

At a glans: metastatic prostate cancer disguised as penile squamous cell carcinoma; a case report

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Background: The incidence rate of prostate adenocarcinoma in the United States was 112 per 100,000 in 2019. Men aged 65 to 74 years had a higher incidence rate (638 per 100,000), and 70% of the cases were detected locally (confined to the primary site) per the United States Cancer Statistics. While rare, prostate adenocarcinoma metastasis to the penis has variable presentation and potentially atypical histology that may require immunohistochemical, biomarker, and genetic analysis for confident diagnosis.

Case Description: We present a 56-year-old patient with advanced prostate cancer post-chemoradiation and androgen deprivation therapy with an uncommon site of metastasis to the penis. The clinical presentation and progression of the disease led to surgical removal and

frozen section analysis. Initial pathologic assessment proved equivocal in the distinction between metastatic prostatic carcinoma versus primary penile squamous cell carcinoma. Diagnostic difficulty due to ambiguous histomorphological features was attributed to the loss of intrinsic prostatic protein markers in metastatic post-treatment cases. Immunohistochemistry and detailed biomarker analysis eventually aided diagnosis.

Conclusions: This report illustrates some of the gross and microscopic histological ambiguity that can obfuscate immediate diagnostic certainty of origin of rapidly growing cutaneous penile lesion in the context of existing prostate cancer, while elaborating on immunohistochemical and genetic markers that can increase otherwise elusive diagnostic certainty. Early patient education and intervention represent sites of potential improvement in management of similar cases.

Key Words: metastatic prostate cancer, penile metastasis, case report, differential diagnosis, immunohistochemistry, castrate-resistant prostate cancer, rare metastasis

Introduction

The incidence of metastatic prostate carcinoma to the penis is relatively low, with around 200 cases reported in the literature.¹ High on the differential

diagnosis should be a primary penile malignancy, specifically squamous cell carcinoma, which typically presents as a distinguishable outgrowth.¹ Here, we present a case of metastatic prostate cancer to a penile site initially visualized at the glans, in a polymetastatic patient who had received androgen deprivation therapy with unusual histological appearance. The aim is to expand on the current literature regarding presentation, histology, diagnosis, and prognosis of this rare phenomenon. Clinical correlation with detailed immunohistochemistry and biomarker analysis made diagnosis possible.

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This study was approved by the ethics committee of Boston Medical Center by means of an exception given the conditions noted in the attached ethics statement. The handwritten informed consent was obtained from the patient's spouse and legal representative. This study was prepared according to the CARE case report guideline and a CARE checklist was provided.² Please see Supplementary Material S1 for more details.

Case Presentation

We present a 56-year-old male with a family history of prostate cancer in his father and known primary prostate cancer who underwent evaluation at Boston Medical Center for urinary retention. No initial penile abnormalities were noted, but he later developed metastasis to the glans (Figure 1).

Twenty months before the emergence of his painful penile lesion, he presented to his primary care physician with eight months of worsening right pelvic pain, increasing fatigue, two months of sleep-disruption and mobility-impairing pain, with a twelve pound weight loss. His initial work-up revealed a prostate-specific antigen (PSA) of 660 ng/mL. He was referred to urology at Boston Medical Center, where a skeletal X-ray showed multiple lytic lesions and lymphadenopathy. A bone scan done one week later revealed mixed sclerotic and lucent thoracolumbar lesions with significant bone destruction, representing extensive bone metastases. Extensive bilateral retroperitoneal and pelvic lymphadenopathy was also noted and a subsequent nodal biopsy demonstrated metastatic prostatic adenocarcinoma. He was started on degarelix and abiraterone, after which a 90% drop in his PSA was noted within 3 months, resulting in a transition from degarelix to leuprolide. He then underwent palliative radiation therapy and 6 months later, multiple cycles of docetaxel.

He had a gradually increasing PSA and an increasing number of pelvic and sacral metastatic sites despite chemotherapy and androgen deprivation therapy (ADT). In just over a year, metastatic spread to the lumbar spine was treated with spinal radiation therapy and transition from docetaxel to cabazitaxel. New bilateral lung nodules, hepatic lesions, and bone progression were noted. During this time, he experienced his first episode of urinary retention. Within three months, during a second episode of urinary retention, a painful herpetic-appearing lesion on the right glans near the meatus was observed. A week later, at his void trial, the lesion had progressed to a

fungating exophytic lesion at the ventral meatus with vertical extension into the corporal tissue and potential urethral involvement. Given his polymetastatic disease, he was offered a biopsy and possible partial penectomy to balance metastatic control and quality of life. He was taken to the operating room soon after for a biopsy, with frozen section consultation revealing solid nests of minimally atypical basal and parabasal cells with ample eosinophilic cytoplasm and well-defined cellular borders favoring a moderately differentiated invasive squamous cell carcinoma (Figure 2). Given this histology, he underwent concurrent partial penectomy.

