Malignant paraganglioma of the urinary bladder in a 44-year-old female: clinicopathological and immunohistochemical study of a rare entity and literature review

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Summary

Paraganglioma of the urinary bladder is a rare pathologic entity with no definitive histological, immunohistochemical or molecular features to determine its malignant potency. 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 less than 30 being malignant. We present a case of malignant paraganglioma of the urinary bladder in a 44-year-old woman. The patient's symptoms were painless hematuria and micturitional headache. The tumor presented the characteristic "zellballen" pattern of growth and immunohistochemically was positive for all neuroendocrine markers. The patient underwent partial cystectomy and the following two postoperative years were uneventful. The literature on paraganglioma of the urinary bladder, analyzing the histological, immunohistochemical and molecular characteristics, is reviewed.

Key words: Paraganglioma; Urinary bladder; Malignant.

Introduction

Paraganglioma of the urinary bladder is a rare entity, constituting less than 1% of all primary bladder tumors and 10% of extra-adrenal intraabdominal paragangliomas [1]. There are no histological, immunohistochemical, ultrastructural or molecular criteria that can help in the distinction between malignant and benign tumors and malignancy is mainly determined by clinical criteria. We present a case of malignant paraganglioma of the urinary bladder in a 44-year-old female patient.

Case Report

A 44-year-old woman was admitted in the Surgical Clinic of our hospital (Department of Urology) with the symptoms of painless hematuria for the last six months and episodes of headaches occurring during urination. The patient's history and clinical examination revealed no other pathology. Cystoscopy showed a papillary, ulcerated neoplasm emerging from the right lateral wall of the urinary bladder. Clinical diagnosis was that of urinary papilloma, but a biopsy was performed, and it revealed a neuroendocrine neoplasm, most compatible with paraganglioma, infiltrating the bladder wall. The patient underwent partial cystectomy with lymphadenectomy. Histological findings were that of a neoplasm arranged in nests, separated by thin fibrovascular trabeculae and of polygonal cells with granular cytoplasm, without significant nuclear polymorphism nor high mitotic index. The neoplasm invaded the deep muscularis of the bladder. Neoplastic cells were strongly positive for neuroendocrine markers such as neuron specific enolase (NSE), chromogranin and synaptophysin, whereas S-100 protein revealed the presence of a limited number of sustentacular cells. Negative staining for epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) confirmed the diagnosis of paraganglioma. The lymph nodes were free of disease. The following two postoperative years were uneventful and there was no further follow-up by the clinicians.

Discussion

The term paragangliomas describes neoplasms arising in the paraganglia, regardless of their location. Five groups of paraganglia are recognized: adrenal medulla, branchiomeric, intravagal, aorticosympathetic and visceral-autonomic paraganglia, the last four being categorized as extra-adrenal paraganglias. This distinction is based on anatomic distribution, innervation and microscopic structure [2].

The composition of all paraganglias consists of two cell types: neuroepithelial (pheochromocytes or chromaffin cells in the adrenal medulla, chief cells in the extra-adrenal paraganglia) and sustentacular or type II cells. Neuroepithelial cells originate from the neural crest (neuroectoderm) during embryonic life along with other elements of the autonomic nervous system and migrate to their final destination [2]. The adrenal medulla represents the largest complex of chromafin cells. Paragangliomas arising in this anatomic site are commonly defined as pheochromocytomas.

The extra-adrenal paraganglia are divided into two major categories: those related to the parasympathetic

Revised manuscript accepted for publication September 21, 2006

nervous system (branchiomeric, intravagal) composed of non-chromaffin cells, with chemoreceptive function and situated mainly in the head, neck and mediastinum and those related to the sympathetic nervous system (aortic sympathetic, visceral autonomic), composed of chromaffin cells and localized in the retroperitoneum, along the thoracolumbar paraaortic region and within blood vessels and numerous visceral organs (urinary bladder, liver hilus, interatrial septum of the heart, mesenteric vessels) [2, 3].

The chief cells of the paraganglia are arranged in well-defined nests (zellballen), separated by thin fibrovascular septae. They are also surrounded by a rim of sustentacular cells and their cytoplasm contains neurosecretory granules of catecholamines. Immunohistochemically, they stain with neuroendocrine markers NSE, chromogranin and synaptophysin, while sustentacular cells are positive to the S-100 protein.

