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Recurrent high grade serous endometrial cancer with brain metastases: Immunotherapy confers improved quality of life and survival

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1. Introduction

In the United States, over 65,000 women are diagnosed with endometrial cancer annually (Bogani et al., 2021 Jul). In recent years; the incidence of endometrial cancer has been rising, and it is projected to continue to rise due to increased life expectancy, obesity, and the use of estrogen in hormone replacement therapy. High grade serous carcinoma of the endometrium accounts for over 40 % of cancer-related deaths despite representing less than 10 % of endometrial cancers (Bogani et al., 2021 Jul). The 5-year survival rate for stage III is 20–30 %; and stage IV is 5–15.

In patients with either type of endometrial cancer, the evidence of metastatic disease is an indicator of a poor prognosis. Common sites of metastases include the pelvic and *para*-aortic lymph nodes, lungs, bones, peritoneum, bladder, and rectum (Kurra et al., 2013). It is rare for this form of cancer to metastasize to the brain. The rates of metastasis are not well established; but one study found rates to be less than 3.2 % (Piura and Piura, 2012); and is the presence of brain metastasis is associated with low survival rates (Kurra et al., 2013).

Risk factors for disease recurrence include advanced stage, histological type, and lymphovascular space invasion (Anderson, 2003). Recurrence rates for Stage III and IV are 37.5 % and 66.7 %; respectively (Mahdy et al., 2024). Typical sites of recurrence are pelvic and *para*-aortic nodes; vagina, peritoneum, and lungs. Atypical sites are intra-abdominal organs, bones, brain, abdominal wall, and muscle (Kurra et al., 2013). Recurrence predominately occurs within 2–3 years following initial treatment; and treatment depends heavily on local vs distant recurrence (Anderson, 2003).

On average, patients with endometrial cancer with brain metastases often have a less than 2-month median survival rate after diagnosis without treatment. However, in patients who undergo whole brain radiotherapy (WBRT) alone, their median survival is 3 months. In patients who undergo multimodal therapy, including surgery and whole brain radiotherapy with close imaging follow-up, studies have shown that this can be extended to a median survival of 8 months (Kato et al., 2021).

Here, we present a case of a patient with recurrent high-grade serous adenocarcinoma of the endometrium with multiple brain metastases whose neurologic status remained intact, and brain metastatic lesions remained stable on immunotherapy for over two and a half years.

2. Case report

This 53-year-old woman was initially diagnosed with grade 2

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endometrioid endometrial adenocarcinoma. She underwent surgical staging with robotic hysterectomy, bilateral salpingo- oophorectomy, bilateral pelvic sentinel node biopsy, and bilateral pelvic and periaortic node dissection. Final pathology showed stage IIIC2 high grade serous endometrial adenocarcinoma with 2 positive left *para*-aortic lymph nodes. Tumor testing revealed intact expression of mismatch repair proteins: MLH-1, MLH-2, MSH-6, PMS-2. Molecular profiling of the tumor revealed HER2/neu positive, ER/PR negative TP53 mutated, and PDL1.

Following surgical staging the patient received adjuvant sandwich therapy, which included three cycles of carboplatin and paclitaxel, followed by whole pelvic radiation and then three additional cycles of carboplatin and paclitaxel.

Twelve months following completion of therapy, the patient presented to her gynecologic oncologist with vague gastrointestinal symptoms. The work up uncovered post-operative seromas that required drainage and new lung lesions. She underwent biopsy of the lung lesion, which confirmed recurrent high grade serious carcinoma of the endometrium. The patient was enrolled on a clinical trial where she received 6 cycles carboplatin and paclitaxel as well as the investigational drug AL3818 followed by 8 cycles of maintenance therapy with AL3818 (anlotinib) only. This drug is a receptor tyrosine kinase inhibitor that has multiple targets including vascular endothelial growth factor receptors, platelet derived growth factor, fibroblast growth factor, and more.

While still on maintenance therapy, 9 months after last chemotherapy, the patient developed neurological symptoms. She presented to the Emergency Department with significant dizziness, generalized weakness, gait instability, and headaches. Neurologic work-up revealed several metastatic lesions (Fig. 1) in the left posterior temporal lobe and right cerebellar hemisphere and mild T2 FLAIR hyperintensity in the left posterior temporal lobe. The patient's lesions were deemed to be inappropriate for surgical intervention. The recommendation and subsequent choice of treatment was to continue with WBRT followed by systemic therapy. She underwent WBRT for two weeks and received 30 Gy (Gy) of WBRT in 10 fractions. In addition to the WBRT, she was prescribed six months of memantine to aid in cognitive preservation due to the inability to spare the hippocampus in her WBRT treatment plan.

