Original Research Article

A study on surface epithelial tumors of ovary with special reference to histogenesis

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Abstract

Aim & Objective: To study the clinico-pathological features of various surface epithelial tumors of ovary with special emphasis on their Histogenesis.**Methodology:** This is a prospective study conducted from July 2018 to July 2020, at Katuri Medical College & Hospital, Guntur. Cases diagnosed as ovarian tumors and received at the Department of Pathology were included in the present study. Relevant clinical and laboratory data was collected.**Results:** A total of 120 cases of Surface Epithelial tumors were diagnosed and taken under study. They amount to almost 83% of the total ovarian tumors (100 cases). Multiparous women predominated the list accounting for 100 of the 120 cases. Tumors were from sizes ranging from 2.5 cms to 30 cms and had varied appearances on cut-section being cystic with unilocular and multilocular. Benign lesions predominated over malignant ones, numbering 100 out of 120 cases. Two cases of Atypical proliferative serous tumor were reported. Among the three cases of STIC, one cases was of Papillary type and two others were Flat type.**Conclusion:** 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.

Keywords: Mucinous tumors, Surface epithelial, Ovary, Proliferative tumors.

Introduction

Surface epithelial tumors comprise the majority of ovarian tumors in adult women.[1] The Ovarian carcinogenesis model has been in a dynamic state of evolution assimilating the contemporary advances and emerging concepts in filed of Pathology. The recent concepts of ovarian carcinogenesis classify Surface Epithelial tumors of Ovary 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. [2] 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. High-grade serous and possibly endometrioid carcinomas most probably arise from surface epithelial inclusion glands. Low-grade serous carcinomas probably arise in a stepwise fashion in an adenoma–borderline tumor–carcinoma sequence from typical to micropapillary borderline tumors to low-grade invasive serous carcinoma.[2] It is likely that most low-grade, relatively indolent ovarian carcinomas of serous, mucinous and endometrioid type arise from pre-existing cystadenomas or endometriosis whereas most high-grade serous carcinomas arise without an easily identifiable precursor lesion.[1] Some of the greatest challenges in detecting and treating these tumors stem from its heterogeneous nature. Hence, an appropriate classification that incorporates the morphological and clinical heterogeniety of these tumors has to be followed.

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The present study will thus elucidate the recent WHO classifation of these tumors and use it in the segregating the tumors reported in our study, so that further study on the histogenesis of these tumors can be carried out in a scientific manner.

Aim & Objective

To study the clinico-pathological features of various surface epithelial tumors of ovary with special emphasis on their Histogenesis.

Materials and Methods

This is a prospective study conducted from July 2018 to July 2020, at Katuri Medical College & Hospital, Guntur. Cases diagnosed as Ovariantumors and received at the Department of Pathology were included in the present study. Relevant clinical and laboratory data was collected.

Tissue received was processed by routine paraffin processing and stained using H&E stains. Immunohistochemistry was done wherever necessary. Records of clinical and radiological data wherever available, were correlated and the results were compared.

In cases of Ovarian serous carcinomas, all tissue from both fallopian tubes is submitted for histologic examination to identify tubal intraepithelial carcinoma (TIC), especially in 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.[1]

Routine tissue processing by Section cuttingand Staining techniques Hematoxylin and Eosin[3,4].

Immuno-histochemistrty

Immunohistochemistry is performed using a combination of microwave oven heating and standard streptavidin-biotin-peroxidase complex, using the Dako kit[4].

Inlusion Criteria

All surface epithelial tumors of Ovary as confirmed by Histopathological examination were included in the study.

Exclusion Criteria

- All other ovarian tumors of non-surface epithelial type
- Biopsy samples of Inadequate or small size

Results

A total of 120 cases of Surface Epithelial tumors were diagnosed and taken under study. They amount to almost 83% of the total ovarian tumors (100 cases).The various clinical, gross and microscopic features were noted.

