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

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A B S T R A C T

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 (Tubectomy) 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

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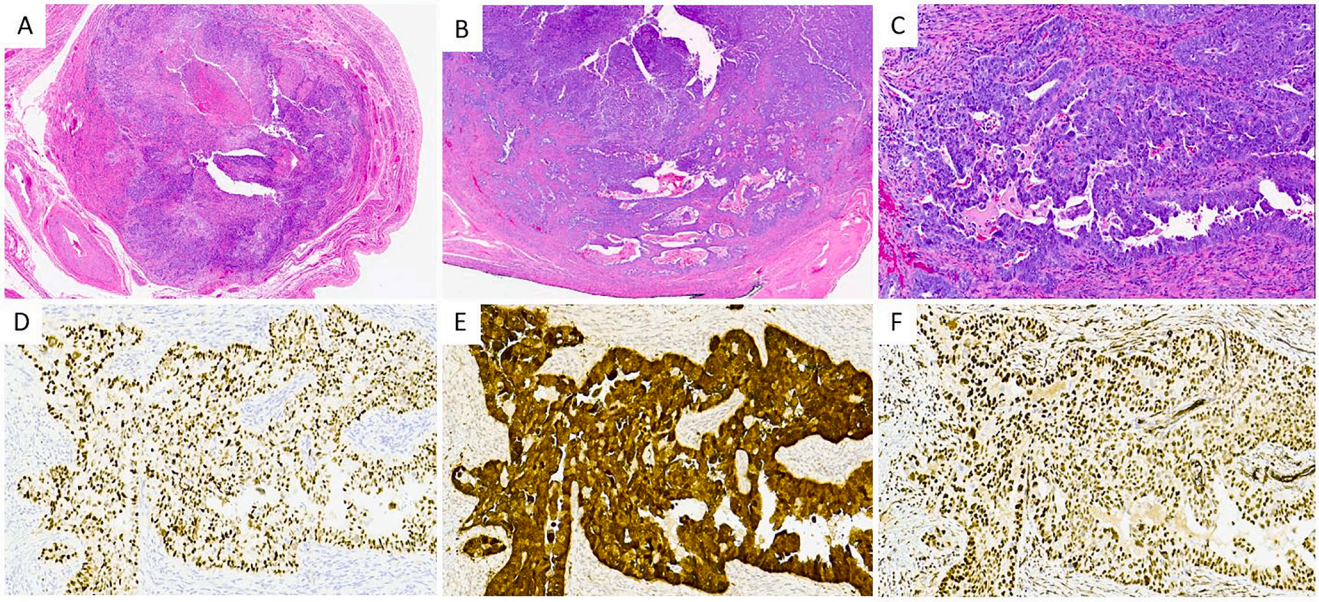

Fig. 1. Salpingectomy and hysterectomy pathology. High-grade serous carcinoma involving the proximal end of the fallopian tube with tubal wall invasion (A) and the uterine fundus with myometrial invasion (B). The serous carcinoma showed typical histomorphology characterized by marked nuclear pleomorphism (C) and stained diffusely and strongly positive for p53 (D), p16 (E), and WT-1 (F) immunohistochemical stains.

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 intraluminal 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 childbearing. 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 IC 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 IB fimbrial carcinoma 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 IIIA 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 (plicae of single fimbria) STIC STIC	Fimbria (6), ampulla (1)
Laki et al. 2007	89 BRCA + RRBSO	3	0	Stage IA FT carcinoma Stage IA FT carcinoma Stage IIIC 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 Focus of STIC STIC (2.2 mm)	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 IIIC serous FT adenocarcinoma (5 cm) 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	Fimbria (2) Not specified (8)
Lavie et al. 2016		2	0		

(*continued on next page*)

Table 1 (*continued*)

