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Case Report

De-Escalated Adjuvant Treatment for Advanced MMR Deficient Mixed Endometrioid/Clear Cell Endometrial Carcinoma with PD-1 Inhibition Alone: A Case Report

Danielle M. Blemur[a] Ravali A. Reddy[a] Susan M. Lang[b] Malte Renz[c]

[a]Department of Obstetrics and Gynecology, Stanford University, Stanford, CA, USA; [b]Gynecologic Oncology Division, Stanford University, Stanford, CA, USA; [c]Department of Gynecology with Center for Oncological Surgery, Charité – Universitätsmedizin Berlin, Berlin, Germany

Keywords
Mixed epithelial endometrial carcinoma · MMR deficiency · Adjuvant pembrolizumab

Abstract
Introduction: Advanced mixed epithelial endometrial carcinomas are rare high-grade cancers with a poor prognosis. A clear cell component infers relative chemotherapy insensitivity, likely further increased by p53 wild type status and MMR deficiency. PD-1 inhibition for MMR deficient endometrial cancers has been recently added to first-line adjuvant treatment in combination with platinum-based chemotherapy. Information on de-escalation of adjuvant treatment to PD-1 inhibition alone without chemotherapy is sparse. ***Case Presentation:*** Here, we present a patient with advanced stage mixed epithelial endometrial carcinoma, a clear cell component and MMR deficiency who underwent de-escalated adjuvant treatment with PD-1 inhibition alone without simultaneous chemotherapy. ***Conclusion:*** Histotype-agnostic adjuvant monotherapy with checkpoint immune inhibitors alone appears to be a highly effective even in the rare mixed endometrial carcinomas if MMR protein deficient as described in this case report.

Correspondence to:
Malte Renz, renzmalt@stanford.edu

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Highlights

- Advanced mixed epithelial endometrial carcinomas are high grade and have a poor prognosis.
- A clear cell component, MMR deficiency, and p53 wild type status may increase chemo-insensitivity.
- Histotype-agnostic, de-escalated with first-line adjuvant PD-1 inhibition can result in a long recurrence-free interval.

Introduction

Mixed epithelial endometrial carcinomas are rare and account for only 3% of all endometrial cancers. According to the 2020 WHO (World Health Orgainzation) classification, they are composed of two or more distinct histotypes, at least one of which is serous or clear cell [1, 2]. Thus, mixed endometrial carcinomas are considered high-grade with a poor prognosis. Furthermore, a clear cell carcinoma component may infer chemotherapy insensitivity [3], possibly enhanced by p53 wild type status and mismatch repair protein deficiency (MMRd) [4], thereby decreasing treatment options. Since The Cancer Genome Atlas (TCGA) study of endometrial cancers [5] the importance of molecular subtypes for prognosis and treatment has been increasingly recognized. The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) recently updated the endometrial cancer staging to incorporate such molecular subtypes [6]. Histotype-agnostic treatment with PD-1 (programmed cell death protein 1) inhibition for MMRd cancers has been promoted from second-line treatment of recurrent metastatic endometrial cancer to first-line adjuvant treatment in combination with platinum-based chemotherapy. De-escalation of adjuvant therapy in MMRd cancers to PD-1 inhibition alone without additional chemotherapy appears to have a sound biological rationale but has not yet been tested in larger clinical trials.

Here, we present a patient with advanced stage mixed endometrial carcinoma with a clear cell component, p53 wild type, and MMR deficient, who underwent upfront minimally invasive debulking surgery followed by 1 year of de-escalated adjuvant single agent pembrolizumab alone without chemotherapy. Despite the initial pelvic peritoneal spread, excellent treatment response to tumor debulking and checkpoint immune inhibition was noted. The patient remains recurrence-free, 14 months at the time of publication. Adjuvant treatment was complicated by autoimmune myocarditis, which resolved with high-dose corticosteroids.

Case Report

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540357). A 67-year-old nulligravida with hypertension and hypothyroidism presented to the primary gynecologist with postmenopausal bleeding in the setting of hormone replacement therapy for 20 years. Since the patient declined an office endometrial biopsy, a hysteroscopy, dilation, and curettage were performed in the operating room. Final pathology showed a mixed epithelial endometrial carcinoma with a clear-cell carcinoma component.

