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Case Report

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Uncharted Territory: Journey of a Mullerian Tumor to the Brain, A Case Report

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ABSTRACT

Introduction: Ovarian cancer is one of the most common gynecological cancers in the United States. Common sites of distant metastasis from ovarian cancers and other cancers of Mullerian origin include the liver, pleura and lungs. However, metastasis to the brain remains exceptionally rare, ranging from 0.49 to 6.1%. Hence, the scarcity of such cases poses significant diagnostic and management challenges.

Case Presentation: We present a case of an 80-year-old female who at the time of initial diagnosis presented with complaints of right leg pain, shortness of breath and cough. Imaging studies were remarkable for a pulmonary embolism, 2.5 cm mediastinal mass, pleural effusions, omental caking and an occlusive thrombus in the right greater saphenous vein. Malignancy was suspected in the setting of hypercoagulability. Biopsy of the omentum and pleural cytology revealed a high grade ovarian serous carcinoma. The patient received neoadjuvant chemotherapy followed by cytoreductive surgery and additional chemotherapy afterwards. She demonstrated good response to treatment with follow up PET without evidence of disease. Over the next four years, the patient was intermittently placed on chemotherapy when found to have elevated CA125 levels and PET scan showing small volume disease mostly in the pelvis.

Six-years later, the patient presented to the oncology clinic with complaints of dizziness and imbalance for the past month. MRI brain showed a new left cerebellar mass with vasogenic edema and obstructive hydrocephalus. However, restaging CT chest, abdomen and pelvis showed minimal to no disease, with the only possible foci being a 1.2 cm paraaortic lymph node. The patient underwent left suboccipital craniotomy and cerebellar tumor resection with pathology showing metastatic carcinoma consistent with spread from a Mullerian primary.

Conclusion: This case emphasizes the diagnostic complexity and evolving clinical course of Müllerian tumors. In a patient with a history of Mullerian tumor and new onset neurological symptoms, differential diagnosis should include metastasis to the brain, even with minimal to no active pelvic and systemic disease burden.

Keywords: Intracranial Metastasis, Mullerian Brain Metastasis, Mullerian Brain Tumor, Mullerian Tumor, Case Report

Introduction

Historically, carcinomas of the ovaries, fallopian tubes, and peritoneum were treated as distinct clinical entities. However, recent advancements in molecular biology and histopathology have demonstrated a shared origin in the Müllerian epithelium, leading to their reclassification as a spectrum of Müllerian-derived tumors. This understanding prompted the 2014 revision of the FIGO staging system, which now encompasses ovarian, fallopian tube, and primary peritoneal carcinomas under a unified framework [1,2].

High-grade serous carcinoma (HGSC) is the most prevalent and aggressive subtype, representing more than 70 percent of all epithelial ovarian cancers. It typically presents at an advanced stage, often with widespread peritoneal dissemination, ascites, pleural effusions, and involvement of the omentum [3,4]. Thromboembolic events, including deep vein thrombosis and pulmonary embolism, are common initial manifestations and are attributable to the hypercoagulable state associated with malignancy [5,6].

While peritoneal and thoracic metastases are well recognized in HGSC, central nervous system (CNS) involvement remains rare. Brain metastases occur in fewer than 2 percent of cases,

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typically in patients with high-grade tumors and advanced-stage disease [7,8]. These metastases may present metachronously, often several years following initial diagnosis and apparent remission. Clinical presentation can be nonspecific, leading to delayed recognition and diagnosis [9].

Therapeutic management of brain metastases from Müllerian tumors poses significant challenges due to the restrictive nature of the blood-brain barrier, which limits the efficacy of many systemic chemotherapeutic agents [10]. Consequently, treatment is often multimodal and tailored to individual patient factors, including performance status, extent of CNS and systemic disease, and presence of neurologic compromise.

We present a case of FIGO stage IV high-grade serous carcinoma that recurred as an isolated cerebellar metastasis years after initial remission, with minimal systemic or pelvic disease burden at the time of intracranial metastasis. This case highlights the atypical metastatic pattern and underscores the importance of considering CNS involvement in patients with Müllerian tumors presenting with new neurologic symptoms.

Case Presentation

An 80-year-old female with a medical history of diverticulosis and benign paroxysmal positional vertigo (BPPV) initially presented to the hospital in 2017 with right leg pain, shortness of breath (SOB), and cough. Initial evaluation at the time revealed a left pleural effusion, atelectasis, and a 2.9 cm prevascular mass. Subsequent imaging identified a mild pulmonary embolism, bilateral pleural effusions, ascites, and a thrombus in the right greater saphenous vein. Anticoagulation with heparin was initiated, and the patient was referred to hematology-oncology for further evaluation of suspected malignancy in setting of hypercoagulable state.

