

Histopathological analysis of ovarian tumours and overexpression of HER2/neu in ovarian carcinomas

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Abstract

Introduction: Ovarian carcinoma is a serious disease prevailing in women and is the fifth most common malignancy. It is the second most common gynecologic malignancy, and the fifth leading cause of cancer death in women in developed countries. The absence of any specific symptoms, the location of the ovaries which are deeply seated and are relatively inaccessible and without any specific markers, ovarian carcinoma is difficult to detect early. HER2 (human epidermal growth factor receptor-2) proto-oncogene encodes protein belonging to epidermal growth factor receptor (EGFR) tyrosine kinase receptor family.

Aims and Objectives: 1) Clinicopathological analysis of ovarian tumours 2) To study the overexpression of HER2/neu in ovarian carcinoma

Materials and Methods: This was a retrospective and prospective study carried out in the Department of Pathology, Dr D.Y. Patil Medical College, Pune. A total of 134 ovarian tumours were received for histopathological examination. The sections of all the tumours were stained by hematoxylin and eosin stain. The malignant tumours were also stained using HER2/neu antibody following the immunohistochemical (IHC) procedure.

Observation and Results: Of the total 134 ovarian tumours, 103 (77%) were benign tumours and 31 (23%) were malignant tumours. The most common type of ovarian tumours was Surface epithelial stromal tumours (71.7). Overexpression of HER2/neu was seen in 6.4% of malignant tumours.

Conclusion: Histopathological study is important in diagnosis of ovarian tumours and predicts their prognosis. HER2/neu can be a good prognostic marker with scope for targeted therapy, requiring further evaluation in a larger sample size.

Introduction

Ovary is the commonest site of neoplastic and non-neoplastic lesions which present in childhood to postmenopausal age group and account for the most common cause of hospital admissions. Ovarian tumors account for about 30% of female genital tract tumour lesions. These ovarian tumours arise from surface epithelium, sex cord stroma and germ cells. Within each category there are several histological subtypes.¹ Knowledge of morphology and age specific characteristics can help refine the diagnosis. Indirectly it can also suggest the prognosis and management of these tumors. Prognosis of the tumors can also be predicted from the degree of differentiation of the tumors. Also, the laterality of the tumors indicates their nature. The newer techniques in imaging and genetics have evolved. Despite this, the diagnosis of ovarian tumors primarily depends on histopathological examination. The complex nature, unpredictable behavior; prognosis and controversial management make ovarian neoplasms a difficult problem

for a gynaecologist. Hence a review of ovarian tumours is very important.¹

The second most common gynecologic malignancy is ovarian carcinoma which is also a common cause of gynecologic cancer death and it is the fifth leading cause of cancer death in women in developed countries.² In India, ovarian carcinoma is the third most common cancer after breast and cervical cancer. Every year, more than 22,000 women worldwide are diagnosed with epithelial ovarian cancer and 15,000 die of it.³

HER2 in Ovarian Cancer

20–30% patients with ovarian carcinoma show HER2 overexpression. Berchuck et al first established that HER2 overexpression is associated with poor survival in advanced stages of epithelial ovarian cancer. According to this study, patients who showed HER2 overexpression had significantly worse prognosis than patients who showed normal expression. In addition, patients who showed high

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HER2 expression were less likely to have a complete response to the primary therapy or have a negative laparotomy, when done second time with normal serum CA125 levels preoperatively. Although HER2 overexpression has been found to be associated with poorer prognosis, there is limited use of HER2 directed therapies.⁴ Currently there is very little reported data of HER2 protein expression in ovarian cancer tissue in India. Hence this study is conducted to evaluate HER2/neu status in our patients with ovarian carcinoma.

Materials and Methods

This study was carried out in the Department of Pathology, Dr D.Y Patil Medical College, Pune following approval from the institute ethics committee. A total of 134 cases received for histopathological examination during the period August 2014 to September 2018 were included in our study. Patients who had received prior radiation or chemotherapy were excluded.

The sections of tissue underwent routine processing and staining was done using hematoxylin and eosin stain. The 2016 WHO Classification was used to classify the ovarian tumours.⁵ Immunohistochemical staining was done using HER2/neu prediluted rabbit monoclonal antibody (BioGenex) on all malignant ovarian tumours. Scoring of HER2/neu expression was done on a scale of 0 to 3+⁶ where

0 = no membrane staining,

1+ = complete membrane staining in <10% of the expressing cells,

2+ = faint complete membrane staining in >10% of the expressing cells,

3+ = strong complete membrane staining in >10% of expressing cells.