Preoperative computer tomography (CT) imaging did not identify any extrauterine disease. The patient underwent staging surgery with robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, infra-colic omentectomy, and sentinel lymph node injection. During the surgery peritoneal implants in the pelvis were seen, biopsied and confirmed

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carcinomatous by intraoperative frozen section. Since the peritoneal lesions were confined to the small pelvis and the upper abdomen appeared disease-free, peritonectomies of the right pelvic sidewall and posterior cul-de-sac were performed as well as excisions of a left uterosacral and right pararectal nodule. At the end of the surgery, complete cytoreduction had been achieved with no visible disease.

Final pathology showed a stage IIIA high-grade mixed clear cell/endometrioid endometrial adenocarcinoma with 20% clear cell and 80% endometrioid. The endometrioid component was grade 1. Twenty-seven percent myometrial invasion and no lymphovascular space invasion were noted. The peritoneal implants, the left uterosacral and right pararectal nodule both showed only the endometrioid component, whereas the implants on the ovary contained the clear cell component. On immunohistochemistry, estrogen and progesterone receptors were highly expressed in the endometrioid component (ER/PR 3+, 90%) and absent in the clear cell component. Mismatch repair proteins MLH1 (mutL homolog 1)/PMS2 (postmeiotic segregation increased 2) were deficient in both components due to MLH1 promoter hypermethylation. p53 wild type was noted in both components.

Given the advanced stage, pelvic peritoneal spread, and high-grade histology of the disease the patient was counseled on adjuvant therapy. Since the patient was apprehensive to both chemotherapy and radiation therapy, immunotherapy options were discussed and through shared decision making, the patient elected for off-label use of adjuvant single agent pembrolizumab. From March to December 2022, 12 cycles of adjuvant pembrolizumab treatment were completed, i.e., nine 3-weekly cycles of 200 mg and three 6-weekly cycles with 400 mg pembrolizumab. positron emission tomography/CT imaging after cycle 6 showed no evidence of disease.

The adjuvant treatment course was complicated by splenic infarcts, a stroke, and lymphocytic myocarditis requiring prednisone therapy. After 5 cycles, the patient presented with left upper quadrant pain and was found to have splenic infarctions. Worsening thrombocytosis and elevated inflammatory markers were noted; apixaban was started. Prior to cycle 12, following several missed doses of apixaban, the patient presented with left arm flaccid paralysis and was found to have a right cerebrovascular accident on magnet resonance imaging. Neurology recommended continuation of apixaban as well as the initiation of aspirin and statin therapy. The symptoms resolved completely with no residuals.

Prior to cycle 13, the patient presented to the cardiology oncology clinic with complaints of palpitations with no reduction in activities of daily living. Elevated troponins to 1,238 ng/L and brain natriuretic peptide of 1,059 pg/mL were noted, prompting admission for expedited workup. A transthoracic ECHO (echocardiography) showed mildly reduced left ventricular systolic function with an ejection fraction of 46%. A cardiac catheterization was performed with no evidence of occlusive coronary artery disease. An endomyocardial biopsy was obtained and revealed several perivascular collections of mononuclear cells with rare myocyte damage meeting criteria for lymphocytic myocarditis. The patient was started on a high-dose prednisone taper. Troponins normalized and a repeat ECHO showed an improvement in (left ventricular ejection fraction to 55%. Because of these severe side effects and no evidence of disease on imaging, pembrolizumab was discontinued. The patient underwent observation. Recent positron emission tomography/CT imaging showed no evidence of disease, and the patient remained disease-free for 14 months at the time of publication.

Discussion

Immunotherapy with immune checkpoint inhibition might be a therapeutic option even in the adjuvant setting for mixed endometrial carcinomas with a clear cell component, especially if MMRd. Defective mismatch repair proteins, a DNA (deoxyribonucleic acid)

single-strand repair system, result in so-called hypermutated cancers with a high amount of neoantigens and an active tumor microenvironment. Increased immunogenicity is the rationale for immune checkpoint inhibition in MMRd cancers, although there is emerging evidence that patients with promoter hypermethylation of MMR proteins might benefit less from immunotherapy than patients harboring MMR protein germline mutations [7]. Neoantigens trigger migration and activation of tumor infiltrating lymphocytes (TILs). In endometrial clear cell carcinomas, high levels of TILs have been observed [8]. The presence of TILs was found to be a good prognostic factor, likely because TILs mediate the anti-tumor response.

