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Case Report

Oligometastatic Squamous Cell Transformation From Metastatic Prostate Adenocarcinoma Treated With Systemic and Focal Therapy: A Case Report

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ABSTRACT

Transformation to squamous cell carcinoma (SCC) after initial treatment of a primary prostate adenocarcinoma is rare and typically results in rapid treatment-refractory disease progression and death. Here, we present a case of a 70-year-old man who was initially treated with prostatectomy and radiotherapy, and later developed bone metastases. After commencing systemic therapy with androgen deprivation therapy (ADT) and apalutamide, his prostate-specific antigen (PSA) declined to undetectable levels, yet short-interval imaging demonstrated oligo-progression at T4, with biopsy specimen demonstrating pure SCC. Molecular profiling of both the primary prostate tumor and T4 demonstrated alterations in *TMPRSS2-ERG*, *TP53*, and *FOXA1* confirming site of origin, with loss of *RNF43* in the squamous metastasis. He was treated with stereotactic body radiation therapy to the SCC metastasis and continued on ADT and apalutamide with stable disease for a year post-radiation. This case highlights the importance of imaging to detect non–PSA-producing metastatic disease, the utility of radiation therapy in oligo-progression, and use of molecular profiling to provide insights into the pathogenesis of histologic transformation.

Keywords: squamous, prostate, *TMPRSS2-ERG*, stereotactic body radiation therapy (SBRT)

INTRODUCTION

Primary squamous cell carcinoma (SCC) of the prostate is a rare entity that typically portends a poor prognosis. Squamous transformation after initial treatment of a primary prostate adenocarcinoma is even less common, with such an event often resulting in treatment-refractory progression and death from disease.

Comprehensive genomic profiling of prostate adenocarcinoma with later squamous transformation can help resolve diagnostic dilemmas and suggest potential therapeutic interventions. It can also provide key insights into the fundamental biology and potential drivers of this phenomenon, especially when the analysis conducted involves comparisons of the primary adenocarcinoma and the metachronous transformed metastasis. To date, there are limited studies that report genomic results of paired primary prostate adenocarcinoma and a metastatic squamous site. We present a radiologic and genomic analysis of a case of metastatic, squamous cell–transformed prostate cancer.

CASE DESCRIPTION

According to institutional policy, this report was exempt from ethical review and the patient provided consent to publish the case. As seen in Figure 1, this 70-year-old man underwent a radical prostatectomy that revealed Gleason 4+3 pT4N1 disease, with a postoperative prostate-specific antigen (PSA) of 0.337 ng/mL. He

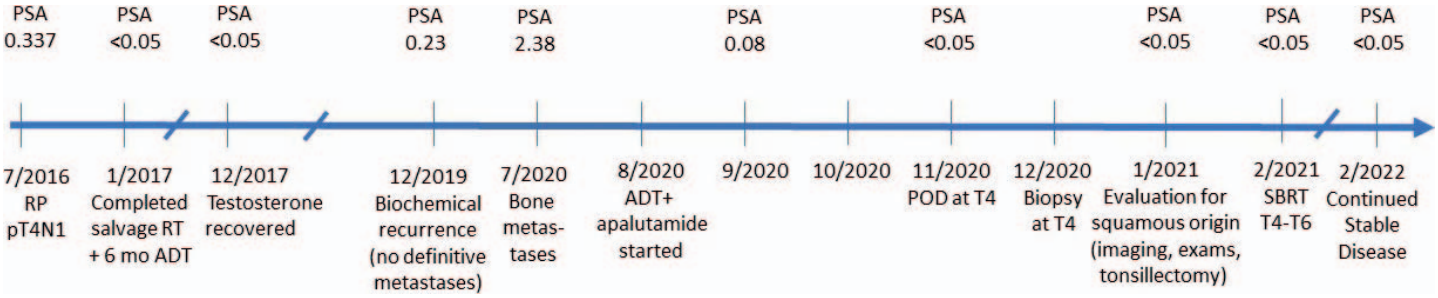

Figure 1. Timeline. RP, radical prostatectomy; POD, progression of disease.

received 6 months of androgen deprivation therapy (ADT) along with salvage radiotherapy to the prostate bed and nodes. His PSA decreased to undetectable levels and remained undetectable for 2 years after testosterone recovery. He developed biochemical recurrence, then a more rapid PSA doubling time, and was restaged with a PSA of 2.38 ng/mL.

