Non-Functional Paraganglioma of Urinary Bladder - A Rare Entity

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Abstract
Paragangliomas or extra-adrenal pheochromocytomas are uncommon tumors which can be seen in retroperitoneum, thoracic region and head and neck area. Primary paraganglioma of urinary bladder is extremely rare and accounts for less than 0.05% of all bladder tumors. They usually present with the symptoms of catecholamine overload and rarely can be non-functional. Histological examination is gold standard and immunohistochemistry can help in difficult cases especially for non-functional paragangliomas. We report a case of 35 years old female presenting with hematuria, difficulty in micturition and lower abdominal pain for three months. Abdominal ultrasound and cystoscopic examination revealed a mass in urinary bladder. Transurethreal resection of tumor was performed and histopathological examination revealed paraganglioma of urinary bladder. Surgery and post-operative period remained uneventful. Patient remained symptoms free at a follow-up period of three months.

Keywords: Catecholamine, Hematuria, Micturition, Paraganglioma, Urinary bladder.

Introduction
Paragangliomas are similar to pheochromocytomas in a sense that they arise from chromaffin cells of sympathetic chains but differ from them on the basis of location. As they develop outside the adrenal medulla, they are also called the extra-adrenal pheochromocytomas.1 The rate of occurrence of these tumors is only 9-23% and they can be found in any location especially abdomen, skull base, mediastinum, neck and peri-aortic area.2 Primary paragangliomas of urinary bladder are quite rare and account for less than 0.05% of all bladder tumors and 6% of all paragangliomas.3,4 Like pheochromocytomas majority of paragangliomas also manifest themselves through classical symptoms of catecholamine overload including headache, hypertension, fainting, palpitations and at times with ventricular arrhythmias.2,5 Non functional paragangliomas are usually discovered incidentally through radiographs or while investigating some other issue and can be confused with multiple mass lesions of the area. Limited numbers of such cases are discussed in medical literature and their biological behavior and prognosis is yet to be defined. Present report describes a case of 35 years female with non functional paraganglioma of urinary bladder which puzzled the pre-op diagnosis and final diagnosis was made possible on histological examination.

Case Presentation
A 35 yrs female resident of remote village of Punjab presented with hematuria, difficulty in micturition and episodes of lower abdominal pain since three months. She had no history of hypertension, episodic headache or palpitations. Abdominal ultrasound revealed a 20x17 mm mass in right lateral wall of urinary bladder at 10/11,0'clock position. A provisional diagnosis of mass lesion ranging from (papilloma/malignancy) was made and further correlation with cystoscopic examination and biopsy was advised. No signs of any metastasis to other abdominal organs were found on ultrasonography (Figure 1). Cystoscopic examination confirmed the ultra-sonographic findings and decision of its transurethreal resection was made. Surgery remained uneventful with no massive bleeding or hypertensive crisis and post-operative recovery was satisfactory. Histopathological examination of specimen revealed tumor cells showing classical nesting or Zellballen pattern. Tumor cells had round to oval vesicular nuclei with salt n pepper chromatin. Nests of tumor cells were separated by fibrous septa and surrounded by sustentacular cells. No pleomorphism, necrosis, large nests or tumor spindling was seen. Mitotic rate was 2/10 HPF and no atypical mitosis was seen (Figure 2). To confirm the morphological diagnosis a panel of immunohistochemical stains was applied including Chromogranin Synaptophysin, CD-56, Pan CK, Ki-67 and S-100. Chromogranin Synaptophysin, CD-56 showed diffuse positivity in tumor cells while S-100 was positive in

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sustentacular cells surrounding the tumor nests. Pan CK was negative and Ki-67 index was <2% (Figure 3). IHC confirmed the histological diagnosis. Patient was discharged after a week of surgery and her course of recovery was unremarkable. At a follow-up period of three months, she was symptoms free with no evidence of recurrence.

**Discussion**

Pheochromocytomas are uncommon tumors and only 10% of them are found at extra-adrenal locations. Common sites include jugular foramen, mediastinum, carotid body and periaortic region. Bladder paragangliomas are rare and thought to arise from embryonic rests of chromaffin cells located within the bladder wall. Young females in their twenties or forties are affected the most. First case of bladder paraganglioma was reported in 1953 followed by limited number of cases till date. Pathogenic mechanism behind their development is still unclear. Most of them are hormonally active and clinically present with headache, tachycardia, sweating and paroxysmal hypertension, particularly during micturition. However, non-functioning paragangliomas are rare and more difficult to diagnose due to non-classical presentation. Clinically, the patient provided no history of hypertension, headache or flushing that would suggest a diagnosis of paraganglioma.

For majority of asymptomatic bladder paragangliomas, definitive diagnosis requires histological examination. Histological features of tumor are similar to adrenal pheochromocytomas with cells growing in classical nested or Zellballen pattern. High grade urothelial carcinoma with nesting pattern is top differential. Immunohistochemical staining is needed for definitive diagnosis. Chromogranin, and NSE highlights neural tissue and neuroendocrine cells while CK negativity excludes urothelial carcinoma. For current case a positive staining of Synaptophysin, CD56, Chromogranin in tumor nests and S-100 in sustentacular cells was consistent with paraganglioma. Around 5-15% of the paragangliomas of the urinary bladder are said to be malignant. Like PASS (Pheochromocytoma of the Adrenal Gland Scaled Score) scoring system for pheochromocytomas, no histological criterion is yet established for paragangliomas to differentiate between benign and malignant tumors. Only the appearance of local invasion or distant metastases confirms that the tumor has malignant behavior. The parameters of PASS scoring system including necrosis, mitosis, large nests monotony, spindling and high grade nuclear atypia can also be used in these cases to suggest high malignant propensity of tumor. Ki-67 index may help to identify rapidly proliferating tumors with increased chances of recurrence. For current case it was <2% favoring its less proliferative nature.

Management of choice is surgical resection, including transurethral resection and partial or total cystectomy. For patients with functional paragangliomas especially those exhibiting paroxysmal hypertension during micturition, preoperative management is mandatory to stabilize hypertension before surgery. Alpha blocking agents or calcium channel blockers are used for two weeks to inhibit the release of catecholamine and to expand the blood volume. Regular follow-up is vital to detect recurrences. It includes cystoscopy, plasma or urinary tests, imaging study and must be lifelong. No understanding has yet been established for frequency of these measures but at least an annual follow-up for asymptomatic patients is suggested.

**Conclusion**

Non-functional paraganglioma of urinary bladder is a rare entity, which can often be confused with other urothelial malignancies. Definite diagnosis requires histological examination and sometimes aid of immunohistochemistry. No histological criterion is yet, set to define malignancy and only local invasion or distant metastasis can help in this
regard. After surgical resection, long-term annual follow-up is suggested for all cases.

References