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Case report

Brain metastasis in advanced serous borderline tumor of the ovary: A case presentation☆

Madhuri Martin[a], Rachel N. Grisham[a,b], Gulisa Turashvili[c], Darragh F. Halpenny[d], Carol A. Aghajanian[a,b], Vicky Makker[a,b,*]

[a] Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Medicine, Weill Cornell Medical College, New York, NY, USA
[c] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[d] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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1. Introduction

Ovarian neoplasms are defined on a spectrum that includes borderline, low-grade, and high-grade tumors. A two-tier classification system is used to grade serous neoplasms as low grade or high grade—two tumor types with distinct molecular, pathologic, and clinical features. Serous borderline tumors represent a premalignant lesion with the ability to progress to low-grade serous carcinoma (LGSC) (Bodurka et al., 2012).

Serous borderline tumors and LGSCs are slow-growing tumors, with a relatively indolent course compared to that of high-grade serous carcinomas. Borderline tumors account for approximately 15% of all primary ovarian neoplasms, and 65% of these ovarian borderline tumors are of serous histology (Jones, 2006; Skírnisdóttir et al., 2008). One-third of women diagnosed with serous borderline tumors are younger than 40 years of age. LGSCs also are most commonly seen in young women, with a mean age at diagnosis of 55.5 years (Skírnisdóttir et al., 2008; Kaldaway et al., 2006). Approximately 33% of serous borderline tumors are associated with peritoneal implants, and in the recent 2014 World Health Organization (WHO) classification system, any invasive foci are now considered peritoneal LGSC, as these tumors display similar biological behavior (Shih and Kurman, 2004; Singer et al., 2003; Seidman and Kurman, 2000). Studies aimed at exploring the underlying genetic profiles of these malignancies have found that both serous borderline tumors and LGSCs express *BRAF* and *KRAS* mutations (Kaldaway et al., 2006). According to the National Comprehensive Cancer Network, the standard treatment for surgically staged borderline epithelial tumors with non-invasive implants is observation. For those with invasive implants, the standard of care also is observation or consideration of systemic treatment, as is recommended for the treatment of LGSC.

Brain metastasis is an extremely rare secondary site of ovarian cancer metastasis, with an incidence of 1–2.5%, associated with an extremely poor prognosis. While studies have shown a much higher prevalence of brain metastasis in grade 3 (83%) versus grade 1 or 2 tumors (17%), no reported case has been found specifically in patients with serous borderline tumor of the ovary (Cohen et al., 2004). Here, we report on a patient who had been diagnosed with recurrent serous borderline tumor with micropapillary architecture, invasive and non-invasive implants, and metastasis to the brain. According to our institutional policies, this case report has obtained Institutional Review Board exemption.

2. Case description

We report on a 41-year-old female who presented a few months prior to her diagnosis of serous borderline tumor of the ovary. The patient had experienced abdominal bloating for which she was referred to gastroenterology. In May 2008, an ultrasound revealed multiple uterine subserosal fibroids, the largest a right posterior subserosal

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* Corresponding author at: Gynecologic Medical Oncology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York 10065, NY, USA.
E-mail address: makkerv@mskcc.org (V. Makker).

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fibroid measuring 2.3 × 2.6 × 2.2 cm, ascites, and a large heterogeneous solid pelvic mass measuring 11.8 × 7.0 × 8.7 cm.

In June 2008, the patient was referred to Memorial Sloan Kettering Cancer Center (MSK). A computed tomography (CT) scan of the chest, abdomen and pelvis (CAP) revealed extensive peritoneal carcinomatosis, ascites, peritoneal and omental implants measuring up to 1.9 × 1.2 cm in the subdiaphragmatic space, and bilateral complex cystic and solid adnexal masses (6.9 × 5.7 cm on the right, 6.6 × 6.3 cm on the left). In addition, several bilateral pulmonary nodules were noted, along with bilateral hilar lymphadenopathy (2.3 × 1.1 cm on the left, 2.8 × 2.6 cm on the right) and mediastinal lymphadenopathy (2.4 × 1.3 cm). The patient underwent an optimal surgical debulking involving an exploratory laparotomy, with drainage of 10 L of ascites, total abdominal hysterectomy, bilateral salpingo-oophorectomy, en bloc culdesectomy, coloproctostomy, omentectomy, appendectomy, pelvic lymphadenectomy, and the insertion of an intraperitoneal (IP) port. The largest visible mass remaining after surgery measured < 0.5 cm, and there were up to 20 such masses left after surgery.

