Cutaneous Metastasis of an Undiagnosed Prostatic Adenocarcinoma

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PRACTICE **POINTS**

- Cutaneous metastasis of prostate cancer can have various manifestations and portends a poor prognosis.
- New skin lesions that develop in patients with a high clinical suspicion for prostate cancer warrant consideration of cutaneous metastasis.

To the Editor:

Cutaneous metastasis of prostate cancer is rare and portends a bleak prognosis. Diagnosis of the primary cancer can be challenging, as skin metastasis can mimic a variety of conditions. We report a case of metastatic prostatic adenocarcinoma confirmed via biopsy of a new skin lesion.

A 97-year-old man presented to the dermatology clinic for routine follow-up of psoriasis. During the visit, a family member mentioned a new bleeding lesion on the left shoulder. It was not known how long the lesion had been present. Four months prior, the patient had a prostate-specific antigen (PSA) level of 582 ng/mL (reference range, 0-6.5 ng/mL), and computed tomography of the chest had shown innumerable pulmonary nodules in addition to lymphadenopathy of the left axilla, clavicle, and mediastinum. The imaging was ordered by the patient's urologist as part of routine workup, as he had a history of obstructive renal failure and was being monitored for an indwelling catheter. Two months later, a bone scan ordered by the urologist due to high PSA levels showed extensive osteoblastic metastatic disease throughout the axial and proximal appendicular skeleton. The elevated PSA levels and findings of pulmonary and osteoblastic metastasis suggested a diagnosis of metastatic prostatic adenocarcinoma, but no confirmatory biopsy was performed following the imaging because the patient's family declined additional workup or intervention.

Physical examination at the current presentation revealed an 8-mm brown papule with an overlying blue-white veil (Figure 1). There were no other skin findings. Primary differential diagnoses included metastatic prostate cancer, nodular melanoma, and traumatized seborrheic keratosis. A shave biopsy of the lesion showed multiple glandular structures infiltrating the dermis lined by monomorphic epithelial cells with prominent eosinophilic nucleoli (Figures 2 and 3). Focal cribriform architecture of the glands was present as well as dermal hemorrhage and a lymphohistiocytic infiltrate (Figure 2A). Interestingly, in-transit vascular metastases were confirmed with the support of ERG, CD34, and CD31 immunohistochemical staining of the vessels.

Immunohistochemical staining was positive for PSA (Figure 2B), NKX 3.1, and ERG in the invasive glandular structures, which also displayed patchy weak staining

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The authors have no relevant financial disclosures to report.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the US Government.

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Cutis. 2025 January;115(1):E7-E9. doi:10.12788/cutis.1162

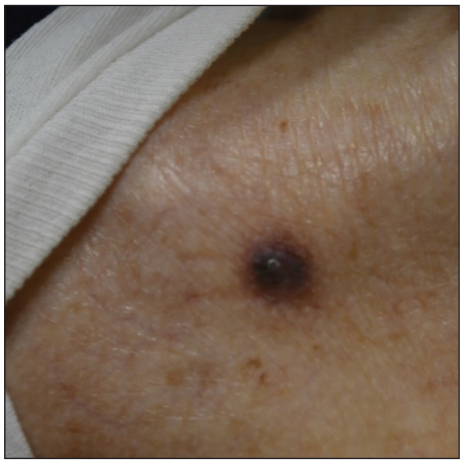

FIGURE 1. Cutaneous metastasis of prostate cancer manifesting as a singular brown papule on the left shoulder.

with AMACR. Staining was negative for prostein, cytokeratin (CK) 7, CK20, CK5/6, p63, p40, CDX2, and thyroid transcription factor 1. These findings were consistent with a diagnosis of cutaneous metastatic prostatic adenocarcinoma. Next-generation sequencing showed trans-membrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog (*TMPRSS2-ERG*) fusion compatible with the positive ERG immunohistochemical staining. The patient and family declined any treatment due to his age, comorbidities, and rapid decline. He died 2 months after diagnosis of the skin metastasis.

