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Case Report

Post-therapeutic squamous cell transformation of a metastatic prostate adenocarcinoma with comparison of molecular profiles: a case report and review of the literature

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Abstract: Transformation of primary prostate adenocarcinoma to squamous cell carcinoma after initial treatment with chemotherapy and hormonal therapy is extremely rare and typically results in rapid treatment-refractory disease progression and death. Here, we present a case of a 64-year-old man who was initially diagnosed with metastatic prostate adenocarcinoma (positive PSA and NKX3.1 stains, total PSA 747.2 ng/ml) to the thoracic spine (T8) in 2019. The patient received androgen deprivation therapy and chemotherapy with good response (PSA 2.53 ng/ml). In 2022, the patient had a tumor resection from the left humerus with a consequent fracture. Pathology showed pure squamous carcinoma without any adenocarcinoma component (PSA and NKX3.1 stains negative and weak p504s stain, PSA 19.82 ng/ml). Given the patient's history of metastatic prostate adenocarcinoma and no history of any other malignancies, a diagnosis of squamous carcinoma transformed from prostate adenocarcinoma was rendered. The patient passed away in 2023. Molecular profiling identified the same *TP53* mutation and two variants of uncertain significance in both specimens, suggesting the same primary. However, there was *CCND3* amplification and absence of the *TMPRSS2*::*ETV4* fusion in the 2022 specimen, which may be associated with squamous transformation and poor prognosis. A microarray might be beneficial to confirm loss of the *TMPRSS2*::*ETV4* fusion. This case illustrates the rare occurrence of squamous transformation in prostate adenocarcinoma and the aggressive clinical course, and need for more therapy guidance and prognostic studies. It also highlights the importance of molecular profiling to provide insights into the pathogenesis of histologic transformation.

Keywords: Squamous transformation, metastatic, prostate adenocarcinoma, molecular profiling, *CCND3, TMPRSS2::ETV4* fusion

Introduction

As one of the most prevalent cancers in men in the United States, prostate adenocarcinoma places a significant burden on the health system [1]. Prostate cancer accounts for 27% of cancer diagnoses in men, and is the most common solid tumor in men worldwide [2, 3]. The two mainstays of treatment of localized cancer include surgery and radiotherapy. Up to 17% of patients develop metastatic disease, with the most common site of metastasis being bone (84%), followed by distant lymph nodes, liver, and thorax [4]. In recurrent or metastatic disease, androgen deprivation therapy (ADT), androgen signaling inhibition (ARSI) and chemotherapy comprise the standard medical treatment [5]. The majority of patients with metastatic prostate cancer who receive standard treatment develop "castration resistance", i.e. resistance to anti-androgen therapy, which is associated with a very poor prognosis [6]. Median survival for men with prostate cancer is 3-4 years depending on the treatment [7]. Recent developments include the use of poly-ADP ribose polymerase (PARP) inhibitors in tumors with homologous recombination repair pathway alterations [8].

Transformation of primary prostate adenocarcinoma to squamous cell carcinoma after initial treatment with chemotherapy and hormonal

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therapy is extremely rare and typically results in rapid treatment-refractory disease progression and death. The serum prostate-specific antigen (PSA) in cases of squamous transformation commonly shows values within the normal range [9, 10].

Comprehensive genomic profiling of metastatic prostate adenocarcinoma with subsequent squamous transformation has the potential to help understand the pathogenesis and guide therapeutic interventions. It can also suggest the potential drivers of the transformation, especially when comparing the molecular profile of the original metastatic prostate adenocarcinoma with the component of squamous transformation. To date, there are very few studies reporting the genomic profile of metastatic prostate adenocarcinoma with squamous transformation. Due to its rarity, we present an interesting case of prostate adenocarcinoma with its paired metastatic, squamous cell-transformed component, each with genomic analysis.

