A case of cutaneous metastatic prostate carcinoma as initial evidence of neuroendocrine differentiation

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Introduction

Prostate carcinoma is the most common non-cutaneous malignancy and the second leading cause of cancer-related mortality in men, second only to lung cancer. Mortality in prostate carcinoma typically occurs in the context of metastatic disease in castration-resistant prostate cancer (CRPC), which is defined as disease progression despite androgen deprivation therapy. Most cases of metastatic prostate carcinoma are due to local extension (e.g. into seminal vesicles) or distant metastases to bone. Cutaneous metastasis is rare, estimated in less than 0.1% of cases.

Cutaneous metastatic prostate carcinoma typically presents late in the disease course as single or multiple nodules in the inguinal region and anterior thighs. Other locations have been reported as well, including the chest, abdomen, and less commonly, the scalp, face, and periumbilical area. Diverse clinical presentations have been described, including inflammatory, sclerodermoid, cellulitic, or zosteriform appearances, and lesions range from asymptomatic to ulcerative and painful. This clinical variability may result in delayed recognition on the part of clinicians. Here, we present a case of cutaneous metastatic prostate carcinoma with neuroendocrine differentiation.

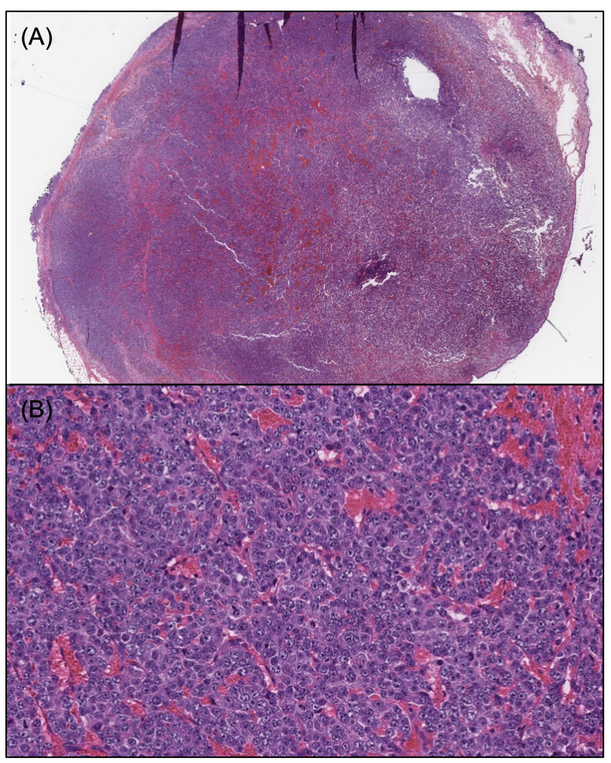

Figure 1. *Excisional biopsy of the left upper chest nodule revealed a large mass in the dermis (A, original magnification x 40). The tumor was deeply infiltrative and consisted of monomorphous cells with hyperchromatic nuclei, fine granular cytoplasm, and indistinct cell borders (B, original magnification x 100).*

Case Description

A 69-year-old man with a history of metastatic prostate carcinoma on leuprolide and enzalutamide presented to his colorectal surgeon with an erythematous nodule on his left upper chest that had been growing in size over four weeks. The nodule, which was thought be an infected cyst, had been incised and drained several months prior with subsequent recurrence.

Two years prior to the appearance of the chest nodule, the patient had been diagnosed with prostate acinar adenocarcinoma with a Gleason score of 8 (4 + 4). His initial prostate biopsy demonstrated androgen sensitivity and was negative for the neuroendocrine (NE) markers synaptophysin and chromogranin A. He was shortly thereafter found to have extensive metastases to the retroperitoneal lymph nodes, liver, bilateral lungs, and bones on CT imaging, and was thus determined to be stage IVB. He had disease progression on docetaxel, and therefore was switched to leuprolide and enzalutamide.

Excisional biopsy was performed of the left chest nodule and showed a large, non-ulcerated, deeply infiltrative mass separated from the epidermis by a thin grenz zone. The mass was composed of sheets of poorly differentiated, monomorphous cells infiltrating through the dermal collagen and extending into the subcutaneous tissue, with focal geographic and cellular necrosis. The cells had indistinct cell borders and contained hyperchromatic nuclei with prominent nucleoli, and a small amount of fine, granular cytoplasm. Numerous mitotic figures were present. Lymphovascular invasion was not identified (Fig. 1A-B). Although there was no evidence of glandular differentiation, given the patient's known history of metastatic prostate carcinoma, a cutaneous metastasis was suspected. Immunohistochemical (IHC) stains were performed and showed diffuse positivity for prostatic acid phosphatase (PAP), androgen receptor, and NKX3.1 (Fig. 2A-B). Additionally, there was scattered positive staining for synaptophysin (Fig. 3) and chromogranin, markers of NE differentiation. The patient was diagnosed with cutaneous metastatic prostate carcinoma with neuroendocrine differentiation. He was restarted on docetaxel as his metastatic disease continued to worsen. He died four months later.

