Neuroendocrine transformation of prostate adenocarcinoma with corpora cavernosa metastases

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FOSS H, RAGAM R, KELLY WK, GOMELLA LG. Neuroendocrine transformation of prostate adenocarcinoma with corpora cavernosa metastases. *Can J Urol* 2022;29(6):11399-11401.

We report the case of a 61-year-old male with metastatic prostate cancer who presented with urinary retention secondary to subdermal penile and corpora cavernosa metastases with neuroendocrine transformation of his metastatic hormone sensitive prostate cancer. We highlight the presentation, diagnosis, and management of this rare condition.

Key Words: neuroendocrine prostate cancer, neuroendocrine transformation, small cell carcinoma, genomics, RB1 loss

Introduction

Neuroendocrine prostate cancer (NEPC) is a rare morphologic variant of prostate cancer with high rates of metastasis and poor survival.[1] Although de novo neuroendocrine prostate cancer is possible, this only accounts for less than 2% of prostate cancers.[2] It more often arises due to selective pressure from androgen deprivation therapy (ADT) or novel androgen receptor-axis-targeted therapies (ARAT) used for advanced prostate cancer treatment.[1] Given the increasing use of ADT with ARATs, the incidence of NEPC has been increasing.[1] It has a poor response to further AR directed therapies and is considered an aggressive variant of castrate resistant prostate cancer.[3] Additionally, it is often only transiently responsive to taxane or platinum based chemotherapy.[3] Here, we present a case report of a male with metastatic prostate adenocarcinoma treated with ADT plus enzalutamide who developed neuroendocrine transformation with metastases to the liver and penile corporal bodies.

Accepted for publication November 2022

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Case report

The patient is a 61-year-old male with history of obesity and diabetes with severe diabetic peripheral neuropathy who originally presented with worsening lower urinary tract symptoms and was noted to have a nodular and firm prostate on digital rectal exam with a PSA of 2.3. Staging studies with an MRI, CT, and bone scan showed locally advanced prostate cancer with bladder wall invasion, right hydronephrosis, abdominal lymph node metastases, and bone metastases (T12 vertebral body and right sacroiliac joint). He ultimately underwent transrectal prostate biopsy and transurethral resection of a bladder mass with pathology showing Gleason 5+5 prostate adenocarcinoma with lymphovascular invasion and invasion into detrusor muscle, consistent with pathologic T4 disease. Immunohistochemical analysis and next generation sequencing showed genomic findings of RB1 loss of exons 3-27 and TMPRSS2-ERG gene fusion. Biomarker findings were notable for low tumor mutational burden (0 Muts/Mb) and microsatellite stability. He was subsequently initiated on degarelix and enzalutamide given his multiple co-morbidities including his symptomatic diabetic peripheral neuropathy. His PSA quickly nadired to < 0.1 ng/mL and he was transitioned from degarelix to leuprolide.

His right hydronephrosis became symptomatic and continued to progress, ultimately requiring an indwelling double J ureteral stent. Despite his worsening hydronephrosis, his staging scans showed interval improvement of his bulky pelvic lymphadenopathy with stable bone disease, and his PSA remained undetectable.

Approximately 1 year after initiation of therapy for his prostate cancer, he began to complain of worsening lower urinary tract symptoms with increasing urinary frequency and post-void dribbling, culminating in acute urinary retention managed with an indwelling foley catheter. He also noted a new firm nodule on the left side of his penis at this time. His exam was notable for a 2 cm firm subdermal nodule within the left dorsal mid penile shaft and firm/nodular proximal corpora cavernosa bilaterally, Figure 1. His PSA remained undetectable at this time. He was taken to the operating room for biopsy of the penile mass as well as suprapubic tube placement. Cystoscopy demonstrated a shaggy appearing urethra with compression of the urethra at the level of the left penile

