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Original Research Article

Clinicopathological spectrum of ovarian neoplasms in pre and post menopausal Indian women

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ABSTRACT

Background: Ovarian cancers are the third most common cancers in women trailing behind cervical and breast cancer. Various molecular insults are seen in hereditary cancer syndromes that results in different morphological types of ovarian cancer.Accurate histological typing suggests screening of the first degree relatives and also targeted therapy for the same. Age specific incidence rate showed that ovarian cancer increases from 35 years of age and peaks between 55 to 64 years of age.

Materials and Methods: Present study was conducted to know the clinical and histopathological spectrum of ovarian neoplasms. To correlate the histopathological subtype with the pre and post menopausal age group. This is a retrospective observational study of 196 cases found over 2.5 years during January 2018 to June 2020.

Results and Discussion: Surface epithelial tumors(SET) are commonest in our study (benign 50%, borderline 6% and malignant 17%) followed by germ cell tumors (12%), sex cord stromal tumors (9%), secondary tumors (5%) and mixed epithelial and mesenchymal tumor (0.5%). Benign SET and germ cell tumors are significantly associated with premenopausal age whereas malignant SET has significant association with post menopausal age. However sex cord stromal tumors did not show any significant association with both the groups. Bilateral involvement was commonest with secondary tumors followed by malignant SET. Mean age of presentation was 41 years with maximum cases presenting in 4^{th} and 5^{th} decade. Various histomorphological parameters were evaluated in detail along with immunohistochemistry(IHC). Inhibin negativity helped to differentiate sertoliform variant of endometrial carcinoma from sertoli cell tumor. WT1 positivity in serous carcinoma ruled out poorly differentiated endometrioid carcinoma in two cases. Thirteen cases show extraovarian spread. Synchronous neoplasms of female genital tract (fibroma with uterine endometrial carcinoma and Brenner with basaloid carcinoma cervix) were found. Collision tumors (sex cord stromal tumors with germ cell tumors) were also found in present study.

Conclusion: Using WHO classification, ovarian tumors can be precisely subcategorized into different morphological subtypes. However overlapping features may need IHC to pinpoint the correct diagnosis. Age specific occurrence of different morphological subtypes may suggest other ancillary investigations and different treatment modalities

1. Introduction

Ovarian cancers are comprised of 3.4 % cases of total cancers and caused 4.4% mortality in females as per the recent study done by Bray et al. when studied in 20 regions worldwide.[1] As per the Indian cancer registries, ovarian cancers are the third most common cancer trailing behind cervical and breast cancer. Various molecular insults are seen in different hereditary cancer

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syndromes such as hereditary breast and ovary cancer syndrome (HBOCS) and Lynch syndrome that leads to development of different morphological types of ovarian cancer.[2] Accurate histological typing of ovarian tumors suggests screening of the first degree relatives for these cancer syndromes and also suggests targeted therapy for the same.[2] Age specific incidence rate showed that ovarian cancer increases from 35 years of age and peaks between 55 to 64 years of age.[3] Mean age of menopause in India ranges from 41.9-49.4 years in different studies with average being 45 years.[4,5] Epidemiological evidence has suggested a link between menopause and ovarian cancer risk. Few studies in the literature have specifically compared subtypes of ovarian neoplasms with age of menopause according to WHO classification.[6,7] Ovarian neoplasms present late in the course of disease with diverse morphology with relatively mild or vague symptoms. Many a times detected incidentally or with metastasis. Family history and nulliparity play important role in etiopathogenesis. Early accurate diagnosis is crucial for better management and good prognosis.[8] Prognosis of ovarian tumors is dependent on histological subtype, tumor stage and grade. Histological subtyping is done with WHO classification and International Federation of Gynaecology and obstetrics staging system.[9]

2. Aims and Objectives

Present study was conducted to know the clinical and histopathological spectrum of ovarian neoplasm in this region. To study the histomorphological parameters in detail with respect to the stage of disease and to correlate the histopathological subtype with the pre and post menopausal age group in particular.

