

Paraganglioma of the urinary bladder mimicking urothelial carcinoma: a case report

Çiğdem Öztürk¹, Hasan Güçer², Seher Çetinkaya Altuntaş³, Oğuzhan Okcu²

¹Department of Pathology, Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkey; ²Department of Pathology, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Turkey; ³Department of Endocrinology, Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkey

ABSTRACT

Paragangliomas of the urinary bladder are rare tumors and can mimic urothelial carcinomas due to some features and can be misdiagnosed. A 71-year-old female was seen for hematuria and there was a solid lesion that measured 3 cm on the urinary bladder at cystoscopy. Treatment approaches for paraganglioma and urothelial carcinoma are very different from each other; therefore differential diagnoses should be made carefully. Although immunohistochemical studies are helpful in differential diagnosis, they may cause misdiagnosis in some cases. In this article, we will discuss the clinical, histomorphological, and immunohistochemical differences between paraganglioma and urothelial carcinomas under their differential diagnosis.

Keywords: Paraganglioma, urothelial carcinoma, GATA-3, tyrosine hydroxylase

Paraganglioma of the urinary bladder is a neuroendocrine neoplasm that is rare and accounts for 0.06% to 10% of all bladder tumors that develops from Chromaffin cells located in the bladder wall. It is divided into functional (chromaffin) or nonfunctional (non-chromaffin) according to catecholamine expression in the whole body. In the urinary bladder, findings related to catecholamine secretion can be seen in patients with functional paraganglioma. While some of the patients may be asymptomatic, hematuria and lower urinary tract symptoms may develop rarely [1].

Paragangliomas of the urinary bladder can mimic urothelial carcinomas and misdiagnose. In this article, we will discuss the important morphological, clinical, and immunohistochemical studies in differential diagnosis.

CASE PRESENTATION

A 71-year-old female was seen in the urology clinic for hematuria for over a week duration. She had a history of thyroidectomy for papillary carcinoma 5 years ago and well-controlled hypertension for 10 years with drugs. Her blood pressure values were around 120/80 before the operation. For further assessment cystoscopy was performed and there was a solid, invasive lesion on the right lateral wall of the urinary bladder. Macroscopically, the tumor which measured 3 cm, infiltrated the detrusor muscle. Transurethral resection was performed.

Microscopically, the tumor was composed of nests of cells with monotonous nuclei and large granular amphophilic cytoplasm. Nests were surrounded by a

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Address for correspondence: Çiğdem Öztürk, MD., Recep Tayyip Erdogan University Training and Research Hospital, Department of Pathology, İslampaşa Mah., 53020 Merkez, Rize, Turkey. E-mail: dr.ozturkcigdem@gmail.com, Phone: +90 464 212 30 09, Fax: +90 464 212 30 15



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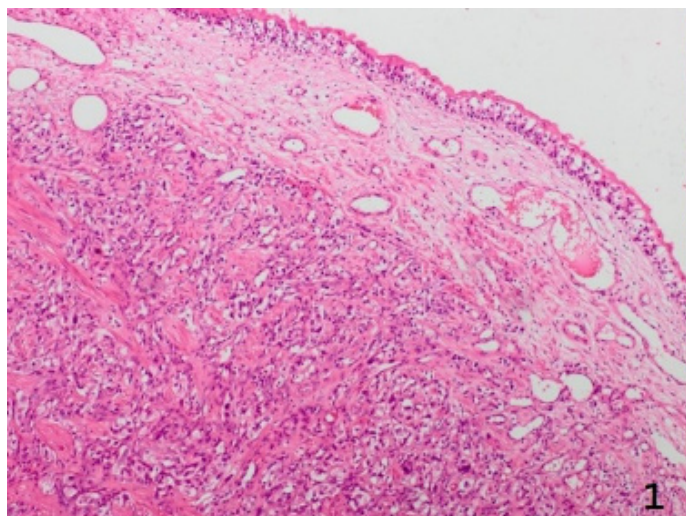


Fig. 1. Neoplastic proliferation below the normal urothelial epithelium (HE×40).