Neither pure endometrial clear cell carcinomas nor mixed endometrial carcinomas were included in the original TCGA study on endometrial cancer [5]. Subsequent studies reported a frequency of MMR protein deficiency in pure endometrial clear cell carcinomas, ranging widely from 0% to 69% [9–14]. More recently, 10% of pure clear cell carcinomas have been described to be MMR protein deficient [8, 15]. Based on these numbers, MMR deficiency might be more frequent in mixed epithelial endometrial carcinomas with a clear cell component. Köbel et al. [16] reported MMR deficiency in mixed endometrioid/clear cell in up to 66%.

An early phase II trial showed an immune-related objective response rate of 71% in 7 MMR deficient metastatic non-colorectal cancers including 2 endometrial cancer patients [17]. Subsequently, the objective response rate in a variety of metastatic MSI-H cancers was found to be 25–71% [18]. The Keynote-158 trial showed an objective response rate of 57% in 233 MMRd endometrial cancer patients [19]. Even in cases refractory to chemotherapy, single agent pembrolizumab was reported to be effective [20]. Subsequently, PD-1 inhibitors have been tested in the first-line adjuvant setting combined with chemotherapy. The phase III trials RUBY [21] and NRG-GY018 [22] showed benefit of adding PD-1 inhibitors to adjuvant chemotherapy for advanced stage endometrial cancers, especially in the MMRd population. It is thought that priming with chemotherapy results in enhanced neoantigen release and thereby makes immunotherapy more effective. On the other hand, in the first-line setting, the immune system has not yet been compromised by prior lines of chemotherapy which also may increase the efficacy of immunotherapy. Furthermore, surgery itself might be a sufficient trigger for neoantigen release, thereby providing synergy for immune checkpoint therapy.

Information on de-escalated single agent PD-1 inhibition without additional chemotherapy in the adjuvant setting is sparse with pertinent randomized trials still recruiting. First data of the LEAP-001 trial (NCT03884101) were just recently presented. The trial randomized advanced stage (and recurrent) endometrial cancer patients to pembrolizumab and lenvatinib versus carboplatin/paclitaxel in the first-line adjuvant setting [23]. In the MMR protein deficient subgroup, progression-free and overall survival were found to be prolonged with pembrolizumab and lenvatinib compared to chemotherapy [24]. KEYNOTE-C93/GOG-3064/ENGOT-en15 (NCT05173987) randomizes patients with MMR protein deficient advanced or recurrent endometrial cancers to single agent pembrolizumab or platinum-based doublet chemotherapy [25]; the DOMENICA trial (NCT05201547) employs dostarlimab in this setting [26]. Results of these latter phase III trials are expected in the next few years.

For MMRd endometrial cancers stage IB/II with substantial lymphovascular space invasion or stage III, the green arm of the multicenter RAINBO (NCT05255653) phase III trial compares adjuvant radiation therapy with and followed by durvalumab (PD-L1 inhibition) to radiation therapy alone [27].

Pembrolizumab can be associated with immune-mediated adverse events, which can affect any organ system or tissue, are generally low-grade, manageable and resolve with time. Any-grade toxicities occur in up to 20% of patients and include fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, abdominal pain, nausea, and hypothyroidism. Immune-mediated adverse reactions can however be severe or even fatal including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, myositis, or myocarditis [28].

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In summary, we presented evidence for histotype-agnostic adjuvant treatment with checkpoint immune inhibitors alone even in the rare mixed endometrial carcinomas if MMR protein deficient. Pending phase III trial results, single agent pembrolizumab in MMRd mixed endometrial cancer appears to be a highly effective adjuvant treatment strategy. Patients need to be observed for immune-related side effects including lymphocytic myocarditis.

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. 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 have no conflicts of interest to declare.

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Author Contributions

Danielle Blemur: investigation, data curation, writing – original draft. Ravali A. Reddy: data curation, review and editing. Susan Lang: investigation, writing – review and editing. Malte Renz: conceptualization, investigation, writing – review and editing.

Data Availability Statement

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

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