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SPECTRUM OF MORPHOLOGICAL CHANGES AND PREVALENCE OF “P53 SIGNATURES” IN TUBAL FIMBRIAL EPITHELIUM IN GENERAL POPULATION AND IN PATIENTS WITH PELVIC SEROUS CARCINOMAS

Gayatri Ravikumar^{1†} --- Julian Crasta²

^{1,2}Department of Pathology, St.John's Medical College, Bangalore, Koramangala, Sarjapur Road, Bangalore, India

ABSTRACT

Aim: Pelvic serous carcinomas (PSCs) are very aggressive malignancies and present at advanced stage. A paradigm shift in the origin and pathogenesis of PSCs occurred when precursor lesions were found in the Fallopian tube fimbria in the prophylactic bilateral salphingo-oophorectomy (PBSO) specimens from BRCA positive patients. The knowledge of various benign and reactive alterations in the Fallopian tube is mandatory to distinguish these lesions from the true neoplastic changes. The study therefore aims to see the spectrum of morphological changes in the Fallopian tube epithelium (FTE) and to know the incidence of the various precursor lesions and p53 signatures in the tubal fimbria. Method: The study included 102 Fallopian tubes from patients undergoing salphingo – oophorectomies for gynaecological indications. The fimbrial end along with one cross section was embedded and examined for stromal and architectural changes, epithelial features and inflammatory infiltrates. IHC for p53 and Ki67 was done to assess the presence of precursor lesions. Results: The mean age of patients' was 49.9yrs. Family history of breast/ovarian cancer was present in 5 cases. Histopathology showed fibrosis (30%), Walthard nest (36%), Wolfian duct remnants(14.7%), pigmentosis tubae(1%) , infiltration by metastatic carcinoma(7%),reactive atypia(6%), metaplasia(16%), tufting(46%),lymphocytes (9%) and plasma cells (2%). SCOUTS were seen in 12%, p53 signature and STIC in 6% and 4% respectively. Tuboperitoneal junction was identified in 15 cases and showed transitional metaplasia. Conclusion: The study describes the different morphological changes in the Fallopian tube in our population. The prevalence of cytological and molecular alterations leading to malignancy was low in general population.

Keywords: Fallopian tube, Morphological changes, p53 signatures, SCOUT.

[†] Corresponding author

Contribution/ Originality

The paper's primary contribution is finding that completely sampling the tubal fimbria with one cross section is a good practice to identify early precursor lesions which may otherwise go undetected. Knowledge of reactive /benign cellular proliferations is mandatory to help distinguish them from these precursor lesions.

1. INTRODUCTION

Pelvic serous carcinomas (PSCs) are one of the most lethal gynaecological malignancies. They include high grade ovarian serous carcinomas, Fallopian tube carcinomas and peritoneal serous carcinomas. These tumours are known to be very aggressive and clinically present as advanced stage tumours. Histologically no evidence of precursor lesion are noted and are thought to arise de novo. The origin of these ovarian tumours was thought to be from the ovarian surface epithelial inclusion cysts. However, this lacks substantial evidence especially in high grade serous carcinoma.

The prophylactic bilateral salphingo-ophorectomy (PBSO) specimens from BRCA positive patients showed early precursor lesion (serous tubal intraepithelial lesions and carcinomas) along with molecular alterations(p53 signatures), thought to be the earliest genetic change associated with PSCs in the fimbriated end of the Fallopian tube. This finding made a paradigm shift in understanding the pathogenesis of these tumours. Studies are increasingly being undertaken to detect the early lesions in patients with or without BRCA mutation to understand the tumorigenesis of serous cancers. Therefore the Fallopian tube which was once an under sampled specimen in pathology practice is now on the focus light.

The knowledge of various benign and reactive alterations in the Fallopian tube like reactive epithelial atypia, benign proliferations and benign papillary lesions is mandatory to distinguish these lesions from the true neoplastic changes [1]. It is important to know the true incidence of the precursor lesions so that optimal screening and preventive methods can be employed. Herzog and Dinkelspiel [2]. As on date there are no effective screening test to detect early precursor lesions in the tubal epithelium. If the precursor lesions are proved beyond doubt by larger studies, salphingectomy would be effective preventive management for risk reduction. The preneoplastic lesions can be identified and are defined by immunohistochemical evaluation with p53 and Ki-67. The study therefore aims to record the spectrum of morphological changes in the Fallopian tube epithelium (FTE) and to know the incidence of the various precursor lesions and p53 signatures in the tubal fimbria.