The partial penectomy specimen revealed a single 2.5 × 2.1 × 1.7 cm tan-white, ill-defined, and moderately friable mass grossly involving the entire glans, located 2 mm from the urethral meatal opening (Figure 3A). No satellite nodules, ulceration, erythema, papillary or wart-like projections were noted on the surface. On bivalving the specimen, the mass did not invade the urethra but was less than 1 mm away from the closest aspect, and 2 mm from the amputated surgical margin (Figure 3B).

Permanent sections revealed cohesive epithelioid cells arranged in an organoid pattern with central open spaces filled with necrotic debris and eosinophilic material (Figure 4A,B). The cells were stratified columnar and cuboidal in morphology with high mitotic activity (39 mitotic figures per 10 high-power fields), cytoplasmic vacuolization, and loss of differentiation. Bizarre pleomorphic nuclei, coarse chromatin, irregular nuclear outlines, and prominent nucleoli suggested a higher-nuclear-grade tumor than initially suspected (Figure 4C). Lymphovascular invasion was evident (Figure 4D), and perineural invasion was not identified on the levels examined. The squamous mucosa overlying the tumor had no evidence of dysplasia (Figure 4E).

To further categorize the tumor, immunohistochemical studies were performed, which showed that the tumor cells were focally positive for prostatic tumor suppressor homeobox protein NKX3.1 and prostate-specific membrane antigen (PSMA), but negative for E26 oncogene homolog (ERG) and PSA (Figure 5). The tumor cells were diffusely immunoreactive for p16 (nuclear and cytoplasmic), but not for p40. Further studies showed positive staining for cytokeratin 7 (patchy), cytokeratin 5/6 (focal), and AE1/AE3, and negative staining for cytokeratin 20, p63, GATA-3, uroplakin, cytokeratin 903, and TTF-1 (Figure 6). Tumor suppressor, phosphatase and tensin homolog (PTEN) exhibited loss of expression, p53 was mutant type (null phenotype), and there was loss of RB1 expression. The ki-67 proliferation index