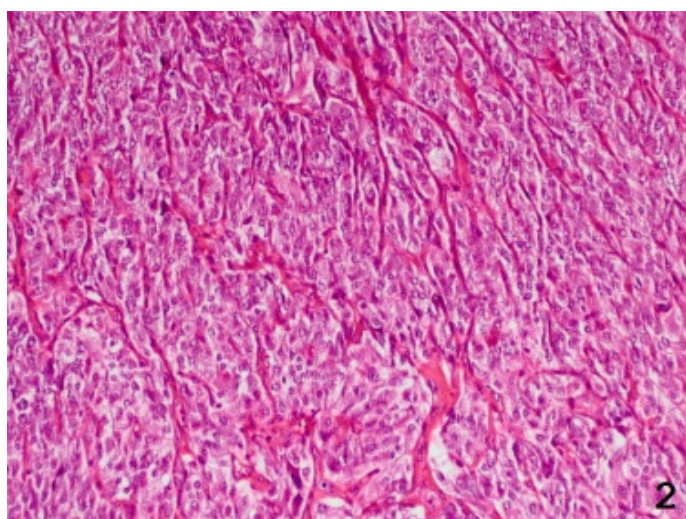


Fig. 2. Classic Zellballen configuration consisting of nests surrounded by thin fibrovascular connective tissue (HE×200).

thin, fibrovascular connective tissue in a classic Zellballen configuration. The tumor invaded through the muscularis propria. No angioinvasion, lymphatic and

perineural invasion was observed in the tumor and no mitotic activity and necrosis were seen. The overlying urothelium was normal (Figs. 1, 2, and 3). The tumor cells were strongly positive for neuroendocrine markers Chromogranin A, Synaptophysin and INSM-1 on immunohistochemistry. S100 protein high lights sustentacular cells. The tumor was negative for cytokeratins. Tyrosine hydroxylase was positive and there was no loss in succinate dehydrogenase B immunohistochemically. The Ki67 proliferation index was about 2-3%. Additionally, the tumor was positive for GATA-3 (Fig. 4). The patient was evaluated postoperatively by an endocrinologist. No pathology was found on physical examination. Laboratory results were normal reference ranges. 18 FDG Positron emission tomography (PET-CT) was done on the patient for metastasis no metastases were detected. The patient's hypertension has been well controlled in her follow-up and was evaluated as essential hypertension.

DISCUSSION

Paragangliomas of the urinary bladder are extremely rare tumors and numerous cases of paraganglioma misdiagnosed as urothelial carcinoma have been reported in the literature [1]. The distinction between paraganglioma and urothelial carcinoma is extremely important because of the different treatments. Even when paraganglioma invades the muscularis propria, partial cystectomy is sufficient; muscle-invasive urothelial carcinomas are treated with radical cystectomy. Patients with paraganglioma may be differentiated from patients with urothelial carcinoma by their age and clinical characteristics [2]. Paraganglioma is seen 1-2 decades younger than urothelial carcinoma. If paraganglioma is functional, symptoms due to cat-

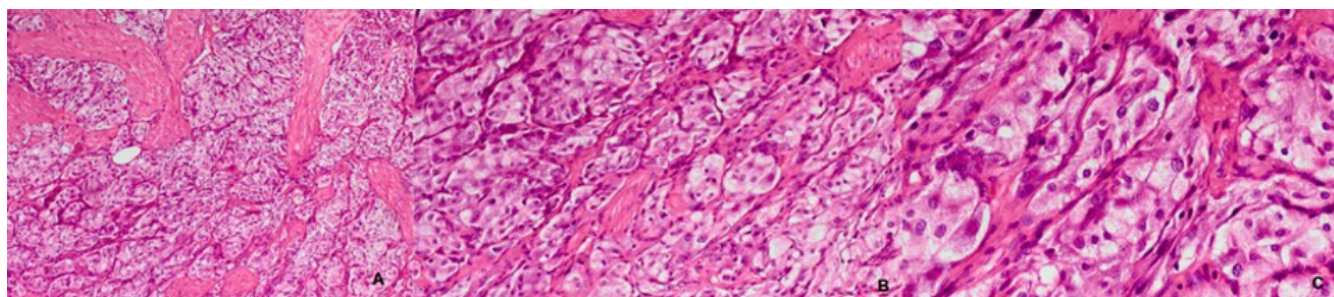


Fig. 3. Monotonous tumor cells with large granular amphophilic cytoplasm invading the muscularis propria (A:100×HE, B:200×HE, and C:400×HE).

