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Case Report

Stage IV endometrial carcinoma: a case report on multiple biomarkers and the emerging role of immunotherapy

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ABSTRACT

Endometrial carcinoma (EC) is a common cancer with a poor prognosis in advanced stages. Despite recent development in therapies, the optimal choice for Stage IV EC with multiple mutations remains debated. Immunotherapy has come up as a promising approach, particularly targeting the PI3K/AKT/mTOR pathway, which is associated with aggressive disease. A 68-year-old African American female with a history of diabetes, hypertension, and postmenopausal bleeding was diagnosed with Stage IV B serous type endometrial carcinoma. Imaging revealed lung and lymph node metastases. The patient received 9 cycles of carboplatin and paclitaxel followed by a radical hysterectomy. Tumour profiling revealed HER2/neu amplification, PIK3CA, and TP53 mutations. Despite microsatellite stability (MSS) and proficient mismatch repair (pMMR), she was started on pembrolizumab (200 mg every 3 weeks) and lenvatinib (20 mg daily). The patient is currently in her third cycle and responding well to treatment. This case highlights the potential of immunotherapy in advanced EC with multiple biomarkers. Although pembrolizumab was initially approved for MSI-H/dMMR cases, its combination with lenvatinib has shown efficacy in pMMR/MSS patients. The case underscores the need for personalised treatment strategies based on molecular profiling, with emerging therapies targeting HER2, TP53, and PIK3CA.

Keywords: Endometrial carcinoma, Pembrolizumab, Lenvatinib, Immunotherapy

INTRODUCTION

Endometrial carcinoma (EC) is the fourth most common cancer in women in the United States. In 2024, approximately 68,000 new cases and 13,250 deaths were expected in the US alone.[1] The 5-year survival rate of EC significantly decreases as the stage progresses, with a rate of 86.3% for Stage I to 28.2% for Stage IV, according to the Danish Gynecological Cancer Group.[2]

Despite recent advances in systemic therapies, the optimal treatment approach for patients with Stage IV EC with multiple mutations remains a debate. As the pathogenesis of EC becomes clearer, it became evident that immune cells and cytokines play an anti-tumor role in the endogenous setting, making EC a good candidate for immunotherapy.[3]

It was recently shown that increased PI3K/AKT/mTOR signalling is associated with aggressive disease and poor prognosis regardless of EC type. This has led to the pursuit of the PI3K/AKT/mTOR pathway as a target for drug design in clinical trials.[4] In this case report, we describe a patient with Stage IV B endometrial carcinoma with HER2/neu, PIK3CA and TP53 positive biomarkers who is undergoing immunotherapy with pembrolizumab and lenvatinib. We discuss the rationale for this approach, clinical outcomes observed and highlight the other potential Immunotherapy agents in the management of this case.

CASE REPORT

A 68-year-old African American female with a medical history of type 2 diabetes mellitus, hypertension, hypercholesterolemia, and glaucoma presented to her primary care physician with symptoms of postmenopausal bleeding, white foul-smelling vaginal discharge, and a non-productive dry cough. She also reported occasional pelvic and vaginal pain that had been present for 2 months. The patient was sexually inactive. A pelvic ultrasound was performed which revealed a 10 cm heterogeneous fibroid uterus with an 8 mm thickened hyperechogenic endometrium as well as a 2.4 cm irregular fluid collection in the superior uterus. A pap smear performed during the same visit revealed the presence of atypical glandular cells, suggesting a possible neoplastic pathology.

A chest CT revealed multiple bilateral pulmonary nodules, suspicious for metastatic lesions. The patient underwent an endometrial biopsy which confirmed the presence of serous type endometrial adenocarcinoma. A whole-body PET/CT scan confirmed the diagnosis of stage IV endometrial carcinoma (cT1aN1M1) with a high suspicion of multiple pulmonary metastasis and left internal iliac regional lymph node metastasis. The definitive confirmation of the pulmonary metastasis was obtained via CT guided lung biopsy, which confirmed the presence of poorly differentiated serous papillary endometrial adenocarcinoma.

The patient was started on a neoadjuvant chemotherapy regimen consisting of 9 cycles of carboplatin and paclitaxel. The patient developed febrile neutropenia after the 6th cycle, hence the patient was given filgrastim and the chemotherapy was halted for 3 weeks. After the 9th cycle of neoadjuvant chemotherapy, a subsequent CT scan with contrast was performed on the chest, abdomen, and pelvis. The CT scan revealed a thickened and ill-defined endometrium measuring 3.3 cm, a fibroid uterus, a left internal iliac lymph node measuring 0.6 cm and numerous bilateral irregular solid nodules in the lungs measuring up to 7 mm.