Age distribution

Age of presentation ranged from 13 years to 75 years with mean being 40.33 years.

Table 1: Age distribution

Age Group	Number of Cases
<21	3
21-30	32
31-40	30
41-50	27
51-60	12
>60	16

Parity

Multiparous women predominated the list accounting for 100 of the 120 cases with the remaining 20 cases being Nulliparous women.

Mensturation Status

Out of 120 cases, 40 were in Post-menopausal phase, Two cases in Pre-menarche phase and 78 in menstruating phase**.**

Hormonal Contraception

History/Current usage of hormonal contraception was seen in 45 of the 120 cases.

Gross appearances

Tumors were from sizes ranging from 30 cms to 2.5cms and had varied appearances on cut-section being cystic with unilocular and multilocular, some of them having both soild and cystic areas; while a few of them received in piecemeal. Few of these tumors showed visible papillary excrescences and mucoid areas.

Behavioral Spectrum:

Benign lesions predominated over malignant ones, numbering 100 out of 120 cases. Two cases of Atypical proliferative serous tumor were reported.

Histological Spectrum

Among benign tumors, Mucinous Cystadenoma predominated with 45 of the cases.

Table 2: Benign Tumors types

Benign tumor type	No. of cases
Mucinous Cystadenoma	45
Serous Cystadenoma	35
SeromucinousCystadenoma	6
Serous Cystadenofibroma	14

Malignant Tumors

Both Mucinous and Serous tumors were not in equal numbers in the present study.

Table 3: Malignant Tumors

Morphological Type	Frequency
High Grade Papillary Serous Carcinoma	6
Micropapillary Serous Carcinoma	2
Mucinous Carcinoma	9
Seromucinous Carcinoma	1
Endometrioid Adenocarcinoma	1
Sertoliform variant of Endometroid carcinoma	1

Tubal Status

Using the morphological criteria for evaluating the tubal dysplasia, following results were obtained.

Table 4:Tubal Lesions

Tubal Lesion	No. of cases
Atypical changes	2
STIC	3

Among the three cases of STIC, one cases was of ***Papillary type*** and two others were ***Flat type***.

Discussion

Worldwide, ovarian cancer is the sixth most common cancer in women and the seventh most common cause of cancer death. There are about 204,000 new cases and 125,000 deaths annually[5]. Ovarian cancer rates increase with age. The annual incidence steadily increases from less than 3 per 100,000 in women age less than 30, and plateaus at 54 per 100,000 in the 75–79-year age group with the median age of women with Ovarian cancer being 63 years at diagnosis[6]. Many studies have shown that age is an independent prognostic factor[7,8]. Its high mortality is primarily due to difficulties in diagnosing early stage disease. Although the 5 years survival rate for stage I ovarian cancer is >90%, stage I diagnoses are more often the exception than the rule. Most patients (~75%) present with advanced stage (III/IV) tumors, for which the 5 years survival rate is a dismal 30%.[7,5] Furthermore, there are no tell-tale physical signs of the disease. Typical symptoms—which include abdominal

discomfort, bloating, gas, nausea, and urinary urgency—are vague and often mistaken for gastrointestinal problems[9,10].

Accordingly, the view that ovarian cancer begins in the ovary and spreads systematically to the pelvis, abdomen, and then distant sites is being challenged and the concept that ovarian carcinoma, over time, progresses from well to poorly differentiated does not appear to be valid. [1] Mounting clinicopathologic and molecular genetic data have led to the proposal of a new model of ovarian carcinogenesis. This model divides surface epithelial tumors into two broad categories:[11]

1. Type I with gradual adenoma- carcinoma sequence
2. Type II which arise denovo.

Recent data, however, suggest that high-grade serous carcinomas, which constitute majority of Type-II tumors, arise from intraepithelial carcinomas, the majority of which have been detected in the tubal fimbriae[12].