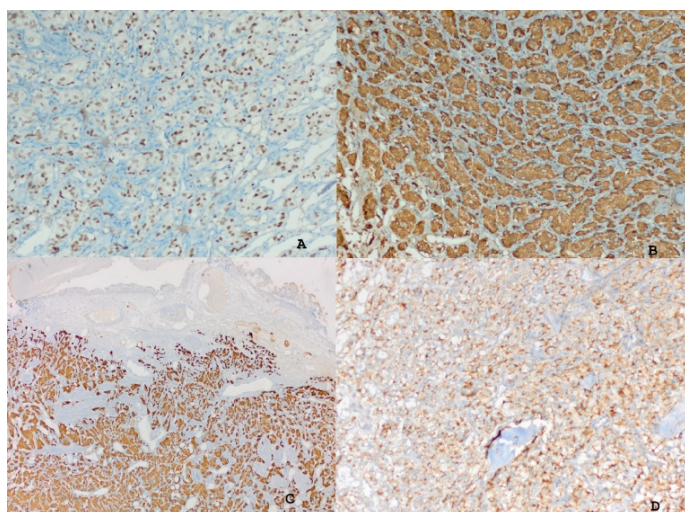


Fig. 4. (A) and (B) Immunohistochemically GATA-3 and Synaptophysin positivity in tumor cells (Anti GATA-3×200, Anti Synaptophysin×200), (C) Strong tyrosine hydroxylase positivity in tumor cells beneath the urothelium (Anti Tyrosine Hydroxylase×40), and (D) No loss of SDHB was seen by immunohistochemistry in tumor cells (Anti SDHB×200).

echolamine secretion can be seen in patients. Macroscopically, paragangliomas are lobulated and well-circumscribed, while urothelial carcinomas show an infiltrative appearance [3]. Our case was a 71-year-old patient and urothelial carcinoma was considered during the cystoscopic examination.

Paraganglioma may be confused with nested variant urothelial carcinoma because of their nest structures; therefore, zellballen structures in the histopathological examination are very helpful in diagnosis. The majority of tumors have the characteristic zellballen pattern consisting of nest structures separated by thin fibrovascular septa at least focally [4].

More than half of the cases with paraganglioma have muscularis propria invasion without a desmoplastic reaction. In urothelial carcinomas, a stromal reaction is expected to accompany muscle invasion, even if it is focal. Our case was also invasive to muscularis propria, but there was no accompanying stromal response, it consisted of zellballen structures in large areas. Tumor cells in paraganglioma always have large basophilic and granular amphophilic cytoplasm and uniform smooth chromatin. Sometimes pleomorphic or bizarre cells that are considered neuroendocrine atypia can be observed. These cells can be confusing for urothelial carcinoma, but the absence of mitosis supports the diagnosis of paraganglioma [5].

Immunohistochemical studies are very useful in the differential diagnosis of paraganglioma and urothelial carcinoma. Whereas urothelial carcinomas are always positive for various keratins such as CK7 and CK20, paragangliomas are not stained with keratins. Insulinoma-associated protein 1 (INSM-1), a nuclear transcription factor used in the detection of neuroendocrine differentiated cells and tumors, may be helpful in the differential diagnosis between paragangliomas and urothelial carcinomas [6]. In our case, INSM-1 was positive in tumor cells, while it was negative in urothelial cells.

GATA-3 which demonstrate urothelial differentiation has been reported to be positive in many tumors and urinary bladder paragangliomas as well as urothelial carcinomas. Therefore, using GATA-3 may cause a misdiagnosis [7]. Similar to the cases reported in the literature, GATA-3 positivity was observed in our case. Therefore, in the differential diagnosis of urothelial carcinoma, other immunohistochemical studies, and all morphological and clinical findings should be evaluated together.

