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Case report

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

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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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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.

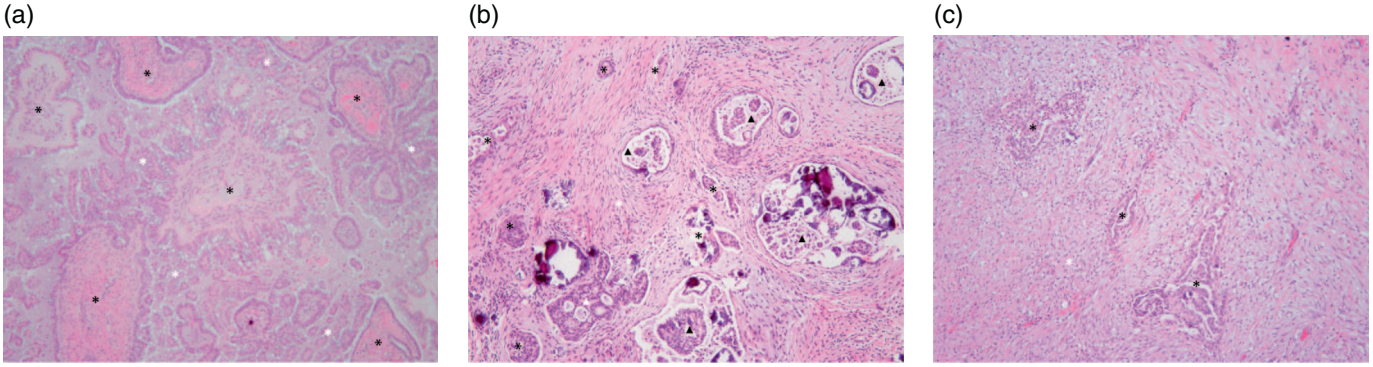

Fig. 1. A. Serous borderline tumor with micropapillary features. The tumor is comprised of large papillae with well-developed fibrovascular cores (black asterisks) surrounded by thin, delicate papillae with length > 5 times the width and scanty fibrovascular support (white asterisks). The area of micropapillary 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]).