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LETTER TO THE EDITOR

Aggressive Paraganglioma of the Urinary Bladder with Local Recurrence and Pelvic Metastasis

Koo Han Yoo[1,2] · Taesoo Choi[2] · Hyung-Lae Lee[2] · Min Jeong Song[3] · Benjamin I Chung[1]

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Abstract

Many pheochromocytoma and extra-adrenal paraganglioma are benign, but some are malignant. Pheochromocytoma of the Adrenal gland Scaled Score analyzed the histological characteristics of the tumor. Tumors with a Pheochromocytoma of the Adrenal gland Scaled Score of 4 or higher have a higher risk of recurrence. This pattern is thought to be applicable to paraganglioma as well, and to future patient follow-up efforts. We report a recurrent and metastatic paraganglioma of the urinary bladder.

Keywords Paraganglioma · Urinary bladder · Neoplasm metastasis

Pheochromocytoma and extra-adrenal paraganglioma are identical diseases that occur in neural crest tissues and are named differently depending on their anatomical location [1]. The World Health Organization (WHO) decided to assign pheochromocytoma exclusively for tumors occurring in the adrenal medulla, and defined extra-adrenal paraganglioma as tumors occurring in other tissues. Patients with pheochromocytoma and extra-adrenal paraganglioma complain of symptoms (e.g., high blood pressure, headache, sweating, tremor, palpitations, and pale face). The cause of these symptoms is excessive catecholamine secreted by the tumor. These symptoms occur when excessive catecholamines are released through excessive physical exertion, labor, anesthesia, surgery, or urination. Such excessive catecholamine secretion can be utilized in diagnosis. Using plasma-free fractionated metanephrine in 24-h urine, the diagnostic rate reports low sensitivity (77%–90%) but a high specificity (98%) [2]. In addition, computed tomography (CT) or magnetic resonance imaging can confirm the anatomical location of the tumor as well as the tumor size and contrast. Recently, iodine I 123 - metaiodobenzylguanidine scintigraphy has been utilized for diagnosis with improved sensitivity (80–90%) and specificity (95–100%).

Surgical treatment is the principle treatment for pheochromocytoma and paraganglioma [3]. However, preoperative treatment such as phenoxybenzamine (a nonselective alpha-antagonist) is required to suppress excessive catecholamine secretion. Metastatic or recurrent pheochromocytoma, and extra-adrenal paraganglioma require further treatment after surgery. Palliative therapy that can be selected after removal of all visible tumors can be considered for chemotherapy, target therapy, or radiation therapy. Chemotherapy is difficult to prolong survival, but can help relieve symptoms. Eighteen patients after 22 years of follow-up with a regimen based on cyclophosphamide, vincristine, and dacarbazine, showed a complete response rate of 11%, a partial response rate of 44%, a biochemical response rate of 72%, and a median survival of 3.3 years. Target therapy does not yet produce meaningful results. Studies with the mammalian target of rapamycin (mTOR) inhibitor everolimus have been published, but the results have been somewhat disappointing. Radiation therapy is currently the most widely used. 131I-MIBG radiation therapy is applicable to patients with MIBG-avid metastases. Phase 2 trials utilizing high-dose 131I-MIBG radiation therapy involving 49 patients demonstrated the following: 8% had a complete response, 14% had a partial response, and the estimated five-year survival was 64% [4]. Herein, we report a recurrent and metastatic paraganglioma of the urinary bladder.

