Research Article

Association of high-grade serous ovarian carcinoma with intraepithelial carcinoma of fallopian tube

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Abstract

Background: The cumulative evidences, both clinicopathological and molecular in the past decade that high-grade serous ovarian carcinoma results from clonal expansion of secretory cells of the distal fallopian tube, rather than ovary. We explored this relationship based on morphological and immunohistochemical studies of a lesion designated "serous tubal intraepithelial carcinoma" (STIC), which closely resembles high-grade ovarian serous carcinoma. This tubal lesion is the plausible origin for pelvic serous carcinomas.

Objective: To study the association between ovarian serous carcinoma and STIC.

Material and Methods: We studied 44 consecutive cases of epithelial ovarian carcinomas from February 2013 to January 2015, including 29 serous, 12 mucinous, and 3 endometrioid. Complete examination of fallopian tubes from each case was done according to serial sectioning and extensive examination of fimbria (SEEFIM) protocol. All the cases were grouped into high-grade serous (27 cases), and non-high-grade serous (17 cases) groups. Immunostaining for p53 and MIB-1 was done on the sections from ovary and fallopian tube.

Results: STIC lesion was identified in fallopian tubes from 10 cases of high-grade serous group (37%) while no STIC was identified in non-high-grade serous group. Eighty percent% of the STIC identified were confined to the fimbria of fallopian tube. Results from both groups were compared using chi square test. A statistically significant association was found between high-grade serous carcinoma group and STIC ($P = 0.013$).

Conclusion: STIC coexists with a significant number of high-grade serous carcinoma cases and further studies are needed to elucidate etiological significance of STIC in high-grade serous carcinoma.

KEY WORDS: High grade serous carcinoma (HG-SC), serous tubal intraepithelial carcinoma (STIC), fallopian tube, SEE-FIM.

Introduction

Ovarian carcinoma is one of the most lethal cancers. The reason for high mortality in these patients is mainly because no effective screening method is available for its early detection and most cases show minimal symptoms in the early phase of disease. Accordingly, ovarian cancer present at an advanced stage.

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It has now become clear that the biggest obstacle in early detection of ovarian cancer was poor understanding of its pathogenesis. Although many theories have been proposed to describe how the ovarian mesothelium could undergo metaplasia and dysplasia, perhaps the greatest gap in understanding the process of ovarian carcinogenesis from ovarian surface epithelium (OSE) is the recognition of a true precursor lesion of high-grade carcinoma in the ovary. For decades, researchers kept their focus on ovary for early detection of high-grade serous ovarian carcinoma; in spite of efforts for its early detection, the overall survival of such cases have not improved much in last 50 years. In recent past, many histopathological studies have provided new evidence that fallopian tube mucosa may be the source of most high-grade serous ovarian carcinomas. The basis for this hypothesis was the finding of a lesion in the fallopian tubes of women with genetic predisposition for ovarian carcinoma, designated as "serous tubal intraepithelial carcinoma" (STIC), which has molecular,

immunohistochemical, and morphological similarities with high-grade serous ovarian carcinoma. To further support this hypothesis, STIC was also detected in the fallopian tube mucosa of women who do not have genetic predisposition for ovarian carcinoma. More recently, Kindelberger et al. found that over 70% of sporadic (non hereditary) ovarian and peritoneal high-grade serous carcinomas showed fallopian tube mucosal involvement by STICs, suggesting that STICs may be potential precursors for sporadic as well as hereditary high-grade serous carcinomas.[1] Strong p53 positivity in STICs and high-grade serous ovarian carcinoma shows a clonal relationship between them, further supporting the above observation. There are very few studies in this regard specially in Indian context; hence, we planned to study the association between ovarian serous carcinoma and STIC.

Materials and Methods

The study was conducted in the Department of Pathology, SMS Medical College, Jaipur, during the year 2014. Of the total 44 cases of ovarian carcinoma studied, 27 cases were high-grade serous carcinoma and remaining 17 were non-high-grade serous carcinoma cases. The specimens received were fixed in 10% formalin for histopathological examination. They were examined and processed according to the standard guidelines. The fallopian tubes were serially sectioned and extensively examined according to SEEFIM protocol. Multiple paraffin-embedded sections from tumor and fallopian tubes were made in usual manner and stained by hematoxylin and eosin. Representative sections from fallopian tube were processed for p53 and MIB-1 immunostaining by routine immune staining procedure. High-grade ovarian carcinoma from same case was taken as positive control for immunostaining. Tubal Intraepithelial lesions are first assessed by morphology, followed by immunohistochemistry.

