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Case report

Unconventional success: Achieving long-term remission with pembrolizumab in recurrent high-grade endometrial carcinosarcoma

Anaiya G. Singh [a,*], Viraj S. Panchal [b], Suvarna Guvvala [c], Richard P. Mansour [c]

[a] Department of Internal Medicine, LSU Health Shreveport, 1541 Kings Hwy, Shreveport, LA 71103, United States
[b] Department of Medicine, Smt. N.H.L. Municipal Medical College and SVPISMR, Ahmedabad, Gujarat 380006, India
[c] Department of Hematology Oncology, Feist-Weiller Cancer Centre, LSU Health Shreveport, 1501 Kings Hwy, Shreveport, LA 71103, United States

1. Introduction

Endometrial carcinosarcoma (EC), or malignant mixed Müllerian tumor (MMMT), is a rare, aggressive high-grade endometrial cancer that makes up about 2 % to 5 % of gynecological cancers but is responsible for approximately 16 % of uterine cancer-related deaths.(Gonzalez Bosquet et al., 2010) This aggressive tumor is distinguished by its biphasic composition, combining malignant epithelial (carcinomatous) and mesenchymal (sarcomatous) elements, contributing to a high degree of tumor heterogeneity. This intratumor heterogeneity, with mixed carcinoma and sarcoma features, results in a clinically challenging and aggressive cancer with a poor prognosis, often resistant to standard therapies.(Matsuo et al., 2018).

While many patients with early-stage disease achieve successful outcomes with surgery alone or in combination with chemotherapy or radiotherapy, effective treatment options remain limited for those with advanced-stage disease or recurrent presentations. Standard therapies, such as carboplatin and paclitaxel, are often insufficient for long-term disease control in these cases, demanding additional, often experimental, therapies due to a high risk of metastasis and limited response to standard treatments.(Amant et al., 2005).

Around 30 % of primary and 13–30 % of recurrent cases of endometrial cancer patients have tumors exhibiting high microsatellite instability (MSI) and mismatch repair deficiency (dMMR). Microsatellite instability (MSI) is a condition marked by genetic hypermutability due to a deficiency in the DNA mismatch repair (dMMR) system, which normally corrects replication errors. MSI serves as an indicator of dMMR and is associated with a hypermutable cellular state, characterized by numerous genetic mutations. MSI can be classified into MSI-high (MSI-H), MSI-low (MSI-L), or microsatellite stable (MSS) based on the extent of instability. This high mutation rate in MSI-H tumors leads to increased PD-L1 expression, elevated tumor mutational burden (TMB), and greater lymphocyte infiltration—making these tumors particularly susceptible to immune checkpoint inhibitors (ICIs) like pembrolizumab. Based on early phase II clinical trials, pembrolizumab, a PD-1 inhibitor, showed promising results in dMMR tumors, leading to its approval in MSI-H and dMMR cancers, including endometrial carcinoma. However, Pembrolizumab has also demonstrated potential in treating proficient mismatch repair (pMMR)/microsatellite stable (MSS) endometrial carcinoma, despite pMMR tumors typically having lower mutation rates and fewer immune-responsive features compared to MSI-H/dMMR tumors. (Eskander et al., 2023).

Here, we present the case of a 62-year-old woman initially diagnosed with stage T1aN0M0 high-grade endometrial carcinosarcoma with stable microsatellite status (MSS) who experienced multiple recurrences, including metastatic spread to the lungs, managed initially with carboplatin and paclitaxel. Despite recurrence and progression, the patient demonstrated an exceptional long-term response to pembrolizumab immunotherapy, with sustained disease control and absence of detectable disease five years after initiating therapy. This case demonstrates the potential of pembrolizumab to achieve durable response in recurrent high-grade endometrial carcinosarcoma, in a histologic subtype traditionally excluded from clinical trials, and suggests a need for broader consideration of immunotherapy in aggressive endometrial carcinosarcoma subtypes.

2. Case

A 62-year-old woman was initially diagnosed with high-grade endometrial carcinosarcoma, characterized by papillary serous endometrial adenocarcinoma with malignant mesodermal mixed tumor with heterologous elements. Her disease was staged as T1aN0M0 with stable microsatellite status. The patient underwent six cycles of carboplatin and paclitaxel (Carbo/Taxol) chemotherapy, without adjunct radiation therapy and achieved a good response.

