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Histopathology

IMMUNOHISTOCHEMICAL STUDY OF HER2/ neu EXPRESSION IN OVARIAN EPITHELIAL CARCINOMAS

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ABSTRACT **Introduction:** Human epidermal growth factor receptor 2 (HER2/neu) plays an important role in tumour cell proliferation and metastasis. Among the protooncogenes, Her-2/neu has been reported to be over expressed in approximately 15–30% of ovarian tumors.Although normal ovarian epithelium may express HER2/neu, it is overexpressed in approximately one third of patients of ovarian cancer. Recently various studies on the prognostic significance of Her-2 neu overexpression in epithelial ovarian cancer suggest chemotherapy resistance , poor prognosis and decreased survival benefit.The measurement of serum Her2 is also used in predicting response to Herceptin therapy. **Materials And Methods:** The cross sectional study was conducted in the department of pathology, siddhartha medical college , Vijayawada over a period of 24 months from July 2018- June 2020 . sample size includes 36 histopathologically diagnosed malignant cases .The immunohistochemical analysis assessed the expression pattern of the Her2/neu protein in these tumors. **Results:** Serous carcinoma constitutes 55.6%, mucinous 39%, endometrioid 3.8% and mixed tumors constitute 2.6%of all malignant surface epithelial ovarian tumors. Total 36 cases of surface epithelial tumors were subjected to immunohistochemical analysis with Her2neu. Among the histological subtypes22.2% of serous type showed positivity and 11.1% of mucinous carcinoma,5.5% of endometrioid tumors and 2.7%of mixed tumors were Her2 neu positive.

Conclusion:

- Her2neu expression was only 41 % in contrast to several other studies and histological types have significant association with decreased survival of the patient's expression was observed to increase in the advanced stages of cancer.
- A higher proportion of serous compared to mucinous carcinomas was also observed to be HER2/*neu* positive.

KEYWORDS : HER2 / neu , Immunohistochemical , Ovarian epithelial carcinomas.

INTRODUCTION:

Epithelial ovarian cancer (EOC) is considered the second most common malignancy in women[1]. Early detection of cases and the provision of early treatment of cases may go a long way to reduce the prevalence of Ovarian cancer cases in India[2].The relatively poor prognosis of ovarian cancer is due to the lack of detection at an early stage and the limited application of effective therapies for advanced-stage disease[3]. Among the protooncogenes, Her-2/neu has been reported to be overexpressed in approximately 15–30% of ovarian tumors.

This glycoprotein is thought to regulate cell proliferation either through its binding to an unknown ligand that acts as a growth factor or, more likely, through its capability to induce the phosphorylation of the tyrosine kinase portion of its intracellular domain and the other EGF receptor family members which it binds to form heterodimers[4]. The Her-2/neuprotooncogene, located on chromosome 17q21 gene, also known as c-erb-B2,is a component of a family of growth factor receptors that includes epidermal growth factor[5]. It plays a role in cell differentiation and proliferation (EGFR,Her-2/neu overexpression has also been demonstrated in many different human neoplasms, including breast,lung, gastrointestinal, prostate, kidney, liver, and bladder cancer).[6] In normal tissues, HER2/neu expression has been demonstrated predominantly in epithelial cells, however the physiological function of HER2/neu like that of peptide growth factor receptors. However, in human malignancies, HER2/neuamplification & overexpression rather than point mutation has been noted[7].Trastuzumab is a humanized monoclonal antibody that targets the HER2extracellular domain and thereby inhibits the proliferation of Her2neu positive tumor cells. The measurement of serum Her2 is also used in predicting response to Herceptin therapy[8]. Ovarian carcinoma exhibits a wide range of morphological phenotypes. Since more than 90% of ovarian cancers are of epithelial cell origin, various genetic alterations occur during the malignant transformation of ovarian epithelial cells. HER2/neu overexpression in breast and ovarian cancer is closely related to the aggressive behaviour of this subset of cancers. Recently various studies on the prognostic significance of Her-2 neu overexpression in epithelial ovarian cancer suggest poor prognosis and decreased survival benefit.This study is undertaken given evaluating the incidence, age, clinical features, histopathological and Her2 expression in ovarian epithelial tumors.

