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Case Report

Exceptional Response to Pembrolizumab in a Mismatch Repair-Deficient Aggressive Prostate Cancer with Somatic EPCAM, MSH2, and MSH6 Co-Deletion: A Case Report

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Mismatch repair-deficient prostate cancer · Prostate cancer · Molecular profiling · Immune checkpoint inhibitors

Abstract
Mismatch repair-deficient (dMMR) prostate cancer (PCa) is a rare (1–5%) but highly actionable molecular subgroup of PCa, vulnerable to immune checkpoint inhibitors. Our case of sporadic *dMMR* PCa due to large monoallelic co-deletion of *EPCAM*, *MSH2*, and *MSH6* features a clinically aggressive disease presentation and a major response to pembrolizumab. We report a 65-year-old patient with primary metastatic PCa, Gleason score 5 + 5 = 10, with penile and lymph node metastases at diagnosis. Patient showed rapid progression on first-line ADT and enzalutamide. Tumor next-generation sequencing (*NGS*) revealed microsatellite instability and a tumor mutational burden of 40.8 mutations/megabase. Immunohistochemistry showed co-loss of *MSH2* and *MSH6*. Review of NGS row data confirmed large monoallelic deletion in chromosome 2p, including *EPCAM*, *MSH2*, and *MSH6*. No germline alterations in mismatch repair genes were detected. Patient showed excellent response to pembrolizumab, which is still ongoing. We conclude that early molecular tumor profiling is essential to enable personalized management of advanced PCa, especially in patients with aggressive or atypical disease course.

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Introduction

Prostate cancer (PCa) is the most commn cancer and the fifth leading cause of cancer death in male adults. Recent advances in molecular tumor profiling and precision oncology treatment have relevantly contributed to modify the treatment landscape of metastatic PCa. Main targetable genomic alterations in PCa are related to DNA damage response, which are found in up to 25% of metastatic PCa. These alterations include defects in the homologous recombination repair, the Fanconi anemia, and the mismatch repair pathways. Mismatch repair deficiency (dMMR) leads to increased predisposition to cancer and can be due to germline, somatic, and/or epigenetic alterations. dMMR or microsatellite instability (MSI-H) is reported in approximately 1–5% of all PCa [1, 2]. Patients with dMMR/MSI-H PCa are usually diagnosed with more aggressive disease and show generally worse responses to conventional treatment as compared to the overall PCa patient population [3]. However, dMMR/MSI-H confers vulnerability to immune checkpoint inhibitors (ICIs) [4]. Previous studies in dMMR/MSI-H PCa showed variable but generally high response rates to ICIs, including durable remissions [4]. In PCa, screening for loss of MMR proteins on the immunohistochemistry (IHC) level is not systematically established [2]. In patients with aggressive or unusual disease presentation, early molecular tumor profiling might identify actionable molecular alterations and spare ineffective and toxic treatment. We report a sporadic case of dMMR/MSI-H PCa associated with a monoallelic large co-deletion of *EPCAM*, *MSH2*, and *MSH6*. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534177).

Case Presentation

A 65-year-old male patient was referred to our center with a symptomatic progression of an aggressive metastatic prostate adenocarcinoma. At diagnosis, the patient presented with Gleason score (GS) 5 + 5 = 10 and metastases to regional lymph nodes and glans penis, hence being classified as stage IVB according to the AJCC staging system 8th Edition (2018). Prostate-specific antigen (PSA) at time of diagnosis was 169.3 µg/L. The patient received first-line treatment with leuprorelin and enzalutamide 160 mg/day, leading to an initial PSA decrease to 21.5 µg/L. However, 7 months from treatment start, an increase in PSA was observed. F^{18}-prostate-specific membrane antigen-positron emission tomography/computer tomography (F^{18}-PSMA-PET/CT) confirmed disease progression with appearance of new bone lesions and progression of lymph node metastases. The patient was suffering from intense left-sided groin pain, as well as hypesthesia and paresthesia along the ipsilateral L5 segment due to nerve compression from lymph node metastases. Second-line chemotherapy with docetaxel 75 mg/kg every 3 weeks was initiated, and the patient was referred to the radiation oncology department. Palliative radiotherapy with 30 Gray was delivered to the primary tumor, to a penile metastasis, and to the pelvic lymph nodes. Despite two cycles of docetaxel, PSA continued rising up to 117 µg/L, along with worsening of pain.