Paraganglioma of the urinary bladder constitutes less than 1% of all primary bladder tumors (0.06 to 0.5%) and 10% of extra-adrenal intraabdominal paragangliomas [1]. Zimmerman *et al.*, were the first to report paraganglioma of the urinary bladder in 1953. Since then, almost 180 paragangliomas have been reported in the literature, with less than 30 being malignant.

The origin of paraganglioma of the bladder is uncertain. Some authors have indentified small nests of paraganglionic tissue in the muscularis propria and in the deep layers of the submucosa of the trigone, anterior and posterior wall of the bladder, while others believe that paragangliomas arise from embryonic rests of chromaffin cells in the sympathetic plexus of the detrusor muscle [2].

The mean age of occurrence is 41 years (range 11 to 78 years) and the prevalence is almost the same in both sexes [2]. The most common symptom of presentation is hematuria and about 50% of the cases present with symptoms resulting from catecholamine excess, such as paroxysmal or sustained hypertension, palpitation, headache and blurred vision. Occasionally, paragangliomas are multifocal in the bladder and are associated with extravescical paragangliomas [4]. A familial case and a unique case of synchronous occurrence with intestinal carcinoid have also been reported. Other associations include renal cell carcinoma, neurofibromatosis, polycystic bilateral disease of the kidney and carcinoma of the urinary bladder [3].

A preoperative diagnosis of a tumor is made in the presence of symptoms. The confirmation of the diagnosis is based on co-evaluation of the levels of catecholamines and their metabolites in a 24-hour urine test. If these levels are increased, I-metaiodobenzylguanidine (I-131 MBIG) scintigraphy demonstrates elevated uptake in the tumor area that persists for days. Excretory urogram, arteriography, ultrasonography and cystoscopy could be helpful for a preoperative diagnosis. At cystoscopy the tumor is usually visualized as a submucosal nodule, with or without overlying ulcerated mucosa (sometimes giving misleadingly the impression of hemangioma due to intense suburothelial vessel density) or as a pedunculated mass projecting into the bladder lumen. Biopsy is not recommended because of the risk of provoking a hypertensive episode, unless the patient is under proper medical treatment. In the majority of the cases though, a correct diagnosis of paraganglioma is difficult due to the absence of hormonal activity.

Histologically, paraganglioma of the urinary bladder mimics, in most cases, the structure of normal paraganglia. Tumor cells are usually organized in small nests (zellballen) separated by thin fibrovascular septae, but they may also grow in a diffuse pattern. Individual cells have abundant eosinophilic granular cytoplasm and centrally or eccentrically located nuclei. Atypical nuclei and vascular invasion may occasionally be seen, but they should not be taken as evidence of malignancy. Mitotic figures and necrosis are not often encountered. Stroma may be very abundant, often with a hyalinized quality [2]. Most urinary bladder paragangliomas are not well circumscribed and may mingle with bundles of smooth muscle fibers of the muscularis propria, without a desmoplastic reaction. This appearance simulates malignancy but cannot be considered as invasion [4]. Cellular elements similar to normal sustentacular cells are rare or may be totally missing. The normal relationship of nerve fibers to chief cell nests also does not exist [1].

Immunohistochemically, neuroendocrine markers as chromogranin, synaptophysin and neuron specific enolase (NSE) highlight the tumor ("chief") cells [5], whereas sustentacular cells stain with S-100 and G-FAP (glial fibrillary acid protein). Some investigators have reported immunoreactivity to neuropeptide Y and enkephalin, somatostatin , calcitonin, gastrin, serotonin and glucagone, vimentin, as well as VIP [5]. Tumor cells are not reactive to cytokeratin 7 and 20, high molecular weight cytokeratins AE1/3, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA) and p53 [2,5]. Cell proliferation index MIB-1 (Ki-67 antigen) is not supportive of rapid multiplication of the tumor cells, even in cases that are obviously clinically malignant [4].

Flow cytometry shows a DNA diploid pattern in tumors with clinically benign behavior, whereas aneuploid and tetraploid/polyploid patterns are observed in malignant, metastatic tumors. The tetraploid pattern is frequently observed in the most aggressive clinical forms [4]. Patients with previously diagnosed benign paraganglioma and DNA diploidy, who present recurrence of the tumor with lymph node or distant metastases, show DNA aneuploidy.

