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Case report

A report of Bell's Palsy triggered by leptomeningeal metastases from recurrent high grade serous ovarian cancer

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1. Introduction

In the United States, epithelial ovarian cancer accounts for more deaths than all other gynecologic malignancies combined. It is the fifth leading cause of cancer deaths among women, yet only accounts for 3% of cancers in women (Jemal et al., 2011). There are no adequate screening tests for ovarian cancer and the clinical symptoms are often nonspecific. Consequently, up to two-thirds of patients are diagnosed with advanced disease (Johnson, 1993). Distant metastases beyond the abdomen and pleural cavity are rare. Cerebral metastases are exceedingly uncommon and have been described in less than 2% of cases (Miller et al., 2011). Central nervous system metastases involving the leptomeninges (LM) are even rarer, with only a few reported cases in the literature (Toyoshima et al., 2017). The presentation of LM metastasis is highly variable, however most patients present with acute, progressive neurological deficits (Yust-Katz et al., 2013). In this case report, we discuss a woman with a history of high grade serous ovarian carcinoma who presented with acute onset of unilateral Bell's palsy and was found to have leptomeningeal metastases from her ovarian cancer.

2. Case description

A 56-year-old G2P2002 Caucasian female was diagnosed with stage IIIC high grade serous carcinoma of the ovary after initial referral for a 10 × 8 × 14 cm adnexal mass and CA-125 of 5005 U/mL. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, pelvic and para aortic lymph node dissection, and radical tumor debulking to optimal cytoreduction. She was subsequently enrolled in a clinical trial and received carboplatin (AUC 6) and paclitaxel (175 mg/m^2) every third week and a daily PARP (Poly (ADP-ribose) polymerase) inhibitor or placebo. Following completion of six cycles, she had a complete clinical response on imaging and her CA-125 normalized to 18.7 U/mL. She was placed on bevacizumab consolidation therapy per study protocol. After one cycle of bevacizumab, her CA-125 rose to 65.8 U/mL and a PET scan was negative for recurrence.

After 2 cycles of consolidation therapy with bevacizumab, she presented for a routine visit and complained of left sided facial numbness and drooping of her left eyelid and mouth. Symptoms had been present for several weeks but acutely worse for one day. Emergent magnetic resonance imaging (MRI) was negative for stroke or intracranial lesions (Fig. 2). Initial suspicion was for viral etiology and Bell's Palsy was clinically diagnosed. She was prescribed prednisone and valacyclovir.

She was seen for follow up one week later due to worsening symptoms. CA-125 level was noted to increase to 103.3 U/mL. A referral was made to Neurology and they performed a lumbar puncture (LP). Cytology confirmed presence of malignant cells favoring adenocarcinoma from her primary ovarian malignancy (Fig. 1). She was offered hospice or weekly intrathecal methotrexate (IT-MTX) with an Ommaya reservoir. She declined Ommaya reservoir and elected to pursue treatment with weekly LP's. She tolerated the IT-MTX well with minimal side effects for 9 total cycles. From a peak of 168.4 U/mL, her

