

Case - Stage IV penile small-cell neuroendocrine carcinoma

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INTRODUCTION

Penile cancer is rare and exhibits significant geographic variability, affecting 0.1-1 men per 100 000 in highly developed countries, and up to 6.8 men per 100 000 in Brazil.¹⁻³ Mortality is similarly variable, ranging from 0.15 per 100 000 in Canada to 0.4-3.4 per 100 000 in several South American, African, and Southeast Asian countries.⁴ The most significant risk factor is human papillomavirus (HPV) infection, particularly strains HPV 16, 6, and 8, with a global meta-analysis revealing a prevalence of 50.8% in penile cancer and 79.8% in penile intraepithelial neoplasia.⁵ Age between 50-60 years, lichen sclerosis, balanitis, obesity, and smoking are other significant risk factors, while circumcision and vaccination against HPV are protective factors.^{1,2,5}

Approximately 95% of penile cancers are squamous cell carcinoma arising from the prepuce and penile glans.^{1,2} Primary non-squamous cell cancer of the penis is exceedingly rare, and can include basal cell carcinoma, melanoma, sarcoma, or extramammary Paget's disease.⁶⁻⁹ Small-cell neuroendocrine carcinoma (SCNC) of the penis is nearly absent from the literature, with only four cases arising from the penile urethra, and only one of penile origin, with a lack of clinicopathologic details.¹⁰⁻¹⁴ This article presents the first detailed case report of primary penile SCNC.

CASE REPORT

A 64-year-old male of East African origin presented to the emergency department (ED) with difficulty urinating and a several-week history of ulcerative penile lesions. Swabs done by his primary care physician were negative for gonorrhea, herpes simplex virus 1 and 2, and hepatitis. The patient voided after receiving intra-

venous hydration and was therefore discharged with an outpatient referral to the infectious disease service.

He returned to the ED three days later with 48 hours of gross hematuria, straining, and dysuria. He was afebrile, with no nausea or vomiting. He presented with a visibly swollen left leg and reported one week of right flank discomfort. He was found to have left inguinal lymphadenopathy measuring 3.6 cm on ultrasound. He was discharged with urgent urology clinic followup.

He presented to the urology clinic in a wheelchair one week later with voiding dysfunction, including diminished flow and dysuria, daily gross hematuria, and new urinary incontinence. He reported worsening of the swelling in his left leg. His physical exam revealed a 7 mm non-bleeding ulcerative lesion at the urinary meatus, firm underlying corporal bodies extending to the proximal midshaft, and left-sided inguinal lymphadenopathy with left lower leg pitting edema.

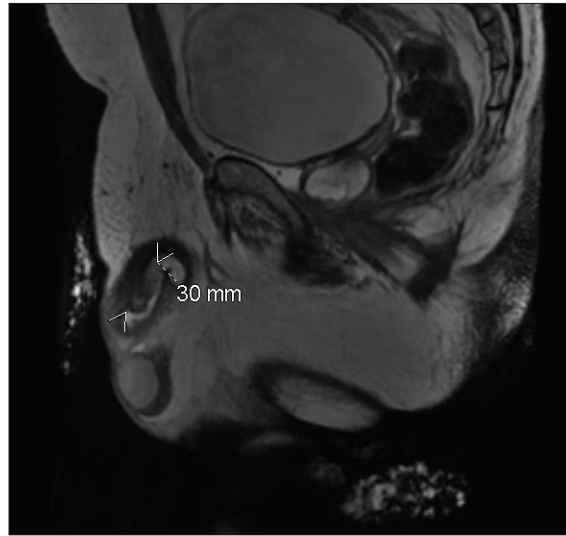
Past medical history is notable for stage 5 chronic kidney disease secondary to diabetic nephropathy, hypertension, obstructive sleep apnea, and gout. He is a lifelong non-smoker. He completed treatment for latent tuberculosis in 2023 and had prior hepatitis B infection with antibodies from the prior year, suggesting immunity. Past surgical history is relevant for a buried peritoneal dialysis catheter inserted in 2022 and prior bilateral inguinal hernia repairs. A clinic punch biopsy of his penile lesion was performed, and he was admitted for expedited workup of suspected invasive penile carcinoma.

