Ovarian cancer arising from the proximal fallopian tube in a patient with a BRCA2 mutation

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ABSTRACT

Patients with BRCA mutations are at high risk of high grade serous ovarian cancer. A paradigm shift has resulted in the current understanding that many cases of ovarian cancer actually arise from the fimbriated fallopian tube. The case presented here involves fallopian tube carcinoma arising from the cornua of the uterus in a BRCA2 carrier. This case suggests that pathologic analysis of risk-reducing bilateral salpingo-oophorectomy (RRBSO) specimens via serial sectioning and extensively examining the fimbriated end (SEE-FIM) may be insufficient to diagnose all occult lesions of interest. This case also provides a new consideration in the ongoing debate over the role of concurrent hysterectomy at time of RRBSO in BRCA carriers.

1. Introduction

People with BRCA mutations have a significantly elevated lifetime risk of developing high grade serous ovarian cancer (HGSOC) (Kuchenbaecker et al., 2017). Due to the lack of effective ovarian cancer screening and aggressive disease behavior, several professional organizations, including the National Comprehensive Cancer Network (NCCN), Society of Gynecologic Oncology (SGO), American College of Obstetricians and Gynecologists (ACOG), recommend risk-reducing bilateral salpingo-oophorectomy (RRBSO) at age 35–45. The role of concurrent hysterectomy at time of RRBSO is an area of active research. For patients with BRCA1 mutations, there is some evidence of an increased risk of serous endometrial carcinoma. Shu et al. (2016) demonstrated an increased incidence of serous/serous-like endometrial cancers in BRCA1 carriers (observed to expected ratio 22.2) after undergoing RRBSO. The NCCN guidelines recommend that the physician should discuss with patients the consideration for concurrent hysterectomy with regards to hormone replacement therapy (HRT). Data demonstrates that patients who have undergone hysterectomy and receive estrogen-only HRT have a lower incidence of breast cancer compared to those receiving combined estrogen and progesterone HRT (Kotsopoulos et al., 2018; Marchetti et al., 2018). Currently, RRBSO alone remains the standard of care.

Rapid uptake of RRBSO following the cloning of BRCA1/2 in the 1990s afforded pathologists the surgical specimens that led to the paradoxical observation that most ovarian cancers begin in the fallopian tube and not the ovary (Callahan et al., 2007; Finch et al., 2006; Piedimonte et al., 2020; Reade et al., 2014; Walker et al., 2015). Studies evaluating occult cancers and precursor lesions at time of RRBSO including serous tubal intraepithelial lesions (STIL) and serious tubal intraepithelial carcinoma (STIC) lesions demonstrate that the majority of cases arise in the distal end of the fallopian tube, usually the fimbria or ampulla (Callahan et al., 2007; Finch et al., 2006; Piedimonte et al., 2020).

The fallopian paradigm for HGSOC pathogenesis has motivated several trials of salpingectomy followed by interval oophorectomy for women with BRCA mutations. The delayed oophorectomy is appealing to women who are concerned about surgical menopause and the associated health risks (including increased risk of heart disease, osteoporosis and cognitive impairment) but still desire HGSOC risk reduction. There are currently five ongoing clinical trials evaluating salpingectomy followed by delayed oophorectomy: Women Choosing Surgical Prevention (WISP), Early Salpingectomy (Tubeectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA), TUBectomy With Delayed Oophorectomy in High Risk Women to Assess the Safety of Prevention (TUBA-WISP-II), A Study to compare Two Surgical Procedures in Women With BRCA1 Mutations to Assess Reduced Risk of Ovarian Cancer (SOROCK), and Prophylactic Salpingectomy with...
Delayed Oophorectomy. A sixth trial is evaluating radical fimbriectomy, in which a portion of the ovary adjacent to the fimbria is resected along with the entire tubal length.

We present a case of a patient with HGSOC and a BRCA2 mutation. Pathologic examination of her fallopian tubes, ovaries, and uterus suggests that HGSOC originated in the fallopian tube at the cornua of the uterus. This case demonstrates the importance of removing the maximal tubal length at time of RRBSO and suggests that detailed pathologic analysis of the proximal fallopian tube should be considered in addition to standard of care analysis via sectioning and extensively examining the fimbriated end (SEE-FIM).

