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Case report

Metastatic epithelial ovarian cancer to Meckel's cave with leptomeningeal spread at time of diagnosis



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ABSTRACT

Background: Brain metastasis occurs in 1–2.5% of epithelial ovarian cancer (EOC) cases and carries a poor prognosis. Typically, brain metastases arise 2–3 years following the primary diagnosis of EOC. Malignant spread to the brain discovered at the time of initial ovarian cancer presentation is exceedingly rare with minimal reported cases in literature.

Case: This is a rare case of highly aggressive EOC in a previously healthy 32-year-old woman with evidence of brain, bone, and vertebral metastasis at the time of initial diagnosis. This is the first reported case of EOC with spread to Meckel's cave with symptoms consistent with trigeminal nerve disruption. The disease rapidly progressed through radiation and front-line chemotherapy.

Conclusion: This report highlights the first reported case of EOC with invasion of Meckel's cave—present at time of diagnosis. Consistent with most cases in the literature of brain metastasis in the setting of EOC, our patient had a highly aggressive tumor associated with a poor prognosis. With better primary management of EOC, along with increased overall survival in EOC patients following spread to the brain secondary to multimodal therapies, we can continue to expect increasing numbers of brain metastasis with uncommon sites of recurrence.

1. Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecologic malignancy in the United States with an incidence of 22,530 new cases annually as of 2019 (EER Cancer Stat Facts, 2020). EOC is a highly aggressive malignancy with the majority of cases presenting with disease spread beyond the ovary at the time of diagnosis. Brain metastasis are rare in ovarian cancer; with an estimated incidence of 1–2.5% (Mayer et al., 1978; Pectasides et al., 2006). Patients with EOC-associated brain metastases have a poor prognosis with a median overall survival ranging between 6 and 12 months. Typically, brain metastases arise 2–3 years after the diagnosis of ovarian cancer. Brain metastasis discovered at the time of initial ovarian cancer presentation is exceedingly rare with minimal reported cases in literature (Izquierdo et al., 1992; Matsunami et al., 1999).

Ovarian cancer with brain metastases most commonly involves the cerebral hemisphere, but spread to the cerebellum, falx cerebri and spinal cord has also been reported (Pectasides et al., 2006). Tumors of

Meckel's cave—a dural recess in the posteromedial portion of the middle cranial fossa which incorporates the proximal rootlets of the trigeminal nerve—are exceptionally rare. Meckel's cave tumors make up less than 1% of all intracranial tumors with the most common being primary tumors including trigeminal schwannomas and meningiomas (Mewes et al., 2001). Metastatic disease to Meckel's cave is even more rare. Only a handful of cases have ever been reported in the literature with primary malignancy sites including breast, colon, kidney, prostate, lymphocytic, thyroid, esophagus, cervix, and endometrium. (Hooker et al., 2018; Soni, 2010; Reshko, 2018; Cerase, 2011; Wang et al., 2016; Sudha et al., 2019). Here we describe a report of a young woman with metastatic EOC to the femur, vertebrae, and Meckel's cave with leptomeningeal spread, all found around the time of initial diagnosis. This is the first reported case of ovarian cancer with metastasis to Meckel's cave.

2. Case report

A 32-year-old nulligravida woman with no prior medical history

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initially presented to her primary care provider with complaints of lower back pain, abdominal bloating, and urinary changes. The patient underwent magnetic resonance imaging (MRI) of the spine to evaluate for suspected disc herniation, however, the MRI revealed a 3.0×2.3 cm enlarged, left periaortic lymph node. She then underwent computed-tomography (CT) imaging of the abdomen and pelvis demonstrating a $14.3 \times 10.0 \times 10.4$ cm adnexal mass with malignant appearing retroperitoneal and left pelvic sidewall lymphadenopathy and omental caking (Fig. 1A). Her CA125 was 437.0 U/mL. Positron Emission Tomography (PET) demonstrated multiple hypermetabolic osseous lesions in the axial and appendicular skeleton suspicious for metastatic disease with L1 and L3 lesions possibly extending into the spinal canal; PET imaging also showed hypermetabolic mesenteric, retroperitoneal and pelvic lymph nodes (Fig. 1D).

