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Surface Epithelial Tumors of Ovary: Clinicopathological Study of 100 Cases

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Abstract:
Introduction: Tumors of ovary have an amazingly diverse pathology, the variety being more than other organ. Owing to their large number and difficulty in diagnosing them at an early stage, we have chosen to study theSurface epithelial tumors which account for 2/3rd of all ovarian neoplasm.
Aim: The aim of the study was to determine the incidence of Surface epithelial tumors of ovary amongst all ovarian tumors received and to assess their clinical presentation, gross and histomorphological features.
Materials and Methods: This study is a retrospective study of 100 cases of surface epithelial tumors diagnosed in the department of pathology over a period of 2 years in a tertiary care center. Detailed clinical data was reviewed.Grossing was done as per standard grossing protocols. Tissues were processed routinely and stained with Haematoxylin and eosin (H&E) stained. Special stains and IHC (Immunohistochemistry)was done wherever required. Final histological diagnosis was given as per WHO classification of ovarian tumors (2014).
Results: Surface epithelial ovarian tumors accounted for 71.43% of primary ovarian tumors of which 83% were benign, 8% were borderline, and 9% were malignant. The commonest symptoms were pain in abdomen, abdominal lump, and menstrual abnormality. The commonest surface epithelial tumor was Serous tumor(57%) followed by Mucinous tumor (38%), Brenner tumor (2%), Seromucinous tumor (2%), endometrioid tumor (1%). Bilaterality was seen in only 2% of cases and both were diagnosed as Serous carcinoma. Metastasis was seen in 2 cases, both of them were high grade Serous carcinoma.
Conclusion: The panorama of ovarian neoplasm is vast, diverse and complex. As concepts change, newer entities are published and criteria are better defined. To conclude we recommend histopathological examination of every ovarian mass as pre-operative imaging modalities like ultrasonography and gross morphology of tumors is not definitive. Targeted therapy depending on the type of tumor is essential to improve outcome in cases of ovarian tumors emphasizing the need for histopathological examination and grading in every case of ovarian tumor.
Study Design: Observational Study
Keywords: Epithelial, Tumors, Ovary &Clinicopathological.

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1. INTRODUCTION

The source of female reproductive capacity, the ovary is the product of complex histogenesis with multi-potential cellular elements having intricate biochemical functions. The number and complexity of tumors that arise in the ovary are a constant source of confusion to the pathologists and gynecologists alike. As per Surveillance Epidemiology and End Results (SEER) cancer statistics 2010-2012 data, 1.3% women have a lifetime risk of developing ovarian cancer at some point in their lives. [1]

Worldwide ovarian cancer is the sixth most common cancer in women and seventh most common cause of cancer death. [2]

Ovaries being deep seated organs, their neoplasm defy early detection causing them to be an important cause of mortality in India.

Owing to their large number and difficulty in diagnosing them at an early stage of the disease, we have chosen to study the surface epithelial tumors; which account for 90% of all ovarian carcinomas and 2/3rd of all ovarian neoplasm. [3] The aim of study was to determine the incidence of surface epithelial ovarian tumors and to assess clinical presentation,gross and histomorphological features.

2. MATERIALS AND METHODS

This study is a retrospective study of 100 cases of surface epithelial tumors diagnosed in the department of pathology over a period of 2 years(1st June 2015 to 31st May 2017) in a tertiary care center. Detailed clinical data was reviewed to get information about the age, clinical presentation, laterality, tumor marker, radiology finding and surgical procedure done.

Grossing was done as per standard grossing protocols. Tissues were processed routinely and stained withHaematoxylin and eosin (H&E) stained. Special stains and IHC was done wherever required. Final histological diagnosis was given as per WHO classification of ovarian tumors (2014).