The patient underwent an omental biopsy which confirmed the diagnosis of high-grade serous carcinoma. She was then started on neoadjuvant chemotherapy, followed by cytoreductive surgery. Post-treatment PET imaging demonstrated no evidence of disease, with CA-125 levels significantly reduced.

Six years after the initial diagnosis, the patient presented to the oncology clinic for follow up, however now reported new-onset dizziness and loss of balance. The patient was admitted to the hospital and a brain MRI was performed which revealed a 3.5 × 3.2 × 2.2 cm left cerebellar mass associated with vasogenic edema (Image A) and obstructive hydrocephalus (Images B & C). In light of above findings, neurosurgery was consulted and she underwent left suboccipital craniotomy and tumor resection. Pathology of the intracranial mass confirmed metastatic high-grade mucinous carcinoma consistent with a Müllerian primary. Restaging CT chest showed no evidence of metastatic disease. CT abdomen and pelvis demonstrated postsurgical absence of the uterus and ovaries, and a nonspecific 1.2 cm paraaortic lymph node-overall consistent with minimal systemic or pelvic disease burden.

A detailed risk versus benefit discussion was carried out with patient and family and a decision was made to treat the patient with a trimodal approach including emergent surgery, followed by fractionated stereotactic radiation to the surgical bed and chemotherapy.

About a year later, the patient presented to the ED with complains of excruciating abdominal pain. CT abdomen pelvis revealed a circumferential obstructing mass at the cecum, several perirectal lymph nodes, mechanical small bowel obstruction due to cecal mass, lateral left costophrenic angle pleural-based nodule measuring 11x 7 mm, and new 5 mm right lower lobe anterior basal pulmonary nodule. Surgical oncology was consulted who determined patient was not a surgical candidate. Palliative care was consulted, and after multiple goals of care discussion, the patient and family decided to transition to hospice care.

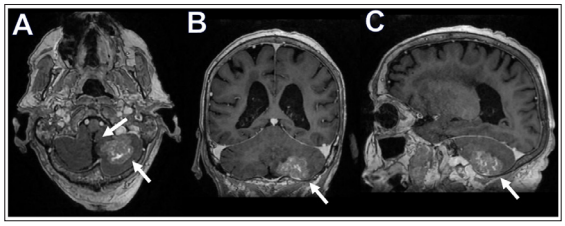

Image A: Inferior Left Cerebellar Mass with Surrounding Vasogenic Edema Causing Mass Effect on the Fourth Ventricle

Image B and Image C: Cerebellar Mass Causing Mild Obstructive Hydrocephalus

Discussion

Ovarian cancer is the second most common gynecological cancer in the USA, and has shown to result in more deaths than any other cancer of the female reproductive system [11]. Approximately 90% of ovarian cancers are malignant epithelial tumors or carcinomas, with High-Grade Serous Carcinoma (HGSC) being the most common subtype, accounting for around 70% of all cases [3-8]. However, due to the indolent and aggressive nature of the disease, 80% of patients are diagnosed with advanced metastatic stage disease at the time of diagnosis [5-9].

Common sites of distant metastasis from cancer of Mullerian origin include the liver, pleura and lungs. The spread of these cancers is widely believed to occur via peritoneal circulation through ascites formation or by direct extension [5-6]. Therefore, accumulation of ascites can significantly increase the likelihood of metastatic disease [6]. Development of brain metastasis from a Mullerian primary tumor is rare, ranging from 0.49 to 6.1%, but seen more commonly in patients with high grade tumors categorized at higher stages per the FIGO staging system [7-9]. In fact, a literature review by Borella et al. showed that most patients with ovarian cancer with metastasis to the brain, had a high-grade serous carcinoma as the primary tumor, followed by the endometrioid, mucinous and clear cell histotypes [7]. In a study conducted by Cohen et al, where 8225 patients with ovarian cancer were studied, showed that brain metastasis developed in only 0.9% of the patients. Out of these, 83% were those diagnosed with high grade ovarian tumors and 81% of the total patients the cancer was categorized as FIGO stage 3 or 4 at time of initial diagnosis [8]. Similarly, our patient was also diagnosed with stage IV high grade serous carcinoma on initial presentation which based on previous literature like mentioned above, increases risk of intracranial metastasis. However, what sets our case apart is the relatively rare phenomenon of Mullerian brain metastasis in the presence of minimal pelvic and systemic disease burden. Whereas, a literature review by Pakneshan et al. showed that at the time of diagnosis of intracranial metastasis, the