The patient had a biopsy of a left retroperitoneal lymph node showing metastatic serous adenocarcinoma consistent with Mullerian primary origin. Immunohistochemistry was positive for CK5, CK7, PAX8, p53, WT1 and negative for TTF1, CDX2, CK20, OCT4 and GATA3. The patient underwent multi-gene panel germline genetic testing which was negative for any pathogenic variant including *BRCA1/2*. Tumor profiling demonstrated that the tumor was mismatch repair proficient, microsatellite stable and had somatic mutations in *PTEN*, *SUFU*, *TP53*.

The patient was treated with radiation therapy to palliate her back pain. Radiation was administered to L1-L5 and her left proximal femur to 2000 cGy in 5 fractions. She then received systemic chemotherapy, Carboplatin and Paclitaxel with Zoledronic Acid due to her known bone metastases. Roughly six weeks after initial presentation, and two days after receiving her first cycle of chemotherapy, she began to experience new facial numbness of the right cheek along the V2-3 distribution, along with paresthesia of the upper extremities bilaterally. MRI of the brain demonstrated an enhancing tumor within the right Meckel's cave measuring up to 1.3×0.6 cm with abnormal enhancement of the right trigeminal nerve consistent with leptomeningeal spread (Fig. 1C-1D). She underwent a lumbar puncture and cerebral spinal fluid was negative for carcinoma. The lumbar puncture was repeated four weeks later with and the cerebral spinal fluid was positive for malignant cells consistent with adenocarcinoma.

The patient completed three cycles of carboplatin, paclitaxel, and zoledronic acid. Her CA125 trend continued to climb to 2,253.0 U/mL following the third cycle. Additionally, her neurologic symptoms continued to worsen. Repeat brain MRI demonstrated new left sigmoid sinus and transverse sinus thrombosis for which she was started on therapeutic enoxaparin. Brain radiation was considered, however, because the patient's clinical status rapidly deteriorated, she was not a