2. MATERIAL AND METHODS

A total of 102 Fallopian tubes from cases of consecutive abdominal hysterectomies with bilateral salphingo – ophorectomy, received in the Department of Pathology, St.John's Medical College, from August 2011 were included. Hysterectomy specimens for obstetric conditions were

excluded and only gynaecological indications for both benign and malignant conditions were included. The study was approved by the Institutional Ethics committee (IERB study no.66/2011)

The Fallopian tubes were amputated at the infundibular region and fimbriae were sectioned longitudinally to get maximum exposure of the Fallopian tube epithelium (FTE). One cross section of the tube was taken (modified SEE-FIM protocol). Haematoxylin and eosin stained slides were examined histologically and the lesions were classified into three categories 1. Stromal and architectural alterations 2. Reactive epithelial changes 3. Inflammatory cell infiltrates 4. Neoplastic alterations.

The stromal and architectural alterations included: fibrosis, intramuscular oedema, luminal contents, inclusion cysts, Walthard nests, pigmentosa tubae, Wolffian duct remnants, endosalpingosis and infiltration with metastatic carcinoma. The reactive epithelial changes included: epithelial atypias, metaplasia (mucinous/squamous/transitional), epithelial stratification and tufting. The inflammatory infiltrates recorded were lymphocytes, mast cells, plasma cells and neutrophils.

All the samples were evaluated immunohistochemically by polymer technique. The primary antibodies included p53 (monoclonal p53, clone DO-7, DAKO) and Ki-67(monoclonal Ki-67, antigen MIB-1, DAKO). p53 positivity was interpreted as nuclear staining of 2+ to 3+ intensity and Ki-67 was graded as percentage of cells showing nuclear staining. Various preneoplastic lesions were defined as follows: [3, 4]

Secretory cell outgrowths (SCOUTS): 12 or more continuous secretory cells without intervening ciliated cells negative for p53 and Ki-67 “p53 signatures”: 12 continuous secretory cell nuclei without atypia but showed p53 immunostaining and had a low Ki-67 index.

Serous tubal intraepithelial carcinoma (STIC): Cells exhibit nuclear atypia with nuclear stratification, hyperchromasia and mitotic figures with aberrant p53 expression and high proliferative (Ki-67) index.

Serous tubal intraepithelial lesion (STIL): When either the morphology was suspicious /atypical with aberrant p53/Ki-67 or when the morphology was not suspicious for STIC but showed high p53 positivity and increased Ki-67.

3. RESULTS

102 consecutive Fallopian tube samples from 51 patients whose age ranged from 36years to 80 years with a mean of 49.9 years were included in the study. Family history of breast/ ovarian cancer was present in 5 patients. Commonest indication for TAH-BSO was leiomyoma (36%). Other indications are enumerated in Table1. The various non-neoplastic alterations seen according to the frequency of the findings are listed in Table 2. The most common stromal and architectural alterations observed were Walthard rests followed by fibrosis and Wolffian duct

remnants with dilated lymphatics. Metastatic carcinoma was found in 7% of cases. Pigmentosis tubae was seen in one case. (Figure 1)

The most common reactive epithelial changes observed were epithelial tufting/stratification and transitional metaplasia. Reactive atypia was observed in 6% of cases. Inflammatory infiltrates were less commonly seen with a predominance of lymphocytes. The tuboperitoneal junction was identified in 15 cases and showed dilated lymphatic channels and transitional metaplasia in all the cases. (Figure 2)

The neoplastic precursor lesions were mainly in seen in tubes excised for non-neoplastic conditions and are summarised in Table 3. All the reported lesions were recorded in the fimbrial end of the tube. The most common lesion observed was SCOUTS with no expression of p53 and <2% Ki-67 index which was seen in 12 cases of which only 1 was OSC. P53 signatures were seen in 6 cases of which 2 had ovarian serous carcinomas and 4 were non neoplastic conditions. STIC was seen in 3 cases of which two were serous carcinomas. (Figure 3). There was no case of STIL in this study. Although there were 9 cases of ovarian high grade serous carcinomas, only 3 cases had these precursor lesions in the fimbriated end. Neoadjuvant chemotherapy (NACT) was administered in 3 cases. The p53 staining was not seen even within the neoplastic cells in cases where NACT was given, but one of them showed p53 signature.