Pathology revealed a stage IIIC serous borderline tumor involving both ovaries. The right ovary exhibited small, scattered foci of micropapillary architecture. There was extensive tumor involvement of the peritoneum in the form of both invasive and non-invasive implants; 3 of 8 left pelvic lymph nodes and 1 of 1 appendiceal lymph nodes showed extensive and large foci of tumor involvement with stromal response. Non-invasive, desmoplastic implants of serous borderline tumor were seen involving the uterine serosa and peritoneal reflection. The cul-de-sac showed implants of serous borderline tumor, indeterminate in nature. The myometrium showed adenomyosis and multiple leiomyomata. The peritoneal fluid was positive for malignant cells (Fig. 1A–C).

In July 2008, the patient was started on adjuvant intravenous (IV) carboplatin/paclitaxel chemotherapy followed by modified IV/IP cisplatin/paclitaxel chemotherapy. Since then, the patient has received several lines of systemic treatment (Table 1). Additional biopsies to assess for transformation to a high-grade invasive serous carcinoma were not performed at the time of recurrence.

In November 2014, the patient reported a loss of taste and smell for which she saw an ENT specialist. In March 2015, the patient underwent magnetic resonance imaging (MRI) of the brain, which revealed at least 7 sub-centimeter foci of enhancement within the right paramedian convexity, parietal lobe, right perinsular and right periventricular brain parenchyma, the left temporal lobe, along the ependymal surface of the left frontal horn of the lateral ventricle, and within the infratentorial medial right cerebellum. The largest focus of abnormal enhancement, measuring 1.0 × 0.8 cm, abutted the dural surface of the posterior media left parietal lobe (Figs. 2 and 3). While a biopsy of these lesions to confirm metastasis over primary tumor was not performed, the appearance on MRI was consistent with metastatic disease. The patient was given 20 fractions of whole brain radiation therapy (WBRT) (4000 cGy) from March to April 2015. A post-radiation MRI in May 2015 revealed complete resolution of her brain metastasis, with no new findings. The most recent brain MRI in May 2017 revealed no new metastasis. Most recently, the patient progressed on bevacizumab and topotecan. A CT CAP revealed new metastatic disease extending from

Table 1
The patient's systemic treatment history.

Date of treatment	Therapy type	CA-125 level
July 2008–October 2008	IV paclitaxel, carboplatin, IV/IP paclitaxel, cisplatin	Pre-Surgical: 1479 Pre-tx: 462 Post-tx: 106
January 2009–March 2009	Letrozole	Pre-tx: 65 Post-tx: 220
March 2009–April 2009	Liposomal doxorubicin	Pre-tx: 220 Post-tx:652
May 2009–October 2010	Gemcitabine, bevacizumab	Pre-tx: 822 Post-tx:132
December 2010–January 2011	Carboplatin	Pre-tx: 172 Post-tx:1331
February 2011–September 2011	Bevacizumab, oral metronomic cyclophosphamide	Pre-tx: 658 Post-tx: 156
October 2011–May 2012	Gemcitabine, bevacizumab	Pre-tx: 156 Post-tx: 133
Treatment break		
January 2013–May 2013	Pimasertib (MEK1/2 inhibitor), voxtalisib (PI3K, mTOR inhibitor)	Pre-tx: 257 Post-tx: 147
June 2013–January 2014	Bevacizumab	Pre-tx: 130 Post-tx: 317
February 2014–October 2014	Gemcitabine, bevacizumab	Pre-tx: 317 Post-tx: 436
Treatment break		
April 2015–October 2016	Paclitaxel, bevacizumab	Pre-tx: 845 Post-tx: 349
October 2016–January 2017	Leuprolide	Pre-tx: 349 Post-tx: 1100
February 2017–May 2017	Bevacizumab, topotecan	Pre-tx: 1225 Post-tx: 994
June 2017-Present	Pemetrexed	Pre-tx: 994 (Most Recent)

IV, intravenous; tx, treatment.