Case description

A 64-year-old Grenadian male was referred to the clinic in 2019 with worsening abdominal pain and right lower extremity weakness. He underwent abdominal/pelvic computed tomography (CT) scan two days earlier, which showed multiple lytic lesions of the sacrum and pelvis with an enlarged prostate gland. For the previous 2 days, he had sharp pain that started in the lower back with radiation through the right leg down to the toes, accompanied with decreased sensation in the distal foot. The patient also had lower urinary tract symptoms and worsening overflow incontinence. Magnetic resonance imaging (MRI) of the cervical, thoracic and lumbar spine demonstrated a T8 spinal tumor extending to the epidural space with severe canal stenosis and cord deformity with signal change from T7-T9. There were also multiple nodular lesions varying in size in all lobes of both lungs, with enlarged mediastinal and hilar lymph nodes, identified on chest CT scan. Laboratory examination showed that the serum PSA level was markedly elevated (747.2 ng/ml, normal: 0-4 ng/ml). A subsequent biopsy obtained from the T7-T8 laminectomy showed metastatic carcinoma. Immunohistochemical studies revealed that the tumor cells were positive for cytokeratin AE1/AE3, PSA and NKX3.1, and negative for CK7, CK20, CD45, GATA3, p63, TTF1 and PAX8, consistent with a prostatic primary.

At that point, hormonal treatment using a luteinizing hormone-releasing hormone (LHRH) analog (leuprorelin), antiandrogen antineoplastic agents (bicalutamide, abiraterone), and an antimicrotubular antineoplastic agent (docetaxel) was started. Serum PSA level gradually decreased to within the reference range after 19 months of treatment (2.52 ng/ml, normal: 0-4 ng/ml).

In 2022, the patient was brought to the hospital after falling down at home and was found to have a left distal humerus fracture. The left humerus X-ray showed a pathologic fracture with a 6 cm-long lytic metastasis in the distal left humerus. The CT scan found an expansile intramedullary mass in the left distal humeral diaphysis with associated cortical breakthrough, consistent with osseous metastasis in the setting of known metastatic prostate cancer. There was also an associated comminuted, predominantly transverse, pathologic fracture of the distal left humerus. The biopsy obtained from the left distal humerus lesion revealed metastatic carcinoma with prominent squamous differentiation. The tumor was positive for cytokeratin AE1/AE3, CAM 5.2, p40, p504s (weak) and negative for NKX3.1, PSA, ERG, and AR. The patient's previous history of metastasis to the thoracic spine and the weak p504s staining suggested squamous carcinoma transformed from prostate adenocarcinoma post hormonal treatment. The PSA level during this period gradually increased again to 19.82 ng/ml, though still much lower than the PSA level before the initial treatment. The antiandrogen agent enzalutamide was added to the therapy. The patient passed away in 2023.

The first specimen from the thoracic spine was sent for solid tumor panel using next-generation sequencing (NGS) at Sema4 in 2019, which identified a clinically significant variant in the TP53 gene and a clinically significant *TMPRSS2::ETV4* fusion. In 2022, the specimen collected from the left distal humerus was sent for NGS analysis, and the results showed *CCND3* amplification but absence of the *TMPRSS2::ETV4* fusion. However, the same

Table 1. Molecular alterations in the two samples

Alteration	2019 sample (thoracic spine T7-8)	2022 sample (left distal humerus)
TP53 p.C182Afs*65	50% VAF	21% VAF
TMPRSS2(1)::*ETV4*(3) fusion	111,684 reads	Not detected
SETD2 p.S572P	51% VAF	42% VAF
FANCA p.M203V	58% VAF	46% VAF
CCND3 amplification	Not detected	9 copies

VAF: variant allele fraction.

TP53 mutation was identified as well as two variants of uncertain significance (VUS) that matched the original specimen, suggesting the same primary (**Table 1**). Though the two VUSs could be germline, the *TP53* mutation is likely somatic given the variant allele fraction and patient age. The *CCND3* amplification and absence of the *TMPRSS2::ETV4* fusion in the 2022 specimen may be associated with squamous transformation and poor prognosis. A microarray would be a potential next step to confirm loss of the *TMPRSS2::ETV4* fusion.