3. RESULTS

Table 1: Subtyping of Surface Epithelial Tumors

		Number of cases	Total %	% within subtypes
Serous Tumors (N=57)	**Benign**	52	52	91
	Borderline	02	02	04
	Malignant	03	03	05
Mucinous Tumors (N=38)	**Benign**	29	29	76
	Borderline	06	06	16
	Malignant	03	03	08
Endometrioid Tumors (N=1)	**Benign**	-	-	-
	Borderline	-	-	-
	Malignant	01	01	100
Brenner Tumors	**Benign**	02	02	100

(N=2)	**Borderline**	-	-	-
	Malignant	-	-	-
SeromucinousTumors (N=2)	**Benign**	-	-	-
	Borderline	-	-	-
	Malignant	02	02	50
Total		100	100	

Table 2: Age distribution of ovarian tumors

AGE IN YEARS		**12-20**	**21-30**	**31-40**	**41-50**	**51-60**	**61-70**	**>70**
Serous Tumors (N=57)	**Benign**	04	16	14	06	05	07	-
	Borderline	-	01	-	-	-	01	-
	Malignant	-	-	-	01	01		01
Mucinous Tumors (N=38)	**Benign**	01	10	11	03	02	02	-
	Borderline	-	01	02	03	-	-	-
	Malignant	-	-	02	-	-	-	01
Endometrioid Tumors (N=1)	**Benign**	-	-	-	-	-	-	-
	Borderline	-	-	-	-	-	-	-
	Malignant	-	-	-	-	01	-	-
Brenner Tumors (N=2)	**Benign**	-	-	-	01	-	01	-
	Borderline	-	-	-	-	-	-	-
	Malignant	-	-	-	-	-	-	-
Seromucinous Tumors (N=2)	**Benign**	-	-	-	-	-	-	-
	Borderline	-	-	-	-	-	-	-
	Malignant	-	01	-	01	-	-	-
Total (N=100)		05	29	29	15	09	11	02

Table 3: Clinical presentation of ovarian tumors

Clinical Presentation		**Pain in abdomen**	**Abdominal lump**	**Menstrual abnormality**	**Asymptomatic**	**Others**
Serous Tumors (N=57)	**Benign**	29	08	07	07	07
	Borderline	01	02	-	-	-
	Malignant	02	01	-	-	01
Mucinous Tumors (N=38)	**Benign**	18	11	03	01	03
	Borderline	04	06	-	-	-
	Malignant	03	01	-	-	-

Endometrioid Tumors (N=1)	**Benign**	-	-	-	-	-
	Borderline	-	-	-	-	-
	Malignant	-	-	-	01	-
Brenner Tumors (N=2)	**Benign**	01	01	-	-	-
	Borderline	-	-	-	-	-
	Malignant	-	-	-	-	-
Seromucinous Tumors (N=2)	**Benign**	-	-	-	-	-
	Borderline	-	-	-	-	-
	Malignant	01	01	-	01	-
Total		59	31	10	10	11

Table 4: Serous tumors

Characteristics		**Benign N=(52)**		**Borderline N=(2)**	**Malignant N=(3)**
		Cystadenoma N=(46)	**Cystadenofibroma N=(6)**		
External surface	**Smooth**	46	6	02	-
	Bosselated	-	-	-	01
	Capsular breach	-	-	-	02
Cut surface	**Cystic**	46	5	1	-
	Solid	-	-	-	-
	Cystic>solid	-	1	1	2
	Solid>cystic	-	-	-	1
loculations	**Unilocular**	41	6	1	2
	Multilocular	5	-	1	1
Necrosis	-	-	-	-	2

Haemorrhage	-	-	-	-	3
Papillae on cut surface	-	-	-	1	2

Table 5: Mucinous Tumors

Characteristics		**BeingnCystadenoma N=(29)**	**Borderline N=(6)**	**Malignant N=(3)**
External surface	**Smooth**	26	06	01
	Bosselated	03	-	02
	Capsular breach	-	-	-
Cut surface	**Cystic**	28	04	-
	Solid	-	-	-
	Cystic> solid	01	02	03
	Solid > cystic	-	-	-
Loculations	**Unilocular**	10	-	01
	multilocular	19	06	02
Necrosis	-	-	-	02
Haemorrhage	-	-	02	03
Papillae on cut surface	-	-	02	01

During our study period of two years, total 140 specimens of Ovarian tumors were received, amongst which 100 cases were diagnosed to be Surface Epithelial tumors amounting to 71.4% and hence being the commonest ovarian tumor to occur. It was followed by germ cell tumors whereas metastatic tumors to the ovary were the least commonly occurring tumors.

