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ER PR EXPRESSION IN NON-GERM CELL OVARIAN CARCINOMA

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ABSTRACT

Context: Hyperestrogenia is an important risk factor for ovarian cancer. The detection of ER, PR receptors in ovarian cancer provides further evidence that ovarian carcinoma are hormone dependant and therefore are amenable to hormone therapy.

Settings and Design : Cross-sectional study .

Aim: The present study thus aims to study ER, PR expression in non-gem cell ovarian carcinoma and to correlate it with histopathological and clinical features.

Material and Methods: 30 consecutive cases of non germ cell ovarian cancer between January 2005 to December 2012 were retrieved from the records of the Pathology Department at PSGIMS&R. The paraffin-embedded H & E slides of the 30 cases were examined. The clinical details and histological type, grade of the neoplasm were observed. Immunohistochemical staining for ER and PR was done.

Results: ER, PR were frequently expressed by serous, endometriod, mucinous carcinoma and granulosa cell tumor. Clear cell, undifferentiated carcinoma and malignant Brenner tumor lacked receptor expression. An increase in PR expression from Grade 1 to Grade 3 epithelial ovarian carcinoma was noted with a fall in PR expression with increasing stage . A fall in ER expression and a mild increase in PR expression was observed in post menopausal ovarian carcinoma

Conclusion: ER, PR expression was frequently seen in serous, endometriod, mucinous carcinoma and granulose cell tumor. The frequency of PR positive epithelial ovarian carcinoma increased with increasing grade of the tumor while the loss of PR expression was associated with a higher stage.

KEY WORDS: ovarian carcinoma, Estrogen Receptor , Progesterone Receptor.

Introduction:

Ovarian Cancer is one of the most aggressive malignancies of the female genital tract, ranking below carcinoma of cervix and endometrium in our country[1]. It is the sixth most common cancer and the fifth leading cause of cancer related death among women in the developed countries[2]. The detection of ER, PR receptors in ovarian cancer provides evidence that ovarian carcinoma are amenable to hormone therapy. Various hormone therapies such as antiestrogens, progestins have been used in recurrent and / or chemo resistant ovarian cancer patients[3]. Ovarian neoplams can be broadly classified into their major categories - germ cell tumors, surface epithelial tumors and sex cord tumors. The latter two express steroid receptors - ER, PR and therefore hormone therapy is used for the malignant category of these tumors. In contrast to breast tumors, little information is availabe in the literature regarding ER, PR expression in ovarian neoplasms. Further, no extensive studies have been done across the Indian population. Therefore the present study .

Material and Methods:

30 consecutive cases of non germ cell ovarian cancer between January 2005 to December 2012 were retrieved from the records of the Pathology department at PSG IMS&R. The paraffin-embedded H & E slides of the 30 cases were examined. The histological type and grade of the neoplasm wereobserved. Clinical details which included the age, hormonal status, stage of tumor were recorded. The representative slides were selected in each case. Immunohistochemical staining for ER and PR was done [4]. Paraffin embedded sections were cut at approximately 4 micrometer, floated on to Poly-L-Lysine coated slides. Antigen retrieval is done by pressure cooking in citrate buffer (pH -6.0) for 10 min. Following Peroxidase block, the sections were incubated with primary and secondary antibodies for 1 hr each.Super enhancer and super sensitive poly- HRP were added to enhance the reaction. The Antibody solutions used were DAKO - Monoclonal Rabbit Anti-Human ER clone and monoclonal mouse anti-human PR clone. The chromogen in the colour development solution was 3'3' diaminobenzidine (DAB).

Breast tissue was used as positive control and the negative control was the same tissue incubated without primary antibody. ER.PR nuclear staining was evaluated using the Allred score[5]. This method takes into consideration both the proportion of positive cells and the intensity of staining. The association between receptor expression and type ,grade, stage, menopausal status were analysed by Chi square test.