Tumor tissue DNA next-generation sequencing (NGS) from a penile metastasis (TruSight Oncology 500®, Illumina, Cambridge, UK) revealed MSI-H (49 out of 123 microsatellites instable) and a tumor mutational burden (TMB) of 40.8 mutations per megabase. However, no pathogenic mutations within the mismatch repair (MMR) genes were detected. In agreement with the high TMB, multiple other mutations, including mutations in *TP53*, *JAK1*, *PTEN*, and *PIK3CA*, were detected.

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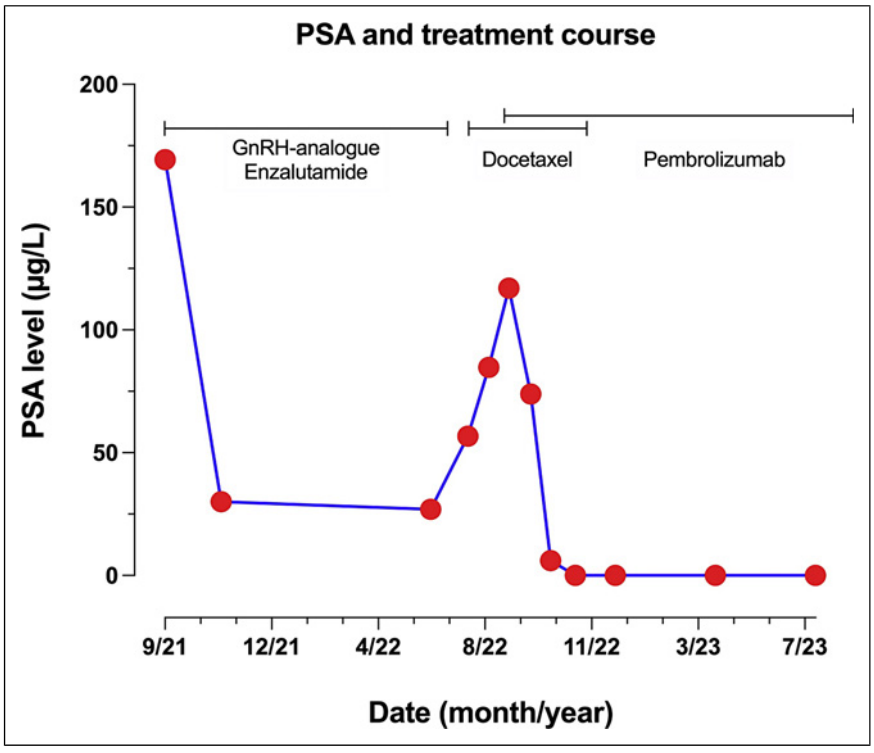

Fig. 1. Schematic illustration of received treatment lines and PSA levels over disease course. Rapid PSA decline is observed following initiation of treatment with the ICI pembrolizumab.

Based on the finding of MSI-H, pembrolizumab 200 mg every 3 weeks was added to the ongoing docetaxel treatment supported by safety data from the KEYNOTE-365 and KEYNOTE-921 studies [5, 6]. Following first dose of pembrolizumab, serum PSA declined progressively, remaining below 0.1 µg/L for the last 9 months (Fig. 1). Treatment with docetaxel was discontinued after 6 cycles, and 15 cycles of pembrolizumab have been administered to date. The patient remains asymptomatic. Subsequent imaging with CT revealed a very good partial response. IHC analysis of the MMR proteins on the initial metastatic biopsy was retrospectively performed showing complete loss of protein expression of MSH2 and MSH6 (Fig. 2). Exon coverage analysis of NGS data revealed a monoallelic large deletion in chromosome 2p, leading to loss of *EPCAM*, *MSH2*, *MSH6*, and *FANCL* (gen. loc.: 47,600,589 to 58,456,936) (Fig. 3a). Patient family history was unremarkable with no first- or second-degree relatives known to be diagnosed with cancer. Germline testing showed absence of pathogenic or likely pathogenic variants in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2*.