Results

Total 44 cases of ovarian carcinoma were studied and they were divided into high-grade serous (n = 27) and non-high-grade serous group (n = 17). Tubal lesion was identified in 10 high-grade serous carcinoma cases out of 27 (37.04%). None of the non-high-grade serous carcinoma group had evidence of tubal lesion. Tubal lesion was situated in fimbrial end of fallopian tube in eight cases out of ten(80%). A statistically significant association was found between high-grade serous carcinoma and occurrence of STIC lesion in the fallopian tube as STIC was identified in 10 cases out of 27 high-grade serous ovarian carcinoma cases(37.04%) with a *P* value of 0.013.

Discussion

Traditionally,fallopian tubes were considered less important in adnexal pathology. However,past decade witnessed the emergence of evidences, including clinical-pathological and molecular findings, in support of the hypothesis that high-grade serous ovarian carcinoma develops from the clonal expansion of the secretory cells in the fallopian tube, rather than the ovary,[1–5] Examination of prophylactic salpingo-oophorectomys pecimens from BRCA mutation carriers should ideally reveal some precursor lesion in the ovary. In contrary to this, in early serous carcinomas, STIC lesions have been shown to involve fallopian tube mucosa. Piek et al.[6] were the first to describe “dysplastic changes or tubal dysplasia,” which was later described as tubal lesions in transition (TLIT)[7,8] in the fallopian tubes in BRCA mutation carriers.

Many subsequent studies confirmed the presence of STIC in the fallopian tube mucosa of BRCA mutation carries who underwent prophylactic salpingo-oophorectomy procedures.[2,9–12] The incidence of STIC lesion in these studies was between 2% and 17%, and STICs were typically located in distal fallopian tube mucosa (in 100% cases). Kindelberger et al. thoroughly examined the fallopian tubes from 55 consecutive cases of serous carcinoma and concluded that over 70% of serous carcinomas shows involvement of endosalpinx and 50% contains STIC. For confirmation of shared origin of the serous ovarian carcinoma and coexisting STICs, they further analyzed TP53 mutation in five cases. Identical mutations were detected in both sites in all five cases.[1]

Another study by Carlson et al. examined 45 cases of primary peritoneal serous carcinoma and found that 9 out of 26 cases (34.6%) with incomplete tubal sampling and 9 out of 19 cases (47.4%) that underwent complete examination of the tube had STIC.[5]

In a study done by Liang et al.[13] TIC was identified in 44% cases of high-grade serous ovarian carcinoma when they compared tubal involvement by STIC in high-grade serous carcinoma with other type of epithelial ovarian carcinoma.

Przybycin et al. identified STIC in 59% cases (24 in 41 cases) of high-grade serous carcinoma and none of the other case (endometrioid, mucinous, high grade not otherwise specified) shows presence of STIC. In their study, STIC was found to be located in the fimbrial mucosa in 92% of cases.[14]

A recent study done by Morrison et al. in 2015,on fallopian tubes removed for nonprophylactic indication (in non-BRCA-1, BRCA-2 carrier patients), identified STIC lesions, some of which were associated with microscopic foci of high-grade serous carcinoma in the ipsilateral ovary. The study demonstrates the potential for complete examination of fallopian tubes and ovaries to identify STIC and early invasive serous carcinoma.[15]

The above-mentioned findings and many other similars tudies give support to the hypothesis that STICs, which typically always located in the fimbria, may be the source of high-grade serous ovarian carcinoma in both BRCA mutation carriers as well as in sporadic ovarian cancer. In our study we examined 44 cases of ovarian carcinoma for which bilateral salpingo-oophorectomy was done. As BRCA mutation analysis is not available in our institution,there was no prophylactic salpingo-oophorectomy specimen in our study. Intraepithelial

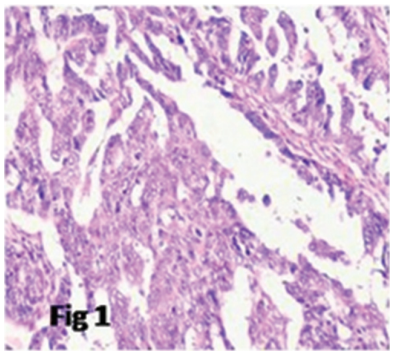

Figure 1: 200x HE staining showing high grade serous ovarian carcinoma.

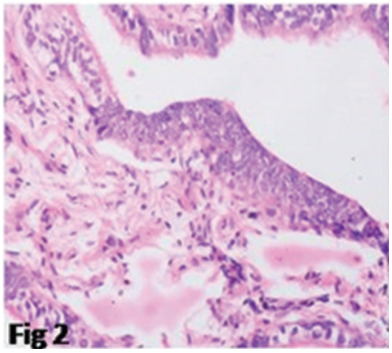

Figure 2: 200x HE staining showing a suspicious for STIC lesion in fallopian tube on morphology.

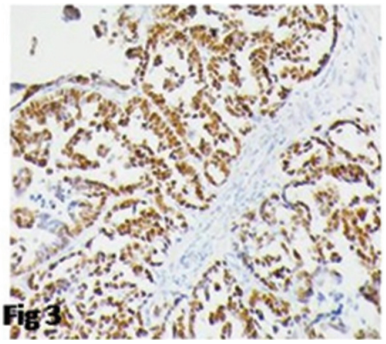

Figure 3: 200x Showing positive P53 staining in High grade serous ovarian carcinoma.