3. Materials and Methods

This is a retrospective observational study of 196 cases found over 2.5 years during January 2018 to June 2020. All cases diagnosed as ovarian neoplasm on histology were included in the study. Ovarian specimens were obtained from excision of unilateral or bilateral ovaries with or without hysterectomy and with or without omental or peritoneal biopsy. The gross specimens were analyzed for parameters such as external surface, cut surface, contents of cysts, color and consistency of tumor, other significant findings in uterus, cervix, fallopian tubes, omentum or peritoneal biopsy and intra-abdominal lymph-nodes if provided. Relevant tissue sections were processed after adequate formalin fixation and stained with hematoxylin and eosin stain on 3-5 micron paraffin embedded sections. Non neoplastic inflammatory lesions such as follicular cyst, luteal cyst, paratubal cysts, tuberculosis and tubo-ovarian abscesses were excluded which were found during the study period. Clinical parameters such as age, signs and symptoms were noted from the case record form. Cases were analyzed according to the 2014 WHO classification given by Robert Kurman and colleagues. Histopathological findings were noted and data was entered in MS Excel sheet. Immunohistochemical evaluation is sought where there was more than one differential diagnosis on morphology. Minimum sample size was calculated 163 using absolute precision 7% and confidence level of 95%. Data is expressed in frequency and percentages. Categorical data was compared by performing Chi square test. For small sample Fisher Exact test was used. $P<0.05$ was considered as statistical significance. Analysis was done using software STATA version 14.0. Institutional ethics committee permission was obtained.

4. Results

Total 196 cases of ovarian neoplasms were studied during the study period. Cases were sub-classified into the categories given in WHO 2014 classification and percentage out of total and percentage of bilateral cases was calculated.Table 1

Median age of presentation was 41 years with the youngest patient of 4 years presented with torsion of mature cystic teratoma and oldest patient presented with mucinous cystadenoma in 80 year old female. Mean age was 41.75±14.77 years. Table 2

Median age of benign surface epithelial tumors which comprises of maximum numbers of cases (100) in our study was 40 years. Whereas median age of borderline surface epithelial tumors and malignant tumors of ovaries was 46 years. Germ cell tumor presented earlier in life with median age of 29 years. Commonest presenting symptom was abdominal pain (60%) followed by mass in abdomen (38.5%) with few cases incidentally detected during evaluation of other gynecological problems. Torsion of ovarian cyst is one of the commonest reasons for acute abdominal pain seen in 4 of our cases.Table 3

Bilateral presentation was seen in 19 cases comprising of 9 cases of malignant and 4 cases of benign surface epithelial tumors along with 6 cases of metastatic tumors. Percentage of bilaterality is significantly associated with malignant surface epithelial tumors with P value 0.0005.

13 cases presented with omental and peritoneal metastasis comprised of 8 malignant surface epithelial tumors, 2 Krukenberg tumors, one MMMT, one case of YST with immature teratoma and one case of YST. Table 4

4.1. Surface epithelial tumors

One case of HGSC shows presence of serous tubal intraepithelial carcinoma (STIC) which is the precursor lesion for the same. Two patients having omental metastasis had received 6 cycles of chemotherapy before debulking surgery.

Table 1:

Histopathology category and percentage out of total	subtypes in the category	No. of cases	%	b/l cases with Percentage of bilaterality in the same category
Benign surface epithelial tumors 50.5%	Serous cystadenoma (SCA)	46	23	3(7)
	Serous adenofibroma (SA)	3	1.5	
	Mucinous cystadenoma (MCA)	49	25	1(2)
	Benign Brenner tumor	2	1	
Borderline surface epithelial tumors 6%	Borderline serous tumor (BST)	3	1.5	
	Borderline mucinous tumor (BMT)	5	3	
	Borderline serous tumor micropapillary variant (BST MP)	2	1	
Malignant surface epithelial tumors 17%	High grade serous carcinoma (HGSC)	15	8	6(40)
	Low grade serous carcinoma (LGSC)	6	3	2(33)
	Endometrioid carcinoma (EC)	5	2.5	
	Clear cell carcinoma (CCC)	1	0.5	
	Mucinous carcinoma (MC)	5	2.5	1(20)
	Transitional cell carcinoma (TCC)	1	0.5	
Sex cord stromal tumors 9%	Adult granulosa cell tumor (AGCT)	9	4.5	
	Juvenile granulosa cell tumor (JGCT)	2	1	
	Fibroma	2	1	
	Fibrothecoma	4	2	
	Mixed sex cord stromal tumor retiform with heterologous elements	1	0.5	
Mixed epithelial and mesenchymal tumor 0.5%	Carcinosarcoma	1	0.5	
Secondary tumors 5%	Krukenberg tumor	7	3.5	4(57)
	Mets of endometrioid carcinoma	3	1.5	2(67)
Germ cell tumors 12%	Mature cystic teratoma (MCT)	19	9.5	
	Immature teratoma	1	0.5	
	Dysgerminoma	1	0.5	
	Yolk sac tumor (YST)	1	0.5	
	Mixed germ cell tumor (YST+MCT) and (YST+ immature teratoma)	2	1	

Table 2: Age wise distribution.

