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Study of tubal intraepithelial neoplasia (TIN) in various ovarian tumours.

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Abstract – *Serous tubal intraepithelial carcinoma (STIC), an early lesion limited to the epithelium of the fallopian tube and firstly identified from specimen obtained by prophylactic salpingo-oophorectomy. Histopathological features of STIC include a variable combination of epithelial stratification, loss of cellular polarity, irregular luminal surface, pleomorphism,loss of cilia,nuclear rounding, increased nucleo-cytoplasmic ratio, prominent nucleoli and mitotic figures. Recently described lesions overexpressing p53 in the distal tubes of mutation carriers, and non carriers, have been proposed as histological precursors of high grade serous carcinoma (HGSC). A careful histological examination of ovaries and fallopian tubes prophylactically resected from BRCA1/BRCA2 mutation carriers has provided clues to the existence of cancer precursor lesions in women genetically predisposed to high grade serous carcinoma, and they have been identified not in the ovary, but in the distal tubal epithelium. Present study was undertaken to observe the histological changes in the fallopian tubal epithelium in various ovarian tumours.*

Key words- *Tubal Intrepithelial Neoplasia, Serous tubal Intraepithelial Carcinoma, Ovarian tumours.*

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I. Introduction-

Pelvic high grade serous carcinomas, including ovarian, tubal, and primary peritoneal carcinomas receive much attention from clinicians and researchers because of their usually advanced stage at presentation, rapid rogression, poor prognosis and high fatality rate. Serous tubal intraepithelial carcinomas , a lesion limited to the epithelium of the fallopian tube and first identified from specimens obtained by prophylactic salpingo-oophorectomies, have provided some insight into high grade serous carcinoms(HGSCs). Accumulating evidence suggest that the distal fallopian tube is a potential primary site of the origin of primary ovarian or pelvic carcinoma.[1]

II. Method and material

This study was carried out in the department of pathology, NKP Salve Institute of medical sciences, Nagpur.
Study Design: Prospective hospital based cross sectional study

Study Location: This was a tertiary care teaching hospital based study done in Department of Pathology, at.NKP
Salve Institute of Medical sciences, Nagpur.
Study Duration:.2 years
Sample size: 63 cases of ovarian tumor..

All patients operated for ovarian neoplasms with salpingo-Oophrectomy are included in this study. Two to three sections from distal(fimbrial) end of the same sided fallopian tube were studied. The fallopian tubes were sectioned using a protocol designated to section and extensively examined the fimbriae(SEE-FIM protocol). This protocol entailed amputation of each fimbria at the infundibulum, longitudinal sectioning of the fimbria and extensive cross sectioning of theremainder of the tube. For control, fallopian tube sections studied from hysterectomy cases without ovarian tumors or cases of hysterectomy done for prolapse of uterus or leiomyoma without any obvious tubo-ovarian or peritoneal pathology.
Inclusion criteria- All operated cases of Ovarian neoplasms with salpingo-Oophrectomywere included in this study.
Exclusion Criteria-Known cases of tubal malignancy will be excluded from the study.

Table 1 : Ovarian Tumours in various age groups

Sr.No.	Age Group	No. of Patients
01	0-10	Nil
02	11-20	01
03	21-30	17
04	31-40	11
05	41-50	21
06	51-60	06
07	61-70	07
08	71-80	Nil
	Total no.	**63**

Table 2: Types of Ovarian tumours

Sr.No.	Benign – total no. of cases	Borderline- total no. of cases	Malignant- total no. of cases `
01	Serous cystadenoma - 15	Atypical proliferative serous tumour – 01	Low grade serous carcinoma-03
02	Mucinous cystadenoma-09	Atypical proliferative mucinous tumour-04	High grade serous carcinoma-10
03	Dermoid cyst - 05	Borderline Seromucinous tumour-01	Seromucinous Carcinoma-01
04	Ovarian fibroma-01		Mucinous cystadenoma carcinoma -05
05	Fibrothecoma - 01		Malignant mixed mulleriantumour -02
06			Krukenbergtumour -01
07			Immature teratoma-01
08			Dysgerminoma -01
09			Adult granulosa cell tumour-02
10	**Total =31**	**Total = 06**	**Total = 26**

