Case Report

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Primary urethral squamous cell carcinoma: a unique manifestation of a penile tumor

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Abstract

This case report describes a unique manifestation of a primary urethral squamous cell carcinoma (SCC) as the underlying pathology in an 80-year-old male patient who underwent partial penectomy due to an enlarging penile mass. Persistent pain in the right knee was discovered to be a pathologic fracture using magnetic resonance imaging. Computed tomography-guided biopsy confirmed metastatic SCC. Whole-body positron emission tomography revealed systemic dissemination to multiple sites. Orthopedic knee replacement was performed in combination with local radiotherapy. Palliative chemotherapy was rejected due to poor performance status. Primary urethral SCC is rare and an uncommon cause of advanced penile cancer. These findings could be of great interest to clinicians for two reasons. First, a tumor's appearance can be misleading. Consequently, histological work-up in accordance with clinical guidelines is necessary for accurate diagnosis. Second, a more comprehensive investigation is required when clinical symptoms persist despite the use of conventional treatment. Our case is an instance in which persistent pain masked the presence of downstream metastasis. We believe that these aforementioned points are of significant clinical importance and present a salient learning opportunity.

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Introduction

Penile cancer is rare (incidence <1/100,000 men).[1] There are several well-known risk factors associated with the development of penile cancer, including phimosis, smoking, multiple sexual partners, and early age at first intercourse.[1] Furthermore, human papilloma virus (HPV)-related carcinogenesis is reported in more than one-third of all cases.[1]

Although penile cancer might be expected to be the underlying cause of a penile mass, a primary urethral carcinoma as the origin can be revealed by histology. Primary urethral carcinoma has several predisposing factors in common with penile cancer but is 6 times less frequent (incidence approximately 1.6/1,000,000 men).[2] Although squamous cell carcinoma (SCC) constitutes the vast majority (>95%) of penile cancer, it comprises approximately 20% of all primary urethral carcinomas.[1,2]

Herein, we present an unusual case of a man in whom a primary urethral SCC was the underlying cause of penile cancer.

Case presentation

An 80-year-old man presented with symptomatic urinary retention due to an enlarging penile mass. In the preceding 3 months, the patient had experienced intermittent gross hematuria. Furthermore, he reported the presence of non-traumatic pain in the right knee during the prior 2 weeks; notably, he complained of load-dependent pain corresponding to an 8 on a numeric rating scale (i.e., from 0 = no pain at all, to 10 = most pain imaginable). Physical examination also revealed palpable lymph nodes in the right groin. Although the patient was fully aware of these changes, he felt embarrassed and delayed medical attention until his condition became almost unbearable for him.

First, a percutaneous suprapubic cystostomy was placed, which immediately relieved urinary retention. Then, conventional X-rays of the right knee were conducted; however, these did not show any pathology (Figure 1a). With adequate analgesia, the patient was able to strain his right leg without any restriction. The following day, tumor staging using computed tomography showed nodal enlargement in the right groin, but found no organ or other nodal metastasis (cT3 cN2 cM0). Partial penectomy was performed shortly after. Histology (Figure 2a–c) revealed a pT3 G2 primary urethral SCC.

A couple of days after the surgery, the patient reported persistent pain in the right knee despite the administration of adequate analgesia. Thus, magnetic resonance imaging (Figure 1b) was performed, which revealed a pathologic fracture of the distal femur. Computed tomography-guided biopsy verified metastasis (Figure 2d–f). Using whole-body positron emission tomography (Figure 1c), systemic dissemination to multiple sites became evident (i.e., pT3 cN2 cM1). Considering all findings, we discussed this case at length during our multidisciplinary tumor board. As a result, total knee arthroplasty was performed 2 weeks later, in combination with local radiotherapy for presenting symptomatology and ambulation. Palliative chemotherapy was

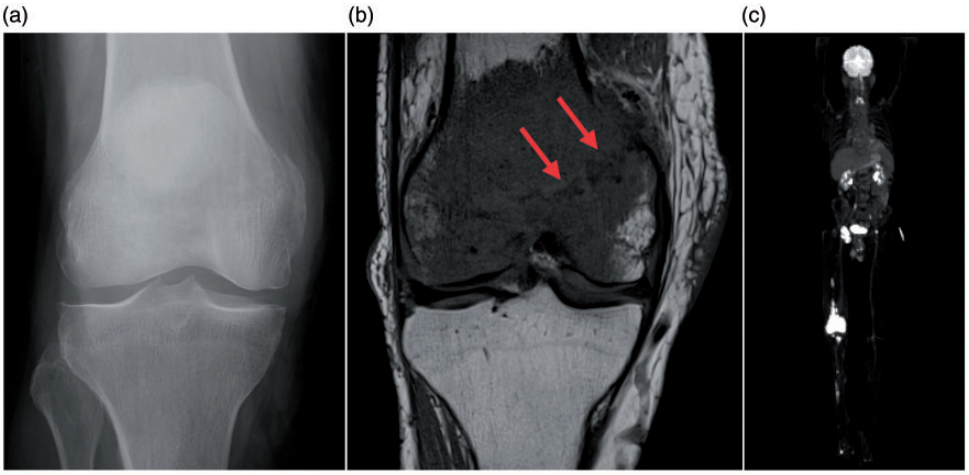

Figure 1. a: Plain film radiographs (anterior posterior view) of the right knee demonstrating no obvious pathology. b: Coronary T1-weighted magnetic resonance imaging of the right knee showing extensive metastasis with cortical infiltration and a fracture line of the medial femur condyle (arrows). c: Whole-body positron emission tomography scan displaying dissemination to multiple sites: bilateral inguinal lymph nodes, right femur, right fibula, right tibia, and right fourth metatarsal bone.