4. DISCUSSION

The Fallopian tube is one of the common surgical specimens received in the histopathology laboratory. Routinely, sampling one cross section of the tube was considered adequate unless indicated. With fallopian tube arising as a novel site for origin of pelvic serous carcinomas, as evidenced in by the findings noted in BRCA positive women undergoing PBSOs, extensive sampling of the tube has been widely advocated. The SEE FIM (Sectioning and Extensively Examining the Fimbriated end) protocol is recommended for all Fallopian tubes from PBSO patients in western countries. In developing countries and underdeveloped countries, testing for BRCA status is expensive and completely sampling the tube may not be cost effective in salpingectomies done for non-malignant cases.

A modified protocol for sampling the Fallopian tube was followed in this study. The entire fimbrial end was sampled along with one cross section of the tube. As the inception of precursor changes (p53 expressing SCOUTS) are known to occur in the fimbriated end than in the rest of the tube as shown in the studies by [Lee, et al. \[5\]](#) and [Chen, et al. \[6\]](#) the fimbriated end was sampled completely along with one cross section of the tube. [\[5, 6\]](#) This modified protocol was validated in [Rabban, et al. \[7\]](#) study on 522 women with low risk for ovarian cancer. [Rabban, et al. \[7\]](#) Therefore this modified protocol is more apt for general sampling of the FT when BRCA status is not known and in FTs removed for non malignant indications.

The fimbriated end is more prone to damage as the epithelium changes from mesothelium to FTE at this site. This junction known as tuboperitoneal junction (TPJ) is proposed as the site for

origin of PSCs as is the role of any other epithelial junctions like cervical squamocolumnar, anorectal, gastro oesophageal junctions in carcinogenesis. Seidman, et al. [8] studied 228 Fallopian tubes from both unselected cohort and those from risk reducing salpingo oophorectomies, where they found dilated lymphatics and transitional metaplasia as the most common finding. TPJ was identified in 15 cases in the present study and the findings were similar to Seidman, et al. [8] studies. [8, 9]

The incidence of the early precursor lesions which include p53 signatures, indicating DNA damage, SCOUTS, STIL and STIC, is low in both general population and in patients with ovarian serous carcinomas as seen in the present study. The p53 signatures are seen in secretory cells which have undergone DNA damage as evidenced by γ -H2AX nuclear staining. Lee, et al. [5] This cell injury is thought to be non BRCA mediated and is seen in equal frequency in BRCA negative women. [5, 6, 10] observed that SCOUTS were identified in similar frequency in both BRCA positive asymptomatic women and in tubes removed for non malignant indications. Chen, et al. [6] The present study also had a similar incidence of both p53 signatures and SCOUTS. These changes are thought as BRCA independent alterations. Carcinogenesis results due to multiple mutations occurring sequentially and BRCA mutation may play a role in the later steps downstream in pelvic serous carcinoma tumorigenesis.

Various other studies in BRCA positive women has shown varying incidences of these precursor lesions in the FTE ranging from 2.2% [11] 6% [12] to 38% [13]. [11-13] IHC staining for p53 protein may be negative in about 10-15% of cases. The IHC staining identifies only the mutated p53 protein resulting due to missense p53 gene mutations and if mutations occur upstream of the segment targeted by IHC or when there is a non sense mutation, the end product is a truncated mutated protein will be undetected by IHC as the proteins are very unstable. [4, 14, 15] The staining pattern is different from wild type p53 which is seen as weak scattered positivity. Crum [4] In the present study some of the ovarian carcinomas have overgrown the FT fimbria by forming a tubo-ovarian mass, rendering the identification of fimbrial end difficult.

