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TO STUDY THE EXPRESSION OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR AND HER-2-NEU RECEPTOR IN EPITHELIAL OVARIAN TUMORS

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ABSTRACT

Background: Epithelial ovarian tumors represent the most common category of ovarian neoplasms and exhibit diverse biological behavior, ranging from benign to malignant lesions. Hormonal receptors such as estrogen receptor (ER) and progesterone receptor (PR), along with growth factor receptor HER-2/neu, have been implicated in tumorigenesis, progression, and prognosis of ovarian cancer. Immunohistochemical (IHC) evaluation of these markers provides insight into tumor biology and may guide therapeutic decision-making.

Objective: This study aimed to assess the expression of ER, PR, and HER-2/neu in epithelial ovarian tumors and to correlate their distribution across benign, borderline, and malignant categories.

Materials and Methods: A total of 50 epithelial ovarian tumors were studied, including 8 benign, 9 borderline, and 33 malignant cases. Immunohistochemistry was performed to evaluate ER, PR, and HER-2/neu expression.

Results: Among the 50 cases, benign, borderline, and malignant tumors comprised 16%, 18%, and 66% respectively. Most benign cases occurred in the 31–40 years age group, borderline tumors in 41–50 years, and malignant tumors also peaked in 41–50 years. ER expression was positive in 5 benign, all borderline, and 30 malignant cases. PR positivity was seen in 3 benign, 4 borderline, and 28 malignant tumors. HER-2/neu overexpression was restricted to malignant tumors (5 cases), with no positivity in benign or borderline groups.

Conclusion: ER and PR expression was observed across all categories but was more frequent in malignant tumors, whereas HER-2/neu positivity was exclusive to malignancies. These findings suggest that ER and PR may have prognostic significance, while HER-2/neu expression could serve as an indicator of malignant potential.

Keywords: Epithelial ovarian tumors, Estrogen receptor, Progesterone receptor, HER-2/neu, Immunohistochemistry

INTRODUCTION

Ovarian carcinoma is the sixth most frequent malignancy among women and the fourth leading cause of cancer-related mortality in females[1]. These tumors comprise a wide spectrum, each with distinct histological, biological, and genetic profiles that determine their behavior and clinical outcomes. Ovarian neoplasms predominantly occur in peri- and postmenopausal women, with

advancing age being the most important risk factor. The rising incidence of ovarian cancer around menopause has been linked to depletion of oocytes, reduced circulating estrogen, and increased secretion of gonadotropic hormones, particularly luteinizing hormone (LH)[2]. Other recognized risk factors include nulliparity, delayed childbearing, early onset of menarche, and late menopause[3]. Benign ovarian cysts can develop at any age, but they are most commonly encountered during reproductive years and account for nearly 90% of ovarian tumors[4]. These lesions generally present in younger women aged 20–45 years, whereas borderline tumors are more often seen in slightly older individuals. Malignant ovarian tumors, in contrast, are typically diagnosed in women between 45 and 65 years of age[5].

Estrogen and progesterone are crucial ovarian hormones that exert their effects via specific receptors[6]. Both hormones, along with their receptors, have been implicated in the pathogenesis of ovarian cancer[7]. The HER-2/neu oncogene has also been identified as a key factor in several malignancies, with overexpression being associated with poor prognosis and reduced survival[8]. With the advent of immunohistochemistry (IHC), it is now possible to evaluate ER, PR, and HER-2/neu expression in routinely processed tissue specimens. Previous studies have demonstrated variable patterns: ER expression tends to be lower in benign tumors, whereas PR is more often expressed in malignant lesions. Higher ER and PR positivity has been observed in serous carcinomas, postmenopausal cases, advanced stage, grade 3 tumors, and those associated with ascites. HER-2/neu, on the other hand, is generally negative in benign tumors but shows positivity in malignant, serous, and high-grade tumors with ascites. Additionally, CA-125 levels are significantly elevated in malignant, serous, advanced-stage tumors, particularly in those with ER and HER-2/neu positivity[9]. These findings support the role of estrogen in tumor promotion, mediated through ER and PR regulation, while HER-2/neu overexpression restricted to malignant tumors suggests its carcinogenic role and utility in distinguishing borderline from malignant lesions. Collectively, these markers may provide valuable information for tumor differentiation and prognostication[10].