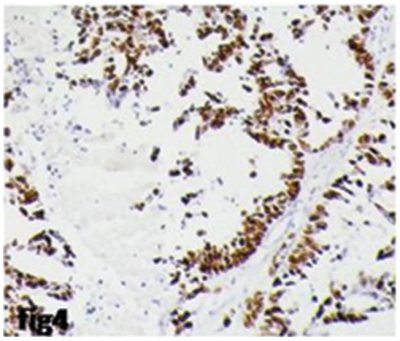

Figure 4: 200xShowing high MIB-1labelling index in serous ovarian carcinoma.

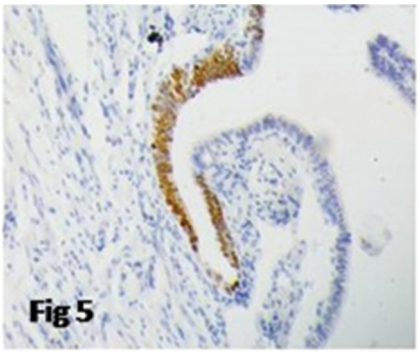

Figure 5: 200x STIC lesion showing P53 positivity.

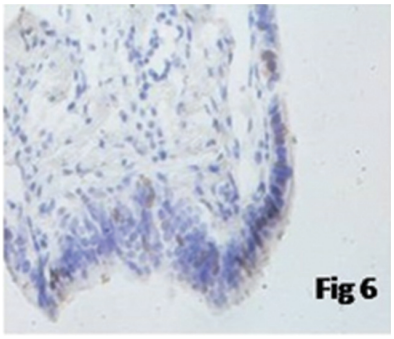

Figure 6: 400x MIB-1 index in STIC lesion.

lesions are first assessed by morphology, followed by immunohistochemistry for p53 and Ki-67 labeling index.

The approach followed in the interpretation of lesions is that proposed by Vang et al. (described below).[16]

For morphologic interpretation of STIC, following cytologic abnormalities were noted:

1. nuclear enlargement,
2. hyperchromasia,
3. irregularly distributed chromatin,
4. nucleolar prominence,
5. mitotic activity,
6. apoptosis,
7. loss of polarity, and
8. epithelial tufting.

If any of these abnormalities are present, lesion is categorized as suspicious for STIC. And if minor cytological abnormalities or no cytological abnormality found, an interpretation of “Not Suspicious for STIC” is made.

On performing Immunohistochemistry, the lesion that is categorized as suspicious for STIC may show either of

two patterns:(1)more than 75% cells in the lesion show diffuse strong positivity for p53 and(2)total absence of staining (0% labeling index), which is due to mutated abnormal protein that cannot be detected by p53 antibodies.

Both the above patterns of p53 staining were considered positive while a lesion that show weak nuclear staining or cytoplasmic staining was considered as negative for p53 staining.

For the assessment of Ki-67 index, a cutoff value of 10% was taken. In a morphologically suspicious lesion, more than 10% Ki-67 labeling index was considered high-Ki-67 index. A Ki-67 proliferation index of <10% is considered "low." Normal fallopian tubal mucosa almost always has a Ki-67 labeling index of less than 2%.

For a foci that is morphologically not suspicious for STIC is considered p53 positive if it shows diffuse strong p53 positivity in 12 or more epithelial cells in continuity.

If all three criteria were met(morphologically suspicious lesion, p53 positivity, and high-Ki-67 labeling index), tubal lesion is diagnosed as STIC, and if two criteria out of three are present it is diagnosed as serous tubal intraepithelial lesion(STIL). Tubal lesion showing only p53 positivity is diagnosed as p53 signature.

A statistically significant association of STIC with high-grade serous ovarian carcinoma in our study indicates that STIC may have some role in the pathogenesis of high-grade serous ovarian carcinoma. Further studies are needed to clarify the role of STIC as a putative precursor lesion for high-grade serous ovarian carcinoma,which may have profound implications for early detection, prevention, and treatment.

Although no method of STIC detection has been established short of surgical resection, the future may hold novel methods of epithelial ovarian carcinoma screening. With improved understanding of STIC and its role in carcinogenesis, there may be opportunities for developing screening methods and biomarker identification.

Furthermore, since most of BRCA-related carcinomas of ovary originate in the fallopian tube, consideration may be given to performing a risk-reducing salpingectomy especially in young patients.

A rigorous approach in evaluating such cases will allow the accumulation of data with long-term follow-up for guiding management recommendations.

Conclusion

STIC coexists with a significant number of high-grade serous carcinoma cases and further studies are needed to elucidate etiological significance of STIC in high-grade serous carcinoma.

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