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Case Report

Complete Response to Pembrolizumab in a Patient with Castration-Resistant Prostate Cancer with Both BRCA Positivity and a High Frequency of Microsatellite Instability: A Case Report

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Keywords
Castration-resistant prostate cancer · Microsatellite instability · Pembrolizumab · Case report

Abstract
Introduction: There have been few reports of patients for whom a cancer gene panel test for solid tumors revealed the simultaneous presence of BRCA mutation and microsatellite instability (MSI)-high status. BRCA mutations have been reported in 13% of castration-resistant prostate cancer (CRPC) patients, and 3.1% of prostate cancer cases are MSI-high/mismatch repair deficient. ***Case Presentation:*** A 71-year-old man with a history of urinary retention was referred to our department for clinically suspected prostate cancer and a high prostate-specific antigen (PSA) level (141 ng/mL). MRI revealed features of prostate cancer invading the bladder, seminal vesicles, and rectum. A histopathological examination of a transperineal needle biopsy specimen obtained from the prostate revealed adenocarcinoma. Bone scintigraphy revealed multiple metastases. The patient was treated with abiraterone acetate combined with androgen deprivation therapy followed by local radiation. Rectal wall thickening and lymph node metastasis were also observed, and docetaxel was administered. A cancer gene

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panel test was positive results for BRCA2 mutation with a MSI-high. After six courses of docetaxel, lymph node enlargement was observed and olaparib was initiated. Two months later, the metastatic lesions showed enlargement and the PSA level increased. Subsequently, pembrolizumab was administered. At 2 to the patient months after the initiation of pembrolizumab administration, PSA levels decreased to <0.025 ng/mL and the rectal lesions and lymph node metastases disappeared. The patient was continuing to receive pembrolizumab without any apparent adverse events or exacerbations, 9 months after initiation. ***Conclusion:*** We herein report a case in which pembrolizumab treatment resulted in a complete response in a CRPC patient with both a BRCA2 mutation and an MSI-high status.

Introduction

There have been few reports of patients for whom a cancer gene panel test for solid tumors revealed the simultaneous presence of BRCA mutation and microsatellite instability (MSI)-high status [1]. We herein report a case in which pembrolizumab treatment achieved a complete response in a patient with bone metastasis of castration-resistant prostate cancer (CRPC) at approximately 18 months after the initiation of abiraterone treatment, and for whom an oncogene panel test demonstrated the simultaneous presence of BRCA2 mutation and an MSI-high status.

Case Presentation

The patient was a 71-year-old Asian Japanese man with a history of hypertension. He had no psycho-socioeconomic history nor a family history of hereditary breast or ovarian cancer-related or Lynch syndrome-related cancer. In October 2019, he visited the urology department with the chief complaint of urinary retention and was referred to our department for further examination due to a relatively high prostate-specific antigen (PSA) level of 141 ng/mL. Pelvic MRI revealed an irregularly-shaped neoplastic lesion centered on the prostate gland and extending into the bladder, seminal vesicles, perineum, and anorectal muscles, which showed low signal intensity on T2-weighted imaging and high signal intensity on diffusion-weighted imaging. No significant pelvic lymphadenopathy was observed. A prostate needle biopsy revealed adenocarcinoma with a Gleason score of 5 + 5 = 10 (Fig. 1). Bone scintigraphy and computed tomography (CT) revealed bone metastasis without visceral metastasis (Fig. 2a). Based on the LATITUDE high-risk criteria, abiraterone acetate combined with degarelix was introduced, and intensity-modulated radiation therapy (55 Gy/20 fr) was administered. At 4 months after the initial treatment, the patient's PSA level decreased to 0.144 ng/mL, and both the primary and metastatic tumors shrank (Fig. 2b). At 18 months after the initial treatment, his PSA level increased to 2.869 ng/mL, and docetaxel (30 mg/m^2 every 2 weeks) was administered. The liquid CDx Cancer Genome Filing cancer gene panel test showed the presence of a BRCA2 mutation with an MSI-high status (Table 1). After six courses of docetaxel, olaparib was introduced; however, CT showed enlargement of the prostate at 2 months after the initiation of olaparib (600 mg/day) treatment, and his PSA level increased to 15.69 ng/mL. Subsequently, pembrolizumab (200 mg every 3 weeks for 3 cycles, and then 400 mg every 6 weeks for 3 cycles) was administered to the patient. His PSA level decreased, and CT showed that the LNs had decreased in size (Fig. 2c, d, 3, 4). We monitored