In the present era with FT fimbria emerging as the novel site harbouring the premalignant molecular and morphological changes for the devastating high grades serous carcinomas, it becomes absolutely necessary to examine the fimbriated end thoroughly. Lauchlan *et al* proposed the theory of second Mullerian system for any Mullerian epithelium found outside the primary Mullerian system. [16, 17] In many studies it is noted that all STICs do not progress to carcinomas and not all carcinomas have STIC. In a significant number of HG -OSCs, no STIC was identified even after extensively sampling the Fallopian tube, [18] probably due to overgrowth by the tumour in the FT, as evidenced by the present study. It becomes mandatory to sample the fimbriated ends in all specimens of FT to identify these early lesions. Herzog and Dinkelspiel have suggested that bilateral salpingectomy with ovarian retention (BSOR) as a new standard for ovarian cancer risk reduction and examination of the tubes should be extended to the

general population also. Herzog and Dinkelspiel [2] They suggest that when the true incidence of these precursor lesions are known, effective screening and preventive strategies can be developed.

With the on going studies on completely sampling the fimbriated end on the tube, which is likely to be extended to the general population, it is pertinent for the pathologist to identify these early precursor lesions distinctly from the reactive/ benign cellular alterations which at present date do not have any clinical implications. Knowledge of these lesions will help to distinguish them from the potentially malignant lesions. A limited literature is available describing the reactive changes in the FT. Hunt and Lynn studied 287 FTs in general population undergoing hysterectomy with salphingo-oophorectomies for various gynaecological and obstetric indications, found similar reactive alterations in the FTE, although the inflammatory cell infiltrates and intramuscular oedema was more frequent. This could be attributed to inclusion of tubes from patients with obstetric indications and sampling only 3 cross section of the tube. Hunt and Lynn [19] study on 522 low risk patients(low risk for BRCA) undergoing TAH BSO for benign indications , found STIC in 4 cases, STIL in 2 cases and atypical proliferations in 9 cases. They also advocate the modified protocol for sampling the FT and complete examination of tubal fimbria in all patients who undergo TAH BSO to detect these early changes, even if there is no clinical suspicion for BRCA mutation. [7]

In conclusion, the fimbriated end of the FT should be completely sampled along with one cross section of the tube in all patients undergoing TAH BSO, to identify the early putative precursor lesions, which would otherwise go undetected with the current method of tubal sampling. This modified protocol is more cost effective than the SEE FIM protocol in general population. Identifying the tuboperitoneal junction is recommended as a good practise as the neoplastic change is thought to arise here, although there is no conclusive evidence in literature. The reactive/ benign cellular proliferations should be known to distinguish them from the precursor lesions. Although the clinical relevance of these precursor lesions and p53 signatures are not known at this date and are still in the research status, identifying and reporting these lesions is a good exercise to understand the pathogenesis of pelvic serous carcinomas, to develop early detection and preventive modalities for the same.

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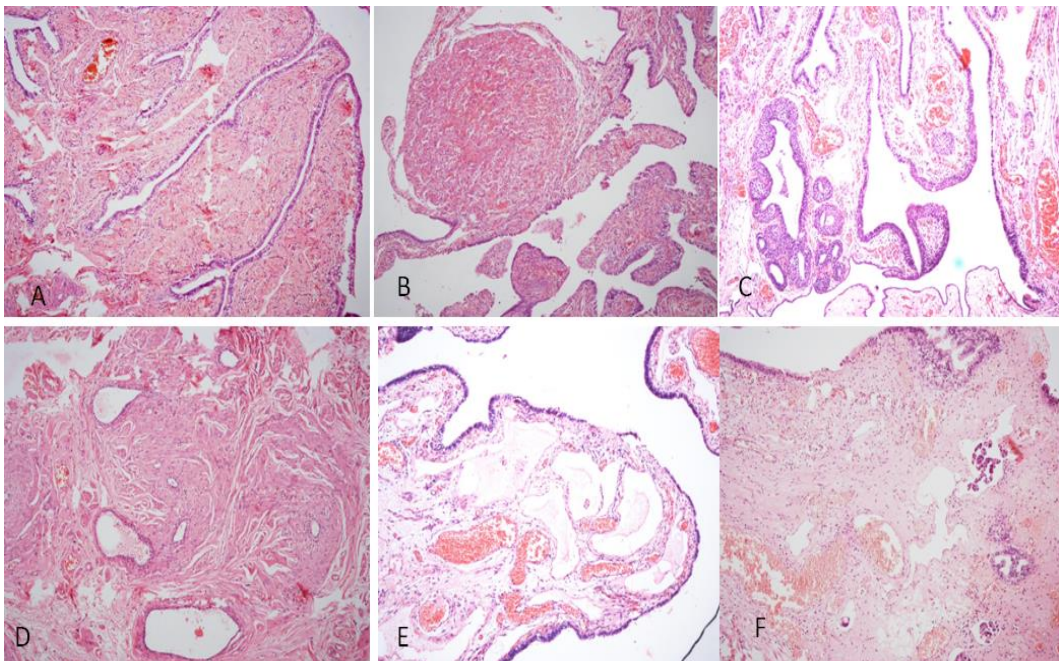


