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Original Research Article

Clinicopathological study of benign and malignant ovarian tumours and the role of HER2/neu and ER expression in these tumours

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ABSTRACT

Background: Ovarian cancers represent the 6th most common cancer among females and are the most common cause of death from gynaecological cancers in the world. The aim is to do clinicopathologic study of ovarian tumours along with evaluation of the expression of estrogen receptor (ER) and human epidermal growth factor receptor (HER2/neu).
Methods: A total of 85 cases of ovarian tumors were studied and immunohistochemistry was performed with specific antibodies against ER and HER2/neu as per standard protocol.
Results: In present study, surface epithelial tumours were the commonest type comprising 64 cases (75.2%), followed by Germ cell tumours, 17cases (20%) and sex cord stromal tumours, 04 cases (4.8%).Among the surface epithelial tumours , ER-positive cases were higher in malignant (71.4%) tumours as compared to borderline tumours (33.3%) and benign tumours (7.7%) while Her2/neu positive cases were higher in borderline (66.7%) tumours as compared to malignant tumours (42.9%) and benign tumours (15.3%).Among the germ cell tumours, ER expression was positive in 62.5% cases of mature teratoma while HER2/neu expression was positive in only 12.5% cases of mature teratoma. None of the sex cord stromal tumours showed positive expression of ER and HER2/neu.
Conclusions: Positive expression of estrogen receptors is seen predominantly in surface epithelial malignancies and in mature teratoma. It proves the mitogenic role of estrogen in ovarian tumours. Her-2 neu was expressed mainly in malignant tumours. This suggests their carcinogenic role. This also helps in differentiating borderline and malignant tumours.

Keywords: Epithelial ovarian tumours, ER, Her2/neu

INTRODUCTION

Ovarian cancers pose one of the greatest challenges to the clinicians and pathologists worldwide because they exhibit heterogenous clinical behavior and wide range of histo-pathological patterns. Early ovarian cancers might go undetected because they cause minimal or no symptoms. Most of the cases of ovarian malignancies are detected in stage III or stage IV when cure is difficult.[1] The 5-year survival rates are only 18-22% for advanced stage of ovarian cancers. As there has been increase in life expectancy, corresponding increase in incidence of ovarian cancers is expected. Thus, research on early detection and better treatment options becomes important in public health issues.

The risk of developing ovarian cancer is increased four folds in women with affected first degree relatives.[2] Age is also one of the significant risk factors. Epithelial ovarian cancer accounts for 90% of ovarian malignancies. With the development of immunohistochemistry and fluorescent in situ hybridization, there has been emphasis

on targeted therapy. Estrogen receptors and HER2/neu are two such targets.

In the present study, authors aim to study the relation of ER and HER2/neu expression with tumor type, tumor grade, prognosis and clinico-pathologic factors. Although it is a single institution-based study, it might serve as a reference in the development of therapeutic agents and assessment of prognosis. The present study was done with the following aims and objectives of this study were based on to find out the frequency distribution of ovarian tumors in and around LLRM medical college, Meerut, Uttar Pradesh. To study clinico-pathologic correlation with histological subtypes of various ovarian tumors, to analyze the immunohistochemical profile of HER2/neu and ER in various ovarian tumors with special reference to surface epithelial tumors.

METHODS

The present prospective and retrospective study was done in the department of pathology, in collaboration with department of obstetrics and gynecology, LLRM Medical college, Meerut, Uttar Pradesh, India attached to SVBP Hospital, Meerut, Uttar Pradesh, India.

For prospective study, all the new cases referred from department of obstetrics and gynecology of SVBP hospital attached to LLRM medical college, Meerut, India approximately in one-year duration (i.e. from May 2017 to August 2018) were studied.

For the retrospective study, slides and blocks available in the department of pathology, LLRM medical college, Meerut, which were histologically diagnosed as ovarian tumors were retrieved from histology archives and reviewed.

The test population comprised of 85 patients diagnosed with ovarian neoplasm after undergoing preliminary Trucut biopsy/open biopsies, and subsequently underwent surgery.

For IHC study, nuclear staining for ER and membrane staining for Her2neu was considered. Data was analyzed with the help of appropriate computerized statistical methods. The IHC staining was studied in correlation with clinico-pathologic factors of ovarian tumors which include age, histological type, tumor grade, tumor stage and CA-125 levels. Histological grading was done for epithelial tumors using the MD Anderson cancer center grading system.