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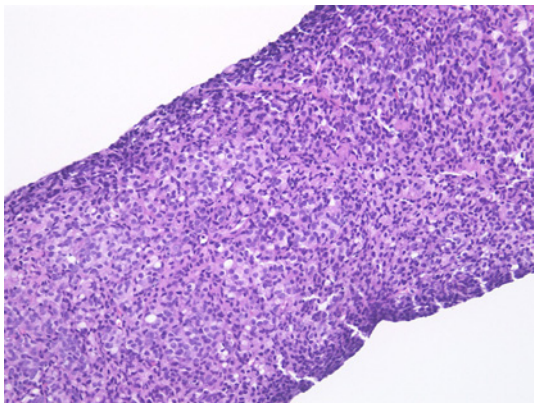

Fig. 1. HE staining of the prostate needle biopsy specimen. Gleason score 5 + 5 = 10, adenocarcinoma. Pattern 5 adenocarcinoma consisting mainly of enriched foci containing seal cell-like carcinoma cells.

his laboratory data, including PSA levels, every month and also performed CT every 3 months. His PSA level continued to fall to less than 0.025 ng/mL, and no recurrence was observed at 9 months after the initiation of pembrolizumab treatment. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary file (for all online suppl. material, see https://doi.org/10.1159/000540419).

Discussion

There have been few reports of prostate cancer with the simultaneous presence of BRCA2 mutations and an MSI-high status. BRCA mutations have been reported in 13% of CRPC patients, and 32 (3.1%) of 1,033 prostate cancer cases are MSI-high/mismatch repair deficient (dMMR) [2, 3]. Sokol et al. [4] reported that 3,446 (1.6%) of 212,417 patients who underwent oncogene panel testing had an MSI-high status. Among these 3,446 patients, 678 (19.7%) had BRCA mutations; this rate, which was 5.3% higher than that in the non-MSI-high group. In prostate cancer patients with BRCA mutations, an MSI-high status was observed in 12.8% of patients with BRCA1 mutations and 3.4% of patients with BRCA2 mutations. Although the overall number of patients with BRCA mutations and an MSI-high status is small, a certain number of patients with BRCA mutations also have an MSI-high status. If olaparib is ineffective after a companion diagnosis of BRCA, a gene panel test might provide an opportunity to detect MSI-high cases.

In the PROfound study, patients with mCRPC with BRCA1, BRCA2, or ATM mutations had significantly longer overall survival with olaparib than with enzalutamide or abiraterone with a hazard ratio of 0.42 after adjusting for crossover cases [5, 6]. In particular, for BRCA mutation cases, the olaparib group showed a significantly longer median OS in comparison to that of the control group (20.1 vs. 14.4 months, HR = 0.63). Based on these results, olaparib was indicated for patients with mCRPC with BRCA mutation-positive mCRPC in Japan. In this case, the patient also had a positive BRCA2 mutation; thus, olaparib was administered, but it was ineffective.

This case showed an MSI-high status based on a liquid biopsy. A previous study showed that immune checkpoint inhibitors are extremely clinically effective in treating patients with MSI-high prostate cancer [3, 7]. In the KEYNOTE-158 trial, pembrolizumab was effective in 34.3% of patients with MSI-high/dMMR non-colorectal solid cancer, including 6 patients with prostate cancer [8]. Abida et al. [3] reported that 6 of 11 mCRPC patients with MSI-high/dMMR who received anti-PD-1/PD-L1 therapy showed a reduction in PSA levels and that 4 showed an imaging response [5]. In our patient, rectal bleeding and bowel movements improved early after the initiation of pembrolizumab, along with his imaging findings.