Following WBRT, the decision was made for our patient to begin immunotherapy with oral lenvatinib 20 mg daily and pembrolizumab 200 mg infusions every three weeks. Like AL3818 (anlotinib), lenvatinib is also a receptor tyrosine kinase inhibitor with several drug targets whereas pembroluzumab is a PD-1 checkpoint inhibitor. While on immunotherapy, our patient continued to have evidence of lesion stability of her brain metastases on surveillance scans every three months. Fifteen months after the diagnosis of brain metastases and initiation of immunotherapy, our patient began to have a growth of single nodules in her lungs that underwent treatments of stereotactic body radiation therapy (SBRT) at one month, seven months, and 11 months following discovery of the initial lung lesion. All lung lesions were radiated with 50 Gy in 5 fractions. Additionally, she had an isolated liver lesions identified and treated with SBRT at 6 months and 11 months following discovery of the lung lesion. The liver lesions also received 50 Gy in 5 fractions. Patient continued lenvatinib and pembrolizumab throughout radiation therapy. Her clinical status remained stable during this time, and in Fig. 2, one can see the patient's brain metastases in the left posterior temporal lobe and right cerebellar hemisphere as well as the T2 FLAIR hyperintensity in the left posterior temporal lobe remain largely unchanged on surveillance imaging.

Following 31 months of immunotherapy, and four months after our patient's last SBRT treatment to lung nodules, the patient's lung function began to significantly decline. She was hospitalized with bilateral pleural effusions with significant progression of disease in her lungs. Given the clear progression, the immunotherapy was discontinued. Her performance status rapidly declined, and she pursued hospice care and passed away in peace at home with her family at her side.

In total, she received a total of 44 cycles of lenvatinib and pembrolizumab. During this time, she had minimal neurologic deficits and maintained a good quality of life. She was able to ambulate, speak, and recall short- and long-term memories as well as perform her activities of daily life with minimal assistance. One month prior to her passing and thirty-two months following initial diagnosis of her brain metastases, she received her routine MRI brain (Fig. 3) which revealed her brain metastases to the left posterior temporal lobe and right cerebellar hemisphere and T2 FLAIR hyperintensity in the left posterior temporal lobe remain unchanged on lenvatinib and pembrolizumab throughout her disease progression.

3. Discussion

Metastases to the brain from all endometrial cancers is rare with an incidence of roughly 0.7 % and only 1100 total documented cases in the literature (Kato et al., 2021). The prognosis for patients with endometrial cancer once they have been found to have brain metastases is very poor as many patients' neurocognitive capabilities decline rapidly.

Bhambhvani et al. evaluated 158 patients with primary endometrial cancer across 11 studies and found that the median survival for patients once they were diagnosed with brain metastases was 4.5 months (Bhambhvani et al., 2021). On average; the median number of brain

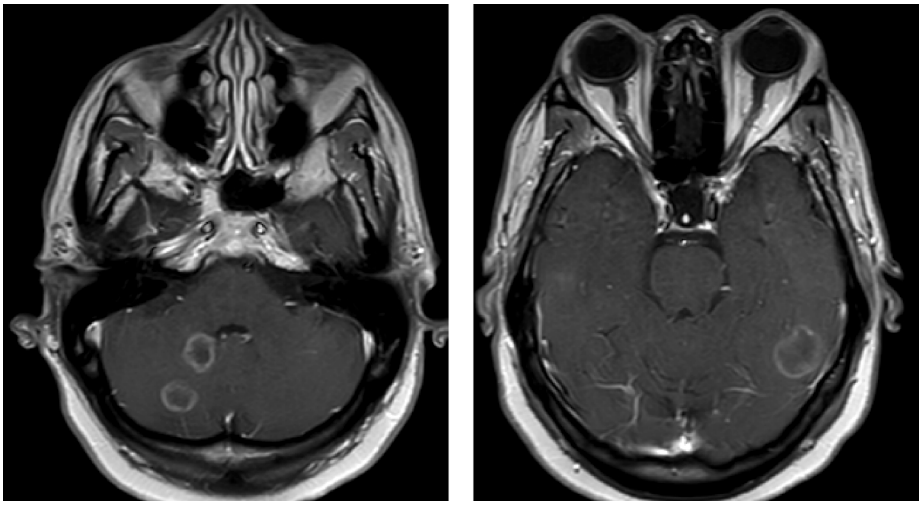

Fig. 1. September 23, 2020 Patient's initial axial T2 MRI brain demonstrating evidence of metastatic disease to the brain. Lesions are present within the left posterior temporal lobe and right cerebellar hemisphere. T2 FLAIR hyperintensity present in the left posterior temporal lobe.