✉ Koo Han Yoo
yookoohan@khu.ac.kr

[1] Department of Urology, Stanford University Medical Center, Stanford, CA, USA

[2] Department of Urology, School of Medicine, Kyung Hee University, 892, Dongnam-ro, Gangdong-gu, Seoul 05278, South Korea

[3] Department of Pathology, Kyung Hee University Hospital at Gangdong, 892, Dongnam-ro, Gangdong-gu, Seoul 05278, South Korea

Eight years ago, a 53-year-old man was admitted to the emergency room with lower abdominal pain. A CT scan was performed on the bladder dome and a 5 cm-enhanced tumor was removed. Macroscopically, the tumor was a 4.5 × 4.5 × 4 cm sized well-circumscribed, exophytic, round mass involving the bladder wall (Fig. 1a). The cut surface showed reddish brown color with fibrous septa, and multifocal hemorrhage and necrosis were identified. Microscopically, the tumor cells were typically arranged in distinct nests (Zellballen) (Fig. 1b). They were separated by a vascular network or fibrous septa. The cells were polygonal and had eosinophilic cytoplasm. Nuclear pleomorphism was prominent and mitosis was observed up to 8/10 HPF (Fig. 1c). Atypical mitosis was also observed. The sustentacular cells surrounding periphery of the nest were immunopositive for the S100 protein. The chief cells showed immunopositivity for neuroendocrine markers, including: CD56, chromogranin A, and synaptophysin.

After follow-up loss, the patient came to the hospital with a recent onset of lower abdominal pain and difficult urination.