Approximately 2 months after the completion of neoadjuvant chemotherapy, the patient underwent a radical hysterectomy. The pathology results revealed the presence of a high-grade endometrial carcinoma of mixed endometrioid and serous type, myometrial invasion (0.4 cm out of 1.1 cm) and extensive lymph vascular invasion. The results of tumour profiling are shown in Table 1. During postoperative month 1, the patient developed postoperative vaginal bleeding for which she received a short course of external radiation therapy (4000cGy) to the vagina in 15 fractions. The radiation therapy was administered in a 3-week cycle (5 days a week). The patient has been started on an immunotherapy regimen consisting of 200 mg IV pembrolizumab every 3 weeks for 12 cycles along with a 20 mg oral lenvatinib daily for 30 days, and she is currently in her 3rd cycle and is doing well.

Table 1: Tumour profiling of the post-surgical tissue sample.

Biomarker	Result
Mismatch repair status	Proficient (Intact)
MSI	Stable
ERBB2 (Her2/Neu)	Amplified
PIK3CA	Pathogenic variant exon 21 (p.H1047R)
TP53	Pathogenic variant exon 7 (p.R248W)
ER and PR	Negative
MLH1, MSH6 & MSH2	Intact nuclear expression
PD-L1 (SP142)	Negative
PTEN	Positive

DISCUSSION

In this case report, we present a female patient diagnosed with suspected stage IV endometrial cancer (EC) who underwent neoadjuvant systemic chemotherapy followed by a hysterectomy. The patient's imaging results showed possible inguinal lymph node metastasis as well as multiple bilateral pulmonary metastasis (T1aN1M1). The decision to initiate neoadjuvant chemotherapy, which consisted of 9 cycles of carboplatin and paclitaxel, was made in consideration of the patient's advanced age and multiple cardiovascular comorbidities, including type 2 diabetes mellitus, hypertension, and hypercholesterolemia.

This treatment approach is recommended by the National Comprehensive Cancer Network (NCCN) guidelines for advanced EC cases where primary debulking is not feasible.[5] A retrospective cohort study in the US demonstrated that surgery following chemotherapy resulted in significantly longer progression-free survival (PFS) and overall survival (OS) in advanced EC patients compared to no surgery. Another study showed that neoadjuvant chemotherapy followed by surgery had a higher short-term survival rate in women with metastatic EC compared to primary debulking surgery.[6,7]

Our patient had pMMR, MSS, ERBB2 amplification, and TP53 and PIK3CA mutations in her post-surgical tissue samples. Prior to May 2017, there was no standard of care for patients who failed frontline neoadjuvant chemotherapy. In May 2017, FDA approved single-agent pembrolizumab for MSI-H/dMMR EC.[8] Later in 2019, the FDA approved the combination of pembrolizumab and lenvatinib, with the KEYNOTE-775 trial showing significant improvement in PFS and OS among patients with advanced EC, regardless of MMR status.[9] Our patient was prescribed pembrolizumab 200 mg for 12 cycles and lenvatinib 20 mg PO for 30 days to reduce her mortality risk and treat any residual tumour following chemotherapy and surgery. HER2neu amplification, TP53 mutations, and PIK3CA mutation are also potential targets in our case. HER2 is often overexpressed in ECs, and some studies

have shown that targeting HER2 with paclitaxel, carboplatin, and trastuzumab can improve progression-free survival in advanced EC patients. TP53 mutations are associated with a poorer prognosis in advanced ECs, but there are currently no immunotherapy agents that specifically target TP53.[10,11] PIK3CA mutations are highly prevalent in EC, and various classes of agents, including rapalogs, PI3K isoform-specific inhibitors, and mTOR-specific catalytic inhibitors, are being developed to treat EC. A Phase 1a clinical trial by Juric et al, evaluated the safety and efficacy of alpelisib in breast and other PIK3CA gynaecological cancers. The trial found that only EC achieved a complete response with the targeted therapy.[12]

Precision medicine has shown promising results in gynaecological oncology for downstaging tumours in advanced-stage diseases. Predictive molecular biomarkers are expected to provide new therapeutic strategies for managing EC patients, improving efficacy and safety.

However, there is a lack of clear guidelines for treating EC patients with multiple druggable targets, and many questions remain unanswered. These include how to manage patients who are both Her2neu positive and pMMR positive, how to prioritise immunotherapy in patients with multiple targets, whether to administer multiple drugs concurrently, and whether alpelisib is effective in EC patients. Addressing these questions is crucial to improving patient care and outcomes.

CONCLUSION

A stage IV B EC patient with multiple genetic mutations, including HER2neu, PIK3CA, and TP53 positive, was treated with pembrolizumab and lenvatinib despite stable MSI and proficient MMR status. Preclinical evidence suggested these mutations may confer sensitivity to immunotherapy. Further studies are needed to explore the role of genetic testing in guiding treatment decisions for patients with MSS/pMMR EC. The multidisciplinary approach for EC involves various treatment modalities such as surgery, chemotherapy, and targeted therapy. Tumour profiling has provided important information about genetic defects for personalised treatment

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