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Case Report

Durable Complete Response to Sequential Administration of Mitoxantrone Followed by Anti-Programmed Cell Death Protein 1 Antibody in a Patient with JAK1 Mutated Refractory Prostate Cancer

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Abstract

Checkpoint blockade immunotherapy for several common solid tumors has been rapidly incorporated into patient care. The current challenge is to understand why a large proportion of cancer patients do not respond to cancer immunotherapy, and how this understanding can be translated into the rational design of combinatorial cancer immunotherapy strategies aimed at maximizing success of immunotherapy. Here we report a patient with chemotherapy refractory metastatic castration-resistant prostate cancer (mCRPC) complicated by obstructive uropathy and partial bowel obstruction due to a large pelvic mass. A comprehensive genomic profiling of his tumor confirmed high tumor mutational burden, JAK1 inactivating mutation and a mismatch repair gene defect. He was given two cycles of mitoxantrone followed by anti-programmed cell death protein 1 antibody pembrolizumab. The patient had complete radiographic and PSA remission. To our knowledge, this is the first case of a patient with mCRPC with JAK1 inactivating alterations demonstrating a dramatic response to chemoimmunotherapy. This early clinical observation suggests that sequential administration of mitoxantrone followed by anti programmed cell death protein 1 antibodies is safe and effective in refractory prostate cancer. This novel strategy warrants further prospective clinical investigation.

BACKGROUND

Immune checkpoint inhibitors have evolved as a critical component of the treatment of multiple tumor entities including renal cell carcinoma, bladder cancer, non-small cell carcinoma, and melanoma [1-4]. However, there has been limited success with immune checkpoint inhibitors in patients with prostate cancer [5-7]. Even in cases where there is supporting evidence that immune checkpoint inhibitors are effective, only a minority of patients respond to the treatment [8]. Currently available biomarkerssuch as PD-L1 expression, tumor mutation load (TML), microsatellite instability (MSI)/mismatch repair deficient (dMMR) status, and mutational burden show incomplete predictive performance. While such biomarkers have prognostic implications, they have not been established as predictive markers [9,10]. Researchers are now assembling a list of features that may confer resistance to anti-PD-1 and anti-PD-L1 therapy [8,11]. One of these mechanisms is that mutations in JAK 1/2 in patients with melanoma and colon cancers have been shown to induce primary resistance to PD-1 blockade by downregulating PD-L1 expression [12-14]. These limited data suggest that *JAK1* mutations may be used as a negative selective predictive biomarker for immune blockade therapy.

There is a growing interest in combining anti-PD-1 and anti-PD-L1 agents with other treatments to expand the clinical benefit of this promising therapy. However, combination strategy face both clinical (increased risk of toxicities) and economic challenges (prohibitive cost). We are interested in developing a novel, alternative approach: giving anti-PD-1 and anti-PD-L1 treatments in tandem, sequentially with other cancer therapy.

Historically, chemotherapy was thought to compromise immune responses by way of lymphocyte lysis. However, there are emerging evidences that chemotherapy can induce immune modulatory effects that could facilitate the induction of antitumor immunity [15]. Mitoxantrone, a non-cell cycle-

specific anthraquinone anticancer drug, induces cell apoptosis by inhibiting DNA synthesis [16]. Recent studies have indicated that cancer cells treated with mitoxantrone can undergo immunogenic cell death (ICD) and initiate antitumor immune responses [17,18].

Here, we present a JAK1 inactivating mCRPC patient who had a durable complete response to sequential chemoimmunotherapy. Our strategy presented here may open new doors to personalized prostate cancer therapy and worthy of further investigation in prospective trials.

CASE REPORT

A 56 year old African American male with metastatic castration resistant prostate cancer came to our cancer center with rapid disease progression despite previous treatment with casodex, lupron, docetaxel, abiraterone acetate, and enzalutamide.

Four years prior to this admission, he was initially diagnosed with localized $T1_c$ N0 M0 prostate cancer with Gleason score of 6 (3+3). His Prostate-specific antigen (PSA) at the time of diagnosis was 10.7. The recommendation at that time was prostatectomy; however, he did not pursue any active therapy.