Amongst the Surface Epithelial tumors of ovary, Serous tumors (57%) were the most commonly occurring tumors.

Most of the Serous, Mucinous and Brenner tumors were benign amounting to 91%, 76% and 100% respectively.Asagainst, all the Endometrioid and the Seromucinous tumors diagnosed were malignant. Age wise incidence of various tumor have been summarized in table-2

It was observed that Surface Epithelial tumors mostly presented with pain in abdomen (59 cases) followed by lump in abdomen (31 cases).

It was observed that Serous tumors ranged in size from 2 cm to 17 cm whereas Mucinous tumors ranged in size from 2 cm to 40 cm.
Benign tumors generally presented with smaller masses (6-10 cm) whereasmalignanttumorspresented with larger masses (16-20 cm).
Only 2% cases presented with masses measuring > 26 cm; both of which were mucinous tumors.
Grossly none of the subtype had showed papillae over external surface. All benign and borderline serous tumors had smooth external surface. 2 out of 3 cases of malignant serous tumor show capsular rupture which upgrades the TNM and FIGO staging because of its prognostic implications. Most of benign mucinous tumors also has smooth external surface. 3 out of 29 had bosselated surface which might be because of accumulation of fluid. All borderline tumors were smooth externally. 2 out of 3 malignant mucinous tumors had bosselation which indicate that there are few solid area within a cyst. External surface of maximum surface epithelial tumors were smooth (90%). In our study 2 out of 9 malignant cases showed capsular breach externally accounting for 22%.It was seen that the majority (84%) of cases were purely cystic on cut surface. Only one case (Brenner Tumor) had a solid cut surface. Most of the benign SETs are cystic. Presence of solid component is seen in borderline and malignant tumors. Serous tumors were predominantly unilocular while mucinous tumors were predominantly multilocular. Most of the serous tumors had a serous content and most of the mucinous tumors had thick gelatinous mucinous contents.
All the tumors showed typical microscopic features except for a single case of serous cystadenofibroma with focal epithelial proliferation, benign mucinous cystadenoma with focal nests of transitional epithelium.Metastasis was seen in 2 cases of high grade serous carcinoma to organs like liver, stomach, appendix, omentum.

4. DISCUSSION

Surface epithelial tumors are derived from the ovarian surface epithelium which develops from the coelomic epithelium (modified mesothelium) which lines the ovary.[4] Surface epithelial tumors of ovary can arise directly from surface epithelium and can grow outwardly, but more often they originate from inclusion glands, thus accounting for the cystic (endophytic) nature of most of these tumors.[5] At menopause, the ovarian surface epithelium extends into the stroma to form inclusion glands. This inclusion gland may become cystic and these rarely occur in early reproductive life and puberty. Epithelial tumors can arise from surface epithelium as well as this inclusion gland.These tumors become solid when they contain a large stromal component or when malignant cells within them proliferate.
The ovarian surface epithelium, when involved in metaplastic or neoplastic conditions, often undergoes a mullerian differentiation; as a result, it may produce any of the adult structures formed by the mullerian ducts, including tubal, endometrial, and endocervical mucosa, singly or in combination.[6]Most of these tumors are composed of more than one cell type.
They are usually classified based on the predominant cell type.[4] When the tumors are composed of two or more of the five major cell types (serous, mucinous, endometrioid, clear cell and transitional) and the second or third predominant cell type together account for >10% of tumor epithelium, they are termed as seromucinous tumors. This group of tumor is a new entity among ovarian cancer within the WHO of Female genital tract (2014) classification. Earlier they were termed as mixed tumors.

Differentiation and extent of proliferation of the epithelium form the basis of classification of surface epithelial tumors. They also exhibit an intermediate borderline category referred to as "tumors of low malignant potential". There is a need to categorize some tumor as "borderline" to allow a more conservative management. This term has more relevance in serous and seromucinous tumors as there are significant amount of cases, which are associated with extra ovarian implants but still, have a favorable prognosis. Diagnosis of borderline tumor is based on histological examination of primary tumor regardless of extra ovarian extension. Better survival is seen in patients with borderline tumor when compared to its malignant counterpart. [7]

Of the total number of ovarian tumors received during the study period (140), the majority were Surface Epithelial tumors (71.43%) followed by germ cell tumors (20%) and sex cord stromal tumors (6.43%). The least number of tumors were metastatic tumors to the ovary accounting for only 2.14% of all cases, which is consistent with studies done by Badge et al[8], Mondal et al [9], Neha et al.[10]

Benign surface epithelial tumors were common than the malignant surface epithelial tumors.