Approximately four years later, she experienced a recurrence with

* Corresponding author.
E-mail addresses: anaiya.singh@lsuhs.edu (A.G. Singh), virajpanchal611@gmail.com (V.S. Panchal), suvarna.guvvala@lsuhs.edu (S. Guvvala), richard.mansour@lsuhs.edu (R.P. Mansour).

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metastatic spread to the lungs. She was re-treated with Carbo/Taxol and showed a positive response. Subsequently, after completing 10 months of Carbo/Taxol therapy, she was transitioned to biweekly paclitaxel, which successfully managed the disease for an additional 2.5 years. A PET scan done two years later revealed stable disease with a suspicious right hilar node, which was monitored. However, a year later, PET imaging indicated progression, showing an enlarged and more avid right hilar lesion. The patient was referred to interventional pulmonology, and an ultrasound-guided endobronchial FNA of the station-7 lymph node confirmed metastatic carcinosarcoma.

Due to failure of conventional chemotherapy, the decision to start immunotherapy was taken and the patient was initiated on pembrolizumab (Keytruda). PET scans six months and one year later, demonstrated no active disease. However, treatment was paused after receiving six months of immunotherapy, coinciding with cycle 16 due to elevated liver function tests (LFTs), which subsequently normalized. Further PET scans repeated every 6 months revealed no evidence of active malignancy. The patient completed three years of Keytruda, with complete remission and no further noted side-effects.

The patient has had regular follow-up PET scans without evidence of recurrence. The patient continues to exhibit a complete absence of detectable disease five years after initiating Keytruda therapy, with regular monitoring and imaging studies to identify any potential disease recurrence.

3. Discussion

Through this case, we highlight the efficacy of pembrolizumab in achieving a desired clinical outcome in terms of remission in a patient with recurrent high-grade endometrial carcinosarcoma (EC) with microsatellite-stable (MSS) status. It is not well-established on the efficacy of immune checkpoint inhibitors (ICIs) in treating MSS-type tumors which are less mutation-prone and are typically considered “cold” with fewer neoantigens and immune infiltrates compared to microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) endometrial carcinomas which have shown promising results with ICIs. (Mulet-Margalef et al., 2023; Cai et al., 2024; Halla, 2022) The uniqueness of our case was the prolonged improved response to pembrolizumab in treating high-grade, aggressive endometrial cancers like carcinosarcoma which makes it necessary to rethink the role of ICIs as traditionally such cancers would exhibit poor response to standard treatments and excluded from clinical trials.

Traditionally, endometrial carcinomas were classified according to their morphological features. They were subsequently divided as (1) Type 1 Endometrioid carcinoma, which is the most common subtype associated with estrogen exposure and has a favorable prognosis, (2) Type 2 which includes Serous carcinoma and Clear cell carcinoma which are linked with p53 mutation and are high grade with aggressive behavior and poor prognosis.(Bokhman, 1983) However, this classification is limited due to its reproducibility and fails to capture biological diversity. The newer classification uses molecular profiling with morphological features which classified them in (1) polymerase epsilon (POLE)-ultra mutated, associated with high mutation rate and favorable prognosis (2) Microsatellite instability-high (MSI-H), often linked with lynch syndrome (3) Copy-number low (CN-low) and (4) Copy-number high (CN-high) associated with p53 mutations, genomic instability, and poor prognosis.(Yen et al., 2020; Cancer Genome Atlas Research Network).

The conventional treatment for endometrial carcinoma involves a combination of surgery, radiotherapy, and chemotherapy depending on the stage and histological grading. For early-stage endometrial carcinoma surgery is the preferred treatment which involves total hysterectomy and bilateral salpingo-oophorectomy, for those patients who are at risk of metastases, pelvic and *para*-aortic lymphadenectomy or sentinel lymph node mapping is done for further treatment decisions.(Concin et al., 2021; Kovacevic, 2021) Adjuvant radiotherapy is added to reduce the risk of recurrence. For those patients with intermediate to high-intermediate risk, vaginal brachytherapy is a standard option that effectively prevents local recurrences with fewer side effects compared to pelvic radiotherapy.(Concin et al., 2021; Seagle et al., 2017) Patients with high-risk and advanced stages platinum-based chemotherapy such as carboplatin and paclitaxel are commonly used. Chemotherapy may be combined with radiotherapy where local and systemic disease management is required.(Powell et al., 2022).