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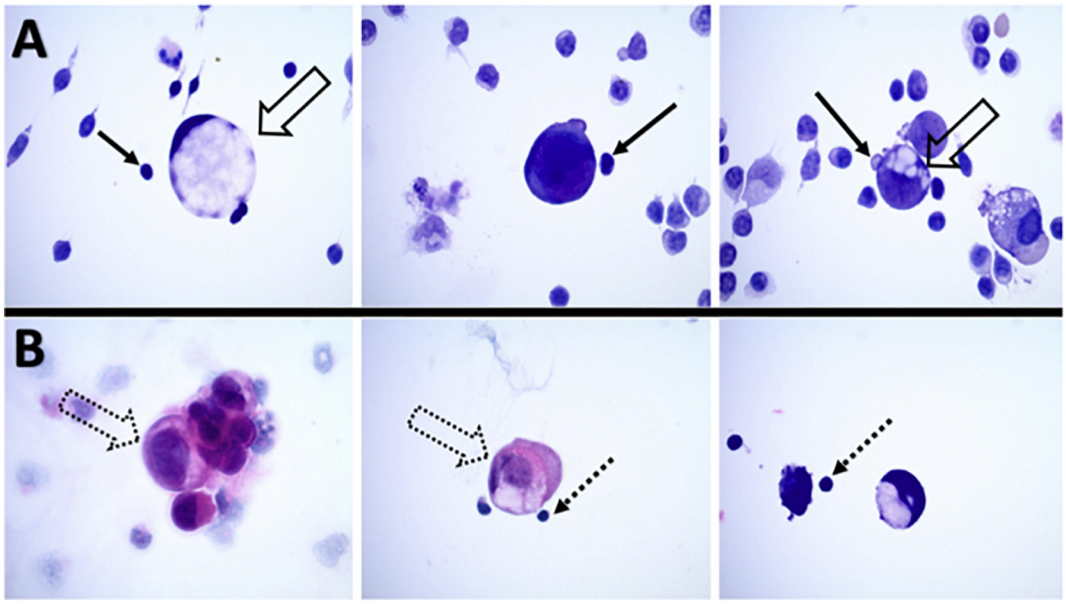

Fig. 1. (A) (60×) Diff-Quik stained cerebrospinal fluid (CSF) cytospins demonstrates large, atypical cells with intracytoplasmic mucin (open arrows) and hyperchromatic nuclei, consistent with metastatic adenocarcinoma. Background lymphocytes (solid arrows) reveal the marked enlargement of the malignant cells with atypical nuclei by comparison. (B) (60×) Follow-up CSF cytology demonstrates persistence of involvement by adenocarcinoma. The pleomorphic cells with irregular nuclei are readily appreciated on Papanicolaou stain (open-dashed arrows), and the marked enlargement of the malignant cells is again appreciated compared to background lymphocytes (dashed arrows).