RESULTS

Ovarian tumors constituted 1.4% (85/6000) of total surgical specimens of female patients submitted (Table 1).

Most ovarian tumors,29 cases (34.1%) were ranged between 21-30 years followed by 25 cases (29.4%) between 31-40 years, (Table 2) shows distribution of ovarian tumors according to WHO classification (Table 2).

Out of total 85 cases of ovarian tumors, surface epithelial tumors were the commonest type comprising 64 cases (75.2%), followed by germ cell tumors, 17cases (20%) and sex cord stromal tumors,04cases (4.8%) (Table 3).

Out of total 85 cases, immunohistochemistry was performed on 37 cases only (43.5% cases), of which 23 cases (62.1%) were of surface epithelial tumors,10 cases (27.0%) of germ cell tumors and 4 cases (10.9 %) of sex cord stromal tumors.

ER expression was based on the proportion of cells in a given tumor specimen exhibiting distinct nuclear immune positivity as well as intensity of staining (Negative <10% and positive>10%).Her-2/neu grading 0 and 1+ were considered as negative and 3+ as positive, 2+ was considered to be equivocal.

Table 1: Year wise distribution of total number of ovarian neoplasm(n=85) in comparison with the total number of surgical specimens of female patients submitted(n=6000).

Period	Total number of surgical specimens of female patients	Total number of malignant cases in females	Total number of ovarian tumours	Percentage of ovarian tumours out of total cases submitted%
January-December 2012	1000	300	11	1.1
January-December 2013	900	200	08	0.9
January -December 2014	800	200	08	1
January- December 2015	1200	400	16	1.3
January-December 2016	900	350	16	1.8
January-December 2017	700	400	13	1.9
January August-2018	500	150	13	2.5
Total	6000	2000	85	1.4

Table 2: Age wise distribution of various ovarian neoplasms(n=85).

Age in years	No. of cases	(%)
<10	1	1.3
11-20	8	9.4
21-30	29	34.1
31-40	25	29.4
41-50	12	14.1
51-60	8	9.4
>60	2	2.3
Total	85	100

Table 3: Overall distribution of various ovarian neoplasms according to who histological classification(n=85).

Ovarian neoplasm	No. of cases	(%)
Surface epithelial tumors	64	75.2
Serous tumors	46	54.1
Benign	40	
Borderline	02	
Malignant	04	
Mucinous tumors	11	12.9
Benign	07	
Borderline	02	
Malignant	02	
Seromucinous tumour	04	4.7
Transitional cell tumour	02	2.3
Endometrioid tumour	01	1.2
Germ cell tumor	17	20
Mature teratoma	13	15.4
Dysgerminoma	02	2.3
Yolk sac tumour	02	2.3
Sex cord stromal tumor	04	4.8
Granulosa stromal cell tumour	03	
Sertoli stromal tumor	00	
Leydig cell tumour	01	
Total	85	100

Table 4: Frequency of expression in benign, borderline and malignant surface epithelial tumors(N=23).

Type of tumour	No. of cases	Positive cases (number and %)	Equivocal and negative (number and percentage)
Benign	13	01 (7.7)	12 (92.3)
Borderline	03	01 (33.3)	02 (66.7)
Malignant	07	05 (71.4)	02 (28.6)
Total	23	07 (30.4)	16 (69.6)

ER-positive cases were higher in malignant (71.4%) tumors as compared to borderline tumors (33.3%) and benign tumors (7.7%). The difference in ER positivity in different histopathological types was found to be statistically significant (P <0.001) (Table 4).

ER positivity was higher for serous tumors (33.3%) as compared to mucinous tumors (4.2%) and the difference in ER positivity of mucinous andserous was found to be statistically significant (P < 0.001) (Table 5).

Her2/neu positive cases were higher in borderline (66.7%) tumors and malignant tumors (42.9%) as compared to benign tumors (15.3%). The difference in Her2 positivity between borderline and malignant cases was not statistically significant (Table 6).

Table 5: Frequency of ER expression in various subtypes of ovarian tumors (N=23).

HPE diagnosis	ER positive cases (number and%)	ER negative cases (number and %)
Serous (n=15)	05 (33.3)	10 (66.7)
Mucinous (n=05)	01 (4.2)	04 (95.8)
Seromucinous (n=1)	00 (0)	01 (100)
Brenner tumor (n=2)	01(4.2)	01(95.8)
Total (n=23)	07 (30.4)	16 (69.6)

Table 6: Frequency of HER2/NEU expression in benign, borderline and malignant ovarian tumors (N=23).