We also did a literature search focusing on the squamous transformation that occurred after a LHRH agonist hormone therapy. To the best of our knowledge, our patient is the third case presenting a pure squamous differentiation resulting from the transformation of a prostate adenocarcinoma after injection of an LHRH agonist (**Table 2**) and the first case with molecular testing results.

Discussion

Squamous cell transformation associated with metastatic prostate cancer is a rare entity that accounts for less than 1% of all prostate malignancies [5]. Although there are a few case reports of squamous cell transformation to date, it has been more commonly seen in primary prostate adenocarcinoma rather than metastatic prostate adenocarcinoma. It usually affects males in the 6th or 7th decade with a worse prognosis and early metastasis to bone, lungs and liver [11]. Prior evidence suggested that the squamous histology could arise months to years after hormonal treatment or radiotherapy. The PSA level and clinical symptoms are limited in suggesting the diagnosis of squamous cell differentiation but the patient's condition deteriorates more aggressively.

The cause of squamous cell differentiation is unclear [6]. Some literature suggests that the origin could be prostatic, bladder urothelial squamous cell metaplasia, or squamous differentiation within a primary adenocarcinoma of the prostate [12]. It has also been proposed that an adenocarcinoma could undergo squamous cell differentiation under hormonal treatment.

Our case is unique in that the patient had metastatic prostate adenocarcinoma when the cancer was originally identified. A molecular panel at that time identified the *TP53* mutation and two VUSs. After 19 months of hormonal treatment, when the tumor had squamous transformation, the molecular panel showed the same *TP53* mutation and the same VUSs, suggesting the same primary for both specimens. However, there was *CCND3* amplification and absence of the *TMPRSS2::ETV4* fusion in the later specimen after hormonal therapy, which might suggest that *CCND3* amplification and loss of the *TMPRSS2::ETV4* fusion may be associated with squamous transformation. In a prior study, Autio and McBride showed loss of *RNF43* in the squamous metastasis after initial ADT of a primary prostate adenocarcinoma [5]. Identifying the genetic changes with a molecular panel is very critical in guiding the systemic treatment. Recent advancements in treatment include PARP inhibitors (indicated for homologous recombination deficient tumors), docetaxel, and radio-ligand therapies [9, 13-15]. However, due to the significant change in histology and even molecular alterations in the component with squamous differentiation, clinical trials of different treatment modalities may be indicated for this rare subtype.

Overall, post-therapeutic squamous cell transformation in metastatic prostate adenocarcinoma is a rare entity requiring pathologic and immunohistochemical confirmation. The radiology results and clinical symptoms also need to be correlated. This case illustrates an example of squamous transformation in metastatic prostate cancer and the aggressive clinical course, and need for better therapies and prognostic studies. It also highlights the importance of molecular profiling to provide insights into the pathogenesis and treatment of squamous histologic transformation in a metastatic pros-

Table 2. Disparities between our case and other cases

Criteria	Our case	Quasim's case (2014)	Ichaoui's case (2019)
Age (y)	64	65	71
Initial Gleason score ADC	Unknown	4+5=9	3+3=6
Hormone treatment (Tx)	LHRH analogue (leuprorelin) and antiandrogen agent (bicalutamide, abiraterone)	LHRH analogue (leuprorelin)	LHRH analogue (triptorelin) and antiandrogen agent (bicalutamide)
PSA level (ng/ml) before Tx	747	84.5	2.7
PSA level post Tx	2.53	0.4	0.04
Duration of transformation (y)	1.6	1.5	9.5
Bone scan	Positive	Negative	Negative
Prognosis	DWD	Unknown	AWD
Molecular testing	Available	Unknown	Unknown

DWD: death with disease; AWD: alive with disease.

tate adenocarcinoma. While providers have multiple effective therapeutic options to treat metastatic prostate cancer patients, it is always necessary to consider the standard therapy as well as targeted therapies, along with the patient's comorbidities and preferences [13].

Disclosure of conflict of interest

None.

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