Materials And Methods :

- The cross sectional study was conducted in the department of pathology at Siddhartha medical college over a period of 24 months From July 2018- June 2020.
- Ethical approval was obtained from institutional ethics committee.

Inclusion Criteria:

1. Cases diagnosed as epithelial ovarian carcinoma among specimens received in the Department of Pathology, SMC, Vijayawada between July 2018 and June 2020.
2. All age groups are included in this study

Exclusion Criteria:

1.All non-neoplastic lesions of the ovary
2.Benign& Borderline tumors of the ovary
3.Non epithelial malignancies (sex cord-stromal tumors& germ cell tumors) of the ovary.
4. Recurrent & metastatic malignancies of the ovary.

Immunohistological Evaluation And Quantification:

Samples scored as 0/+1 were considered to be negative for HER2/neu expression,2+ weakly positive, and +3 strongly positive.

Table 1: HER 2 NEU Scoring Based On Scoring System

Score report	HER2 protein assessment	Staining pattern
0	Negative	No staining is seen / membrane staining ≤10% of invasive tumor cells
1+	Negative	Faint / barely perceptive membrane staining detected in >10% of invasive tumor cells
2+	Equivocal	Weak to moderate complete membrane staining in ≥ 10% of invasive tumor cells or ≤ 30% with strong complete membrane staining
3+	Positive	Strong complete membrane staining in ≥ 30% of invasive tumor cells

RESULTS:

In the study period of 2 years from 2018 to 2020, a total of 92ovarian specimens were received in the Institute of Pathology, GGH of Obstetrics& gynecology for histological examination. Of these surface epithelial ovarian cancer accounted for 84 cases with a percentage of 91.3. The total number of benign, borderline, malignant cases was 42,6, and 36 respectively. Thus, the distribution of benign tumors was 50%, border line tumors 7.1 % and malignant tumors were 42 % among the surface epithelial ovarian cancer specimens. Serous carcinoma constitutes 55.6%, mucinous 39% endometrioid 3.8% and mixed tumors constitute 2.6%of all malignant surface epithelial ovarian tumors.

Fig 1: Mucinous carcinoma (A,B,C&D)

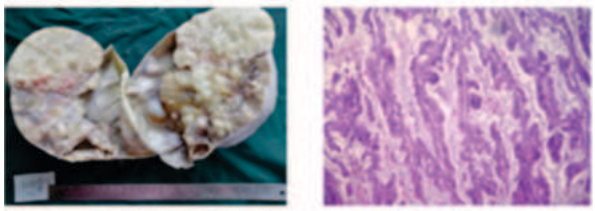


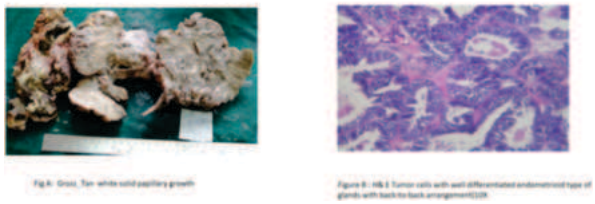
Fig A: GrossFleshy white solid and cystic mucinous area

FigB: H& E Confluent growth of complex interconnecting papillae(10X)

Fig C: Alcian blue staining of Mucinous carcinoma

Fig D : IHC. Strong cytoplasmic membrane staining for Her 2 neu

Fig 2: Endometrioid carcinoma (A,B)



Ovarian cancers had a peak incidence in the age group of 41-50 years. The Youngest age of presentation of ovarian cancer was 21 years in this study, with a mean age of 47 yrs.