2. Case

Our patient is a 72-year-old with family history of breast cancer in her mother, with end-stage renal disease due to diabetes and hypertension and prior bilateral robotic nephrectomy for left renal cell carcinoma who underwent transabdominal renal transplant. No imaging was obtained in the period immediately prior to her transplant. Her postoperative course was complicated by a small bowel obstruction (SBO). On post-operative day 12 she underwent diagnostic laparoscopy and was noted to have an inflamed appendix adherent to the renal allograft. The appendix was removed, and final pathology demonstrated a high-grade adenocarcinoma positive for cytokeratin-7 and PAX8, and negative for TTF-1 and cytokeratin-20, suggesting metastatic disease from a gynecologic primary site.

The patient underwent robotic-assisted total hysterectomy and bilateral salpingo-oophorectomy one month after diagnosis. She was noted to have peritoneal implants in the abdomen and pelvis that were completely resected, but otherwise had no visible disease. Pathologic exam demonstrated HGSOC, FIGO Stage IIIb. Tumor was identified at the proximal portion of the left fallopian tube, consisting of an intra-luminal mass invading the fallopian tube wall and left uterine fundal wall, extending to within 0.5 mm of the uterine serosa (Fig. 1). No foci of STIC or STIL were identified throughout the tube, and the fimbriated end was completely uninvolved. Immunohistochemical stains showed that the tumor cells were diffusely positive for p53 (Fig. 1D) and p16 (Fig. 1E), consistent with high-grade serous carcinoma. The tumor cells were also diffusely positive for WT-1 (Fig. 1F), which is typical of tubal origin. The patient had genetic testing that identified a BRCA2 mutation (c.5946delT). She underwent adjuvant chemotherapy with single agent carboplatin; however, she recurred within six months of completing treatment. She died due to complications of recurrent disease and recurrent SBO.

3. Discussion

RRBSO is the standard of care for BRCA1/2 carriers for ovarian cancer risk reduction. ACOG, SGO, and the NCCN all concur that carriers of BRCA1/2 mutations should be recommended to undergo RRBSO by age 35–40 (age 40–45 for BRCA2), or at time of completion of child-bearing. As RRBSO has become increasingly common, a growing body of evidence has emerged demonstrating that HGSOC likely develops in the distal fallopian tube. There is now significant evidence, especially from specimens analyzed via SEE-FIM protocol after RRBSO, that HGSOC develops in the fimbriated end of the fallopian tube in a stepwise fashion through the accumulation of multiple mutations (Reade et al., 2014). The current prevailing theory of HGSOC pathogenesis is that cells progress through the p53 signature (benign-appearing tubal epithelium with a p53 mutation) to STIL and STIC lesions (epithelial stratification, nuclear atypia, active proliferation), and eventually to invasive carcinoma with invasion of the basement membrane (Reade et al., 2014; Walker et al., 2015).

Much of this evidence is based on the discovery of occult carcinoma and pre-cancerous lesions in the fallopian tube at the time of RRBSO. A systematic review of 24 studies including a total of 6283 patients (4473 BRCA1/2 carriers) found 75 patients with occult tubal carcinoma at time of RRBSO in addition to 93 patients with STIC/STIL (Piedimonte et al., 2020). Table 1 (adapted from Piedimonte et al. (2020)) details the histologic findings and location of occult carcinomas from studies included in the systematic review. Although not all of the original studies describe the location of the lesion within the tube, of those that did, 52 cases were located within the fimbriated end of the fallopian tube. Of the six cases located elsewhere in the tube, 5 were located in the non-fimbrial (ampulla or isthmus) portion of the tube, and one arose in the ampulla.

The case reported here is unique due to the site of origination of the patient’s tumor in the proximal fallopian tube and adjacent cornua with an uninvolved fimbriated end. This case highlights the importance of...
Table 1
Location and Type of Occult Tubal Lesions at time of RRBSO (Table adapted from Piedimonte et al., 2020).