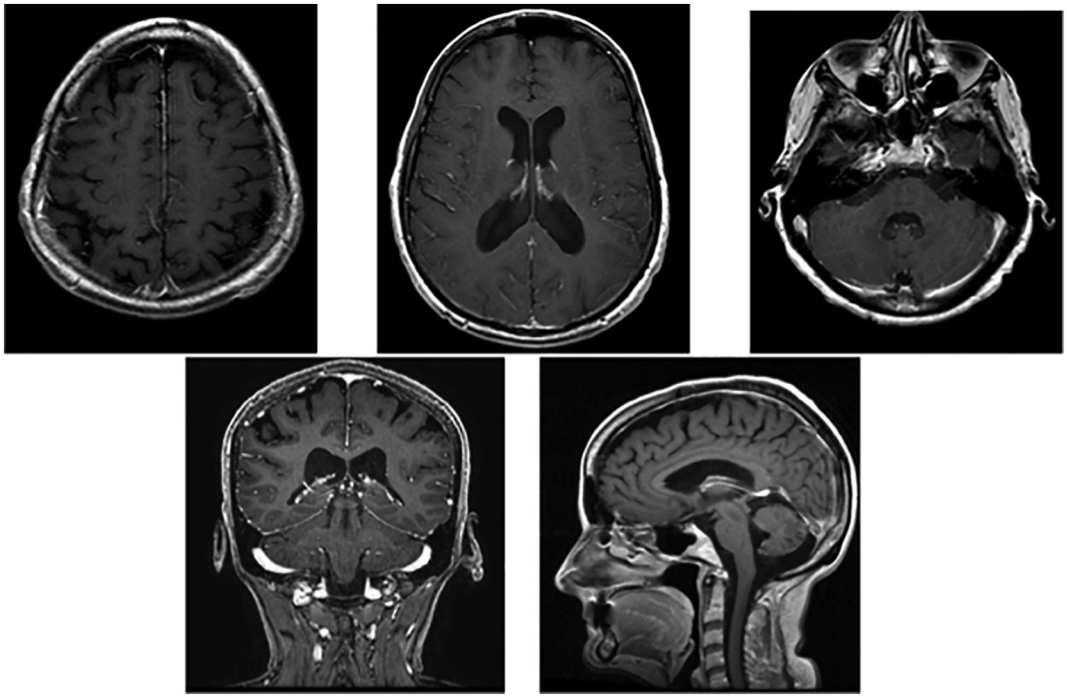

Fig. 2. Pertinent T-1 post contrast MRI images in axial, coronal and sagittal. Findings of images include: (Jemal et al., 2011) central and cortical volume loss with widening of ventricular spaces. (Johnson, 1993) No intra-axial or extra-axial masses, abnormal enhancement or signs of increased intracranial pressure (Toyoshima et al., 2017) No pathologic enhancement after gadolinium administration.

CA-125 decreased to 69.4 U/mL.

After 9 cycles of IT-MTX was completed, she began having dysphagia to both solids and liquids. An MRI revealed stable pattern of cranial nerve enhancement, a more confluent pattern of T2/FLAIR hyperintense signal within the bilateral corona radiata and centrum semiovale, and stable to slight interval increase in parenchymal volume loss (Fig. 3). Regardless of the reassuring MRI, the patient continued to have worsening dysphagia, necessitating percutaneous endoscopic gastrostomy tube (PEG) placement and she experienced a decline in her performance status to an ECOG of 2. The patient declined hospice care at this time and was referred to Radiation Oncology and began whole brain radiation therapy (WBRT). She received 2 treatments of 200 cGy/fraction for 15 fractions to a total dose of 3000 cGy to the whole brain. Simultaneously, the base of skull and cranial nerves received 250 cGy/fraction for 15 fractions to a total dose of 3750 cGy. She was then transitioned to hospice care 16 weeks after LM diagnosis and died