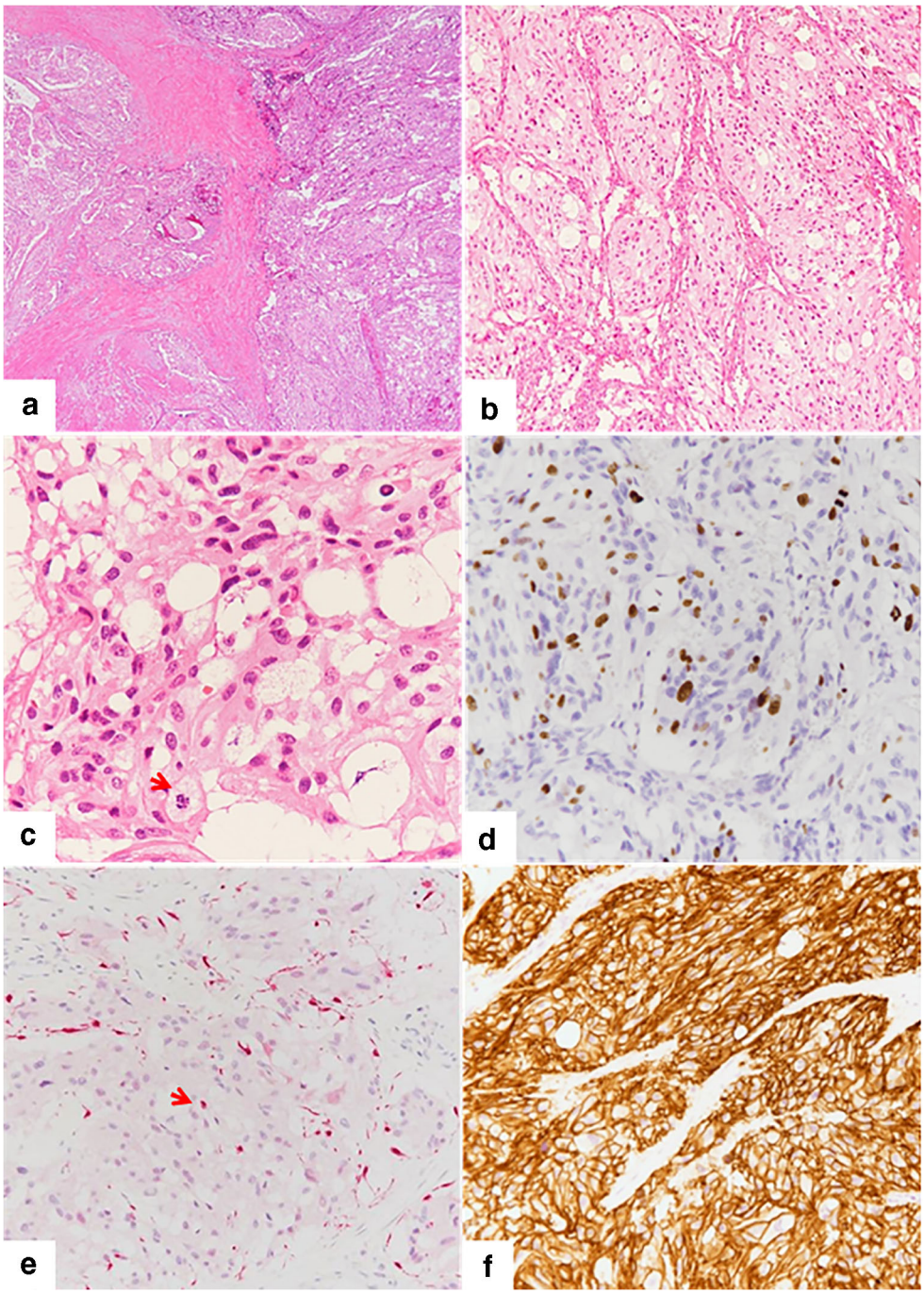

Fig. 1 Microscopic features. The tumor infiltrates into proper muscle layer (**a**). In low magnification, the tumor is composed of nested islands of eosinophilic cells with fibrovascular septa (Zellballen pattern) (**b**, ×100). The tumor cells have round to oval nuclei and prominent nucleoli. Nuclear pleomorphism and mitosis (arrow) are frequent (**c**). The Ki-67 labeling index is approximately 10% (**d**, ×200). The sustentacular cells are highlighted by S100 immunostain (**e**, *arrow*, ×200) and chief cells show immunopositivity for synaptophysin (**f**, ×100)

After CT scan, we performed a surgical removal of a 3 cm tumor on the urinary bladder and enlarged Lt obturator LN. Macroscopically, the removed tumor appeared to be a well-defined lobulating firm mass measuring 2.3 × 2 × 1.8 cm. Sections of the tissue were identified heterogeneously yellow to tan with focal hemorrhage. Microscopically, the tumor demonstrated invasion into the muscle layer. There was necrosis inside the tumor and angiolymphatic invasion was extensively present. Tumor cell differentiation had a mitotic activity of 6/10 HPF and marked pleomorphism. Immunohistochemical staining revealed CD 56 (+), chromogranin A (+), synaptophysin (+), and S-100 (+), with Ki67 being approximately 10% (Fig. 1d, e, f). The recurrent tumor showed identical histologic features to those of the primary tumor. The tumor invaded the muscle layer. Extensive angiolymphatic invasion was identified and occasionally tumor emboli obstructing of the entire lumen of the vascular space was observed. Removed Rt obturator LN was identified as a polypoid soft mass, measuring 1 × 0.9 × 0.9 cm. Microscopically, metastatic paraganglioma in vascular space was identified. Finally in our case, Pheochromocytoma of the Adrenal gland Scaled Score (PASS) was 12 points. The patient planned radiation therapy after confirming wound healing. A total of 55 Gy / 25 fractions were administered to the whole pelvis for 4 weeks. Six months later, a CT scan was performed, which showed a lack of recurrence.

Follow-up is critical for cancer patients after surgery and treatment, which helps physicians understand the nature of the tumor recurrence or progression. Most of the pheochromocytoma and extra-adrenal paraganglioma have low malignant potential. However, some of them (3–8%) have a malignant pattern. Several researchers have sought to characterize the recurrence and progression of pheochromocytoma. Several features showing malicious patterns were identified and analyzed, including: large tumor size, increased number of mitoses, DNA aneuploidy, and extensive tumor necrosis- all of which were identified as significant factors. PASS analyzed the histological characteristics of the tumor (invasion, large nests or diffuse growth, focal or confluent necrosis, high cellularity, tumor cell spindling, cellular monotony, increased mitotic figures, atypical mitotic figures, profound nuclear pleomorphism, and hyperchromasia) [5]. If the tumor has a PASS of 4 or higher, the risk of recurrence and progression is high. This pattern is thought to be applicable to paraganglioma as well, and to future patient follow-up efforts.

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Compliance with Ethical Standards

Ethics Declarations

Conflict of Interest The authors declare that there is no conflict of interest.

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