Aside from nonmelanoma skin cancer, prostate cancer is the most common cancer and the second leading cause of cancer-related deaths among men in the United States.[1] It most commonly metastasizes to the bones, nonregional lymph nodes, liver, and thorax.[2] Metastasis to the skin is very rare, with only a 0.36% incidence.[3] When prostate cancer does metastasize to the skin, the prognosis is poor, with an estimated mean survival of 7 months after diagnosis of cutaneous metastasis.[4] Our patient's survival time was even shorter—only 2 months after diagnosis of cutaneous metastasis, likely the result of his late diagnosis.

Clinically, cutaneous metastasis of prostate cancer can manifest as a wide variety of lesions; in one report of 78 cases, 56 (72%) were hard nodules, 11 (14%) were single nodules, 5 (7%) were edema or lymphedema, and 5 (7%) were an unspecific rash.[4] Diagnosis of cutaneous metastasis of prostate cancer can be challenging, as it often is mistaken for other skin conditions including herpes zoster, basal cell carcinoma, angiosarcoma, cellulitis, mammary Paget disease, telangiectasia, pyoderma, morphea, and trichoepithelioma.[5] In our patient, the clinical appearance of the lesion resembled a nodular melanoma. Thus, in patients with a history of prostate cancer, it is important to keep cutaneous metastasis in the differential when examining the skin because of the prognostic implications. Cutaneous metastasis of prostate cancer often indicates a poor prognosis.

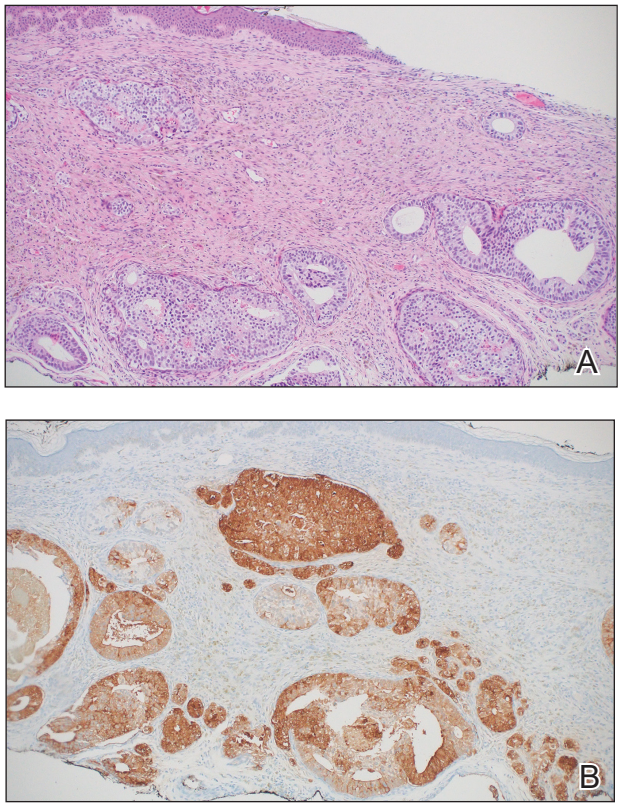

FIGURE 2. A shave biopsy highlighted an invasive glandular infiltrate with a background of a lymphohistiocytic infiltrate on low-power view (H&E, original magnification ×100)(A) with positive stain for prostate-specific antigen (original magnification ×100)(B). These findings were consistent with a metastatic prostatic adenocarcinoma involving the dermis.

In a report of 78 patients, the most common sites of skin metastasis for prostate cancer were the inguinal area and penis (28% [22/78]), abdomen (23% [18/78]), head and neck (16% [12/78]), and chest (14% [11/78]); the extremities and back were less frequently involved (10% [8/78] and 9% [7/78], respectively).[4] Generally, cutaneous metastasis of internal malignancies involves the deep dermis and the subcutaneous tissue. It is common for cutaneous metastases to show histologic features of the primary tumor, as we saw in our patient. In a case series with 45 histologic diagnoses of cutaneous metastases from internal malignancies, 75.5% (34/45) of cases showed morphologic features of the primary tumor.[6] However, this is not always the case, and the histologic appearance may vary. Metastatic prostate cancer may manifest as sheets, nests, or cords and often may have nuclear pleomorphism with prominent nucleoli.[7]

Immunohistochemical staining can help make a definitive diagnosis and differentiate the source of the tumor. Prostate cancer metastases often will stain positive for NKX3.1, PSA, AMACR, ERG, PSMA, and prosaposin, with PSA being the most specific marker.[7,8] In our patient, no prostate biopsy had been performed, thus the skin biopsy was the diagnostic tissue for the prostatic adenocarcinoma.