| Reference       | Sample                                      | Invasive Tubal Carcinoma at time of RRBSO | STIC/STIL at time of RRBSO | Histologic Finding                                                                 | Tubal Location                  |
|-----------------|---------------------------------------------|------------------------------------------|---------------------------|-------------------------------------------------------------------------------------|----------------------------------|
| Leeper et al. 2002 | 30 BRCA + or HR patients undergoing RRBSO | 1                                        | 2                         | Right STIC, 8 mm Early invasive FT carcinoma, 7 mm STIC < 1 cm                      | Not specified                    |
| Agoff et al. 2004 | 7 HR patients undergoing prophylactic TAH-BSO | 1                                        | 3                         | Stage 1 invasive FT carcinoma (invades stalk only), 7 mm Stage IC STIC, single malignant cells in tubal lumen, 8 mm Stage 1A focus of STIC, 2 mm Stage 1A fimbrial STIC, 4 mm | Fimbria (1)                      |
| Olivier et al. 2004 | 90 RRBSO (BRCA + or HR)                     | 3                                        | 0                         | Stage IA FT endometrioid adenocarcinoma, grade 2 Stage IIIB FT Pap serous adenocarcinoma Stage IV poorly diff fallopian tube/ovarian adenocarcinoma | Not specified                    |
| Finch et al. 2006 | 490 BRCA + RRBSO                           | 3                                        | 0                         | Stage IIB 5 cm tumor attached to right tubal fimbria Stage IIA fimbrial carcinoma  | Fimbria (3)                      |
| Lamb et al. 2006 | 113 HR/BRCA + RRBSO                        | 1                                        | 4                         | FT HG microinvasive pap serous adenocarcinoma (invades stalk) Fallopian tube containing focal HG carcinoma in situ Fallopian tube containing focal HG carcinoma in situ Fallopian tube containing focal HG carcinoma in situ Fallopian tube carcinoma in situ | Not specified                    |
| Callahan et al. 2007 | 122 BRCA + RRBSO                          | 4                                        | 3                         | Stage IIA invasive serous fimbrial carcinoma (omentum, peritoneum, uterine serosa positive) Stage IC grade 2 endometrioid fimbrial carcinoma Stage IIA invasive grade 2 serous fimbrial carcinoma (1 mm) + ovarian implant (3 mm) Stage II invasive grade 2 endometrioid tubal carcinoma STIC (pilae of single fimbria) STIC | Fimbria (6), ampulla (1)          |
| Laki et al. 2007 | 89 BRCA + RRBSO                            | 3                                        | 0                         | Stage IA FT carcinoma Stage IA FT carcinoma Stage IIIA FT carcinoma | Not specified                    |
| Hirst et al. 2009 | 45 BRCA + and HR RRBSO                     | 3                                        | 1                         | Distal FT microinvasive serous carcinoma (0.3 mm) Poorly differentiated serous FT carcinoma (2.5 mm) FT invasive carcinoma with associated STIC (2.7 mm) STIC (1 mm) | Fimbria (4)                      |
| Rhiem et al. 2011 | 175 BRCA RRBSO                             | 1                                        | 0                         | Microinvasive carcinoma of distal FT, stage IA | Not specified                    |
| Manchanda et al. 2011 | 308 HR and BRCA + RRBSO                  | 1                                        | 9 STIC 10 STIL            | Stage IA invasive serous FT carcinoma | Fimbria (2)                      |
| Powell et al. 2011 | 111 BRCA + RRBSO                          | 4                                        | 5                         | FT HGSC (2.7 mm, 1.7 mm) T HGSC (6 mm) FT serous carcinoma (12 mm) FT serous carcinoma (2.2 mm) Focus of STIC STIC (3 mm) Focus of STIC | Not specified                    |
| Yates et al. 2012 | 136 BRCA + RRBSO                          | 1                                        | 3                         | 2 foci STIC (1.7 mm, 0.4 mm) 2 foci STIC (1 mm, 0.4 mm) STIC (2 × 3 mm) HGSC FT (2 mm) | Fimbria (4)                      |
| Mingels et al. 2012 | 226 BRCA + RRBSO (105 BRCA- controls)     | 2                                        | 14                        | 2 invasive tubal ca 14 STIC | Fimbria (11) Non-Fimbrial (Isthmus or ampulla) (5) |
| Sherman et al. 2014 | 996 RRBSO BRCA+/HR                        | 6 (1 HR, BRCA neg)                       | 4                         | Stage IIC serous FT adenocarcinoma (5 mm, 2.5 mm ovarian lesion) Stage IIC serous FT adenocarcinoma (5 mm) Stage IA FT adenocarcinoma (1 cm) Stage IA serous FT adenocarcinoma (microscopic focus) Stage IC serous FT adenocarcinoma (microscopic foci ovaries/FT) Stage IA microscopic focus in left FT Microscopic STIC focus x4 pts | Not specified (8)                |
| Lavie et al. 2016 | 2                                          | 0                                        |                           |            |                                        |                                  |