- Hence, we have undertaken 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 from our institutional perspective.
- Our study aimed to elucidate and document the various clinico-pathological features of various surface epithelial tumors of ovary to get an insight into their Histogenesis, has yielded us a total of 120 cases.
- We, hereby discuss and also compare the results of our study with many eminent workers in the field of Gynaecological pathology and document the concordance or discordance accordingly.

Age of Presentation

The age distribution in our study showed maximum number of cases in third decade of life. With the least number of cases being recorded in first two decades of life.

The percentage of cases reported in first two decades of life in our study was 3% which is in concordance with all the three studies listed here. The share of cases reported in the third decade of life is 26.66% which is much higher than that reported by R Jha and S Karki[13] (10.7%), Modepalli N et al[14](15.8%).

Parity

A large chunk of cases in our study was from the multiparous women. The proportion of nulliparous women in our study (14.2%) is on par with that of Saeed M et al[15], but is lesser when compared with that of Fatimah Zahra[16].

Behavioural spectrum

Benign Tumors, accounting for 83% of the tumors in our study, predominated over malignant and Borderlinetumors. We present a tabular comparison of our study with a few similar studies conducted.

The Proportion of Benign cases in present study (83%) shows good concordance with that of **GG Swamy et al[17]** (80.2%) but is much higher than that of **Ghartimagar D et al[18]**(74.4%).

Table 5: Age wise distribution of Behavioural Spectrum

Age Group	Frequency	
	Benign	Malignant
<20yrs	4	-
21-30	25	6
31-40	30	2
41-50	16	10
51-60	10	2
>60yrs	13	-

In our study the extremes of age (<20 and >60yrs) didn't show any malignant tumors.The peak incidence of malignant tumors in our study was in 5^{th} decade of life (41-50yrs). This is in concordance with that of Zubair M et al.,[19] and Rajagopal Let al.[20]

Histological Spectrum

Benign Tumors

Among the Benign tumors, the Mucinous tumorspredominated our study.

Serous Cystadenoma

- Thirty five cases of Serous Cystadenoma showed the cyst wall lined by mostly flattened to occasionally cuboidal to low columnar cells with few cases showing papillary excrescences.
- There was no evidence of atypia or stratification in these cases confirming their benign nature.

Serous Cystadenofibroma

Fourteen cases of Serous Cystadenofibroma showed broad fibrous papillae lined by a single layer of flattened to cuboidal and in few cases tubal type of epithelium protruding into the cystic cavity. And, due to the absence of dysplasia or stratification, benign nature of these tumors was established.

Mucinous Cystadenoma

Forty-five cases of Mucinous Cystadenoma were composed of glands and cysts lined by simple non-stratified mucinous epithelium containing goblet cells with small, bland, and uniform nuclei and cytoplasm containing abundant lightly basophilic mucin. The absence of overt proliferation, atypia and stratification with preserved polarity of the cells ruled over more grave diagnoses.

Sero-mucinous Cystadenoma

Six cases of Cystic tumors lined by both Serous and Mucinous elements were identified. The mucinous lining was of Endocervical type with papillary architecture.

The share of Mucinous Tumors in the present study (45%) is much lower than that of GG Swamy et al[17](81.67%), but is much higher than that of Ghartimagar D et al[18](25.4%).

Borderline Tumors

There were two cases of borderline tumors in our study both of them of Borderline Serous type. These cases displayed extensive epithelial tufting and stratification exceeding more than 10% of tumor. The cells displayed features of atypia including moderate pleomorphism, hyperchromasia with prominent nucleoli. The lower incidence of borderline tumors in the present study might be a chance occurrence. Neverthless, this definitely should motivate thorough inspection, sampling and discussion of this spectrum of Seroustumors.

Histological Spectrum of Malignant Tumors

- The present study shows equal proportion both Serous and Mucinous Carcinomas among malignancies.

High Grade Papillary Serous Carcinoma

The six cases of High-Grade Serous Carcinomas showed Complex branching and Soild patterns of growth comprising of cells showing marked atypia, high mitotic index often greater than 20/10 HPF with frequent bizzare atypical mitoses. Bizzare tumor gaint cells coupled with psammomatous calcifications and areas showing obvious invasive patterns of growth with areas of confluent necrosis.

