Small-cell carcinoma of the penile urethra: a case report and a short review of the literature

Introduction

The diffuse neuroendocrine-cell system (DNS) consists of a wide variety of cells that are present in the central and
Peripheral nervous system and in many classic endocrine organs. These cells share the ability to produce many biologically active amines, peptides and other substances (such as neuron-specific enolase, chromogranins, synaptophysin and Leu-7). Cells and neoplasms of the DNS are divided into two groups: those of the neural type and those of the epithelial type which includes neuroendocrine tumors (NETs) from numerous sites. The major categories of morphologically identifiable NETs are carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma and small-cell carcinoma. Nineteen percent of NETs are located in the gastrointestinal tract or in the bronchopulmonary tree [1]. Cases of small-cell carcinoma in other sites are rarely reported.

We report a case of a small-cell carcinoma arising from the distal urethra, one of the most infrequent locations of a primary NET in the urogenital tract, describe its clinical, histological and immunohistochemical presentation and discuss its management.

The differential diagnosis of this entity includes a heterogeneous group of neoplasms such as neuroblastoma, carcinoid, small-cell variant of osteosarcoma, primitive neuroectodermal tumor, Merkel cell tumor (MCC) and metastatic small-cell carcinoma. In our case, the differentiation from a MCC was rather difficult and additional immunohistochemical staining proved to be very helpful in this case. MCC is a rare skin tumor of a highly malignant nature which is usually located in the head and neck area and on the extremities (sun exposure) [2]. MCC, similar to other small-cell malignancies, is a radiosensitive and chemosensitive disease. Radiotherapy and/or chemotherapy is indicated in patients with clinically (and usually pathologically) noticed lymph nodes because of the high risk of regional relapse following surgery alone [3]. Patients treated aggressively with surgery and locoregional radiotherapy have ~50% chance of cure. In the review reported by Tai et al. [4], the most commonly used chemotherapy regimens were cyclophosphamide/doxorubicine (or epirubicin)/vincristine and etoposide/cisplatin (or carboplatin) combinations with overall response rates of 75% and 60%, respectively.

Concerning the neuroendocrine malignancies of the male genital tract there is an absolute lack of knowledge about the optimal management because of the limited number of reported cases in this area. Neoplasms of the distal urethra can be successfully managed surgically even if regional lymph nodes are involved. For tumors arising in the proximal urethra surgery has included penectomy and prostavesiculecctomy, penectomy, cystoprostatectomy and supravesical diversion and pelvic lymphadenectomy. In analogy with primary NETs in other areas, platinum-based chemotherapy may be an option for patients presenting with metastatic disease [5]. The definitive role of chemotherapy and radiotherapy in the adjuvant setting after surgery, however, remains uncertain.

case report

A 57-year-old man with a history of herniated lumbar disc, deep venous thrombosis and nephrolithiasis presented with a left inguinal mass which had been noticed for 4 months and had become painful in the last two weeks. Three months before presentation he experienced an episode of urinary tract infection. There was no weight loss, fever, night sweat or fatigue. Familial history elicited a mother with metastatic bladder cancer and a brother with a brain tumor. Clinical examination revealed the man in a good general condition (World Health Organization performance status 0) and a nontender palpable left inguinal mass, measuring 4.0 × 3.0 cm. Digital rectal examination was normal. Routine blood analyses were negative, as were marker tests including neuron-specific enolase, carcinoembryonic antigen, chromogranin, human chorionic gonadotropin and α-fetoprotein. An excisional biopsy of the lymph node was carried out and the histologic examination showed a small-cell neuroendocrine carcinoma with immunoreactivity for pan-cytokeratin, cytokeratin 20 and chromogranin, while there was only a weak immunoreactivity for Leu-7 and no reactivity for CD45. Furthermore, dense core granules were demonstrated by electron microscopy. Because of these findings the diagnosis of a Merkel cell carcinoma was initially made [6]. More extensive clinical examination revealed the presence of a tumor of the distal part of the penis and purulent discharge from the urethral meatus was noticed. Computed tomography of the thorax and abdomen showed no evidence of disease. Positron emission tomography (PET) did not reveal the primary tumor site, however the scan was performed only rostral to the pelvis. Whole body scintigraphy with 111-In-Octreotide (Octreoscan®) finally confirmed the presence of a lesion in the penis. The patient underwent a distal penectomy and left inguinal lymph node dissection. Histological examination of the penectomy specimen demonstrated a small-cell carcinoma of the penile urethra which infiltrated into the corpus spongiosum (pT2pN2M0). This time the neoplastic cells were immunoreactive for NCAM, chromogranin and synaptophysin, but not for Leu-7 and CK20 (Figure 1A and B). The only lymph node found at surgery at that time did not contain tumor cells.

