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Original Article

Estrogen and Progesterone Receptor Expression in Epithelial Ovarian Cancers and Their Correlation with Histologic Subtypes, Grades and Immnuoexpression

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Context: Ovarian cancer is the most fatal gynecological malignancy and its major burden is shared by Epithelial Ovarian Cancers (EOC). Total 85% of all ovarian cancers belonged to EOC. Despite knowing the involvement of Estrogen and Progesterone in their carcinogenesis, complete understanding of how they transform ovarian surface epithelium (OSE) is still unknown. Their associations with EOC may differ by different subtypes and grades which can be helpful in determining the hormonal need of each. This knowledge can also be valuable for targeted hormonal therapies comparable to those already established in carcinoma breast.
Objective: To evaluate Estrogen and Progesterone receptor expression in various histologic subtypes and grades of Epithelial Ovarian Cancers.
Materials and Methods: Total 82 cases of EOCs including both ovarian biopsies and surgical resections were collected, processed and stained. Hematoxylin and Eosin (H&E) stained slides were examined and histological sub typing of EOC was done. Both Serous and Non-Serous carcinomas were graded. Immunohistochemistry was performed on selected sections to evaluated ER, PR immunoexpression. Extent of immunostaining was noted and graded as 0 to 4+ on the basis of percentage of nuclear staining of tumor cells.
Results: Total number of cases were 82 (n=82). Median age was 48 years. Most common histologic subtype was Serous carcinoma. The commonest grade among Serous carcinoma was high grade and maximum cases of Non- Serous carcinomas belonged to poorly differentiated (G3) category. ER immunoexpression was observed in 61% of total cases. Correlation of ER immunoexpression with various subtypes of EOC proved to be statistically significant with Endometrioid subtype showing maximum immunoreactivity. Among various grades low grade Serous carcinoma proved to be most immunoreactive for ER. PR expression was observed in 41.5% of cases with Serous carcinomas most immunoreactive for PR. Correlation of PR immunoexpression with grades of Serous carcinoma was statistically significant with maximum number of low grade Serous positive for PR.
For combined ER/PR expression 38% cases were ER+/PR+, 22% were ER+/PR-, 4% were ER-/ PR+ and 36% were ER-/ PR-. Correlation of ER/PR immunoexpression with total cases (n=82) was statistically significant, 64% of total cases showed immunoreactivity for either ER or PR. Correlation of ER/PR immunoexpression with histologic subtypes was also statistically significant with most ER+/PR+ cases belonged to Serous and Endometrioid subtypes while most cases of Mucinous and all cases of Clear cell and undifferentiated carcinomas belonged to ER-/PR- category.
Conclusions: A variable expression of ER and PR was noted in EOC among different subtypes and grades. Most cases showed ER immunoexpression, its association with postmenopausal status, link to non-clear cell carcinomas and frequent relation with low grade tumors. These findings strengthen the hypothesis that low grade tumors require ER for tumor initiation and progression, high grade tumors are independent of sex steroids. In contrast to ER smaller number of EOC were positive for PR. They were associated with premenopausal status and low grades of Serous and Non-Serous carcinomas. These findings are consistent with the fact that epithelial malignancies are associated with decreased PR immunoexpression which is gradually lost as tumor progresses from low to high grade. Much lower immunoreactivity of both receptors for Mucinous tumors and absolutely no immunoreaction for Clear cell carcinoma favor the hypothesis that they are distinct morphological and epidemiological entities separate from non-clear cell carcinomas.
Keywords: Estrogen receptor (ER), Progesterone receptor (PR), Epithelial Ovarian Cancer (EOC), Ovarian Surface Epithelim (OSE)

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Introduction

Ovarian cancer is the most common and lethal malignancy of female genital tract. It is ranked seven among the most common malignancies worldwide and fifth in developed nations. Globally the cumulative incidence rate is calculated to be 6.3 new cases per 100,000 females. [1]Five year prevalence rate of females living with ovarian cancer is calculated to be 22.6 per100, 000 women worldwide. [2] It is the third most common malignancy and the top most gynecological cancer in Pakistan.[3, 4]

