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Case Report

Exceptional Response to Pembrolizumab for Treatment of Metastatic Chemorefractory Endometrial Carcinoma in a Patient with Lynch Syndrome: A Case Report

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Keywords
Pembrolizumab · Advanced endometrial cancer · Lynch syndrome

Abstract
Advanced endometrial cancer is associated with poor outcomes and few treatment options exist. Recently, the US Federal Drug Administration approved pembrolizumab for the treatment of endometrial cancers that are deficient in mismatch repair and have high microsatellite instability (MSI). Lynch syndrome is an autosomal dominant disease that causes MSI-high endometrial cancer. We report a case of a 46-year-old woman with Lynch syndrome and advanced endometrial cancer who experienced progressive disease after treatment with chemotherapy with carboplatin and paclitaxel. She was then treated with single-agent pembrolizumab and had an exceptional response. She was noted to have a significant decrease in the size of a large uterine mass extending into the vagina and vulva, as well as decrease in the size of lymphadenopathy. Data are limited at this time for patients with Lynch syndrome treated with single-agent pembrolizumab. Our case report seeks to add to the body of literature that suggests that this patient population may particularly benefit from this novel therapy.

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Introduction

Microsatellite instability (MSI) is a molecular tumor phenotype associated with approximately 30% of endometrial cancers [1]. It is defined by the gain and/or loss of nucleotides from microsatellite tracts and these changes can arise from deficiencies in the mismatch repair (MMR) system [1]. MSI is typically the result of either a germline mutation in the MMR system, as in the case of Lynch syndrome, or a somatic hypermethylation of the *MLH1* promoter. Thus, both MMR deficiency and MSI-high status are hallmark features of Lynch syndrome.

Lynch syndrome is an autosomal dominant disease that is caused by a germline mutation in MMR genes, including *MLH1, MSH2, MSH6, and PMS2* [2]. Women with Lynch syndrome have a 15–46% lifetime risk of developing colorectal cancer, 43–57% lifetime risk of endometrial cancer, and 10–17% lifetime risk of ovarian cancer, depending on which gene is mutated. For those with an *MLH1* gene mutation, the risks are 46%, 43%, and 10%, respectively [3]. Prior studies have shown that the average age at diagnosis of Lynch syndrome-associated endometrial cancer is 47–49 years (range 26–87) [4], compared with 60 years in the general population. Lynch syndrome-associated endometrial cancers are typically of endometrioid histology, and the tumors are more often located in the lower uterine segment [5].

Treatment options for women with advanced endometrial cancer, both sporadic and Lynch syndrome-associated, are known to be limited, with a 5-year survival of 20% in those with distant metastatic disease [6]. As such, there has been ongoing interest in novel therapeutic targets for the treatment of advanced/metastatic endometrial cancer. One such target is the programmed death (PD-1) receptor which, when bound to programmed death ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells, leads to inhibition of the immune response, including antitumor activity [7]. Pembrolizumab is a monoclonal anti-PD-1 antibody that blocks this interaction and has been shown to have response in patients with multiple tumor types, and was approved in May 2017 for the treatment of MSI-high solid tumors [7]. PD-L1 overexpression is a predictive biomarker for anti-PD1 therapy, and it is thought that endometrial cancer cells have this overexpression in 25–100% of cases [8]. Additionally, high tumor mutational burden, which increases production of tumor-specific neoantigens, has also been a predictive biomarker for anti-PD-1 therapy, and this feature has been associated with MMR-deficient/MSI-high tumors [9]. We present a case of a patient with Lynch syndrome with an advanced endometrial cancer who had an exceptional response to single-agent pembrolizumab.

Case Presentation

A 46-year-old Hispanic woman presented with a 1 year history of abnormal vaginal bleeding. An endometrial biopsy was performed that showed an undifferentiated carcinoma. CT imaging demonstrated a 10 cm endometrial mass with myometrial invasion, extension to the left ovary and distal vagina, and enlarged bilateral iliac and left inguinal lymph nodes with no evidence of distant metastatic disease.