also considered; however, it was not initiated due to the patient's poor performance status (i.e., grade 3 of the Eastern Cooperative Oncology Group, ECOG).[3]

Thus, the patient was discharged but followed up regularly for replacement of the suprapubic catheter and clinical evaluation. Although his performance status improved to an ECOG grade 2 over the next 2 months, the patient declined palliative chemotherapy. Four months after initial presentation, he underwent palliative radiotherapy to manage symptomatic bilateral lymph node enlargement of the groin. As a consequence of his progressive disease, the patient's condition deteriorated significantly and he was placed in a hospice to receive the best palliative care possible. The patient succumbed to his illness, 6 months after initial presentation.

Discussion

Primary urethral SCC is a very uncommon cause of penile tumors.[2] Whereas primary urethral carcinoma is very unlikely to occur in adults under the age of 45 years, its highest incidence rate is often reported in individuals at 75 years and older.[2,4] In men, who are approximately three times more frequently affected than women, primary urethral SCC can develop from predisposing factors such as urethral strictures, chronic urethral irritation and inflammation, or sexually transmitted diseases, such as HPV-associated condylomata.[2] Although chronic inflammation and HPV infection are also common risk factors for penile cancer,[1] the prevalence of HPV in the male urethra is much lower.[5]

The European Association of Urology (EAU) guidelines on primary urethral carcinoma recommend diagnostic urethrocystoscopy with biopsy for primary assessment [level of evidence (LE) 3, grade of recommendation (GR) B], as crucial information regarding tumor extent and location, as well as subtype classification, can be determined through histological examination.[2] Interestingly, in contrast to penile cancer,

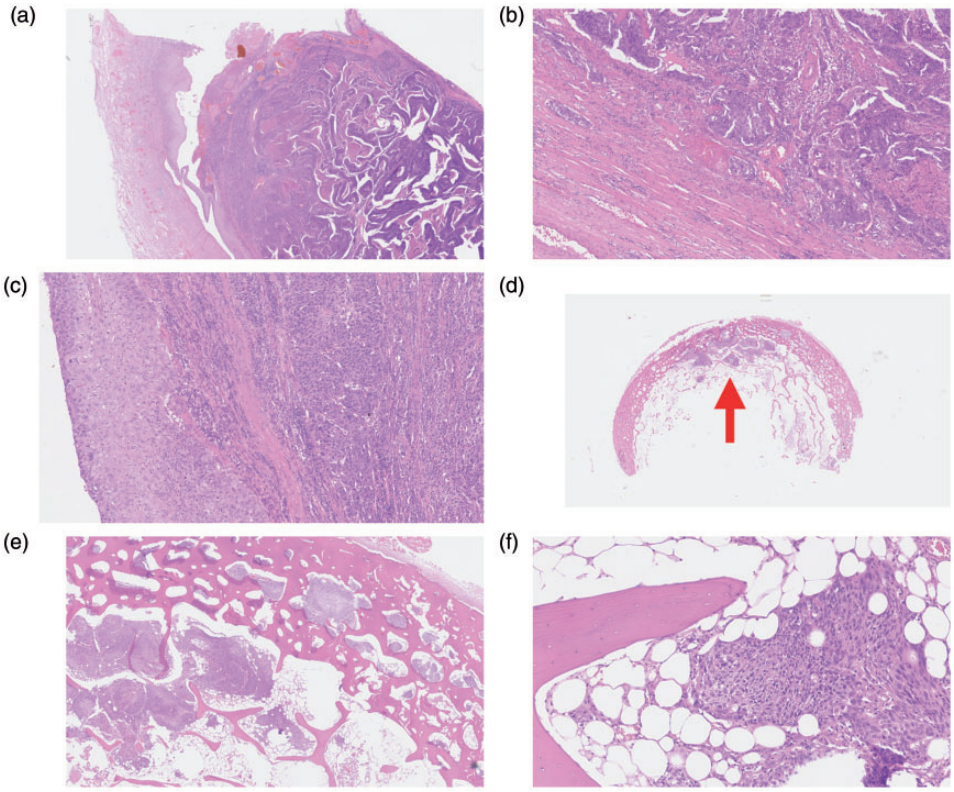

Figure 2. Representative microscopic images of primary urethral squamous cell carcinoma and femoral bone metastasis using hematoxylin and eosin staining. a: Partial penectomy specimen – overview with squamous cell carcinoma (original magnification, OM). b: Partial penectomy specimen with blood vessel invasion of squamous cell carcinoma (10× OM). c: Partial penectomy specimen with squamous cell carcinoma in situ (left side) and penile invasion (right side) (10× OM). d: Core bone biopsy overview with metastasis (arrow) of the right femoral bone (OM). e: Femoral bone metastasis with cortical involvement (2× OM). f: Femoral bone metastasis with focal spindle cell-like morphology (20× OM).

