Review Article

Serous Tubal Intraepithelial Carcinoma: Emerging Trend in Ovarian Neoplasm: A Must Know for a Pathologist

Abstract

Among all gynecological malignancies, ovarian cancer is associated with the highest rate of mortality. Most ovarian carcinomas have been suggested to originate from the ovarian surface epithelium or postovulatory inclusion cysts formed after follicular rupture and repair. Over the past decade, a new model has emerged to explain the origin of epithelial tumors of the ovary and the fallopian tube now appears to play a central role; however, there is now compelling evidence that many epithelial pelvic cancers, especially high-grade serous carcinomas of the ovary/peritoneum, begin in the mucosa of the fallopian tube as serous tubal intraepithelial carcinoma.

Keywords: *Fallopian tube, ovary, serous tubal intraepithelial carcinoma*

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What Should Be Known?

Among all gynecological malignancies, ovarian cancer is associated with the highest rate of mortality. It is estimated that there will be >1,40,000 deaths per year worldwide.[1] Although many surgical techniques and chemotherapies have been developed for ovarian carcinoma, the prognosis remains poor, with a 5-year survival rate of 45%.[2] Most ovarian carcinomas have been suggested to originate from the ovarian surface epithelium or postovulatory inclusion cysts formed after follicular rupture and repair.[3] According to the incessant ovulation hypothesis, every ovulation creates a wound, and the surface ovarian epithelial cells are then repaired by increased proliferation. This may increase the likelihood for DNA damage and carcinogenic mutations.[4] However, this hypothesis is inconsistent with the observation that the patients with polycystic ovarian syndrome who have decreased ovulatory cycles appear to have an increased ovarian cancer risk.[5] Nevertheless, attempts to define a precursor lesion from this tissue have always failed.

Over the past decade, a new model has emerged to explain the origin of epithelial tumors of the ovary and the fallopian tube now appears to play a central role. Pathologists have always paid little attention to the fallopian tube; however, there is now compelling evidence that many epithelial pelvic cancers, especially high-grade serous carcinomas (HGSCs) of the ovary/peritoneum, begin in the mucosa of the fallopian tube as serous tubal intraepithelial carcinoma (STIC). This is independent of the fact, whether or not the patient has BRCA mutation and has an increased risk of breast and ovarian cancers. Pelvic HGSC can be diagnosed in an early stage, now if the pathologists focus their attention to fallopian tubes and look for STIC lesions. These lesions are in the mucosa of the fimbriae of fallopian tubes. These tubal tumors are microscopic, high grade, and resemble HGSC are usually noninvasive and harbor p53 mutations as in advanced stages of HGSC. STIC is found in almost 60% of women with ovarian or peritoneal HGSC only if the tubes are carefully processed for complete microscopic examination.[6]

These features suggest that all these pelvic HGSC first start in the mucosa of the fallopian tube as STIC and shed these tumor cells which then get implanted on the ovary and peritoneum where they progress to form large tumors.[7] One more hypothesis suggests that these benign mucosal cells from the fallopian tube get shed onto the ovary during ovulation and get entrapped in the ovarian tissue near

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the ruptured ovarian follicle which later on form epithelial inclusion glands and cysts in the ovary, which may later transform into HGSC.

Molecular studies are identifying the sequence of events which lead to the transformation to STIC in fallopian tubes and HGSC in the ovary. P53 appears to play a major role. In women, who do not have BRCA germline mutations, there may be a risk-reducing role for removing fallopian tubes during abdominal surgery done for any other indication or for performing salpingectomy instead of tubal ligation for sterilization.[8]

How Are Serous Tubal Intraepithelial Carcinoma Lesions Diagnosed

Traditionally, the technique of taking one cross section from the middle of the fallopian tube and not from the nonfimbriated end for histopathologic examination should be discouraged because these STIC lesions are present in the fimbriated end of the fallopian tube and can be missed on traditional grossing techniques. After proper grossing, a pathologist should be aware of the diagnostic criteria for tubal carcinoma, in particular STIC.

Currently, the diagnosis of these STIC lesions depends on a combination of morphology and immunohistochemistry. The morphologic criteria are severe nuclear atypia, mitosis, and loss of polarity of the mucosa of the tube (i.e. stratification, piling up, and tufting). There should also be a loss of normal specialized features of tubal mucosa such as cilia, terminal bars, and peg cells. The immunohistochemical criteria are aberrant P53 and MIB1 staining. Aberrant P53 staining is defined as either diffuse, strong nuclear expression, or complete absence of any staining in any nuclei. Normal mucosal epithelium should exhibit patchy week nuclear P53 expression. Aberrant MIB1 staining simply means that the percent of cells that exhibit nuclear expression in the lesion is noticeably higher than the small percent of cells in the adjacent normal mucosa (some authors suggest 10% or more is sufficient to call aberrant). When both the criteria are met the diagnosis of STIC can be made. If invasion into the underlying stroma is present, then a diagnosis of invasive tubal HGSC can be made. Occasionally, some tubal proliferations may show partial criteria but not all criteria for STIC; some suggest naming them as serous tubal intraepithelial lesion. Their management still remains to be ascertained.

Difficulties in Diagnosis

It is possible for metastasis from either primary gynecological tumor outside the tube (endometrium and cervix) or primary nongynecological tumors (colorectal and breast) to grow in the fallopian tube and mimic STIC. Primary gynecological tumors should be PAX8 positive, whereas nongynecological carcinomas are PAX8 negative. In addition, STIC should be WT1 positive, whereas nonserous carcinomas of the gynecological organs are WT1 negative. PAX8 and WT1 are useful when trying to differentiate STIC from metastatic carcinoma of other sites.

Differential Diagnosis

The differential diagnosis of STIC includes a variety of benign proliferations, metaplasias and reactive alterations to inflammation, hemorrhage (endometriosis), or prior treatment (radiation and chemotherapy).

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Conflicts of interest

There are no conflicts of interest.

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