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Case Report

Characteristics of ovarian tumors of low malignant potential in BRCA mutation carriers: A case series

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1. Introduction

In 2015, ovarian cancer remains the most fatal gynecologic malignancy in the United States (Siegel et al., 2015). Genetic components are becoming more important considerations in the etiology and pathophysiology of ovarian cancer development and progression (Jayson et al., 2014). Breast cancer susceptibility genes (BRCA) 1 and 2 are among the major tumor suppressor genes and the germ line deletion or mutation of BRCA 1 and 2 are known to be associated with an increased risk of various types of cancer, including ovarian cancer (Foulkes, 2008). Generally, ovarian cancer arising in BRCA 1 and 2 mutation carriers is high-grade serous ovarian cancer with aggressive tumor behavior and presents with metastatic advanced disease (George and Shaw, 2014).

Ovarian borderline tumors or tumors of low malignant potential (LMP) are one of the histologic subtypes of epithelial ovarian tumors, and certain types of oncogene mutations such as KRAS and its downstream signaling BRAF are reported to be associated with the development of ovarian LMP tumor (Sood et al., 2010; Mayr et al., 2006). Ovarian LMP tumor with a KRAS mutation is also known to progress or recur as low-grade serous ovarian cancer that has distinct clinical and molecular characteristics compared to high-grade serous ovarian cancer (Diaz-Padilla et al., 2012). However, investigation into an association between BRCA mutation and ovarian LMP tumors has been limited. The aim of the study was to describe the clinical and histologic characteristics of ovarian LMP tumors in BRCA mutation carriers.

2. Patients and methods

After Institutional Review Board approval at University of Southern California, medical records of five cases of ovarian LMP tumors in women with BRCA mutations were examined. These cases were based on provider's recall but not on thorough screening of consecutive ovarian LMP tumors in our institution. These five patients had surgery and postoperative care at the Los Angeles County Medical Center or the Norris Cancer Center. These hospitals are categorized as tertiary care institutions and provide gynecologic oncology care. Between said institutions, the approximate annual number of surgeries performed for gynecologic malignancies is 300. Both institutions provide support with expert gynecologic pathologists who review our pathology.

Among identified cases, the following information was abstracted: (*i*) demographic, (*ii*) surgical treatment, (*iii*) tumor characteristics, (*iv*) BRCA testing results, and (*v*) survival outcomes. For demographic data, age at diagnosis of ovarian LMP tumor, ethnicity, past medico-surgical history, pregnancy history, family history, and body mass index were abstracted. Information for surgical treatment included date of and type of surgery. Tumor characteristics included histologic type of ovarian LMP tumor, extent of metastasis, and the International Federation of Gynecology and Obstetrics (FIGO) stage reclassified per the most recent classification (Prat, 2014). In addition, archived histopathology slides (hematoxylin and eosin staining, and immunohistochemistry staining) were retrieved and reviewed by a gynecologic pathologist to confirm the diagnosis of an ovarian LMP tumor and to rule out any evidence of invasive disease. The pathologist was blinded for clinical information. Additional BRAF or KRAS testing was not

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performed for the study. For genetic testing results, the type of BRCA gene mutation (BRCA1 *versus* BRCA2) and the location of the mutation foci were abstracted from medical records. For treatment pattern and survival outcome, type of postoperative treatment (chemotherapy and/or radiotherapy, if received) and progression-free survival (time interval between surgery for ovarian LMP tumor and the date of recurrence of last follow-up) and overall survival (time interval between surgery for ovarian LMP tumor and the date of death or last follow-up) were determined.

Descriptive analysis for collected variables was performed. Continuous variables were expressed with mean (±standard deviation [SD]) or median (range). Categorical or ordinal variables were examined with Fisher's exact test expressed with odds ratio (OR) and 95% confidence interval (CI). Post-hoc analysis was made between the current case series and previously reported study in the literature: a recent Surveillance, Epidemiology, and End Results (SEER) database study to represent population-based cohort (n = 6017) (Lesieur et al., 2011); and a large-scale multicenter study to represent histopathology cohort (n = 950) (du Bois et al., 2013). Of note, these two studies do not have information for BRCA results in their study populations. All statistical analyses were two-tailed and *P* values of less than 0.05 were considered as significant.