III. Results

63 consecutive cases of ovarian tumours were evaluated. Patients ranged from 11years to 70 years of age(Table1).Most common age group was 41 to 50 years.Out of Total 63 casesof ovarian tumours,31 werebenign,6 borderline and 26 malignant.Benign tumours did not show Tubal intraepithelial neoplasia (TIN).Various malignant tumours were HGSC, LGSC, Mucinous cystadenocarcinoma, Seromucinous Carcinoma, Mixed mulleriantumor,Krukenberg'stumor, dysgerminoma, immature teratoma and granulosa cell tumour. (Table2). HGSC was most common malignant tumor.Out of 10 cases of HGSC, 4 were positive for TIN (Figure1to3). Second common malignant ovarian tumor was Mucinous cystadenocarcinoma. Mucinous cystadenocarcinoma did not show TIN. Low grade serous carcinoma was 3rd common malignant tumor in frequency. Out of three cases of LGSC, one case was positive for TIN. Other malignant tumours did not show TIC.Histopathological features of STIC include a variable combination of epithelial stratification, loss of cellular polarity, irregular luminal surface, pleomorphism,loss of cilia,nuclear rounding, increasednucleo-cytoplasmic ratio, prominent nucleoli and mitotic figures. TIN predominantly involved the distal fallopian tube, involving the fimbriae. In one case of bilateral HGSC, TIN was present in both tubes. In our study we got TIN in 4 cases(40%) of HGSC and one case of LGSC. No other tumours showed foci of TIN/STIC. In the present study TIN positivity is less as compared to other studies.

IV. Discussion

The incidence of STIC has primarily been studied with known BRCA mutations or a strong family history of breast or ovarian cancer and is estimated to be in the range of 0.6 to 6%.[2-4] Wethingtonet al found the incidence of STIC in women undergoing risk reducing salpingo- oophorectomy(RRSO) at a single institution to be 2%, this is consistent with prior reports in the literature. All patients in this study had a known BRCA mutation or high risk personal or family history.[3] Kindelberger DW et al [5] studied fallopian tubes in a consecutive series of pelvic serous carcinomas, and entailed complete examination of the fallopian tubes with special attention given to the fimbrial end(SEE-FIM). Cases positive (group A) or negative(group B) for endosalpinx (including fimbria) involvement, were subclassified as tubal, ovarian, or primary peritoneal in origin. Coexisting TIC was recorded in groupA when present and p53 mutation status was determined in 5 cases. Of 55 evaluable cases, 41(75%) were in group A; including tubal(n=5), peritoneal(n=6), and ovarian (n=30)carcinomas. Foci of TICs were identified in 5 out of 5, 4 of 6, and 20 of 30 respectively. Ninety-three percent of TICs involved the fimbriae. Five of 5 TICs and concurrent ovarian carcinomas contained identical p53 mutations. Thirteen of 14 cases in group B were classified as primary ovarian carcinomas, 10 with features supporting an origin in the ovary. Overall 71% and 48% of ovarian serous carcinomas had TIC. The tumor suppressor gene, TP53 is mutated in 80%of BRCA- mutation –linked ovarian/tubal carcinomas, and p53 mutations have been identified in early stage and in situ serous carcinomas, indicating a key role for altered p53 function in serous carcinogenesis.[6,7] Lee et al have documented p53 mutations in 12 out of 12 cases of tubal intraepithelial Carcinoma.[8] High grade serous carcinomas frequently overexpress p53, and there is no difference in the frequency of p53 staining between hereditary and sporadic serous carcinomas.[9,10] Tubal

intraepithelial carcinoma has in the past been defined as a lesion characterized by replacement of normal tubal epithelium by malignant cells, with increased nuclear/cytoplasmic ratio, nuclear pleomorphism, disorganized growth and increased proliferation. Jarboe et al recently added two additional criteria to the definition, including the absence of ciliated cells and presence of prominent nucleoli.[11] In the present study, only on the basis of morphology we diagnosed the cases of STIC/TIN. TIN was identified in 4 cases (40%) out of 10 cases of high grade serous carcinoma and 1 case (33.33%) out of 3 cases of low grade serous carcinoma. However direct evidence regarding STIC as the precursor of HGSC is still tantalizing. Along with morphology, Ki67 and p53 are necessary. So further studies with large number of cases and molecular genetic studies are required.