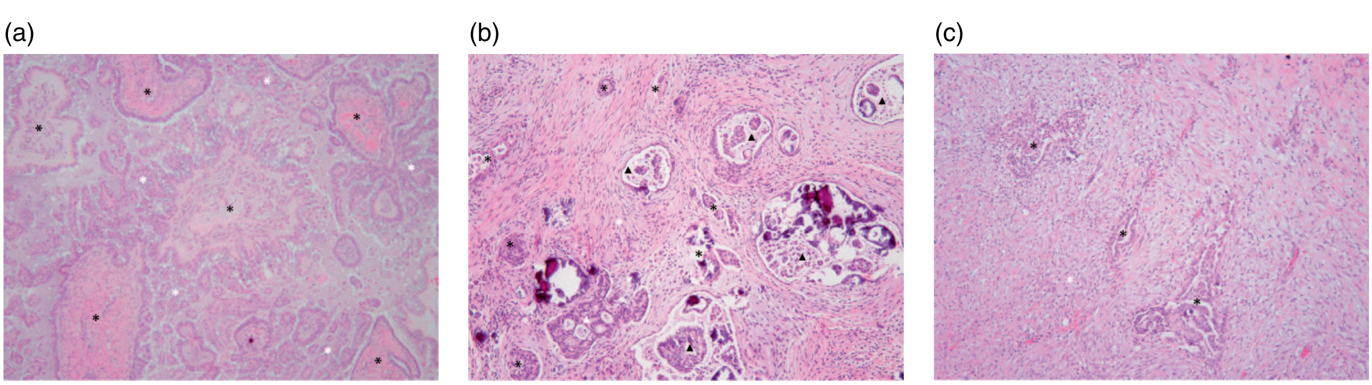

Fig. 1. A. Serous borderline tumor with micropapillary features. The tumor is comprised of large papillae with well-developed fibrovascular cores (black asterisks) surrounded by thin, delicate papillae with length > 5 times the width and scanty fibrovascular support (white asterisks). The area of micropapillary growth pattern spans > 5 mm in diameter. B. Invasive implant. The tumor consists of irregular to round glands of varying size (black asterisks), haphazardly infiltrating dense fibrous stroma (white asterisk), and surrounded by clear spaces. Some glands exhibit micropapillary (black arrowheads) or cribriform architecture (white arrowhead). The glands contain serous and mesothelial-type cells with moderate cytologic atypia. C. Non-invasive desmoplastic implant. Irregular gland-like structures (black asterisks) are embedded in an abundant inflamed and edematous (granulation tissue-like) stroma (white asterisk) in a linear orientation. The gland-like structures are lined by one to several layers of epithelial and mesothelial-type cells displaying abundant eosinophilic cytoplasm and mild cytologic atypia. (hematoxylin & eosin stain; original magnification × 100 [all panels]).

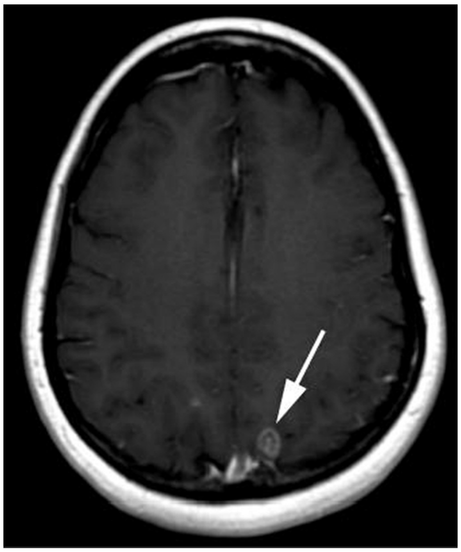

Fig. 2. T1 weighted MRI of the brain obtained after administration of intravenous gadolinium demonstrating a ring enhancing metastasis in the posterior left parietal lobe.

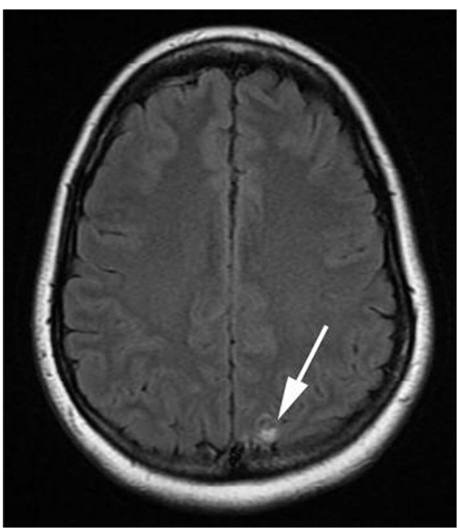

Fig. 3. Fluid attenuation inversion recovery MRI image of the brain demonstrating focal high signal in the posterior left parietal lobe in the same location as the ring enhancing metastasis in Fig. 2.

the right urinary bladder to the ileum of the right lower quadrant. The patient was started on pemetrexed, and is currently on this treatment regimen.

3. Discussion

Brain metastasis from primary ovarian cancer is a rare phenomenon, with fewer than 600 cases reported in the literature. The most common cases of brain metastasis have been seen in patients with advanced-stage (III/IV), poorly differentiated epithelial serous carcinoma; however, to our knowledge, no cases have been reported specifically for serous borderline tumors with invasive implants (Piura and Piura, 2011).

