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Original Research Article

Histopathological study of epithelial ovarian tumors with special reference to human epidermal growth factor receptor-2/NEU and CA-125 expression

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ABSTRACT

Background: Ovarian cancer is the second most common gynecologic malignancy. The aim of the study was to evaluate the tissue expression of HER-2/NEU and CA-125 in various epithelial ovarian carcinoma and assess the prognostic significance.
Methods: A retrospective study was done in 76 cases of ovarian tumor. IHC was done in 16 cases of epithelial ovarian cancer with HER-2/NEU and CA-125.
Results: Total number of cases were 76. Out of these 76 cases, 22 cases were malignant. 16 cases were malignant epithelial ovarian cancer. The highest incidence of malignant tumor was seen in the 41-50 years age group with 9 cases (11.84%). Out of 11 serous adenocarcinoma, 9 cases (81.8%) showed tissue expression of CA-125 and rest 2 cases (18.18%) did not show expression. All the 5 cases (100%) of mucinous adenocarcinoma did not show any tissue expression of CA-125. HER-2/NEU expression was positive in 7 out of 16 cases that is 43.75% and negative expression was seen in 9 out of 16 cases that is 56.25% of cases. Maximum HER-2/NEU positivity is seen among grade 3 tumors, that is (62.5%) (5 out of 8 cases).
Conclusions: The incidence of epithelial ovarian tumors are more common. The tissue expression of CA-125 on malignant epithelial ovarian tumors was studied, which showed positive expression in serous cystadenocarcinomas, but not in mucinous cystadenocarcinoma. HER-2/NEU expression was seen to be increasing with advanced grade of the tumors.

Keywords: Epithelial ovarian cancer, HER-2/NEU, CA-125

INTRODUCTION

Ovarian cancer is the second most common gynecologic malignancy and the major cause of gynecologic cancer death.[1] In most of the population based cancer registries across India, ovary is the third leading site of cancer among women, trailing behind cervix and breast.[2] According to WHO histological classification based on the most probable tissue of origin, ovarian tumors are broadly classified under- (a) surface epithelial-stromal tumors; (b) sex cord-stromal tumors; (c) germ cell tumors; and (d) metastatic cancer from non-ovarian primary.[3] Epithelial ovarian cancer accounts for about 80-90% of all ovarian malignancy and about 60% of all ovarian tumors. Traditionally the five main subtypes of epithelial ovarian cancer are serous, mucinous, endometrioid, clear cell and transitional cell (Brenner type) tumors.[4] HER-2 (human epidermal growth factor receptor-2) protooncogene encodes a transmembrane glycoprotein belonging to EGFR tyrosine kinase receptor family. Over-expression of HER-2 initiates intracellular signalling pathways involved in cell proliferation, differentiation, migration and apoptosis.[5]

CA-125 (MUC 16) is a high molecular weight, membrane associated mucin, which is aberrantly expressed in advanced serous epithelial ovarian carcinoma.[6] CA-125 is the gold standard tumor marker in ovarian cancer. Serum level of CA-125 is used to monitor response to chemotherapy, relapse and disease progression in ovarian cancer patients.[7]

The aim of the study was to evaluate the tissue expression of HER-2/NEU and CA-125 in various epithelial ovarian carcinoma and assess the prognostic significance.

METHODS

The study was done for a period of one year from December 2018 to November 2019. This was a retrospective study done in the department of pathology, Silchar Medical College and Hospital. Ethical approval was taken from the ethical committee of Silchar Medical College and Hospital and it was approved in terms of scientific researches and patient ethics. 76 cases of ovarian tumor specimens were included in the study.

Inclusion criteria

All patients irrespective of age with ovarian masses were included in the study.

Exclusion criteria

Non-neoplastic mass was excluded from the study.

Samples were collected using stratified random sampling technique. All the data were analyzed using Microsoft excel 2013 and figures were inserted using Microsoft word 2013.

After fixation with 10% neutral buffered formaldehyde, the specimen was grossed using standard protocol. The sections were paraffin embedded and stained with hematoxylin and eosin (H and E). IHC study was done in malignant tumors of epithelial origin. Appropriate sections were prepared on poly-L-lysine coated slides for IHC using CA-125 and HER-2/NEU following standard protocol. The CA-125 stains the cell membrane. A positive HER-2/NEU IHC reaction was considered in the presence of brown membrane staining.

RESULTS

In this study, a total number of 76 ovarian tumor specimens were obtained, out of which 52 (68.42%) were benign, 2 (2.63%) were borderline and 22 (28.94%) were malignant (Table 1).

The tumors were categorized according to different age groups as shown in Table-2. The highest incidence of malignant tumors was seen in the 41-50 years age group with 9 cases (11.84%) (Table 2).

Table 1: Number of cases.