Although ER, PR, and HER-2/neu have been extensively studied in ovarian tumors worldwide, data from our population remain scarce. Since tumor biology and patient characteristics can vary across regions, local evaluation is essential. Assessing these markers may aid in distinguishing benign, borderline, and malignant tumors, provide prognostic information, and potentially guide targeted therapeutic strategies.

MATERIAL AND METHODS

The present study titled “To Study the Expression of Estrogen Receptor, Progesterone Receptor and Her-2-Neu Receptor in Epithelial Ovarian Tumors” was carried out in the Department of Pathology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Kashmir, over a period of five years (2010–2015). The study included both retrospective cases (three and a half years) and prospective cases (one and a half years). A total of 50 cases of epithelial ovarian tumors were analyzed, comprising 33 malignant, 9 borderline, and 8 benign tumors. The benign cases were selected randomly for inclusion. Clinical data such as age, parity, menopausal status, and available preoperative CA-125 levels were retrieved from medical records.

All surgical specimens received were fixed in 10% neutral buffered formalin. Gross examination included assessment of tumor size, external and cut surface characteristics, and sampling from representative areas at 1 cm intervals. Tissue samples were placed in stainless steel cassettes, labeled, and subjected to routine histopathological processing. The tissue blocks were dehydrated in graded alcohols (50%, 70%, 90%, and absolute ethanol), cleared in xylene, and embedded in paraffin wax. Sections of 3–5 μm thickness were cut using a rotary microtome and mounted on glass slides coated with Mayer’s albumin. Routine Hematoxylin and Eosin (H&E) staining was performed for histopathological evaluation and tumor classification according to WHO criteria.

Immunohistochemistry (IHC): Immunohistochemistry (IHC) was performed on paraffin-embedded tissue sections to assess the expression of estrogen receptor (ER), progesterone receptor

(PR), and HER-2/neu. Sections were deparaffinized, rehydrated through descending grades of alcohol, and subjected to antigen retrieval. Endogenous peroxidase activity was blocked, followed by incubation with primary antibodies against ER, PR, and HER-2/neu. Detection was carried out using a standard streptavidin–biotin peroxidase method with diaminobenzidine (DAB) as chromogen, and counterstaining with hematoxylin.

Evaluation of Staining: Estrogen receptor (ER) and progesterone receptor (PR) positivity was defined by the presence of distinct nuclear staining in tumor cells, while HER-2/neu expression was assessed by membranous staining intensity and percentage of positive cells, using established scoring criteria. Appropriate positive and negative controls were included for each batch of staining.

Data Analysis: Tumors were categorized into benign, borderline, and malignant groups, and correlations were made between receptor expression and clinicopathological parameters such as age, histological type, grade, and stage. Statistical analysis was performed using chi-square test and p-values <0.05 were considered significant.

RESULTS

A total of 50 cases of epithelial ovarian tumors were analyzed during the study period. Among these, 8 cases (16%) were benign, 9 cases (18%) were borderline, and 33 cases (66%) were malignant. Benign tumors were most frequently encountered in women aged 31–40 years, borderline tumors peaked in the 41–50 years age group, while malignant tumors showed their highest incidence in the same 41–50 years range. The youngest patient in this series was a 20-year-old female diagnosed with serous cystadenocarcinoma, whereas the oldest was a 75-year-old woman with the same diagnosis. Overall, the incidence of epithelial ovarian tumors increased with advancing age.

