Combined DNA repair defects in testicular metastasis from prostate cancer sensitize to immune checkpoint blockade

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Abstract

Testicular metastasis in prostate cancer is uncommon and may be a culprit of widespread disease which portends a worse prognosis. Little is known about the molecular biology of metastases to the testicles and whether there is any role for targeted therapeutics. Here we report a case of prostate cancer recurring with testicular and lung metastases. Targeted sequencing of the patient’s left testicular tumor after orchiectomy disclosed inactivating mutations in the CDK12 and ARID1A genes, and MSH2 and MSH6 loss resulting in high microsatellite instability and high tumor mutational burden. The patient experienced a complete radiographic and prostate-specific antigen response at 12 weeks of PD-1 immune checkpoint blockade with pembrolizumab and continues uninterruptedly on treatment. Molecular characterization of this rare phenotypic subtype of prostate cancer in larger studies may help deliver precision therapies with the potential to improve outcomes.

Keywords: ARID1A mutation; CDK12 mutation; DNA repair; Immune checkpoint inhibitor; Mismatch repair deficiency; Prostate cancer; Testicular metastasis

1. Introduction

Testicular metastasis may present as a solitary site of malignant neoplasms or be part of more diffuse metastatic disease.[1] Prostate cancer represents the most common primary, followed by renal cell, colon, urothelial, and lung cancer.[2] Detection of testicular metastases is usually guided by local symptoms and may be enabled by use of scrotal ultrasonography, which is the imaging modality of choice.[3] In rare cases, it may be an incidental finding on high sensitivity imaging, such as 68Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (PET/CT).[4]

Various mechanisms of metastatic spread of prostate cancer to the testis have been demonstrated in large autopsy studies, including retrograde venous or lymphatic extension, arterial embolism, and spread through the lumen of the vas deferens.[5] Nevertheless, the molecular biology of testicular metastasis from prostate cancer is unknown.

In this study, the clinical and molecular characteristics of a patient with unilateral testicular and bilateral lung metastases from prostate cancer are presented. The patient relapsed after prior definitive radiation and androgen deprivation therapy.

2. Case presentation

A 78-year-old Asian man with history of very high-risk prostate adenocarcinoma (Gleason sum of 8, prostate-specific antigen [PSA] 15.42ng/mL, clinical T4 disease with prostate fixation to the levator muscles) presented with left testicular discomfort and palpable mass, 8 months after treatment with prostate/pelvic irradiation and androgen deprivation therapy. His PSA was 11.3 ng/mL, rising on castrate levels of testosterone (22.15 ng/dL) after a nadir of 0.05 ng/mL. A scrotal ultrasound disclosed an underlying mass measuring 3.8 cm × 1.9 cm occupying most of the left testicle with internal vasculature (Fig. 1a). Staging CT scans of the chest, abdomen, and pelvis showed multiple bilateral large lung masses consistent with metastatic disease (Fig. 1b–d).

A bone scan was negative for metastatic bone disease. The patient underwent left orchiectomy and histopathology was consistent with high-grade prostate adenocarcinoma.

The patient’s testicular tumor underwent DNA sequencing with use of a targeted panel consisting of 324 genes as well as introns of 36 genes involved in rearrangements, and assays for loss of heterozygosity, microsatellite instability (MSI) and tumor mutational burden (TMB). Interestingly, several deleterious mutations and copy number variations in numerous DNA repair and chromatic remodeling genes were found, among other pathogenic molecular alterations in cancer genes (Table 1). These included cyclin-dependent kinase 12 (CDK12) G1271fs*23, loss of MSH2, MSH3 K383fs*32, loss of MSH6, ARID1A S2269L, ARID1A Q766fs*67, ARID1A P1175fs*5. Additionally, high MSI was detected and a high TMB was reported (132 muts/ Mb).

The patient’s family cancer history was significant for soft tissue sarcoma in his father who was diagnosed and died at age 45. Germline genetic testing with use of a broad panel of 67 genes associated with hereditary cancers was negative for any pathogenic variants.
Based on these findings, the patient was started on the anti-PD-1 monoclonal antibody pembrolizumab at a dose of 200 mg intravenously every 3 weeks. Assessment of response at 12 weeks after initiation of immunotherapy showed a barely detectable PSA of 0.01 ng/mL (Fig. 2) and a complete resolution of patient's lung tumors on CT scans (Fig. 3). The patient has tolerated treatment well without any immune-related or other toxicities and continues to receive pembrolizumab.