Groups	No. of cases	Percentage (%)
Benign	52	68.42
Borderline	2	2.63
Malignant	22	28.94

Table 2: Age group.

Age group (years)	Benign	Borderline	Malignant
0-10	0	0	1
11-20	6	0	0
21-30	14	0	1
31-40	20	0	4
41-50	10	2	9
51-60	2	0	7

In this study, 45 cases (59.21%) were epithelial tumors, 25 cases (32.89%) were germ cell tumor, 5 cases (6.57%) were sex cord stromal tumors and 1 case (1.31%) was metastatic tumor. In this study, among the benign tumors, mature cystic teratoma was the commonest, accounting for 22 cases (28.94%) followed by serous cystadenoma, accounting for 18 cases (23.68%) and mucinous cystadenoma, accounting for 8 cases (10.52%). In the malignant group, serous cystadenocarcinoma accounted for 11 cases (14.47%) of which the papillary variety was the commonest (Table 3). In the benign epithelial tumor group, serous cystadenoma accounted for 18 cases (23.68%) was the commonest. In the malignant group, papillary serous adenocarcinoma was the commonest, 7 cases (9.21%).

Table 3: Frequency of different histological types of ovarian tumors.

Histological types	No. of cases	Percentage (%)
Benign		
Serous cystadenoma	18	23.68
Mucinous cystadenoma	8	10.52
Mature cystic teratoma	22	28.94
Fibroma	3	3.94
Benign brenner	1	1.31
Borderline		
Brenner borderline	1	1.31
Serous borderline	1	1.31
Malignant		
Papillary serous adenocarcinoma	7	9.21
Serous cystadenocarcinoma	4	5.26
Mucinous cystadenocarcinoma	5	6.57
Granulosa cell tumor	2	2.63
Dysgerminoma	1	1.31
Yolk sac tumor	2	2.63
Metastatic tumor (Krukenberg tumor)	1	1.31

There were total 16 malignant surface epithelial ovarian tumors, 11 serous adenocarcinoma and 5 mucinous adenocarcinoma. Out of 11 serous adenocarcinoma, 9 cases (81.8%) showed tissue expression of CA-125 and rest 2 cases (18.18%) did not show expression. All the 5 cases (100%) of mucinous adenocarcinoma did not show any tissue expression of CA-125 (Table 4).

Table 4: Type of tumor.

Type of tumor	No. of cases	CA-125 (+)	CA-125 (-)
Serous adenocarcinoma	11	9	2
Mucinous adenocarcinoma	5	0	5
Total	16	9	7

Expression of HER-2/NEU with histopathologic type and grade was studied. HER-2/NEU expression was positive in 7 out of 16 cases that is 43.75% and negative expression was seen in 9 out of 16 cases that is 56.25% of cases (Table 5-6).

Table 5: HER-2/NEU status.

HER-2/NEU status	No. of cases	Percentage (%)
Negative	9	56.25
Positive	7	43.75
Total	16	100

Table 6: Histological type.

Histological type	HER-2/NEU (+)	HER-2/NEU (-)
Serous adenocarcinoma	5	6
Mucinous adenocarcinoma	2	3

From Table 7, it is seen that out of 16 cases, 3 cases (18.75%) were grade 1, 5 cases (31.25%) were grade 2 and 8 cases (50%) were grade 3. Maximum HER-2/NEU positivity is seen among grade 3 tumors, that is 62.5% (5 out of 8 cases) (Table 7). HER-2/NEU expression was found to be increasing with increase of grade.

Table 7: Distribution of tumors according to Universal grading system of ovarian cancer was done.

Grade	No. of cases	Percentage (%)	Negative	Positive
1	3	18.75	2	1
2	5	31.25	4	1
3	8	50	3	5
Total	16	100	9	7

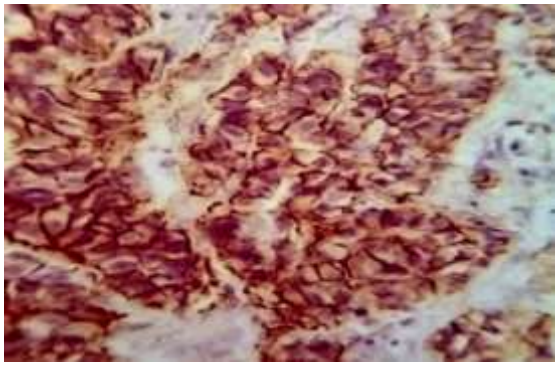

Figure 1: HER-2/NEU positivity seen in serous cystadenocarcinoma in 40X under microscope.