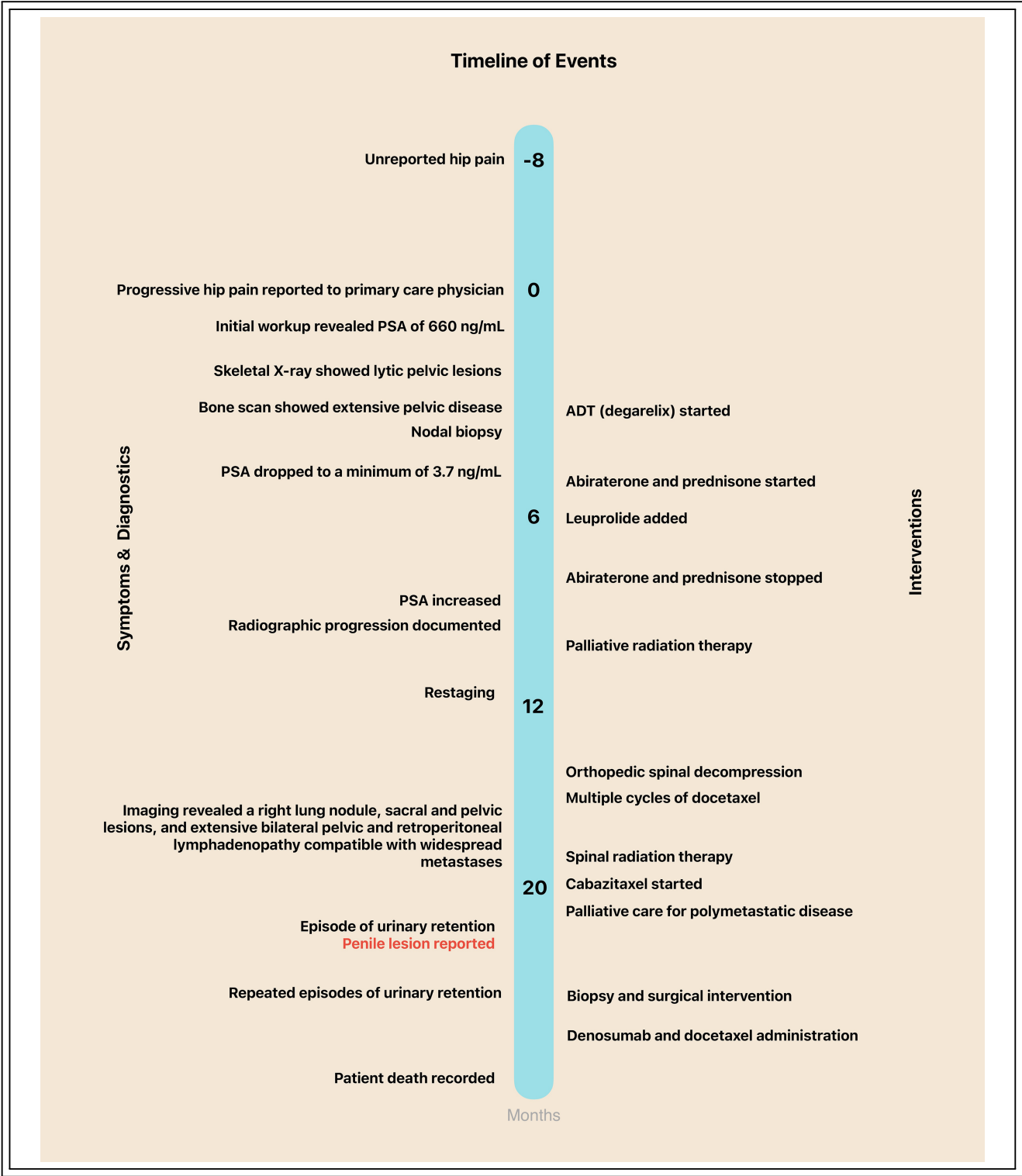


FIGURE 1. Timeline of patient presentation, management, and outcome.

