Cutaneous metastasis as the first sign of small-cell cancer: An unexpected presentation in a patient with concurrent prostate cancer

Yana Kost, BA, Daiva M. Mattis, MD, PhD, Ahava Muskat, BS, Roya Nazarian, MD, Bijal Amin, MD, Haiying Cheng, MD, PhD, and Beth N. McLellan, MD

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INTRODUCTION

Cutaneous metastasis as the first sign of malignancy in a patient with no other clinical symptoms is extremely rare.[1] We report the case of a patient presenting with a solitary groin metastasis as the initial manifestation of small-cell carcinoma (SCC) of likely pulmonary origin.[2] Of note, the patient was concurrently receiving radiotherapy (RT) treatment near the groin for stage IIC (cT1cN0M0) high-risk prostate adenocarcinoma. Studies suggest that RT may stimulate previously circulating tumor cells to hone to the skin, which may explain the unusual site of the cutaneous metastasis. Our report demonstrates the diagnostic power of skin biopsy, which led to a new diagnosis of metastatic SCC in this case.

Abbreviations used:

NEPC: neuroendocrine prostate cancer
RT: radiotherapy
SCC: small-cell carcinoma

CASE REPORT

A 58-year-old African American man with a 15-pack year smoking history and stage IIC high-risk prostate adenocarcinoma treated with 6 months of androgen deprivation therapy and ongoing intensity-modulated RT presented to our dermatology clinic with a 2-week history of a rapidly enlarging, painful left groin nodule. Examination revealed a tender, erythematous 3-cm nodule with central erosion and purulent odorous drainage (Fig 1, *A*). The nodule developed 4 weeks after RT initiation for prostate cancer at a standard dose of 41.4 Gy in 23 fractions, with treatment planned for 77.4 Gy in 43 fractions. The patient tolerated RT well and denied constitutional symptoms. A shave biopsy was conducted as part of the differential diagnosis, which included keratoacanthoma and cutaneous metastasis.

Biopsy demonstrated clusters and sheets of basaloid cells with fine stippled chromatin, minimal cytoplasm, nuclear molding, and crush artifact (Fig 2). The presence of mitoses and apoptotic cells was frequent, and an area of ulceration with adjacent necrosis was present. Immunohistochemical stains showed tumor cells negative for S100/MelanA, CD45, and CDX2, ruling out melanocytic, hematopoietic, and gastrointestinal carcinoma, respectively. Prostate markers (PSA, PSAP, PSMA, and NKX3.1) were negative. Tumor cells were positive for AE1/AE3 cytokeratins, synaptophysin, and TTF-1, most consistent with metastatic poorly differentiated SCC. Negative CK20 and positive TTF-1 stains excluded cutaneous neuroendocrine carcinoma. Ki-67 expression was seen in nearly 100% of the cells, indicating aggressive disease.

To assess for primary malignancy site and metastases, a whole-body ^{18}fluorine-labeled fluorodeoxyglucose positron emission tomography/computed tomography scan was conducted. The scan revealed multiple fluorodeoxyglucose–avid sites, including a

From the Division of Dermatology, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York.
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Correspondence to: Beth N. McLellan, MD, Department of Medicine, Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, 3411 Wayne Avenue, Bronx, NY 10467. E-mail: bmcllela@montefiore.org.

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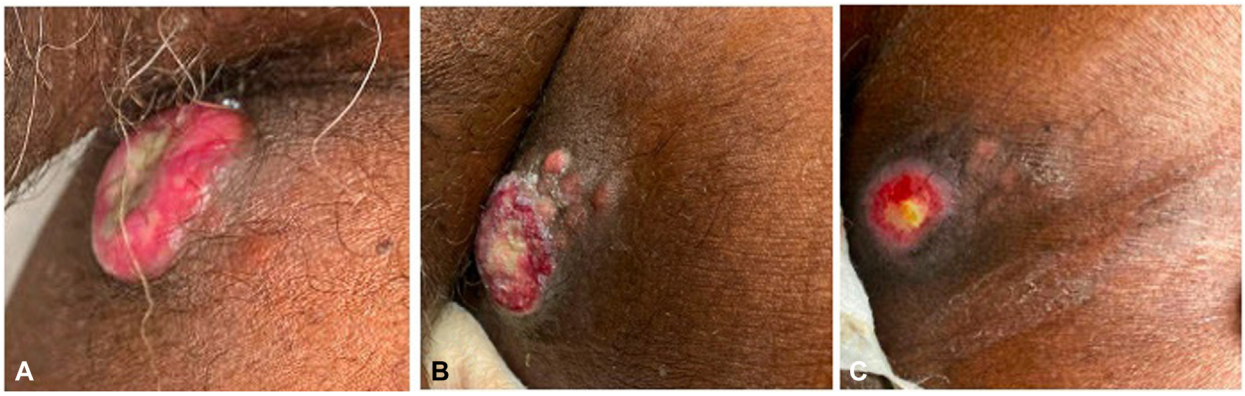

Fig 1. Cutaneous metastasis. **A,** The patient's groin demonstrated a solitary, erythematous, well-circumscribed nodule with central erosion and purulent drainage. **B,** Follow-up revealed a flatter, indurated, eroded nodule with hemorrhagic crust but with several new surrounding pink papules. **C,** After 2 chemotherapy cycles, the lesion showed significant improvement in healing with minimal drainage and regression of surrounding papules.