Figure-1. Stromal and architectural alterations in Fallopian tube fimbria. A- Fibrosis of the plica, B- Pigmentosis tubae, C- Walthard cell rest, D- Wolfian duct remnants, E- Dilated lymphatics, F- Metastatic carcinoma within lymphatic channels. (Hematoxylin and Eosin Staining, original magnification, X4)

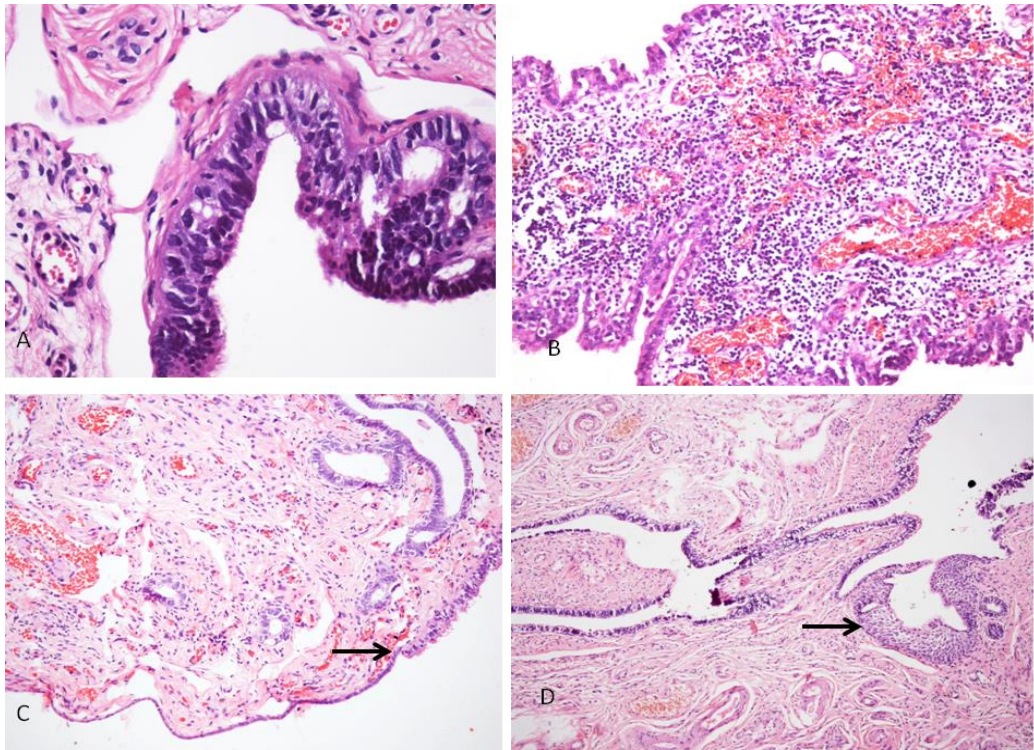


Figure-2. Reactive epithelial changes and inflammatory infiltrate. A- Reactive atypia,(Hematoxylin and eosin , original magnification X 20) B- Inflammatory cell infiltrate,(Hematoxylin and eosin , original magnification X 20) C-Tubo peritoneal Junction (arrow)(Hematoxylin and eosin , original magnification X 4) D- transitional metaplasia (arrow)(Hematoxylin and eosin , original magnification X 10)

