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Original Research Article

Study of immuno-histochemical markers ER, PR and Her2/neu in ovarian neoplasms

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ABSTRACT

Background: Among genital malignancies, ovarian cancer has the most increased mortality rate. ER, PR and HER2/neu expression levels depend on tumour histologic grade, stage of disease and age group. Aim of the study was to study the clinic-pathological parameters in ovarian tumours with reference to age, histologic type and grade and their correlation with ER, PR and HER2/neu status.
Methods: The prospective study of 2 ½ years was conducted on 100 resected ovarian tumour specimens from June 2017 to December 2019 received in the department of pathology, JLN medical college, Ajmer. Sections were examined for presence of ovarian tumour, histological type, grade and for ER, PR and HER2/neu status, immunohistochemistry was done.
Results: Out of 100 cases, 72 cases were benign, 03 cases were border-line and 25 cases were malignant. Serous tumors were most common among all epithelial tumors (61%). Malignant cases showed maximum positivity with ER, PR and HER2 as 61.76%, 68% and 100% respectively. ER, PR and HER2/neu positivity in serous epithelial tumors was 76.47%,84% and 90% and in mucinous tumors was 20.59%, 12% and 10% respectively. Majority of positive ER, PR and HER2/neu receptors was observed in age groups of >40 years as 64.71%, 64% and 85% respectively. ER, PR and HER2/neu positivity seen in higher grade and stage tumors as 76.19%, 76.47% and 70% in grade 3 and stage 3 tumors respectively.
Conclusions: The higher expression of ER, PR and HER-2/Neu is associated with progression of invasive cancer, higher grade and stage of ovarian tumors, higher age group, and multiparty.

Keywords: Ovarian cancer, Immunohistochemistry, Genital malignancies

INTRODUCTION

Ovarian cancer is one of the most frequent cancers in female patients[1]. Among genital malignancies, ovarian cancer has the most increased mortality rate. The low survival is due to the lack of symptoms in early stages. Therefore, the diagnosis is delayed and the prognosis is poor. About 80% are benign, these occur mostly in young women between the ages of 20 and 45 years. Borderline tumours occur at slightly older ages. Malignant tumours are more common in older women between the ages of 45 and 65 years. The most common symptoms include: Bloating, pelvic or abdominal pain, urinary symptoms such as urgency or frequency, and heaviness in abdomen.[2]

The initial assessment of patients with suspected ovarian cancer, following the initial history-taking, physical

examination, laboratory results, pelvic ultrasound, preferably using colour Doppler are done. It has been shown that ER and PR expression levels depend on tumour histologic grade and the stage of the disease, and are variable between tumours of the same grade.[3]

The ER and PR expression levels correlate with ovarian cancer patients' survival. The HER-2/Neu gene is amplified and/or over expressed in 25%-30% of human ovarian cancers and is associated with progression of invasive cancer, poor prognosis and resistance to chemotherapy. Immunohistochemistry is helpful in vast number of cases to resolve the diagnostic dilemma.[4]

Aims and objectives

The aim and objectives of the study was to determine the clinic-pathological parameters in ovarian tumours with special reference to age, histologic type and grade and evaluate the role of immune-histochemical profile of ER, PR and HER2/Neu in ovarian neoplasms and also correlate the results of immunohistochemistry with clinic-pathological parameters.

METHODS

The prospective study of 2 and ½ years was conducted on 100 surgically resected ovarian tumours samples from June 2017 to December 2019 received in the department of pathology, Jawahar Lal Nehru medical college and associated groups of hospital, Ajmer. Non-neoplastic lesions and metastatic lesions of ovary were excluded.