Staging investigations included computed tomography (CT) of the chest, abdomen, and pelvis, which revealed widespread lymphadenopathy, including cervical and supraclavicular nodes, and metastatic nodal disease throughout the abdomen. Pelvic magnetic resonance imaging (MRI) (Figure 1) revealed a penile mass within the distal corpus spongiosum measuring 31x17 mm and associated dilatation of the penile urethra. Bone scan and CT spine were both unremarkable.

All viral swabs and serology, including HPV, returned negative, along with negative blood and urine cultures, with no infectious source identified on his staging scans. Four days after admission, there was evidence of pancytopenia, ongoing acute kidney injury with creatinine of 643, and a potassium of 5.7 requiring hemodialysis. He continued to deteriorate despite hemodialysis, developing delirium and persistent pancytopenia requiring platelet transfusions. This raised concern for hemophagocytic lymphohistiocytosis. He

KEY MESSAGES

- Penile cancer is a rare disease, with squamous cell carcinoma accounting for 95% of cases, and human papillomavirus infection being the most significant risk factor.
- Small-cell neuroendocrine carcinoma of the penis is hypothesized to arise from pluripotent stem cells of the penile urethra and is identical in microscopic appearance to small-cell lung cancer.
- There are no treatment guidelines specific to penile small-cell carcinoma, but reports in the literature have used a combination of surgery, platinum-based chemotherapy, and radiation, with limited success.



Figures 1. Sagittal T2 penile magnetic resonance image with contrast. Image quality was limited by significant movement secondary to patient confusion. The penile urethra is distended proximal to a distal penile urethral mass, measuring approximately 31 x 17 mm, showing T2 heterogeneous (predominantly hyperintense) signal (300/85) with ulceration on the penile tip.

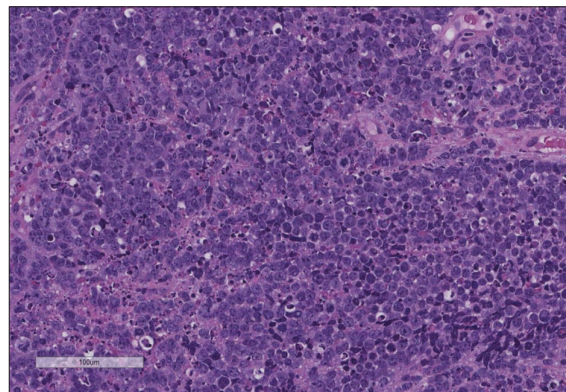


Figure 2. Hematoxylin and eosin-stained section of penile mass showing tumor cells with scant cytoplasm, round to oval nuclei with nuclear molding, fine granular nuclear chromatin, brisk mitotic activity, and scattered apoptotic bodies.

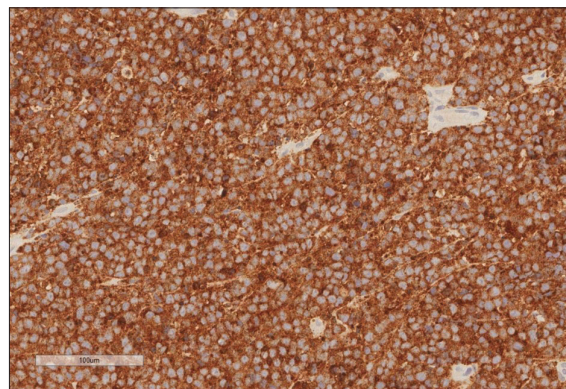


Figure 3. The same tumor cells showing immunoreactivity for synaptophysin.

was assessed by the benign hematology service and oral dexamethasone was initiated.