Age group	No of cases	Percentage %
0-10 years	4	2 %
11-20 years	5	2.5 %
21-30 years	39	20 %
31-40 years	47	24 %
41-50 years	48	24.5 %
51-60 years	32	16.5 %
61-70 years	18	9 %
71-80 years	3	1.5 %

Table 3:

Signs and symptoms	Percentage %
Pain in abdomen	60
Mass in abdomen	38.5
Asymptomatic	12
Torsion	2
Gastrointestinal symptoms	6.5
Abnormal uterine bleeding	1
Infertility	2

Table 4:

Histological diagnosis	No of cases presented in stage III/IV
HGSC	3
LGSC	2
Mucinous carcinoma	1
Carcinosarcoma (MMMT)	1
YST	1
Krukenberg tumor	2
Endometrioid carcinoma	2
YST + immature teratoma	1

Mean age of diagnosis is 43 years in mucinous carcinoma which is one decade earlier than high grade serous carcinoma 54 years and half decade earlier than low grade serous carcinoma 49 years. One patient of mucinous carcinoma presented as bilateral masses.

Foci of endometriosis was seen in two cases of endometrioid carcinoma which is considered as the precursor lesion for primary endometrioid carcinoma of ovary. In our study two patients of endometrioid carcinoma also had history of treatment for infertility owing to polycystic ovary disease (PCOD). Out of this one case was having endometrioid carcinoma with areas resembling sex cord stromal tumor. One was bilateral ovarian metastasis from sertoliform endometrioid endometrial carcinoma with omental metastasis.

We had two cases of borderline serous tumor with micropapillary architecture.

One case of Brenner tumor was incidentally detected in a patient of basaloid squamous cell carcinoma of cervix.

We found one case each of clear cell carcinoma, transitional cell carcinoma and carcinosarcoma (MMMT) during study period.Figures 1, 2 and 3

4.2. Germ cell tumors

Maximum numbers of germ cell tumor were seen in pre-menopausal age group. Most of them were mature cystic teratoma (MCT). One case of MCT also showed foci of struma ovarii. Two cases were mixed germ cell tumor comprised of one YST with MCT and another immature teratoma with small component of YST with omental metastasis of immature neuroectodermal tubules and neural cells (gliomatosis peritonei). One case of dysgerminoma was seen in 22 year old female.

4.3. Sex cord stromal tumors

Median age of adult granulosa cell tumor was 44 years while two cases of juvenile granulosa cell tumors were seen in below 20 year age group. We had one case of mixed sex cord stromal tumor retiform pattern with heterologous elements in 45 year old female. One case of fibroma was incidentally detected in a patient of endometrial carcinoma and one patient of fibrothecoma has atypical endometrial hyperplasia.Figure 4

4.4. Secondary tumors

Out of seven cases of krukenberg tumor 4 were metastasis from gastric carcinoma, one is from rectosigmoid signet ring cell carcinoma and one is from breast infiltrating duct carcinoma as confirmed from the past history and other investigations.

Numbers of cases in each major morphological category were compared between pre and post menopausal age group which is taken as 45 years in Indian women and P value calculated.Table 5

Table 5:

Morphological category	No of cases in premenopausal age	No of cases in post menopausal age	P value
Benign surface epithelial tumor	71	32	0.005
Borderline surface epithelial tumor	8	2	0.318
Malignant surface epithelial tumor	11	22	<0.001
Germ cell tumor	21	3	0.005
Sex cord stromal tumor	10	8	0.570

5. Discussion

Mean age of diagnosis is similar to the study of Nalini Modepalli, SK Mondal.[8,10] surface epithelial tumors are commonest in our study (67.5%) followed by germ cell tumors (12%) and sex cord stromal tumors (9%). Similar observation was seen in other studies.[8,11] Mucinous cystadenoma was the commonest tumor followed by serous cystadenoma and mature cystic teratoma similar to study done by Mankar et al.[12] Borderline mucinous tumor was commonest in borderline category as seen in Neha Gupta et al, Garg et al study.[11,13] Mean age of diagnosis of malignant surface epithelial tumors are in accordance with Singh N, Gilk CB study.[2] Jung et al found significant association of benign and malignant surface epithelial tumor in pre