On receiving the specimens in 10% neutral buffered formalin, a systematic gross examination was performed. Gross features like size, shape, colour, external appearance on cut section and contents were noted.
The tumors were cut at various levels and adequate tissue slice (<5 mm) submitted which were routinely processed 3-to-5-micron sections were cut from paraffin embedded blocks. These sections were routinely stained with Harri's H and E stain and was examined for presence of ovarian tumour, histological type, and grade.[11]

For immuno-histochemistry, the primary antibody used was estrogen receptor, progesterone receptor and Her2/Neu receptor along-with positive and negative controls. The positive control for ER, PR and HER2/neu, fibro-adenoma tissue section was taken.

The IHC staining was studied in correlation to clinic-pathologic factors of ovarian tumours which include age, laterality, parity, histological type, tumour grade, tumour stage.

RESULTS

A total of 100 ovarian tumors were studied, out of which 72% are benign, 3% borderline and 25 % malignant.

Out of 100 studied ovarian tumors, 60% are epithelial tumors, 33% are germ cell tumors, and 7% are sex cord tumors. Out of epithelial tumors, 55% tumors are benign, 5% are border-line and 40% are malignant. Out of germ cell tumors, 96% are benign and 4% are malignant. Out of sex cord tumors, 100% are benign tumors.

Serous tumors are most common among all epithelial tumors (61%). Out of total 37 serous tumors, 49% are benign. Serous adenocarcinomas are the most common malignant tumor accounting for 32% of all epithelial tumors and 51% of serous tumors. Out of total 21 mucinous tumors, 72% are benign, 14% are borderline and 14% are malignant. One case of endometrioid tumor and poorly differentiated tumor is present.

Majority (96%) of germ cell tumors are mature cystic teratoma, 4% are dysgerminoma but yolk sac tumors and malignant mixed germ cell tumors are not found.

Among sex cord stromal tumors, most common tumor is fibroma (72%) followed by granulosa cell tumor (14%) and stromal Leydig cell tumor (14%). None of the case of granulosa theca cell tumor is found.

Out of total positive estrogen receptors (34), 61.76% was positive in malignant cases (Figure 1) followed by 32.35% in benign cases and rest 5.88% in borderline cases. While out of total positive progestrone receptors (25), 68% was positive in malignant cases (Figure 2) followed by 32% in benign cases. Out of total positive HER2 receptors (20), 100% was positive in malignant cases whereas benign and borderline cases are negative for HER2/neu.

ER positivity in serous epithelial tumors is 76.47%, in mucinous tumors is 20.59% and in endometrioid tumor is 2.94%. PR positivity seen in serous tumors is 84%, in mucinous tumors is 12% and in endometrioid tumor is 4%. HER2/NEU positivity is seen in 90% of serous tumors and 10% of mucinous tumors. Rest brenner, sex cord stromal tumors and mature cystic teratomas do not show any ER, PR and Her2/neu positivity. No significant difference was observed of Status of ER, PR and Her2/neu and classification of ovarian tumors (Table 1).

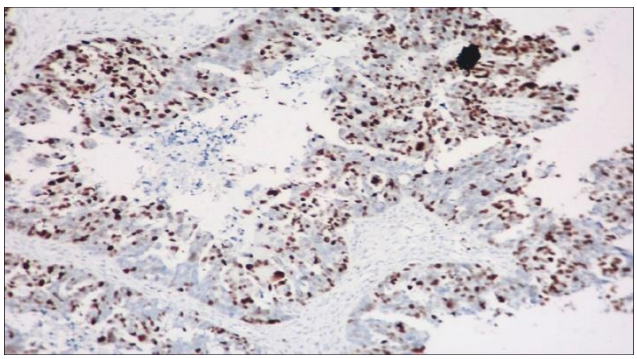

Figure 1: Malignant papillary serous tumour showing ER positivity with IHC score 6 (400X).