3. Discussion

Mismatch repair (MMR) mutations are infrequent in prostate cancer and their incidence in various studies ranges from 1.2% to 8.1%. Besides implications for familial cascade genetic testing for Lynch syndrome in a subset harboring germline gene defects in the canonical MMR pathway (MSH2, MSH6, MLH1, PMS2), these patients demonstrate aggressive clinical and pathological features, such as high Gleason grade, enrichment in intraductal histology, and presence of visceral metastases. Nevertheless, they appear to respond to hormonal therapies, as well immune checkpoint inhibitors, with the anti-PD-1 monoclonal antibody pembrolizumab being the first tissue-agnostic immunotherapy that was approved for solid malignancies of any primary with MMR deficiency or and high MSI.

CDK12 loss can occur in 3% to 7% of patients with advanced prostate cancer and is characterized by an aggressive clinical behavior, including high-grade Gleason ≥8, shorter time to metastasis, and development of castration-resistance.

Table 1
Somatic alterations (pathogenic) in testicular metastasis from prostate cancer: microsatellite instability-high, high tumor mutational burden of 132muts/Mb.

| Gene   | Alteration(s)       |
|--------|---------------------|
| AR     | H877Y, R877L        |
| ERBB2  | R678Q               |
| PTEN   | L576*F, R1300       |
| ARID1A | S236L, T708fs*67, P1175fs*5 |
| CDK12  | G1271fs*23          |
| PKD1C2B| L104R               |
| RNK43  | G659R*4              |
| ABL1   | P441L               |
| BCCR1L1| A1168fs*56          |
| CARD11 | S622M               |
| CD73A  | R1316fs*61          |
| CDKN1B | G659fs*60           |
| CEBPA  | P238fs*137          |
| CTCF   | T204fs*28           |
| FAM121B| L896fs*23           |
| FLT3   | N897D               |
| FUBP1  | S111*43             |
| GPRM3  | R183C               |
| HNFA1A | P291fs*           |
| MLL2   | G773*157            |
| MSH3   | K389fs*232          |
| PAX5   | P358fs*31           |
| SETD2  | R1407fs*5           |
| SPOP   | Y87C                |
| SPOR   | Y87C                |
| TPS3   | S268N               |
| MSH2   | Loss                |
| MSH6   | Loss                |

Figure 1. (A) Scrotal ultrasound showing an enlarged left testicle 5.1 cm × 2.4 cm × 3.1 cm mostly occupied by an intratesticular mass measuring 3.8 cm × 1.9 cm with internal vasculature; (B) chest computed tomography showing multiple bilateral large lung masses consistent with metastatic disease (arrows) including: 5.6 cm × 4.0 cm mass in the posterior segment of the right upper lung, 5.4 cm × 3.5 cm pleural-based mass laterally in the right middle lung; (C) 4.4 cm × 2.0 cm mass laterally in the right lower lobe with a small right pleural effusion; (D) 4.2 cm × 4.1 cm left upper lobe mass.
inactivating mutations have been associated with elevated neoantigen burden\(^\text{[10]}\) and favorable responses to PD-1 inhibitors, but poor responses to hormonal and taxane therapies and PARP inhibitors.\(^\text{[11]}\) ARID1A is a chromatin remodeling gene that can harbor truncating mutations in various neoplasms, including 8% of prostate cancers.\(^\text{[12]}\) Recent evidence supports a causative link between ARID1A-deficiency and compromised MSH2 recruitment at sites of DNA damage in tumors, resulting in MSI and high TMB,\(^\text{[13]}\) which may confer longer median progression-free and overall survival to these patients after immune checkpoint blockade.\(^\text{[14]}\)

This case represents the first attempt to describe the molecular landscape of prostate cancer that metastasizes to the testicle(s). This infrequent site of visceral metastasis may not only be associated with other synchronous visceral metastases (e.g., lung) but also with several co-occurring DNA repair gene defects (MSH2, MSH6, CDK12, ARID1A). These molecular findings have direct clinical and therapeutic implications. Although this patient had intact germline copies of these genes, it may be postulated that the combination of these heterozygous alterations might confer higher sensitivity to immune checkpoint inhibition compared to each one alone, given prior excellent responses in patients harboring tumors with biallelic inactivations of MMR or CDK12.\(^\text{[7,10]}\) Further molecular studies are warranted to elucidate whether co-occurring DNA repair alterations are enriched in this rare prostate cancer phenotype and whether responses to immune checkpoint blockade may be durable and translate into a significant overall survival benefit.

Figure 2. PSA levels at the end of each cycle of pembrolizumab. PSA=prostate-specific antigen.
Acknowledgments
None.

Statement of ethics
The study was approved by the Institutional Review Board of Weill Cornell Medicine, 7/17/19, protocol number # 1302013582. This study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient has given his written informed consent to publish this case (including publication of images).

Conflicts of interest statement
The author has no conflicts of interest to declare.

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Author contributions
Panagiotis J. Vlachostergios provided direct patient care, conceptualized and designed this study, acquired, analyzed and interpreted clinical and molecular data, drafted and revised the manuscript.

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