In May 2016, he developed urinary frequency. His PSA went up to 87, and a digital rectal exam (DRE) was abnormal. A computed tomography (CT) scan showed large pelvic mass 10 cm x 6.2cm x 8.5cm abutting and invading the rectum. No evidence of bone metastases per a Skeletal Scintigraphy (bone scan). A pelvis MRI (magnetic resonance imaging) scan showed a large infiltrating 7 x 7 x 10 cm pelvic mass invading the rectum posteriorly and the posterior bladder wall anteriorly, involving the muscularis layer of both bladder and rectum. A positron emission tomography (PET) scan showed a 7.1 x 7.0 x 9.1 cm irregular hypermetabolic pelvic mass abutting the rectum posteriorly and the posterior bladder wall anteriorly, with probable direct invasion of bladder and rectum. There was also moderate to severe hydronephrosis. He underwent bilateral nephrostomy tube placement. Needle biopsies of the pelvic mass showed prostate adenocarcinoma with Gleason score of 9 (5+4). Tumor cells exhibited reactivity with antibodies directed against prostatic specific antigen and did not exhibit reactivity with antibodies directed against PSAP, CK7, CK20. He was started on Lupron. He was subsequently treated with docetaxel, abiraterone acetate, enzalutamide, and cabazitaxel.

On 5/12/2017, the patient was admitted for partial large bowel obstruction secondary to tumor mass effect. Computed tomography (CT) of the abdomen and pelvis large heterogeneously enhancing pelvis mass measuring 7.5 x 9.4 x 10.2 cm in transverse, anterior posterior and craniocaudal dimensions. The mass appears to arise from the prostate, and extends to the pelvic sidewalls without involvement of the musculature or vessels. It has invaded the bladder, predominantly the posterior wall; however, there is diffuse circumferential bladder wall thickening with adjacent fat stranding. There is encasement of the rectosigmoid colon, posteriorly. There were multiple prominent retroperitoneal lymphadenopathy. The patient underwent laparoscopic diverting loop sigmoidostomy. He was also seen by urologist and subsequently underwent transurethral resection of the prostate (TURP), which showed high-grade carcinoma consistent with prostatic origin (Figure 1). Tumor cells exhibited reactivity with antibodies directed against prostatic specific antigen and did not exhibit reactivity with antibodies directed against PSA, Prostatic acid phosphatase (PAP), CK7, CK20, p63, synaptophysin, CD56, S-100, or CD45. Mismatch repair proteins were tested for and showed intact MLH 1 and PMS 2, but there was no nuclear staining for MSH 2 or MSH 6.

The tumor tissue was further evaluated with next generation gene sequencing to evaluate for specific mutations. The tumor molecular profiling revealed microsatellite instability and high tumor mutation burden, including mutations in PTCH1, PI3K, JAK1, TP53, and PTEN. The tumor mutation burden (TMB) was 46 Muts/Mb. In addition, one or more variants of unknown significance (VUS) in 41 genes were detected in this patient's tumor, including genes involved in cell cycle and PI3K pathways.

Unfortunately, the patient's clinical condition was deteriorating rapidly. His PSA went up dramatically to 210. Mitoxantrone was started and then stopped after two cycles due to febrile neutropenia. He was subsequently started on pembrolizumab at 200 mg every 3 weeks based on the findings of molecular testing. After two administrations, the patient's disease-related symptoms such as weight loss and pain dramatically improved. His PSA came down to an undetectable level. Magnetic resonance imaging (MRI) scan showed complete radiographic remission (Figure 2). The patient tolerated therapy well without side effects. He remains alive in complete remission so far for more than 14 months.

DISCUSSION

We describe here a previously heavily treated patient who demonstrated a dramatic, durable complete response to mitoxantrone followed by pembrolizumab after having failed multiple lines of therapy. To our knowledge, this is the first reported case of prostate cancer successfully treated with sequential administration of a chemotherapy agent and a PD-1 inhibitor. Our case study highlights several interesting points. First, patients with aggressive prostate cancer generally do not have trials immediately ready for them; hence, individual case report can be critical to stimulating further investigation and to informing clinical management. Second, the patient's tumor had MSIH and high mutational burden, suggesting that these genomic characteristics are important for selecting patients for anti PD1 immunotherapy in diseases beyond colorectal cancer. Most interestingly, our patient had a remarkable response to sequential administration of a chemotherapy agent and a PD-1 inhibitor, despite JAK1 inactivating alterations that have recently been implicated in resistance to anti PD1 agents [12-14].

Metastatic castration-resistant prostate cancer at times remains a lethal disease, and effective therapy is still lacking. To date, there has been very little data published on the use of immune checkpoint inhibitors in patients with mCRPC [5,6]. Mismatch repair mutation has been described in prostate cancer. Deficient mismatch repairs (dMMR) tend to be present

