A rare case of malignant paraganglioma of urinary bladder

Vinaya B. Shah, Amit T. Bhandare
Department of Pathology, T N Medical College and B Y L Nair Hospital, Mumbai, Maharashtra, India

Address for correspondence:
Dr. Vinaya Shah, Flat No. 38, Bldg No. 2, Government Quarters, K. K. Marg, Haji Ali, Near Mahalaxmi Race Course, Mumbai - 400 034, Maharashtra, India. E-mail: shahvinaya@yahoo.com

ABSTRACT
Paraganglioma of the urinary bladder is a rare pathologic entity with no definitive histological, immunohistochemical or molecular features to determine its malignant potential. Malignancy is essentially determined by the presence of deep local invasion, invasion of adjacent structures and lymph node or distant metastases. So far, up to 180 cases of paraganglioma have been reported, with <30 being malignant. A 50-year-old male presented with painless hematuria for 6 months. Cystoscopic biopsy of the bladder mass was given as invasive urothelial carcinoma. Patient underwent radical cystectomy with pelvic lymphadenectomy. The gross morphological brown discoloration of mass on formalin fixation was suspicious of paraganglioma and was confirmed on immunohistochemistry. The diagnosis of malignant paraganglioma was made based on regional lymph node metastases. We describe a rare case of a patient with malignant urinary bladder paraganglioma with main differential diagnostic considerations on the histomorphology.

KEY WORDS: Gross morphology, lymph node metastases, malignant paraganglioma

INTRODUCTION
Paraganglioma of the urinary bladder represent <1% of bladder tumors and 6% of all paragangliomas.[1] Of these, only 10% show malignant behavior.[2] There is neither exact histological proof nor are there immunohistochemical features for the diagnosis of malignancy. The absolute criterion for malignancy is the presence of local recurrence, regional lymph node metastases or distant visceral metastases. To the best of our knowledge, approximately 30 malignant cases being reported thus far in the literature.[3]

We present a rare case of malignant paraganglioma in a cystectomy specimen which was missed on cystoscopic biopsy.

CASE REPORT
A 50-year-old, nonhypertensive, nondiabetic presented with painless hematuria since 6 months. He had no other symptoms. Routine blood tests and routine physical examination were unremarkable. Computed tomography (CT) scan showed a mass in left lateral wall of the urinary bladder. Cystoscopic biopsy of the mass was performed at a private hospital and was referred to our institute with the diagnosis of muscle invasive urothelial carcinoma. Subsequently, patient underwent radical cystectomy along with pelvic lymphadenectomy.

Gross
A large polypoidal mass 4 cm × 3 cm with a smooth surface was seen protruding into the bladder lumina and the depth was 1 cm infiltrating the muscle layer.

Cut surface in the fresh state was smooth, tan gray and fleshy. After formalin fixation, mass darkened to a mahogany brown and yellow [Figure 1]. Tissue sections were stained with routine hematoxylin and eosin stain.

Microscopy
The tumor was composed of nests of tumor cells surrounded by fibrous septae with fine vascular channels with tumor infiltrating the muscularis propria. Other areas were edematous with tumor cells forming trabeculae and cords. The main cells were large with moderately clear to eosinophilic cytoplasm and indistinct cell borders. The nuclei were round to oval with a small, but distinct nucleolus. Nuclear pleomorphism was observed in focal areas. There was no necrosis and no mitoses seen [Figure 2a and b]. The histopathological features were consistent with nested variant of urothelial carcinoma. The gross discoloration of mass to yellow-brown color in formalin made us suspect the possibility of paraganglioma. Silver stains that is, reticulin stain highlighted the typical zell-ballen pattern [Figure 2c]. Immunohistochemical staining...
was performed with antibodies against chromogranin and synaptophysin, which was positive, confirming the diagnosis of paraganglioma [Figure 2d].

The other markers AE1/AE3 was negative ruling out urothelial carcinoma. There was metastases in the left obturator lymph node signifying its malignant behavior.

Follow-up positron emission tomography/CT scans remained negative 14 months after the surgery. Urine catecholamine levels at 2 and 6 months postoperatively were within normal range.

**DISCUSSION**

Paraganglioma of the urinary bladder accounts for <1% of bladder tumors,[1] and its biologic behavior is uncertain. Malignant paraganglioma of the urinary bladder constitutes 10% of all the bladder paragangliomas,[1,2] highlighting its rare occurrence.