Only 5% benign surface epithelial tumors occured below the age of 20 years. This finding correlates with that of Nageswararao et al[11] and Talwelkar et al[12] which state that such tumors were uncommon before menarche. This may suggest that we should exclude other types of ovarian tumors before making a diagnosis of SETs at this young age.

The peak incidence of surface epithelial tumors occurred in third and fourth decades of life with only 2% comprising those above the age of 70 years. The comparative study by Nageswararao et al[11] andTalwelkar et al [12] showed a peak incidence in the fourth decade and in third decade respectively.

In our study benign tumors commonly occurred in third and fourth decade, borderline tumors in fifth decade and malignant tumors after fourth decade of life. This shows slight but definite increase in the occurrence of malignant tumors with age and these findings are similar to the study by Nageswararao et al[11]. This could suggest that transformation from the benign to the malignant tumor type may occur over time in a few tumors by progressive increase in degree of epithelial abnormality.

From the table-3 it is evident that pain in abdomen was the most common presenting complaint followed by lump in abdomen, which is similar to study by Talwelkar et al[12]According to the literature, benign tumors are generally painless unless there is sudden increase in size, torsion, infarction etc. Menstrual abnormalities like amenorrhoea, hypomenorrhoea, abnormal uterine bleeding, menorrhagia, oligomenorrhoea, post menopausal bleeding were found to be the most common complaints in benign serous and mucinous tumors. Mucinous cystic tumors are amongst the tumors which stimulate the ovarian stroma to luteinize and to produce steroid hormones; effects that simulate those of typical functioning tumors of the ovary. These tumors are most common among those causing virilization in young women during pregnancy. [4]

Two cases of benign serous tumors were related to pregnancy. One presented with missed abortion and other was a post partum female. Generally cases diagnosed during pregnancy present acutely along with torsion and hemorrhage. It is difficult to diagnose such lesions during pregnancy as the large gravid uterus hampers adequate palpation of the coexisting adnexal mass. [13]

Amongst the patients who were asymptomatic, most were diagnosed to have benign serous tumors which are comparative to the study by Tindal et al.[14]

Out of 100 cases studied, only 2% cases were bilateral which was concordant with Shreya et al [15], Talwelkar et al [12].The significance of bilaterality in ovarian tumors is that it strengthens the concept of the "extended mullerian system" wherein the close relationship of the ovarian mesothelium and the mullerian duct during embryogenesis is postulated as the reason for the common type of response of both the ovarian surface and the mullerian duct derivatives in adulthood, leading to similar pathogenesis in both.
Our finding is consistent with that of literature which states that the malignant serous tumors are most common SETs to be bilateral.
Determining the bilaterality in mucinous SETs is of outmost importance as bilaterality favors the diagnosis of metastatic mucinous ovarian tumors over the primary ovarian mucinous tumor. In our study all the 3 cases of mucinous carcinomas presented with unilateral masses.

In the present study the tumors ranged in size from 2cm to 40 cm. The smallest tumor had a size of 2 cm in diameter that was seen in 51 year old female and diagnosed as benign serous cystadenoma and in 27 year old female as benign mucinous cystadenoma.
The largest tumor measured 40 cm which was diagnosed as benign mucinous cystadenoma in 33 year old female. These findings correlate with Shreya et al.[15] Overall it was observed that benign serous tumors are usually small and the mucinous tumors present as huge masses.
Most of the benign tumors ranged in size from 6 to 10 cm, borderline tumors 11 to 20 cm and malignant tumors 11 to 20 cm.

