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Metastatic primary neuroendocrine carcinoma of the genitourinary tract: A case report of an uncommon entity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 59
Final Diagnosis: Neuroendocrine carcinoma of urinary bladder
Symptoms: Dysuria • hematuria
Medication: –
Clinical Procedure: MRI • cystoscopy
Specialty: Urology • oncology

Objective: Rare disease

Background: Neuroendocrine carcinomas of the genitourinary tract are rare but distinct and important entities because they are very aggressive tumors and are usually advanced or metastatic at the time of diagnosis. A high index of suspicion must be held by the pathologist viewing the specimen, as it can easily be misdiagnosed as a high grade urothelial carcinoma. Specific, proven treatment algorithms have been formulated over the years for the latter, whilst neuroendocrine carcinomas of the genitourinary tract are rare and treatment regimes have not yet been proven to show a significant improvement in survival in the majority of cases, so accurate diagnosis is important.

Case Report: We report the case of a 59-year-old man who presented with a short history of dysuria and frank hematuria. Imaging and cystoscopy revealed a large exophytic mass in the base of the urinary bladder, which extended into the bladder neck. Metastatic deposits were already present in his liver and vertebrae. Histology revealed a neuroendocrine carcinoma.

Conclusions: A comprehensive review of the existing literature regarding this rare but aggressive tumor is presented, including advances in classification, pathogenesis, and treatment.

Key words: bladder • neuroendocrine carcinoma • small cell

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Background

Neuroendocrine carcinomas of the genitourinary tract are much less common than traditional-type epithelial carcinomas in this locality. They are more common in elderly men and are aggressive tumors that are usually metastatic at the time of presentation and as such have a worse prognosis. Unfortunately, because of the rarity of this entity, no definitive treatment algorithms have yet been put forward. We present a case of this rare malignancy that was metastatic at the time of diagnosis.

Case Report

A 59-year-old hypertensive, diabetic man presented to the University Hospital of the West Indies (UHWI) with a 3-week history of dysuria and frank hematuria. Investigations done prior to his presentation to hospital included an abdominopelvic ultrasound, which revealed 2 bladder masses in the region of the posterior-lateral base, as well as a moderately enlarged prostate with evidence of mild bilateral hydronephrosis. The liver contained 2 nodules. His blood prostate specific antigen (PSA) level was 8.06 ug/L. The patient gave a history of smoking but did not quantify this.

Cystoscopy was undertaken and a broad-based, flat, irregular bleeding tumor was visualized in the bladder base and trigone extending into the neck. Evacuation of clots and a transurethral resection of the bladder tumor were performed. However, post-operatively, he continued to have frank hematuria and returned to the surgical unit 2 days later for fulguration.

MRI done subsequently revealed thickening of the posterior wall of the bladder with an associated irregular exophytic mass. A normal prostate was not appreciated and this was thought to be in keeping with the patient's previous history of a transurethral resection of the prostate gland (TURP). It was noted, however, that the mass extended inferiorly to fill this region. A flat plane was appreciated between the mass and the rectum. Bilateral hydronephrosis was noted. Multiple enlarged iliac lymph nodes were seen as well as multiple liver nodules. Deposits consistent with the appearance of a tumor were also noted in the lumbar vertebrae.

Despite marked cautery artifact, the biopsy of the bladder mass revealed extensive transmural infiltration of the bladder wall by sheets, nests, and trabeculae of malignant cells exhibiting numerous abnormal mitoses and large areas of necrosis (Figure 1). Immunohistochemistry revealed intense positivity for neuroendocrine markers, specifically neuron specific enolase [NSE] and chromogranin (Figure 2). There was negative staining for cytokeratin and prostate-specific antigen (PSA). These features were in keeping with a poorly differentiated neuroendocrine tumor. Neither a focus of origin nor *in situ* urothelial carcinoma was identified in the biopsy. No other concurrent carcinoma was identified in the specimen examined.

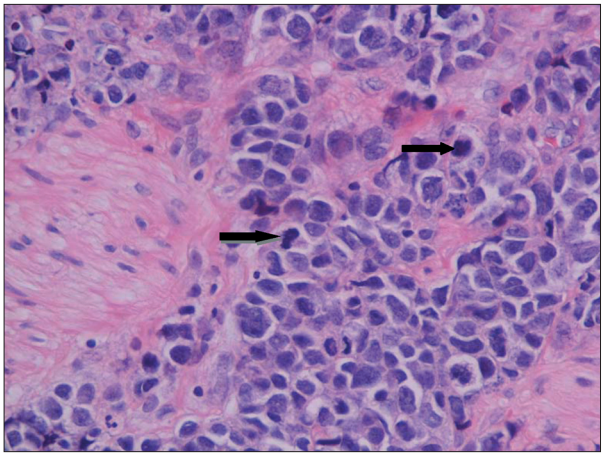

Figure 1. Nests and trabeculae of tumor cells exhibiting mitoses (arrows). [Hematoxylin and eosin, ×400].

