CLINICAL VIGNETTE

Metastatic Prostate Cancer with BRCA2 Mutation without Skeletal Metastasis

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Introduction

Prostate cancer is a global health problem, affecting millions of men worldwide, ranking as the second most common male malignancies. The global incidence of prostate cancer is over 1.2 million and over 350,000 will die of the disease.[1] The most common site of metastasis is the skeleton and the vast majority of patients will develop bone metastasis. Prostate cancer spread from regional lymph nodes to the bone is usually the first metastasis site. Mutations in DNA repair pathway genes such as BRCA2 appear to increase the risk of developing prostate cancer and are associated with a more aggressive phenotype. We present a patient with extensive castrate-resistant prostate cancer with the absence of any bone involvement. He was later found to have a BRCA2 mutation.

Patient History

The patient is a 65-year-old man who was initially diagnosed in his native country of Peru after evaluation of an elevated PSA level. His PSA was 45 ng/mL and prostate biopsy showed Gleason 4+4 adenocarcinoma with extensive prostate involvement and neural invasion. In early 2020 he was treated with bilateral orchiectomy but did not undergo a prostatectomy. Postoperatively, his PSA dropped to 0.1 ng/mL.

He relocated to Los Angeles about 2 years ago. He presented to an emergency department with painless hematuria and RLQ and pelvic discontent. He also reported decreased appetite, and weight loss. Past medical history included hypertension and his only other surgery was an appendectomy. He was a smoker and drank occasional wine. Family history was negative for cancer. A CT scan showed a lobulated lesion in the area of the prostate with multiple soft tissue masses around the perirectal region, suggesting enlarged lymph nodes. Tumor invasion of the rectum was suspected. The liver showed multiple rim-enhancing lesions throughout both the right and left lobes, measuring up to 3.5 cm, consistent with metastases. The spine showed some degenerative changes but there was no evidence of metastasis in any of the bones.

He was referred for outpatient care to Medical Oncology. His PSA was 25 ng/mL and testosterone level were less than 6 ng/dL. Pelvic MRI showed a very large, infiltrative prostate cancer with direct extension into the surrounding peri-prostatic tissue and rectum. Multiple regional lymph nodes were abnormally enlarged. He was symptomatic from the extensive pelvic disease, and was seen by Radiation Oncology for palliative radiation therapy. Because of the unusual presentation with extensive liver disease, without bone metastasis, liver biopsy was performed to rule out small cell prostate cancer or a second primary cancer metastasis. Pathology confirmed metastatic adenocarcinoma consistent with prostate origin. In addition, an 18F-fluciclovine PET-CT scan was performed as a more sensitive way of detecting bone metastasis. This demonstrated tracer uptake in his liver metastases and pelvic disease, increased since his prior CT scan, but again no evidence of bone metastasis.

Next generation sequencing on his tumor specimen and germline genetic testing both revealed a pathogenic BRCA2 mutation, which predicted cancer responsiveness to PARP (poly ADP ribose polymerase) inhibitors. Given data indicating patients without bone metastasis are less likely to respond to androgen deprivation therapy alone, he was treated with chemotherapy, docetaxel 75 mg/m^2 intravenously every 3 weeks for 6 cycles. He was subsequently started on therapy with enzalutamide (androgen receptor inhibitor) and rucaparib (PARP inhibitor). The patient's cancer-related symptoms resolved and his PSA became undetectable. Repeat 18F-fluciclovine PET-CT scan showed complete resolution of the neoplastic hypermetabolic activity. He continues to do well without progression on therapy one year after his ED presentation.

Discussion

This case is unusual because there was no evidence of bone involvement by prostate cancer despite widely metastatic disease, even when staged using an 18F-fluciclovine PET-CT scan. It also highlights the aggressive nature of prostate cancer associated with BRCA2 mutations and the use of PARP inhibitors that capitalize on its impaired DNA repair pathway.