Results

The present study deals with histopathological examination of ovarian tumors and evaluation of HER2/neu status in malignant ovarian tumours. During the duration of the study, a total 134 cases were studied out of which 103 (77%) were benign tumors and 31 (23%) malignant tumors.

Maximum number of cases (38 cases, 28.4%) were found in the age group 30-40 years followed by age group 20-30 years (29 cases, 21.6%) (Table 1). Abdominal pain was the commonest clinical presentation (88 cases, 66%) followed by lump in abdomen (46 cases, 34%).

Surface epithelial tumors were the commonest in our study (71.7%), followed by germ cell tumors (20.2%) and sex cord stromal tumors (4.5%) (Table 2). Among the malignant cases, tumors arising from surface epithelial layer were maximum (75.9%) in our study followed by germ cell tumor (17.2%) (Table 3). The commonest benign tumor was serous cystadenoma (48 cases, 46.8%) followed by mucinous cystadenoma (30 cases, 29.3%). Mature cystic teratoma was the most common Germ cell tumour. (13.6%)

After analysis of the morphological subtypes of malignant tumors in our study, mucinous cystadenocarcinoma (Figure1) was the most common (12 cases, 38.9%) followed by serous cystadenocarcinoma (5

cases, 16.3%) (Table 4). There were 3 cases (9.6%) of malignant Brenner tumor. Immature teratoma, transitional cell carcinoma, granulosa cell tumor (Figure2) and high-grade Non-Hodgkin Lymphoma (Fig. 3) comprised of 2 cases (6.4%) each.

The most common tumors in our study are of the surface epithelial-stromal subtype, of which 76% were benign and 24% malignant. The most common surface epithelial stromal tumors were serous in nature (52%) followed by mucinous tumors (36.5%). However, in regard to malignant surface epithelial neoplasms, the mucinous tumors (52.2%) outnumbered the serous tumors (21.7%). The other surface epithelial tumors noted in our study were Brenners tumor-benign and malignant, endometrioid tumor, transitional cell tumor and one malignant epithelial tumor.

In our study, out of 31 malignant ovarian tumours, 2(6%) cases of mucinous cystadenocarcinoma showed 2+ membranous positivity for HER2 (Figure 4) while others were negative (Table 5).

Table 1: Age wise distribution of ovarian tumours

Age group	Number of patients	Percentage (%)
13-15	2	1.5
15-20	9	6.7
20-30	29	21.6
30-40	38	28.4
40-50	27	20.2
50-60	16	12
>60	13	9.6
Total	134	100.0

Table 2: Frequency of various ovarian tumours by morphology

Type of tumor	Number of patients (n=134)	Percentage (%)
Surface Epithelial Stromal Tumours	96	71.7
Sex cord Stromal tumour	6	4.5
Germ cell tumour	27	20.2
Miscellaneous tumours	1	0.8
Tumour- like conditions	2	1.4
Lymphoid and hematopoietic tumours	2	1.4

Table 3: Different morphological subtypes of benign tumours of ovary

Type of tumour	No. of cases	Percentage
Serous cystadenoma	48	46.8
Mucinous cystadenoma	30	29.3
Mature cystic teratoma	14	13.6
Serous cystadenofibroma	2	1.9
Brenner Tumour	2	1.9
Fibroma	2	1.9
Mixed type cystadenoma	2	1.9
Benign sertoli cell tumour	1	0.9
Lutenized thecoma	1	0.9
Fibrothecoma	1	0.9
Total	103	100

Table 4: Different morphological subtypes of malignant tumours of ovary

Type of Tumour	No. of Cases	Percentage
Mucinous cystadenocarcinoma	12	38.9
Serous cystadenocarcinoma	5	16.3
Malignant Brenner tumour	3	9.6
Immature Teratoma	2	6.4
Transitional cell carcinoma	2	6.4
Granulosa cell tumour	2	6.4
High grade Non-Hodgkin lymphoma	2	6.4
Dysgerminoma	1	3.2
Tubulopapillary adenocarcinoma endometrioid type	1	3.2
Squamous cell carcinoma	1	3.2
Total	31	100

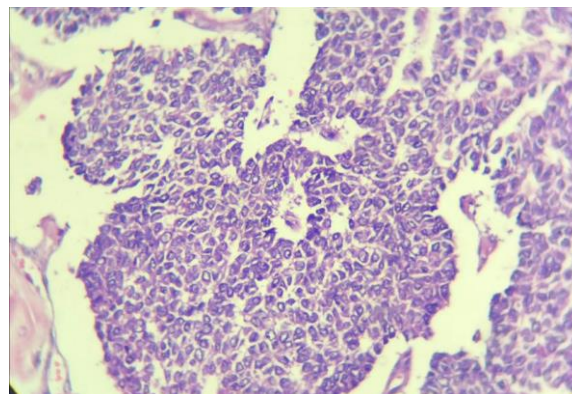


Fig. 2: Photomicrograph of Adult granulosa cell tumour showing nuclear grooves (H&E, x400).