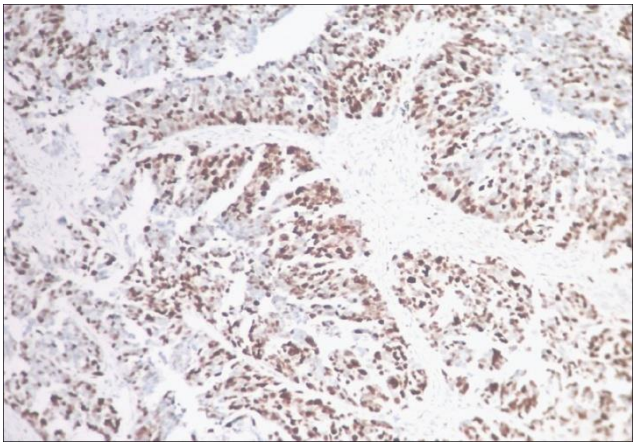

Figure 2: Malignant papillary serous tumour showing PR positivity with IHC score 6 (400X).

Epithelial tumors and sex cord tumors were significantly more in >40 years of age groups (70% and 57.14% respectively) as compared to germ cell tumors which was significantly more (87.88%) in <40 years of age groups.

Majority of positive ER, PR and HER2/neu receptors was observed in age groups of >40 years as 64.71%, 64% and 85% respectively (Table 2).

Although the unilateral tumors were more in epithelial tumors (60%) and germ cell tumors (72.73%) as compared to sex cord tumors (42.86%).

Epithelial tumors (81.67%) and sex cord tumor (71.43%) was statistically more significant in multipara as compared to germ cell tumors (24.24%), whereas germ cell tumors are common in nullipara women.

Bilateral positivity of the receptors was observed in majority of cases. ER positive were 64.71% bilateral, PR receptors were 64% while HER2/NEU receptors showing bilateral positivity in 85%.

Positivity of the receptors was observed in majority of multipara cases. ER positive were 85.29% of multipara, PR positive were 88% of multipara while HER2/NEU receptors of multipara were 100%.

Out of total malignant surface epithelial tumors, serous tumors were 36.84% as grade 2, while 63.16 % as grade 3. Malignant mucinous and endometrioid tumor were 100% as grade 3.

ER, PR and HER2/neu positivity seen in higher grade tumors (Figure 3-5) as 76.19%, 76.47% and 70% in grade 3 tumors respectively (Table 3).

Out of total malignant surface epithelial tumors, serous tumors were 36.84% as stage 2, while 63.16% as stage 3. Malignant mucinous, endometrioid tumor 100% stage 3.

ER, PR and HER2/neu positivity seen in higher stage tumors 76.19, 76.47 and 70% stage 3 tumors respectively.

Table 1: Status of ER, PR and Her2/neu in ovarian tumor.

Variables	ER		PR		HER2/ NEU		P value LS
	N	%	N	%	N	%	
Serous (37)	26	76.47	21	84	18	90	
Mucinous (21)	7	20.59	3	12	2	10	
Endometrioid (1)	1	2.94	1	4	0	0.00	0.697NS
Brenner (0)	0	0.00	0	0.00	0	0.00	
SCST (7)	0	0.00	0	0.00	0	0.00	
MCT (32)	0	0.00	0	0.00	0	0.00	
Total	34	100	25	100	20	100	

Chi-square=2.209 with 4 degrees of freedom; p=0.697.

Table 2: Status of ER, PR and Her2/neu according to age.

Age group (Years)	ER		PR		HER2/NEU		P value LS
	N	%	N	%	N	%	
<40	12	35.29	9	36	3	15	0.233NS
>40	22	64.71	16	64	17	85	
Total	34	100	25	100	20	100	

Chi-square=2.998 with 2 degrees of freedom; p=0.223.

Table 3: Status of ER, PR and Her2/neu according to grade of tumor.

Grade of tumor	ER		PR		HER2/NEU		P Value LS
	N	%	N	%	N	%	
Grade 2	5	23.81	4	23.53	6	30	
Grade 3	16	76.19	13	76.47	14	70	0.872NS
Total	21	100	17	100	20	100	

Chi-square=0.273 with 2 degrees of freedom; p=0.872.