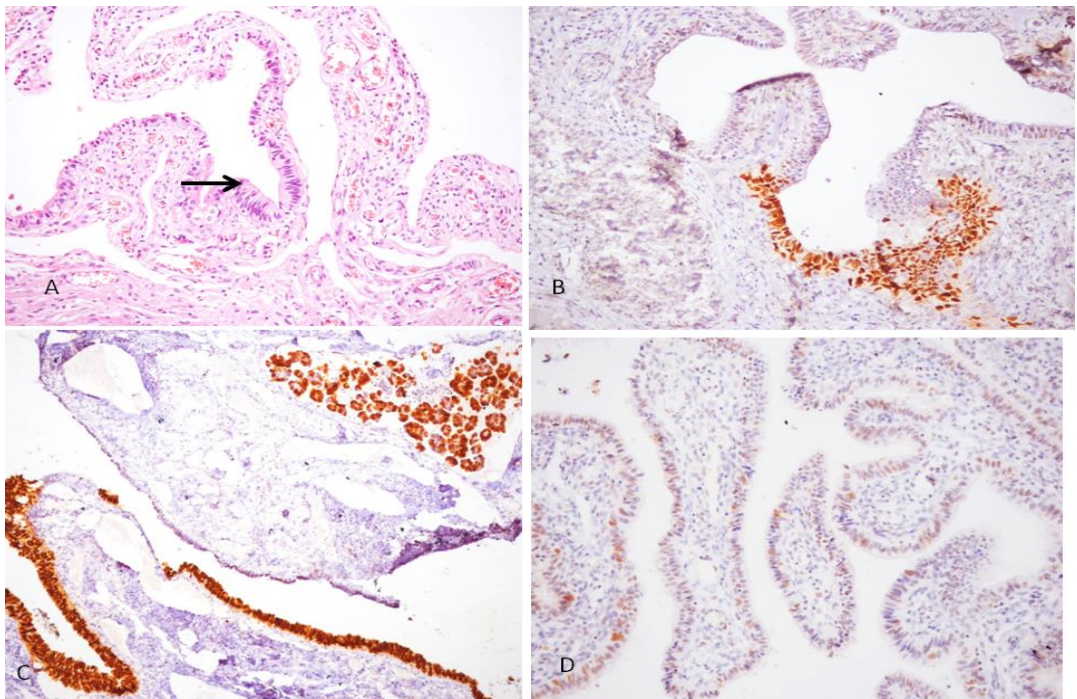


Figure-3. Neoplastic alterations. A- Secretory cell outgrowth(SCOUT)(arrow)(Haematoxylin and eosin , original magnification X 4) B- p53 signature(IHC, original magnification X 4) C- Serous tubal intraepithelial carcinoma(IHC, original magnification X 4) D- Normal Fallopian tube fimbria expressing wild type p53 staining (IHC, original magnification X 4)

Table-1. Clinical indications for surgery (some cases had more than one indication)

Clinical indications for surgery	Number of cases
Leiomyoma	18
Dysfunctional uterine bleeding	8
Non neoplastic endometrial indications(polyp/hyperplasia)	3
UV prolapse	4
Benign ovarian cysts(serous/mucinous/endometriotic)	7
Uterine malignancy(endometrial Ca/MMMT/LMS)	6
Cervix cancer	5
Ovarian cancers	10

(MMMT- malignant mixed Mullerian tumour,LMS- leiomyosarcoma)

Table-2. Histological findings in the Fallopian tube

Histological Findings	Frequency of occurrence
Stromal and Architectural alterations	
Fibrosis	30%
Intramuscular edema	6%
luminal contents	4%
Inclusion cysts	8%
Walthard nests	36%
Pigmentation tubae	1%
Wolffian duct remnants	14.7%
Decidualized stroma	Nil
Endosalpingiosis	Nil
Infiltration with metastatic carcinoma	7%
Epithelial characteristics	
Atypia	6%
Metaplasia	16%
Epithelial tufting/stratification	46%
Inflammation	
Mast cells	Nil
Plasma cells	2%
lymphocytes	9%

Table-3. Distribution of Precursor lesions in the Fallopian tube

Precursor Lesions	Ovarian serous carcinomas(9cases)	Non neoplastic cases
SCOUTS	1	11
P53 SIGNATURES	2	4
STIC	2	1

6 cases of OSC did not show any precursor lesions

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