Morphologically ovarian tumors are divided into three main types including: Surface Epithelial-Stromal tumors, Germ cell tumors and Sex cord-Stromal tumors. Surface Epithelial-Stromal tumors are by far the most common and important group.[5]They are divided according to cellular morphology in to Serous, Mucinous, Endometrioid, Clear cell, Brenner, Transitional and mixed cell types. Each group has a proliferation spectrum of benign, borderline and invasive or malignant categories. The malignant categories of Surface Epithelial group are called Epithelial Ovarian Cancers (EOC). They comprise 85-90% of all ovarian cancer cases in the Western world.[6]Similarly EOCs predominate over other ovarian malignancies in Pakistan and Serous cyst adenocarcinomas are the commonest among all with a percentage of around 30-38%. [7]

Various risk factors have been identified to shed light on their etiology and pathogenesis. Most important of them all is positive family history. Other factors include early menarche, nulliparity, late menopause and advancing age. Use of oral contraceptives, pregnancy and late age at first or last child birth are associated with a lower risk.[8]Based on these risks various theories had been proposed in the past including theorem of "incessant ovulation", effects of gonadotropins and the effect of ovarian aging leading to follicular depletion. However, none of them provides a solid clue regarding the subject.[9]

During recent years the origin of tumor cells was questioned and it was proposed that origin of certain types of EOC is not Ovarian Surface Epithelium(OSE) rather they have originated from distal end of fallopian tubes e.g. Serous carcinomas, from endometriosis e.g. Endometrioid and Clear cell carcinomas and from transitional epithelial nests e.g. Transitional cell, Brenner tumors.[10]New molecular pathogenetic model for EOC divide them into 2 broad categories, Type I and II. Type I tumors include low-grade Serous, Endometrioid, Clear cell, Mucinous and Brenner tumors. They are generally indolent, stage 1 tumors characterized by mutations of KRAS, BRAF etc but rarely TP53 and are stable genetically. Type II tumors include high-grade Serous, Endometrioid, malignant mixed tumors and Undifferentiated carcinomas. They are aggressive, present in advanced stage and have a very high frequency of TP53 mutations.[10]

Estrogen and Progesterone are charged with a proper role in carcinogenesis but detail of their gimmickry is not fully known. It is hypothesized that Estrogen has an impact on the growth and differentiation of OSE where it acts as a mitogen and causes increase cellular proliferation. Contrary to Estrogen, Progesterone has a protective influence over OSE. It exerts its actions through promotion of apoptosis, and inhibition of DNA synthesis and cell division. [9]Their actions are mediated through specific nuclear receptors along with an additional intracellular trans-membrane receptor for Estrogen. Various isoforms of both receptors have been identified including Estrogen receptor (ER-α)/ (ER-β) and Progesterone receptors PR-A/PR-B.These isoforms are normally expressed in primary cultures of normal OSE while malignant epithelial cells of ovary have altered expression of these receptors. A notable lower mean immunoexpression of ER-β and PR (but not ER-α) is seen in ovarian cancer tissue when compared with normal OSE.[11]

Variability of ER, PR expression is also observed in relation to histological subtype, grade and stage of tumor with highest expression in Serous and Endometrioid carcinomas. An association of ER expression is noted with older age, non-Clear cell carcinomas and high-grade tumors, while PR expression is noted in non-Clear cell carcinomas with better response to chemotherapy and progression-free survival. A group of ER negative and PR positive (ER-, PR+) carcinomas (10% of all tumors) showed a superior prognosis and long term survival when compared with other combinations (ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-) of ER and PR expression.[12]

To study ER, PR expression in various subtypes and grades of EOC help us identify hormone dependency of each subtype. It may also help in developing a rationale to establish the role of endocrine treatment in EOC..

Material & Methods

Total 82 cases of EOCs including both ovarian biopsies and surgical resections were collected from 2012 to

2016. Available demographic details like age, menopausal status etc were also noted. Specimens were processed and stained. Hemotoxylin and Eosin (H&E) stained slides were examined and histological sub typing of EOC was done. Serous carcinomas were graded as low and high grade based on two tier grading system while Non-Serous carcinomas were graded as GX (Cannot be assessed), G1 (Well differentiated), G2 (Moderately differentiated), G3 (Poorly differentiated) and G4 (Undifferentiated).

