positive sustentacular cells

Thus, by collective evidence from morphology, histology and immunohistochemical study, diagnosis of paraganglioma was confirmed. As excised pelvic lymph nodes showed invasion by tumor, diagnosis of Malignant Paraganglioma was concluded.

Discussion

In 1953 Zimmerman et al. reported the first case of urinary bladder paraganglioma.⁷ Bladder paragangliomas are rare and represent 6 % of all paragangliomas and less than 1 % of all bladder tumors.^{8,9} Malignancy is present in approx. 10% of pheochromocytomas and 5-20% of paraganglioma.¹⁰ Although definitions of malignancy vary, it is usually defined as the presence of distant metastases, as even tumors that locally invade adjacent organs may maintain an indolent course. Malignant tumors do not differ histologically or genetically from benign tumors, however, they tend to be larger and secrete more dopamine than benign lesion.¹¹⁻¹² Five year survival rates of patients with malignant pheochromocytoma are between 36-60%.¹³ Paraganglioma occur more frequently in women than in men mainly in second and third decade.

There are 2 types of paraganglioma: Sympathetic and parasympathetic. Sympathetic paraganglioma arise from sympathetic paraganglia that lie along paravertabral and para aortic axis in close relation to sympathetic trunk extending from near the superior cervical ganglion high in neck to abdomen and pelvis. There include adrenal medulla and organ of zuckercandle. Small numbers of paraganglioma originate in tiny paraganglia lying in connective tissue

adjacent to pelvic organs. Parasympathetic paraganglioma are found in head and neck region close to vascular structures and branches of 9th and 10th nerve which includes carotid body, intravagal and jugulo tympanic tumors.¹⁴

Contraction of bladder muscularis and changes in bladder pressure during micturation lead to systemic release of catecholamine and eventually to intermittent hypertension during or after micturation.¹⁵ Classic triad of episodic hypertension, persistent hematuria and postmicturition syncope is virtually diagnostic but seen only in functional tumor i.e secreting catecholamines. Furthermore headache, palpitation, diaphoresis, dysuria, anxiety and recurrent cystitis may occur. Non functional tumors can be asymptomatic. Painless hematuria may be the one persistent complain in these cases. So that they can be easily missed out.

Diagnostic work up includes biochemical study on 24-hour urine and serum concentrations of VMA, epinephrine, norepinephrine and metanephrine; specimens must be drawn during attacks to avoid false negatives. Other diagnostic works up include cystoscopy, abdominal sonography, CT scan and I¹³¹-MIBG scan, which is the most usefoll tool in the diagnosis of extra adrenal tumors arising from the paraganglion system or in metastatic lesions.

Grossly these tumors are well circumscribed nodules or nodular aggregates that can be found anywhere in bladder wall. On microscopy, tumor cells are arranged in zellballen¹⁶ pattern and are surrounded by fibrous network rich in blood vessels. Pleomorphism, mitotic figures and bizzare nuclear forms (which do not necessarily reflect a higher grade of malignancy) may also be seen. Moreover, tumors that contain a large number of aneuploid or tetraploid cells are more likely to recur.¹⁷⁻¹⁸ On immunohistochemistry chief cells of tumor are positive for neuroendocrine markers such as chromogranin and synaptophysin. Sustentacular cells are positive for S-100 but negative for cytokeratins including CK-7 and CK-20. This characteristic differentiates paraganglioma from urothelial carcinoma and carcinoids which are positive for cytokeratins and melanoma which are positive for Melan-A and HMB-45.

The main differential diagnosis for paraganglioma of urinary bladder are granular cell tumor, nested variant of urothelial carcinoma, metastatic large cell neuroendocrine carcinoma and malignant melanoma. Histologically, granular cell tumor is characterized by nests of round to polygonal cells separated by bundles of mature collagen. The lack of zellballen growth pattern and fine vascular stroma, absence of sustentacular staining pattern for S-100 and negative immunostaining for chromogranin readily distinguish granular cell tumor from paraganglioma. The nested variant of urothelial carcinoma is characterized by infiltrative growth of deceptively benign nests and/or tubules of urothelial cells. These urothelial tumors are

likely to be associated with carcinoma in situ or non invasive papillary urothelial carcinoma whereas the urothelium overlying paraganglioma is normal, reactive or ulcerated. It is distinguished from paraganglioma by lack of fine vascular network and the negative immunostaining for S-100 and chromogranin. It stains positively with CK-7 nad CK-20. Distinction between these two is critical because of different therapeutic options. Immunohistochemical studies is useful in differential diagnosis of large cell neuroendocrine carcinoma as it also stains positively with neuroendocrine markers but stain negatively with S-100. Awareness of these uncommon tumor is critical to avoid misinterpretation.

The most effective management for paraganglioma is surgical resection either by transurethral resection or partial or total cystectomy. The perioperative treatment and preparation is important particularly for the patients presenting with classical symptoms of paraganglioma like paroxysmal hypertension. It is necessary to stabilize hypertension prior to surgery by using alpha blockers or calcium channel blockers to inhibit release of catecholamine and expand the blood volume. With the advances in laproscopic techniques laproscopic partial cystectomy is the treatment of choice. Due to multilayer involvement of bladder wall, open surgery to perform partial cystectomy is recommended. In tumor measuring less than 2-3 cm in size without deep parietal infiltration, trans urethral resection is considered to be feasible. Regular follow-up is necessary to detect late recurrences. It is done by cystoscopy, urinary or plasma tests and imaging studies.

In summary malignant paraganglioma of urinary bladder is an uncommon tumor with no reliable histologic criteria that could distinguish between benign from malignant paraganglioma. Praganglioma though rare should be considered in differential diagnosis of usual and unusual variants of urothelial carcinoma. In addition to histology for differential diagnosis pathologist should also consider gross morphological appearance which may aid an important clue to suspect paraganglioma.

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