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Pathology

STUDY OF IMMUNO-HISTOCHEMICAL MARKER HER2/NEU RECEPTOR IN OVARIAN NEOPLASMS

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ABSTRACT Among genital malignancies, Ovarian Cancer has the most increased mortality rate. HER2/neu expression levels depend on tumour histologic grade and stage of disease and are variable between tumours of the same grade. We studied the clinicopathological parameters in ovarian tumours with reference to age, histologic type and grade and their correlation with HER2/neu status. The prospective study of 2 ½ years was conducted on 100 resected ovarian tumour specimens from June 2017 to December 2019 received in the Department of Pathology, JLN Medical College, Ajmer. Sections were stained and examined for presence of ovarian tumour, Histological type, grade and for HER 2/neu status, immunohistochemistry was done. Out of 100 cases, 72 cases were benign, 03 cases were borderline and 25 cases were malignant. 60% were of surface epithelial neoplasm, followed by germ cell tumors. Serous tumors were most common among all epithelial tumors (61%). Malignant cases showed maximum100% positivity with HER2. HER2/neu positivity in serous epithelial tumors was 90% and in mucinous tumors was10%. Majority of positive HER 2/neu receptors was observed in Age groups of >40 years as 85%. HER2/neu positivity seen in higher grade and stage tumors as 70% in grade 3 and stage 3 tumors respectively.The higher expression of HER-2/Neu is associated with progression of invasive cancer, higher grade and stage of ovarian tumors, higher age group, and mulitparity.

KEYWORDS : Ovarian cancer, Immunohistochemistry, Genital malignancies.

Introduction:

Ovarian cancer is one of the most frequent cancers in female patients[1]. Among genital malignancies, Ovarian Cancer has the most increased mortality rate. The low survival is due to the lack of symptoms in early stages. Therefore, the diagnosis is delayed and the prognosis is poor. About 80% are benign, these occur mostly in young women between the ages of 20 and 45 years. Borderline tumours occur at slightly older ages. Malignant tumours are more common in older women between the ages of 45 and 65 years. The most common symptoms include: Bloating, pelvic or abdominal pain, urinary symptoms such as urgency or frequency, and heaviness in abdomen.[2]

The initial assessment of patients with suspected ovarian cancer, following the initial history-taking, physical examination, laboratory results, Pelvic ultrasound, preferably using colour Doppler are done. [3]

The HER-2/Neu gene is amplified and/or over expressed in 25%-30% of human ovarian cancers and is associated with progression of invasive cancer, poor prognosis and resistance to chemotherapy. Immunohistochemistry is helpful in vast number of cases to resolve the diagnostic dilemma.[4]

Aims and objectives:

To study the clinicopathological parameters in ovarian tumours with special reference to age, histologic type and grade and evaluate the role of immune-histochemical profile of HER2/Neu in ovarian neoplasms and also correlate the results of immunohistochemistry with clinicopathological parameters.

Materials and methods:

The prospective study of 2 and ½ years was conducted on 100 surgically resected ovarian tumours samples from June 2017 to December 2019 received in the Department of Pathology, Jawahar Lal Nehru Medical College and Associated Groups of Hospital, Ajmer. Non-neoplastic lesions and metastatic lesions of ovary were excluded.

On receiving the specimens in 10% neutral buffered formalin, a systematic gross examination was performed. Gross features like size, shape, colour, external appearance on cut section and contents were noted.

The tumors were cut at various levels and adequate tissue slice (<5mm) submitted which were routinely processed 3 to 5micron sections were cut from paraffin embedded blocks. These sections were routinely stained with Harri's H & E stain and were examined for presence of ovarian tumour, Histological type, and grade.

For Immuno-histochemistry, the primary antibody used was Her2/Neu receptor along-with positive and negative controls.

The positive control for HER2/neu, fibroadenoma tissue section was taken.

The IHC staining was studied in correlation to clinicopathologic factors of ovarian tumours which include age, laterality, parity, histological type, tumour grade, tumour stage.

Results:

A total of 100 ovarian tumors were studied, out of which 72% are benign, 3% borderline and 25 % malignant.