Our patient had a recurrence of endometrial carcinosarcoma despite being on carboplatin and paclitaxel, where her disease progressed over time to involve metastatic spread to the lungs. The disease trajectory aligns with the aggressive nature of carcinosarcomas. These carcinosarcomas have the components of both epithelial and mesenchymal cells responsible for their intratumor heterogeneity and increase the resistance to standard chemotherapy.(Leskela et al., 2019) The sustained response that was obtained with pembrolizumab in our patient suggests that immune-based therapy can play an important role in transforming the management of the patient and potentially increasing the survival in patients with recurrent or metastatic carcinosarcoma which are limited with treatment options.(Eskander et al., 2023; Gupta et al., 2022).

MSI-H/dMMR markers are regarded as the markers for the efficacy of ICI therapy, however, our case had an absence of such markers yet the patient was able to attain remission.(Du and Liu, 2022) The higher tumor mutational burden (TMB) and the expression of PD-L1 is linked with the expression of the dMMR/MSI-H phenotype which can be treated with pembrolizumab.(Cho et al., 2021) While some MSS tumors may still benefit from pembrolizumab.(Diaz et al., 2022) Our patient had a benefit from the use of pembrolizumab which may raise intriguing questions on factors that are yet to be identified which may influence the immune responsiveness and have a role in the tumor’s microenvironment related to its immunogenicity, particularly for carcinosarcomas. One of the proposed mechanisms could be the expression of PD-L1 in certain MSS tumors due to the formation of a neoantigen and the presence of tertiary lymphoid structures in the tumor microenvironment. (Haddox et al., 2024; Wu et al., 2024).

Furthermore, in our case, pembrolizumab was administered with careful monitoring to attain therapeutic benefits even in the presence of elevated liver function tests. Managing various adverse events of ICIs, the American Society of Clinical Oncology suggests close monitoring of patients with grade 1 toxicities except for some neurologic, hematologic, and cardiac toxicities, while it becomes imperative to suspend ICIs for grade 2 and 3 toxicities and use corticosteroids to prevent further damage.(Brahmer et al., 2018).

While this case offers valuable insights into the potential efficacy of pembrolizumab in microsatellite-stable (MSS) high-grade endometrial carcinosarcoma, there are several limitations that should be acknowledged. Notably, next-generation sequencing (NGS) was not performed, and therefore, tumor mutational burden (TMB) and other actionable genomic alterations remain unknown. Additionally, HER2 testing was not conducted on the original tumor specimen, as this was not routinely performed at the time of diagnosis. The initial pathology report confirmed the presence of both papillary serous and sarcomatous elements consistent with carcinosarcoma; however, a precise quantification of each component was not available. Despite these limitations, the sustained clinical response to pembrolizumab in the absence of typical predictive biomarkers such as MSI-H or dMMR underscores the need to further explore the immunogenic potential of select MSS tumors.

4. Conclusion

Through this case report, we highlight the notable long-term response to pembrolizumab in a patient with recurrent, metastatic MSS endometrial carcinosarcoma. Our patient remained disease-free even after five years after initiation of pembrolizumab therapy which highlights the necessity of reevaluating immunotherapy for rare, aggressive cancers with limited treatment options, such as endometrial

carcinosarcoma. Additional research is needed to explore the role of predictive biomarkers beyond MSI status to identify patients who can benefit from the use of ICIs in challenging cancer types like endometrial carcinosarcoma.

CRediT authorship contribution statement

Anaiya G. Singh: Writing – original draft, Project administration, Methodology, Investigation, Data curation. **Viraj S. Panchal:** Writing – original draft, Resources. **Suvarna Guvvala:** Writing – review & editing, Project administration, Conceptualization. **Richard P. Mansour:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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