At her initial gynecologic oncology visit, she was noted to have significant left buttock and labial swelling, erythema, and pain as well as leukocytosis. There was concern for a perirectal abscess, and she was therefore taken to the operating room for debridement with extensive tumor noted. She clinically improved after debridement and antibiotics but required prolonged hospitalization followed by multiple subsequent readmissions. During this time, she was unable to void due to obstruction from the tumor and required an indwelling Foley

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catheter. Tumor testing was performed and was notable for MSI-high status. There was loss of nuclear expression of *MLH1* and PMS2. Hypermethylation testing of the MLH1 promoter was negative. She underwent genetic counseling and testing and was positive for a pathogenic variant in *MLH1* (c.1011dup, p.Asn338GInfs*24), confirming a diagnosis of Lynch syndrome. Of note, the patient had a family history that was notable for several male relatives with colon and/or stomach cancers, but she was uncertain of the details.

The patient was subsequently treated with chemotherapy (carboplatin and paclitaxel). Following two cycles of chemotherapy, she was noted to have progression of the tumor with almost complete occlusion of the vagina. Her treatment was therefore changed to single-agent pembrolizumab (200 mg given intravenously every 3 weeks). After just two cycles of treatment, she was noted to have an exceptional response (Fig. 1a, b), with h further significant reduction in tumor size with each subsequent chemotherapy cycle (Fig. 1c, d). She remains on treatment with CT scans confirming a significant decrease in the size of her uterine mass, vaginal mass, and lymphadenopathy with no new sites of metastasis. As shown in Figure 2, the uterine mass decreased in size from 13.1 × 7.5 × 14.8 cm to 4.7 × 2.4 × 2.4 cm after 12 cycles of single-agent pembrolizumab.

Overall, she has tolerated pembrolizumab well. Following her third cycle of treatment, she developed transient hyperthyroidism followed by hypothyroidism which is being managed by the endocrinology service. Her Foley catheter has since been removed after three cycles of treatment, and she is now fully active with no limitations to her daily activities. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000530154).

Discussion

Outcomes for patients with advanced or progressive endometrial cancer are poor [6], and treatment options have thus far been limited. Pembrolizumab is a relatively new therapeutic option for these patients; however, data on its use in patients with Lynch syndrome are limited. Thus, this case report seeks to add to the body of literature regarding use of this agent in this population. Though several studies have been performed looking at pembrolizumab and endometrial cancer, they are limited by small sub-cohorts of patients or patients treated with pembrolizumab in combination with another agent [8].

Results from the KEYNOTE-158 trial, a phase II study of pembrolizumab in patients with previously treated, advanced noncolorectal MSI-H/MMR deficient cancers, showed an objective response rate (ORR) of 34.3% with a median progression-free survival of 4.1 months and median overall survival of 23.6 months [10]. In this study, 27 tumor types were represented, and 49 patients (21% of the cohort) had endometrial cancer with an ORR of 57.1% [10].

In 2020, Makker et al. [11] published results from KEYNOTE-146 pertaining to the endometrial cohort and showed the combination of lenvatinib and pembrolizumab 200 mg IV every 3 weeks was associated with an ORR of 63.6% in patients with MSI-high tumors and 36.2% in patients with MSI-stable tumors. They thus concluded that this combination had promising activity in advanced endometrial cancer regardless of MSI status. Building on these promising findings, the NRG trial-GY018 trial is evaluating pembrolizumab in addition to carboplatin/paclitaxel in patients with stage III/IV or recurrent endometrial cancer [12], while the ongoing KEYNOTE-B21 trial seeks to address the efficacy of pembrolizumab in addition to adjuvant chemotherapy for patients with advanced endometrial cancer in the upfront setting [13].

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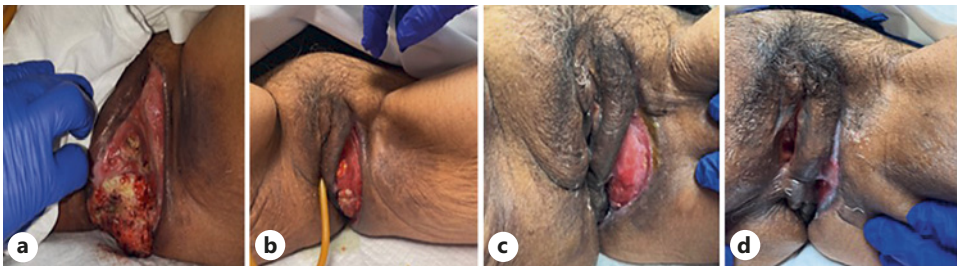

Fig. 1. Left buttock area, on single-agent pembrolizumab. From left to right: (**a**) prior to start of pembrolizumab, (**b**) after 2 cycles, (**c**) after 3 cycles, and (**d**) after 4 cycles.