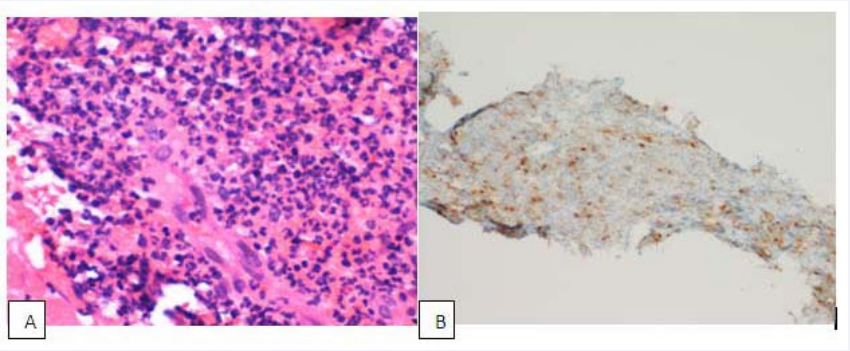

Figure 1 Histopathological findings of the tumor from transurethral resection of bladder tumor showed high-grade carcinoma consistent with prostatic origin on H&E (A). Tumor cells exhibit reactivity with antibodies directed against prostatic specific antigen (B).

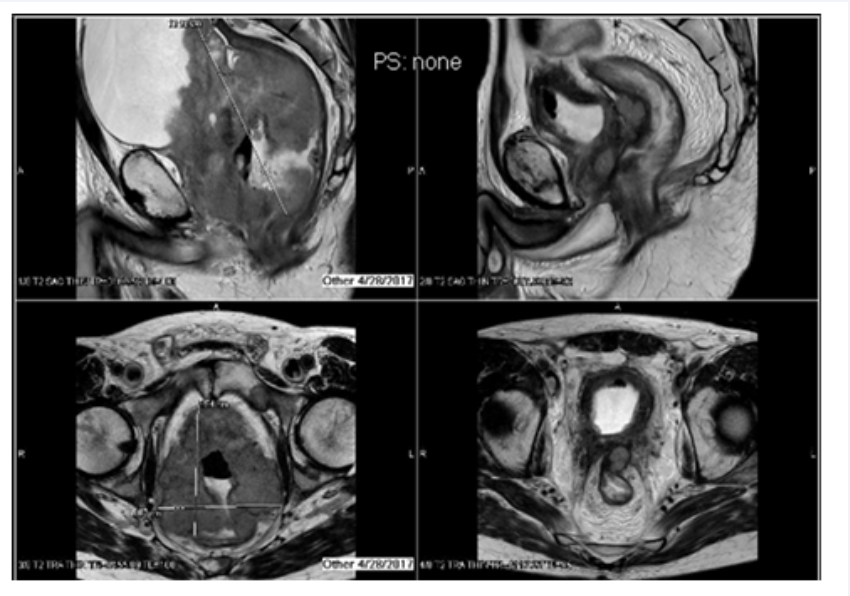

Figure 2 Magnetic resonance imaging (MRI) scan showed complete radiographic remission: before start of chemoimmunotherapy (left) and after chemoimmunotherapy (right).

in aggressive, high-grade, lymph node-positive, and recurrent prostate cancer [19-22]. On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various microsatellite instability (MSI)-high or mismatch repair-deficient solid tumors, pembrolizumab was approved by the Food and Drug Administration for the treatment of cancer patients whose tumors had deficient mismatch repair gene (dMMR) [23]. However, mutations in JAK 1/2 in patients have been shown to induce primary resistance to PD-1 blockade by downregulating PD-L1 expression, which is a potential barrier to effective treatment of JAK 1/2 mutated tumors with PD-1 blockade monotherapy [12-14].

Despite recent excitement surrounding cancer immunotherapy, most patients don't respond to immune checkpoint inhibitors. There is a growing interest in combining these agents with other treatments to expand the clinical benefit of this promising therapy. Given their immunomodulatory properties, conventional chemotherapy drugs are interesting candidates to combine with immunotherapy – a concept termed chemoimmunotherapy [24]. Besides the immunogenic effects on tumor cells, mitoxantrone can also promote rapid dendritic cell differentiation which may support the development of a strong immune response [25,26]. In our case, prostate cancer cells that succumb to the lethal effect of mitoxantrone can serve as a therapeutic vaccine and stimulate the host immune system to attack other tumor cells. We hypothesized that, the clinical benefit of monotherapy with PD-1 or PD-L1 inhibitors may be improved by giving anti-PD-1 and anti-PD-L1 treatments sequentially with mitoxantrone. To our knowledge, this is the first case of a patient with mCRC with JAK1 inactivating alterations demonstrating a dramatic response to chemoimmunotherapy.

CONCLUSION

Our patient showed excellent clinical, biochemical, and radiologic response to sequential mitoxantrone and PD-1 inhibition with pembrolizumab as the fifth line agent. Our strategy presented here will be tested in a prospective clinical

trial in our institution which hopefully opens new avenues for the treatment of advanced prostate cancer.

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