

Fallopian tube pathology – New findings: A review

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Abstract

Pathology of fallopian tube, a small organ, is now emerging as a center of interest in gynecological pathology. Non-neoplastic and neoplastic lesions with importance on the emerging tubal serous carcinoma literature are reviewed to emphasize, in women with family history of carcinoma, the necessity of careful examination of fallopian tube.

Introduction

The fallopian tube has usually revealed only incidental curiosities with no clinical significance and only few conditions needing expert pathology opinion. This organ is now receiving greater attention due to the observation of early malignancies. This new interest is reflected in ovarian cancer prevention strategies. Hence, it is important to know the various changes, both normal and abnormal in fallopian tubes and to distinguish them from the worrying carcinomas.

Non-neoplastic lesions

Metaplasias are regarded as focal epithelial changes into another cell type. A common type is focally accentuated secretory vacuoles which are seen frequently in the fallopian tube. Mucinous metaplasia is another common type in the tube. They are associated with chronic inflammation and with Peutz–Jeghers syndrome.^[1] Arias-Stella reaction is seen with intrauterine pregnancy. Walthard cell rests due to transitional metaplasia are commonly seen near the columnar mesothelial junction. They arise from reserve cells here and are p63 positive.^[2]

Acute and chronic salpingitis sometimes can show enlarged nuclei and hyperchromasia. The maintained polarity and ciliated cells are helpful in identifying metaplasias from more worrisome proliferations. Salpingoliths are rare and seen in <5% of fallopian tubes, frequently non-specific when associated with chronic

salpingitis but are a clue to examine more deeper sections as they may be linked to low-grade serous borderline tumors of the ovary or peritoneum.^[1]

Three types of complex epithelial proliferations are described as follows:

1. Florid epithelial hyperplasia, associated with salpingitis, is a mimic of neoplasms. The epithelial architecture disruption gives a cribriform growth appearance. The disrupted mucosal-submucosal interface delivers epithelium into the submucosal lymphatics. The background inflammation and the continuing transition from non-atypical to atypical epithelium help in characterizing this process from malignancy.
2. The adenofibromas are commonly found in the fimbrial portion. The evidence of stromal differentiation with both inhibin and CD10 positivity is unusually similar to the ovary. The stimulus for both tubal and ovarian tumors may be the same.
3. The papillomas are seen as small distinct detached papillae in the lumen. Being self-limited, their uniform architecture and bland cytomorphology tell them apart from rare papillary serous tumors. This does not dismiss their probable relationship to serous tumors, but they are benign.^[2]

Neoplastic Lesions

With the rising awareness about the fallopian tube as an origin of pelvic serous carcinoma, it has gained attention of pathologists

for precursor conditions. Both ovarian high-grade and low-grade serous carcinomas are initiated not from the ovary, but from the fallopian tube, is an emerging concept from recent studies.^[3]

Serous carcinomas that are primary to the fallopian tube have been recognized for more than 10 years. In spite of traditional guidelines laid down to categorize a tumor as adnexal serous carcinoma, most are being classified as ovarian.^[4]

The evidences cited now in favor of primary fallopian origin are as follows:

1. The dysplastic, intraepithelial lesions predominantly identified in fallopian tube and not in the ovaries in risk-reducing salpingo-oophorectomy specimens of women at increased risk for ovarian carcinomas.^[5]
2. Identical TP53 mutations in the tubal intraepithelial neoplasia and their concurrent ovarian carcinomas suggest a common origin.
3. Few TP53 mutations in the fallopian tube are lacking in the ovary, suggesting that either the lesions are multifocal or developed initially in the tube.^[6]
4. Comparative analysis of chromosomal changes by FISH in the tubal and synchronous ovarian lesions demonstrated likeness supporting a common, monoclonal origin.^[7]
5. Sustenance for the concept that the serous neoplastic process begins in the fallopian tube rather than ovary is the range of putative and perhaps non-obligate precursor lesions identified in the fallopian tube.^[2]