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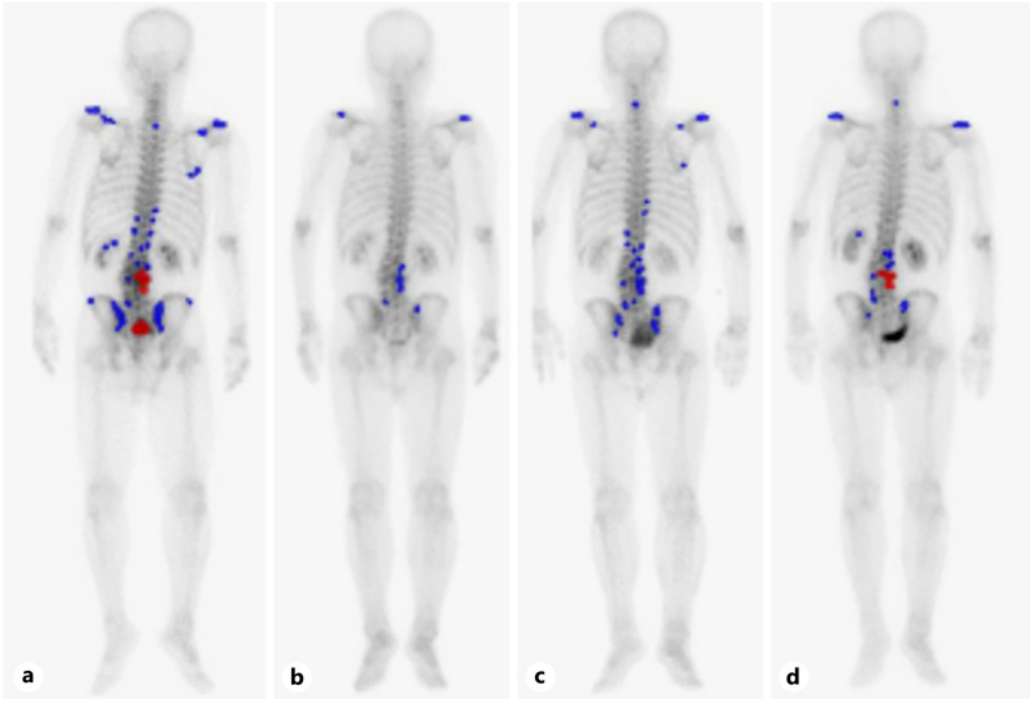

Fig. 2. Bone scintigraphy findings in initial (**a**), post-1st-line treatment (**b**), pre-olaparib (**c**), and post-olaparib (**d**) status.

Table 1. Genomic findings

Gene	Amino acid change	VAF
BRCA2	S2371 fs*21	0.0019
MLH1	Y157 fs*15	0.017
	D450 fs*41	0.052
MSH2	Y408*	0.043
MSH6	F1088 fs*5	0.012
PMS2	–	–
AR	T878A	0.067
RB1	Q762*	0.054
TP53	S215g	0.0073
PTEN	–	–

VAF, variant allele frequency.

Sokol et al. [4] reported that olaparib was ineffective and that pembrolizumab was effective in 2 patients with BRCA mutation-positive and MSI-high prostate cancer. They suspected that when a BRCA mutation and MSI-high overlap, the BRCA mutation is monoallelic, meaning that only one of the alleles is expressed (monoallelic) and is less likely to result in a homologous recombination repair defect than a biallelic BRCA mutation, which expresses both alleles.

Monoallelic BRCA mutations are thought to occur due to a high number of oncogene mutations due to an MSI-high status, suggesting that PARP inhibitors would be ineffective and that immune checkpoint inhibitors may be effective. In the present case, the variant allele

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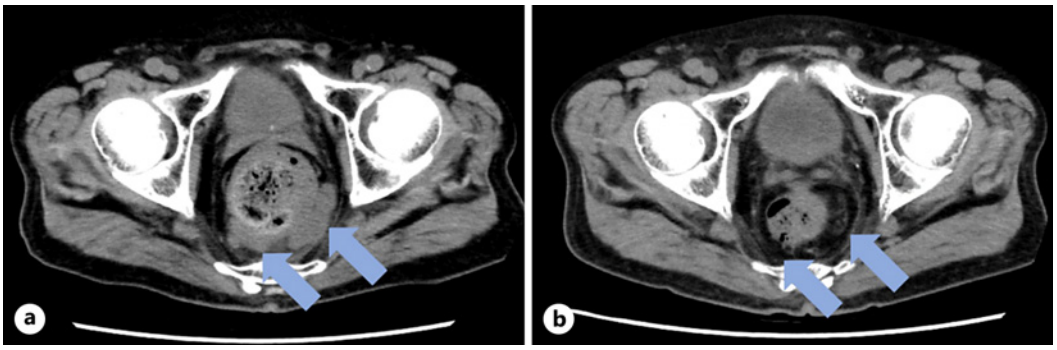

Fig. 3. Axial non-contrast CT. The pre-pembrolizumab (**a**) and post-pembrolizumab (**b**) statuses.