Table 5: HER2 status in ovarian carcinoma

Cases	HER2 Status		Total
	Positive Cases	Negative Cases	
Frequency	2	29	31
Percentage	6.4	93.6	100

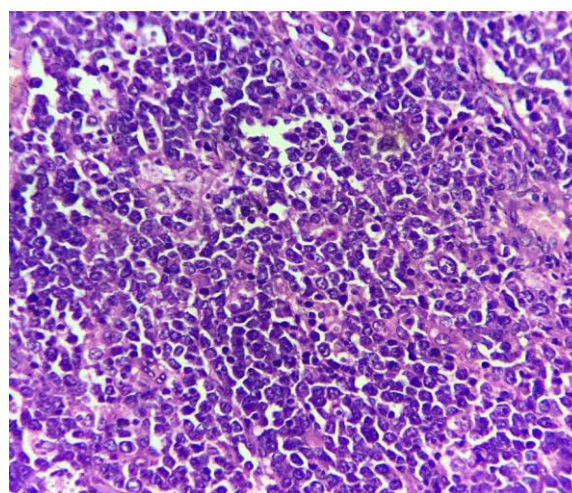


Fig. 3: Photomicrograph of ovarian non-hodgkin lymphoma shows diffuse sheets of small round cells with hyperchromatic nuclei (H&E, x400).

Table 6: Comparison with previous studies of HER2/neu protein overexpression in ovarian carcinoma

Group	Year	Total number of cases	HER2 Protein over expression%
Hogdall EV et al	2003	181	13.30%
Bookman MA et al	2003	837	11.40%
Camilleri-Broet et al	2004	95	15.80%
Lee CH et al	2005	102	4.90%
Mano MS et al	2004	72	8.30%
Tuefferd M et al	2007	320	12.80%
Steffensen KD et al	2008	99	14.10%
Vermeij J et al	2008	31	19.40%
McAlpine et al	2009	33	18.20%
Yan et al	2011	17	35.30%
Chay et al	2013	113	27.40%
Missaoui N et al	2014	14	14.30%
Verma N et al	2018	22	62.80%
Present study (2018)	2018	31	6%

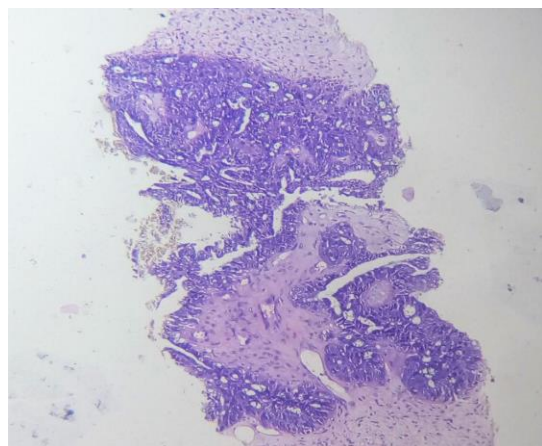


Fig. 1: Photomicrograph of Mucinous cystadenocarcinoma showing mucinous lining epithelium (H&E, x100).

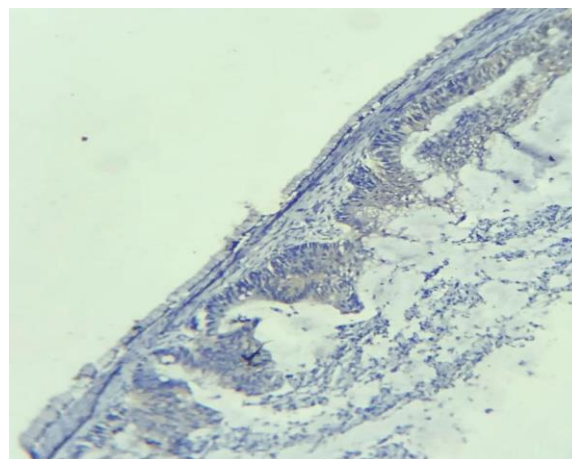


Fig. 4: Photomicrograph showing Mucinous cystadenocarcinoma HER2/neu IHC stain membranous 2+ positivity of many cells (IHC, x100).