The positron emission tomography (PET) ^{18}F-FACBC (fluorine 18 fluciclovine [anti-1-amino-3–^{18}F-fluorocyclobutane-1-carboxylic acid]) (Axumin, Blue Earth Diagnostics Inc.) scan, bone scan, and magnetic resonance imagining (MRI) of the total spine showed the patient had evidence of metastases at T4, T6, and the left fourth rib (Figs. 2A, B). He was started on ADT and apalutamide, an androgen receptor inhibitor, with decline in PSA to undetectable levels. A restaging PET ^{18}F-fluciclovine scan performed 3 months later demonstrated resolution in avidity of prior metastatic disease except for new uptake in the T4 transverse process, confirmed on MRI of the thoracic spine. This lesion was biopsied; pathology was consistent with a pure metastatic SCC, positive on immunohistochemistry for p16 and p40 and negative for *NKX3.1* and GATA-3. Human papillomavirus high-risk test was negative. A core from the bone metastasis that had not been decalcified was sent for next-generation sequencing using MSK-IMPACT, an FDA-approved 468-gene oncopanel.

The patient underwent a thorough comprehensive and dermatologic exam (given a history of superficial SCC). He underwent imaging inclusive of computed tomography of the neck and chest/abdomen/pelvis, fluorodeoxyglucose (FDG) PET, and MRI of the rectum. FDG PET demonstrated avidity at T4 as well as the tonsil, whereas other sclerotic bone metastases were non–FDG-avid. A simple tonsillectomy was performed given the FDG avidity in the tonsil and was consistent with benign inflammation.

Molecular profiling of the T4 lesion revealed somatic mutations in *TP53* (exon8p.P278R), *FOXA1* (exon2p.L260Cfs*6), and *TMPRSS2-ERG* fusion exons (TMPRSS2 exons 1-2 and ERG exons 4-11). Subsequent analysis of the primary prostate tumor from the original prostatectomy showed identical *TP53*, *FOXA1*, and *TMPRSS2-ERG* alterations with the addition of a point mutation in *RNF43* (exon2.p.G26A) that was lost in the squamous-transformed metastasis. No new alterations were discovered in the SCC metastasis relative to the primary tumor, although the allele frequency of *FOXA1* was slightly higher (0.05 in the primary adenocarcinoma and 0.37 in the SCC metastasis).

Evidence suggested the patient's prostate adenocarcinoma had transformed into an SCC at a focal metastatic site. He was treated with stereotactic body radiotherapy (SBRT; 2700 cGY over three fractions to T4-T6) with ongoing ADT and apalutamide. He continued surveillance FDG PET imaging and labs every 3 months; he remains without any radiographic or biochemical progression 12 months after the completion of his SBRT (Fig. 3).

DISCUSSION

Squamous cell histology associated with prostate cancer is a rare entity representing less than 1% of all prostate cancers; it has been more commonly reported from primary prostate tumors rather than later metastatic transformation.[1] Prior reports have described these tumors arising after radiotherapy or hormonal therapy, anywhere from months to years later.[2] Often the diagnosis is made after clinical symptoms prompt attention, such as bladder outlet obstruction from a locally advanced tumor.

Although case reports are sporadic, a series of 33 cases with squamous histology reported 21 occurring with a prior diagnosis of adenocarcinoma.[3] Histologically, 8 of 33 were pure SCC whereas most were adenosquamous histology. It has been speculated that the SCC may arise from multipotential prostate adenocarcinoma cells given antecedent hormonal therapy and radiotherapy, rather than evolution from a benign squamous metaplasia.

Paired genomic analyses of the primary prostate adenocarcinoma and metastatic SCC offer insights into pathogenesis. Data from other cases and our own case suggest a high proportion harbor *TMPRSS2-ERG* fusions.[4–6] This finding may reflect the high-risk nature of these prostate tumors at diagnosis, of which *TMPRSS2-ERG* is already known to be associated, or it may be implicated in the biology of transformation.

Lara et al[6] compared the primary and metachronous SCC and adenocarcinoma deposits and found loss of *CDKN2A/B*; specific to the SCC was a *CIC* (G133C)