External surface of majority of surface epithelial tumors was smooth (90%), followed by bosselated external surface (8%). Only 2% cases showed capsular breach. None of our case had surface papillae.
Both the cases having capsular breach were high grade serous carcinoma. Both cases showed distant metastasis. Capsular breach increases the stage of the tumor, thereby amounting to poorer prognosis.[16] In our study, out of 83 benign tumors 79 had smooth external surface. All borderline tumors presented with smooth external surface. Most of the malignant tumors (4/9) had bosselated external surface.
Mucinous tumors (5/38) showed more of external bosselation than serous tumors (1/57). Thus, external bosselation may indicate that the tumor is multiloculated or may have a lobulated cut surface
Documentation of surface papillae is also of outmost importance since they are associated with an increase frequency of peritoneal implants. [4] However no surface papillae were seen in any of our cases.

In the present study 84% cases were cystic (79% were benign, 5% were borderline). Only one case which had a completely solid cut surface was a case of Brenner tumor. The other case of Brenner tumor and a case of Endometrioid tumor showed solid cystic cut surface with predominant solid component.
One case of benign mucinous tumor which showed focal component of Brenner tumor had a focal solid area within cystic area.
Maximum number of malignant tumor (7/9) were solid cystic with predominant cystic component, which was consistent with study of Shreya et al. [15]
Thus as evident in the literature, malignant tumors exhibit capsular breach, variegated appearance with solid areas showing hemorrhage and necrosis, while benign tumors do not.

In our study serous tumors especially the benign, and also of the malignant ones were usually unilocular as mentioned in the literature. [4,17]

Mucinous cystic tumors in our study were usually multilocular**;** literature review confirms the same. [16] Generally benign cystadenomas show uniform cyst wall thickness. Cystadenofibromas show increased wall thickness or firm nodular areas or papillary projections. We had 6 cases of serous cystadenofibromas. One of them showed nodular area.

Detail analysis of gross features, identifying any unusual areas and sampling them is of great importance. Adequate sampling of the SETs is crucial, more so in cases of mucinous tumors. This is because they are typically heterogeneous and can harbor occult foci of carcinomas. Moreover they are associated with various other tumors.

As seen in table –1 serous tumors were the most frequently occurring tumor as seen in studies by Talwelkar et al [12] and Shreya et al [15]. We had more cases of seromucinoustumors(2%) than this study;which might be because according to recent WHO classification the tumors with 2 or more mullerian cell types, all accounting for at least 10 % of the epithelium as seromucinous tumors. Parenthetically, it should be noted that besides seromucinous carcinomas, which can show a variety of cell types, all the epithelial ovarian tumors can also show mixture of cell types. They are classified by the predominant type but the smaller components can be included in the diagnosis.[17]

Serous Tumors

They are lined by epithelial cells resembling those of fallopian tube, including ciliated cells.

One case showed benign serous tumor showed focal nuclear stratification and atypia. Also it had predominant fibromatousstroma. Therefore it was classified as serous cystadenofibroma with focal epithelial proliferation. As, such areas amounted to less than 10% of the tumor it was retained in the benign category. Cystadenofibromas are a group of benign tumors which have more amount of solid component than cystadenomas. They have nodular projections into their cystic cavities. [16]

Out of 52 benign tumors, 6 cases show stroma which is cellular and fibrous component predominated. It was seen that maximum wall thickness range from 0.1 to 0.4 and was more in tumor diagnosed as adenofibroma.

2 cases displayed extensive epithelial stratification, tufting and detachment of individual cells and clusters, hierarchial branching and were labeled as borderline serous tumors. Stromal invasion was not seen in these cases.

Micropapillae (non hierarchial branching architecture which measure less than 5mm in confluent growth), microinvasion (clusters of cells in stroma with abundant eosinophilic cytoplasm that measures less than 5mm in greatest dimension) were not seen in any of our cases. There were 3 cases of serous carcinoma in which tumor cells were arranged in glandular, papillary and solid patterns. The papillae showed irregular branching with multilayered pleomorphic epithelium with areas of stromal invasion.

One case was diagnosed as low grade serous carcinoma which showed numerous psammoma bodies and stromal invasion as well as it infiltrated the muscularis of fallopian tube.

Two cases which were diagnosed as high grade serous carcinoma which showed

other than pelvic organs. One case showed metastasis to subdiaphragmaticserosal surface of liver and to stomach (antrum and pylorus). Other case shows metastasis to appendix and omentum.

