PARAGANGLIOMA OF THE URINARY BLADDER: A CASE REPORT

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Paragangliomas of the urinary bladder are very rare. To date, there are no reliable methods for predicting their clinical behavior, so long-term follow-up is required. We describe a paraganglioma of the urinary bladder in a 32-year-old male who presented with painless gross hematuria. Abdominal ultrasonography revealed a protruding mass with hematoma over the right lateral wall of the urinary bladder. The tumor was not completely resected by transurethral resection of bladder tumor (TURBT) due to intermingling with the bladder wall. Follow-up I^{131}-metaiodobenzylguanidine was performed 3 weeks after surgery and suspected incomplete resection lesions were noted. Histologic examination of the tumor indicated paraganglioma of the urinary bladder. We also provide a brief review of the literature for comparison.

Key Words: paraganglioma, pheochromocytoma, urinary bladder
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Neoplasms arising from chromaffin cells of the sympathetic nervous system are called pheochromocytomas. Approximately 70% of pheochromocytomas arise in the adrenal medulla. Extra-adrenal tumors identified as pheochromocytomas are referred to as extra-adrenal paragangliomas. These arise predominantly in the retroperitoneum, from the upper abdomen to the pelvic floor. The urinary bladder can also be a primary site of extra-adrenal paragangliomas; 9.8% of extra-adrenal paragangliomas arise from the urinary bladder [1], although paragangliomas account for only 0.06% of all tumors of the urinary bladder [2]. Herein, we describe a 32-year-old male with primary paraganglioma of the urinary bladder and review the literature on the subject.

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CASE PRESENTATION

A 32-year-old male heavy smoker had excellent health until 3 days before admission, when painless gross hematuria with blood clots developed. He visited our hospital for urologic investigation. According to his statement, he had also suffered from voiding with palpitation and headache for 2 years.

Findings on physical examination were not remarkable. Resting blood pressure on admission was 120/70 mmHg and his urine analysis revealed a red blood cell count (RBC) of more than 100/high-power field (HPF), a white blood cell count (WBC) of 10–25/HPF, and protein of more than 300 mg/dl; all other laboratory examinations were unremarkable. Abdominal ultrasound showed a large protruding tumor over the right lateral wall with hematoma extension to the base of the urinary bladder (Figure 1). The maximal diameter of the tumor was 3.0 cm. No lesion was found on imaging studies, including roentgenography of the kidneys, ureter, and bladder (KUB) and chest.

Cystoscopy showed an exophytic tumor with normal covering mucosa from the right lateral wall

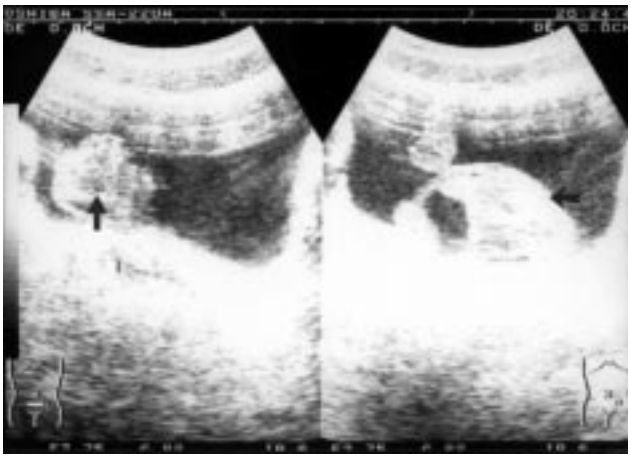

Figure 1. *Pelvic ultrasonography reveals a tumor mass (arrow) over the right lateral wall (left), with blood clots (arrow) over the basal area of the urinary bladder (right).*