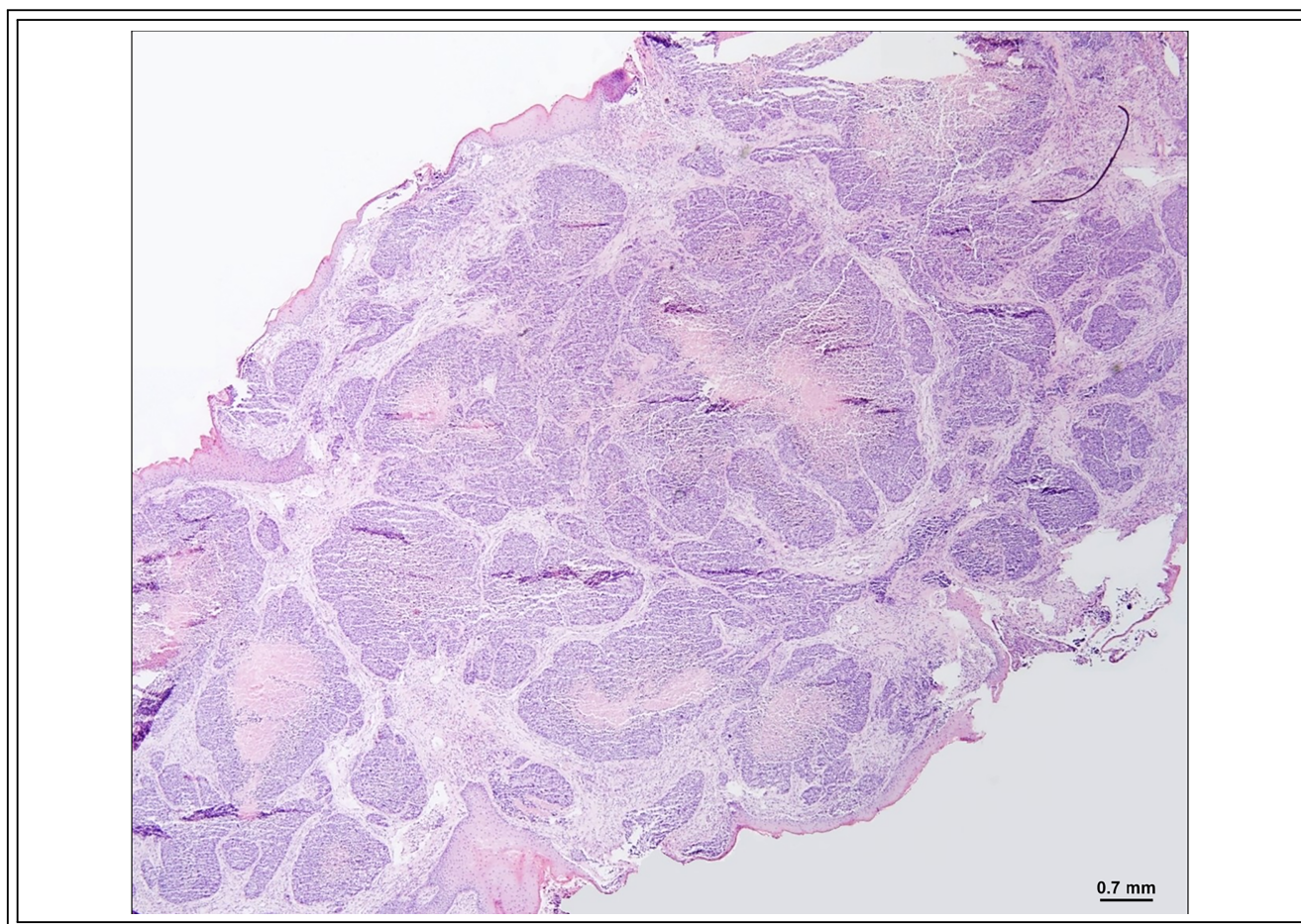


FIGURE 2. Frozen section of penile biopsy showing solid nests of infiltrative cells on H&E (2x).



FIGURE 3. Gross photographs of the lesion. A. Ventral surface of the glans with an exophytic friable mass. B. Paraffin-embedded block of the cut-surface showing the relationship of the mass to the inked (orange) margin.

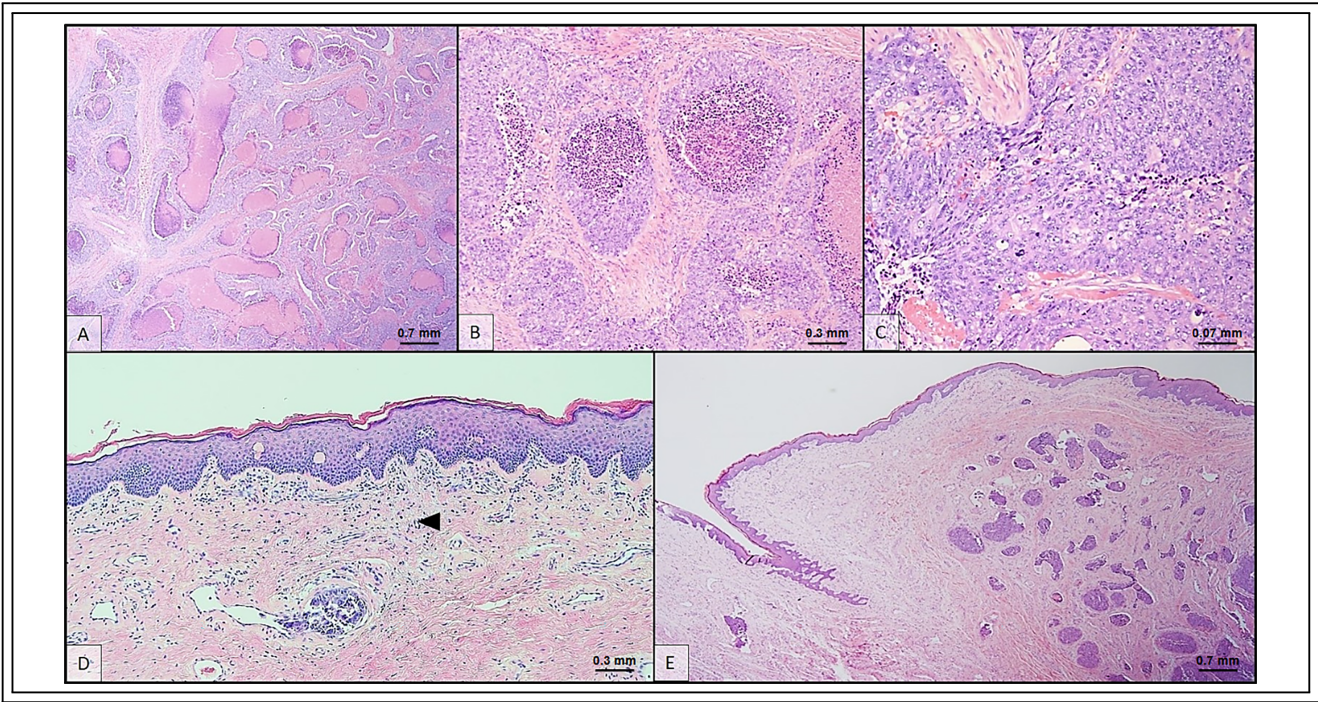


FIGURE 4. H&E-stained sections of the lesion. A. Nested bundles with eosinophilic pools (2x). B. Central necrosis (4x). C. High mitotic activity and pleomorphism (20x). D. Lymphovascular invasion, indicated by arrowhead (4x). E. Normal squamous mucosa without dysplasia overlying neoplastic cells (2x).