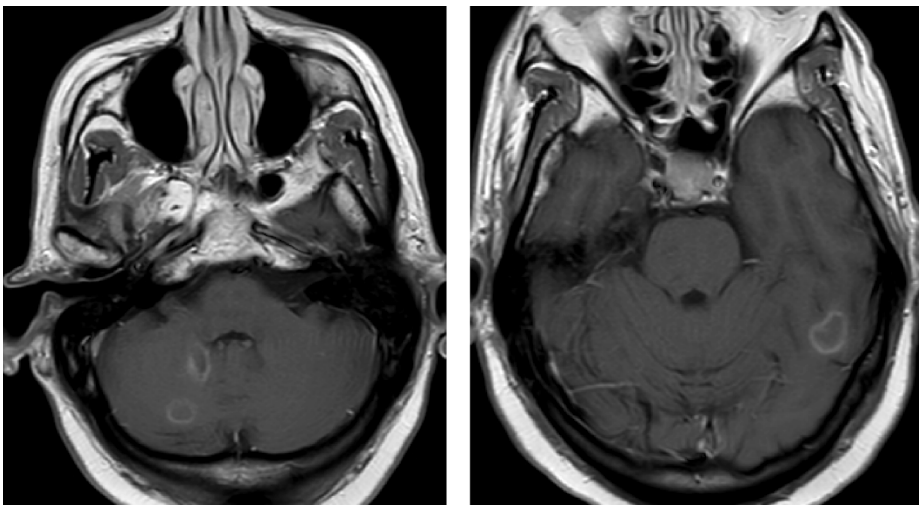

Fig. 2. December 9, 2020 Patient's T2 axial MRI brain status post whole brain radiotherapy (WBRT) displaying lesion stability within the left posterior temporal lobe and right cerebellar hemisphere and unremarkable chanced in the T2 FLAIR hyperintensity in the left posterior temporal lobe.

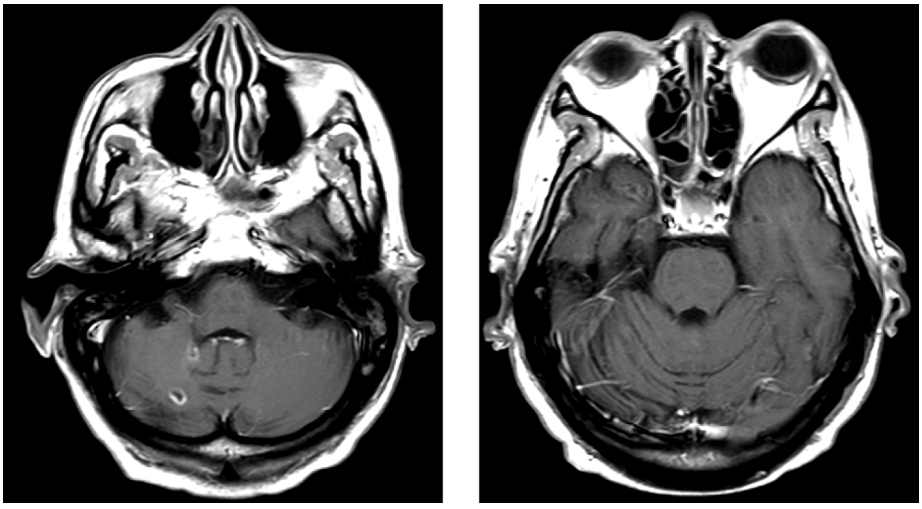

Fig. 3. June 22, 2023 Patient's final axial T2 MRI brain one month prior to passing secondary to declining lung function. This image depicts minimal changes to her left posterior temporal lobe and right cerebellar hemisphere lesions and mildly decreased T2 FLAIR hyperintensity in the left posterior temporal lobe.