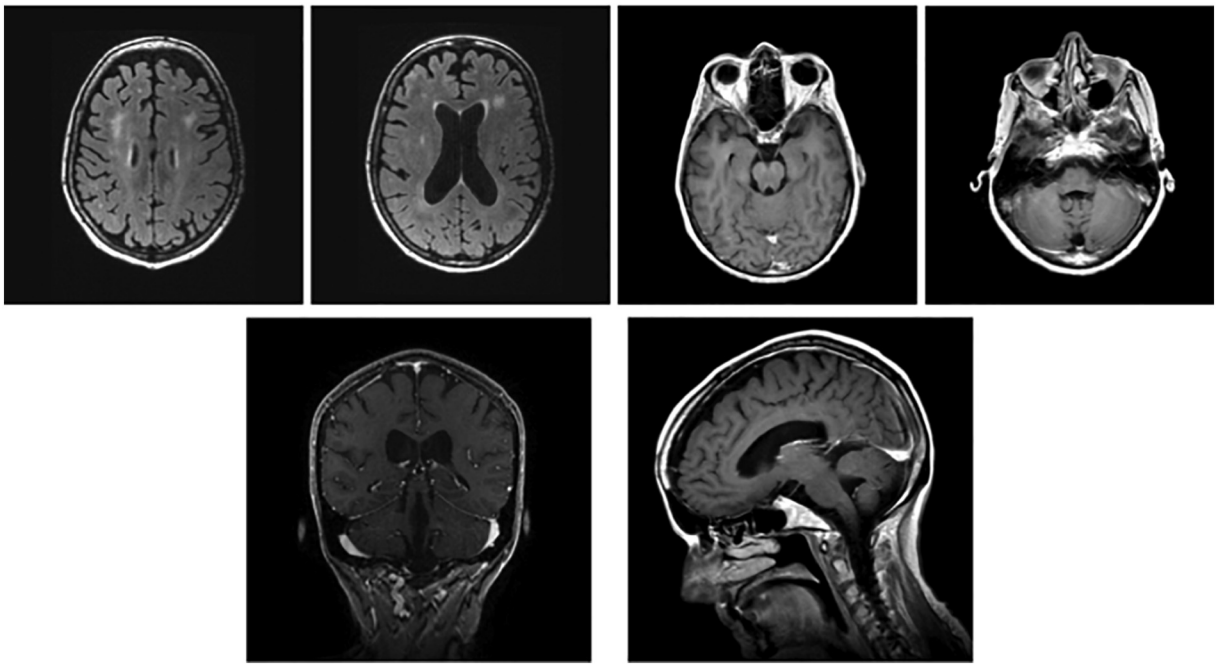

Fig. 3. Pertinent T-2/FLAIR MRI images in axial, coronal and sagittal. Findings include: (Jemal et al., 2011) Stable pattern of cranial nerve enhancement keeping with patient's known leptomeningeal disease. (Johnson, 1993) More confluent pattern of hyperintense signal within the bilateral corona radiata and centrum semiovale which may be related to chemotherapy treatments. (Toyoshima et al., 2017) Stable to slight interval increase in parenchymal volume loss.

13 months after initial ovarian cancer diagnosis Table 1.

3. Discussion

Ovarian cancer usually presents at stage III or greater with the most common sites of distant metastases being the liver parenchyma and pleura. Central nervous system (CNS) metastases can occur with ovarian cancer, but only at a rate of 1.4–2% (Anupol et al., 2002). Most of these cases involve the brain parenchyma, whereas leptomeningeal spread has only been reported in a few case reports.

Leptomeningeal metastases occur in 3%–5% of all cancer cases. Breast, lung, and melanoma are the most common primary tumors that metastasize to the meninges. Only a small number of cases of leptomeningeal metastasis associated with gynecologic malignancy can be found in the literature (Asensio et al., 2009; Delord et al., 1998). Patients usually present with seizures, altered mental status, dementia, autonomic dysfunction, limb weakness/paresthesia and/or bowel and bladder issues (Goto et al., 2008).

There are no case reports that describe Bell's Palsy as the presenting sign of leptomeningeal metastasis from ovarian cancer. Bell's palsy is a temporary paralysis of the facial muscles and is usually caused by trauma or damage to cranial nerve seven (NINDS, 2016). The classic presentation of Bell's Palsy is hemi-facial paralysis causing drooping of the eyelid and corner of the mouth, drooling, dry eye, dry mouth, taste impairment, and/or excessive tearing in one eye. These symptoms typically develop rapidly over 48 h. It is most commonly caused by a viral infection from the herpes family such as varicella zoster virus or the Epstein Barr virus. These viruses can lay dormant in the nerve and cause acute swelling when reactivated, which results in the classic symptoms of Bell's Palsy (Furuta et al., 2001). Possible reasons for reactivation of the virus include trauma, environmental factors, metabolic or emotional disturbances, and immunocompromised states (Kasse et al., 2003). The diagnosis is one of exclusion and is made clinically. A physical exam, thorough history, blood work, and imaging can help narrow the possible cause, which can include stroke, herpes, Lyme disease, sarcoidosis, trauma, and malignancy (NINDS,2016).

The prognosis for patients with leptomeningeal metastases in a setting of a primary ovarian malignancy is very poor. Life expectancy at time of presentation is often weeks to months. Usually, the cause of death in these patients is related to neurological tumor progression (15–87%) or systemic disease burden (10–64%) (Goto et al., 2008). Due to the poor prognosis, if treatment is started, it should be for palliative purposes. Chemotherapy (IV and Intra-CSF) and radiotherapy are the main therapies in leptomeningeal metastases (Leal et al., 2011). Regardless, there is no uniform or standard approach. One of the biggest hurdles in effective therapy for these patients is establishing a therapeutic level of the chemotherapeutic agent in the CSF due to the blood-brain barrier. Therefore, chemotherapy is usually administered intrathecally via an Ommaya reservoir or intra-CSF via repeated lumbar punctures. In the setting of such a poor prognosis, we demonstrate that repeated LP's for intrathecal administration can be safely performed, with a total of 9 treatments.