The cause for fimbria as an ideal site for early tubal carcinogenesis is unclear. It is wide-open to the peritoneal cavity, closely located to the surface of ovary, and merges with the serosal mesothelium, forming a “Mullerian–mesothelial” junction. It exhibits epithelial plasticity and harbors reserve cells or nests of transitional metaplasia. Benign serous cystadenomas and cystadenofibromas arise here. Factors such as ovulation implicated in ovarian carcinogenesis are close to the distal fallopian tube. Whether this situation places more biologic or “genetic stress” on the fimbrial mucosa in genetically susceptible individuals needs to be assessed.^[4]

Documentation of a distinctive preneoplastic lesion is a necessary in pelvic serous cancer prevention. The distal fallopian tube is emerging as the source of “fimbrial-ovarian” serous neoplasia with compelling evidence, so new proposals for pathways to cancer in both organs and newer strategies for cancer prevention are being pursued.^[8] Secretory cells of the epithelium here with a restricted ability to repair DNA damage over time are susceptible to gathering mutations and hence vulnerable to carcinogenesis. They are the source of the precursors and their malignant counterparts.^[9] The role of secretory cells in diseases related to ovarian surface lesions such as endometrioid carcinomas, ovarian clear cell carcinomas, and endometriosis is important.^[10] Secretory cell outgrowths (SCOUTs) are clonal proliferations of these cells and may be associated with p53 mutations (so-called p53 signatures), but the alterations in p53 may be absent also.^[9]

p53 signature, an early step in fallopian tube carcinomas, is histologically normal mucosal epithelium but characterized by ≥ 12 consecutive secretory cells in a linear extent showing strong p53 expression mostly seen in the fimbriated end of the tube and are more in number and multifocal in tubal intraepithelial carcinoma (TIC).^[1] Several features are shared by p53 signatures and TIC such as fimbrial location, secretory cell phenotype, DNA damage, strong nuclear p53 positivity, and sometimes continuity with TIC.^[10]

Ten or more consecutive secretory cells in benign tubal mucosa staining positively for insulin-like growth factor II are considered as “IMP3 signature” and this often occurs in anatomic continuity with serous tubal intraepithelial carcinomas (STICs), suggesting a progressive change from IMP3 signature to STICs, to serous carcinoma. Hence, the overexpression of IMP3 which is normally not expressed in normal adult tissue may be involved in the initial process of tubal or pelvic serous carcinogenesis and IMP3 signature may serve as a hidden preneoplastic biomarker for these tumors in women.^[11]

SCOUTs forming a morphologically distinct stretch of the secretory cell population have been linked to serous neoplasia and serve as a biomarker.^[12]

STICs called also as tubal lesions in transition are non-invasive carcinomas recognized in the fallopian tube. 5–7% of prophylactic salpingo-oophorectomy cases from BRCA carriers show them and 57–100% of them are located in fimbriae. They are defined as secretory cells with striking cellular atypia, positive p53 staining, and a high proliferative index.^[10] STICs at the fimbriae of the tube have been established as precursors of high-grade serous carcinomas by pathological and clinical evidence.^[13] It is a good practice that the remaining fallopian tube should be submitted for histopathological examination before signing out a diagnosis of intraepithelial neoplasia in a routine specimen so as to exclude invasive carcinoma component.^[1]

Primary fallopian tube carcinoma is an uncommon tumor in women younger than 40 years and accounts for nearly 0.7–1.5% of female genital malignancies. Bilaterality is infrequent (3–13%).^[1] This rarity and the clinical presentation which simulates an ovarian cancer, allows a correct pre-operative diagnosis possible only in 4% of cases, and is usually first recognized by pathologists as illustrated in the case of bilateral primary serous carcinoma of the fallopian tube in a 36-year-old female.^[14]