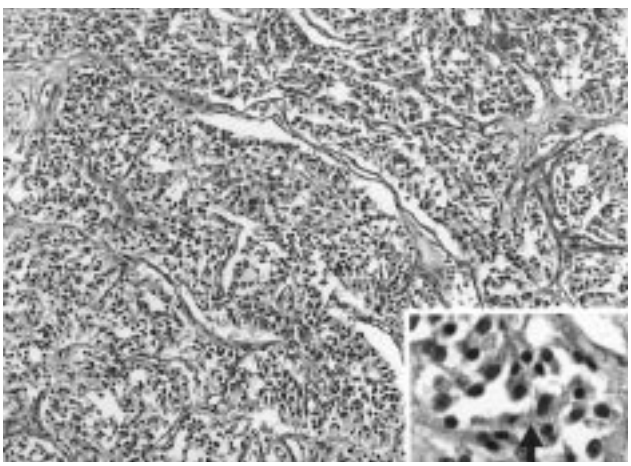

Figure 2. *Tumor cells arranged in characteristic Zellballen pattern around a delicate vasculature. (Hematoxylin & Eosin, original magnification x 100.) Tumor cells are ovoid to polygonal and have a granular cytoplasm (arrow). There is no nuclear anaplasia. (Insert: Hematoxylin & Eosin, original magnification x 400.)*

near the neck of the urinary bladder. Transurethral resection of bladder tumor (TURBT) was performed for suspected tumor of the urinary bladder. During surgery, the surgeon found that the tumor was hypervascular and had involved the muscular wall of the bladder, so the tumor was resected incompletely. Because the mucosa of the bladder neck was abnormal, bilateral prostate biopsy was also performed.

On pathologic examination of the specimen, more than 10 pinkish and elastic tumor fragments were obtained. Microscopic histologic examination showed ovoid to polygonal and slightly spindle-shaped cells with abundant amphophilic to eosinophilic cytoplasm, containing many foamy granules. The nuclei were round and vesicular with occasional mitotic activity. The tumor cells were arranged in a characteristic Zellballen pattern with short, irregular anastomosing sheets around a delicate vasculature (Figure 2). Neither nuclear anaplasia nor vascular invasion were found. Immunohistochemical study demonstrated the presence of neuron-specific enolase, chromogranin, synaptophysin, and S-100 protein but the absence of cytokeratin, vimentin, leukocyte common antigen, and epithelial membrane antigen. Histologic diagnosis was paraganglioma of the urinary bladder.

Electron microscopic study revealed an admixture of light and dark cells with dense-core neurosecretory granules, which were more numerous in dark cells (Figure 3).

Follow-up I^{131}-metaiodobenzylguanidine (MIBG) scan was performed 3 weeks after TURBT and revealed a radioactive focus in the right side of the urinary bladder throughout the serial 24-, 48-, and 72-hour images, even post voiding. The results suggested local residual paraganglioma involving the urinary bladder with low probability of distant metastasis.

Discussion

Paragangliomas of the urinary bladder are rare, with only a few case reports published in Taiwan [3,4]. From the first description by Zimmerman et al in 1953 to 1999, more than 160 cases have been reported

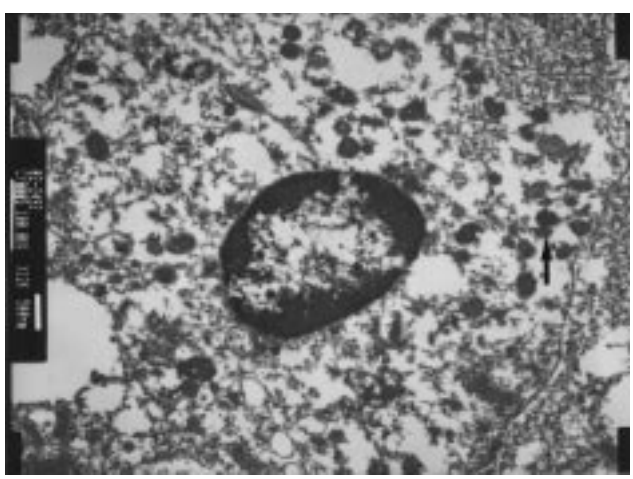

Figure 3. *Dense-core neurosecretory granules (arrow) are found within the tumor cells under the electron microscope. (Original magnification x 12,000.)*

worldwide [5–7]. At diagnosis, patients were between 11 and 84 years old [8]; there were slightly more females than males [9–11]. The tumors originate from neuroectodermal tissue within the bladder wall and common sites are the trigone followed by the dome and bilateral wall [6,11]. Tumors are relatively small, ranging from a few millimeters to 10 cm with an average of 1.9 cm [8].