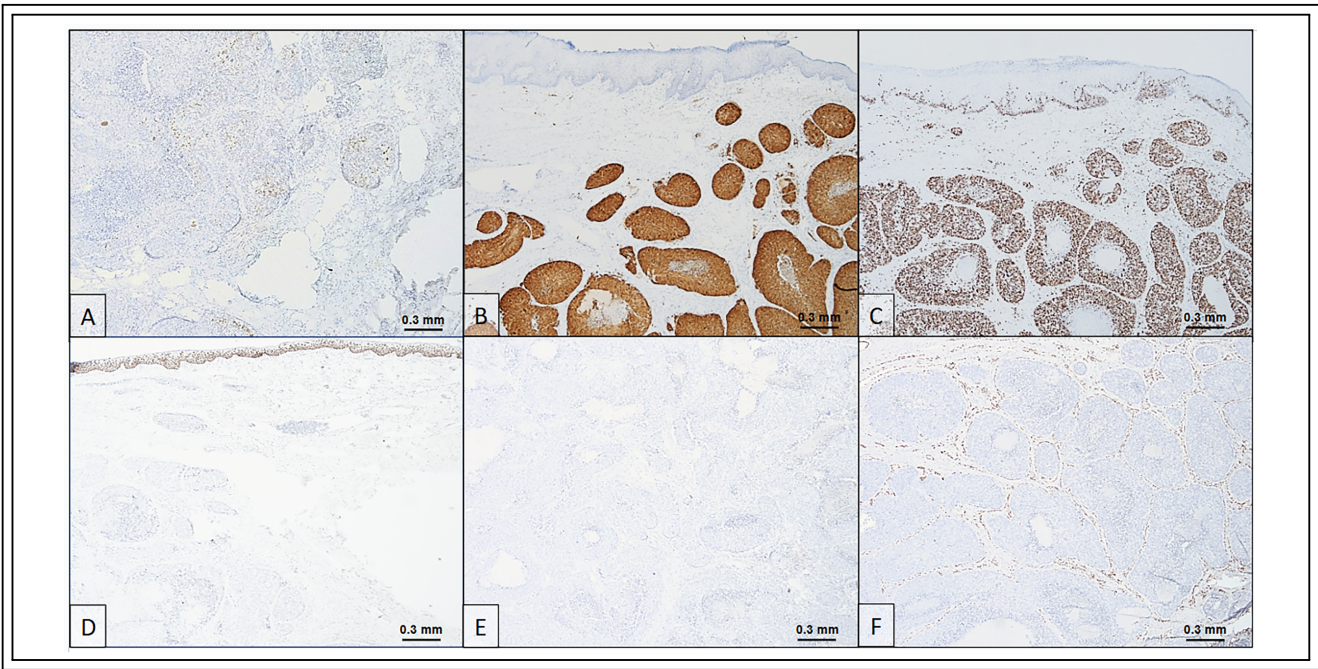


FIGURE 5. Immunohistochemical staining patterns confirming prostatic origin. A. NKX3.1 focal positivity (2x). B. p16 positive cells (notice overlying normal squamous mucosa) (2x). C. High Ki-67 proliferative index (2x). D. p40 negative (2x). E. PSA negative (2x). F. ERG negative (2x).

Immunohistochemistry, Biomarker, and Genetics Results		
Negative	Positive	Molecular
ERG, PSA p40,p63 CK20 GATA-3 Uroplakin CK903 TTF-1	Focal NKX3.1 PSMA CK5/6 Patchy CK7 Diffuse AE1/AE3 ki-67 : 95% (high) p16 (nuclear and cytoplasmic) p53: null phenotype (mutant pattern)	TMPRSS2-ERG fusion Expression loss: <i>PTEN</i>, <i>RB1</i>, <i>PIK3R1</i> High microsatellite instability Tumor mutational burden of 9 per megabase

FIGURE 6. Immunohistochemical, biomarker, and molecular analysis results.

rate was noted to be high (95%). The tumor showed no morphologic evidence of neuroendocrine differentiation based on the equivocal and non-specific immunohistochemical stains for synaptophysin and chromogranin that were performed.

Foundation testing (FoundationOne® CDx) revealed significant biomarker findings, such as a high microsatellite instability status and a tumor mutational burden of 9 per megabase. Loss of *PTEN* and *PIK3R1*, *TMPRSS2-ERG* fusion, and gene alterations such as *RB1* R7fs*24 (variant allele frequency [VAF]—64.2%), and *TP53* V73fs*76 (VAF—69.9%) were found; all of which have potential clinical, diagnostic, and therapeutic implications. Based on our collective findings and following interdepartmental consensus, the final pathological diagnosis was reported as metastatic carcinoma consistent with the patient's known primary prostatic acinar adenocarcinoma.