Another lesion that is important in the differential diagnosis with paraganglioma is metastatic neuroendocrine tumors. Since neuroendocrine markers are positive in both paraganglioma and neuroendocrine tumors, it may cause misdiagnosis if additional immunohistochemical studies are not performed. A useful immunohistochemical marker in this subject is tyrosine hydroxylase which plays role in the biosynthetic pathway of catecholamines [8]. Immunohistochemically staining with tyrosine hydroxylase proves that the tissue is paraganglioma and pheochromocytoma. The negativity of tyrosine hydroxylase in neuroendocrine tumors is very helpful in differential diagnosis, but it should be kept in mind that it may be negative in parasympathetic paragangliomas [9]. In our case, the possibility of neuroendocrine tumor metastasis was excluded with the keratins negativity and tyrosine hydroxylase positivity.

Histopathological characteristics of the tumors can be determined using the GAPP scoring system in determining the metastasis risk of paraganglioma. GAPP criteria consist of architectural patterns, cellularity, presence of comedo necrosis, presence of vascular/capsular invasion, Ki67 labeling, and biochemical evidence of disease [10]. Although the GAPP scoring system shows high accuracy in deter-

mining the metastasis risk of the cases, it has been argued that the succinate dehydrogenase (SDH) gene mutation should be considered in addition to the GAPP criteria in recent studies [11]. Investigation of the status of SDHB immunohistochemically provides common information for all SDHx related diseases. Because any mutation involving one of the SDH subunits and assembly factors leads to destabilization of the protein complex and loss of immunoreactivity [9]. SDHB mutation was studied by immunohistochemical study, which is an easy and practical method in our case, and staining was observed with this marker and it was concluded that there was no mutation in the SDHB gene. When our case was evaluated according to the GAPP criteria, her score was found to be low, but since paraganglioma was not considered clinically at the beginning, biochemical measurement of catecholamine metabolites could be made 10 days after transurethral resection. In this case, the catecholamine level may have decreased to normal limits biochemically due to the resection of the tumor.

In addition to mutation status and GAPP criteria, tumor size and localization are also important in determining the poor clinical course [9]. In our case; no metastasis was detected according to the 18FDG-PET CT result. The functional status of the tumor is not known, but it can be said that the risk of metastasis is low due to the SDHB expression and small tumor size. The 2017 World Health Organization no longer classified paragangliomas as benign, even without metastasis as multifocal and progressive diseases have significant morbidity and mortality [12]. Therefore, how long these patients will be followed is a controversial issue, cases are presenting with metastasis even 20-40 years after diagnosis. For this reason, it is recommended that patients with paraganglioma should be followed for life with catecholamines and their metabolites and imaging methods [13].

More than 40% of patients with paraganglioma have germline mutations involving one of more than 20 genes. A genetic examination is recommended for determining disease progression because it enables early diagnosis and treatment of other family members before complications develop. Our case is an elderly patient, and sporadic mutation was thought to be more likely. A genetic examination was recommended for the patient, but could not be performed due to the patient's socioeconomic conditions.

CONCLUSION

Treatment approaches for paraganglioma and urothelial carcinoma are very different from each other; therefore differential diagnoses should be made carefully. Patients should be evaluated together with all morphological, clinical findings, and immunohistochemical study results. For a correct diagnosis, immunohistochemical studies should be performed in combination with neuroendocrine markers, keratins, and tyrosine hydroxylase.

Authors' Contribution

Study Conception: ÇÖ, HG; Study Design: ÇÖ, HG, SÇA; Supervision: HG, OO; Funding: ÇÖ, OO; Materials: ÇÖ, SÇA; Data Collection and/or Processing: ÇÖ, HG; Statistical Analysis and/or Data Interpretation: ÇÖ, SÇA; Literature Review: ÇÖ, HG; Manuscript Preparation: ÇÖ, SÇA and Critical Review: HG, OO.

Informed Consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images or data.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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