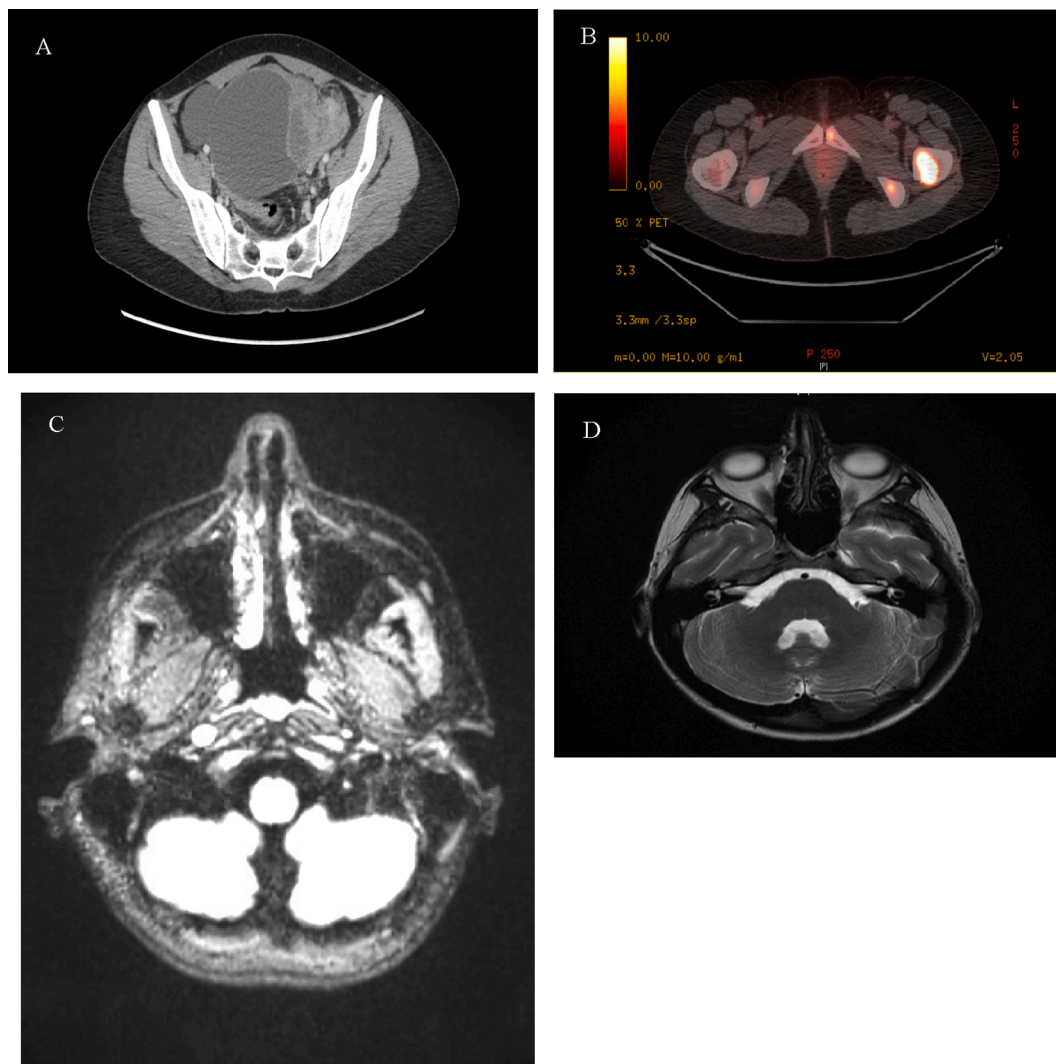


Fig. 1. A computed-tomography (CT) imaging of the abdomen and pelvis demonstrating a $14.3 \times 10.0 \times 10.4$ cm adnexal mass with malignant appearing retroperitoneal and left pelvic sidewall lymphadenopathy with omental caking. B. Positron Emission Tomography (PET) demonstrated multiple hypermetabolic osseous lesions in axial and appendicular skeleton suspicious for metastatic disease with L1 and L3 lesions, lesion of left femur. D MRI of the brain with and without contrast showed an enhancing tumor within the right Meckel's cave measuring up to 1.3×0.6 cm with abnormal enhancement of the right trigeminal nerve.

candidate for other treatment modalities. At 12 weeks from her initial diagnosis she presented to the emergency room in septic shock and passed from respiratory failure two days after hospital admission.

3. Discussion

This is a rare case of highly aggressive EOC in a young, previously healthy 32-year-old woman with evidence of brain, bone, and vertebral metastasis at the time of initial diagnosis. There are several important aspects of this case to consider. First, this is the only published report of ovarian cancer with metastatic spread to Meckel's cave, which presented with symptoms consistent with trigeminal nerve disruption. The average time between diagnosis of ovarian cancer and metastasis to the brain has been reported as roughly 31 months (Stasenکو et al., 2019). In this case, brain metastasis with leptomeningeal spread occurred simultaneously with the primary diagnosis of cancer, something that has rarely been described with less than a handful of reported cases in current literature (Izquierdo et al., 1992; Matsunami et al., 1999). Additionally, this disease progressed rapidly through radiation and chemotherapy. The patient experienced a ten-fold increase in CA125 level after three cycles of first-line chemotherapy with carboplatin and paclitaxel.

Meckel's cave is a natural mouth-shaped aperture in the medial portion of the middle cranial fossa—connecting the cavernous sinus to the prepontine cistern of the posterior fossa. This tiny parasellar structure acts as a key conduit for the trigeminal nerve (CN V), the largest trigeminal nerve. Meckel's cave also contains the three postganglionic rootlets of the trigeminal nerve—ophthalmic (V1), maxillary (V2) and mandibular (V3)—all of which provide sensory innervation to the face and motor function for mastication (Malhotra et al., 2018). MRI is the preferred imaging modality to assess Meckel's cave; protocol should include imaging in three planes with T1- and T2-weighting, short-tau inversion recovery (STIR) and gadolinium-enhanced T1-images with fat suppression (Borges, 2008). Accurate neuroimaging of Meckel's cave and surrounding structures is essential for the early detection of perineural spread of malignancy which impacts prognosis and management (Malhotra et al., 2018).

Metastatic spread to Meckel's cave is hypothesized to occur either from hematogenous dissemination versus perineural invasion from head and neck tumors (Soni, 2010). As the central nervous system (CNS) does not have lymphatic channels, metastasis from distant organs typically reaches Meckel's cave via hematogenous routes. Although the blood brain barrier (BBB) is effective at keeping out infection and therapeutic agents, it is ineffective at preventing the passage of circulating metastatic cells. There are several theories as to how certain malignancies, including ovarian cancer, cross the BBB including disruption of endothelial cells lining the CNS which increases vascular permeability and metastatic cells causing ischemia along the CNS which leads to cerebral auto-regulation and increased vascular permeability (Stewart et al., 1987; Hirano and Zimmerman, 1972).