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Figure1- Photomicrograph showing section of fallopian tube with Focal Tubal epithelial stratification, anisonucleosis and loss of polarity of nuclei.

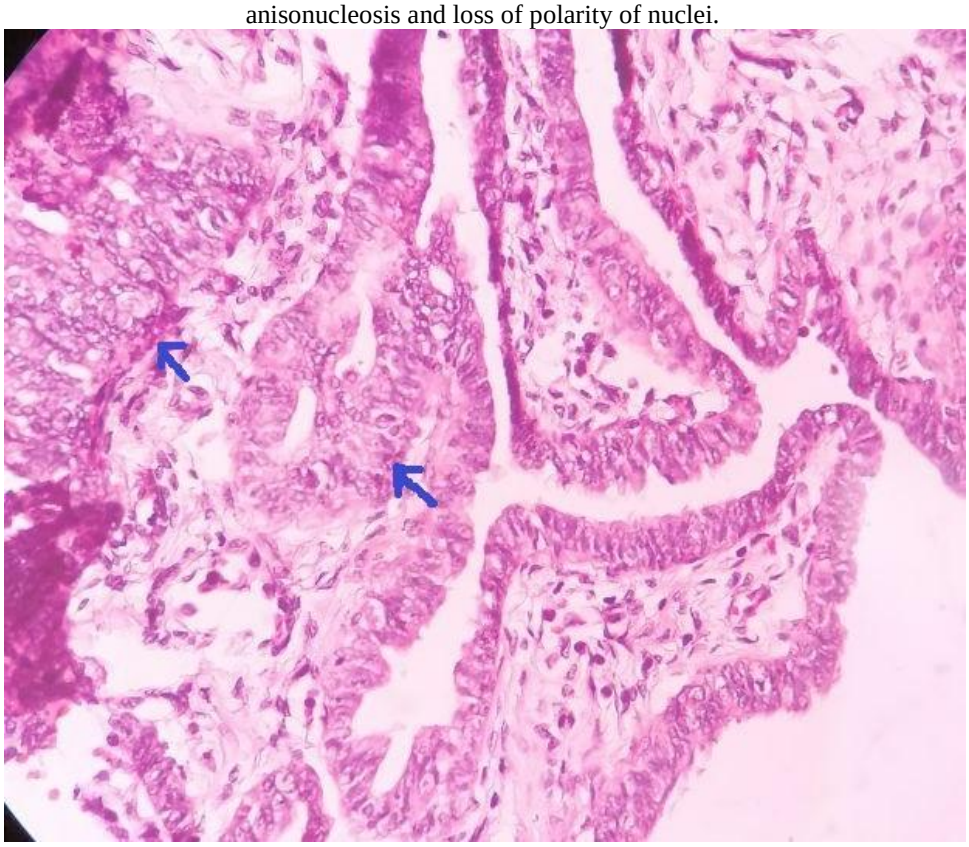


Figure 2-Photomicrograph showing Focal Tubal Intraepithelial Neoplasia (Arrow).