Table 1: Type of Tumour

Tumour Type	No. of Cases (n=50)	Percentage (%)
Benign	8	16
Borderline	9	18
Malignant	33	66
Total	50	100

Of the 50 epithelial ovarian tumors studied, malignant tumors formed the majority, constituting two-thirds of the cases. Borderline tumors represented 18% of cases, while benign tumors were the least common, comprising only 16%.

Table 2: Age-wise Distribution of Benign, Borderline, and Malignant Ovarian Tumors

Age in Years	Malignant		Borderline		Benign		Total
	No.	%	No.	%	No.	%	
11 to 20	1	2	0	0	0	0	**1**
21-30	0	0	1	2	1	2	**2**
31-40	4	8	3	6	5	10	**12**
41-50	15	30	4	8	2	4	**21**
51-60	9	18	1	2	0	0	**10**
61-70	2	4	0	0	0	0	**2**
71-80	2	4	0	0	0	0	**2**
Total	**33**	**66**	**9**	**18**	**8**	**16**	**50**

The age distribution revealed that benign tumors were most frequent in women aged 31–40 years, accounting for 62.5% of all benign cases. Borderline tumors occurred predominantly between 41–50 years (44.44%), while malignant tumors peaked in the same age group, representing 45.45% of all malignant cases.

Table 3: Distribution of Benign, Borderline and Malignant tumors into various histological types			
Tumor Type		**No. of Cases**	**Percentage (%)**
Benign (n=8)	Serous	3	6
	Mucinous	1	2
	Others	4	8
Borderline (n=9)	Mucinous	2	4
	Serous	7	14
Malignant (n=33)	Clear cell Carcinoma	1	2
	Mucinous Cyst Adenocarcinoma	9	18
	Serous cyst Adenocarcinoma	23	46

Histological subtyping demonstrated that serous tumors were the most common across all categories. Among benign tumors, serous cystadenomas predominated. Borderline tumors were also chiefly serous in nature (77.7%). In the malignant group, serous cystadenocarcinoma was the most frequent subtype (69.7%), followed by mucinous carcinoma (27.3%) and a single case of clear cell carcinoma.

Table 4: Diagnosis									
		Benign			**Borderline**		**Malignant**		
		Mucinous	**Others**	**Serous**	**Mucinous**	**Serous**	**Mucinous**	**Serous**	**Clear Cell**
ER	N	0	2	1	0	0	0	3	0
	P	1	2	2	2	7	8	21	1
PR	N	1	3	1	0	4	2	3	0
	P	0	1	2	2	3	6	21	1
HER-2-neu	N	1	4	3	2	7	7	20	1
	P	0	0	0	0	0	1	4	0

The immunohistochemical correlation of ER, PR, and HER-2/neu expression across benign, borderline, and malignant epithelial ovarian tumors revealed significant patterns.

Estrogen Receptor (ER): ER positivity was observed across all categories, though with marked differences. Among benign tumors, 5 of 8 cases showed ER expression, mostly in serous and mucinous variants, whereas 3 were negative. All borderline tumors (100%) demonstrated ER positivity, indicating strong receptor expression at this intermediate stage of neoplastic transformation. In the malignant group, 30 of 33 cases (90.9%) were ER positive, including serous, mucinous, and the single clear cell carcinoma. These results suggest a progressive increase in ER positivity from benign to borderline to malignant tumors, implying a role for estrogen in tumor progression and proliferation.

Progesterone Receptor (PR): PR expression was more variable. In benign tumors, only 3 of 8 cases (37.5%) were positive, reflecting relatively low receptor activity at this stage. Among borderline tumors, 5 of 9 cases (55.5%) showed PR positivity, including both serous and mucinous types. In malignant tumors, however, PR positivity was much higher, with 28 of 33 cases (84.8%) demonstrating expression. This suggests that PR expression is strongly associated with malignant transformation, and in contrast to ER, it shows a sharper rise in malignant cases.