The characteristic symptom complex is associated with catecholamine excess, and includes hypertension, dizziness, headache, tachycardia, and palpitation, triggered by micturition, bladder distension, or sexual intercourse. Painless hematuria, frequency, and dysuria are also common. Biochemical study is based on 24-hour urine and serum concentrations of vanillylmandelic acid (VMA), epinephrine, norepinephrine, and metanephrine; specimens must be drawn during attacks to avoid false negatives. However, Bravo et al found that 50% of their patients with pheochromocytoma had urinary VMA within the normal range [12]. Other diagnostic workups include abdominal ultrasound, computerized tomography (CT) scan, and I^{131}-MIBG scan, which is the most useful tool in the diagnosis of extra-adrenal tumors arising from the paraganglion system or in metastatic lesions.

Paragangliomas of the urinary bladder have histologic features similar to adrenal pheochromocytoma. Tumors are often poorly circumscribed and intermingled with adjacent muscle bundles of the bladder wall. The typical Zellballen pattern (cell clusters) of growth is the most common variant. Trabecular, ribbon, and sarcomatoid patterns have also been reported. Like many other endocrine tumors, bizarre cells are not uncommon. Low-grade transitional cell carcinoma should be included in the differential diagnosis. When tumors have a spindle-cell pattern, differential diagnosis should include Schwann cell and smooth muscle neoplasm.

About 5–15% of urinary paragangliomas are diagnosed as malignant [8]. As in pheochromocytoma, there is no ideal histologic evaluation for the malignant potential of paraganglioma of the urinary bladder. Characteristics such as nuclear atypia, mitotic activity, vascular invasion, and infiltrating growth pattern do not contribute to malignant potential. As noted by Neville, the only absolute criterion for diagnosing malignancy is the presence of tumor in sites where paraganglionic tissue is not normally found [13]. However, it is difficult to tell true metastasis from multifocal development of the tumor in some cases. Even in patients who have developed metastatic lesions, there is still no histologic feature distinguishing between malignant and benign tumors.

Kliewer et al suggested that the presence of sustentacular cells is associated with benign behavior, and that these cells seem to be absent in aggressively metastatic paragangliomas [14,15]. However, Grignon et al indicated that numerous sustentacular cells were present in a case that showed malignant behavior [2]. The same result was noted by Korat et al in one of three malignant extra-adrenal paragangliomas [16]. Anton et al and Pugh [17,18] have suggested that the amount of dopa and dopamine secretion is different in benign and malignant paragangliomas [17]. However, a case of malignant urinary bladder paraganglioma with no increased dopa secretion has been reported [19]. In 1986, a flow cytometry study by Hosaka et al showed that polyploidy or nuclear content are significant predictors of malignant behavior in adrenal pheochromocytomas [20]. Grignon et al studied three urinary bladder paragangliomas and found an aneuploid DNA pattern in two cases and a diploid pattern in the other case [2]. One case with aneuploid DNA was alive and well 7 years after diagnosis and the other died of an unrelated cause. The patient with diploid DNA had local recurrence five times after first surgery. According to this study, DNA ploidy seems not to be a useful predictor of malignancy in urinary bladder paraganglioma [1]. To sum up, there are currently no reliable methods predicting the clinical behavior of urinary bladder paragangliomas, so long-term follow-up is necessary, including measuring blood pressure and catecholamine concentrations and I^{131}-MIBG scanning.

Because of the small number of cases and the smaller number of cases followed up, the prognosis of urinary bladder paraganglioma is not well established. One study revealed a 5-year survival rate of 44% in malignant adrenal pheochromocytomas and that extra-adrenal paraganglioma had worse prognosis than adrenal pheochromocytoma [21]. However, another report showed that urinary bladder paraganglioma had the same prognosis as adrenal pheochromocytoma [22].

Blood pressure control, preoperative hydration, and a skilled anesthesia team are essential to avoid blood pressure dropping off suddenly during surgery.

The surgical treatment for urinary bladder paraganglioma depends on the location and extent of the tumor. TURBT can remove a tumor successfully in some patients. When the location and size do not allow complete transurethral resection, partial cystectomy or total cystectomy with or without pelvic lymph node dissection is considered. In our case, we advised the patient to undergo partial cystectomy or total cystectomy for complete removal of the residual tumor. Due to neither hematuria nor voiding with palpitation and headache after TURBT, he refused further surgical intervention even though he was informed of the possibility of regrowth and the malignant potential of the residual tumor.

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