Micropapillary serous Carcinoma

The two cases of Micropapillary carcinoma in the present study showed a characteristic pattern of papillary branching where the

distal papillary branches were thin and delicate with minimal to absent fibro-vascular core, and were seen emanating abruptly from thick, more centrally located larger papillae without intervening branches of successive intermediate sizes, forming what is described as Non-hierarchial branching papillary patterns.

Mucinous carcinoma

One cases of Mucinous carcinoma in the present study showed the presence of destructive stromal infiltration with haphazard infiltrative pattern of small glands with marked cytologicatypia. Also seen were large areas with confluent glandular pattern with complex interconnecting neoplastic glands.

One case of Seromucinous carcinoma showed papillary patterns of growth with expansile to destructive patterns of invasion showing both serous type epithelium with prominent stratification and also mucinous components

Endometrioid Adenocarcinoma

There were one cases of Endometriod Adenocarcinomas of which one was conventional type and the other was Sertolifrom variant of Endometriod Adenocarcinoma.

Table 6: IHC results of Sertoliform Variant of Endometrioid Carcinoma

Marker	Reaction
Epithelial Membrane Antigen (EMA)	Positive
Vimentin	Weakly positive
Calretinin	Postive
Inhibin	Negative

While the positivity of Epithelial Membrane Antigen (EMA) ruled out the possibility of Sex-cord Stromal tumors (SCST), the positivity of Calretinin again tilted the equation towards SCST. It must be however remembered that in 10% of the cases of Endometrioid Carcinoma, including the sertoliform variant calretinin has shown to be expressed Inhibin by far is the most specific and sensitive Immunohistochemical marker available, the negativity of which will rule out SCST.[1]

The share of Other Surface epithelial malignancies(i.e., Seromicunos and Endometrioid Adenocarcinomas) was 12%, which was very much in concordance with that of Akakpo et al[21] (12%) but very much lower than that of Zubair et al[19] (19.8%) and Fatimah Zahra[16](17.6%).

Tubal Status

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-cililatedcells.

- 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, the were placed under the category of ***"STIC"*** with Flat-***type*** as the morphological sub-type.

Table 7: Relationship of the Surface epithelial tumors of Ovary to tubal status

Surface Epithelial Tumor	Co-existing Tubal Pathology	Number
High Grade serous carcinoma	STIC(Flat)	2
Micropapillary Serous Carcinoma	STIC(papillary)	1
Seromucinous Carcinoma	Atypical changes	1
Mucinous carcinoma	Atypical changes	1

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.,[22] and Tang S et al.[23]

Incidence of STIC among Ovarian tumors

Out of the 120 cases in the present study, STIC was found in 3 cases. Thus, the incidence of STIC coexisting with ovarian tumors in the present study is 2.5%.

Site of the STIC and comparison with other studies

- In our study the location of STIC was as follows
  1. Two cases at Fimbrial end (TPJ or Tubeperitoneal Junction)
  2. One case at the Ampullary region of tube

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[24].,(64%)but slightly more than that of AS Sehdev et al.,[25] (59.4%).

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 and efficient screening and bring down the mortality and morbidity associated with these tumors just following the same path of successful prevention strategies for Carcinoma Cervix.