In the months following the partial penectomy, he developed new pulmonary and liver nodules with significant thromboembolic disease. He was diagnosed with stage IV T2N1M1c metastatic castrate-resistant prostate cancer (metastatic to the liver, lung, penis, and bone with pelvic and retroperitoneal nodal positivity) with progression of disease on hormonal and chemotherapy. His rapid deterioration despite receiving the current standard of care eventually led to his demise in hospice less than two months following surgery.

Discussion

Per the American Cancer Society, penile cancer accounts for less than 1% of all cancers in men in the United States, with an estimated 400 deaths each year.³ According to the World Health Organization's International Agency for Research on Cancer, there were 1964 diagnoses in North America and 37,700 diagnoses globally in 2022.⁴ Primary penile tumors (most commonly squamous cell carcinomas (SCC)) occur at a higher rate than metastatic lesions to the penis. Infrequently, nonsquamous penile malignant neoplasms including basal cell carcinoma, melanoma, sarcomas, and adenosquamous carcinoma have been reported as primary lesions.⁵ SCC accounts for 95% of penile cancers and is subcategorized, the most common subtype being the "usual type" (45% to 65%).³

The usual type is classified under Human Papilloma Virus (HPV)-independent SCC, and is further divided based on the growth pattern as pseudo-hyperplastic, pseudoglandular, superficial spreading, vertical, verruciform, and multicentric.⁶ Of interest, the pseudoglandular pattern is characterized by infiltrative nests with central open spaces lined by atypical, cubical or cylindrical uni- or multi-stratified cells frequently filled with amorphous material containing debris, neutrophilic microabscesses, keratin, and desquamated cells with a comedo-like appearance. Multiple areas of vacuolar clearing are seen within solid nests forming a circumferential

collarette, producing central intraluminal cell sloughing. Frequent vascular and perineural invasion is seen. These specific features of the pseudoglandular pattern of HPV-independent penile SCC share a resemblance to our previously described morphologic picture.⁷ A key difference between the two is the presence of penile intraepithelial neoplasia in the epithelium adjacent to pseudoglandular carcinoma.⁷

There are no robust population-level data giving a single, precise fraction of all penile tumors that are metastatic from non-penile primaries as metastatic penile tumors are reported almost exclusively as individual cases and small series. However, secondary (metastatic) penile tumors are clearly far less common than primary penile cancers, with only about 500 metastatic cases reported as of last count in 2017 compared with thousands of primary penile squamous cell carcinomas.^{8,9}

70% of metastatic penile carcinomas are of genitourinary origin, most frequently bladder urothelial carcinoma.^{8,10} The remaining minority are metastatic colorectal or lung carcinomas, and in extremely rare cases, carcinomas of the stomach, pancreas, liver, tonsil, and nasopharynx have been described (4).⁶ Given the very low fraction of metastatic tumors among all penile tumors, a small percentage (less than 1%) of total penile tumors are attributed to a primary prostatic origin. Tatkovic et al.'s review of 4850 68Ga-PSMA PET/CT examinations of penile tumors revealed an incidence of 0.1% of PSMA-avid prostate cancer lesions.¹¹ PSMA is present in 92% of prostatic adenocarcinoma biopsies.¹² Of note, the incidence of penile metastasis may be underreported or underestimated since current literature consists predominantly of case reports and small-volume case series.

In a recent case series of 109 cases of metastases to the penis, 88% of the patients had a known malignancy, and half of patients were diagnosed with their metastasis to the penis between 1 and 36 months after diagnosis of their primary tumor.¹⁰

Symptomatic presentation can be key to the diagnosis prior to pathological assessment. Associated symptoms include acute urinary retention, penile nodules, ulceration, pain, edema, dysuria, and hematuria.¹⁰

While articles published before 2010 often cite two articles from the 1960s and 1980s in which malignant priapism was found to be the most common presenting symptom of metastasis to the penis, more recent reviews note bothersome nodules or masses, and pain as the two most common presenting symptoms.^{1,10,13} Haddad et al.'s review of about 70 cases showed average cancer-specific survival for patients with and without malignant priapism to be 1.5 and 5.7 months,

respectively, whereas Cocci et al.'s 2017 review of about 70 cases showed the median cancer-specific survival to be 14.5 months.^{8,14} Those with tumors of urologic origin had better cancer-specific survival, at 18 months versus 11, in the case of non-urologic origin. Further, their data showed that those whose penile metastasis initially presented with malignant priapism had worse survival, with an average 20% cancer-specific mortality of 10 months rather than 20.⁸

In two of the most recent systematic reviews from 2016 and 2017, De Luca et al. and Cocci et al., malignant priapism, intermittent or continuous, was found to be reported in 40% of penile metastases from various primary malignancies.^{8,15} The use of Gallium-68 prostate-specific membrane antigen (68 Ga-PSMA) PET/CT might be helpful in this scenario for detecting active penile involvement with the presence of avid lesions.¹¹ The utility of PSMA over PSA in this case is higher since treated refractory metastatic prostate carcinomas are documented to have loss of PSA expression, which is displayed by the immunophenotype described in our case.¹⁶

The most common mechanism of metastatic tumors to the penis is through retrograde lymphatic venous drainage. The penile root (38.8%) and shaft (38.8%) are more commonly involved in comparison to the glans (22.2%) in metastasis.^{8,15} These lesions occur mostly in the central portion of the corpus cavernosum or spongiosum. In contrast, primary penile lesions are mainly localized at the glans. Furthermore, exclusive foreskin involvement is atypical.