3. Results

3.1. Case 1

A 44-year-old nulligravida woman with past medical history only significant for hypertension came to our institution for further work-up following an abnormal cervical cytology test result at an outside clinic. The patient was found to have a strong family history of ovarian cancer. Her sister was diagnosed with ovarian cancer at age 41 and her mother was diagnosed with ovarian cancer at age 37 and subsequently died at age 41. Given the strong family history, the patient was referred for genetic counseling and underwent assessment for a risk-reducing salpingo-oophorectomy. On pelvic ultrasound, however, the patient was found to have bilateral adnexal masses with a serum CA-125 level of 417 U/mL. The patient was referred to a gynecologic oncologist and underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy resulting in complete tumor reductive surgery. The patient was diagnosed with stage IB bilateral ovarian serous LMP tumor associated with stage IIIC ovarian high-grade serous carcinoma. Metastatic sites of high-grade carcinoma included peritoneum, omentum, uterine serosa, peri-rectosigmoid tissue, and one pelvic lymph node. There was serous carcinoma *in situ* seen in the fimbriae. Genetic testing confirmed that the patient had a BRCA1 mutation (2883del4). The patient was prescribed 6 cycles of carboplatin and paclitaxel. The patient currently has no evidence of recurrence (follow-up time, 5.1 months).

3.2. Case 2

A 44-year-old gravida 2 para 2 woman presented with abnormal uterine bleeding and a history of a complex adnexal mass discovered on pelvic ultrasound in an outside country. The mass was presumed to be an endometrioma. Upon presenting to our institution, the patient underwent a pelvic ultrasound and was found to have a persistent complex right adnexal mass with internal echoes and serum CA-125 was 64 U/mL. The patient had a family history significant for a mother with breast cancer at age 63 and a paternal cousin with ovarian cancer at age 50. The woman with ovarian cancer may have had a daughter diagnosed with breast cancer around age 30. She underwent a laparoscopic right salpingo-oophorectomy. Examination of the surgical specimen revealed a 7.1 cm mucinous ovarian LMP, intestinal type. Given this family history, the patient underwent genetic testing and was found to have a BRCA1 mutation (187delAG [c. 68_69del]). She thereafter underwent total laparoscopic hysterectomy and left salpingo-oophorectomy. The histology results were unremarkable. The patent was staged as IA ovarian mucinous LMP tumor. Currently, she has no evidence of recurrence 10.9 months after surgery.

3.3. Case 3

A 49-year-old gravid 3 para 3 woman was previously diagnosed with stage IIIC serous ovarian LMP tumor at age 37. The patient underwent surgery at an outside institution. Surgery included bilateral salpingo-oophorectomy and extensive intra-abdominal resection of serous ovarian LMP tumor of the right and left ovaries. She was found to have invasive implants to the omentum and small bowel. Her surgery was followed by 6 cycles of adjuvant carboplatin and paclitaxel. Due to diagnosis and strong family history, including a sister diagnosed with breast cancer at age 38 who died at age 41 and a father who died of prostate cancer at age 69, she underwent genetic testing and was found to have BRCA1 943ins10deleterious deletion. The patient is currently without evidence of disease (follow-up time, 148.9 months). The patient is currently being assessed for a prophylactic bilateral mastectomy.

3.4. Case 4

A 33-year-old gravida 2 para 2 woman presented to her generalist with complaints of intermittent bloating for 1 year. During work-up and treatment for presumed gastritis, the patient had imaging that showed an ovarian mass. The patient traveled to an outside country to undergo a total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node biopsy, omentectomy, appendectomy, abdominal washings and staging for bilateral adnexal masses. The patient returned to the United States for adjuvant treatment. Pathology slides were reviewed in our institution, and the findings were consistent with stage IIIB serous ovarian LMP tumor with invasive implants to the peritoneum, and pelvic washings were positive for serous ovarian LMP tumor. Upon presenting to our institution two months after the initial surgery, the patient had imaging that showed residual omental nodularity warranting further evaluation with a diagnostic laparoscopy to assess her current disease. The procedure revealed residual disease that was confirmed with biopsies (serous ovarian LMP tumor with a non-invasive implant). She was prescribed chemotherapy with carboplatin and paclitaxel for 6 cycles. Of note, her family history was significant for a mother with colon cancer at age 61 and father with prostate cancer at age 68 as well as a strong history of breast and gastric cancer in extended family. The patient underwent genetic counseling and was found to be BRCA1 del exons 9–12 positive. There is no evidence of recurrence after 9.0 months of follow-up.

3.5. Case 5

This patient presented at age 27 with a strong family history of cancer. Most notably, the patient's sister had serous ovarian cancer at age 40 and was a BRCA2 + E1953X mutation carrier. Her mother was also a BRCA2 + E1953X mutation carrier diagnosed with breast cancer at age 53. The patient was found to have the same BRCA2 + E1953X mutation. While undergoing surveillance, the patient was found to have a 3 cm pelvic mass with multiple papillations. Her serum CA-125 level remained normal. Given the abnormal appearance of the mass, the patient was taken to the operating room for exploration. The patient underwent a laparotomy to remove the broad ligament mass. Pathology revealed a 3 cm lesion consistent with serous ovarian LMP tumor (stage IA). Other operative findings were notable for a unicornuate uterus, normal appearing ovaries and absent left fallopian tube. She was followed with serum CA-125 levels and pelvic ultrasonography. She had one spontaneous abortion followed by a term pregnancy delivered *via* cesarean section. Once completed with childbearing, the patient