Despite the gradual course of this patient's disease, the presence of invasive implants and lymph node involvement suggests a more aggressive form of disease. In a meta-analysis of 97 studies of 4129 patients with serous borderline tumors, invasive peritoneal disease (LGSC) was associated with shorter overall survival. Results showed an overall survival rate of 95.3% for advanced serous borderline tumors with non-invasive implants versus 66% for patients with invasive peritoneal disease (LGSC) (Seidman and Kurman, 2000). Our patient's clinical course is consistent with the histology of her disease.

Lymph node involvement has also been found to be prevalent in 21–29% of patients with serous borderline tumors. A study by McKenney et al. suggested that lymph nodes with nodular aggregates of epithelium > 1 mm in linear dimension significantly correlated with a decrease in disease-free survival, regardless of implant type (McKenney et al., 2006). In a study of 49 patients, however, Lesiur et al. reported that lymph node involvement in patients with advanced borderline tumors did not significantly correlate with improved prognosis (Lesiur et al., 2011). The comparable rate of recurrence was 25% for those with positive lymph nodes and 23.5% for those with negative lymph nodes. In addition, the 10-year and overall survivals between the two groups was not significantly different. While the McKenney et al. study showed that lymph nodes with nodular aggregates led to reduced disease-free survival, the Lesiur study did not specifically delve into the morphology of lymph nodes. The presence of lymph node involvement in predicting survival requires further study; however, there may be specific lymph node types that pose a high risk to patients (McKenney et al., 2006; Lesiur et al., 2011).

Due to the rarity and complexity of this disease, an understanding of prognostic factors in these patients is an ongoing effort. In a study evaluating *KRAS/BRAF* mutational status in 70 patients with serous borderline and LGSC, > 50% of patients were found to have a *KRAS/BRAF* mutation. Specifically, 17 patients were found to have a *KRAS* mutation (G12D or G12 V), 26 had a *BRAF* mutation (V600E), and 32 were wild type for *KRAS* and *BRAF*. Of 26 patients who had received systemic chemotherapy, 2 had *KRAS*-mutant tumors, 0 had *BRAF*-mutant tumors and the remaining had *KRAS/BRAF* wild-type tumors, suggesting that patients with *BRAF* mutation tumors are likely to survive longer than patients with *KRAS* mutant and *BRAF* wild-type tumors (Grisham et al., 2013). Our patient has a *KRAS* G12D mutation and has received multiple lines of chemotherapy for her recurrent disease.

To evaluate treatment options for patients with ovarian cancer and brain metastasis, studies have looked at the use of multimodal therapy (surgical resection and WBRT versus WBRT alone) for better survival (Piura and Piura, 2011). A phase I study evaluating the combined use of bevacizumab and WBRT for patients with unresectable brain metastasis from solid tumors concluded that patients who received bevacizumab at 15 mg/kg IV every 2 weeks in combination with WBRT (30 Gy15 fractions) had a better response than those who received lower doses of bevacizumab. The possible treatment response with bevacizumab has been linked to the anti-angiogenesis of bevacizumab, which may disrupt the cycle between angiogenesis-induced hypoxia and radio-resistance (Lévy et al., 2014).

The use of bevacizumab for LGSC has also been supported by the literature. A retrospective study from MSK was one of the first to propose the use of bevacizumab in combination with chemotherapy as a treatment option for patients with LGSC. This study evaluated the response of 17 patients with LGSC and serous borderline tumors. Six patients with LGSC were found to have a partial response, demonstrating a 55% response rate within the group. No complete response was observed for this group. Of the 4 patients with serous borderline tumors, no complete or partial responses were observed (Grisham et al., 2014).

Survival for patients with brain metastasis is poor; however, the literature on prognostics, survival, and treatment options for patients with epithelial ovarian cancer offers limited applicability to patients with serous borderline tumor or LGSC. As a result, it is important to continue our efforts in determining the etiology and disease course of patients with rare disease types and offer empirically supported treatments.

Conflict of interest statement

Dr. Grisham served on an advisory board for Mateon. Outside the submitted work, Dr. Aghajanian reports personal fees from Oxigene Steering Committee Meetings, as well as personal fees from a Cerulean Advisory Board, Bayer Advisory Board, VentiRx Advisory Board, AstraZeneca Advisory Board, ImmunoGen Advisory Board, and Oxigene Advisory Board. She also reports travel reimbursement from Abbvie for investigator meetings.

Dr. Makker reports personal fees from Eisai Pharmaceuticals Advisory Board. The other authors have no conflicts to disclose.

Consent

According to our institutional policies, this case report has obtained Institutional Review Board exemption.

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