In order to further distinguish between the initially suggested diagnosis of a MCC (on the basis of the lymph node specimen) and the more likely diagnosis of a small-cell NET of the urethra, additional immunohistochemical staining with E-cadherin was carried out on both the initial lymph node specimen and the penectomy specimen. Interestingly, in both specimens E-cadherin expression was primarily membranous and not nuclear (Figure 1C and D), giving further support to the diagnosis of a NET of the urethra [7].

The patient received adjuvant chemotherapy with etoposide, cisplatin and ifosfamide, but refused further treatment after three cycles. Thereafter, locoregional radiotherapy was given to both inguinal regions (52 Gy). Thirty months after diagnosis the patient presented with left-sided enlarged supravacular lymph nodes and had an elevation of his serum neuron-specific enolase (122 ng/ml). A PET scan indicated involvement of both inguinal, retroperitoneal and supraclavicular lymph nodes. Treatment with chemotherapy (carboplatin/etoposide) did not lead to a renewed response; he developed progressive skin metastases, edema of the left arm and right leg, deteriorated rapidly and ultimately died 35 months after diagnosis.
Only since the late 1980s has small-cell carcinoma of the genitourinary system been reported and shown to occur in the prostate, bladder and kidney [8].

NETs occur more frequently in the female genital tract than in the male genital tract; most are uterine small-cell carcinomas or ovarian carcinoids [9]. Primary NETs of the uterine cervix and Merkel cell carcinoma of the vulva have been described rarely [10–12].

Concerning the male genital tract, focal neuroendocrine differentiation in a conventional prostatic adenocarcinoma is not uncommon, but small-cell carcinomas in the prostate are relatively rare. Carcinoids are not uncommon in the testis and should be distinguished from metastatic tumors; however, carcinoids are extremely rare elsewhere in the male genital tract. Small-cell neuroendocrine carcinomas have been reported in the scrotal or penile skin (as Merkel cell carcinoma) but are extremely rare in the penile urethra [9].

Among the different tumors arising in the male urethra, squamous cell cancer is the most frequently occurring histologic type (80%), the remaining being mainly transitional cell carcinoma (15%) and adenocarcinoma or undifferentiated carcinomas (5%). Those arising in the prostatic and membranous part of the urethra (usually transitional cell type) are often associated with bladder tumors, while those arising in the bulbous or penile part (usually of squamous cell type) rarely do. Tumors of the distal urethra usually metastasize to the inguinal nodes, those of the proximal urethra mostly spread to the pelvic nodes. Palpable inguinal nodes occur in ~20% of the cases and nearly always represent metastatic disease [13].

Only four cases of a primary NET of the penile urethra have been described in the literature earlier [14–17]. To our knowledge, a primary neuroendocrine carcinoma of the distal penile urethra with clinically evident regional metastases has never been reported before. The cases reported by Sylora et al. [14], a carcinoid tumor of the mid penile urethra, and Parekh et al. [16], a small-cell carcinoma of the mid penile urethra, were initially recognized as transitional cell carcinomas without inguinal lymph nodes. The case described by Vadmal et al. [15] was indeed a primary NET of the distal penile urethra with regional metastases, but the diagnosis of regional metastases was only evident from radiologic studies and was not evident clinically. The case reported by Rudloff et al. [17] was an extensively disseminated neuroendocrine carcinoma of the proximal urethra but again without palpable lymph nodes at clinical examination.

In our patient, we choose for adjuvant chemotherapy because of the metastatic presentation of the disease and thus assuming a poor prognosis. Radiotherapy was given to both inguinal regions because of the unilaterally involved inguinal lymph node at presentation and the known anatomic lymph node drainage pattern. Nevertheless, the disease recurred at distant sites 30 months after initial diagnosis, and the patient died 5 months later.
The origin of extrapulmonary small-cell carcinoma remains uncertain and multiple theories have been proposed. The mostly accepted theory is that of Kobori and Oota [18], who showed that multiple lines of differentiation of tumors may arise from a multipotential stem cell.

In theory, the primary tumor in our case could have been developed from epithelial Merkel cells of the frenulum as described by Tomic et al. [19]. The urologic examination and the later findings in the pathology specimen all, however, suggested that the pluripotent stem cells of the urethral epithelium, capable of neuroendocrine differentiation, were the most likely source of origin. The initial diagnosis of a MCC became less likely because of the membranous expression of E-cadherin in both the neoplastic cells in the lymph node biopsy and the penectomy specimen. E-cadherin is indeed the most frequently expressed cadherin in MCC, however the pattern of expression is more nuclear rather than membranous. This finding has additional value and potential use in the differential diagnosis of these tumors [7].

**Conclusion**

Malignant neoplasms of the distal penile urethra are usually treated with partial penectomy alone. Adjuvant chemotherapy and radiotherapy to the regional lymph nodes should be considered in case of penile NETs because of their anticipated worse outcome. The present case is of particular interest because it illustrates that very uncommon tumors of the genital tract can present with an inguinal mass, supporting the notion of taking an adequate medical history and performing a good clinical examination.

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