Fallopian Tubes May Play a Role in the Development of Serous Carcinoma of the Ovary and Peritoneum.

Written by Hilary Haefner, PA(ASCP)

Introduction:
In the past, fallopian tubes were usually viewed as organs removed for incidental purposes. Recently, the fallopian tube has been gaining a lot of attention in the pathology world for being a possible key player in the pathogenesis of serous ovarian carcinomas, and specifically primary peritoneal carcinomas. For this reason it is critical to pay close attention to the patient's clinical history, and make sure that fallopian tubes are properly processed.

Serous carcinomas are not only the most malignant tumor of the ovaries, but also attribute to the most deaths. Ovarian serous carcinomas are divided into two major groups: high-grade and low-grade serous carcinomas. High-grade serous tumors of the ovary are associated with a mutation in the tumor suppressor protein, p53, which can be demonstrated using immunohistochemistry (IHC) staining. Recent studies have linked BRCA1 and BRCA2 gene mutations as a major risk factor in the development of ovarian carcinoma. The majority of ovarian cancers found in BRCA-positive women are high-grade serous carcinomas, which more recently are thought to have originated from the fimbriated end of the fallopian tube.

The ovarian surface is the most common place for serous tumors to occur, however, on rare occasions they occur as primary tumors of the peritoneum and are referred to as primary peritoneal serous carcinoma (PPSC). PPSC is classified as diffuse tumor involvement of the peritoneum, little to no involvement of the ovaries, and with no other apparent primary tumor. In PPSC the ovaries appear normal in size, and the involvement of extra-ovarian organs is greater than the involvement of the ovary. If the ovary is involved, it may only be superficially involved and must have no cortical invasion. Clinically, these patients present with ascites, raised CA 125, and sometimes an omental cake, with little to no ovarian involvement. In the past decade, the diagnosis of PPSC has risen from 10% to 18-25% because more physicians are accepting the idea that some ovarian tumors may be originating from other organs, such as the fallopian tube.

Originally, PPSC has been thought to arise from the mesothelium of the ovary that subsequently spreads to the peritoneum, with which it shares a common space. Recently, it has been suggested that the serous tumors of the ovary and peritoneum histologically resemble tumors that one would expect to see in the epithelium from an endodermal-derived organ, such as the fimbriated end of a fallopian tube.

Methodology:
The current protocol for proper examination of a BRCA-positive patient's fallopian tubes is referred to as Sectioning and Extensively Examining the Fimbriated end of the fallopian tube (SEE-FIM protocol). In this protocol, it is required for the tissue to be fixed for at least four hours in 10% buffered formaldehyde. This step is crucial, because it both preserves and makes the tissue firm enough to get thin sections for proper evaluation. The second step is to amputate the fimbriated end of the fallopian tube and section it along the length of the fimbriae. Then the remainder of the fallopian tube is cross-sectioned at 0.2-0.3 cm intervals. The fallopian tube is submitted in its entirety in order to
detect any type of tubal lesion. Additionally, if the ovaries are received they are also sectioned perpendicular to the long axis, at 0.2-0.3 cm intervals. Currently, this protocol is in place for specimens in which the patient is BRCA positive. It may be advisable to use the SEE-FIM protocol in all suspected cases of serous carcinomas, especially for suspected primary peritoneal serous carcinomas, in order to gain a better understanding of the origin of these types of tumors.

Results:
Many times women who present with primary peritoneal serous carcinoma must undergo a de-bulking surgery as part of their treatment. In a surgical report from The Hospital of Central Connecticut at New Britain General, a woman presented with ascites with a cancer of unknown origin (Figure 1). Upon examination, there appeared to be tumor involvement of multiple organs, and the patient underwent a de-bulking surgery to include omentum, right and left pelvic peritoneum, uterus, cervix, bilateral fallopian tubes, and ovaries. The omentum displayed diffuse indurated congested fat, consistent with omental caking (Figure 2C). On sectioning, there was no tumor grossly identified (Figure 2D); however on histological evaluation there were multiple scattered foci of metastatic adenocarcinoma, measuring up to 0.1 cm. The peritoneum also showed microscopic foci of metastatic adenocarcinoma, histologically. The left fallopian tube in this case (Figure 3A) grossly contained a friable, papillary tumor within the middle portion of the tube. Histologically, this tumor was called papillary serous carcinoma (Figure 3B). This tumor involved the left ovary, right ovary, uterine serosa, and myometrial lymphatics.

Figure 1: Ascites fluid of a patient with papillary serous carcinoma of the fallopian tube. 1A: H&E slide, showing malignant cells with some visible mitotic figures. 1B: IHC staining of CK7+ ascites fluid shows that the cells are of genitourinary origin. 1C: positive staining for P53 is common in papillary serous carcinoma. 1D: CA-125 positive staining is common for patients with papillary serous carcinoma.
Figure 2: Omental caking in two separate cases of papillary serous carcinoma. 2A and 2B: show grossly the tumor involving the omentum prior to sectioning (2A) and after sectioning (2B). 2C and 2D: shows the omental caking however on sectioning (2D) the tumor is not apparent grossly but is present microscopically.

Figure 3: Gross picture of papillary serous carcinoma of the fallopian tube along with the histologic pattern of papillary serous carcinoma.

Discussion:
One proposed mechanism suggests that the epithelium of the fimbria develops a p53 mutation leading to tubal intraepithelial carcinoma. The tubal intraepithelial carcinoma undergoes a malignant change to become serous carcinoma, which then can either invade the fallopian tube locally, or proliferate and shed tumor implants to the mesothelial-lined surfaces of the ovary or peritoneum.\(^2\) This is a likely route of transmission due to the close proximity of the fallopian tube and ovary in the body. This mechanism also supports the theory that the fallopian tube is the source for PPSC as well because it shares the same space within the body and has a histological pattern that is more probable to be the source.\(^3\) In the case mentioned above, the patient had papillary serous carcinoma of the fallopian tube, however, presented clinically with symptoms of someone with PPSC. There could be other cases of fallopian tube primary tumors that get diagnosed as PPSC because there was not proper examination of the fallopian tube.
In many cases of ovarian serous carcinoma in which the fimbriated ends of the fallopian tubes have been examined, serous tubal intraepithelial carcinoma (STIC) has also been identified. In one study, it was shown that of patients diagnosed with PPSC, 40% also showed STIC after histological examination of the fallopian tube. This could mean that some women who are diagnosed with PPSC may have a primary fallopian tube carcinoma, rather than a primary peritoneal carcinoma. Additionally, in BRCA-positive women who have prophylactic salpingo-oophorectomies, 1% of those specimens were found to have STIC. For this reason there has been a strong focus on submission of the entire fallopian tubes for patient’s specimens that are BRCA-positive. Thorough histological examination is also crucial because tumors arising in the fallopian tube can be discrete, even on microscopic examination.

**Conclusion:**
As more evidence comes forward about the role that the fallopian tube may play in the development of ovarian cancer and primary peritoneal serous carcinoma, thorough processing is crucial for an accurate diagnosis. Tumors arising in the fallopian tube can be discrete, even on microscopic examination. Since serous carcinoma of the ovary has a morbid prognosis, understanding its origin could provide a new direction in how clinicians treat at-risk patients. Proper histological examination starts at the bench, with proper sampling and sectioning of the fallopian tube by the Pathologists’ Assistant, Pathology resident, and/or the Pathologist.
References