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The Origins of Ovarian Cancer: A Prospective Study to Decipher the Precursor Lesions of Surface Epithelial Neoplasms

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Abstract

Introduction: The rapidly accumulating advances in the field of Pathology lead to the evolution of newer models of Ovarian carcinogenesis, that classify Surface Epithelial tumors into Type-I and Type-II. Type-I are those ovarian tumors, where precursor lesions in the ovary have clearly been described. Type II tumors are those, where such lesions have not been described clearly and tumors may develop de novo from the tubal and/or ovarian surface epithelium, comprising of high grade carcinomas, causing significant mortality. Hence, we undertook the study to identify the precursor lesions of these malignant neoplasms and provide a road-map for early diagnosis. *Aim:* To study the morphological spectrum of ovarian surface epithelial neoplasms with emphasis on tumorogenesis of malignant tumors. *Materials and Methods:* This is a prospective study conducted from July 2015 to July 2017. Cases diagnosed as Ovarian tumors were included in the present study, with special emphasis on extensive examination of fallopian tubes using SEE-FIM protocol. *Results:* Out of 133 cases of Surface Epithelial tumors, malignant tumors accounted for 25 cases and were associated with Serous Tubal Intraepithelial Carcinoma (STIC) in three cases and 'Atypical changes' in two cases. *Conclusion:* The Serous Tumors of the Ovary, may have an identifiable precursor lesion in the form of STIC arising from the fallopian tube, more commonly from the Tubo-Peritoneal Junction at the fimbrial end.

Keywords: Surface Epithelial; Ovary; STIC; Atypical Changes; Malignant; Serous Carcinoma; Tubo-Peritoneal Junction; Fimbrial; Precursor Lesion.

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Introduction

Surface epithelial tumors form the bulk of Ovarian tumors in adult women [1]. The rapidly accumulating advances in the field of Pathology lead to the evolution of newer models of Ovarian carcinogenesis, that classify Surface Epithelial tumors into Type-I and Type-II [1]. Type-I are those ovarian tumors, where precursor lesions in the ovary have clearly been described. These include endometrioid, clear cell, mucinous, low grade serous, and transitional cell carcinomas. Type II tumors are those, where such lesions have not been described clearly and tumors may develop de novo from the tubal and/or ovarian surface epithelium, comprise high grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas [2].

Most deaths from ovarian cancer are caused by tumors of the serous histological type, which are rarely diagnosed before the cancer has spread [3].

However, the overall survival for women with advanced stage mucinous carcinomas is significantly less than that for women with advanced stage serous carcinoma [4]. Hence, we undertook the study to identify the precursor lesions of these malignant neoplasms and provide a road-map for early diagnosis.

Aim

To study the morphological spectrum of ovarian surface epithelial neoplasms with emphasis on tumorogenesis of malignant tumors.

Materials and Methods

This is a prospective study conducted from July 2015 to July 2017. Cases diagnosed as Ovarian tumors were included in the present study. Tissue received was processed by routine paraffin processing and stained using H & E stains. Immunohistochemistry was done wherever necessary. In carcinomas, all tissue from both fallopian tubes is submitted for histologic examination. To maximize the proportion of the fallopian tube mucosa that is accessible for microscopic examination, SEE-FIM protocol is followed which entails sectioning and extensively examining the fimbriated end. The fimbriated end is amputated from the rest of the tube and serially sectioned at 2-mm intervals along the long axis. The entire length of the remaining tube is then cut perpendicular to the long axis (''bread loafed'') at 2-mm intervals [5].

To facilitate the objective evaluation of tubal epithelium, we have applied the following criteria as exemplified by Visvanathan et al. [6].

Morphological criteria for Tubal Atypia and Serous Tubal Intraepithelial Carcinoma (STIC).

1. Nuclear enlargement (>2X nuclear area compared with non-ciliated cells within the focus of interest or in adjacent normal mucosa) and/or nuclear rounding
2. Marked pleomorphism
3. Abnormal chromatin (hyperchromasia and/or vesicular nuclei with prominent nucleoli)
4. ≥1 mitotic figure (either normal or abnormal)
5. Epithelial stratification (>2 cell layers)
6. Nuclear moulding
7. Apoptotic bodies

Morphologic Stratification

Normal/reactive: <2 of the above criteria in any length of non-ciliated cells

Atypical: Two criteria in ≥ 10 consecutive non-ciliated cells or ≥ 2 criteria in <10 consecutive non-ciliated cell.

STIC: >2 diagnostic features in ≥ 10 consecutive non-ciliated cells

Results

A total of 133 cases of Surface Epithelial tumors were diagnosed and taken under study. They amount to almost 72.2% of the total ovarian tumors (184 cases). Age of presentation ranged from 13 years to 75 years with mean being 40.33 years. Benign lesions predominated over malignant ones, numbering 107 out of 134 cases. Two cases of Atypical proliferative serous tumor were reported. Among 25 malignant tumors, Serous Carcinomas and Mucinous carcinomas amounted to 11 cases each. (Table 1 and Figure 1, 2,3).