Out of 100 studied ovarian tumors, 60% are epithelial tumors, 33% are germ cell tumors, and 7% are sex cord tumors. Out of epithelial tumors, 55% tumors are benign, 5% are borderline and 40% are malignant. Out of germ cell tumors, 96% are benign and 4% are malignant. Out of sex cord tumors, 100% are benign tumors.

Serous tumors are most common among all epithelial tumors (61%). Out of total 37 serous tumors, 49% are benign. Serous adenocarcinomas are the most common malignant tumor accounting for 32% of all epithelial tumors and 51% of serous tumors. Out of total 21 mucinous tumors, 72% are benign, 14% are borderline and 14% are malignant. One case of endometrioid tumor and poorly differentiated tumor is present.

Majority (96%) of germ cell tumors are mature cystic teratoma, 4% are dysgerminoma but yolk sac tumors and malignant mixed germ cell tumors are not found.

Among sex cord stromal tumors, most common tumor is fibroma (72%) followed by granulosa cell tumor (14%) and stromal Leydig cell tumor (14%). None of the case of granulosa theca cell tumor is found.

Out of total positive HER2 receptors (20), 100% was positive in malignant cases whereas benign and borderline cases are negative for HER2/neu.

HER2/NEU positivity is seen in 90% of serous tumors and 10% of mucinous tumors (table 1).

Table 1: Status of Her2/neu in ovarian tumors

	HER2/NEU	
	No.	%
Serous (37)	18	90
Mucinous (21)	2	10
Endometrioid (1)	0	0.00
Brenner (0)	0	0.00
SCST (7)	0	0.00
MCT (32)	0	0.00
Total	20	100

Epithelial tumors and Sex cord tumors were significantly more in >40 years of age groups (70% and 57.14% respectively) as compared to Germ cell tumors which was significantly more (87.88%) in <40 years of age groups.

Majority (85%) of positive HER2/neu receptors was observed in Age groups of >40 years (table 2).

Table 2: Status of Her2/neu According to Age

	HER2/NEU	
Age group	No.	%
<40 yrs	3	15
>40 yrs	17	85
Total	20	100

Although the unilateral tumors were more in Epithelial tumors (60%) and Germ cell tumors (72.73%) as compared to Sex cord tumors (42.86%).Epithelial tumors (81.67%) and sex cord tumor (71.43%) was statistically more significant in multipara as compared to Germ cell tumors (24.24%), whereas Germ cell tumors are common in nullipara women.

Bilateral Positivity of the HER2/NEU receptors was observed in 85%.HER2/NEU receptors showing positivity of Multipara were 100%.Out of total malignant surface epithelial tumors, serous tumors were 36.84% as grade 2, while 63.16 % as grade 3. Malignant mucinous and endometrioid tumor were 100% as grade 3.

HER2/neu positivity seen in higher grade tumors as 70% (in grade 3 tumors).Out of total malignant surface epithelial tumors, serous tumors were 36.84% as stage 2, while 63.16 % as stage 3 (table 3). Malignant mucinous and endometrioid tumor were 100% as stage 3. HER2/neu positivity seen in 70% of higher stage tumors.

Table 3: Distribution of Malignant Epithelial Tumors According to Grade of Tumor

Malignant Epithelial Tumors (n= 24)		Grade of Tumor							
		I		II		I		II	
		no	%	No	%	no	%	No	%
1	Serous tumors	0	0	7	36.84	12	63.16	19	100
		0		0		5			
2	Mucinous tumors	0	0	0	0	3	100	3	100
		0		7		14			
3	Endometrioid tumors	0	0	0	0	1	100	1	100
		0		7		16			
	Total	0	0	7	29.17	17	70.83	24	100