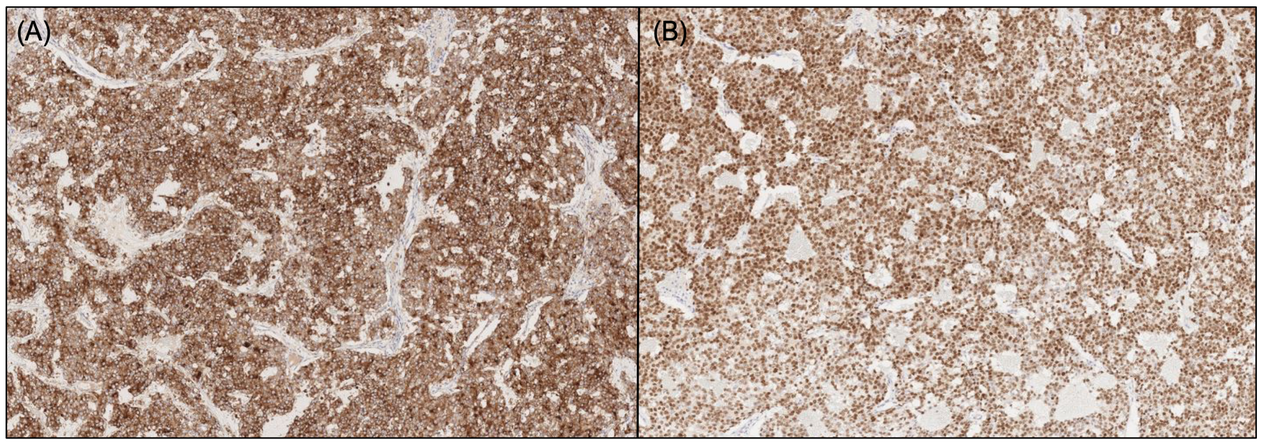

Figure 2. *Immunohistochemistry showed diffuse positivity for PAP (prostatic acid phosphatase) (A, original magnification x 100) and for NKX3.1 (B, original magnification x 100).*

Discussion

Most prostate carcinomas are adenocarcinomas, which are derived from glandular cells dependent on androgens, thus making androgen blockage therapy the mainstay of treatment for advanced and recurrent prostate carcinomas. NE differentiation is a well-recognized phenotypic change by which prostate carcinoma cells transdifferentiate into NE-like cells, which lack expression of androgen receptor and prostate specific antigen and therefore may confer resistance to standard androgen deprivation therapy. NE differentiation is known to be induced by therapeutic agents, including androgen deprivation therapy, docetaxel, enzalutamide, and radiation therapy.

While NE differentiation is common in primary prostate carcinomas, it is rare in metastatic disease. To date, there are only three reported cases of cutaneous metastatic prostate carcinoma demonstrating neuroendocrine differentiation, and two of these cases were from small cell prostate carcinoma. In addition, there is just one case of cutaneous metastasis representing the first evidence of NE differentiation, as in our case.

Cutaneous tumors with neuroendocrine differentiation are almost invariably malignant. The differential diagnosis includes primary cutaneous malignant neuroendocrine tumors – most commonly Merkel cell carcinoma – and metastatic neuroendocrine malignancies. Visceral neuroendocrine carcinomas rarely metastasize to the skin. However, when cutaneous metastases occur, the most frequent primary sites are the gastrointestinal tract and bronchopulmonary system. Therefore, in the work-up of cutaneous tumors with neuroendocrine differentiation, the following IHC studies may be helpful in the appropriate clinical context: cytokeratin 20, TTF-1, and CDX-2 to evaluate for Merkel cell carcinoma, metastatic neuroendocrine carcinoma of bronchopulmonary origin, and metastatic neuroendocrine carcinoma of intestinal origin, respectively.

NE differentiation in prostate carcinoma is important to recognize due to its implications on prognosis and management. When present in primary and metastatic tumors, it is associated with a poorer prognosis, with a two-year survival rate of 35% versus a two-year survival rate of 97% in cases without it. The degree of NE differentiation appears to be directly related to the degree of tumor aggressiveness. This is thought to be due to several reasons, including the fact that NE-like cells can produce peptide hormones and growth factors that promote tumor growth and aggression, and because NE-cells do not proliferate, thus constituting a dormant phenotype resistant to therapy.6 Studies have found that patients with metastatic prostate carcinoma with NE differentiation may have improved clinical outcomes with alternative treatment regimens, such as docetaxel-prednisone followed by abiraterone acetate.