Discussion and Conclusions

With only 1 out of 5 cases harboring an underlying germline alteration, sporadic defects in MMR genes are the most common cause of dMMR/MSI-H in PCa [1–3]. Most frequent alterations are found in *MSH2* and *MSH6*, followed by *MLH1*, *PMS2* [1]. Moreover, by silencing *MSH2* expression, *EPCAM* deletions can cause Lynch syndrome. In PCa, Abida et al. [3] reported that individual cases of dMMR might be acquired along PCa disease progression.

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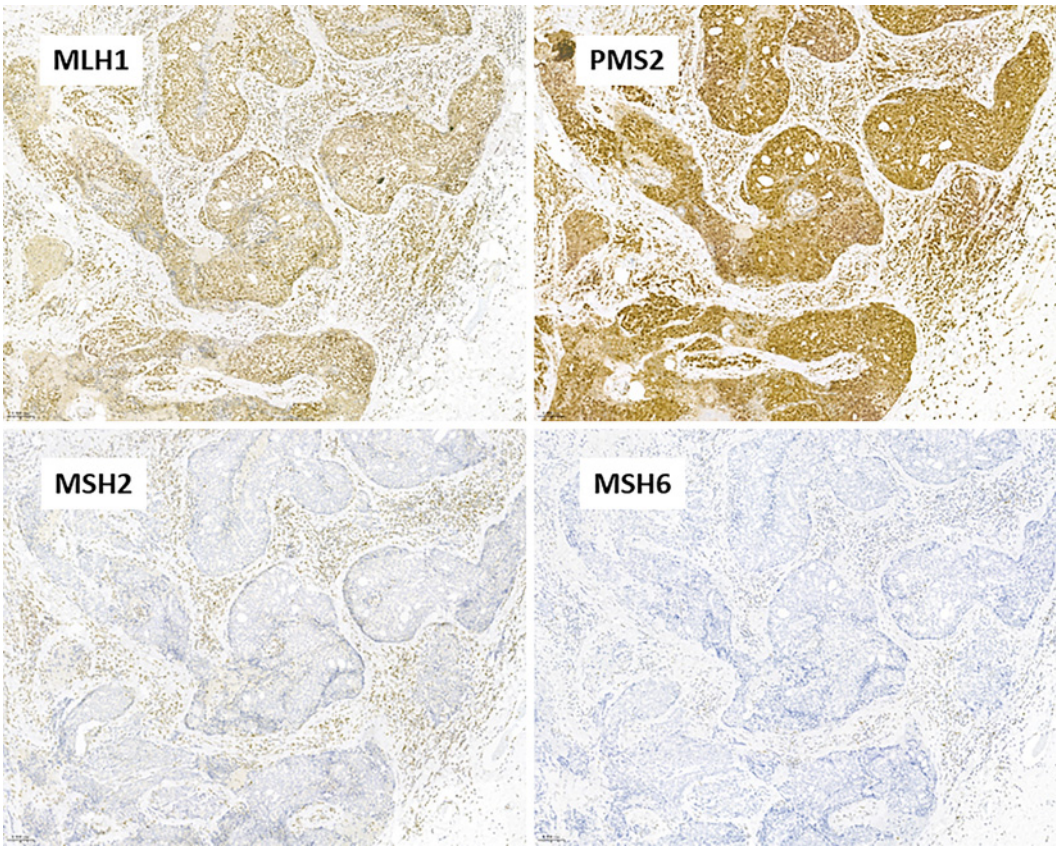

Fig. 2. IHC of the MMR proteins in the PCa tumor sample from a penile metastasis. Loss of MSH2 and MSH6 (2 lower panels) and conserved expression of MLH1 and PMS2 (2 upper panels) are observed.