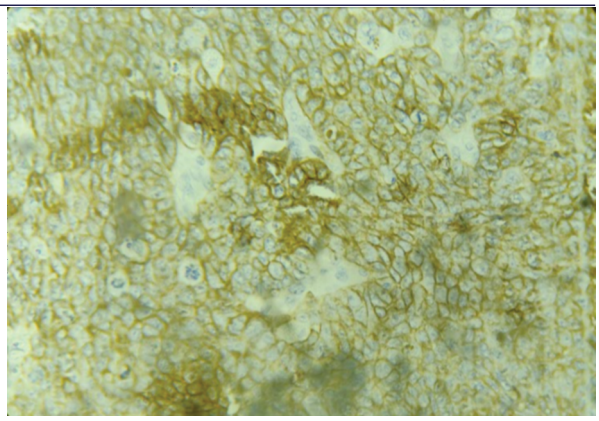

Figure 1: Photomicrograph of malignant serous tumour showing strong Her2 positivity with IHC score 3 (200x)

DISCUSSION

In our study, 72 cases are benign, 03 cases are borderline and 25 cases are malignant. Among the various neoplasms studied, 60% are of surface epithelial neoplasms, followed by germ cell tumors accounting for 33% of all tumors, sex cord stromal tumors accounting 7% of all tumors.

Our results are comparable with results of study done by Bhagya Lakshmi et al (2016)[5] on 42 ovarian tumors, where surface epithelial tumors constituted around 59.5% of all tumors. Similarly, Lubna khan et al (2014)[6] studied 80 operated cases of ovarian tumors and found that benign lesions were more common (75%) the malignant lesions (25%).

In our study serous cyst adenocarcinoma was the most common malignant tumor among all epithelial tumors accounting for 32% of all epithelial tumors and 51% of all serous tumors. Bhagya Lakshmi Atla (2016)[5] and Krigman et al (1994)[7] gave similar results with incidence of 59% and 36% among all epithelial tumors respectively. Serous cystadenoma was the commonest benign tumor (45%). Overall surface epithelial carcinomas were responsible for 52 % and 70 % of all malignant lesions among which serous cyst adenocarcinoma was the most common (45%).[5]

In our study, out of total positive HER2 receptors (20), 100% was positive in malignant cases. This is parallel to study done by Sylvia *etal*.[9]

In our study, HER2/NEU positivity was seen in 90% of serous tumors and 10% of mucinous tumors. Rest brenner, sex cord stromal tumors and mature cystic teratomas did not show any Her2/neu positivity.

MT Sylvia et al (63.6%)[10] reported that Her2/neu was weakly positive/ equivocal in only 3 cases accounting for 7.14% which includes one case each of serous cystadenocarcinoma, mucinous cystadenocarcinoma and clear cell carcinoma . Thus, Her2 expression was seen only in surface epithelial carcinomas.

In our study, Majority of positive receptors was observed in Age groups of >40 years as her2/neu positive 85%. According to Bhayga Lakhsmi Atla et al (2016)[5], Her2/neu had showed positivity in two of the three cases were above 40 years of age.

Bilateral Positively of the receptors was observed in majority of cases. HER2/NEU receptors of Multi para were 100%. Our study is comparable with BhaygaLakhsmi Atla et al (2016)[5] and MT Sylvia et al (2012).[10]

In our study, we observed that HER2/neu positivity seen in higher grade tumors as 70% in grade 3. Majority of HER2/neu positivity seen in higher stage tumors as 70% in stage 3. Our study is comparable with Bhayga Lakhsmi Atla et al (2016)[5] and MT Sylvia et al (2012)[10] showing similar results. As per BhaygaLakhsmi Atla et al (2016)[5] majority of the ovarian carcinomas were of grade 2 and stage 3.

Hellstrom et al (2014)[12] Her-2-neu was negative in all grade 1 tumors and all benign cases, higher in grade 2 and 3 tumors in concordance to previous studies. Most of these tumors had higher association with

ascites suggesting an aggressive tumor type and advanced stages which is similar to the study by Hellstrom et al.[12]Malignant tumors, serous group, and grade 3 tumors had significant higher proliferation index similar to previous results.

CONCLUSION-

Prognosis and management of ovarian cancer are influenced by classic variables such as histologic type and grade, parity, status of hormone receptors HER 2/neu status.

In conclusion, HER2/neu status correlates well with histopathological grading and other clinic-pathological parameters. Hence, immunohistochemical assessment of HER2/neu status along with histopathological grading and staging will guide the clinicians to make correct choice of treatment protocols.

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