Results:

Of the 30 cases of non-germ cell ovarian carcinoma studied, 26 (86.7%) were malignant surface epithelial neoplasms and 4 (13.3%) were sex cord tumors all being adult - type granulosa cell tumor. The most common malignant surface epithelial neoplasm were the serous carcinoma ten cases (33.3%) followed by endometrioid five cases (16.8%), clear cell carcinoma four cases (13.3%) mucinous carcinoma three cases (10%) undifferentiated carcinoma three cases (10%) and a single case (3.3%) of Malignant Brenner(table1)

Either ER or PR expression or both ER and PR co-expression could be demonstrated in 19 of the 30 cases (63.3%) while the remaining 11 cases (36.7%) did not express either ER or PR(Table 2). The 11 receptor negative cases included clear cell carinoma (four cases, 36.4%), undifferentiated carcinoma (three cases, 27.2%), endometrioid carcinoma (one case, 9.1%), mucinous carcinoma (one case, 9.1%) serous carcinoma (one case, 9.1%) and Malignant Brenner tumor (one case, 9.1%).

The grade, stage, hormonal status, location and receptor expression of the epithelial ovarian carcinoma have been summarized in table3 . Ten cases of serous carcinoma comprised of four ER+/PR-, two ER-/PR+, three ER+/PR+ and one receptor negative case. ER expression was thus seen in 70% of the serous carcinoma, while PR expression was seen in 50%. The three cases of mucinous carcinoma included one of endocervical type mucinous carcinoma, while the other two were of intestinal type. The former expressed both ER, PR while the latter were ER-/PR- and ER-/PR+. ER expression was seen in 1 case(33%) and PR expression was seen in 2 cases (66%). (Fig1) Three of the five cases of endometrioid carcinoma (60%) were ER+/PR+, one case was ER-/PR+ (20%) and one other case (20%) was ER-/PR-. There were no ER+/PR- endometrioid carcinoma.60% of the endometrioid carcinoma expressed ER, while 80% expressed PR.(Fig2).

All the four cases of sex cord tumors were adult type granulosa cell tumors constituting 13.3% of ovarian cancers Three of the four cases (75%) were unilateral and stage II tumors. Two of the cases (50%) were observed in postmenopausal age and one in a premenopausal woman. In one of the cases, the hormonal status could not be assessed due to hysterectomy. ER expression was seen in two of the four cases (50%) and PR expression was noted in all the four cases (100%)(Fig3)

ER expression was 70%, 60%, 50% & 33.3% in the serous carcinoma, endometrioid carcinoma, granulosa cell tumor and mucinous carcinoma while PR expression was observed in 100%, 80%, 66.6% and 50% of granulosa cell tumor, endometrioid, mucinous and serous carcinoma respectively. Further ER,

PR coexpression was seen in 60%, 50%, 33.3% and 30% of endometrioid, granulosa cell tumor, mucinous and serous carcinoma in that order. Malignant Brenner tumor, clear cell carcinoma and undifferentiated carcinoma did not express ER and PR receptors(Fig4)

Further ER, PR expression was correlated with stage and the hormonal status as shown in table 4. ER expression was present in seven cases, PR expression in nine cases of stage 2 carcinoma while six cases of stage 3 tumors expressed ER & PR. ER expression was present in nine cases (52.9%) and PR expression in eight cases of premenopausal ovarian carcinoma; ER expression was observed in three cases (25%) and PR expression in six cases (50%) of postmenopausal ovarian tumors.

The association of receptor expression with the grade of the malignant epithelial neoplasms has been shown in table 5. ER expression was seen in two (50%), seven (36.8%) and two (66.6%) cases of grade 1, grade 2 and grade 3 epithelial carcinoma respectively. PR expression as observed in one (25%), eight (42.11%) and two (66.6%) of grade-1, grade-2 and grade-3 epithelial carcinoma in that order. An increase in PR expression with grade was seen (though not significant statistically p= 0.543).

Discussion:

Estrogen and progesterone are hormones secreted by the ovary acting through specific steroid receptors. The expression profiles of Estrogen and Progesterone receptors in tumor tissue has been studied in the malignancies of breast, uterus and prostate in addition to the ovary [6]. In the present study, the ER PR expression patterns across the spectrum of non-germ cell ovarian carcinoma were studied and correlated with histopathological type, grade, FIGO stage and hormonal status.