Immunohistochemistry was performed on selected sections to evaluated ER, PR immunoexpression. Tumor cells were considered positive on the basis of nuclear staining. Immunohistochemical score was based on the percentage or extent of immunostaining regardless of intensity. No nuclear reactivity or few positive tumor cells ≤5% were considered negative. Heterogeneous nuclear reactivity of 6-25% and 26–50% tumor cells was considered positive and scored as 1+ and 2+ while homogenous nuclear staining of 51–75% and 76–100% tumor cells was also considered positive and scored as 3+ and 4+ respectively. Intensity of nuclear staining was also noted but not used for scoring. It was graded as mild 1+, moderate 2+ and marked 3+.

Results

Out of total 82 cases 58 (70.7%) were resection specimen, 15 (18.3%) cases were ovarian biopsies, 5 (6.1%) cases were post-chemotherapeutic resection specimens and 4 (4.9%) were peritoneal nodules. Median age of the patients was 48 years with an age range of 25-83 years. Total 43 (52%) patients were premenopausal while 39 (48%) patients had postmenopausal status.

1- Results based on morphology (Sub-typing and grading):

Total 38 cases (65.5%) were diagnosed as Serous, 9 (15.5%) as Mucinous, 6 (10%) as Endometrioid and 5 (9%) as Clear cell carcinoma. All 9 cases of post-chemotherapeutic resections and peritoneal nodule were diagnosed as Serous carcinoma. Most common histologic subtype was Serous carcinoma followed by Mucinous, Endometrioid, Clear cell and finally undifferentiated carcinoma. Mucinous carcinoma had a comparative younger age range of 20-40 years.

The commonest grade among Serous carcinoma was high grade for 33 cases (55%) as compared to 14 cases (23%) of low grade Serous carcinoma. Similarly, maximum cases of Non-Serous carcinomas were Poorly differentiated (G3). (Figures 1 & 2)

Discussion

The main function of platelets is to regulate haemostasis. Thrombocytopenia i.e. platelet count < 150 x 10^9/l is a most common cause of bleeding. Pathophysiologically, thrombocytopenia is divided into hyperdestructive and hypoproductive thrombocytopenia.[2] Bone Marrow examination is considered as a gold standard in distinguishing between the two categories. As it is an invasive time consuming procedure, in recent year's studies have been done to validate the specificity and sensitivity of MPV as an alternative method. MPV is measured by haematological analyzers. It indicates platelet function. It alters in different manner in different causes of thrombocytopenia. This study included 147 patients of thrombocytopenia. Bone marrow aspiration and biopsy was used as gold standard for classifying into two categories internationally many studies have been conducted on this subject, like the study done by Ntaiob-G in 2008 showed that MPV can be relied for the diagnosis of immune thrombocytopenic purpura. Another study done by Bowles KM and Cooke LJ showed that patients with marrow disease had MPV 8.1fl and without marrow disease 9[5].8fl But in some studies it was seen that 8.1fl cut off value has not high significance with a sensitivity of 67.7% and specificity of 65%. The results of this study showed that MPV with bone marrow disease was 7.3fl and without bone marrow disease was 8.62fl, so they stated that it can be used as an initial indicator but bone marrow aspiration and biopsy remain the gold standard.[15]

Study by Aksoyetal showed that MPV 7.4 fl cut off value has sensitivity 82.7%and specificity 89.6% and can be used in patients of solid tumors as a marker of presence or absence of bone marrow metastasis[16].According to this study MPV of thrombocytopenic patients with bone marrow disease ranges from 7fl to 10.3fl with Mean value of 8.8fl and without bone marrow disease range from 7fl to 12fl with Mean value of 9.72. A value of 8 has no high significance. The most common causes of thrombocytopenia in our study were:

- Megaloblastic Anaemia (n)= 39
- Infective Process (n)=34
- Mixed deficiency Anaemia(n)=29