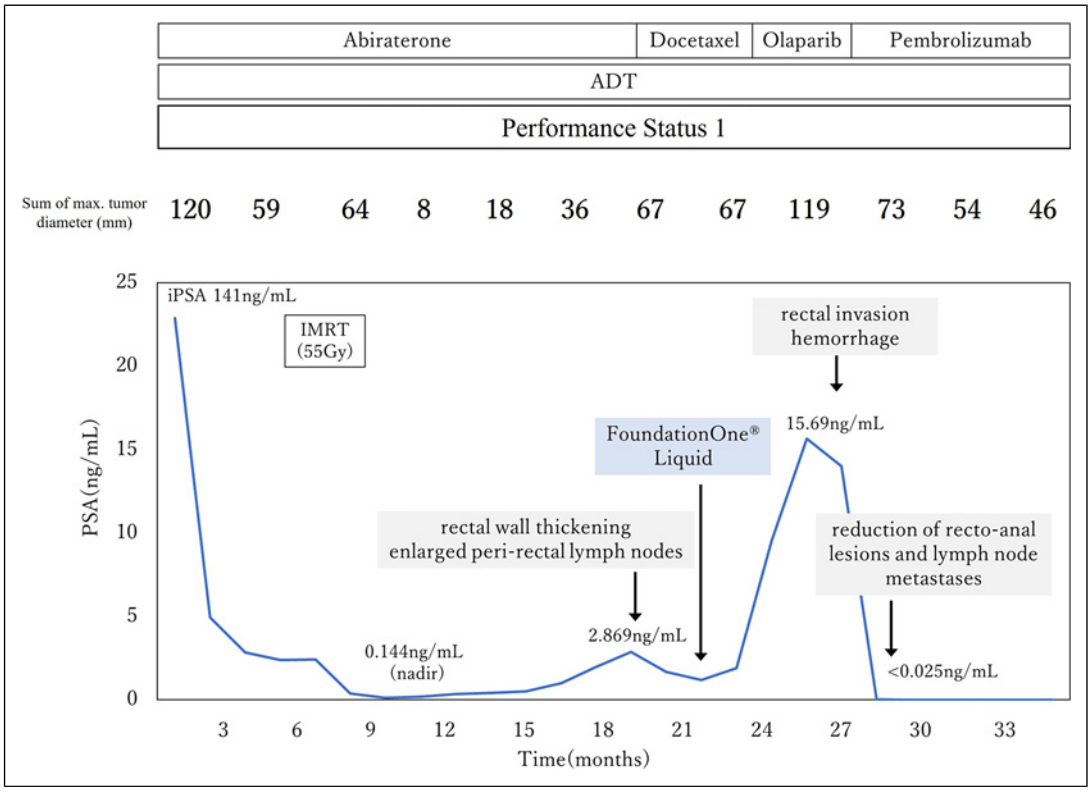

Fig. 4. Clinical course.

frequency of the BRCA2 mutation was 0.19%, which is lower than that of MLH1, MSH2, MSH6, and other mutations, as well as the variant allele frequency of CHIP (clonal hematopoiesis of indeterminate potential) and monoallelic mutations. The truncating mutations in MLH1, MSH2, and MSH6 also suggested that the MSI-high/high-TMB status was caused by mismatch repair gene abnormalities, which may explain why olaparib was not effective. The optimal first-line treatment with pembrolizumab or olaparib in patients with both BRCA mutations and MSI-high remains controversial. In addition, PSMA-positron emission tomography is not presently available in Japan. Thus, adequate imaging modalities or biomarkers are needed. The further accumulation of cases and clinical trials is needed to determine the efficacy of this option.

Conclusion

Here, we presented a case of MSI-high bone metastatic CRPC in which the patient showed a complete response to pembrolizumab treatment at approximately 18 months after the initiation of abiraterone treatment.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest Statement

The authors declare no conflicts of interest in association with the present study.

Funding Sources

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Author Contributions

T.H., K.Y., N.M., T.K., K.M., and H.U. drafted the manuscript. K.Y., N.M., H.H., Y.K., J.A., S.F., J.O., and M.M. performed the experiments.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

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