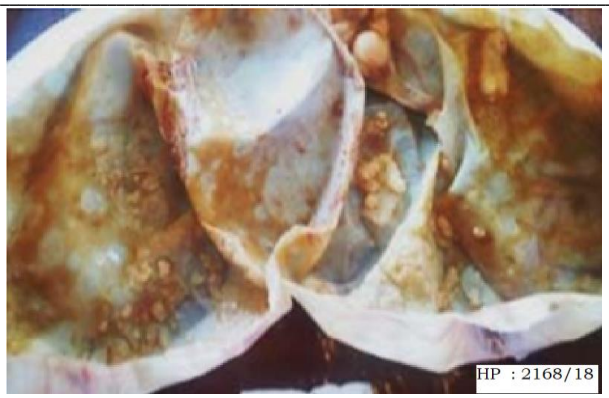

Fig 1: Serous cystadenoma – cut section showing papillary excrescences

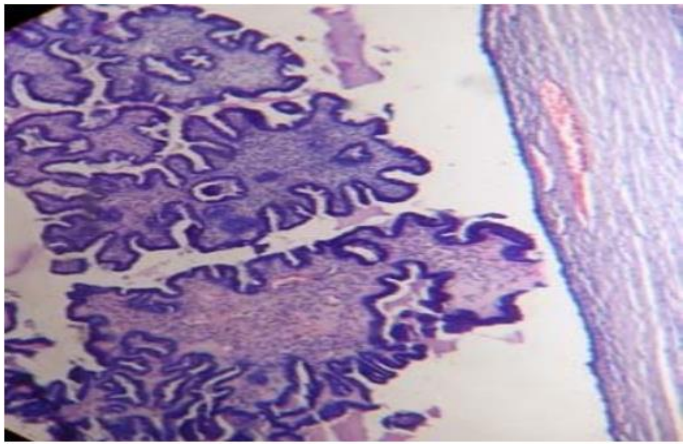

Fig 2: Papillary serous cystadenoma. Papillary fronds lined by benign cuboidalepithelium. H&E, 100x

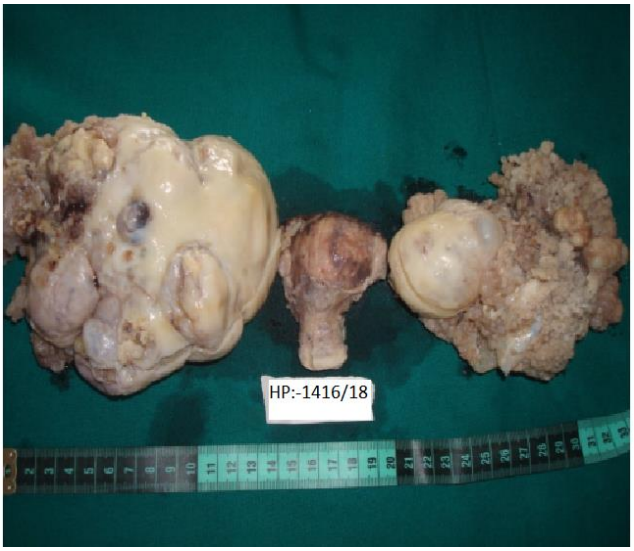

Fig 3: Papillary serous cystadenocarcinoma. Gross picture showing extensivesurface papillary excrescence

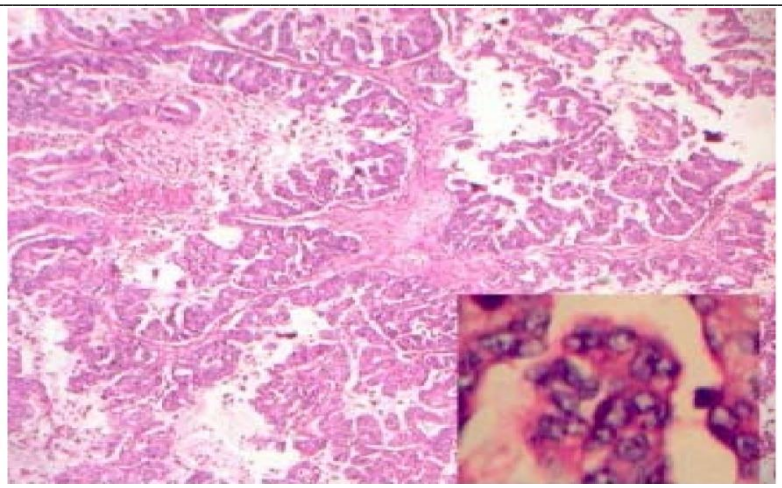

Fig 4: Papillary serous cystadenocarcinoma. Photomicrograph showingpapillary fronds lined by tumor cells. Inset showing large pleomorphic cells.H&E, 100x. Inset 1000x