HER-2/neu: Unlike ER and PR, HER-2/neu positivity was restricted exclusively to malignant tumors. All benign and borderline tumors were negative, whereas 5 of 33 malignant tumors (15.2%) were positive for HER-2/neu. Most of these were serous carcinomas, with a smaller proportion in mucinous carcinoma. The absence of HER-2/neu expression in benign and borderline tumors highlights its potential role as a marker of malignancy and tumor aggressiveness.

DISCUSSION

In this study, malignant epithelial tumours comprised two-thirds of all cases, with serous carcinoma forming the major share and mucinous next, while clear cell was rare. This malignant-predominant profile and serous>mucinous rank order are consistent with multiple classic series[11,12,13,14,15]. In this study, benign tumours peaked at 31–40 years, whereas borderline and malignant tumours clustered at 41–50 years. A similar age pattern was documented by Rhandhawa et al. (1980), who reported the same peaks for benign (31–40) and for borderline/malignant (41–50) tumours[12]. The shift of tumour burden toward peri- and post-menopausal ages aligns with the broader epidemiologic context that ovarian carcinoma is a common and lethal female cancer with risk rising around menopause[1,2].

In this study, benign lesions were chiefly serous cystadenomas with fewer mucinous lesions and several functional cysts, a distribution also reported by Tyagi (1978), Rajagopalan (1982), Prabhakar (1989), and Quintyne (2008)[9,13,14,16]. Borderline tumours were predominantly serous (7/9), matching patterns in Tyagi, Rajagopalan, Prabhakar, Misra, and Quintyne[9,13-16]. Borderline tumours were predominantly serous (7/9), matching patterns in Tyagi, Rajagopalan, Prabhakar, Misra, and Quintyne[9,13-16].

In this study, ER was positive in most benign, all borderline, and most malignant tumours, and PR rose sharply in malignancies; HER-2/neu positivity was confined to malignant tumours. The higher ER/PR expression in serous relative to mucinous tumours concurs with Larry C. Ford et al. (1982) and Agarwal et al. (1986), with similar confirmation by Quintyne (2008) and Sylvia (2012)[10,16-18]. The restriction of HER-2/neu positivity to malignant predominantly serous tumours aligns with Sylvia (2012)[10]. When stratified by diagnostic category, the predominance of ER/PR (and any HER-2/neu) expression in carcinomas over benign/borderline agrees with Bergqvist (1982), Agarwal (1986), Hogdall/MALOVA (2007), and Sujitra Tanvanich (2008)[18-21].

CONCLUSION

In this study, immunohistochemical profiling demonstrated that estrogen receptor and progesterone receptor are expressed across benign, borderline, and malignant epithelial ovarian tumours, with the highest frequencies in malignant lesions, while HER-2/neu expression was confined to a small subset of carcinomas. These patterns support the incorporation of ER/PR assessment into routine diagnostic work-up to aid differentiation and prognostication, and they suggest a potential role for endocrine-based strategies in selected cases. HER-2/neu positivity, although specific for malignancy in this cohort, was infrequent, indicating that HER-2–directed therapies would apply only to a limited subgroup. Overall, integrating this receptor panel with histomorphology may improve risk stratification and inform individualized management.

LIMITATIONS

This analysis was single-centre with a modest sample size and a malignant-predominant case mix, including a small, randomly selected benign subset, which may introduce selection bias and limit generalizability. The design combined retrospective and prospective cases, and pre-analytical variables (fixation time, block age) could have influenced antigen preservation. HER-2/neu interpretation treated 1+ as negative and lacked reflex confirmatory testing (e.g., FISH/ISH), which may underestimate equivocal amplification. Standardized scoring for ER/PR beyond intensity categories and inter-observer reproducibility metrics were not captured. Finally, the study did not include survival or treatment-response outcomes, precluding definitive prognostic or predictive conclusions and underscoring the need for larger, prospective cohorts with outcome correlation.

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