SCC is a less common histological type (i.e., approximately one in four). "Urothelial carcinoma of the urethra" is the predominant histological type of primary urethral cancer.[2] Given the large penile mass, we expected that histological examination would reveal the patient to have a penile SCC. Therefore, we refrained from performing a diagnostic urethrocystoscopy with biopsy.

Comprehensive staging (i.e., computed tomography of the thorax and abdomen) is advised (LE 3, GR B) in all patients with invasive disease (>cT1) to assess whether metastases are present.[2] In our case, computed tomography of the thorax and abdomen did not reveal any organ metastasis, although it showed local nodal enlargement. Interestingly, after the use of MRI for further exploration of the patient's painful right knee, an uncommon site of metastasis was detected. Considering that osteoarthritis is the number one cause of knee pain in adults over 65 years of age,[6] we did not expect to observe a pathological fracture as the cause for the patient's painful right knee. After performance of whole-body positron emission tomography,

systemic dissemination to multiple bony sites became evident. While less frequently reported in primary urethral SCC, regional spread of penile cancer is well-known; the most common routes of systemic spread after passage through regional nodes are pelvic and retroperitoneal nodes, followed by liver and lung.[1]

Radiotherapy (LE 3, GR C) or urethrectomy and urethra-sparing surgery (LE 3, GR B) are recommended treatment strategies for the management of primary urethral SCC in localized stages of cancer.[2] Depending on performance status, patients with locally advanced SCC might benefit from preoperative chemoradiotherapy (LE 4, GR C).[2,7,8] Depending on tumor stage and the patient's performance status, radiotherapy or radical surgery, in combination with chemotherapy, are recommended treatment strategies. For superficial non-invasive penile cancer (Tis), topical chemotherapy, circumcision, laser therapy, or glans resurfacing have all been shown to be beneficial.[1] While organ-sparing treatment (including radiotherapy for lesions <4 cm) is appropriate for localized invasive penile cancer (i.e., ≤T2), partial or total penectomy in combination with neoadjuvant chemotherapy or palliative radiotherapy is recommended for more invasive stages of disease (i.e., T3/T4).[1] Although associated with a high burden of morbidity (up to 50%), radical inguinal lymphadenectomy with adjuvant chemotherapy can be considered in patients with penile cancer and palpable inguinal lymph nodes (cN1/cN2).[1]

When providing patients with treatment options, disease-specific risk factors for survival should be considered. There are multiple predictors for survival in cases of primary urethral carcinoma (LE 3) related to patient (age and ethnicity) and tumor (size, location, stage and grade, nodal stage, presence of distant metastasis, and histological type) characteristics.[2] In contrast, the outcome for patients with penile cancer primarily depends on the histological subtype of the SCC and its association with HPV (in addition to tumor characteristics).[1]

In prior studies, the 5-year overall survival of primary urethral carcinoma ranged from 46%[9] to 54%,[10] with a 5-year overall cancer-specific survival of 68%.[4] When stratified by primary T stage, 5-year overall survival ranged from 63% (≤cT1) to 29% (≥cT3).[9] Although subject to temporal fluctuations,[11] the 5-year overall survival of patients with penile cancer was higher (i.e., between 65%[12] and 70%[13]) than that of patients with primary urethral carcinoma. Independent of the type of cancer (penile or primary urethral), SCC has the highest 5-year relative survival (70% and 69%, respectively), compared with adenocarcinoma (44% and 48%, respectively) or transitional cell carcinoma of the urethra (52%).[10] These findings were confirmed for primary urethral carcinoma, such that SCC had a longer mean survival time than transitional cell carcinoma and adenocarcinoma (i.e., 71 vs. 48 vs. 38 months, respectively).[9] In addition, patients with HPV-positive penile SCC had significantly better 5-year disease-specific survival than those reported as HPV-negative (93% versus 78%).[14] Despite the favorable overall outcome for patients with SCC, survival significantly decreased with age (>75 years) and stage progress, as evident in our case.[12,13] Given the small number of patients worldwide and because of the lack of standardized follow-up guidelines, predictions of long-term outcome for patients with primary urethral carcinoma remain difficult.

Conclusion

This case report describes a unique manifestation of a primary urethral SCC, which is a rare and uncommon cause of an advanced penile tumor. These findings could be of

great interest to clinicians for two reasons. First, a tumor's appearance can be misleading. Consequently, histological work-up, as recommended by clinical guidelines, is necessary for accurate diagnosis. Second, if there is a discrepancy between clinical symptoms and the underlying disease, a more comprehensive investigation is required. Our case demonstrates a corresponding example, wherein persistent knee pain was revealed as an unusual downstream metastasis of a primary urethral SCC. We believe that these aforementioned points are of considerable clinical importance and present an important learning opportunity.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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