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Mucinous Tumor

Mucinous tumors have a lining which consist of columnar cells resembling gastric foveolaror intestinal epithelium, less commonly it can be endocervical type too. In our study benign mucinous tumors comprised 29% of cases. They are lined by a single layer of mucin containing columnar cells.

One of our case show cyst lined by mucin secreting columnar epithelium and foci of nest of transitional epithelium. The origin and relationship between ovarian mucinous and brenner neoplasm is enigmatic. It has been reported that their association with each other ranges from 1% to 16% with a mean of about 9%.[18] A search for early mucinous ovarian tumors has suggested that some of them arise from mucinous inclusions in the medullary hilar area of the ovary or from transitional cell nests similar to those in brenner tumor in the same location.

6% of the cases were of borderline type. They were lined by atypical epithelium of intestinal type. The lining cells were often stratified, generally 2-3 layers and exhibited nuclear atypia. 2 cases of borderline variant also contained mucin granulomas i.e.

mucin in stroma associated with histiocyticand foreign body giant cell reaction. Borderline variant is characterized by absence of capsular or stromal invasion, in contrast to the frankly malignant tumors. 3% of mucinous tumors were malignant which showed both solid and cystic patterns, predominantly showing cystic areas with complex stratification of lining of intestinal epithelium and marked nuclear pleomorphism. The tumor cells were infiltrating into adjacent stroma.

Endometrioid Tumor

We had a single case of endometrioid carcinoma, in a 58 years old asymptomatic female.

Brenner Tumor

We encountered 2 cases of this variant with a classical gross appearance and both were benign showing oval to round irregular nests of transitional type cells within a fibromatousstroma.

Seromucinous Tumor

In our study we came across 2 cases of malignant tumor.

One case showed Mucinous and Serous type of epithelium each types accounting for more than 10% of the epithelium. Stromal invasion was seen.

The other case showed admixture of mucinous and endometrioid components, each accounting for more than 10%. Numerous infiltrating invasive glands lined by atypical nuclei with intracytoplasmicmucin were seen. Mitosis is brisk. Area of necrosis is seen. Both of these tumors were confined to ovary.

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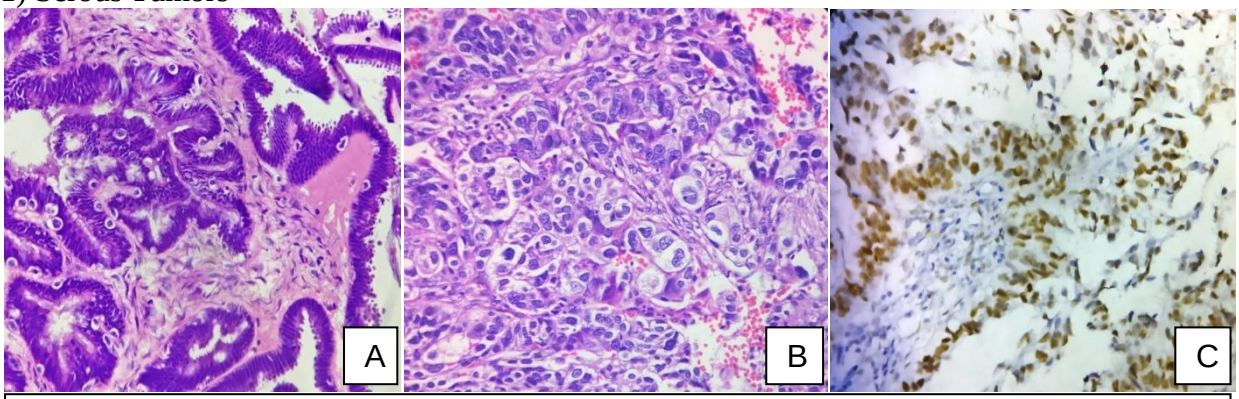
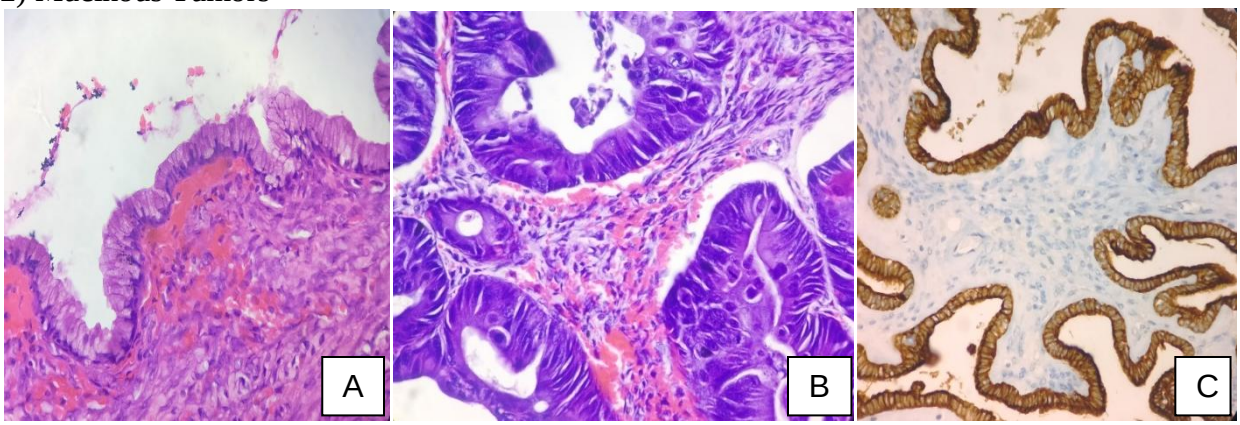
1) Serous Tumors