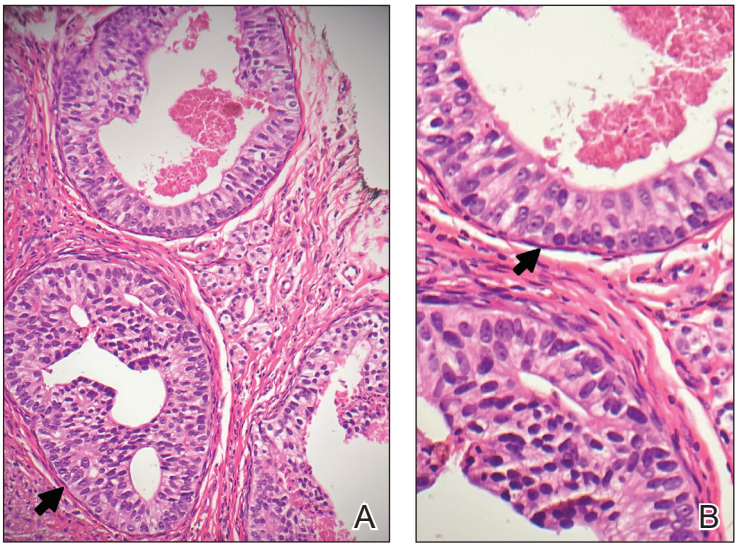

FIGURE 3. Glandular structures were appreciated within the endothelial cell–lined vasculature (arrow)(H&E, original magnification ×200)(A) with highlighting of the nucleolar prominence and endothelial cells (arrow)(H&E, original magnification ×400)(B).

Next-generation sequencing showed a *TMPRSS2-ERG* fusion, which commonly is seen in prostate cancer.[9] A search of Google Scholar using the terms *next-generation sequencing*, *cutaneous metastasis*, and *prostate adenocarcinoma* yielded 3 additional cases of cutaneous metastasis of prostate cancer in which next-generation sequencing was performed.[10-12] One case showed mutations of the tumor protein 53 (*TP53*) and phosphatase and tensin homolog (*PTEN*) genes; one showed just a *TP53* mutation; and one showed inactivation of the breast cancer predisposition gene 2 (*BRCA2*) and amplification of MYC proto-oncogene, BHLH transcription factor (*MYC*) and fibroblast growth factor receptor 1 (*FGFR1*).[10,11,12] While limited by a small number of reported cases, there does not appear to be a repeating mutation to suggest a genetic mechanism of skin metastasis.

The route of cutaneous metastasis of prostate cancer still is unclear, but hypothesized mechanisms include hematogenous or lymphatic spread, direct infiltration, or implantation from a surgical scar.[11] When cutaneous involvement occurs in an area far from the primary tumor, it is thought to be the result of hematogenous spread, which would be consistent with our patient's findings.[13] Given the role of Batson venous plexus as a conduit from the prostate to the vertebral column for metastatic spread and considering the location of the lesion on our patient's back, we hypothesized that the mechanism of metastasis to the skin was from vascular extension of the metastatic foci involving the vertebrae.

Our case highlights the importance of considering cutaneous involvement of prostatic adenocarcinoma in patients with new skin lesions, particularly in the setting of a known or suspected prostate malignancy. Skin metastasis can have a range of manifestations and provides prognostic information that can help determine the course of treatment.

Acknowledgement—The authors would like to thank Isabell Sesterhenn, MD (Silver Spring, Maryland), for her guidance in the genitourinary pathology in our patient.

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