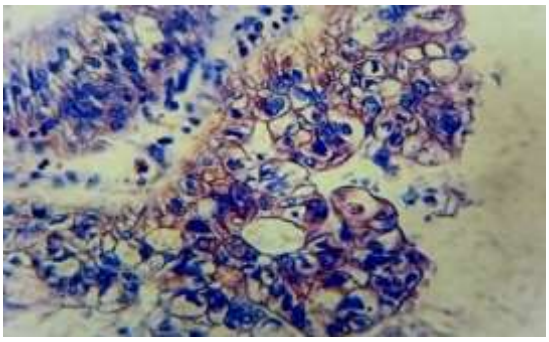

Figure 2: HER-2/NEU positivity seen in mucinous cystadenocarcinoma in 40X under microscope.

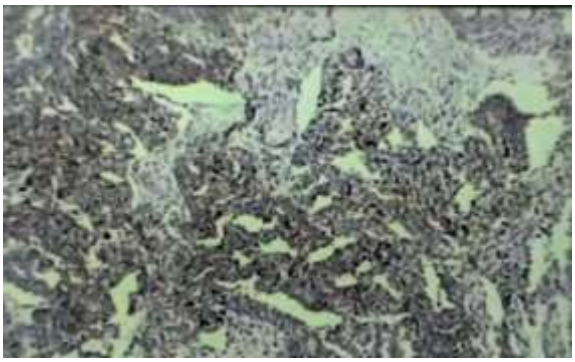

Figure 3: CA-125 positivity seen in serous cystadenocarcinoma in 10X under microscope.

DISCUSSION

The study was carried out in total of 76 patients admitted in Silchar Medical College and Hospital, Silchar who underwent suspected ovarian tumor removal during the period of December 2018 to November 2019. Out of the 76 ovarian tumors, 52 (68.42%) were benign, 22 (28.94%) were malignant and 2 (2.63%) were borderline. Francisco et al (1993) reported 80.7% benign, 16.9% malignant and 2.3% borderline.[8] Rajan (1994) reported 94% tumors as benign and rest as malignant including tumors of borderline malignancy.[9]

The highest incidence of malignant tumor was seen in the 41-50 years age group with 9 cases (11.84%). Gupta et al (1986), Prabhakar et al (1989) and Sarkar (1996) reported the maximum incidence were in third and fourth decades of life which tallies with the observation of our study.[10]

All these 76 tumors were examined histologically and classified into the following broad groups: common epithelial tumor (59.21%), germ cell (32.89%), sex cord (6.57%) and metastatic (1.31%). claude gompel and silverberg (1985) held that epithelial tumor of ovary to be 60% and while sarkar (1996) reported 66.8%.[11,10]

In the present study, an attempt was made to evaluate the immunohistochemical role of CA-125 in detecting malignant epithelial ovarian tumor. 16 cases of malignant epithelial ovarian tumor had 11 serous adenocarcinoma and 5 mucinous adenocarcinoma. Fukazawa et al in their study found that CA-125 was not expressed in ovarian mucinous cystadenocarcinoma but was demonstrated immunohistochemically in 82% of ovarian serous cystadenocarcinomas.[12] Similarly, Neunteufel et al had all mucinous tumors to be CA-125 negative.[13] So, in our study, out of total 11 serous adenocarcinoma, CA-125 was expressed in 9 cases (81.8%) and no expression in mucinous adenocarcinoma.

In our study, HER-2/NEU positive expression was found in 7 out of 16 cases (43.75%) and negative in 9 out of 16 cases (56.25%). Ajani et al study reported 41.3% serous carcinoma were HER-2/NEU positive.[14] Marinas et al had 55.5% HER-2/NEU serous adenocarcinoma positive.[15] In our study, this was 45.45%.

Goel et al had HER-2/NEU positivity of mucinous adenocarcinoma in 66.7%.[5] While Vrabie et al had HER-2/NEU positivity of mucinous adenocarcinoma in 41.66% of cases.[16] In our study this was 40%.

Studies by Ajani et al and Mahdi et al showed HER-2/NEU positivity increased with higher grades of ovarian epithelial carcinoma.[14,17] The above studies are in concordance with the findings of present study.

Limitations

This study had some limitations as the study period was only for one-year duration, long term follow-up of patients was not possible and thus the prognosis of most patients were not known.

CONCLUSION

A tentative conclusion can be drawn from the present study that benign ovarian tumors are more common than the malignant counterpart. Moreover, the incidence of epithelial tumors are more common. The tissue expression of CA-125 on malignant epithelial ovarian tumors was studied, which showed positive expression in serous cystadenocarcinomas, but not in mucinous cystadenocarcinoma.

HER-2/NEU expression was seen to be increasing with advanced grade of the tumors.

As the study period was only for one-year duration, long term follow-up of patients were not possible and thus the prognosis of most patients were not known. However, long term follow-up of these patients are needed with proper management and early detection of recurrences especially by the use of CA-125 in cases of malignant tumors of epithelial origin.

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