Composite Paraganglioma and Neuroblastoma of the Urinary Bladder: A Rare Histopathological Entity

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Key Words

Bladder tumor • Composite tumor • Neuroblastoma • Paraganglioma

Abstract

Paraganglioma of the urinary bladder is an uncommon clinical entity. Neuroblastoma of the urinary bladder is another rare tumor with only 7 reported cases, all in children. This report presents the case of a composite paraganglioma and neuroblastoma in a 45 year-old male who presented with dysuria and flank pain. On the computerized tomography scan, the bladder wall overlying the tumor was smooth and the mass had a large exophytic component. The initial diagnosis was paraganglioma on transurethral resection. Following partial cystectomy and bilateral pelvic lymph node dissection, pathology confirmed a composite tumor consisting of paraganglioma and neuroblastoma. To our knowledge, this is the first report of such a composite tumor involving the bladder.

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Introduction

Paragangliomas, or extra-adrenal pheochromocytomas, are tumors arising from the chromaffin tissue of the paraganglion system, most commonly below the diaphragm. These tumors comprise 15–20% of all pheochromocytomas [1]. Approximately 1% arise from the bladder comprising 0.06% of all bladder tumors. Patients with bladder paraganglioma often present with headache, sweating, palpitations, hypertension, or hematuria. Symptoms may be brought on by voiding, however 27% of these lesions will be nonfunctional.

Neuroblastoma is a common childhood malignancy that is rare in adults. Neuroblastoma of the urinary bladder is exceedingly rare with only six reported cases all in children. To our knowledge, there have been no reports of neuroblastoma involving the bladder in adults [2]. Neuroblastoma may arise from anywhere in the sympathetic nervous system with the most common sites being the adrenals (40%), thorax (15%), and abdomen (15%). These tumors may secrete catecholamines with symptoms similar to paragangliomas or may present with local symptoms depending on the organ involved.

Fig. 1. a. Contrast CT showing 4.4cm extraluminal bladder mass arising of the urinary bladder dome. **b.** Contrast CT showing enlarged lymph nodes in the iliac chains.

Fig. 2. a. Histopathology slide showing monotonous hyperchromatic cells with scant cytoplasm consistent with neuroblastoma. **b.** Histopathology slide showing a Zellballen pattern and abundant cytoplasm consistent with paraganglioma.

Here we report a case of a bladder tumor diagnosed as a composite tumor composed of paraganglioma and neuroblastoma on final pathology following partial cystectomy.

Case Report

A 45 year-old male presented to our university hospital medical center with complaints of flank and abdominal pain and dysuria. None of the typical symptoms of pheochromocytoma such as headaches, blurred vision, flushing, or palpitations were present.

The patient's medical history was significant for Type I diabetes mellitus managed with Metformin 400mg orally daily and long acting injectable insulin (10–20 units twice daily). Clinical examination was unremarkable. A computerized tomography urogram showed a 4.4 cm extraluminal bladder mass at the bladder dome with possible seminal vesicle involvement as well as a 2.3 cm enlarged lymph node in the right iliac chain (fig. 1. a, b).

The patient underwent transurethral resection of this tumor with intraoperative findings of normal bladder mucosa being displaced by an extraluminal mass. The specimen stained positive for synaptophysin and S-100 consistent with paraganglioma. The tumor was negative for P63 and CK. The functional status of the tumor was evaluated with elevated plasma normetanephrine 6.6

(range 0–0.89 nmol/l), urine VMA 27.4 (range 0–7.0 mg/d), urine norepinephrine 2,189 (range 15–80 µg/24h), and chromogranin A 1,495 (range 0–95 ng/ml). MIBG scan was essentially normal with very mild activity in the left adrenal gland. After careful pre-operative optimization of blood pressure with both alpha- and beta-blockade, the patient underwent a partial cystectomy, right ureteral reimplant, and bilateral pelvic lymph node dissection.

The histopathological report showed cells with abundant eosinophilic cytoplasm in a nested pattern. Other areas showed monotonous cells with scant cytoplasm and hyperchromatic nuclei. Mitotic figures varied from 5 mitotic figures/10 HPF in areas of paraganglioma to 36 mitotic figures/10 HPF in the small round blue cell (SRBC) population. The lymph node metastasis was composed predominantly of the SRBC component, but small areas of more typical paraganglioma cells were also present. Immunohistochemical stains were performed and showed positive staining for synaptophysin, CD56, and chromogranin. S-100 was positive in the sustentacular cells in areas of paraganglioma, but was negative in the SRBC component. NB84 showed positive staining within the SRBC population of cells, but was negative in the areas of paraganglioma. Pan-cytokeratin, CAM 5.2, CK 20, desmin, CD45, and CD99 were negative. These morphologic and immunohistochemical findings were determined to be due to a composite tumor composed of paraganglioma and a SRBC component consistent with neuroblastoma (fig. 2. a,b).

In the post-operative period the patient's clinical condition improved. His plasma normetanephrine dropped to 1.01 (range 0–0.89 nmol/l) and chromogranin A to 348 (range 0–95 ng/ml). His blood sugar is well-controlled with a single oral medication.

Discussion

Paragangliomas are extremely rare bladder tumors. Their symptoms are recognizable as those for all pheochromocytomas: headache, flushing, palpitations, syncope. In the case of bladder involvement, these symptoms may be brought on by micturition [3]. On magnetic resonance imaging, paragangliomas appear as round- or oval-shaped intensely enhancing lesions with T1 hyperintensity [4]. The patient in this case report reported no such complaints and so functional testing and further imaging were not performed until histopathological diagnosis of paraganglioma following transurethral resection of bladder tumor. Bladder paragangliomas may be managed with transurethral resection [5], however partial cystectomy is often curative with radical cystectomy reserved for cases in which partial is not feasible. Correct identification of bladder paraganglioma versus the more common urothelial cell carcinoma is paramount.

One report outlined the characteristic histologic features of bladder paraganglioma that may facilitate correct diagnosis [6]. These include a zellballen pattern (diffuse patterns of large polygonal cells in clusters separated by a delicate fibrovascular stroma), muscle invasion with-

out desmoplastic reaction, epithelioid cells with abundant eosinophilic and granular cytoplasm, and a lack of mitotic activity. Paraganglioma will stain positive for chromogranin, synaptophysin, S100, and neuron specific enolase. They stain negative for cytokeratin. Despite these histologic features, the diagnosis remains difficult.

Neuroblastoma is an aggressive tumor derived from neural crest cells of the sympathetic nervous system. While a common childhood tumor, it is an uncommon tumor in adults. It has been reported even less frequently as a composite tumor with paraganglioma and, to our knowledge, never in the urinary bladder [7]. Microscopically, neuroblastoma appears similar to other small round blue cell tumors with poorly defined cytoplasmic borders. They may have Homer-Wright pseudorosettes, neuropil between tumor cells, and alveolar, pseudovascular, or Schiller-Duval body appearance due to hemorrhage. Antibody panels are necessary for diagnosis. They stain positive for chromogranin, synaptophysin, vimentin, neurofilament, neuron-specific enolase, nerve growth factor-receptors, and ALK. They will be negative for p53, CD99, FLI1, desmin, myogenin, keratin, CD45, variable EMA, and variable WT1.

While no cases of composite paraganglioma-neuroblastoma of the urinary bladder have been reported, the literature reveals 6 cases of composite paraganglioma-ganglioneuroma [8]. All of these tumors were non-malignant. However, the case presented here raises the possibility of a composite neuroblastoma. This should raise concerns for an increased risk of malignancy and metastases due to the neuroblastoma component when evaluating patients with neuroendocrine tumors.

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