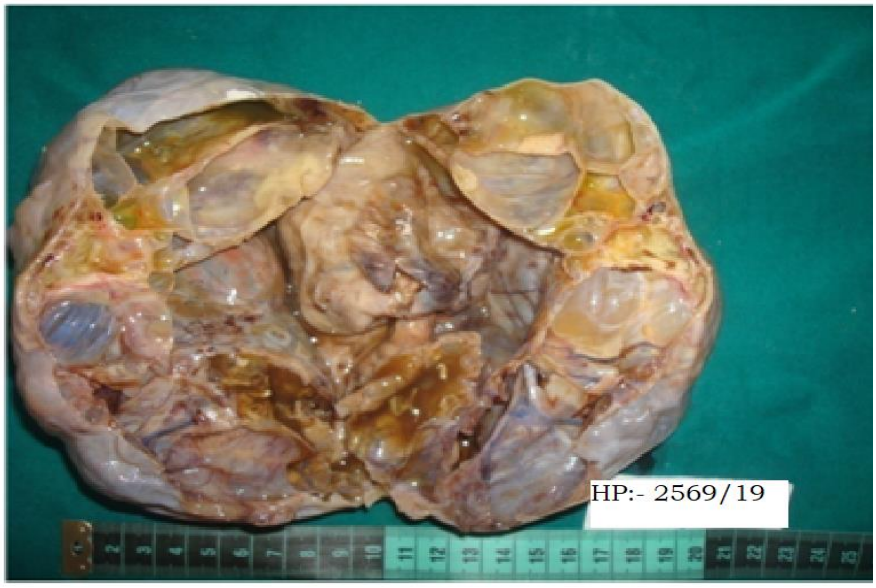

Fig 5: Mucinous cystadenoma. Cutsection showing multiloculated cysts

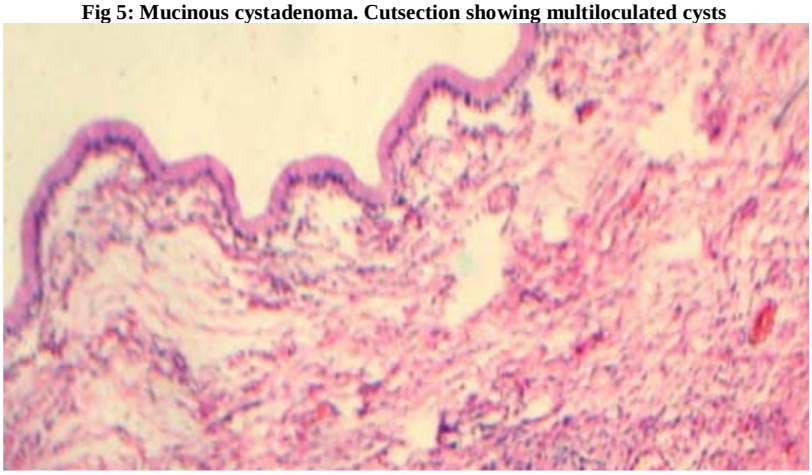

Fig 6: Mucinous cystadenoma . Photomicrograph showing cyst wall lined bytall columnar cells with apical mucin. H&E, 100x

Fig 7:Mucinous cystadenocarcinoma. Cut section showing both solid and cysticareas.