In patients of leukemia, aplastic anaemia and hypocellular marrow the MPV is decreased as compared to megaloblastic anaemia.[17]It was in close

relation with a local study which concludes that in our setup infection and megaloblastic anemia are the most common causes of thrombocytopenia while in another International study it was concluded that 78% cases of isolated thrombocytopenia were of ITP. In this study it was also seen that patients of Megaloblastic anemia had high MPV levels, which was related to an international study with same results.[15,17] Iron deficiency anaemia is usually associated with thrombocytosis. The result of previous studies show that thrombocytopenia is not rare in patients of iron deficiency anaemia.[18]Thrombocytopenia reverses in these patients with the use of iron supplements.[19,20,21]

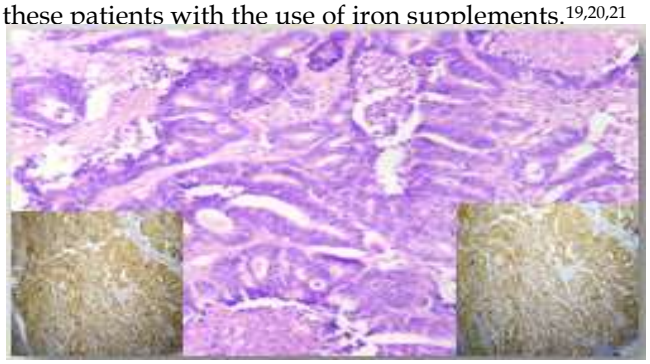

Figure 1: Endometrioid carcinoma (G2) H&E x 100, ER, PR positive immunoexpression (Proportion score 4+, Intensity 3+) IHC x 40

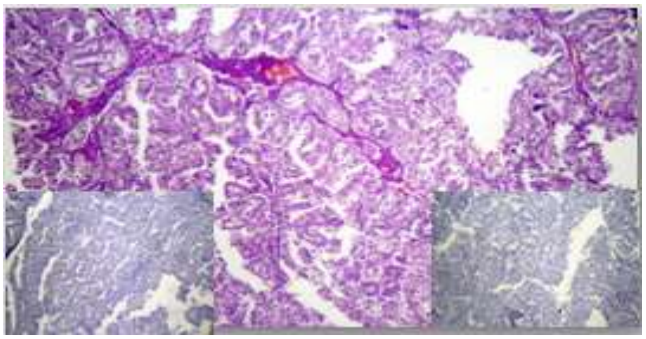

Figure 2: Clear cell carcinoma (G3) H&E x 100 , ER, PR negative immunoexpression (Proportion and Intensity score 0) IHC x 40

2- Results based on immunohistochemical findings:

A- ER immunoexpression:

Positive ER (ER+) immunoexpression was observed in 50 (61%)cases. Total 70% of ER+ cases were >40 years with an age range of 41-60 years. 52% ER+ cases belonged to postmenopausal category.

- **ER immunoexpression among various subtypes of EOC:**

Correlation of ER immunoexpression with various subtypes of EOC was statistically significant (*P* = 0.001).Endometrioid subtype was most immunoreactive for ER with 86% ER+ cases. It was followed by Serous carcinomas with 70% positive cases. Mucinous carcinomas had much lower immunoreactivity for ER with 22% positive cases. All cases of Clear cell and single case of undifferentiated variety showed no immunoexpression for ER.

- **ER immunoexpression among various grades of EOC:**

ER+ immunoexpression was noted in 86% cases of low grade Serous carcinoma as compared to70% cases of high grade Serous carcinomas, similarly maximum ER immunoreactivity was noted among G2 and G3 grades of Endometrioid carcinoma.

- **IHC scoring of ER immunoexpression:**

Out of total 61% ER+ cases,14% were 1+, 26% were 2+,12% were 3+ and 48% were 4+. Intensity of ER immunoexpression was 1+in 8%, 2+ in 48% and 3+ in 44% cases respectively.

B- PR immunoexpression:

Positive PR (PR+) immunoexpression was observed in 34 (41.5%) cases. Total 65% PR+ cases belonged to patients with age>40 years with an age range of 41-60 years. Unlike ER immunoexpression 53% PR+ cases belonged to premenopausal category.

- **PR immunoexpression among various subtypes of EOC:**

PR+ immunoexpression was frequently seen in Serous carcinomas with 48% PR+ cases. It was followed by Endometrioid and Mucinous carcinomas with 43% and 22% PR+ cases respectively. Both Clear cell and undifferentiated carcinomas revealed no immunoreactivity for PR.