An ER expression of 43.3% and a PR expression of 50% was seen in the 30 cases of ovarian carcinoma in our study which included 26 cases of surface epithelial carcinoma and four cases of granulosa cell tumor. Among the surface epithelial carcinoma, ER, PR expression was frequently seen in serous (70%, 50%) endometriod (60%, 80%) and mucinous carcinoma (33.6%, 66.7%). The highest ER, PR co-expression was present in endometrioid carcinoma followed by serous and mucinous carcinoma. A similar pattern of expression has been described by Pulido HA [7] and Hech JL [8] except for a greater expression of PR in mucinous carcinoma in the present study contributed by PR expression in the ovarian mucinous carcinoma of the gastrointestinal type which has not been reported in literature. . Clear cell, undifferentiated carcinoma and malignant Brenner tumor did not express ER, PR receptors . Such a lack of steroid expression in the these categories has been documented [9,10,11].

All four cases of sex cord tumors were granulosa cell tumor with 100% PR expression, 50% ER expression and 50%ER PR co-expression. These findings are in agreement with those of Farinola MA [12]. There was no case of Sertoli – Leydig cell tumor.

A variation in ER, PR expression was seen among the three grade of epithelial ovarian cancer with maximum expression in grade 3 carcinoma. There was a rise (though not statistically significant p=0.54) in the PR expression from Grade 1 through Grade -2 to Grade 3 carcinoma (25% to 42.1% to 66.7%) similar to that described by Hogdoll EV[6]. ER expression also showed a rise from grade-1 to grade -3 (50%to 66%) but a fall in the expression was present in grade 2(36.8%) compared to Grade- 1. This could perhaps be due to the presence of clear cell and undifferentiated carcinoma constituting 31.6% of the grade-2 tumors which did not express either ER or PR. Our findings therefore partly coincided with those of Teufel[13] who found greater ER expression in grade 2 and grade 3 carcinoma compared to grade 1.

Assessing the relation between FIGO stage and steroid receptor expression, we found in the present study that there was a decrease in both ER as well as PR expression in stage III (40% expression of ER, PR) carcinoma compared to stage II carcinoma (ER 46.7% and PR 60%). The fall in PR expression with increasing stage was moderate(from 60% to 40%, but not statistically significant (p = 1.06).This fall in PR expression has been observed in other studies[6] **.**There were no stage I and stage IV carcinoma in the present study.

A fall in ER expression (52.9% to 25%) and a mild increase in PR expression (47% to 50%) in post menopausal ovarian carcinoma as observed in the current study contradicted the findings of Hecht JL[14] who noted a moderate increase in ER+ and PR- ovarian carcinoma in post menopausal women.

CONCLUSION:

The expression of either ER or PR or their co-expression suggests a better outcome compared to (ER negative / PR negative) absence of both receptor expression .PR over expression has associated with a favourable prognosis. In the present study, Serous, Endometrioid , Mucinous carcinoma and granulosa cell tumour frequently express ER PR and are therefore would benefit from hormone therapy. The frequency of PR positive epithelial ovarian carcinoma increased with increasing grade of the tumor . The loss of PR expression was associated with a higher stage of ovarian carcinoma. With the advent of a wide range of hormone drugs - antiestrogen, progestins, GnRH analogs effective management has become possible. These drugs may be used either alone or in combination with chemotherapeutic regimens.

Table 1: Distribution of non-germ cell ovarian cancers:

Non - germ ovarian cancer	No of Cases (n=30)	%
1. Malignant surface epithelial neoplasms:		
(i) Serous Carcinoma	10	33.3
(ii) Endometrioid carcinoma	5	16.8
(iii) Clear Cell carcinoma	4	13.3
(iv) Mucinous carcinoma	3	10.0
(v) Undifferentiated carcinoma	3	10.0
(vi) Malignant Brenner	1	3.3
2. Sex cord tumor:		
Granulosa cell tumor	4	13.3

Table 2: Pattern of ER PR expression in non germ cell ovarian cancers:

ER PR Expression	No of Cases (n=30)	%
ER + / PR -	4	13.3
ER - / PR +	6	20.0
ER + / PR +	9	30.0
ER - / PR -	11	36.7

Table 3: Showing the grade, stage, Hormonal status, location and ER, PR expression of the Epithelial ovarian Carcinoma:

