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 (Poulkes, 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 in 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 medical-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...
performed for the study. For genetic testing results, the type of BRCA gene mutation (BRCA1 versus BRCA2) and the location of the mutation loci 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 (interval time between surgery for ovarian LMP tumor and the date of recurrence of last follow-up) and overall survival (interval time 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 studies 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 IIIIC 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 gravid 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 patient 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 gravida 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 deleterons 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 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 unicorne 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...
underwent a prophylactic supracervical hysterectomy and bilateral salpingo-oophorectomy at age 39. No abnormalities were noted in her uterus, ovaries or pelvic washings. Fourteen years after her ovarian LMP tumor diagnosis, the patient has not recurred.

3.6. Case series summary

Patient demographics are shown in Table 1. Mean age of the five women at ovarian LMP diagnosis was 37 years of age (SD ± 7.6). The majority of women were non-obese (80%) and premenopausal at ovarian LMP tumor diagnosis (100%). None of the patients was Jewish. All women had a family history of breast and/or ovarian cancer (100%). All women except one underwent BRCA testing at the time of ovarian LMP tumor diagnosis (80%). None of the patients had a personal history of any other type of malignancy. For tumor laterality, a half of ovarian LMP cases were bilateral (50%), and there was one case of ovarian LMP tumor found in the broad ligament associated with a unicornuate uterus. The majority of cases had BRCA1 mutation (80%).

Characteristics of histopathology results and treatment patterns are shown in Table 2. All but one ovarian LMP tumor case consisted of serous histology subtype (80%). Advanced-stage disease (FIGO stages III–IV) was seen in 40% of the cases, and those with advanced-stage disease had invasive implants of serous ovarian LMP. The two cases with invasive implants received adjuvant chemotherapy with carboplatin and paclitaxel for 6 cycles after surgery. There was one case with non-invasive implants. There was one case of serous ovarian LMP tumor that had a synchronon FIGO stage IIIC high-grade serous ovarian cancer, and she received systemic chemotherapy after surgery for this indication. With median follow-up time of 10.9 months, there was no case of recurrent disease or secondary malignancy reported.

4. Discussion

Our case descriptions highlight unique characteristics of ovarian LMP tumors in BRCA mutation carrier women. Because the BRCA gene family plays an important role in double-strand DNA homologous recombinant repair mechanisms (Foulkes, 2008), loss of tumor suppressor function in BRCA mutation carrier women may hypothetically result in an increased risk of tumor progression of ovarian LMP tumor. Invasive implants represent one aggressive feature of ovarian LMP tumors, and the majority of invasive implants are usually seen in serous ovarian LMP tumors (du Bois et al., 2013). In this case series, 50% (2 out of 4 cases) of serous ovarian LMP tumors had invasive implants. The incidence of invasive implants in our case series seems to be higher than the incidence reported in other large-scale studies of serous ovarian LMP tumors (2.3%, 23 out of 644 cases, OR 27.0, 95% CI 3.6–200, P = 0.008) (du Bois et al., 2013). In addition, large proportion of women in our series presented with advanced-stage disease of serous ovarian LMP tumor (proportion of FIGO stage III–IV disease, 40%, 2 out of 5 cases) when compared to a population-based study but this did not reach statistical difference (16.3%, 615 out of 5909 cases, OR 5.74, 95% CI 0.96–34.4, P = 0.088) (Lesieur et al., 2011). Taken together, our case series may suggest that ovarian LMP tumors in BRCA mutation carrier women have more aggressive features, particularly in the presence of invasive implants. Another hypothetical link between BRCA mutation and ovarian LMP tumors is tumorigenesis. In a review of the literature, there were no BRCA1 and 2 mutations reported in ovarian LMP tumors in recent studies in non-Jewish populations while approximately 4% of women with ovarian LMP tumors were associated with BRCA mutation (Boyd et al., 2000; Pal et al., 2005; Gotlieb et al., 2005). Whether or not BRCA mutation carrier women have an increased risk of ovarian LMP tumor is not answered in the current study, and this clinical entity merits further investigation.

In the five cases in our study, the mean age at ovarian LMP diagnosis was 37 years, which is younger than the mean age at ovarian LMP tumor diagnosis in the general population. Among 6017 ovarian LMP cases reported in a population-based study, the mean age of ovarian LMP tumor diagnosis was reported as 48 years (Lesieur et al., 2011). This trend may hold true because BRCA1 mutation carriers have a younger age at onset of ovarian cancer than those with sporadic ovarian cancer (mean age of ovarian cancer diagnosis, BRCA1 carrier versus BRCA2 carrier versus wild type, 54 years versus 62 years versus 63 years old) (Boyd et al., 2000;
Prat et al., 2005). Collectively, if ovarian LMP tumor is diagnosed in a patient of young age with a strong family history for breast or ovarian cancer, there might be a possibility that the patient carries a BRCA mutation.

In one of our cases, serous ovarian LMP tumor co-existed with a high-grade serous ovarian cancer (Case 1). In general, serous ovarian LMP tumor is known to progress to low-grade serous ovarian cancer when the patient carries the KRAS mutation (Prat, 2014). KRAS status was not known in Case 1. However, a recent detailed clonality analysis showed that there is a possibility of progression of serous ovarian LMP tumor to high-grade serous ovarian cancer although it is a rare event (Dehari et al., 2007). Our case suggests that a BRCA mutation may be involved in the progression of serous ovarian LMP tumor to high-grade serous ovarian carcinoma.

Our cases of ovarian LMP tumor in BRCA mutation carriers revealed serous histology to be dominant (80%, 4 out of 5 cases) and this was consistent with other large-scale studies that showed serous histology to be dominant (67%, 640 out of 955 cases, OR 1.90, 95% CI 0.21–17.1, \(P = 1.0\)) (Boyd et al., 2000). Similarly, the proportion of BRCA1 to BRCA2 mutation carriers was BRCA1 dominant (80%) in our case study. This trend was similar to what is reported in the literature (proportion of BRCA1 and 2 mutations in invasive ovarian cancer, 63% versus 37%) (Pal et al., 2005).

In summary, our case series suggests that ovarian LMP tumors in BRCA mutation carriers may have distinct clinical and histopathological characteristics. Although this is a case series and limited by the small sample size, our findings would suggest that genetic counseling and BRCA testing should be considered in woman with newly diagnosed ovarian LMP tumors who exhibit young age and aggressive tumor characteristics, such as invasive implants. In addition, when ovarian LMP tumor is diagnosed, a thorough family history for cancer, specifically focusing on breast cancer and ovarian cancer, should be completed in order to further identify patients who meet criteria for genetic testing. The possible relationship between LMP ovarian tumors and BRCA mutation presents an opportunity for development, and additional studies are warranted to validate and expand on our findings.

**Disclosure**

The authors declare that there is no conflict of interest for the study.

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