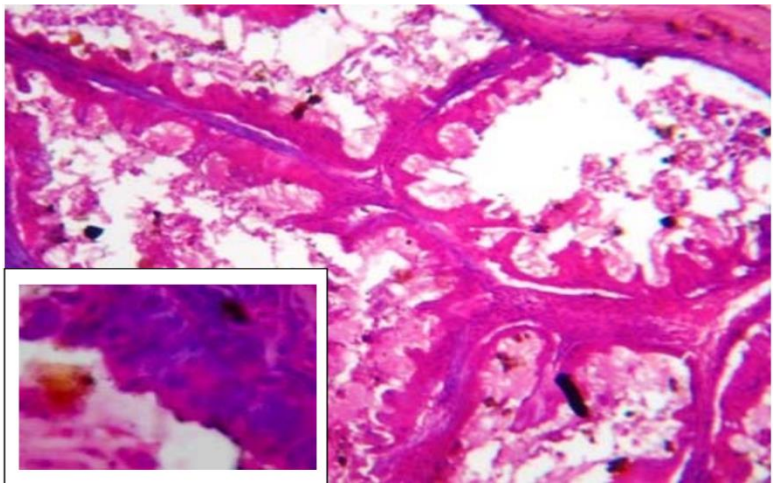

Fig 8: Mucinous cystadenocarcinoma. Inset showing stratified columnarepithelium with hyperchromatic nuclei. H&E, 100x, Inset 400x

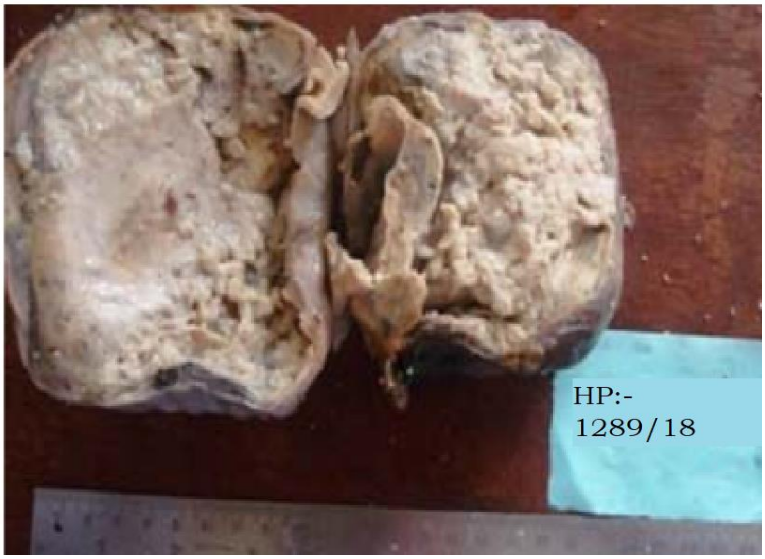

Fig 9:Endometrioid carcinoma – cut section showing both solid and cysticareas

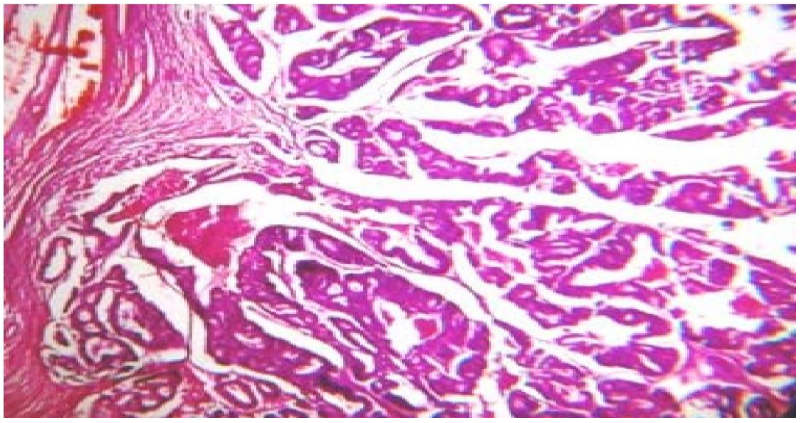

Fig 10: Endometrioid carcinoma. Tumor cells in glandular pattern. H&E, 100x

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