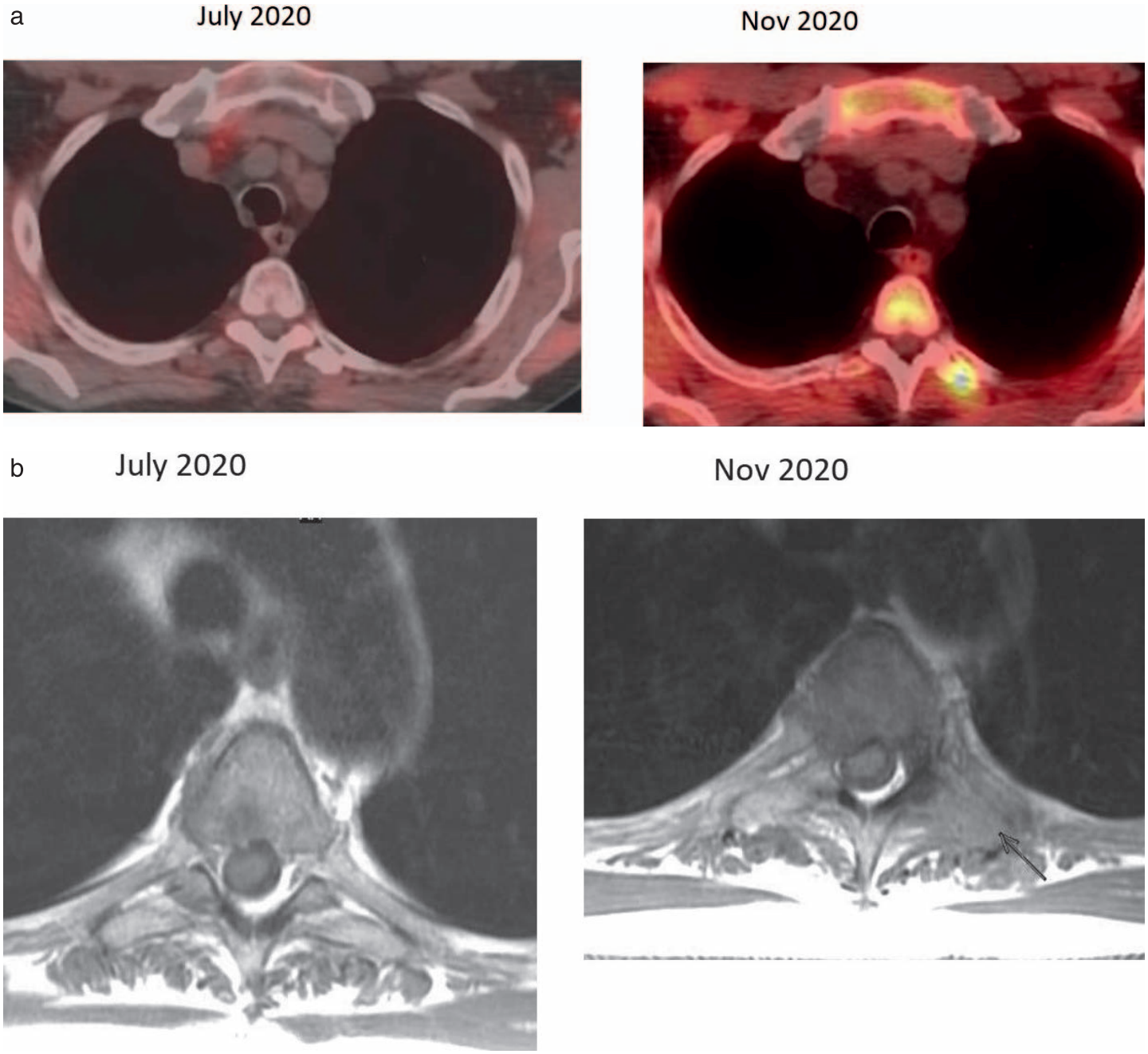

Figure 2. Routine imaging performed July 2020 and November 2020 demonstrating radiographic progression at T4 reflective of squamous cell metastasis. (A) PET fluorine 18 (^{18}F)-fluciclovine; (B) MRI of the spine. In the right panel, the arrow points to the progressive T4 posterior element. PET, positron emission tomography; MRI, magnetic resonance imaging.

mutation. *CIC* is a transcriptional repressor that constitutively represses certain genes targeted for activation by the EGFR/RAS/MAPK pathway. Lau et al[7] found a *CTNNB1* mutation in their analysis of a transformed SCC. In our own analysis, we found that a *RNF43* mutation present in the primary adenocarcinoma was lost in the squamous deposit, but otherwise identical. The significance of *RNF43*, an E3 ubiquitin ligase that negatively regulates WNT signaling, is uncertain. In our case, many of the molecular features in the primary adenocarcinoma were retained in the SCC, and transformation may occur through lineage plasticity in response to selective treatment-related pressure.

Lineage plasticity refers to the ability of a cell to shift from a committed developmental pathway to another, creating a new phenotype, which may occur through selective treatment pressure.[8] This shift has been described with the more common neuroendocrine prostate cancer but may similarly apply to SCC transformation. Both the original primary adenocarcinoma and