Close to 80% of prostate cancer patients who develop metastatic disease will exhibit bone metastasis. In autopsy cases of metastatic prostate cancer, 90% demonstrated bone metastasis, compared to 46% lung metastasis and 25% liver metastasis.[2] Complications of bone metastasis include bone pain, pathologic fractures, spinal cord compression, and symptomatic hypercalcemia. Osteoblastic bone metastases are more common in prostate cancer but, can be osteolytic, or mixed.[3] Adult bone homeostasis is achieved by osteoclast resorbing bone and osteoblast depositing new bone, leading to a constant remodeling that maintains the integrity of bone. In bone metastasis, greater

osteoblast activity leads to osteoblastic lesions while greater osteoclast activity leads to osteolytic lesions. Bone appears to be the favorite site for prostate cancer cells to spread and inhabit. In prostate cancer progression, cells shed from the primary tumor invade blood vessels and spread throughout the body, but preferentially migrate to the bones of the axial skeleton, where red marrow is most abundant.[4,5]

Prostate cancer's tropism for bone is related to interactions between prostate cancer cells and the bone microenvironment, consisting of mineralized bone matrix, osteoclasts, osteoblasts, and other cell types. Parathyroid hormone-related peptide is secreted by tumor cells and upregulates receptor activator of nuclear factor kappa-B ligand (RANKL) production and down-regulates osteoprotegerin (OPG) production by osteoblasts, which activate osteoclast formation and promote bone resorption.[3,4,6,7] Bone reabsorption can release growth factors from the bone matrix, such as transforming growth factor-beta (TGF-beta), and increase extracellular calcium, which promotes cancer cell growth and a more aggressive cancer phenotype.[5] This leads to a vicious cycle of bone metastasis and cancer growth. Another important contributor to bone metastasis is bone morphogenetic protein (BMP), part of the TGF-beta super family which is synthesized by both osteoblasts and prostate cancer cells. Members of this BMP family appear to stimulate osteoblastic activity and lead to osteoblastic metastasis as well as promote prostate cancer growth.[4,8,9] There are a variety of other growth factors and cytokines that also participate in the interaction between prostate cancer cells and the bone microenvironment, though their role is less defined than those already discussed.

Prostate cancer cells have an intrinsic quality that gives a strong predilection for metastasizing to the bone. This case report highlights the unusual circumstance of metastatic prostate cancer without detectable bone metastasis. One can question whether our patient's BRCA2 mutation contributed to his cancer lacking predilection for bone metastasis. BRCA1 and BRCA2 are genes that code for DNA repair proteins and were originally associated with hereditary breast and ovarian cancer syndrome. Pathogenic BRCA2 mutations in particular also increase risk of developing prostate cancer, with one meta-analysis reporting a relative risk of 2.1 in Ashkenazi Jewish BRCA2 carriers and 4.4 in non-Ashkenazi Jewish European descent BRCA2 carriers.[10] Pritchard et al[11] found BRCA2 mutations in 5.3% of their study of patients with metastatic prostate cancer. BRCA2 mutated prostate cancers have been characterized as having a higher Gleason score, being more likely to metastasize, and being more likely to lead to death, compared to non-BRCA2 mutated counterparts.[12] The aggressive behavior of BRCA2 mutated prostate cancer can be attributed to its global genomic instability and genomic alteration in pathways involving WNT, mTOR, and MYC, among other pathways.[13] National Comprehensive Cancer Network guidelines recommend germline genetic testing for pathogenic mutations in patients with prostate cancer with any of the following criteria: 1) metastatic disease, 2) non-metastatic high-risk disease, 3) family history sufficiently suspicious for hereditary breast and ovarian cancer syndrome, or 4) Ashkenazi Jewish ancestry.[14] Genetic testing can also be considered in individuals with a first-degree relative meeting these criteria. There are therapeutic implications for the presence of BRCA mutations in metastatic prostate cancer and it is now standard of care using next generation sequencing. PARP inhibitors impair DNA repair pathways and lead to cancer cell apoptosis, particularly in cancer cells already deficient in DNA repair proteins. Therapy with PARP inhibitors such olaparib and rucaparib have improved outcomes, including improved progression-free survival with olaparib, in patients with metastatic castration-resistant prostate cancer and BRCA mutations, with recent FDA approval.[15] Our patient is currently on therapy with rucaparib and appears to be responding well. Greater understanding of the biology of metastatic prostate cancer, including those with BRCA2 mutations, and ongoing clinical trials will hopefully lead to further improvement in the management of these patients.

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