Table 1: Histological Spectrum of Malignant Tumors

Histological Type	Number
High Grade Papillary Serous Carcinoma	8
Micropapillary Serous Carcinoma	3
Mucinous Carcinoma	11
Seromucinous Carcinoma	1
Endometriod Adenocarcinoma	1
Sertoliform variant of Endometroid carcinoma	1

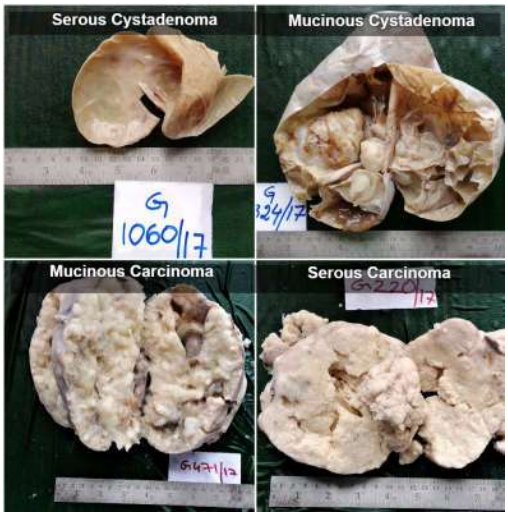

Fig. 1: Gross Pictures of various Surface epithelial tumors of Ovary

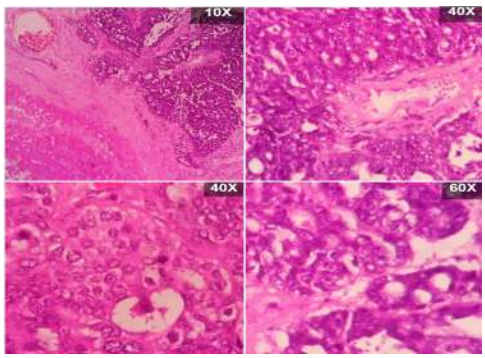

Fig.2: Serous Carcinoma- showing papillary formations and marked nuclear atypia with mitiotic activity

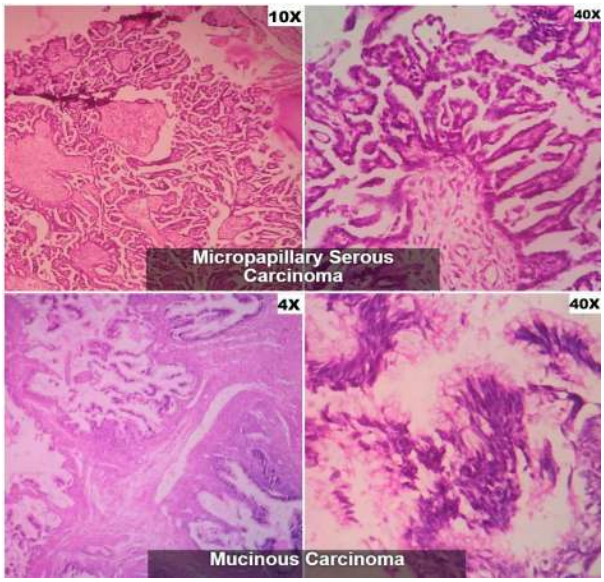

Fig. 3: Micropaillary And Mucinous Carcinoma showing non-hierarchical branching patterns and mucin filled cells with destructive stromal infiltration respectively

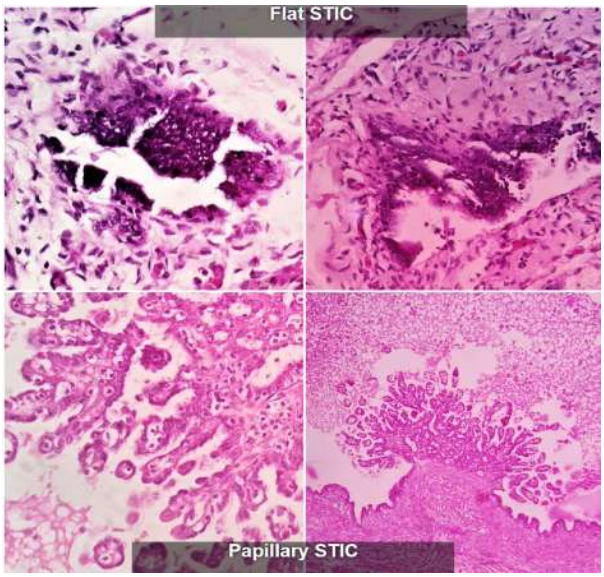

Fig. 4: Serous Tubal Intraepithelial Carcinoma, flat type and papillary type, showing epithelial stratification and abnormal chromatin

Using the morphological criteria for evaluating the tubal dysplasia, we have identified two cases of "Atypical changes" and three cases of "STIC". (Table 2). Among the three cases of STIC, one case was of *Papillary type* and two others were *Flat type*. (Figure 4).