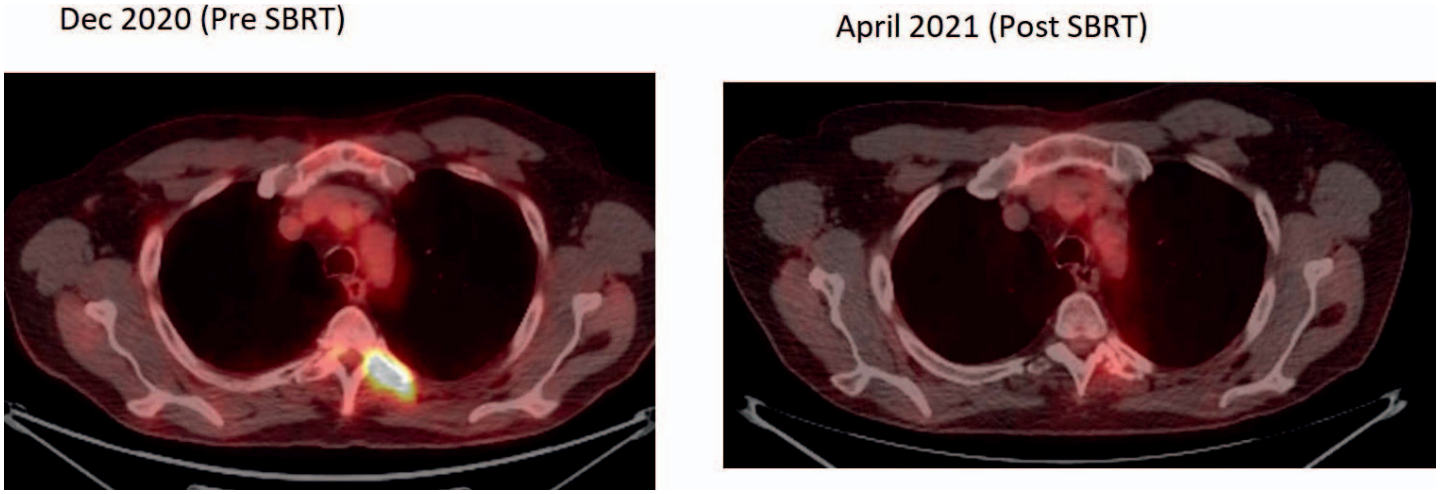

Figure 3. FDG PET imaging pre- and post-SBRT to the T4 squamous metastasis. FDG, fluorodeoxyglucose; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

metastatic SCC harbored a somatic alteration in *FOXA1*. *FOXA1* is a pioneering transcriptional cofactor reported in 11% of prostate cancers and is associated with metastatic recurrence.[9,10] In addition, *FOXA1* R219 mutations are enriched in metastatic tumors with neuroendocrine differentiation.

This case is unique in that the patient has had a relatively favorable ongoing response to a conservative treatment strategy upon discovery of the squamous metastasis, a shift that has been reported to portend an aggressive clinical course. It may be that the biology of this SCC was less aggressive, with retention of p16, which is thought to be more favorable in squamous non–small cell lung cancer, or it may be more radiation-sensitive; the incidental nature of its discovery on routine imaging might also suggest it was an early event that made a focal intervention more successful.

Highlighted in this case is the utility of imaging in hormone-sensitive prostate adenocarcinoma irrespective of PSA level. National Comprehensive Cancer Network guidelines suggest bone imaging every 6–12 months for this patient population, although imaging practices in the community vary. Although increased frequency of imaging is not warranted given the rarity of SCC transformation, clinical suspicion in a patient with a new symptom should prompt additional imaging despite an undetectable PSA level. Additionally, pseudoprogression or "flare" response characterized by new lesions on bone scan is not uncommon with androgen receptor inhibitors; close follow-up imaging is thus important if new lesions are detected, to differentiate between true progression and pseudoprogression. In the case presented here, an MRI was able to delineate progression with marked diffusion elevation, reflective of true progression. PET ^{18}F-fluciclovine was used at the time of biochemical recurrence in this patient, which reflects one of several imaging modalities available for this patient population; however, it should be noted that the repeated PET ^{18}F-fluciclovine at 3 months would not be standard, and access to this modality for repeat measurement can vary by insurers. Of note, prostate-specific membrane antigen (PSMA) PET is generally believed to be a more sensitive imaging tracer for biochemical recurrence although it may not have captured the T4 metastasis as readily given the lack of target antigen in a squamous transformation.

Limitations of this case include the lack of biopsy procedure of one of the responding, non–FDG-avid sclerotic metastases, which is presumably adenocarcinoma. Dense sclerotic metastases can be more challenging to yield a specimen sufficient for molecular profiling, and therefore a biopsy procedure of a responding metastasis (adenocarcinoma) was not performed. Strengths of this case include parallel molecular profiling, a contemporary approach to treatment, and the uniquely favorable prognosis to date in contrast to other cases of squamous cell transformation of prostate adenocarcinoma.

CONCLUSIONS

Overall, squamous cell transformation from prostate adenocarcinoma remains a rare entity requiring pathologic confirmation, imaging, and clinical correlation. This case highlights the use of genomic profiling to validate the diagnosis on a patient level and may help to elucidate the mechanisms of transformation from prostate adenocarcinoma to variant histologies warranting study on a larger scale.

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