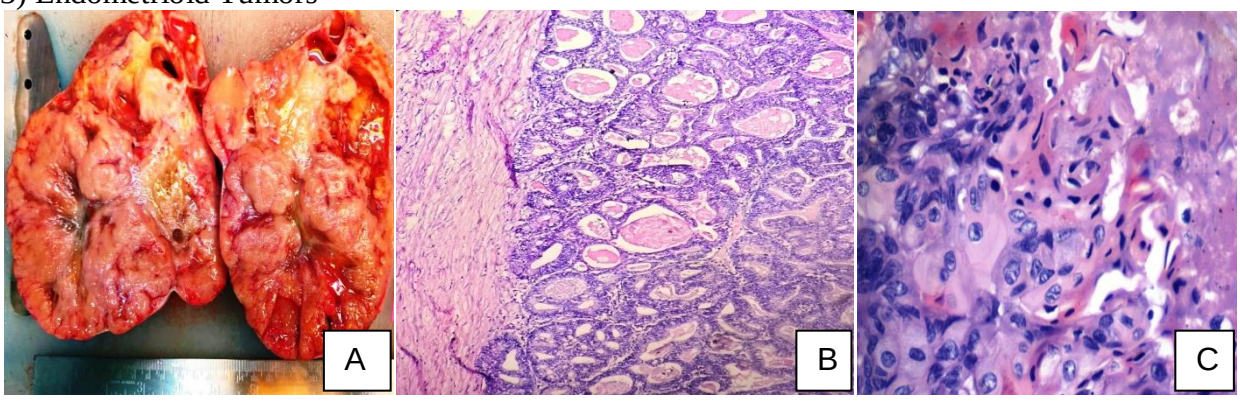
[A]-Histology showing Serous borderline tumor with hierarchical branching pattern lined by cuboidal to columnar epithelium with minimal cytological atypia (H&E×400) [B]-Histology showing low grade Serous carcinoma with complex papillary pattern of arrangement with cells showing moderate nuclear atypia. Stromal invasion was seen, however no necrosis was identified (H&E×400) [C]-Histology showing High grade Serous carcinoma confirmed by nuclear expression of WT1 (H&E×400)

2) Mucinous Tumors



[A]-Histology showing Mucinous cystadenoma with cyst lined by gastrointestinal mucinous cells with minimal or no cytological atypia (H&E×400) [B]-Histology showing Mucinous carcinoma with stromal infiltration, marked cytological atypia and brisk mitosis (H&E×400) [C]-Histology showing CK7 cytoplasmic positivity (H&E×400)