Early detection of leptomeningeal metastases in the setting of ovarian cancer is important to minimize neurological deficits. Additionally, even though treatment is palliative in nature, early detection can help maintain the patients' quality of life by decreasing sequelae from CNS disease. As demonstrated here, leptomeningeal metastases can have varied presentations including acute onset of Bell's Palsy, and therefore the practitioner must maintain a high degree of suspicion when evaluating patients with neurological complaints.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

The authors have no conflicts of interest

Table 1
Six cases of gynecological malignancies with leptomeningeal metastasis summarized

Author	Demographic	Primary Location	Symptom	Mode of Diagnosis	Treatment	Prognosis
Patel, et al. (In present)	56 yo white F	Ovarian	Left-sided Bell's palsy	(1) Negative MRI (2) Positive LP for malignant cells	Weekly intrathecal methotrexate; Whole brain radiation	Deceased 16 weeks after diagnosis of leptomeningeal disease
Asensio et al. (2009)	72 yo F	Uterine	Progressive sacrococcygeal pain, left-sided sciatica pain, leg weakness	(1) Negative brain CT (2) Negative brain MRI (3) Positive LP for malignant cells	Intrathecal methotrexate	No clinical benefit of intrathecal methotrexate; patient deceased of pneumonia
Asensio et al. (2009)	63 yo F	Cervical	Peripheral facial paralysis and right hearing loss	(1) Small calcified area on brain CT (2) Negative LP for malignant cells (3) Leptomeningeal enhancement on spine MRI (4) Repeat LP positive for malignancy	Radiation therapy to leptomeningeal disease, followed by radiation therapy to bulky disease	Deceased 3 weeks after completion of radiation therapy
Asensio et al. (2009)	54 yo white F	Cervical	Dizziness and ataxia	(1) Intraventricular lesion on brain CT (2) Multiple nodular lesions involving cerebellum, protuberance, thalamus, ventricular system on brain MRI (3) Negative LP x 3 for malignancy (4) Suspicious mediastinal lesions, multiple bone/liver metastases on PET	Palliative radiation therapy; cisplatin and etoposide systemic chemotherapy	Chemotherapy stopped because of infectious toxicity; deceased 7 months after diagnosis of neurologic dissemination
Goto et al. (2008)	60 yo F	Ovarian	Gait instability, dizziness, nausea, right temporal headache	(1) Negative brain MRI (2) Enhancement of cauda equina on spine MRI (3) Positive LP for malignant cells	Intrathecal methotrexate	Deceased after 19 cycles of intrathecal methotrexate
Delord et al. (1998)	57 yo F	Ovarian	Parasthesia and deafness	(1) Negative brain CT (2) Negative brain MRI (3) Positive LP for malignant cells	Intrathecal methotrexate	Deceased 2 days after initiation of therapy

Abbreviations: year-old (yo); female (F); Magnetic Resonance Imaging (MRI); lumbar puncture (LP); computed tomography scan (CT); Positron emission tomography scan (PET)

Author contributions

Each author was actively involved in revisions of the report and approved the final version for submission. The individual contributions are listed below.

Khilen B. Patel: Organized data, figures and drafted the report

Anna Gaidis: Contributed to written drafted report

Thomas Z. Thompson: Pathologist who prepared the images for the report

Angela Stephens: Contributed to written draft of report and reviews

Heather Williams: Contributed to written draft of report and reviews

Bunja Rungruang: Provided gynecologic oncology care for the patient, recognized the educational value of publishing the case, and highlighted key teaching points.

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