Metastatic Prostate Cancer in a *RAD51C* Mutation Carrier

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A man, aged 61 years, with a history of hypogonadism and family history of cancer experienced persistent urinary difficulties with no visible prostate abnormalities. Laboratory testing and diagnostic imaging revealed a primary lesion in the prostate with lymph node involvement and multiple bone metastases. Treatment with androgen-deprivation therapy, 17,20-lyase inhibition, and bisphosphonates for 7 months was unsuccessful in preventing disease progression, but second-line chemotherapy and continued androgen-deprivation therapy improved prostate specific antigen levels. During the patient's second treatment regimen, his daughter received a diagnosis of breast cancer. The patient's daughter underwent genetic testing for oncogenic mutations, and it was discovered that she carried a mutation in *RAD51C*, a gene encoding a protein involved in DNA repair and genomic maintenance. Subsequent genetic testing of the patient revealed mutation in *RAD51C* as well. For patients with metastatic prostate cancer who are unresponsive to standard treatment and who have a positive family history of cancer, genetic testing may be warranted to develop alternative treatment regimens for the patient and guide family discussions regarding cancer risk. Targeted agents like poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors may be a consideration in prostate cancer patients with DNA repair mutations and with refractory disease.

Keywords: *RAD51C*; Metastatic; Prostate cancer

Although the incidence of prostate cancer in the United States has been rapidly declining since 2010, prostate cancer is still the most common cancer in men, with an estimated number of 161,360 new cases and an estimated 26,730 deaths to occur in 2017.¹ The two major risk factors for prostate cancer are age and genetics. A patient with a first-degree relative diagnosed with prostate cancer has a two- to four-fold increased risk of developing the disease.² Familial clustering is noted with prostate cancer, and it is estimated that between 5% and 10% of prostate cancer cases are probably caused by hereditary mutations in prostate cancer susceptibility genes.³⁻⁵ Current evidence from case-control and cohort studies, and population- and hospital-based series suggests an association between germline mutations and prostate cancer. For example, germline mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* increase risk of prostate cancer by 2.5 to 8 fold.⁶ With the development of next-generation sequencing (NGS), multiple genes can be sequenced and analyzed for mutations.

RAD51C encodes a DNA repair protein that may play a role in reproductive organ cancer development. Meindl et al^{7,8} first identified this gene as a predisposing factor for breast and ovarian cancer in 2010, but there is no evidence of *RAD51C* mutations in patients with prostate cancer reported in the literature. We present a case of metastatic prostate cancer in a man with a pathogenic mutation of *RAD51C* that was diagnosed after genetic testing.

Case Description

A man, aged 61 years, with a past medical history of hypertension and hypogonadism experienced an acute urinary retention and bladder outlet obstruction in February of 2015. He failed several attempts of voiding trial and managed with intermittent urinary catheterization and antibiotic for suspected prostatitis. His family history is significant for multiple cancers including prostate, ovarian, and breast cancers (Figure 1).

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Figure 1. Pedigree analysis of cancer

Since the patient continued to experience symptoms of urinary retention and difficulties emptying the bladder, he underwent additional testing. A digital rectal examination revealed a smooth normal-sized prostate with no palpable nodules; however, an elevated prostate specific antigen (PSA) level (16.2 ng/mL) was detected. With persistent symptoms and continued elevated PSA (16.2 ng/mL) after adequate treatment for suspected prostatitis, he underwent prostate biopsy that revealed a diffuse infiltrative adenocarcinoma that was predominantly on the right side, with high grade single cell infiltration. Eight of the 12 biopsies had a Gleason score of 5+4=9. The patient was further evaluated for metastases with computed tomography (CT) imaging of the abdomen and pelvis and a bone scan. The CT highlighted multiple nodules on the periaortic, pelvic, and iliac lymph nodes with the largest nodule measuring 5.3x2.2 cm, while the bone scan visualized diffuse multiple bone metastases.

To treat the metastatic disease, the patient was enrolled in the clinical trial S1216, a phase III randomized trial comparing androgen-deprivation therapy and 17,20-lyase inhibition with TAK-700 (orteronel) against androgen-deprivation therapy and first-generation nonsteroidal anti-androgen drug bicalutamide in patients with newly diagnosed metastatic hormone-sensitive prostate cancer. After treatment randomization, the patient received gonadotropin-releasing hormone (GnRH) agonist leuprolide (22.5 mg) every 3 months and orteronel (300 mg) twice daily for 28 days every month per trial protocol. The patient also received bisphosphonates for bone metastasis. Serial PSA levels and bone scans were done to ascertain response to treatment. After six cycles of orteronel, the patient's PSA level was elevated from 4.0 ng/mL to 8.4 ng/mL, and a bone scan showed significant interval metastatic progression from September 2015 to April 2016. The patient was discontinued from the trial due to disease progression.