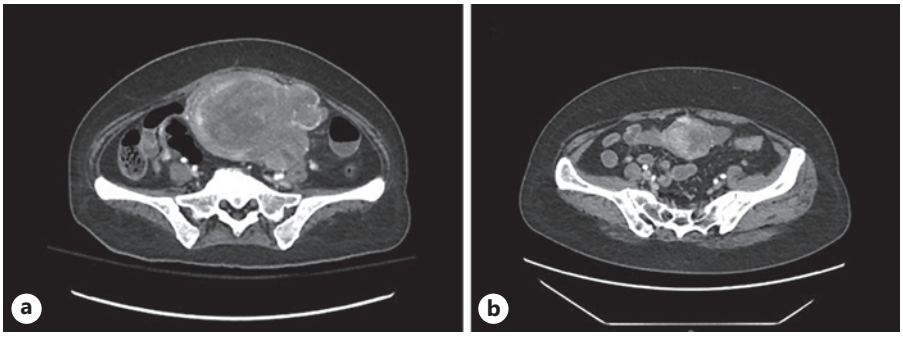

Fig. 2. CT evaluation of uterine mass. From left to right: (**a**) prior to the start of pembrolizumab (13.1 × 7.5 × 14.8 cm), (**b**) after 12 cycles of pembrolizumab (4.7 × 2.4 × 2.4 cm).

The majority of data assessing the efficacy of immunotherapy in MSI-high tumors does not differentiate between sporadic *MLH1* promoter methylation and germline Lynch syndrome. It is unknown if MSI leads to equivalent immune activation regardless of its origin. A study by Pakish et al. [9] found an increase in CD8+ cells and activated cytotoxic T lymphocytes in the stroma of Lynch syndrome cases as compared to sporadic cases, suggesting differences in response to immunotherapy and highlighting the need for more research in this area.

At this time, data specific for patients with Lynch syndrome treated with pembrolizumab are largely limited to case reports. In one such report, a patient with uterine serous carcinoma and Lynch syndrome sustained a partial response to pembrolizumab and has remained asymptomatic and stable for 2 years at the time of publication [14]. In 2021, Bellone et al. [15] published data from a phase 2 study of single-agent pembrolizumab for recurrent "Lynch-like" (i.e., somatically acquired MMR mutations) and sporadic endometrial cancer (i.e., biallelic methylation of *MLH1* gene promoter). In their small cohort of 24 evaluable patients, six were noted to have somatically acquired MMR mutations and no patients had germline mutations. Patients with somatically acquired MMR mutations had an ORR of 100% versus 44% in patients with sporadic endometrial cancer; the 3 year progression-free survival was 100% in this cohort versus 30% in the sporadic endometrial cancer cohort [15]. This finding was corroborated by preliminary data from Borden et al. [16], which demonstrated that women with endometrial cancer with *MLH1* hypermethylation had an ORR of 25.0% compared to 66.7% in women with germline/somatic MMR deficient endometrial tumors.

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Conclusion

In summary, our case of a patient with MSI-high chemorefractory, advanced endometrial cancer with an exceptional response to pembrolizumab is notable given her history of Lynch syndrome. Tumors associated with Lynch syndrome are MSI-high and this therefore may be a patient population can particularly benefit from immunotherapy treatment with pembrolizumab.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of Interest Statement

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter of materials discussed in this manuscript.

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Author Contributions

Dr. Samantha Batman is the primary author who wrote the majority of the manuscript. Drs. Kathleen Schmeler, Alejandro Rauh-Hain, Michaela Grinsfelder, Ross Harrison, Monica Avila, Han Cun, and Jeffrey How are gynecologic oncology faculty and fellows who treated the patient. Drs. Xiaohong Wang and Nidhi Tandon are pathologists who reviewed the case and performed the tumor testing. Amir Jazaeri and Emily Hinchcliff are gynecologic oncologists who provided technical expertise for the manuscript. Dr. Schmeler served as the primary mentor for Dr. Batman and oversaw and contributed to the writing of the manuscript. All authors reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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