For the MSI-H/dMMR PCa, scarce retrospective clinical data suggest more aggressive disease course paired with higher GSs and more advanced disease stage at presentation. Our patient presented with a biologically highly aggressive disease with a GS of 10 and penile metastases at diagnosis. Data on response to conventional treatments point to poor clinical outcomes [3, 7]. Indeed, the patient reported here progressed only 7 months after initiation of a first-line treatment despite androgen deprivation with an LHRH agonist and enzalutamide. Data from a retrospective cohort of dMMR/MSI-H PCa patients showed a median treatment duration on abiraterone or enzalutamide of 9.9 months (range: 3.0–34.5) in the metastatic castration resistant (mCRPC) setting [3]. In the ENZAMET trial, 62% of patients in the enzalutamide arm remained on treatment at 3 years [3, 8].

For dMMR/MSI-H PCa, previous studies reported variable response rates to ICIs (Fig. 3b) [4, 7]. The pivotal KEYNOTE-158 study reported tumor-agnostic responses in solid cancers with dMMR/MSI-H [4]. An overall response rate (ORR) of 34.3% was observed for the 6 patients with metastatic PCa. For these patients, the median overall survival was 23.5 months (95% CI: 13.5–not reached) [9]. In this study, IHC or 5 microsatellite loci PCR panel was used to determine the dMMR/MSI status [9]. Based on these results, pembrolizumab received approval for dMMR/MSI-H metastatic PCa refractory to one previous treatment line. Retrospectively, Lenis et al. [10] identified 26 patients with dMMR/MSI-H or TMB-high metastatic PCa, detected by the MSK-IMPACT NGS panel and treated with immunotherapy. The study reported a decline in PSA level of more than 50% (PSA50 response) in 65% of patients, with a median progression-free survival (PFS) of 41 months for dMMR/MSI-H patients and of

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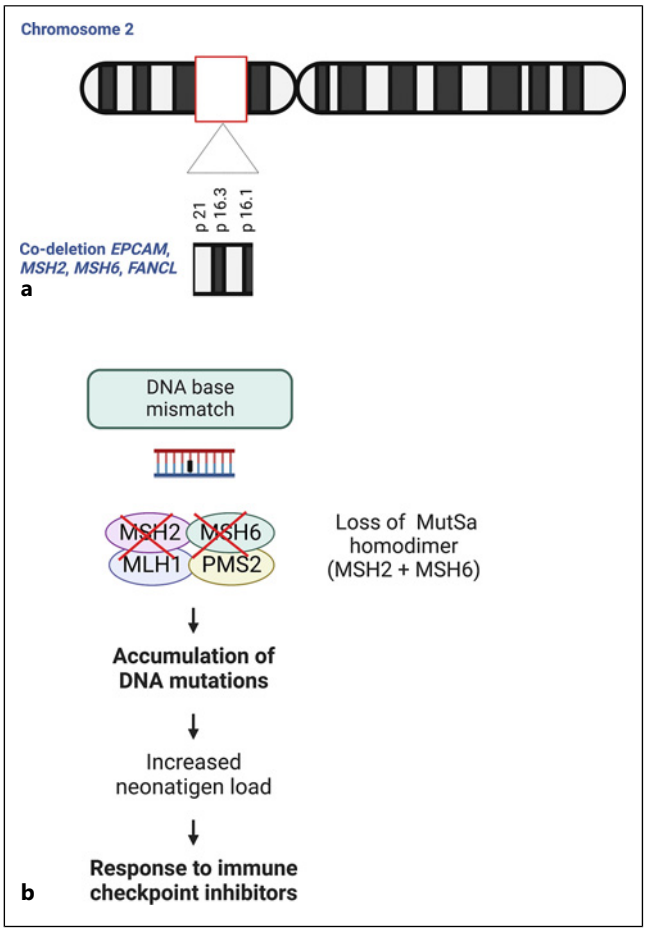

Fig. 3. a Schematic illustration of large monoallelic co-deletion in chromosome 2p, including genomic loci of *EPCAM*, *MSH2*, *MSH6*, and *FANCL*. **b** Loss of function in the MMR DNA repair pathway leads to accumulation of DNA mutations and increased neoantigen load, leading to responses to ICIs.