Malignant paraganglioma cannot essentially be differentiated from benign bladder paragangliomas based on gross anatomy or histology, and the malignant behavior is determined based on deep local invasion, lymph node involvement, or metastases either locally or to distant organs.[1] No reliable histologic criteria exist to distinguish malignant from benign neoplasms.[2,4] Some authors have suggested that the presence of necrosis, angiolymphatic invasion, and increased number of mitotic figures was associated with unfavorable outcomes for patients with paraganglioma.[2,5] The features of necrosis, vascular invasion, or mitotic figures were uncommon or rarely seen in paraganglioma of the urinary bladder as also observed in our case.

The main differential diagnostic considerations for paraganglioma of the urinary bladder are granular cell tumor, nested variant of urothelial carcinoma, metastatic large cell neuroendocrine carcinoma, and malignant melanoma. The distinctive clinical, histologic, and immunohistochemical findings usually permit a definitive diagnosis.[6] Few cases of granular cell tumor of the urinary bladder have been reported.[7] Histologically, granular cell tumor is characterized by nests of round to polygonal cells separated by bundles of mature collagen. The lack of zell ballen growth pattern and fine vascular stroma, the absence of sustentacular staining pattern for S-100 protein, and negative immunostaining for chromogranin readily distinguish granular cell tumor from paraganglioma of the bladder. The nested variant of urothelial carcinoma is characterized by infiltrative growth of “deceptively benign” nests and/or tubules of urothelial cells.[8] It is distinguished from paraganglioma by the lack of a fine vascular network and the negative immunoreactivity for S-100 protein and chromogranin. The presence of positive immunostaining for neuroendocrine markers observed in paraganglioma of the bladder often raises the possibility of metastatic large cell neuroendocrine carcinoma in the differential diagnosis. However, necrosis, numerous mitotic figures, and cellular anaplasia were not seen in paraganglioma. Immunohistochemical studies may be useful in difficult cases. Large cell neuroendocrine carcinoma is positive for cytokeratin and negative for sustentacular staining of S-100 protein. Awareness of these uncommon tumors is critical to avoid misinterpretation. As in many endocrine tumors, occasional bizarre nuclei may be seen [Figure 2b]. Their chromatin appears smudged and hyperchromatic without mitoses, typical of degenerative atypia rather than the atypia of a high-grade malignant tumor. Paragangliomas of the bladder can invade deeply into the muscle or show vascular invasion. Invasive urothelial carcinoma on occasion grow in a nesting pattern reminiscent of paraganglioma. However, these urothelial tumors are likely to be associated with carcinoma in situ or noninvasive papillary carcinoma, whereas the urothelium overlying a paraganglioma is normal, reactive, or ulcerated. In cases in which the authors have seen paragangliomas misdiagnosed as urothelial carcinoma, the major histologic features that led to the incorrect diagnosis included a diffuse growth pattern, focal clear cells, necrosis, and muscularis propria invasion, with significant cautery artifact compounding the diagnostic problems.[9] Distinction between paraganglioma and urothelial cancer is critical because of different therapeutic options, with paragangliomas treated by transurethral resection of bladder mass or partial cystectomy.

Paragangliomas usually react with antisera to neuron-specific enolase, synaptophysin, and chromogranin and are negative with...
antibodies to various keratins. In contrast, invasive urothelial carcinomas are positive for CK7, CK20, and a high-molecular-weight cytokeratin. The classic triad of episodic hypertension, persistent hematuria, and postmicturition syncope is virtually diagnostic but is seen in functional tumors that is, catecholamine secreting tumors. Nonfunctional tumors can be asymptomatic. Painless hematuria is another commonly reported symptom as seen in our case. Role of chemotherapy and radiotherapy are not well defined. Because bladder paragangliomas are likely to recur and to metastasize, life-long follow-up with annual measurement of catecholamine levels is essential.

In summary, malignant paraganglioma of the urinary bladder is an uncommon tumor with no reliable histologic findings that could distinguish benign from malignant paraganglioma. Paraganglioma, though rare should be considered in the differential diagnosis of usual and unusual variants of urothelial carcinoma.

Beyond differential diagnosis on histology, pathologists should also consider the gross morphological appearance, which may aid as an important clue to suspect paraganglioma.

REFERENCES


How to cite this article: Shah VB, Bhandare AT. A rare case of malignant paraganglioma of urinary bladder. Indian J Pathol Microbiol 2015;58:235-7.

Source of Support: Nil, Conflict of Interest: None declared.