majority of the patients (57.3%) had multiple brain lesions, with concurrent extracranial metastasis in 49.8% of cases involving liver (20.7%), lung (20.4%), lymph nodes (12.6%), bones (6.6%) and pelvic organs (4.3%) [12]. Whereas, in our patient's case, at the time of diagnosis of intracranial disease, the patient's restaging CT chest abdomen and pelvis was remarkable for only minimal to no disease, with the only other area of possible active disease being a nonspecific 1.2 cm para-aortic lymph node. This phenomenon underscores the importance of maintaining a high suspicion of intracranial metastasis for any patient with a history of Mullerian tumor presenting with new onset neurological symptoms, irrespective of extracranial disease burden.

However, regardless of disease burden at time of diagnosis, overall prognosis for patients with metastasis of ovarian cancer to the brain has been noted to be poor, with median survival time of 6.27 months (95% CI, 4.48-8.06 months) after diagnosis of intracranial metastasis [8,9]. Therefore, the main goal of treatment is to help alleviate neurological symptoms and improve quality of life [9,10]. Available treatment modalities include surgery, radiation either Whole Brain Radiation Therapy (WBRT) or Gamma Knife Radiation Surgery (GKRS), chemotherapy, immunotherapy and PARP inhibitors [7-10]. WBRT for many years was considered the mainstay of treatment for metastasis to the brain, allowing it to target both macro and microscopic lesions, therefore remains the treatment of choice for patients with multiple brain lesions [7]. Cohen at al., showed that a combination of surgical resection and whole-brain radiation therapy (WBRT) resulted in a longer survival time (median, 23.07 months) than did WBRT alone (median, 5.33 months) or surgery alone (median, 6.90 months) [8] On the other hand, patients with single lesions who are not surgical candidates, GKRS may be the preferred modality [7-9]. In fact, a retrospective review by Lee et al., revealed that treatment with GKRS resulted in a longer survival time (median, 29 months) than those treated with WBRT (median, 6 months) ($p = 0.0061$), regardless of number of metastases [10].

Finally, the role of chemotherapy in the treatment of brain metastasis remains controversial, due to the inability of many drugs to cross the Blood Brain Barrier (BBB). For the most part, treatment of Mullerian cancers include intravenous administration of carboplatin plus paclitaxel every 3 weeks [4,7]. For recurrent disease i.e. after more than 6 months of disease-free interval, a platinum-based regimen can be proposed especially due to its ability to cross the BBB [4-7]. On the other hand, in refractory cases, pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, trabectedin or weekly paclitaxel, eventually with the addition of an anti-angiogenetic drug, can be considered [4-7]. However, due to a lack of a universally accepted standard of care in cases of Mullerian cancers with metastasis to the brain, treatment is usually patient-centered. Our patient was treated with a trimodal therapy approach including emergent surgery, followed by followed by fractionated stereotactic radiation to the surgical bed and chemotherapy, as research shows, that a combination of surgery with radiation improves outcomes, with median survival up to 20 months to 23 months [6-13]. However, prognosis still varies case by case keeping in mind other factors such as age, functional status and other comorbidities.

Conclusion

This case highlights the rare but important potential for CNS metastases in high-grade serous carcinoma (HGSC) of Müllerian origin, even after prolonged remission and minimal pelvic disease burden. The patient, initially diagnosed with FIGO stage IV disease, responded well to standard therapy and remained in remission for nearly six years. However, she later developed neurological symptoms, and imaging revealed a solitary cerebellar metastasis with obstructive hydrocephalus.

Surgical resection confirmed metastatic Müllerian carcinoma, illustrating that brain metastases can present as delayed, isolated events in HGSC. Due to the limited penetration of systemic therapies across the blood-brain barrier, CNS involvement poses unique diagnostic and therapeutic challenges.

This case underscores the need for continued surveillance regardless of remission, multidisciplinary management involving neurosurgery, oncology, and radiation and greater awareness of neurological progression despite minimal or no pelvic disease burden. Clinicians should remain vigilant for atypical metastatic patterns, particularly in patients presenting with new neurologic symptoms, regardless of systemic disease control.

Disclosures

Conflicts of Interest: The above listed authors have no conflicts of interest to declare.

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