3) Endometrioid Tumors



[A]-Gross showing cut surface with predominantly solid areas [B]-Histology showing well differentiated endometrioid adenocarcinoma with back to back arrangement of glands with little or no intervening stroma (H&E×400) [C]-Histology showing foci of squamous differentiation (H&E×400)

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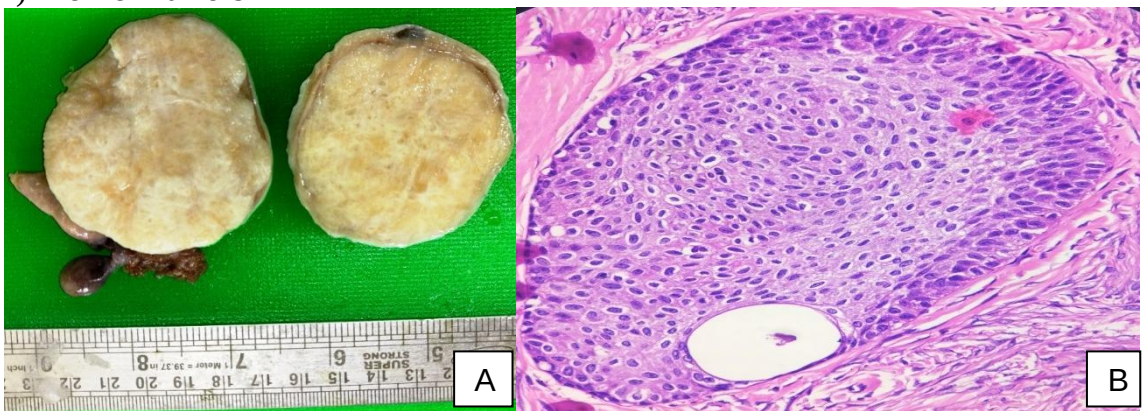
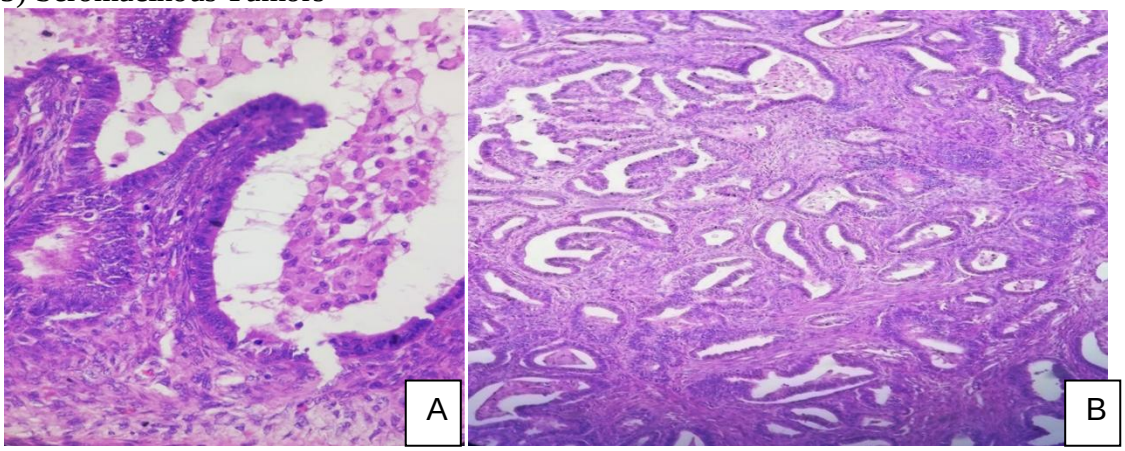
4) Brenner Tumors



[A]-Gross showing well circumscribed homogenous grey white cut surface [B]-Histology shows nests of transitional type epithelium (H&E×400)

5) Seromucinous Tumors



[A]-Histology showing mucinous area with muciphages and apical mucin (H&E×400) [B]-Histology shows high grade endometrioid area (H&E×400)

5. CONCLUSION

Histopathological examination of every ovarian mass is of outmost importance as pre operative imaging modalities of these tumors may not be definitive. In addition histopathological examination and tumor grading helps to tailor the treatment and targeted therapy. Follow up of patients is recommended to assess the usefulness of histomorphological grading and staging in terms of clinical outcomes.

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