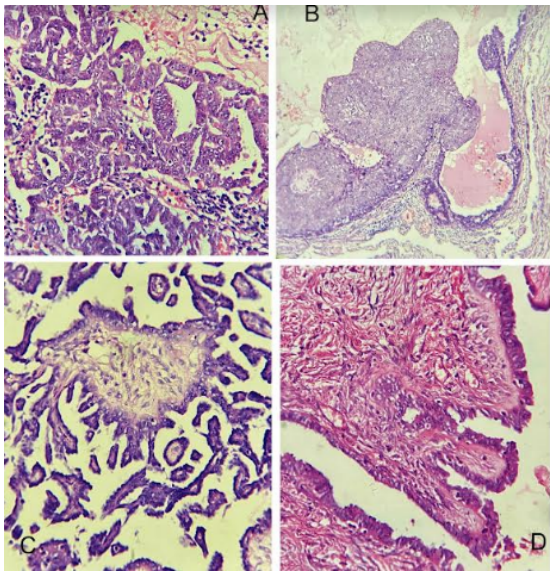

Fig. 1: A: High grade serous carcinoma; **B:** Serous tumor in situ; **C:** Micropapillary serous carcinoma; **D:** Borderline serous tumour

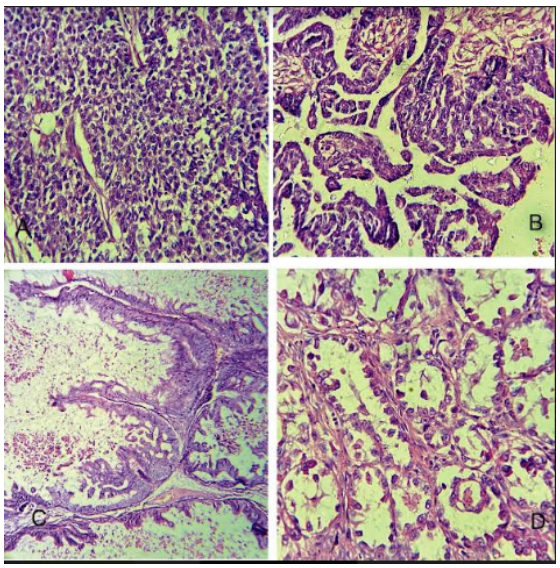

Fig. 2: A: Poorly differentiated endometroid carcinoma ovary; **B:** Low grade serous carcinoma; **C:** mucinous carcinoma; **D:** clear cell carcinoma ovary

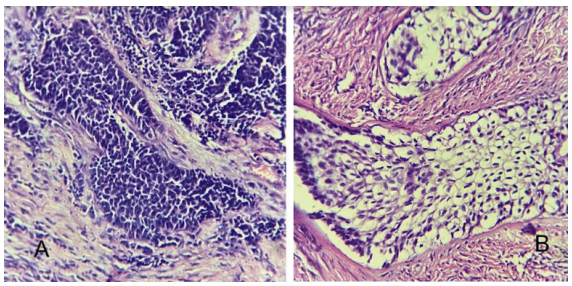

Fig. 3: A: Basaloid carcinoma cervix; **B:** Benign brenner tumor

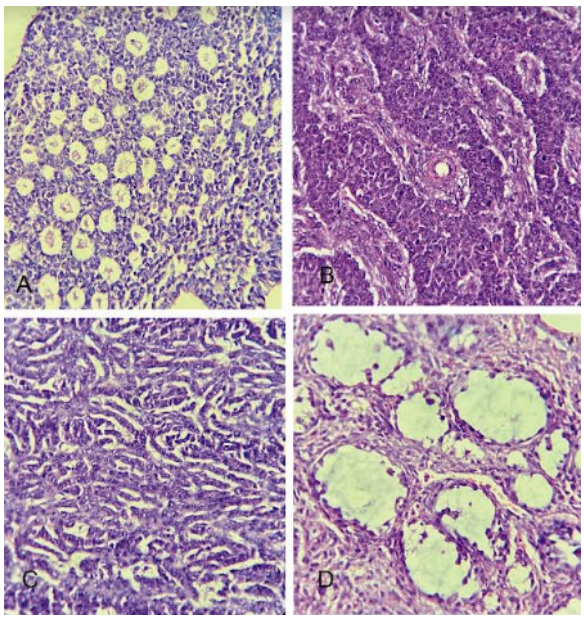

Fig. 4: A: AGCT, Call Exner bodies; **B:** AGCT, pleomorphic granulose cells in sheets; **C:** AGCT, trabecular pattern; **D:** Juvenile granulosa cell tumor.