CHARACTERISTICS	NUMBER OF CASES					
Histopatholgy	**Serous Carcinoma**	**Mucinous Carcinoma**	**endometrioid Carcinoma**	**Clear Cell Carcinoma**	**Malignant Brenner**	**Undiffer-entiated carcinoma**
TOTAL NO. OF CASES	10	3	5	4	1	3
Grade :1	2 (20%)	2 (66.7%)	NIL	NIL	NIL	NIL
2	5 (50%)	1 (33.3%)	5 (100%)	4 (100%)	1 (100%)	3 (100%)
3	3 (30%)	NIL	NIL	NIL	NIL	NIL
Stage: I	NIL	NIL	NIL	NIL	NIL	NIL
II	3 (30%)	2 (66.7%)	5 (100%)	1 (25%)	1 (100%)	NIL
III	7 (70%)	1 (33.3%)	NIL	3 (75%)	NIL	3 (100%)
IV	NIL	NIL	NIL	NIL	NIL	NIL
Hormonal Status:					Nil	2(66.7%
Premenopausal	7 (70%)	1 (33.3%)	4 (80%)	2 (50%)	1 (100%)	1(33.3%
Post menopausal	3 (30%)	2 (66.7%)	1 (20%)	2 (50%)		
Location:					1 (100%)	Nil
Unilateral	5 (50%)	2 (66.7%)	5 (100%)	1 (25%)	Nil	3 (100%)
Bilateral	5 (50%)	1 (33.3%)	Nil	3 (75%)		
Hormone receptor expression					Nil	Nil
ER+ / PR -	4 (40%)	Nil	Nil	Nil	Nil	Nil
ER - / PR +	2 (20%)	1 (33.3%)	1 (20%)	Nil	Nil	Nil
ER + / PR +	3 (30%)	1 (33.3%)	3 (60%)	Nil	1 (100%)	3 (100%)
ER - / PR -	1 (10%)	1 (33.3%)	1 (20%)	4 (100%)		

Table- 4: Showing correlation between FIGO stage of non germ cell ovarian carcinoma, hormone status and ER, PR expression.

CHARACTERISTIC	All cases	ER+/PR-	ER/PR+	ER+/PR+	ER-/PR-
FIGO Stage:					
I	-	-	-	-	-
*II	15	2(13.3%)	4(26.7%)	5(33.3%)	4(26.7%)
**III	15	2(13.3%)	2(13.3%)	4(26.7%)	7(46.7%)
IV	-	-	-	-	-
Hormonal Status:					
Premenopausal	17	3(17.6%)	2(11.8%)	6(35.3%)	6(35.3%)
Post menopausal	12	1(8.3%)	4(33.3%)	2(16.7%)	5(41.7%)

Table-5 : Shows ER, PR expression in different grades of epithelial ovarian carcinoma :

GRADE OF EPITHELIAL OVARIAN CARCINOMA	All cases	ER+/PR-	ER-/PR+	ER+/PR+	ER-/PR-
Grade 1	4	2 (50%)	1 (25%)	0 (0%)	1 (25%)
Grade 2	19	1 (5.2%)	2 (10.5%)	6 (31.6%)	10 (52.6%)
Grade 3	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)

IMAGES :

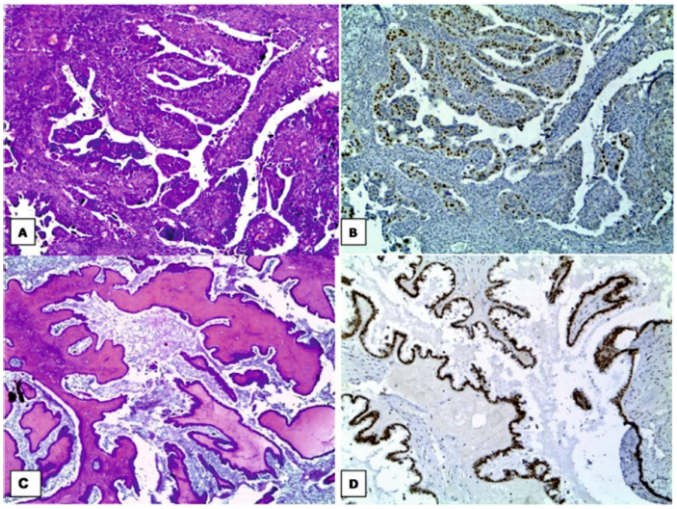

Fig 1A Shows serous ovarian carcinoma (H&E,100X) with strong ER expression in B(100X). C shows Mucinous carcinoma of endocervical type (100X) with strong ER expression in D (100X). A similar PR expression was seen in both cases.