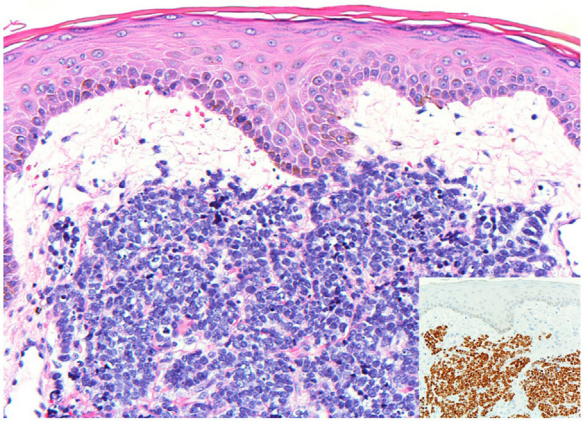

Fig 2. Small-cell carcinoma. The hematoxylin-eosin stained image shows clusters of small rounds to oval basaloid cells with fine stippled chromatin, scant cytoplasm, and nuclear molding. Mitoses and apoptotic cells are abundant. The inset shows a TTF-1 immunohistochemical stained image that is strong and diffusely positive in this same cell population. (Hematoxylin-eosin stain; original magnification: ×200; Inset, TTF-1 stain; original magnification: ×200.)

soft tissue density in the left lung hilum (8.2 × 5.2 cm), mediastinal nodes, a mass in the body of the pancreas (5.8 × 5.2 cm), several foci in the liver, intramuscular right posterior neck, and subcutaneous left medial proximal thigh. Laboratory results revealed normal PSA (0.2 ng/mL), elevated lactate dehydrogenase (308 U/L; reference normal, <240 U/L) as well as leukopenia (0.5 k/μL; reference normal, 1.0-4.8 k/μL), and monocytosis (0.7 k/μL; reference normal, 0.3-0.5 k/μL).

Based on pathology findings, the dominant lung lesions, and widespread disease, the oncology team felt that extensive-stage pulmonary SCC was most probable, although its origin was not confirmed via lung lesion biopsy. The patient completed RT for prostate adenocarcinoma and started treatment with carboplatin, etoposide, and atezolizumab for the newly diagnosed pulmonary SCC. The dermatology team prescribed topical 0.75% metronidazole cream for bacterial colonization. After 1 chemotherapy cycle, the examination revealed a flatter nodule with several new satellite pink papules (Fig 1, *B*) and decreased purulence and odor resolution. After 2 cycles of chemotherapy, the patient had decreased pain, minimal drainage, and regression of surrounding papules (Fig 1, *C*). Imaging revealed a marked decrease in the left hilar mass size to 1.2 × 2.5 × 2.2 cm, with regions previously suspicious for malignancy found to be within normal limits.

DISCUSSION

Cutaneous metastasis as the first presentation of a visceral malignancy is extremely rare.[3] While the pulmonary origin of malignancy was not confirmed, imaging and histologic evidence suggested a pulmonary primary. Of note, the patient's lesion may also represent a cutaneous metastasis of neuroendocrine prostate cancer (NEPC), a rare, aggressive prostate cancer escape variant resistant to androgen deprivation therapy.[4] NEPC is histologically similar to other neuroendocrine tumors; it has high proliferative rates and often lacks prostate cancer marker expression, as seen in the present case.[5] As the SCC variant of NEPC often metastasizes to the lung, it is important to consider the differential of lung SCC in patients with prostate cancer history.[5] Like in our patient, NPEC presents in patients with high-risk prostate

cancer without subsequent PSA elevation.[4,5] TTF-1, found to be positive in our patient, is positive in up to 90% of pulmonary SCC but in <50% of NEPC.[5] NPEC commonly presents with locally invasive bladder or bowel disease and distinct bone lytic lesions, which our patient lacked.[4] Furthermore, NPEC typically presents 39.7 months after a prostate cancer diagnosis, unlike our patient who presented earlier.[6] Finally, response to chemotherapy favors a lung cancer primary.

Interestingly, the metastatic lesion was close to the radiation field for prostate cancer. Several cases of cutaneous metastasis of recurrent primary cancer in the RT field have been reported primarily in breast cancer,[7] but to our knowledge, we report the first case of cutaneous metastasis as the first sign of new underlying malignancy near the RT field. While RT is intended to destroy malignant cells, basic science and clinical data indicate that under some circumstances, RT may stimulate metastasis, providing reasoning for why the cutaneous lesion may have occurred in the groin.[7,8] Proposed mechanisms point to the development of an "immunocompromised district" more susceptible to tumors because of RT-induced vascular damage impeding lymphatic drainage and causing local hypoxia leading to local cytokine upregulation promoting metastasis.[9] Both effects are not limited to irradiated tissues and may affect neighboring cells through gap junctions or soluble factors, a phenomenon known as the radiation-induced bystander effect.[10] Conversely, others describe RT-induced inhibition of distant tumor growth through the abscopal effect.[9] Such studies are limited and more research is needed to determine the effect of RT on metastases.

This case underscores the powerful diagnostic utility of a skin biopsy, which provided initial evidence for an internal malignancy in this case. RT may explain the unusual site of cutaneous metastasis in this presentation. In conclusion, metastatic skin disease should always be considered in patients with cutaneous nodules so that correct diagnosis and treatment to prolong survival may be initiated.

Conflicts of interest

None disclosed.

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