Immunohistochemistry as an adjunct is a helpful aid to cinch the diagnosis. p16 is often used as a surrogate for HPV to depict positivity when expressed in a nuclear block-like pattern.^{17,18} Approximately half of HPV-negative penile cancers are attributed to the oncogenic activation of tumor suppressor *TP53*, and another quarter are due to the loss of *TP53* function, possibly combined with additional oncogenic mutations in *PIK3CA*, *KRAS*, and *HRAS*.¹⁹

FoundationOne[®] CDx is the first FDA (Food and Drug Administration) approved tissue-based broad companion diagnostic (CDx) that is clinically and analytically validated for 324 cancer genes in solid tumors: breast, colorectal, ovarian, prostate, melanoma, and cholangiocarcinoma.^{20,21} Utilization of known therapeutics against clinically significant genomic alterations is extremely helpful since up to 55% of prostate cancer cases are identified to have ERG overexpression.²² This is attributed to gene fusion transcripts of transmembrane serine protease 2 (TMPRSS2) and v-ets erythroblastosis virus ERG, which are present in both early and late-stage prostate cancer.^{22–24}

Targeted treatment for primary penile carcinoma includes surgical excision with or without lymph node dissection, radiation, and/or neoadjuvant chemotherapy.²⁵ Patients with no inguinal node metastases have an 85–100% five-year cancer-specific survival rate.³ Similarly, various palliative treatment options for metastatic prostate carcinoma have been described, including local surgical excision, penile amputation, radiotherapy, or chemotherapy. Regardless of treatment, outcomes remain poor once metastasis has spread to the penis. Nova-Camacho et al.'s review showed a 16-month post-diagnosis all-cause mortality of 53%, Cocci et al.'s data showed a median of 10 months (range 6–18 months), and most patients died within 1 year in yet another study.^{8,10,26} While post-metastasis diagnosis survival has continued to improve over the last 40 years, the high mortality rate therefore often begets palliative therapy as opposed to definitive curative modalities, with the exception of otherwise healthy oligometastatic patients.^{1,27}

Furthermore, neoadjuvant chemotherapy, androgen deprivation therapy, and radiation therapy are documented to cause collapsed glands, small inconspicuous individual tumor cells, cytoplasmic vacuolization, and intraductal/cirriiform growth patterns, loss in luminal glandular spaces (luminal collapse), increased stroma, and nuclear pyknosis.¹⁶ Squamous differentiation has been described following hormonal therapy, radiation therapy, or combination thereof.²⁸ Moreover, the theory of poorly differentiated tumors losing their innate marker expression due to therapeutic pressure pertaining to androgen receptor-driven genes is well-evidenced.²⁹

The clinical presentation with cutaneous penile involvement in a patient with known polymetastatic prostate cancer supports metastatic disease rather than a second primary malignancy. Based on the immunohistochemical and molecular profile, this lesion was metastatic prostate adenocarcinoma with minimal squamous differentiation following androgen deprivation therapy, though the diagnosis was complicated by atypical features noted above. Focal cytokeratin 5/6 positivity is inconsistent with the typical strong cytoplasmic staining found in squamous cell carcinomas. Negativity for p63 and p40 binding, given their above-95% sensitivity and high specificity for squamous differentiation, making penile squamous cell carcinoma very unlikely.³⁰ The *TMPRSS2-ERG* fusion strongly supported prostatic origin, as this is the most common chromosomal aberration in prostate cancer, occurring in 41–43% of prostate cancer metastases and is not found in penile

cancer.³¹ Focal positivity for NKX3.1 and PSMA further supports prostatic lineage, while the negativity for PSA and ERG reflects treatment-related dedifferentiation and normal variation of ERG expression in the setting of common-to-prostate-cancer *TMPRSS2-ERG* fusion, respectively.^{12,32–35} The loss of *PTEN*, *RB1*, and *PIK3CA* regulatory subunit 1, combined with *TP53* null mutation, represents the genomic instability characteristic of metastatic castration-resistant prostate cancer, consistent with the patient's clinical history.^{31,36,37}

The combination of focal prostatic markers (NKX3.1, PSMA), absence of squamous differentiation markers (p40, p63), and molecular alterations (*PTEN* loss, *TP53/RB1* co-deletion, *TMPRSS2-ERG* fusion) collectively establishes the diagnosis as metastatic prostatic adenocarcinoma with high confidence.