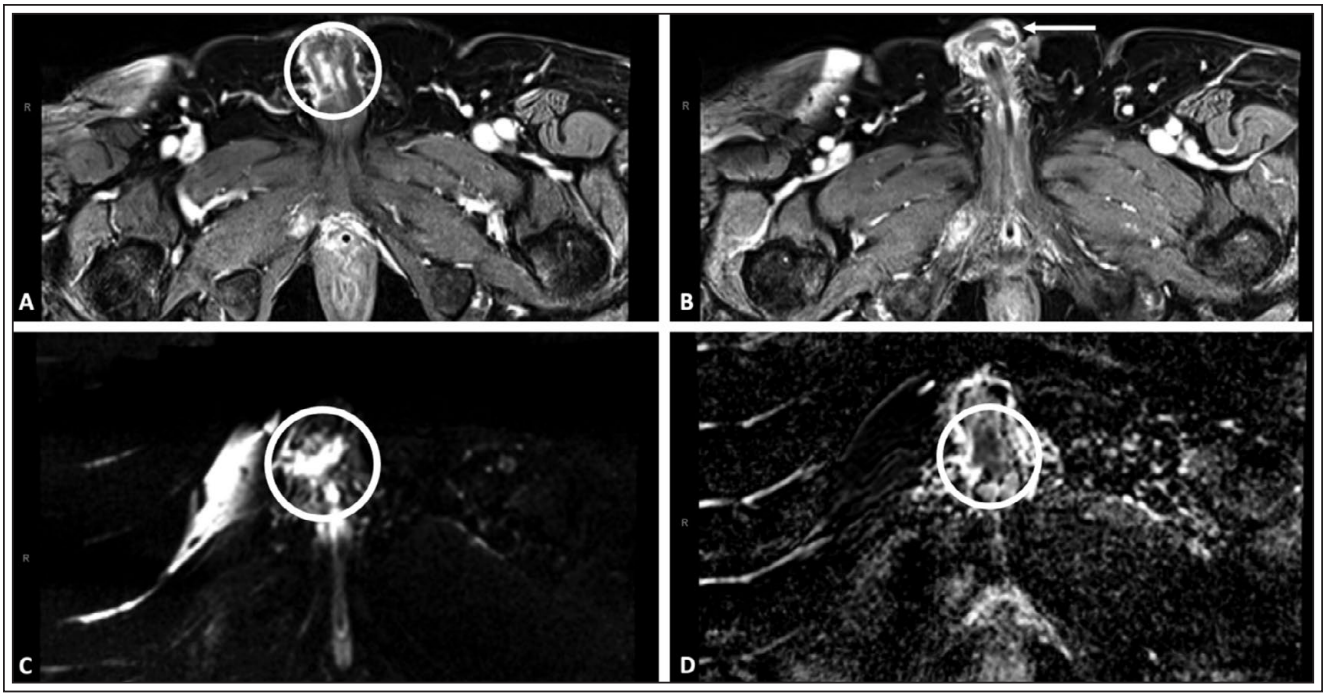

Figure 1. (A) Nodular irregular enhancement in the mid-penile shaft involving the corpus cavernosum and spongiosum on axial post-contrast T1-weighted fat suppressed image. **(B)** 1.1 mm peripherally enhancing subdermal nodule in the left base dorsal penile shaft on post-contrast T1-weighted fat suppressed image. The irregular corporal lesions show restricted diffusion, as evidenced by hyperintensity on diffusion-weighted imaging (DWI) with corresponding deficit on ADC **(C, D)**.

shaft mass. Pathology demonstrated malignant tumor with neuroendocrine features. Immunostains showed tumor cells positive for TTF-1 (thyroid transcription factor 1) and CAM5.2, favoring a small cell carcinoma but not specific for a site of origin. A liquid biopsy was notably positive for TMPRSS2-ERG fusion and RB1 loss of exons 3-27, markers also consistent with his original tumor biopsy. Staging CT at this time showed new metastatic liver disease. Additionally, his chromogranin A level was elevated to 282.2, but was previously within normal limits 1 year prior at the time of diagnosis. Given his disease progression and transformation to small cell phenotype, he was initiated on carboplatin and etoposide chemotherapy.

Interval imaging after initiation of chemotherapy showed decreased liver lesions but the penile lesion was grossly unchanged. Given his initial penile biopsy had insufficient tissue for further somatic genetic testing, he was again taken to the operating room for an excisional biopsy to help direct future therapy. Pathology again demonstrated poorly differentiated carcinoma with high grade neuroendocrine features. Immunohistochemical stain demonstrated aberrant (null) pattern of expression of p53 and RB1. Interestingly, his genetic biomarker testing did not show mutation in either RB1 or p53. However, it did show a likely pathologic variant of gene EPHA2. Unfortunately, shortly after this his disease progressed despite treatment with development of brain metastases as well as worsening obstructive nephropathy requiring left percutaneous nephrostomy tube placement. Ultimately, he was transitioned to hospice care after a goals of care discussion with the patient and his family.

Discussion

Neuroendocrine transformation of prostate cancer is a rare but highly aggressive progression of advanced prostate cancers. A study conducted by Ostano et al looked at molecular features of prostate tumors that may anticipate neuroendocrine transformation of prostate adenocarcinomas and found that tumors with the highest levels of chromogranin A and perineural invasion showed higher likelihood of neuroendocrine transformation.[1] Neuroendocrine transformation should be on the differential for patients with progressive disease despite a normal PSA, especially in those with a history of prior or active treatment with ADT or ARAT.

Genomic testing is becoming an increasingly prevalent area of research in relation to prostate adenocarcinoma. Alterations or loss of tumor suppressor genes TP53, RB1, and PTEN portend more aggressive disease.[4] Our patient's immunohistochemical stain demonstrated an aberrant (null) expression of p53 and RB1 and his genomic sequencing was significant for RB1 loss, which has been found promote neuroendocrine differentiation of prostate cancer.[5-7] Genomic testing also identified a TMPRSS2-ERG gene fusion, a mutation thought to play a role in early prostatic carcinogenesis.[8] This gene mutation has also been identified in many prostatic small cell carcinomas (SCC), present in up to 40%-50% of both de novo and treatment-emergent NEPC.[2,9] However, this marker has not been shown to be prevalent in non-prostatic SCC, demonstrating that this can be used as a marker to establish prostatic monoclonal origin of SCC.[2]

Genomic testing is important not only in classifying a specific cancer subtype, but also in identifying therapeutic targets. Currently, those with small cell NEPC are often treated with systemic therapy regimens used in small cell lung cancer (SCLC) with platinum-based chemotherapy given the molecular similarities.[9] Although small cell NEPC may be initially responsive to platinum-based chemotherapy with objective response rates of 50%-60%, the larger clinical challenge is what to offer as second line therapy. Further research is currently being conducted to establish genomic aberrations and epigenetic changes associated with NEPC that could be targeted by immunotherapy.[9] Identifying unique biomarkers with liquid biopsies and genomic testing of metastatic biopsies will prove important in facilitating future clinical trials. □

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