Reference	Sample	Invasive Tubal Carcinoma at time of RRBSO	STIC/STIL at time of RRBSO	Histologic Finding	Tubal Location
	92 BRCA + Ashkenazi RRBSO			Stage IC FT serous papillary adenocarcinoma (foci of vascular invasion, colonic serosal implant) Stage IIB FT HGSC	Fimbria (1) Not Specified (1)
Lee et al. 2017	63 BRCA + RRBSO	3	2	Stage IIIC FT high-grade papillary serous carcinoma Stage IIB FT high-grade papillary serous carcinoma Stage IIIC FT high-grade papillary serous carcinoma STIC x2 pts	Distal Fallopian Tube (5)
Ricciardi et al. 2017	290 BRCA+/121 HR RRBSO	2 (1 BRCA unknown)	7 STIC 8 STIL	Stage IA High grade serous FT carcinoma Stage IIIC High grade serous FT carcinoma (mets to omentum, pelvic and aortic nodes)	Not specified
Zakhour et al. 2016	257 BRCA + RRBSO	3	9 STIC	Stage IA tubal carcinoma Stage IC2 tubal carcinoma Stage IIIA2 tubal carcinoma STIC < 5 mm x9 patients	Fimbria (9)
Giannos 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 I FT cancer STIC x3 patients	Not specified
Blok et al. 2016	471 BRCA+/HR RRBSO	7	0	Stage IC paratubal carcinoma (3 mm) Stage IIIC FT carcinoma (5 mm, RO 6 cm) Stage IIIA FT carcinoma (<1mm) Stage IIB FT carcinoma (2 mm) Stage IIIB FT carcinoma (1.8 cm, 5 cm ovarian mass) Stage IA FT carcinoma (1 mm) Stage IA FT carcinoma (2 mm)	Not specified
Thompson et al. 2018	130 BRCA+/HR RRBSO	1	0 STIC 3 STIL	Stage IC3 high grade serous FT carcinoma	Not specified
Minig et al. 2018	359 BRCA + RRBSO	5	3 STIC	Stage IA FT carcinoma (STIC associated) Stage IA FT carcinoma Stage IIIA1 FT carcinoma (STIC associated) Stage IC1 (STIC associated) Stage IIIA2 (STIC associated)	Fimbria (7) Isthmus (1)

HR = High risk for breast/ovarian cancer, BRCA status negative or unknown; FT = fallopian tube; STIC = serous tubal intraepithelial carcinoma; STIL = serous tubal intraepithelial lesion; HG = high-grade; HGSC = high grade serous carcinoma.

removing a maximum portion of the fallopian tube during RRBSO. Cass et al. (2010) performed a prospective study evaluating the length of tubal epithelium left after a simulated RRBSO during hysterectomy. Tubal epithelium remnants were identified in 73% of the cornua evaluated; the median length of residual tubal epithelium was 6 mm, and the median residual tubal epithelial surface area was 14 mm^2 (Cass et al., 2010).

The case presented in this report, along with data from Cass et al. (2010), suggests that RRBSO may be insufficient to remove the entire tubal epithelium. Concurrent hysterectomy may be considered to ensure that there is no remaining tubal epithelium. Women undergoing RRBSO should be counseled regarding the residual risk of developing HGSOC after RRBSO and the risks and benefits of concurrent hysterectomy. Given the ongoing research into the risks of serous endometrial cancer in BRCA1/2 carriers and possible increased risk of breast cancer in patients taking combined estrogen and progesterone HRT regimens, women desiring maximal risk reduction may choose to undergo concurrent hysterectomy. Although rare, this case demonstrates that primary fallopian tube carcinoma may arise in the proximal fallopian tube, and the tubal site of origin of HGSOC is not limited to the fimbriated end, as was previously thought. Interestingly, for the SEE-FIM protocol, I think it was originally intended for just the fimbriated end but now indicates submission of the entire fallopian tube (and ovaries if present). This case also suggests that SEE-FIM analysis of RRBSO specimens may not be sufficient to identify all lesions of interest. We propose that the entire tubal specimen, including the proximal end, should undergo close pathologic analysis to ensure that precursor lesions and occult carcinoma are not missed in portions of the fallopian tube outside the fimbriated end.

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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