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High-Grade Serous Tumor Arising from Fallopian Tube in a BRCA Mutation Carrier after Prophylactic Oophorectomy

Domenica Lorusso Roberta Di Rocco Maria Mancini
Francesco Raspagliesi

Department of Gynecologic Oncology, Fondazione IRCCS National Cancer Institute, Milan, Italy

Key Words

Ovarian cancer · Fallopian tube · BRCA mutation · Kurman's hypothesis

Abstract

We present the case of a 67-year-old patient with a BRCA1 mutation and breast cancer who underwent prophylactic oophorectomy. After 6 years, an abdominal computed tomography revealed a pelvic mass which proved to be a poorly differentiated serous carcinoma originating from the right residual tube which previously had not been removed during prophylactic surgery. This case report suggests that much effort should be made during prophylactic oophorectomy to completely remove the tubes, especially in light of the recent pathologic theories on the tubal origin of ovarian cancer.

Case Report

A 58-year-old woman was diagnosed with breast cancer in August 1989. She underwent left quadrantectomy and homolateral axillary lymphadenectomy for a pT2N1M0 invasive ductal carcinoma. The hormonal receptor status was negative. In June 1993, a bilateral breast cancer recurrence was diagnosed and cured with demolition surgery and CMF chemotherapy for 8 cycles. Genetic BRCA germline analysis was carried out and BRCA1 mutation was detected. Given that the patient was 67 years old at the time of BRCA mutation diagnosis, a bilateral oophorectomy was proposed, and in June 1998, she underwent a bilateral oophorectomy showing no evidence of disease in the ovaries and tubes. During surgery, massive peritoneal adhesions were detected which complicated the surgical procedure possibly due to a previously undiagnosed pelvic inflammatory disease syndrome (PID).

In October 2004, after an increase in serum Ca-125 levels was registered, an abdominal computed tomography scan was performed evidencing a pelvic 8-cm complex mass reaching the hepatic flexure and the transverse colon. The results of a colonoscopy and a gastroscopy were negative, so the patient

underwent an abdominal longitudinal midline laparotomy with removal of the mass and right hemicolectomy. During surgery, it became evident that the mass was originating from a residual of the right fallopian tube which, inaccurately, had not been removed during the previous prophylactic oophorectomy, probably because of the significant scarring due to the previous PID. The histological report documented a poorly differentiated (G3) serous carcinoma derived from the right residual tube with presence of tumor at the tubal fimbria, complete absence of ovarian stroma, and involvement of the peritoneum of the right colon without muscle and mucosa infiltration (FIGO stage IIIC). After surgery, the patient received 6 cycles of carboplatin AUC6-paclitaxel 175 mg/mq chemotherapy which was completed in April 2005. The patient is still alive and disease free.

Written informed consent was obtained from the patient for publication of this case report.

Discussion

Fifteen to 40% of women with BRCA1/2 mutations present an increased risk of ovarian cancer [1]. The suggested prophylactic surgical approach for women with a family history of ovarian carcinoma or BRCA1/2 mutation is bilateral salpingo-oophorectomy with the intent to reduce the risk of ovarian cancer.

The history of this patient seems to suggest that much attention should be paid during prophylactic salpingectomy to carefully and completely remove the fallopian tubes, even taking away the intrauterine portion of the tubes, as suggested by several authors, due to the risk that a part of the organ might be erroneously left in place and then would represent the originating site of a subsequent neoplastic transformation.

Moreover, a more intriguing scenario is opening up concerning the pathogenesis of ovarian cancer. Recently, Kurman [2] proposed a hypothesis on ovarian cancer origin which suggests that ovarian cancer may represent the metastatic lesion of a tumor with tubal origin.

In 2001, Dutch investigators first described tubal intraepithelial carcinomas, later designated as 'serous tubal intraepithelial carcinomas (STICs)', and occult invasive high-grade serous carcinomas (HGSCs) in the fallopian tube of women with a genetic predisposition to ovarian cancer that closely resembled ovarian HGSC, in the absence of ovarian lesions [3]. It was later proposed that secondary implantation of malignant cells from the tubal carcinoma to the ovary develops into a tumor mass resembling cancer originating in the ovary [4].

The authors proposed that the failure to identify the precursors of ovarian cancer in the past was due to the research of these lesions being concentrated on the ovaries where, logically, they were expected to be, thus explaining why a careful and systematic examination of the fallopian tubes had been neglected [5]. Additional studies, in which the fallopian tubes were completely sectioned using the Sectioning and Extensively Examining the FIMbria (SEE-FIM) protocol, confirmed that STICs and small early invasive tubal carcinomas occurred not only in women with a genetic predisposition to the development of ovarian cancer, but also in 50–60% of women without recognized BRCA mutations [6]. Moreover, in most cases, the tumor lesions were detected in the fimbria, and it has been proposed that the earliest neoplastic changes begin in the secretory-type cells [6]. Further evidence supporting this hypothesis comes from the detection of identical TP53 mutations in STICs and concomitant ovarian HGSCs, indicating a clonogenic relationship between the two lesions [6].

In a series of 342 consecutive gynecologic cancers, STICs were present in 18.8% of women with serous ovarian cancer, while it was not possible to identify these precursor lesions in any other histological subtype [7].

A gene profiling study showing that the gene expression profile of HGSC is more closely related to fallopian tube epithelium than to the ovarian surface epithelium and immunohistochemical studies emphasizing that HGSC expresses PAX8, a Müllerian marker, but not calretinin, a mesothelial marker, lend further support to Kurman's hypothesis [8]. There are no features according to which it is possible to distinguish between primitive tubal carcinomas and ovarian carcinomas originating in the tube and secondarily implanted in the ovary; this aspect further supports the theory that these tumors are not different entities.

The ovary appears not to be the originating site also of endometrioid and clear-cell tumors. Data support the theory that endometrioid and clear-cell tumors arise from endometrial tissue passing through the fallopian tube and being secondarily implanted into the ovary and that mucinous tumors also develop from the tubal-peritoneal junction [9]. We speculate that the detached clusters of endometrial epithelium pass through the tube and are implanted on the ovarian surface where they can develop into 'atypical proliferative serous tumors (APSTs)' or are implanted on the pelvic and abdominal peritoneum to produce noninvasive implants.

The history of our patient is very intriguing: she had both ovaries and the left fallopian tube removed during the prophylactic surgery, while the right tube was erroneously left attached to the uterus, possibly because of the scarring and adhesions related to a previous PID which made it difficult to detect the tube. Six years later, a HGSC originating from the residual tube was diagnosed and completely removed during surgery. The patient was treated with conventional platinum-based chemotherapy and is still alive and disease free.

The impressive extensive disease-free interval of our FIGO stage IIIC patient positively fits the surgical radicality obtained during cytoreductive surgery and the documented increased platinum sensitivity in BRCA mutation carriers [10]. Kurman's theory and our clinical case report possibly suggest that salpingectomy or fimbriectomy alone with ovarian sparing might be sufficient to reduce the risk of ovarian cancer in patients with BRCA mutation and preservation of fertility and hormonal status. At present, this approach needs to be evaluated in randomized clinical trials.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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