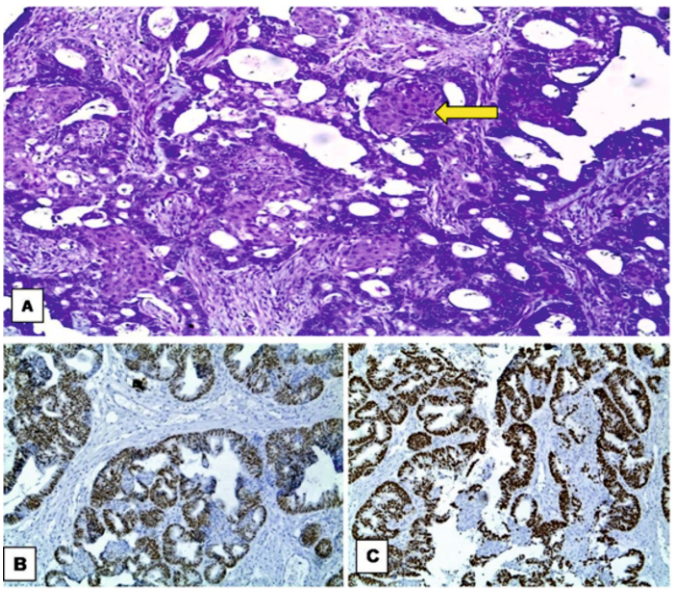

Fig2A Shows grade 2 endometrioid carcinoma with squamous morules (yellow arrow) (H&E,100X) .B shows strong ER expression in 95% of cells (100X).C shows a similar PR expression(100X)

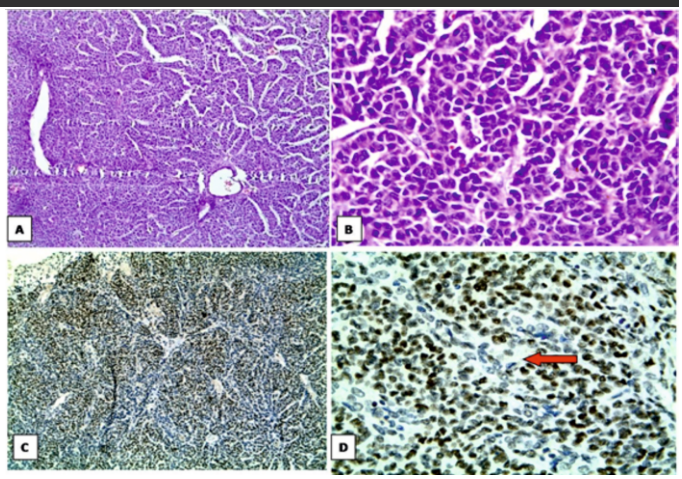

Fig3A and B show granulose cell tumor with cells in sheets and trabecular pattern (H&E 100X,400X). C shows strong ER expression (100X)D shows strong PR expression A nuclear groove is shown by red arrow(100X)

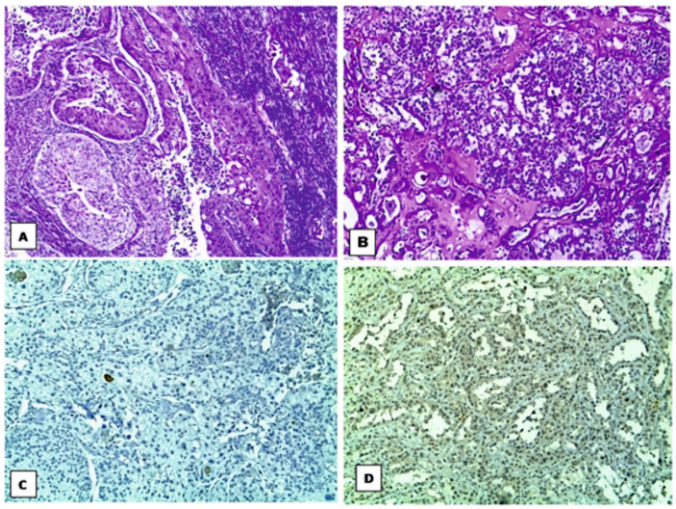

Fig4A shows malignant Brenner tumor(H&E, 100X).B shows clear cell carcinoma (H&E,100X).C and D shows lack of ER expression in these tumors(100X). A similar absence of PR expression was seen .

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