Treatment of paraganglioma includes complete resection of the tumor by transurethral resection, partial cystectomy or radical cystectomy combined with pelvic lymph node dissection, especially in the presence of proven metastasis [3, 6, 7]. Transurethral resection is not always considered as an ideal treatment since the risk of provoking uncontrollable hemorrhage is severe. Cystectomy remains the treatment of choice because the tumor can present local recurrence and there is also the possibility of multifocality [5]. Radiotherapy and chemotherapy have little effectiveness on locally recurrent and

metastatic paragangliomas. Recently though, some investigators have reported that radiotherapy in combination with chemotherapy seems to be effective in cases of malignant paraganglioma with local recurrence or lymph node metastasis. The combined use of radiotherapy and chemotherapy inhibits the tumor's growth and decreases serum and urinary levels of catecholamines [8]. Follow-up in cases of malignant paraganglioma is recommended, by measuring the levels of urinary catecholamines and their metabolites. If they are found elevated, a MIBG scintigraphy needs to be done so that a precise localization of the tumor can be made [3].

Although paraganglioma of the urinary bladder is a rare tumor with characteristic histological and immunohistochemical features, it may be misdiagnosed as urothelial cancer. Morphologic characteristics that may create confusion are a diffuse or nested growth pattern that mimics urothelial carcinoma and its nested variant, invasion of the muscularis propria and presence of necrosis or artifact changes induced by the transurethral resection [9, 10]. In addition, due to its rarity, paraganglioma is not often placed among the possible diagnostic choices of pathologists evaluating bladder tumors [9]. Metastatic prostate cancer to the urinary bladder can grow in solid nests and has uniform nuclei, but unlike paraganglioma, it is positive for cytokeratins, prostate-specific antigen and prostate-specific phosphatase [9]. Metastatic renal cell carcinoma also has a nested pattern of growth and thin vascular septae, but the positivity for cytokeratins, epithelial membrane antigen (EMA), CD 10 and RCC antigen and the negativity for neuroendocrine markers can be helpful in the differential diagnosis of paraganglioma [10]. Granular cell tumor, although extremely rare in the urinary bladder, must be included in the differential diagnosis when facing a tumor with an unusual pattern of growth. Metastatic large cell neuroendocrine carcinoma and malignant melanoma, as well as carcinoid tumor, are other entities that need to be taken into consideration. In any case, the presence of a zell-ballen pattern and fine vascular network, insignificant cellular anaplasia or high mitotic index, along with the characteristic immunohistochemical profile, should contribute to the recognition of paraganglioma. Diagnosis is facilitated if the clinical symptom of catecholamine excess coexists and the preoperative control is suggestive of a hormone-active tumor [10].

About 5-15% of paragangliomas of the urinary bladder are malignant. There are no histologic criteria to determine the malignant potency of a tumor other than the presence of local invasion, lymph node and distant metastases. Necrosis, vascular invasion and number of mitoses have been linked to a more aggressive behavior, but an association between these features and malignancy is not always confirmed. Similarly, the hypothesis expressed by certain investigators that there is an inverse correlation between the density of the sustentacular cells, identified by S-100 and GFAP immunostain or electron microscopy, the intensity of chief cell staining and tumor grade, can not always predict an accurate prognosis. The relationship between these two cell populations is stable in normal paraganglia and benign tumors and a progressive loss of sustentacular cells observed in tumors of increased degree of malignancy may suggest potential future metastases, but the contradictory literature reports do not allow the use of this feature as an absolute prognostic factor [1, 3, 4, 7].

An increase of MIB-1 index and p53 expression is equivocal in case of malignant paraganglioma [5], whereas marked expression of VEGF in tumor cells may constitute a prognostic factor [4].

DNA ploidy cannot be reliable in distinguishing benign from malignant paraganglioma although, in almost all reported cases of malignancy, flow cytometry gives an abnormal pattern [5].

Anton *et al.,* indicated the secretion of 3.4 dihydrophenylalanine (dopa) and dopamine on behalf of the malignant counterpart as a biochemical difference between benign and malignant tumors, but further investigation is needed.

At present, tumor staging and complete resection are the most important prognostic factors in cases of paraganglioma of the urinary bladder. Due to the propensity of local recurrence and development of metachronous metastasis, lifelong follow-up is warranted.

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