Given this, clinicians should have a low threshold for sampling new cutaneous lesions in patients with a known history of prostate carcinoma, even if the morphology is atypical for metastasis. Cutaneous metastatic prostate carcinoma may rarely be the first evidence of NE differentiation. Therefore, IHC markers to evaluate for NE differentiation, including chromogranin A, synaptophysin, CD56, and neuron-specific enolase, should be obtained in the appropriate context.

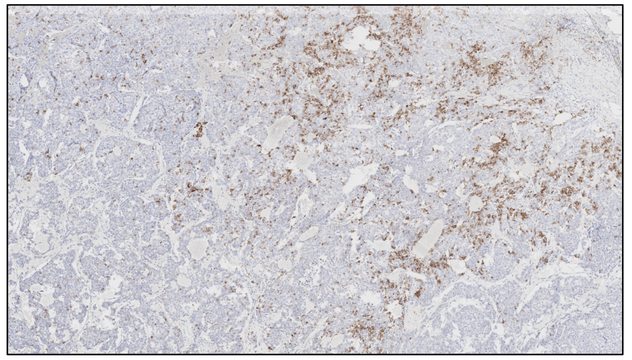

Figure 3. *Immunohistochemistry was also significant for scattered tumor cells with positive staining for synaptophysin (original magnification x 100).*

References

Henley SJ, Ward EM, Scott S, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer. 2020;126(10):2225-2249.

Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. Can Urol Assoc J. 2010;4(6):380-384. doi:10.5489/cuaj.10167.

Brown GT, Patel V, Lee CC. Cutaneous metastasis of prostate cancer: a case report and review of the literature with bioinformatics analysis of multiple healthcare delivery networks. J Cutan Pathol. 2014;41(6):524-528.

Kataria PS, Kendre PP, Patel AA, Dalsaniya S. Cutaneous Metastasis Leading to the Diagnosis of Carcinoma of the Prostate: A Rare Case Report and Review of Literature. Indian J Dermatol. 2018;63(2):182-185. doi:10.4103/ijd.IJD_7_17

Piqué Duran E, Paradela A, Fariña MC, et al. Cutaneous metastases from prostatic carcinoma. J Surg Oncol. 1996;62(2):144-147.

Hu CD, Choo R, Huang J. Neuroendocrine differentiation in prostate cancer: a mechanism of radioresistance and treatment failure. Front Oncol. 2015;5:90.

Patel GK, Chugh N, Tripathi M. Neuroendocrine Differentiation of Prostate Cancer-An Intriguing Example of Tumor Evolution at Play. Cancers (Basel). 2019;11(10).

Munera-Campos M, Bielsa I, Plana-Pla A, Posada R, Quer A, Ferrándiz C. Cutaneous metastases from prostate cancer revealing neuroendocrine differentiation. J Cutan Pathol. 2019;46(12):976-978.

Nelson EC, Cambio AJ, Yang JC, Ok JH, Lara PN, Evans CP. Clinical implications of neuroendocrine differentiation in prostate cancer. Prostate Cancer Prostatic Dis. 2007;10(1):6-14.

Cecen K, Karadag MA, Demir A, Kocaaslan R. Small cell carcinoma of the prostate presenting with skin metastasis: a case report. J Med Case Rep. 2014;8:146.

Kaplan M, Atakan IH, Bilgi S, Inci O. Case report: subcutaneous metastasis from small cell carcinoma of the prostate. Int Urol Nephrol. 2007;39(1):157-160.

Amorim GM, Quintella D, Cuzzi T, Rodrigues R, Ramos-E-Silva M. Cutaneous Metastasis of Neuroendocrine Carcinoma with Unknown Primary Site: Case Report and Review of the Literature. Case Rep Dermatol. 2015;7(3):263-274.

Fernandes R, Matsushita M, Mauad T, et al. Prostate carcinoma with neuroendocrine differentiation: case report and literature review. Rev. Hosp. Clin. 2001;56(5): 153-158.

Di Sant'Agnese PA. Neuroendocrine differentiation in human prostatic carcinoma. Hum Pathol. 1992 Mar;23(3):287-96. doi: 10.1016/0046-8177(92)90110-o. PMID: 1313390.

Fan L, Yang Y, Chi C, et al. Neuroendocrine differentiation markers guide treatment sequence selection in metastatic castration-resistant prostate cancer. Prostate. 2019;79(6):567-573.