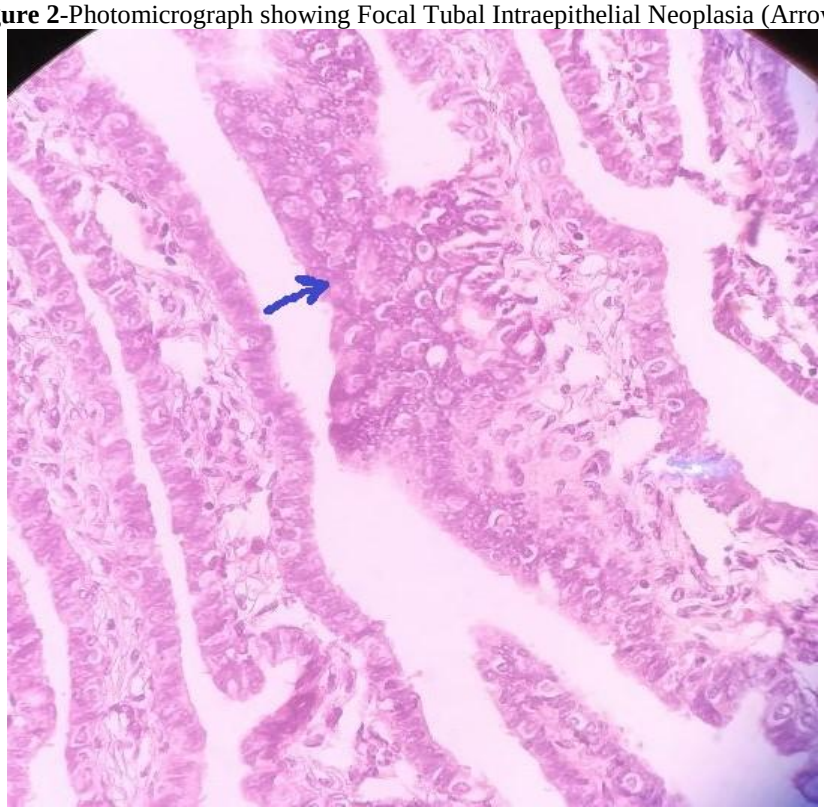
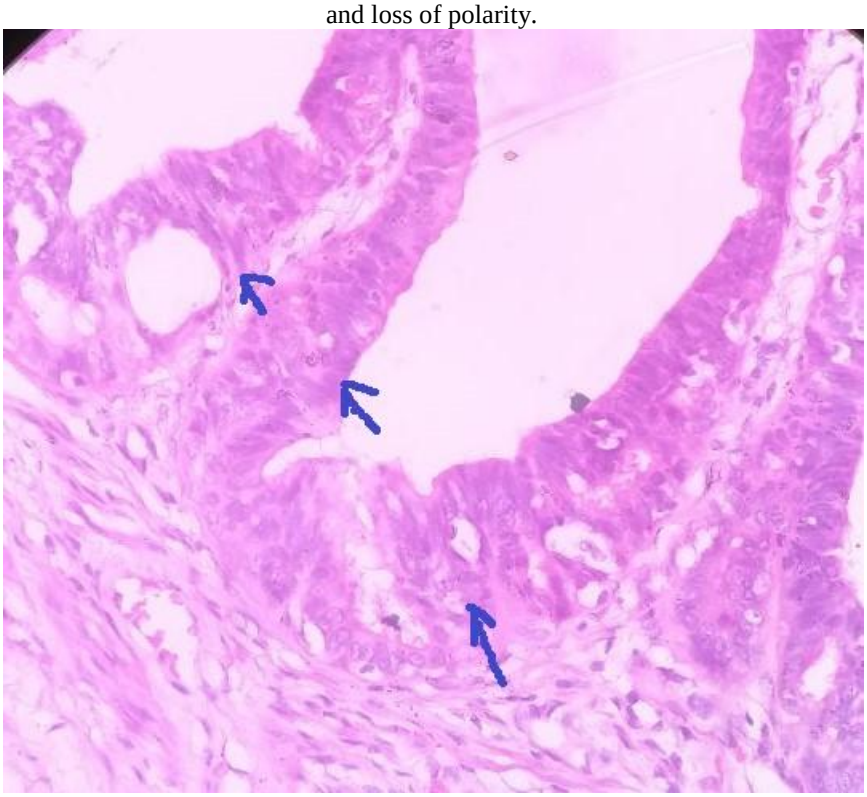


Figure 3- Photomicrograph of fallopian tube showing Focal tubal epithelial stratification, nuclear enlargement and loss of polarity.



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