7 months for the TMB-high patients [10]. Graham et al. [7] reported a PSA50 response in 8 out of 15 (53.3%) dMMR/MSI-H PCa patients treated with pembrolizumab, and after a median follow-up of 12 months, 7 men were still on treatment without progression. Another multi-institutional case series reported PSA responses to immunotherapy in 4 out of 9 (44.4%) patients with MSI-H identified by cell-free DNA NGS, with ongoing response at data cutoff in every responder. Finally, there are no efficacy data supporting the combination of pembrolizumab with docetaxel in the dMMR/MSI-H setting, and therapy with docetaxel could have been omitted in this patient.

Besides this specific molecular subgroup of PCa, several trials in biomarker-unselected PCa patient population failed to report clinically relevant benefit from ICIs in monotherapy, or synergistic effect in combination with androgen receptor pathway inhibitors or chemotherapy. Globally, metastatic PCa is considered as immunologically cold with low presence of infiltrating T-cells. The KEYNOTE-199 trial assessed the efficacy of pembrolizumab monotherapy in androgen receptor pathway inhibitors and docetaxel-pretreated mCRPC population [11]. ORR was low (6% in PD-L1-positive cohort and 3% in the PD-L1-negative cohort), with a duration of response of at least 18 months in 63 and 50% of the responders, respectively [11]. Two responders showed dMMR defects per IHC. The randomized KEYNOTE-921, which assessed the efficacy of the combination docetaxel-pembrolizumab versus docetaxel-placebo in mCRPC patients refractory to novel hormonal agents, failed to show a difference in PFS or overall survival for the combination versus docetaxel monotherapy [6]. The phase 2 CheckMate 650 trial evaluated the

combination of ipilimumab 3 mg/kg and nivolumab 1 mg/kg for four cycles followed by nivolumab maintenance in both pre- and post-chemotherapy mCRPC patients (45 patients in each cohort) [12]. ORR was 25% for chemotherapy-naive patients and 10% in chemotherapy-pretreated cohort [12]. For patients with a TMB higher than the median, ORR was 50%. Radiological PFS was 5.5 versus 3.8 months, respectively (online suppl. Table 1). A recently published meta-analysis of 85 immunotherapy trials in solid tumors showed that treatment with ICIs can potentially achieve higher rates of tumor complete responses as compared to other systemic therapies [13]. However, accurate selection of candidate patients based on molecular tumor profile is essential to optimize the benefit from treatment with ICIs. Moreover, novel emerging biomarkers might further optimize personalization of treatment [14, 15].

As therapeutic landscape is rapidly evolving for metastatic PCa, molecular tumor profiling in case of lack of response or failure of first-line treatment is highly recommended [16]. In the reported case, after progression on enzalutamide, second-line treatment with pembrolizumab could have been initiated immediately, avoiding combination with docetaxel. Preclinical data point to higher PSMA expression in PCa tumors with DNA damage repair alterations, prompting the hypothesis that such patients might respond better to ^{177}Lutetium-PSMA-617 radioligand therapy. Recently, Raychaudhuri et al. presented a monocentric retrospective analysis on efficacy of ^{177}Lutetium-PSMA-617 therapy in patients with and without DNA damage repair alterations [17]. Two patients with alterations in *MSH2* were included, both showing a PSA50 response [17].

In conclusion, dMMR/MSI-H PCa is a rare but highly targetable molecular subtype of PCa. Our case report underlines the relevance of early tumor molecular profiling in PCa patients with aggressive or unusual disease presentation.

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Statement of Ethics

The study was approved by the Ethics Committee of Bern (Kantonale Ethikkommission Bern, BASEC ID 2022-00978). The patient provided written consent for anonymized use of his clinical data. All study procedures were performed in accordance with relevant guidelines, such as the Declaration of Helsinki, as well as local regulations. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. No identifiable images or data are included in this report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No funding for this study has been received.

Author Contributions

The work reported in the manuscript has been performed by the authors, unless clearly specified in the text. Conception and design and writing – original draft: D.H. and D.A.; data curation: D.H., D.A., and J.B.; analysis and interpretation of data and investigation: D.H., M.R., T.G., M.v.G., J.B., and D.A.; writing – manuscript review and editing: D.H., M.R., T.G., J.B., and D.A.; and resources and supervision: D.A. All authors have read and approved the final manuscript.

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.

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