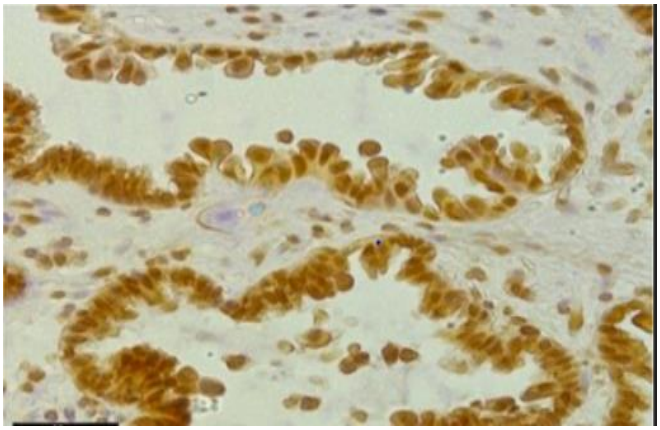

Figure 3: High grade serous tumour showing ER positivity with IHC score 8 (400X).

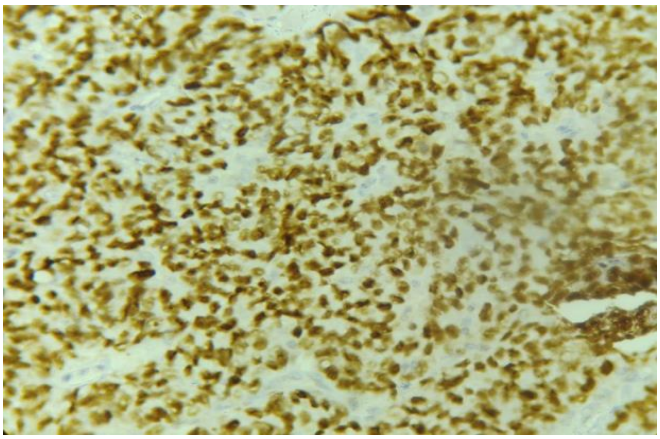

Figure 4: Malignant serous tumour showing PR positivity with IHC score 8 (400X).

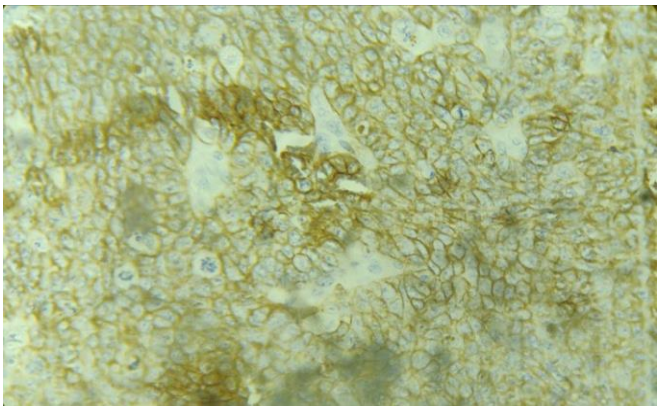

Figure 5: Malignant serous tumour showing strong Her2 positivity with IHC score 3 (200X).

DISCUSSION

In our study, 72 cases are benign, 3 cases are borderline and 25 cases are malignant. Among the various neoplasms studied, 60% are of surface epithelial neoplasms, followed by germ cell tumors accounting for 33% of all tumors, sex cord stromal tumors accounting 7% of all tumors.