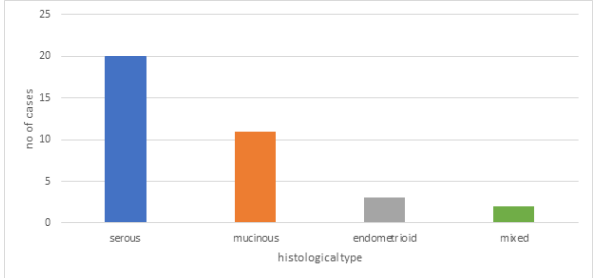


Chart 1: Distribution Of Histological Subtypes Of Ovarian Tumors

Among the 36cases, 11cases (30.5) were reported in the age of 41-50yrs and 18 cases (50 %) were reported in the age of 51-60 yrs. Only 5.5% of the cases presented in the 2nd to 3rd decades of life.

Ovarian tumor distribution according to their histological subtypes was showing Table-2. 55.5% of serous carcinoma, 33.6%of mucinous, 5.5% Endometrioid and 5.5 of mixed type tumor was observed.

Results Of Immunohistochemical Studies

Of the total, 36 cases were subjected to immunohistochemical analysis with Her2neu. The age of the patients ranged between 31 and 70 with a mean of 48.2 yrs. There were 2 cases (5.5%) below 40 years of age and 34 cases (94.5%) for more than 40 years. 16 cases (44.4%) were located in the left ovary, 18 cases (50%) in the right ovary, and 2 cases (5.5%) were bilateral tumors. Grossly, 24 cases (66.6%) showed both solid and cystic areas, 2 cases (5.5%) showed solid with papillary excrescences, 2 cases (5.5%) purely solid, 3 cases (8.3%) with solid ,cystic with papillary excrescences, and 5 cases (13.8%) presented as a multiloculated cyst. The tumor ranged in size from 10 cm to 20 cm with the median size of 12.5cm. There were 20 cases (55.5%) with tumor size less than 10cm, 12 cases (33.3%) with tumor size between 10 to 20cm and 4 cases(11.1%) were in size more than 20cm. Histologically, 20 cases (55.5%) belonged to serous type, 3 cases (5.5%) belonged to endometrioid, 11 cases (33.6%) were mucinous, and 2 cases (5.5%) belonged to mixed type. 17 cases(47.2%) were well-differentiated carcinomas, 11 cases (30.5%) showed moderate differentiation and 8cases (22.2%) were poorly differentiated carcinomas. 20 cases (55.6%) belonged to advanced stage; 16 cases (44.4%) were in early stage. In this study group, 26 cases (72.2%) had ascites and 10 cases (27.7%) did not have ascites. Omental involvement was seen in 13 cases (36.2%) and it was absent in 23 cases(63.8%)

DISCUSSION:

In this study, the age of epithelial ovarian cancer patients ranged from 31 to 70 years with the mean age of 47 years. The highest incidence of epithelial ovarian carcinoma (42%) occurred in the 5th to 6 th decade and it constitutes only 5% in 7 th decade. This is in concordance with the study done by Murthy NS et al[9] who observed incidence in the peak age of 55-64yrs and another study done by J K Chan, et al[10] who reported it as a disease of post-menopausal age.

Comparision Of Distribution Of Tumors With Subtypes

According to literature, Serous carcinomas constitute 55.5%, mucinous 33.6%, endometrioid 5.5% of all ovarian tumors. It showed concordance to a study done by Marcela F Paes, et al [11]who showed 30% of serous carcinomas, 13% of mucinous and endometrioid carcinoma**.**

Comparision Of Distribution With Gross Morphology

In this study, among the serous carcinomas, 87.5% presented as a solid papillary pattern, only 85.7 % of cases presented as solid cystic with papillary, 50% cases are solid & cystic. 75% of mucinous carcinoma is presented as multiloculated cysts compared to other types. 66.7 % of endometrioid type showed purely solid areas predominantly, 25% of cases were solid with cystic areas predominantly. This is by the findings observed by Kurman et al. [12]

Comparision Of Ovarian Cancer Grade Distribution

In this study, grade 1 carcinomas were more common than the other grades of distribution. 47.2% of the tumors showed well differentiation. This is in contrast to the study conducted by Marcela F Paes et al[48] who noticed the prevalence of grade II differentiation. The present study also showed an increased number of serous carcinoma with grade II differentiation, mucinous carcinomas with grade I[11].