Diagnostic criteria to differentiate primary fallopian from primary ovarian/endometrial carcinoma were developed by Hu *et al.* and later modified by Sidles. Thus, primary fallopian tube carcinoma is diagnosed if: Grossly, the main tumor arises from the endosalpinx; histologically, the pattern of tumor resembles tubal mucosa; presence of transition from benign to malignant epithelium; and ovary/endometrium are normal or have a much smaller volume of tumor.^[5] Many a times, it is difficult to differentiate primary fallopian tube cancer from ovarian cancer but is necessary now though in the past the management remained the same. On an average, the 5-year survival rate of

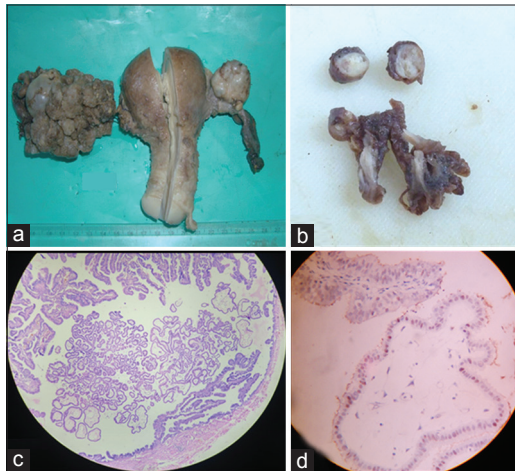


Figure 1: (a) Hysterectomy specimen with bilateral adnexae and the right ovarian tumor, (b) SEE-FIM technique for grossing fallopian tube, (c) Intratubal serous carcinoma (H and E $\times 10$) (d) immunohistochemistry showed p53-positive nuclei in tumor papillae

fallopian tube carcinoma is 50% as compared to ovarian cancer at 77%.^[6]

Do small occult carcinomas/tubal intraepithelial neoplasia/p53 signatures behave in a fashion similar to bulky symptomatic tumors? Is there a need to submit the entire fallopian tube in all routine cases for histopathological examination, to pick up early tubal cancer?

The surgical practice of prophylactic salpingo-oophorectomy for women in BRCA carriers is on the rise and has led to many fallopian tube serous carcinomas being discovered at an early stage. Hence, the fallopian tubes and ovaries should be submitted totally and serial sections are evaluated by a pathologist. The aim is to ensure sectioning and extensive examination of the fimbria sectioning and extensive examination of the fimbria (SEE-FIM protocol). The protocol followed is a fixation for 4 h of the entire tube to decrease loss of epithelium during handling and the distal 2 cm of the fimbriated end transected. The fimbrial mucosa is sectioned longitudinally into four pieces. The remaining tube is sectioned transversely every 2–3 mm into cross-sections. The tubal segments combined with the fully sectioned fimbriated end are submitted in toto^[2] [Figure 1 (unpublished author data)].

New methods for early detection and prevention such as risk-reducing salpingectomy and tubal cytology have been promoted with the understanding of serous carcinoma's origin. Risk-reducing salpingectomies could be performed regularly in women enduring hysterectomies for benign conditions or tubal ligations for sterilization. A possible limitation of the procedure is that it may be unsuccessful when ovaries already have endosalpingiosis, a precursor of ovarian cancer and may progress into ovarian epithelial inclusions and cystadenomas, borderline tumors, and lastly to low-grade serous carcinomas. Tubal exfoliative cytology

to study the epithelial cells from the fimbriated end may be an another method for early detection of ovarian cancer and an effective, minimally invasive means of gaining entry to the fallopian tube, but its current limitation is the lack of standardization.^[15]

Conclusion

Diagnosis at an earlier stage provides better prognosis and survival. Prophylactic bilateral salpingectomy should be considered as an effective method of prevention. Cytology of tubal epithelia may be tried and standardized as an alternative screening method. The entire fallopian tube should be sectioned and thorough pathological review is necessary for the detection of such occult lesions.

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