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Original Article

Expression of Immunohistochemical Markers Estrogen Receptor Alpha, Progesterone Receptor A, Her2-neu, p53, and Ki-67 in Epithelial Ovarian Tumors and Their Correlation with Clinicopathologic Variables

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Abstract

Background: This study aims to assess the expression of estrogen receptor alpha (ERα), progesterone receptor A (PRA), Her-2-neu, p53, and Ki-67 in epithelial ovarian tumors and evaluate their correlation with various clinicopathologic variables.

Materials and Methods: A total of 50 cases of epithelial ovarian tumors received from the department of obstetrics and gynaecology and surgical oncology were included in this study. Immunohistochemistry (IHC) was performed on sections taken from paraffin-embedded tissue blocks. Chi-square test and ANOVA were used for statistical analysis.

Results: Among 50 cases of ovarian epithelial tumors, 26 (52%) malignant, 18 (36%) benign, and 6 (12%) borderline. The median age of patients was higher (53 years) in malignant tumors. ERα had lower expression in benign (27.7%) and PRA had higher expression in malignant (69%) while Her-2-neu and p53 were negative in benign tumors. ERα and PRA had higher expression in serous (57.1% and 53.6%), postmenopausal (83.3% and 70%), advanced stage (55.6% and 53.3%), Grade 3 (44.4% and 40%), and tumors with ascites (77.8% and 53.3%). Her-2-neu and p53 were negative in benign and higher in malignant (23% and 58%), serous (66.7% and 67%), Grade 3 (57% and 35%), and tumors with ascites (71% and 88%). Ki-67 had a significant higher expression in malignant (52 ± 28) and Grade 3 tumors (72 ± 20) as compared to benign tumors (4 ± 2).

Conclusion: The difference in expression of these markers among benign, borderline, and malignant tumors reveals their role in differentiation and prognostication of ovarian tumors. Ovarian tumors are extremely heterogeneous as proved by the lack of coexpression of these markers. Tumors with adverse prognostic factors express ERα and PRA; this supports the mitogenic role of estrogen and estrogenic regulation of PR. Her-2-neu and p53 are expressed only in malignant tumors supporting their role in the differentiation of borderline and malignant tumors. Similarly, differential expression of Ki-67 in tumors with adverse prognostic factors would help in prognostication and differentiation.

Keywords: Carcinogenic role, Her-2-neu, Ki-67, p53, Prognostic factors, Steroid receptors

INTRODUCTION

Ovarian carcinomas account for the greatest number of deaths from malignancies of the female genital tract and are the fifth leading cause of cancer fatalities in women. Heterogeneity of ovarian tumors makes it difficult to understand their pathogenesis, response to therapy, and prognosis.[1]

The study of various molecular markers, mutations, and oncogenes gives insight into their pathogenesis and contributes to developing targeted treatment modalities. The main aim is to accurately classify ovarian tumors as per their type, grade, and stage to have better treatment protocols and long-term prognosis.[2]

The aims of this study were to evaluate the expression of five molecular pathways, namely estrogen receptor alpha

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(ERα), progesterone receptor A (PRA), Her-2-neu, p53, and Ki-67 by immunohistochemistry (IHC) and correlate them with clinicopathologic prognostic factors of ovarian tumors, namely age, histological type, tumor grade, stage, and the presence of ascites.

MATERIALS AND METHODS

The study was performed on 50 cases of epithelial ovarian tumors received from the department of obstetrics and gynecology and surgical oncology in the department of pathology. The hematoxylin and eosin stained sections from the tumor specimens were studied and diagnosis was made. 4 μm sections were taken from representative area of paraffin-embedded tissue blocks for IHC which was performed according to heat-induced epitope retrieval method with antibodies against ERα, PRA, Her-2-neu, p53, and Ki-67. Informed consent was obtained from all the participants and clinical details were collected as per pro forma. Statistical analysis was done by Chi-square and ANOVA tests using the Statistical Package for the Social Sciences software.