Table 2: Tubal Dysplasia

Tubal Lesion	No. of cases
Atypical changes	2
STIC	3

Table 3: Relationship of the Surface epithelial tumors of Ovary to tubal status in the present study

Surface Epithelial Tumor	Co-existing Tubal Pathology	No.
High Grade serous carcinoma	STIC(Flat)	2
Micropapillary Serous Carcinoma	STIC(papillary)	1
Seromucinous Carcinoma	Atypical changes	1
Mucinous carcinoma	Atypical changes	1

Discussion

The origin and pathogenesis of epithelial ovarian cancer has perplexed investigators for decades. Ovarian cancer is, in fact, the most lethal gynaecologic malignancy [2]. In many cases, symptoms may not even present until the tumor has reached an advanced stage and hence, frequently nicknamed, as the "Silent killer" [7,8,9]. Advances in molecular biology correlated with morphologic studies have led to the proposal of a new model of carcinogenesis, that the origin of ovarian carcinoma may rather be the fallopian tube in many cases, a finding which has important clinical ramifications [1]. Hence, we have undertook this study of Surface epithelial tumors of Ovary with an emphasis on examination fallopian tubes for any premalignant lesions to throw light on their histogenesis.

The proportion of malignant cases in present study (18%) was much higher than *Modepalli N et al.* [10] (12.1%) and *GG Swamy et al. [11]* (12.8%), but much lower than that of *Ghartimagar D et al. [12]* (22.6%). The examination of co-existing tubes which were received as a part of Salpingo-oopohorectomies and Hysterectomies coupled with bilateral salpingo-oophorectomies in accordance with the methodology described earlier, for evaluation of tubal dysplasia, yielded us with a total of five cases showing significant pathology.

Two of these cases showed the following features

1. Epithelial stratification (>2 cell layers)
2. Abnormal chromatin (hyperchromasia with prominent nucleoli)

These two features were present in greater than ten consecutive non-ciliated cell, which clearly delineates them from "Reactive/normal" category, but, were insufficient to be placed in the *"STIC"* category as it required the presence of more than two features in more ten consecutive non-cililated cells.Hence, these two cases were placed in the *"Atypical changes"* category.

Of the remaining three cases, two cases showed

1. Epithelial stratification (>2 cell layers)
2. Abnormal chromatin (hyperchromasia with prominent nucleoli)
3. Marked pleomorphism

These changes were present in clusters of solid nests of more than 10 consecutive non-ciliated cells along the tubal lining, limited to epithelium and not invading into epithelial structures. Hence, they were placed under the category of *"STIC"* with Flat-*type* as the morphological sub-type. The last case showed the changes of STIC coupled with papillary pattern of growth of neoplastic cells. And hence, was placed in the category of "Papillary STIC".(Ref. Figure-4). The percentage of STICs in the present study (2.2%) is comparable with that of E.E.K. Meserve, et al. [13], (2%) and is slightly more than that of Jeffrey D. Seidman [14] (0.8%). But, our finding is very much less than that of M. JJM. Mingels et al. [15], (6.2%). This disparity is attributable to the very fact that the cohort of study of M. JJM. Mingels et al., is exclusively of BRCA positive women, who are known to have high rates of STICs as evident in the works of Vaughan H.M. et al. [16], and Flinch A et al. [17].

In the present study, STICs were found in association with only Serous Neoplasms, but not with non-serous neoplasms. This finding is consistent with that of E.E.K. Meserve, et al. [13], and Tang S et al. [18] (Ref. Table- 3: Relationship of the Surface epithelial tumors of Ovary to tubal status in the present study).

The percentage of STICs discovered in the fimbrial end of the fallopian tube in the present study (66%) were very much in concordance with that of M. JJM. Mingels et al. (64%)but slightly more than that of AS Sehdev et al. [19] ≥ (59.4%). Jeffrey D. Seidman [14] has documented the presence of STIC at and in the immediate vicinity of the recently described junction of the peritoneum and the fimbrial epithelium of the fallopian tube.

Conclusion

We, hereby conclude, from the findings of the present study, that the Serous Tumors of the Ovary, may have an identifiable precursor lesion in the form of Serous Tubal Intraepithelial Carcinoma (STIC) arising from the fallopian tube, more commonly from the Tubo-Peritoneal Junction (TPJ) at the fimbrial end. Further studies, elaborating the intrinsic, finer and subtle pathways of progression from STIC to Invasive Serous carcinomas and identifying the precursors lesion from other Epithelial tumors of Ovary, may enable us to identify these precursor lesions before-hand, provide a frame-work for rapid andefficient screening and bring down the mortality and morbidity associated with these tumors just following the same path of successful prevention strategies for Carcinoma Cervix.

Conflict of Interest

The Authors declare that they have No conflicts of Interests.

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