(continued on next page)
The median residual tubal epithelial surface area was 14 mm$^2$; the median length of residual tubal epithelium was 6 mm, and the tubal epithelium left after a simulated RRBSO during hysterectomy. Removing a maximum portion of the fallopian tube during RRBSO. Cass et al. (2010) performed a prospective study evaluating the length of intraepithelial lesion; HGSC.

Tubal epithelium remnants were identified in 73% of the cornua evaluated; the median length of residual tubal epithelium was 6 mm, and the tubal epithelium left after a simulated RRBSO during hysterectomy. Cass et al. (2010) performed a prospective study evaluating the length of intraepithelial lesion; HGSC.

Stewart et al. 2019

Blok et al. 2016

Stage IA tubal carcinoma (2 mm) Stage IIC tubal carcinoma Stage IIIA tubal carcinoma

Stage IIA2 tubal carcinoma

Minig et al. 2018

Case report 1 BRCA1 RRBSO 1 0 High grade serous tubal carcinoma (1 mm) Fimbria (1)

Stewart et al. 2019

183 BRCA+ /HR RRBSO 1 3 Stage IFT cancer STIC x3 patients

Minig et al. 2018

359 BRCA + RRBSO 5 3 STIC Stage IA FT carcinoma (STIC associated) Stage IIA1 FT carcinoma (STIC associated)

Stage IIC (STIC associated)

Fimbria (7)

Informed consent

Informed consent for this case report was obtained from the patient’s next-of-kin, and permission was granted to allow the patient’s information to be used in this case report.

Declaration of Competing Interest

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References

Callahan, M.J., Crum, C.P., Medeiros, F., et al., 2007. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 25 (25), 3985–3990. https://doi.org/10.1200/JCO.2007.12.2622.

Cass, I., Walts, A., Karlan, B.Y., 2010. Does risk-reducing bilateral salpingo-oophorectomy leave behind residual tube? Gynecol. Oncol. 117 (1), 27–31. https://doi.org/10.1016/j.ygyno.2009.12.023.

Finch, A., Shaw, P., Rosen, B., Murphy, J., Narod, S.A., Colgan, T.J., 2006. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol. Oncol. 100 (1), 58–64. https://doi.org/10.1016/j.ygyno.2005.06.065.

Kotsopoulos, J., Gronwald, J., Karlan, B.Y., et al., 2018. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol. 4 (8), 1059–1065. https://doi.org/10.1001/jamaoncol.2018.0211.

Kuchenbaecker, K.B., Hopper, J.L., Barnes, D.R., et al., 2017. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 317 (23), 2402–2416. https://doi.org/10.1001/jama.2017.7112.

Marchetti, C., De Felice, F., Boccia, S., et al., 2018. Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A meta-analysis. Crit Rev Oncol Hematol. 132, 111–115. https://doi.org/10.1016/j.critrevonc.2018.09.018.

Piedimonte, S., Frank, C., Laptite, C., Quaiattini, A., Goltieb, W.H., 2020. Ovulat Tubal Carcinoma After Risk-Reducing Salpingo-oophorectomy: A Systematic Review.
Reade, C.J., McVey, R.M., Tone, A.A., et al., 2014. The fallopian tube as the origin of high
grade serous ovarian cancer: review of a paradigm shift. J Obstet Gynaecol Can. 36
(2), 133–140. https://doi.org/10.1016/S1701-2163(15)30659-9.

Shu, C.A., Pike, M.C., Jotwani, A.R., et al., 2016. Uterine Cancer After Risk-Reducing
Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations.
JAMA Oncol. 2 (11), 1434–1440. https://doi.org/10.1001/jamaoncol.2016.1820.
Walker, J.L., Powell, C.B., Chen, L.M., et al., 2015. Society of Gynecologic Oncology
recommendations for the prevention of ovarian cancer. Cancer. 121 (13),
2108–2120. http://doi.org/10.1002/cncr.29321.