Over the next week, the patient continued to receive frequent hemodialysis, platelet transfusions, and dexamethasone, with only mild and transient improvements in delirium. Approximately two weeks from his initial presentation, the medicine team initiated empiric intravenous antibiotics with piperacillin-tazobactam due to worsening level of consciousness and suspicion of infection. The following day, a suprapubic catheter was inserted for gradual onset urinary retention, with post-void residual volumes above 500 ml.

The pathology from the clinic biopsy revealed invasive SCNC. There was brisk mitotic activity and tumor necrosis (Figure 2). There was also a small focus of squamous epithelium with cytologic atypia, which was not overtly neoplastic. By immunohistochemistry, the neoplastic cells were positive for synaptophysin (Figure 3), chromogranin, and P16. Tumor cells also stained positive focally for pancytokeratin. The tumor cells were negative for CK7, CK5, CK20, GATA3, P40, and CD45. The proliferation index with Ki67 labelling was >95%. The small portion of squamous epithelium was negative for P16. A left supraclavicular lymph node biopsy was also consistent with metastatic SCNC.

Upon consultation, medical oncology felt there was no role for chemotherapy given the atypical pathology and advanced grade IV disease at presentation. He continued to require hemodialysis, and the prognosis was guarded. A family meeting was held, and the deci-

sion was made to transition to palliative measures. The patient died surrounded by family in the following days from hyperkalemic cardiac arrest.

DISCUSSION

Small-cell carcinoma is an aggressive neuroendocrine cancer that typically arises in lung tissue and is strongly linked to smoking. Pulmonary SCNC most often arises due to a disruption in DNA repair mechanisms from mutations causing loss of tumor suppression genes RB1, TP53, and FHIT.¹⁵ While SCNC accounts for 10-15% of all lung cancers, extrapulmonary SCNC are responsible for only 2.5-5.0% of all small-cell carcinomas.¹⁶ Despite its rarity, extrapulmonary SCNC has been reported throughout the body, including the head and neck, digestive and hepatobiliary tracts, renal collecting system, gynecologic system, and male genitourinary systems.^{14,16} Extrapulmonary SCNC often presents atypically and carries a very poor prognosis, with an overall five-year survival rate of only 13%.¹⁴

With only four cases reported with a penile urethral origin, and one case of penile origin without clinical details, the pathology of penile SCNC is poorly understood. It has been hypothesized that pluripotent stem cells of the penile urethral epithelium are capable of malignant transformation and differentiation into SCNC.^{11,16} Pathologic examination, including morphology and immunohistochemistry, reveals lesions that are indistinguishable from pulmonary SCNC.

The treatment of penile SCNC is also not clearly defined. All four patients in prior case reports of penile urethral SCNC underwent surgical excision, with three of four receiving chemotherapy, and half receiving inguinal nodal dissection.¹⁰⁻¹³ Long-term outcomes were not consistently reported. In a report of 81 patients undergoing surgery for extrapulmonary SCNC, 75% of patients had disease recurrence in a median of six months, despite adjuvant cisplatin-based chemotherapy in 17% and adjuvant radiotherapy in 40%.¹⁴ A recent retrospective study examined extrapulmonary SCNC treated with platinum doublet regimens, including cisplatin or carboplatin combined with 5FU or etoposide, and found an improvement in Ki-67 proliferation index values, but lacked a comparison group.¹⁷ While a treatment protocol is not clearly defined, a combination of surgery, platinum-based chemotherapy, and radiation has been used to treat extrapulmonary SCNC, including penile SCNC.

CONCLUSIONS

Penile SCNC is an exceedingly rare, lethal, and poorly understood variant of penile cancer. We present an

unfortunate case of a patient presenting with advanced, stage IV penile SCNC, who died weeks later. The aggressive nature and lack of a standardized protocol in treating penile SCNC highlight the importance of rapid assessment of any penile lesions with malignant suspicion, including prompt biopsy and appropriate staging.

COMPETING INTERESTS: Dr. Cagiannos has been an advisory board member/speaker/moderator for Bayer, Ferring, Janssen, Knight, TerSera, and Tolmar. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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