metastases was 1.75 lesions. Survival in patients with a single metastatic brain lesion was longer than those with multiple lesions (Kato et al., 2021). There have been multiple studies that displayed evidence for chemotherapy not being effective at improving long-term treatment outcomes in patients with endometrial cancer with brain metastases (Nakagawa et al., 1996). Historically; brain metastases were treated via surgical resection with or without whole brain radiotherapy. Previous studies have showed that increased survival times were more closely associated with surgical tumor removal and whole brain radiotherapy combined when compared to whole brain radiotherapy and chemotherapy. However; not all patients are surgical candidates and those who are surgical candidates may undergo various post-operative complications such as hemorrhage or infection. Thus, WBRT can be utilized as a safer alternative to help slow disease progression. When undergoing WBRT, radiation oncologists design their treatment plans to spare the hippocampus to preserve neurocognitive function (Brown et al., 2020). However; due to the location of this patient's lesions, the hippocampus was unable to be avoided. Given this, our patient concurrently took memantine for 6 months (Duman et al., 2018). Memantine has been demonstrated to be neuroprotective against neurocognitive side effects of brain radiation. In our case; our patient tolerated radiotherapy well and remained neurologically intact without neurocognitive deficits. Despite surgery and WBRT being our current standard practice for treatment, survival is only extended by a median of approximately six months (Kato et al., 2021). Recently; there have been studies to investigate the possibility of using immunotherapy to treat brain metastases and prolong life expectancy. Currently, the standard systemic treatment in patients with recurrent endometrial cancer that is MMR proficient who have progressed after systemic chemotherapy is lenvatinib and pembrolizumab (Mimura et al., 2022). However; there is a paucity of literature describing the effects of immunotherapy on brain metastases.

One of the main challenges to effective drug delivery to the brain is being able to penetrate the blood brain barrier. Current treatment methods of penetrating the blood brain barrier include WBRT and stereotactic radiation therapy like gamma knife therapy (Mehta et al., 2005). These methods target tumors with high doses of radiation and are most effective for small to medium sized lesions. However; the number of lesions is also a factor when deciding which method to utilize (Zhu et al., 2014). In addition to radiation therapies; there are chemotherapeutic options like temozolomide, which is often used to treat glioblastoma, tyrosine kinase inhibitors, or immune checkpoint inhibitors (Mimura et al., 2022; Zhu et al., 2014).

In this case, our patient received radiation, a tyrosine kinase inhibitor, and an immune checkpoint inhibitor as was taking lenvatinib, a vascular endothelial growth factor (VEGF) inhibitor, and pembrolizumab, a PD-1 inhibitor. There is potential for VEGF inhibitors to be effective against brain lesions. It is hypothesized that the brain metastases disrupt the relationship between the astrocyte-endothelial relationship resulting in abnormal vessels allowing them to be distinguishable from normal vessels (NCI, 2016);. This allows for the VEGF inhibitor to accurately identify which vessel receptors to bind to. Currently, there is a limitation in the literature regarding the ability of VEGF and PD-1 inhibitors being able to penetrate the blood brain barrier. There are clinical trials such as the DEFINITY trial researching the ability of pembrolizumab crossing the blood brain barrier (Cormio et al., 1996 Apr). In our case; the patient's treatment regimen maintained her brain metastases for over 2.5 years.

Quality of life for patients with brain metastases can be significantly diminished. Many begin to have generalized weakness, gait instability, and cognitive dysfunctions. Other patients have complained of difficulty with balance, dizziness, confusion, visual disturbances, and seizures [20]. Many patients report having difficulties performing their activities of daily life and require additional assistance whether it be familial involvement, home health, or a skilled nursing facility. Despite being diagnosed with metastatic disease to the brain, this patient did not have many persistent neurologic deficits after initiating treatment. She was able to continue living independently and perform her activities of daily life. This is unique as she was not a surgical candidate and had greater than 2 lesions. These are both prognostic indicators for reduced survival (Kato et al., 2021).

Here we, present a case that adds to the literature by displaying evidence of a patient with recurrent high grade serous carcinoma of the endometrium with lung and brain metastases and multiple negative prognostic indicators who was able to have stability of brain metastases and live for over 2.5 years with a good quality of life. Immunotherapy may contribute to prolonged survival in these patients; however, there needs to be more investigation in order to better understand the treatment effects within the brain.

CRediT authorship contribution statement

Kierany B. Shelvin: Writing – original draft, Data curation, Conceptualization. **Jill Vincent:** Writing – review & editing. **Shawna Morron:** Writing – review & editing, Data curation. **Michael Morin:** Writing – review & editing. **Aaron Mammoser:** Writing – review & editing. **Navya Nair:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Navya Nair is an editorial board member for Gynecologic Oncology Reports and serves on the SGO Board of Directors and is Chair of the SGO Diversity, Inclusion, and Health Equity Committee].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101494.

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