While an increasing level of suspicion for penile metastases in the setting of polymetastatic disease suggests the possibility of earlier detection, a low pre-test probability of metastasis relative to the incidence of all potential penile lesions complicates broad suspicion as a tool for detection. While Devasia et al. estimated that between 120,000 and 190,000 people in the United States are living with metastatic prostate cancer at a given time, only a fraction of those are living with polymetastatic disease more likely associated with penile metastases.³⁸ Early evaluation of emergent lesions presenting with the most common signs of painful mass, nodule, or cutaneous lesion in these higher-risk cases may present an opportunity for a balance of the benefits of earlier detection and the risks of false positives.¹ That is, for those with an established prostate, bladder, or rectosigmoid cancer diagnosis (primary cancers that make up about 80% of penile secondary tumors), a lower threshold for workup of new penile nodules, localized pain, or painful cutaneous lesions may help decrease morbidity of delayed management.

In the case of cutaneous lesions, as many as 50% of men with cutaneous penile cancer delay between 3.5 to 6 months before notifying their physician about their penile lesions.^{39–41} While early management of suspicious cutaneous penile lesions may initially include topical treatments, in the setting of known pelvic malignancy, preemptive patient education and early biopsy may be a viable approach to improving morbidity and survival.⁵

In summary, the distinction between primary squamous cell carcinoma and metastatic prostatic acinar adenocarcinoma is more difficult in patients who have undergone definitive treatment for the latter.⁴² Our initial difficulty in differentiating

between the two was due to atypical morphologic and immunohistochemical expression. Diagnostic limitations were evident, as the initial histology mimicked squamous cell carcinoma, requiring extensive immunohistochemical and molecular analysis to confirm the metastatic prostatic origin following androgen deprivation therapy. Management interventions were constrained by the patient's polymetastatic, castrate-resistant disease, which limited therapeutic options and necessitated a palliative balance between local control (partial penectomy) and quality of life. Follow-up and prognosis were severely limited by the aggressive biology of the disease, as the penile metastasis heralded rapid systemic progression and death within months, underscoring the poor survival associated with this complication. While this represents a helpful example of a rare phenomenon, it is but a single example of varied presentations, and longitudinal appreciation of intervention could not be appreciated, secondary to overall advancement of the patient's disease. Further, as a photograph of the pre-biopsy gross anatomy was not helpful for the patient's care, an image of the early cutaneous lesion is not available to share. Early detection is complicated by the rarity of metastasis to the site, the multitude of alternate etiologies of penile lesions, the frequent difficulty with anatomy visualization by patients, and the delay in patient reporting.

Our initial conundrum in differentiating between the two was due to atypical morphologic and immunohistochemical expression, though diagnosis was made possible with available detailed testing and expertise. Given the limited number of published cases of metastatic prostate cancer to the penis and that 22% of the roughly 200 published cases of prostate cancer metastases to the penis are localized to the glans, this case report further augments knowledge of this phenomenon in literature.

Conclusion

Metastatic prostatic adenocarcinoma to the penis is an extremely rare complication that portends poor survival. Patient education, regular follow-up, and active surveillance are essential for its early detection and management. Here, we presented an atypical penile lesion secondary to metastatic prostate cancer and rapid clinical deterioration in the months prior to the patient's death. Further investigation into this morbid phenomenon is warranted to improve management strategies and survival rates.

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Author Contributions

Conceptualization: Ramya Narasimhan, Joanna Wang, Ricardo Munarriz, Carmen Sarita-Reyes. Writing: Ramya Narasimhan, Kikuye Sugiyama, Joanna Wang, Ricardo Munarriz, Carmen Sarita-Reyes. Editing: Ramya Narasimhan, Kikuye Sugiyama, Joanna Wang, Ricardo Munarriz, Carmen Sarita-Reyes. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

Due to the nature of this research, the participant of this study did not agree for their data to be shared publicly, so supporting data is not available.

Ethics Approval

As a case report, the research involved only retrospective chart review of de-identified data and posed minimal risk to its single participant, and the Boston Medical Center IRB granted a waiver. Written informed consent was obtained from the patient's spouse and legal healthcare proxy. All analysis complied with the Health Insurance Portability and Accountability Act (HIPAA) privacy requirements. This study was prepared in line with CARE case report guidelines whose checklist was submitted.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Materials

The supplementary material is available online at <https://www.techscience.com/doi/10.32604/cju.2026.072310/s1>.

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