Discussion

The study comprising of 134 ovarian tumours was carried out at the Department of Pathology, Dr.D.Y Patil Medical

College, Pune. Histopathological findings were classified according to the revised 2016 WHO Classification of Ovarian tumours.⁵ We also studied the HER2 overexpression on malignant ovarian tumours.

We have compared our results with similar studies in literature. Hence the data available is from different time periods and different geographic regions. In our study majority of patients were in the age group of 30-40 years (28.4%) followed by age group 20-30 years (21.6%). The youngest patient was 14 years old while the oldest was 73 years. These findings were similar to the studies of Singh et al⁷ and Maurya et al⁸ but were not in concordance with the findings of Thakkar et al⁹ who had a majority of cases in the age group of 40-59 years with 53.5%. In our study, benign tumours (77%) were more frequent than malignant tumours (23%). Studies reported by Jarwani et al,¹⁰ Swamy et al,¹¹ Singh et al,⁷ Thakkar et al,⁹ and Maurya et al⁸ corroborated our findings. In the present study surface epithelial tumours were most common comprising 96 cases (71.7%) out of 134 cases. Thakkar et al⁹ reported 73.8% of surface epithelial tumours in their study. 6 cases of sex cord stromal tumours which constituted 4.5% of the total ovarian tumours were reported in our study which was in concordance with a study conducted by Jarwani et al¹⁰ who reported 4.51% cases. In the present study germ cell tumours were the second most common, accounting for 20.2% cases which were similar to 21.7% cases reported by Swamy et al.¹¹ In our study, out of the total 96 surface epithelial tumours 74(77%) were benign and 22 (23%) were malignant. According to Singh et al⁷ out of 80 surface epithelial tumours 67 (83.7%) were benign and 13(16.25%) were malignant. Amongst 27 germ cell tumours in our study 22(81.5%) were benign while 5(18.5%) were malignant. Our findings were comparable to study conducted by Singh et al⁷ where of 32 germ cell tumours 28(87.5%) were benign and 4(12.5%) were malignant. Out of the total 6 sex cord stromal tumours 4(66.6%) were benign while 2(33.33%) were malignant while out of 5 sex cord stromal tumours in study conducted by Singh et al,⁷ 3(60%) were benign and 2 (40%) were malignant. In our study we found a rare case showing primary Burkitt-like lymphoma of the ovary, in which IHC markers were positive for CD45, CD19 and CD10.

The HER2 gene, which is located on 17q11 chromosome, encodes the HER2 protein. This gene is required for intracellular signalling pathways which results in cell growth and differentiation. Amplification or mutation of HER2 gene may be an important factor in tumour pathogenesis. The range for HER2 overexpression in epithelial ovarian carcinoma ranges from 1.8-76%.¹² The wide variation in the range can be due to the use of different antibodies and different techniques. In the present study, HER2 overexpression is seen in 2 (6%) out of 31 malignant tumours. In our study both the mucinous cystadenocarcinomas showed 2+ membranous HER2 positivity. The findings of our study are in concordance with other studies reported in literature (Table 6). HER2 expression can be prognostic significance and is common in

mucinous type of epithelial ovarian carcinoma.¹³ Analysis of HER2 expression has been done on all histological subtypes of ovarian carcinoma and many studies show that HER2 status is not significant in nonmucinous type of epithelial ovarian carcinoma.¹⁴ Trastuzumab therapy would be an option for patients with mucinous carcinoma when the tumor has HER2 overexpression. In some studies overexpression of HER2 was associated with chemotherapy resistance; advanced stage of the disease, poorly differentiated tumours and shortened survival of patient.¹² Verma et al¹² reported that HER2 status may be helpful in treatment outcome by giving an idea about the biological behaviour of the ovarian tumour.¹²

The limitation of our study however, is the small sample size for HER2 analysis and lack of follow-up of cases. Hence, a large population-based, multicentric study using standardised IHC marker and staining technique with facility of follow-up is needed to decide the usefulness of anti-HER2/neu therapy in epithelial ovarian carcinomas.

Conclusion

Histopathological study is important in diagnosis of ovarian tumours and predicts their prognosis. HER2/neu can be a good prognostic marker with scope for targeted therapy. However, there is wide variation of HER2 overexpression in various reported studies, hence, a large sample size, multicentric study with patient follow is proposed to determine the efficacy of HER2/neu targeted therapy for ovarian carcinoma.

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