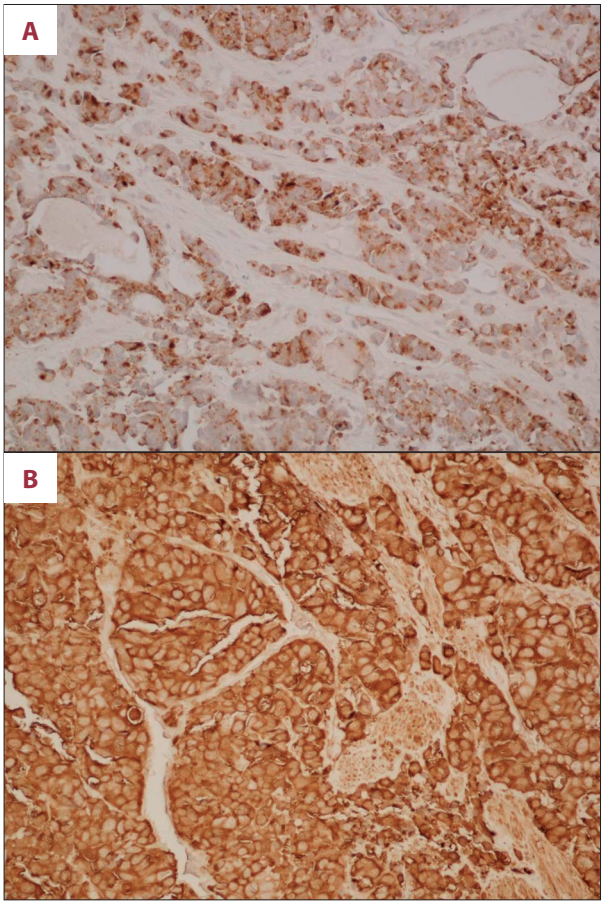

Figure 2. Positive staining for chromogranin (**A**) and neuron specific enolase [NSE] (**B**).

Discussion

Neuroendocrine (NE) neoplasms are a heterogeneous group of tumors arising from neuroendocrine or neurosecretory cells. These cells are scattered throughout various organ systems in the body and secrete a variety of neurotransmitters, neuromodulators, or neuropeptide hormones. The neoplasms that arise from these cells, although showing specific features of the organ of origin, also show features common to all such neoplasms as variably positive staining by neuroendocrine immunohistochemical stains including synaptophysin, chromogranin, and neuron-specific enolase. In addition, they all show the presence of cytoplasmic dense-core granules on electron microscopy.

The new WHO classification divides these neoplasms into neuroendocrine tumors (NTs) and neuroendocrine carcinomas (NCs) [1,2]. NTs correspond to the carcinoids of the old nomenclature, and NCs are divided into low- and high-grade. Atypical carcinoids with local invasion and lymph node metastases are now regarded as low-grade NC, while classic small cell carcinoma (SCC) and large cell neuroendocrine carcinoma qualify as high-grade NC. Our patient would be placed into this latter category of tumors.

Neuroendocrine tumors occur in various sites in the body, most commonly in the lungs and gastrointestinal tract, including the pancreas. Rarely, they also occur in the genitourinary (GU) system, usually in the kidney, prostate, or urinary bladder. The urinary bladder is the most common site for genitourinary extrapulmonary NTs. It is, however, relatively rare, with the first published case appearing in 1981 [3], and accounts for less than 1% of all bladder tumors [4]; since then there have been several case reports and small series published about this entity.

Bladder NC shows a male predominance, with the quoted male: female ratios in the literature ranging from 2:1 to 5:1 [4–9]. The mean age reported in the literature for patients with bladder NC is 60 to 70 years [4–9]. As with traditional urothelial carcinoma, painless hematuria is the most common presentation of patients with bladder NC [6,8,10] and this was the case in our patient. Our index case also gave a history of cigarette smoking, and it has been documented that up to 70% of patients report a smoking history [10].

We propose that this lesion was a primary tumor of the urinary bladder even though on imaging the tumor was seen to extend inferiorly into the region occupied by the prostate gland. There was a verbal history of a previous TURP in this patient for nodular hyperplasia; however, a histology report could not be found. The great majority of the tumor mass was noted within the bladder; also, the tumor was negative for PSA (although up to 60% of primary prostatic NC are negative for this marker [11]). It has been suggested in the existing literature that these lesions be determined to be primary GU lesions based on clinical and radiological grounds, as up to 25–39% of the primary NCs of the GU tract may stain positive for thyroid transcription factor-1 (TTF-1) [11], thought to be a marker of primary pulmonary neoplasms.

Several theories regarding the potential origins of the NTs of the GU system have been put forward. One such is that these tumors are derived from NE cells of the diffuse NE system, which may increase in numbers in reactive conditions. Another is that they are derived from multipotent stem cells [11].

Conclusions

GU neuroendocrine carcinomas are rare entities that generally have a poor prognosis and are usually metastatic at the time of diagnosis, as was the situation with our index case. The optimal therapy for patients with bladder NC is difficult to define because of the rarity of this entity. Age over 65 years and locally advanced or metastatic disease at presentation are thought to be predictors of poor survival, and early treatment with cisplatin-based chemotherapy has been associated with a favorable prognosis [12].

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