Type of tumour	No. of cases	Positive (%)	Equivocal and negative (%)
Benign	13	02(15.3)	11(84.7)
Borderline	03	02 (66.7)	01(33.3)
Malignant	07	03 (42.9)	04(57.1)
Total	23	07 (30.4)	16 (69.6)

In the present study, HER2/neu expression was more in serous tumor (33.3%) and transitional tumor (50%) as compared to mucinous tumor (4.2%) and this difference was statistically significant (Table 7).

Table 7: Frequency of HER2/neu expression in various subtypes of ovarian tumors (N=23).

HPE diagnosis	HER2/neu positive (%)	HER2/neu negative (%)
Serous (n=15)	05 (33.3)	10 (66.7)
Mucinous (n=05)	01 (4.2)	04 (95.8)
Seromucinous (n=1)	00 (0)	01 (100)
Brenner tumor (n=2)	01 (50)	01 (50)
Total (n=23)	07 (30.4)	16 (69.6)

HER2/neu expression was positive in only 1 out of 8 (12.5%) cases of mature teratoma and negative in dysgerminoma and yolk sac tumor. HER2/neu expression was negative in all the cases of sex cord stromal tumors. ER expression was positive in 5 out of 8 cases (62.5%) of mature teratoma and negative in dysgerminoma and yolk sac tumors.ER expression was negative in all the cases of sex cord stromal tumors.

DISCUSSION

In present study, ovarian tumors (benign and malignant) constituted 1.4% of total number of specimens of female patients submitted. Malignant ovarian tumors constituted 0.6% of all malignant tumors in females. This is not in concordance with the study done by Mondal SK et al, where incidence of malignant ovarian tumors was 9.5%.[3] From this, it is evident that frequency of malignant ovarian tumors is much lower (0.6%) in this part of the country as compared to other studies.

In the present study, maximum number of cases (77.6%) were between 21-50 years of age. This age group included 77.6% of tumors. This was in concordance with the study done by Manoja V et al, where 84.5% tumors were included in this age group and Jha R et al, where72.2% cases were present.[4,5]

The incidence of surface epithelial tumors in the present study was 76.5%. Pilli GS et a1, reported slightly lower incidence as 72.9%.[6] Slight lower incidence was also reported by Rashid A et al, as 68.5%.[7] Germ cell tumors constituted 20% of total ovarian tumors. The incidence in the present study was almost similar to Rashid A et al, who reported it to be 23%.[7]

Sex cord stromal tumors constituted 4.8% of total ovarian tumors. Pilli GS et al, and Bodal VK et al, reported as 6.7% and 3.33% respectively.[6,8]

ER expression was higher in borderline and malignant tumors as compared to benign cases which were similar to findings of Damiao et al had reported that benign tumors were negative for steroid receptors and that serous tumors had more expression as compared to mucinous tumors.[9] In present study, ER expression was positive in 62.5% cases of mature teratoma while HER2/neu expression was positive in only 12.5% cases. This is in concordance with the study conducted by Soule et al, where HER2 /neu positivity was only 22.1%. If authors relate the estrogen positivity rate with malignancy rates then authors find that ER positivity rate was higher in malignant and borderline cases (5/7) as compared to benign (1/13;4.7%), thus showing a significant difference (p=0.020). However, on evaluating the sensitivity and

specificity of ER for diagnosis of malignancy it was found to be only 34.5% sensitive but 89.2% specific, thus showing it to be a specific rather than sensitive tool for diagnosis of malignancy.

HER 2/neu and ER expression is high in malignant tumours and shows positivity in high grade malignant tumors mostly commonly in high grade serous tumors (4/7 cases, 42.9%). This is in concordance with Sylvia MT et al, and Goel S et al.[10,11]

CONCLUSION

Together expression of ER and HER2/neu associated with decreased survival rates. These markers may aid in prognostication of ovarian tumors. This study is an institution based one with a small sample size of 85 cases. The results may not actually reflect the original age distribution and histological pattern of ovarian tumors in Indian population. The epidemiological data of developed countries in many aspects differ from the developing nations. This should be standardized to identify reliable prognostic markers in the clinical trial of hormone therapy.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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