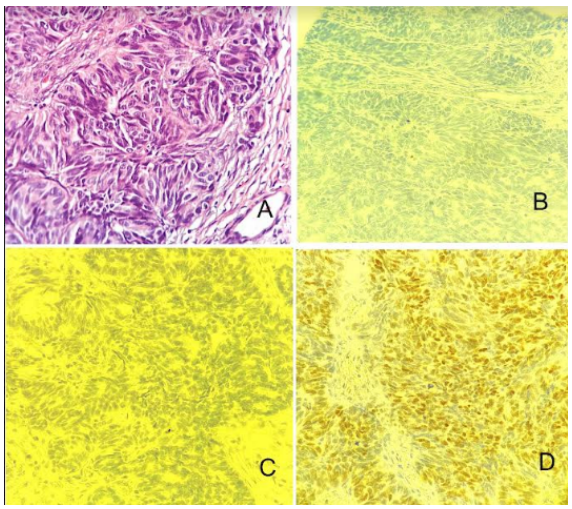

Fig. 5: A: Sertoliform Endometrioid carcinoma, elongated cells forming tubules and sheets; **B:** IHC WT1 negative; **C:** IHC Inhibin negative; **D:** IHC Estrogen receptors positive

and post-menopausal groups respectively in Korean women taking 49 years as age of menopause. Similarly significant association was found between germ cell tumors and sex cord stromal tumors with pre and post-menopausal women respectively.[7] Present study also showed that benign surface epithelial tumors and germ cell tumors are significantly associated with premenopausal age whereas malignant surface epithelial tumors have significant association with post-menopausal age. However sex cord stromal tumors did not show any significant association with both the groups.

Size of the tumor ranged between 5-15 cm in borderline and malignant category in largest diameter. Maximum tumors were predominantly solid except benign surface epithelial tumors which were almost cystic excluding benign Brenner tumor. Maximum size of benign tumor in our study was 25 cm. Pain and lump in abdomen were the commonest presentations as seen in many other studies.[14,15]

2014 WHO classification replaces the three tier system of well, moderate and poorly differentiated serous carcinoma by two separate entities LGSC and HGSC. They present as solid cystic masses with solid areas showing papillary, cribriform and glandular arrangement of cells with nuclear atypia.[16] Number of mitosis were more than 12/10 high power field in HGSC with increase nuclear pleomorphism. LGSC show less than 12 mitosis/10 high power field.[9]

Coexisting Brenner tumor with endometrial carcinoma is well established in literature, however association with cervical carcinomas is mentioned with villoglandular adenocarcinoma.[17–20] Extensive calcification could suggest a long standing existence in the patient in our case.

Two cases of adult GCT and one case of mucinous cystadenoma showed foci of mature cystic teratoma.[9,21] Roth LM suggested simultaneous transformation of germ cells and sex cord derivatives in the histogenesis of mixed germ cell and sex cord stromal tumors of ovary.[22] Prerna Guleria and colleagues studied various morphological parameters in a series of AGCT and compared with proliferation marker on immunohistochemistry. Our study showed presence of more than 10 mitosis/10 high power field along with necrosis and anisonucleosis in one out of nine cases. Call Exner bodies were seen in 4 cases, nuclear grooves in 7 cases. Predominant architectural pattern was diffuse, trabeculae, nests and microfollicular.

Bilateral ovarian metastasis of sertoliform endometrioid carcinoma with omental metastasis showed small hollow or solid tubules surrounded by cellular and fibrous stroma.[23–25]

Immunohistochemistry (Inhibin negative, Estrogen receptor positive and WT1 negative) confirmed the endometrial origin of the tumor and ruled out the sertoli cell tumor in these two cases.Figure 5

6. Conclusion

Present study describes the histopathological spectrum of ovarian neoplasms with respect to age and other clinical parameters at tertiary care hospital in central India. Using WHO classification these tumors can be precisely subcategorized into different morphological subtypes. However overlapping features may need immunohistochemistry to pinpoint the correct diagnosis. Present study reports a rare variant sertoliform endometrioid endometrial carcinoma with bilateral ovarian and omental metastasis in a 30 year old female suffering from polycystic ovarian syndrome. Though synchronous tumors are not rare in female genital tract organs, we report two incidentally detected ovarian masses one is fibroma in a patient of endometrial carcinoma and another one benign Brenner tumor in a patient of basaloid squamous cell carcinoma of cervix.

7. Limitations of Study

Factors that may contribute to the occurrences of various histological subtypes such as parity, hormonal therapy, mutation status, environmental factors are not analyzed. As menopause status of each case was not known age of menopause is taken as 45 years which is the mean age seen in Indian women in many studies.

8. Conflict of Interest

The authors declare no relevant conflicts of interest.

9. Source of Funding

None.

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