At this time, there have only been two gynecologic malignancies reported to have metastatic spread to Meckel's cave. In 2018, Hooker et al. described a case of large cell neuroendocrine carcinoma of the cervix. This patient presented with dental pain, diplopia, and facial droop. She received palliative radiation to her brain for symptomatic control. Due to a decline in functional and mental status, she was not a candidate for chemotherapy. Comfort care was pursued and the patient died two months after diagnosis. (Hooker et al., 2018) The second reported case was in 2019, Sudha et al. describe a case of endometrioid type adenocarcinoma of the endometrium. This patient presented with post-menopausal bleeding as well as pain and numbness of the right cheek and chin. She was treated with palliative whole brain and pelvic tumor radiation with improvement in symptoms and vaginal bleeding; she was asymptomatic at 8 months of follow up. (Sudha et al., 2019)

There have been minimal reported cases of ovarian cancer with brain metastasis at the time of primary diagnosis. In 1992, Izquierdo et al.

described a case of a 60-year-old woman with papillary adenocarcinoma of the ovary with distant spread to the right frontoparietal lobe; she underwent craniotomy with complete resection, total hysterectomy, bilateral salpingo-oophorectomy, six cycles of cisplatin and cyclophosphamide, and whole brain radiation. The patient was without evidence of recurrence at 24 months of follow-up (Izquierdo et al., 1992). In 1999, Matsunami et al. reported a 36-year-old woman with poorly differentiated adenocarcinoma of the ovary (endometrioid type) with invasion of the left frontal lobe. She underwent left frontooccipital craniotomy with resection, total hysterectomy, bilateral salpingo-oophorectomy followed by intraperitoneal cisplatin and six cycles of adriamycin, cisplatin, and cyclophosphamide. The patient was without evidence of recurrence at 12 months of follow-up. (Matsunami et al., 1999)

Studies have reported that *BRCA1/2* status and hormone receptor status of EOC have possible implications with the development of brain lesions. In a 2018 retrospective study of 3,649 EOC patients, Stasenکو et al. found that patients with *BRCA1/2* pathogenic variants were more likely to have isolated brain metastasis as compared to *BRCA1/2* wild-type patients (48% vs. 19%, $p = 0.02$) (Stasenکو et al., 2019). In a 2017 retrospective study, Mittica et al. demonstrated the risk of developing brain metastasis appeared 9.5 times greater in patients with androgen receptor (AR)-negative primary ovarian cancer as compared to AR-positive ($p = 0.013$) (Mittica et al., 2017). However, as cases of ovarian cancer brain metastasis are scarce, the literature remains limited.

Previous literature has reported a median survival of 3–5 months among EOC patients following the diagnosis of CNS metastasis (Larson et al., 1986). In a 2002 retrospective study, Pothuri et al. evaluated the impact of craniotomy in 14 EOC patients with established CNS spread. They found that survival improved among these patients following craniotomy; the median survival following craniotomy was 18 months, the 1-year survival rate was 66%, and the 2-year survival rate was 39% (Pothuri et al., 2002). Given recent improvements in primary control of EOC with surgical and chemotherapeutic advancements—resulting in improved overall survival—studies project a continually increasing incidence of brain metastasis (Pectasides et al., 2006). Additionally, with improved overall survival in EOC patients with CNS metastasis secondary to multimodal therapies, we can continue to expect increasing numbers of brain metastasis with uncommon sites of recurrence.

4. Conclusion

Brain metastasis in the setting of ovarian cancer is uncommon. Furthermore, brain metastasis at the time of diagnosis of EOC is exceedingly rare. This report highlights the first reported case of EOC with invasion of Meckel's cave—present at time of diagnosis. Consistent with most cases in the literature of brain metastasis in the setting of EOC, our patient had a highly aggressive tumor associated with a poor prognosis. Future studies are necessary to better understand the spread of EOC to the CNS in the hopes of improving early detection, symptomatic control and clinical management.

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Declaration of Competing Interest

There are no conflicts of interest for this study to disclose.

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