The patient was next given second line chemotherapy with weekly docetaxel (a multi-target chemotherapeutic agent) and continued leuprolide every 3 months for disease progression. Since the patient tolerated the treatment without significant

concerns, and his PSA levels were decreasing, he was given a total of ten cycles of docetaxel. During this time, he developed worsening shortness of breath due to bilateral pleural effusion in the chest. The pleural fluid analysis was negative for malignancy, which suggested the patient was exhibiting an adverse response to docetaxel. The patient's shortness of breath improved after discontinuing docetaxel and was started on enzalutamide.

In September of 2016, the patient's daughter was diagnosed with breast cancer at the age of 45 and underwent genetic testing with risk factors of high-grade invasive ductal cancer (grade 3/3), diagnosis of breast cancer at young age, family history of metastatic prostate cancer. The patient's daughter discovered that she had a *RAD51C* mutation and underwent prophylactic bilateral salpingo-oophorectomy. The patient was then referred for genetic counseling and testing with a hereditary prostate cancer panel and *RAD51C* mutations based on his pedigree analysis (Figure 1) and daughter's genetic results. The risks, benefits, and limitations of genetic testing were discussed with him, and after informed consent, he underwent multigene testing with the ProstateNext (Ambry Genetics) 14-gene panel and *RAD51C* mutation analysis. The ProstateNext gene panel includes *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51D*, *TP53* (sequencing and deletion/ duplication); *EPCAM* (deletion/ duplication only), which were negative. *RAD51C* mutation testing determined that the patient had a pathogenic heterozygous deletion/duplication mutation in exon 4 and/or the 3' untranslated region (UTR) of *RAD51C*.

The patient's shortness of breath completely resolved after discontinuation of docetaxel. However, his PSA progressively increased while on enzalutamide. Palliative chemotherapy with docetaxel was re-initiated, as he had responded previously. Follow-up CT of the abdomen and pelvis showed worsening of metastatic disease with significant retroperitoneal and pelvic lymphadenopathy. Bone scan revealed new extensive uptake at the right anterior femoral neck and intertrochanteric region. His chemotherapy regimen was changed to carbazitaxel and abiraterone. Despite all efforts,

unfortunately, the patient passed away with generalized weakness and failure to thrive.

Discussion

RAD51C is one of five *RAD51* paralogs (*RAD51B*, *RAD51C*, *RAD51D*, *XRCC2*, *XRCC3*) involved in homologous recombination and repair of double-strand DNA breaks and in the maintenance of genomic stability.⁹⁻¹¹ This gene is localized on the long arm of chromosome 17, region 2, band 3 (17q23) and is associated with Fanconi anemia and susceptibility to ovarian cancer.^{7,12,13} Biallelic mutations in *RAD51C* cause Fanconi anemia and monoallelic mutations are associated with breast and ovarian cancer.⁹ Nonsense, frameshift, spliced, and non-functional missense mutations are also noted with *RAD51C*; however, there is limited evidence of the association of these mutation types with familial breast cancer.^{7,12} *RAD51C* mutations are primarily observed in families with ovarian cancer and breast cancer and are rarely found in families with breast cancer alone.⁷

Mutations in the *RAD51C* gene have a moderate to high penetrance level in carriers.^{7,12} The presence of a *RAD51C* mutation increases a woman's risk of ovarian cancer by 9% by the age of 80 years.^{14,15} Although the prevalence of *RAD51C* mutations are very low in patients with ovarian and breast cancer (1%), mutations in *RAD51C* are noted to be at a higher frequency in families with multiple ovarian cancers.¹⁶

In contrast to women, there does not appear to be an association between *RAD51C* mutations and prostate cancer development in male carriers, though men with metastatic prostate cancer have a higher incidence of germline mutations than men with localized prostate cancer.^{17,18} In a multicenter study of prostate cancer cases, Pritchard et al.¹⁷ detected a *RAD51C* mutation in one man (0.14%) among 82 men who tested positive for germline mutations. Pelttari et al.¹⁹ genotyped 1,083 Finnish prostate cancer patients for *RAD51C* mutations and concluded that there was no association between prostate cancer and *RAD51C* mutations. However, there are studies that have detected an association between aggressive metastatic prostate cancer and patients with germline mutations in DNA repair genes.¹⁸ Treating patients with metastatic prostate cancer that are unresponsive to current therapies with agents that enhance the function of DNA repair proteins may prevent disease progression.

Poly (adenosine diphosphate-ribose) polymerase (PARP) is involved in single stranded DNA break repairs. If the DNA breaks persist during replication, multiple double strand breaks develop leading to cell death.^{10,20} In a randomized study by Mateo et al.,²¹ an observed therapeutic response occurred in 16 patients receiving PARP inhibitors in metastatic castrate resistant prostate cancer with DNA repair defects who failed to respond to standard treatments.

Conclusion

Genetic testing may play a role in identifying novel mutations

in DNA repair genes particularly in the management of metastatic prostate cancer patients who are refractory to standard treatment. Targeted agents like PARP inhibitors might be a consideration in metastatic prostate cancer patients with DNA repair gene mutations like *RAD51C*. Since there is limited information on the involvement of *RAD51C* mutations in prostate cancer, additional studies are needed to address this knowledge gap in the literature.

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