Serous Tubal Intraepithelial Carcinoma or Not? Metastases to Fallopian Tube Mucosa Can Masquerade as In Situ Lesions

Reena Singh, MD; Kathleen R. Cho, MD

Context.—Nonuterine high-grade serous carcinomas (HGSCs) are believed to arise most often from precursors in the fallopian tube referred to as serous tubal intraepithelial carcinomas (STICs). A designation of tubal origin has been suggested for all cases of nonuterine HGSC if a STIC is identified.

Objective.—To highlight that many different types of nongynecologic and gynecologic carcinomas, including HGSC, can metastasize to the tubal mucosa and mimic de novo STIC.

Data Sources.—A mini-review of several recently published studies that collectively examine STIC-like lesions of the fallopian tube.

Worldwide, ovarian carcinoma is the seventh most common cancer and the eighth most common cause of death from cancer in women. High-grade serous carcinoma (HGSC) is the most common and most lethal type of ovarian carcinoma. For many decades it was assumed that HGSCs arise from the ovarian surface epithelium, but in 2001 this line of thinking was challenged by the identification of presumptive HGSC precursors—that is, serous tubal intraepithelial carcinomas (STICs), and occult HGSCs in the fallopian tubes of patients with germline BRCA1 mutations who were undergo prophylactic surgery. Detailed examination of prophylactic specimens in this patient population implicated the tubal fimbriae as the origin of HGSC. Additional evidence of tubal origin of HGSC was provided by several subsequent studies showing STIC with invasive carcinoma confined to the fallopian tube in women without hereditary predisposition to ovarian cancer. Consequently, a recent consensus statement on primary site assignment of tubo-ovarian HGSCs recommends assigning cases as tubal in origin if STIC or invasive mucosal carcinoma is identified in the fallopian tube.

Accepted for publication May 23, 2017.
From the Department of Pathology, University of Michigan Medical School, Ann Arbor.
The authors have no relevant financial interest in the products or companies described in this article.
Presented in part at the New Frontiers in Pathology meeting; October 13–15, 2016; Ann Arbor, Michigan.
Reprints: Kathleen R. Cho, MD, Department of Pathology, University of Michigan, 1506 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200 (email: kathcho@umich.edu).

Conclusions.—The fallopian tube mucosa can be a site of metastasis from carcinomas arising elsewhere, and pathologists should exercise caution in diagnosing STIC without first considering the possibility of metastasis. Routinely used immunohistochemical stains can often be used to determine if a STIC-like lesion is tubal or nongynecologic in origin. In the context of uterine and nonuterine HGSC, STIC may represent a metastasis rather than the site of origin, particularly when widespread disease is present.

both of the STICs associated with HGSCs harbored the identical TP53 mutations found in the matched HGSC. TP53 mutations were also identified in the 2 STICs associated with endometrial carcinoma. In 1 case, the matched endometrial carcinoma lacked TP53 mutation but contained mutations of several genes characteristically mutated in uterine endometrioid carcinomas, including PTEN, KRAS, PIK3CA, MTOR, and ATM. As all of these mutations were absent in the matched STIC, the STIC in this patient was confirmed to be an incidental finding, unrelated to the endometrial cancer. In the fourth case (Figure, A through D), a missense TP53 mutation was identified in the tubal lesion that was not present in the endometrial cancer. However, the tubal lesion also contained mutations of PTEN and CTNNB1, both of which are uncommon in HGSCs. The endometrial carcinoma contained the identical PTEN mutation, confirming a clonal relationship between the tubal and endometrial neoplasms. Interestingly, the endometrial carcinoma harbored a different CTNNB1 mutation than the one present in the tubal lesion. This finding likely represents an example of “convergent evolution” in which mutations of certain genes are recurrently selected for, because they provide affected cells with a strong fitness advantage and/or they cooperate with other preexisting mutations.\textsuperscript{19,20} The findings described above provide compelling molecular evidence that the tubal lesion in the fourth case represents a mucosal micrometastasis from the endometrial carcinoma that mimics STIC. Even more recently, Eckert et al\textsuperscript{21} used whole exome sequencing to analyze tumor samples from 8 women who presented with advanced-stage, sporadic HGSC and underwent primary debulking surgery without having received neoadjuvant chemotherapy. Phylogenetic clustering based on whole exome sequencing data from germline DNA, STIC, and HGSC from 3 sites (fallopian tube, ovary, and omentum) demonstrated STIC to be the HGSC precursor lesion in half of the cases. However, in 2 cases the STICs were identified as mucosal metastases to the fallopian tube rather than HGSC precursors.

Detailed molecular analyses are not necessarily required to demonstrate that the fallopian tube can harbor metastases from other sites in an apparent intraepithelial fashion. For example, Rabban et al\textsuperscript{22} characterized the features of 100 nongynecologic cancers that metastasized to the fallopian
Choosing hormone receptors in association with CK20 and CDX-2 positivity can aid in the recognition of a colon carcinoma metastasis. Because many types of cancers acquire TP53 mutations, reliance on p53 immunostaining alone is insufficient to confirm tubal origin.

Nontubal gynecologic carcinomas can also metastasize to the fallopian tube. A study by Reyes et al suggested that cervical carcinomas can colonize the tubal mucosa and mimic a primary tubal process. At low power, metastatic endocervical adenocarcinoma can share the hyperchromatic appearance of STIC. Unilateral involvement can further add to diagnostic confusion. However, at higher magnification metastatic endocervical adenocarcinoma is characterized by apical mitoses and apoptotic bodies, which will generally be positive for high-risk human papillomavirus by in situ hybridization, and usually does not overexpress p53.

Importantly, p16 is not useful for distinguishing STIC from metastatic endocervical adenocarcinoma because p16 is likely to be overexpressed in both. Finally, Kommoss et al. used histopathology and immunohistochemistry to clarify the relationship between STIC-like lesions and uterine serous carcinoma in 32 cases. On the basis of the histologic and immunohistochemical features, the tubal lesion was considered to represent metastasis from the uterine HGSC in most cases. Only 3 were considered likely to represent an independent tubal primary.

In conclusion, STICs are appropriately considered HGSC precursors, but some apparent STICs actually represent mucosal metastases from tumors arising elsewhere, either within or outside of the female genital tract. The possibility that a tubal intraepithelial carcinoma could represent a metastasis should be considered by practicing pathologists even in the context of HGSC. The accumulated evidence thus far suggests that the presence of STIC in 1 or both fallopian tubes does not provide sufficient evidence for tubal origin of advanced-stage HGSC in a given patient. In many cases, careful attention to morphology and routinely used immunohistochemical stains can be used to distinguish between true STIC and metastases from nontubal primaries.

References