Our results are comparable with results of study done by Atla et al on 42 ovarian tumors, where surface epithelial tumors constituted around 59.5% of all tumors.[5] Similarly, Khan et al studied 80 operated cases of ovarian tumors and found that benign lesions were more common (75%) the malignant lesions (25%).[6]

In our study serous cyst adenocarcinoma was the most common malignant tumor among all epithelial tumors accounting for 37.5% of all epithelial tumors and 54.5% of all serous tumors. Atla et al and Krigman et al gave similar results with incidence of 59% and 36% among all epithelial tumors respectively.[5,7] Serous cystadenoma was the commonest benign tumor (45%). Overall surface epithelial carcinomas were responsible for 52 % and 70% of all malignant lesions among which serous cyst adenocarcinoma was the most common (45%).[5]

In our study, out of total positive estrogen receptors (34), 61.76% was positive in malignant cases followed by 32.35% in benign cases and rest 5.88% in borderline cases. While out of total positive progestrone receptors (25), 68% was positive in malignant cases followed by 32% in benign cases. Out of total positive HER2 receptors (20), 100% was positive in malign ant cases. According to Naik et al the expression of ER was more in malignant tumors (81.25%) than borderline (75%) and benign (24.39%).[8] This is parallel to study done by Sylvia et al.[9]

In our study, ER positivity in serous epithelial tumors is 76.47%, in mucinous tumors is 20.59% and in endometrioid tumor is 2.94%. PR positivity seen in serous tumors is 84%, in mucinous tumors is 12% and in endometrioid tumor is 4%. HER2/NEU positivity is seen in 90% of serous tumors and 10% of mucinous tumors. Rest brenner, sex cord stromal tumors and mature cystic teratomas do not show any ER, PR and Her2/neu positivity.

Sylvia et al (63.6%) reported higher expression for PR while Shilpa et al (27.5%) reported lower PR expression in their study, but still both the studies had higher PR positivity than our study.[10,11] Her2/neu was weakly positive/equivocal in only 3 cases accounting for 7.14% which includes one case each of serous cystadenocarcinoma, mucinous cystadenocarcinoma and clear cell carcinoma. Thus, Her2 expression was seen only in surface epithelial carcinomas.

In our study, majority of positive receptors was observed in age groups of >40 years as ER 64.71%, PR 64% and her2/neu 85% respectively. According to Atla et al ER and PR showed higher expression in age group above 40 years, her2/neu in two of the three cases were above 40 years of age.[5]

Bilateral positively of the receptors was observed in majority of cases. ER positive were 64.71% bilateral, PR receptors were 64% while HER2/NEU receptors positivity. Positivity of the receptors was observed in multipara cases. ER positive were 85.29% of multipara, PR receptors were 88% of multipara while HER2/NEU receptors of multipara were 100%. Our study is comparable with Atla et al and Sylvia et al.[5,10]

In our study, we observed that ER, PR and HER2/neu positivity seen in higher grade tumors as 76.19%, 76.47% and 70% in grade 3 respectively. Majority of ER, PR and HER2/neu positivity seen in higher stage tumors as 76.19%, 76.47% and 70% in stage 3 respectively. Our study is comparable with Atla et al and Sylvia et al showing similar results.[5,10] As per Atla et al majority of ovarian carcinomas were of grade 2 and stage 3.[5]

Hellstrom et al Her-2-neu was negative in all grade 1 tumors and all benign cases, higher in grade 2 and 3 tumors in concordance to previous studies. Most of these tumors had higher association with ascites suggesting an aggressive tumor type and advanced stages which is similar to the study by Hellstrom et al.[12] Malignant tumors, serous group, and grade 3 tumors had significant higher proliferation index similar to previous results.

Limitation

Non-neoplastic lesions and metastatic lesions of ovary were excluded, so status of ER, PR and HER2/neu in these lesios can't be determined.

CONCLUSION

Prognosis and management of ovarian cancer are influenced by classic variables such as histologic type and grade, parity, status of hormone receptors- ER, PR and more recently, HER2/neu status. ER, PR and HER2/neu status correlates well with histopathological grading and other clinic-pathological parameters. Hence, immunohistochemical assessment of ER, PR and HER2/neu status along with histopathological grading and staging will guide the clinicians to make correct choice of treatment protocols.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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