Table 1: Distribution of cases according to histologic types of ovarian tumors

Histological types of ovarian tumors	Number of cases
A. Serous tumors	28
Benign	10
Borderline	4
Malignant	14
B. Mucinous tumors	11
Benign	4
Borderline	1
Malignant	6
C. Endometrioid tumors	
Benign	3
Malignant	2
D. Clear cell tumors	
Borderline	1
E. Brenner tumors	
Benign	1
F. Mixed tumors	
Malignant	4
Serous	2
Mucinous	1
Endometrioid	1

Table 2: Distribution of malignant ovarian tumors according to grade and stage

Grade and/or stage	% (number of cases)
Grade 1	19 (5)
2	31 (8)
3	50 (13)
Stage 1	38 (10)
2	4 (1)
3	35 (9)
4	23 (6)

RESULTS

The median age of patients was higher in malignant and borderline tumors (53 years) in comparison to benign tumors (41 years) [Figure 1].

The most common type is malignant serous tumors [Tables 1 and 2].

Benign tumors show lower expression of ERα (5/18 cases, 27.7%). Serous tumors were the most common type in all three groups (benign, borderline, and malignant). Mucinous tumors, clear cell carcinoma, and mixed tumors were negative for ERα.

PRA showed higher expression in malignant cases (69%, 18/26 cases). Among PRA+malignant tumors, 42% of the cases were serous, 19% were endometrioid, and 8% were mucinous. Clear cell carcinoma was negative.

Her2-neu and p53 expression were negative in benign tumors. Her2-neu and p53 expression were higher in malignant tumors 23% (6/26 cases) and 58% (15/26 cases), respectively.

Ki67 proliferation index was highest in malignant tumors followed by borderline tumors and lowest in benign tumors.

Ascites was present in 21 of the 26 malignant cases (80.77%) [Table 3].

Both ERα and PRA+malignant tumors include 25.2% and Her-2-neu were more coexpressed with PRA as compared to ERα. With regard to p53, 12% were ERα+p53+, 38.2% of cases were p53+PRA+, and 12% of cases were

Table 3: Expression of IHC markers among different tumor types and clinical conditions

IHC markers	Benign	Borderline	Malignant	Serous	Postmenopausal	Advanced stage	Grade 3	Ascites
ER	27.7	50	38	57	83	56	44	78
PR	44	67	69	54	70	53	40	53
P53	Negative	33	58	67	-	-	35	88
Her-2neu	Negative	-	23	66.7	-	57		71
Ki-67	4±2	25±20.8	52±28	64	-		72±20	

ER: Estrogen receptor

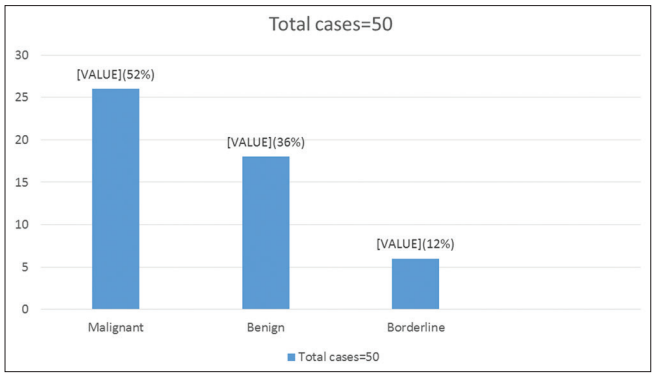

Figure 1: Distribution of cases according to type of tumour

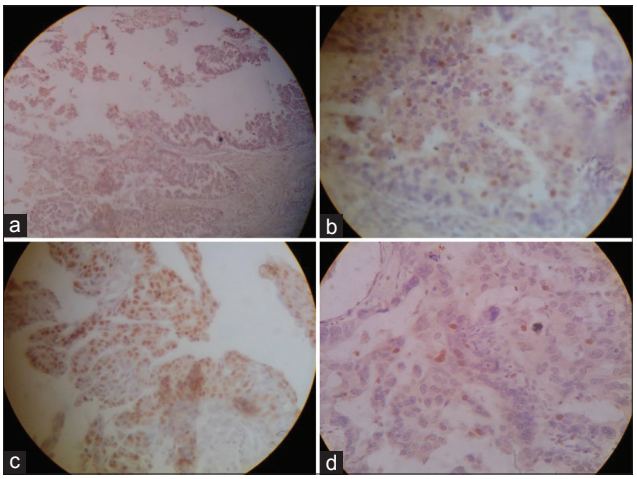

Figure 2: (400x): IHC stained slides showing positivity for markers: (a) ER, (b) PR, (c) p53 and (d) K-67

p53+Her-2-neu+. There was no significant association between the markers [Figure 2].

DISCUSSION

In >90% ovarian cancers, human ovarian surface epithelial cells are the tissue of origin.[3] Similar to previously reported studies, malignant tumors were the most common with serous carcinomas being the predominant type.

In our study, ERα expression was higher in borderline and malignant tumors as compared to benign cases; this was similar to the findings of Sylvia *et al.*[4] and Damiao *et al.*[5] Benign tumors were reported negative for steroid receptors by Agarwal *et al.*[6] Serous tumors, postmenopausal, advanced stages, and tumors with ascites had higher expression of ERα similar to the previous studies.[4,6,7] In our study, majority of Grade 3 tumors showed ERα expression which is in contrast to the studies of Buchynska *et al.*[8] which demonstrated that higher grade tumors had lower expression and Sylvia *et al.*[4] which showed the similar expression in low- and high-grade tumors.

Similar to Sylvia *et al.*, our study also emphasizes the higher expression of PRA similar to ERα in malignant cases, serous tumors, postmenopausal age group, advanced stage, and Grade 3 tumors. This is in contrast to the study by Hecht *et al.*[7] and Lau *et al.*[3] who found no significant association with postmenopausal age group and decrease in PRA expression with Grade 3 and advanced stage tumors, respectively. This higher coexpression of PRA and ERα explains the carcinogenic role of these steroid receptors and role of estrogen in regulating a disease process.[2,8,9]

Both Her-2-neu and p53 were negative in all benign cases, higher expression was seen in Grade 3 tumors, advanced stages, and higher association with ascites which is similar to the previous studies.[4,10-13]

Similar to the previous studies,[14] malignant, serous, and Grade 3 tumors had significant higher proliferation index.

Other variants such as clear cell, mucinous, and mixed tumors are least likely to express ERα and PRA. These findings are in accordance to other studies.[4,15]

Statistically significant correlation was found between the age of patient and ER-PR status which was similar to the finding of Sylvia *et al.*[4]

There was no correlation between expression of ER, PR, and grade of malignant tumor in this study. Similar findings were reported in other series.[4,11]

CONCLUSION

The difference in expression of these markers among benign, borderline, and malignant tumors reveals their role in differentiation and prognostication of ovarian tumors. Ovarian tumors are extremely heterogeneous as proved by the lack of coexpression of these markers. Tumors with adverse prognostic factors express ERα and PRA; this supports the mitogenic role of estrogen and estrogenic regulation of PR. Her-2-neu and p53 are expressed only in malignant tumors supporting their role in the differentiation of borderline and malignant tumors. Similarly, differential expression of Ki-67 in tumors with adverse prognostic factors would help in prognostication and differentiation.

Thus, this study emphasizes the importance of using panel of markers for epithelial ovarian tumors. It also establishes the need for novel markers to further understand the pathogenesis and for accurate prognostication.

The limitation of this study was limited number of cases. Hence, we propose interinstitutional studies to have better understanding of the use of these important markers.

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