Neilsen JS et al[8], studied both uni and multivariate analyses on 4cases of epithelial cancer in Denmark and reported statistical significance between Her2neu positivity and prognostic factors such as older age, advanced FIGO stage, and poorer differentiated grade

In this study15 cases of epithelial ovarian carcinoma showed statistical significance between Her2neu positivity and prognostic factors such as advanced FIGO stage, and poorer differentiated grade.

Correlation Of Her 2 NEU Expression With Other Known Clinicopathological Prognostic Factors

Nisha Marwah[13](2007), conducted a study on 75 cases of ovarian carcinomas. He observed that Her2 neu expression was significantly

associated with high grade epithelial ovarian carcinomas, but the intensity of positivity does not correlate with tumor grade.

This study was conducted on 36 cases of epithelial ovarian carcinomas and observed that HER2 neu expression was significantly associated with high-grade epithelial ovarian carcinomas but the intensity of positivity correlates with tumor grade. Ajani et al [14]The positive expression rate of HER2/*neu* in this study was 16.6%. This is comparable to the rate of HER2/*neu* positivity in EOC, which ranges from 7–50%.A higher proportion of serous (41%) than mucinous (21%) carcinomas was observed to be HER2/*neu* positive in our series. Furthermore, in this study, 21%, 36%, and 42% of HER2/*neu*-positive tumors were grades 1, 2, and 3, respectively. There appears to be increasing HER2/*neu* positivity with higher grades of ovarian carcinoma. HER2/*neu* expression wasobserved to increase in the advanced stages of cancer. A higher proportion of serous compared to mucinous carcinomas was also observed to be HER2/*neu* positive.

In the present study expression rate of HER2/*neu* in this study was 41%. A higher proportion of serous (22%) than mucinous (11%) carcinomas was observed to be HER2/*neu* positive in our series. Furthermore, in this study, 5.5%, 8.3%, and 22% of HER2/*neu*-positive tumors were grades 1, 2, and 3, respectively. HER2/*neu* expression was observed to increase in the advanced stages of cancer. A higher proportion of serous compared to mucinous carcinomas was also observed to be HER2/*neu* positive.

In the present study conducted on 36 malignant ovarian tumors and demonstrated that serous adenocarcinomas showed statistically significant association with HER2 neu among all malignant ovarian tumors with positivity in 22% tumors. There is no direct association of Her2neu positivity with older age, ascitis. There is a direct association of Her2neu expression with advanced stage, high grade, site, size, gross morphology, and histological types.

A study done by MC marinas et al [74]2012 studied 26 serous tumors found that HER2 /neu expression has significant association with serous adenocarcinomas with more intense positivity in high-grade serous adenocarcinomas as compared to low-grade serous adenocarcinomas.

CONCLUSION:

- In this study, the incidence of surface epithelial ovarian carcinoma was higher among all ovarian cancers.
- Most of our patients presented in the perimenopausal age group with a peak incidence in 5 th to 6 th decades of life.
- The most common histological type was serous carcinoma.
- Her2neu expression was only 41 % in contrast to several other studies.
- There was a statistically significant correlation between Her2neu expression and clinico pathological parameters were observed and histological types have significant association with decreased survival of the patient's expression was observed to increase in the advanced stages of cancer.
- A higher proportion of serous compared to mucinous carcinomas was also observed to be HER2/*neu* positive.
- In this study, Her2neu expression appear to have any prognostic value. Hence it needs to consider them as a prognostic marker.

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