- **PR immunoexpression among various grades of EOC:**

Correlation of PR immunoexpression among grades of Serous carcinoma was statistically significant(*P* = .005). Total 86% case of low grade Serous were PR+ as compared to 39% cases of high grade Serous carcinoma, Similarly correlation of PR immunoexpression among grades of Non-Serous carcinoma was also statistically significant (*P* = .007). Maximum cases of PR+ Endometrioid carcinoma belonged to G2 category.

- **IHC scoring of PR immunoexpression:**

Out of total 41% PR+ cases, 32% were 1+, 26% were 2+, 18%were 3+ and 24% cases were 4+. Intensity of PR immunoexpression was 1+ in 6%, 2+ in 23.5%and 3+ in 70.5%cases respectively.

C- Combined ER/PR immunoexpression:

Out of total 82 cases, 38% were immunoreactive for both ER and PR (ER+/PR+), 22% were ER+/PR-, 4% were ER-/ PR+ and 36% were ER-/ PR-.

Correlation of ER/PR immunoexpression with total cases was statistically significant, 64% cases were either positive or negative for both receptors. (*P* = 0.001)

Correlation of ER/PR immunoexpression with histologic subtypes was also statistically significant (*P* = 0.001). Maximum cases of ER+/PR+ cases belonged to Serous and Endometrioid subtypes while most cases of Mucinous and all cases of Clear cell and undifferentiated carcinomas belonged to ER-/PR- category. Correlation of ER/PR immunoexpression with various grades of Serous carcinomas was proved to be statistically significant only for ungraded (GX) and high grade Serous carcinomas with a *P* value of (0.04) and(0.02) respectively.

Table-1: Correlation of ER/PR expression among total cases, histologic subtypes and grades of EOCs (n=82)

	ER Expression	PR Expression		Total
		PR+	PR-	
	ER+	31 (38%)	18 (22%)	50
	ER-	3 (4%)	30 (36%)	32
	Total	34	48	*64% (P = 0.001)*
Histologic subtypes				*(P =0.001)*
Grades				
Serous GX				*(P = 0.04)*
Serous (LG)				(*P* = 0.7)
Serous (HG)				*(P = 0.02)*
Non-Serous G3				(*P* = 0.2)
G4				(*P* = 0.3)

Total 82 cases (n=82) of EOCs were evaluated and majority of them were older than 40 yrs. (41-60 yr).These statistics are in concordance with Hanif M and Aziz Z et al, local studies from Karachi and Lahore with the median age between 47-51 years.[13, 14] Association of malignancy with younger age groups is a common demographic trend in Pakistan and other developing countries. According to statistical data provided by SEER statistical fact sheet (1975-2011) from USA, the median age of affected females was 63-65 years which is around 5- 10 years more than the females of developing nations.[15]

For the study in view Serous carcinoma proved to be the commonest subtype of EOC. This finding is in consonance with many local and international studies.Mucinous carcinomas proved to be the second most common subtype and followed by Endometrioid, Clear cell and undifferentiated carcinomas.This finding is supported by Hashmi AA et al a recent, local study from Karachi according to which a higher incidence for invasive Mucinous tumors is observed in this region with an incidence rate as high as 14.3% as compared to 5% mentioned in Western literature.[16]

Maximum cases of Serous carcinomas were high grade while most of non-Serous carcinomas especially Endometrioid and Clear cell belonged to G3 or poorly differentiated category.Almost half cases of Mucinous carcinoma were graded as G1 or well differentiated.These findings are in accord with Hashmi AA et al according to which high grades, greater incidence of capsular invasion and omental metastasis are associated with Endometrioid and Serous tumors as compared to Mucinous tumors.[16]

ER immunoexpression

It was observed in 61% of total cases.This elevated ER+ immunoexpression had also been described by "Ovarian Tumor Tissue Analysis Consortium" and a Danish group with 81% and 43% of positive cases respectively.[17, 18] Most patients were postmenopausal, this finding is comparable with Tangjitgamol S et al and Liu JF et al, according to which ER immunoexpression had strong association with postmenopausal, older age group with maximum expression near and above 60 years.[12, 19]

Maximum ER+ cases belonged to Endometrioid (86%) subtype followed by Serous carcinomas (70%).These results are comparable with Geisler JP et al having disagreement with few other studies describing Serous carcinomas as most immunoreactive for ER.[20]Lower ER expression in Mucinous carcinomas can be compared with Vang R et al in which no ER immunoexpression had been found in primary ovarian Mucinous carcinomas but few cases of seromucinous types and metastatic endocervical carcinoma exhibit focal and weak ER staining.[21]

Lack of ER+ in majority of Clear cell carcinoma cases is documented by Voutsadakis IA with only 2-4% ER+ cases.[22]A variable expression of ER is seen among different grades. Low grade Serous carcinoma had max. ER+ cases with an IHC score of 4+ as compared to less ER+ cases for high grade with IHC score of 2+. These observations can be compared with Wong KK et al which proposed that higher levels of ER, PR receptors are frequently associated with low grade tumors which mark the importance of gonadal steroids in their pathogenesis.[23]

PR Immunoexpression:

It was observed in 41.5% of total cases. These findings are in concordance with many studies showing lower mean expression of PR in epithelial malignancies. Most cases belonged to premenopausal category. It can be compared with Hecht JL et al which associate increasing age and postmenopausal status with ER+ and PR- tumors.[24]For current study maximum cases of low grade Serous carcinomas were PR+ followed by Endometrioid subtype with max. G3 cases. This finding supports the observation that high grade tumors are associated with loss of PR function.

Based on these facts immunoreactivity for PR can be taken as a differential expression between low and high grade Serous carcinoma and G2 and G3 Non-Serous carcinomas. It is proved to be statically significant in both cases (P = 0.005) and (P = 0.007) respectively. Additionally maximum cases of low grade Serous carcinoma showed 4+ IHC scoring as compared to high grade which had most cases with 1+ score. These findings are comparable with Wong KK and Hecht JL et al and further strengthen the observation that high grade tumors are associated with lower concentration of PR receptors.[23, 24]

Co-expression of ER/PR:

Maximum ER+/PR+ co-expression was found among Serous and Endometrioid carcinomas. These findings are in accord with Arias-Pulido H et al which had Serous and Endometrioid carcinomas as 2 major receptor positive categories.[25]For ER-/PR- category majority were Clear cell and Mucinous carcinomas. This is in accord with many studies, to be considered as different epidemiological entities with less or no receptor activity.

Among grades maximum number of ER+/PR+ cases belonged to low grade Serous and to G2 category, while most high grade Serous and G3 non-Serous tumors were negative for either or both receptor.

Wong KK et al supported these observations by suggesting that high steroid receptor expression is associated with low grade tumors due to their dependency on gonadal steroids to thrive, while high grade tumors are independent of these hormones.[23]

Conclusion

In conclusion, current study suggests a variable expression of ER and PR in EOC.

Data highlighted ER-α immunoexpression among majority of epithelial malignancies, its association with postmenopausal patients, maximum immunoreactivity among non-clear cell carcinomas including Endometrioid and Serous and frequent relation with high grade tumors. All these parameters augment the hypothesis that high ER-α expression is required for initiation and to some extent progression of malignancy. For high grade Serous tumors initiation and progression of malignancy is independent of gonadal steroids.

PR-A immunoexpression was observed in smaller number of epithelial malignancies. It was associated with premenopausal patients, commonly seen in Serous and Endometrioid tumors and had a frequent relation with low grades of both Serous and Non-Serous tumors. These observations are consistent with the hypothesis that PR-A immunoexpression show a marked cutoff in EOCs, commonly expressed in non clear cell malignancies and is totally lost when a tumor progress from low to high grade.

For ER/PR co-expression Endometrioid and Serous carcinomas showed maximum immunoreactivity, Mucinous carcinomas were least immunoreactive for both receptors while Clear cell carcinomas showed no reactivity for them. These findings are in favor of hypothesis which consider them as distinct morphological and epidemiological entities separate from non-clear cell carcinomas.

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B. Experimentation/Study Conduction
C. Analysis/Interpretation/Discussion
D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis