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Study of Different Ovarian Malignancies Based on Histopathology at A Tertiary Hospital

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ABSTRACT

Ovarian carcinoma is a heterogeneous disease. Each of these categories is associated with different genetic risk factors and molecular events during oncogenesis and they also differ dramatically in frequency. Present study was aimed to study different ovarian malignancies based on histopathology and expression of CD44 in malignant surface epithelial tumors of ovary at a tertiary hospital. Present study was single-center, descriptive study conducted all specimens of ovarian carcinoma received in the department during the study period. All cases of malignant surface epithelial tumors were subjected to study of immunohistochemical marker CD44. In present study 204 cases of ovarian malignancies were studied. Majority patients were from age-group of 51-60 years (38.23%) followed by age-group of 61-70 years (22.55%). Only around 13% of the patients were premenopausal, majority were postmenopausal (66.17%). There were 187 cases (91.17%) of surface epithelial tumors. Based on histopathology most common type was serous carcinoma (42.15%), followed by mucinous carcinoma (17.64%), endometroid carcinoma (20.6%) and clear cell carcinoma (8.33%). Majority of the patients presented at stage I, closely followed by patients at stage II. In our study, 35 cases of surface epithelial carcinomas were selected for CD44 expression study. This include 17 cases of serous carcinomas, 5 cases of mucinous carcinomas, 7 cases of endometroid carcinomas, 4 cases of clear cell carcinomas and 2 cases of seromucinous carcinomas. The positive staining of CD44 showed cellular membrane localization. 15 cases showed strong CD44 positivity, 9 cases showed moderate positivity and 7 cases showed weak positivity. From our study we conclude that the surface epithelial carcinomas constituted the major part of ovarian malignancies. We also noticed a positive correlation between tumor grade and CD44 positivity.

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Key Words
Ovarian malignancies, histopathology, tertiary hospital, ovarian cancer

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INTRODUCTION

Ovarian carcinoma is a heterogeneous disease. The histopathological classification of ovarian cancers by WHO categorizes the ovarian tumors with regard to their derivation from coelomic surface epithelial cells, germ cells and mesenchyme[1]. Thus most tumors of the ovary can be placed into one of the three major categories- *epithelial tumors, sex cord-stromal* tumors and *germ cell* tumors[1,2].

Each of these categories is associated with different genetic risk factors and molecular events during oncogenesis and they also differ dramatically in frequency. Out of the ovarian cancers, Surface epithelial cancer is the most lethal gynecological cancer. The very high case fatality rate is partly because the condition usually presents in advanced stages of the disease[3,4].

CD44 is a cell-surface glycoprotein which is involved in cell-to-cell and cell to extracellular matrix interaction. CD44 is encoded by a single gene located on human chromosome 11. Ovarian cancer cells frequently metastasize by implanting on to the peritoneal mesothelial lining of the abdominal cavity. CD44 is also found to have a possible role in this process. Some studies have shown that over-expression of CD44 in ovarian surface epithelial cancers represent tumor aggressiveness and poor prognosis[5,6]. Present study was aimed to study different ovarian malignancies based on histopathology and expression of CD44 in malignant surface epithelial tumors of ovary at a tertiary hospital

MATERIAL AND METHODS

Present study was single-center, descriptive study conducted in Department of Pathology, Government Medical College, Thiruvananthapuram, India. The study was conducted for a period of 5 years from February 2011 to January 2016 for the analysis of ovarian malignancies and for a period of 1 year from February 2015 to January 2016 to study the expression of CD44 in epithelial ovarian cancers. Study approval was obtained from institutional ethical committee.

All specimens of ovarian carcinoma received in the department during the study period were included in the study. Relevant clinical details of the cases were collected. All specimens were received in 10% formalin and gross features like tumor size, intactness of the capsule, nature of the cut surface and stage of the tumor were assessed. Specimens were processed by paraffin embedding and blocks cut serially and H and E-stained sections were prepared.

Microscopic features like histologic type, grade and metastasis were studied. All cases of malignant surface epithelial tumors were subjected to study of immunohistochemical marker CD44. The CD44 staining percentage was graded as 0 [Negative], 1 [Weak/<10%], 2 [Moderate/ 10-50%], 3 [Strong/>50%]. The relation between CD44 expression and tumor grade as well as tumor stage were studied.

Data was entered in the proforma and was tabulated in Microsoft Excel 2010. IBM SPSS statistics version 22.0 software was used to analyze the data.

RESULTS

During this study period a total of 1,909 cases of ovarian tumors were received in our department. Among them 1202 cases were benign, 503 cases were borderline and 204 cases were malignant. The ratio of benign to malignant tumors of ovary obtained in our study was 6:1. In present study 204 cases of ovarian malignancies were studied.

The patients in our study belong to different age group ranging from 11 years to 80 years. Majority patients were from age-group of 51-60 years (38.23%) followed by age-group of 61-70 years (22.55%). Only around 13% of the patients were premenopausal, majority were postmenopausal (66.17%).

Out of 204 malignant ovarian tumors, on basis of origin, there were 187 cases (91.17%) of surface epithelial tumors, 10 cases of sex cord-stromal tumor, 4 cases of germ cell tumor, 1 case of lymphoma. Two cases of metastatic tumor of ovary are included, both having their primary site in GIT.

Based on histopathology most common type was serous carcinoma (42.15%), followed by mucinous carcinoma (17.64%), endometroid carcinoma (20.6%), clear cell carcinoma (8.33%), granulosa cell tumour (3.92%), seromucinous carcinoma (2.45%) and dysgerminoma (1.96%). Staging of all the malignant ovarian tumors were done except for two cases of metastatic tumors. Majority of the patients presented at stage I, closely followed by patients at stage II .None of the patients belonged to stage IV.

In our study, 35 cases of surface epithelial carcinomas were selected for CD44 expression study. This include 17 cases of serous carcinomas, 5 cases of mucinous carcinomas, 7 cases of endometroid carcinomas, 4 cases of clear cell carcinomas and 2 cases of seromucinous carcinomas.

The positive staining of CD44 showed cellular membrane localization. CD44 expression was compared with the menstrual status of the patient, tumor stage and tumor grade. Among the 35 cases the immunohistochemical scores were 3 in 15 cases (42.8%), 2 in 9 cases (25.5%) , 1 in 7 cases (20%) , 0 in 4 cases (11.4%). 15 cases showed strong CD44 positivity, 9 cases showed moderate positivity and 7 cases showed weak positivity.

Table 1: General characteristics

Age groups (years)	No. of patients	Percentage
11-20	3	1.47
21-30	5	2.45
31-40	19	9.31
41-50	42	20.6
51-60	78	38.23
61-70	46	22.55
71-80	11	5.4
Menstrual status		
Premenopausal	27	13.23
Perimenopausal	42	20.6
Postmenopausal	135	66.17

Table 2: Distribution of malignant ovarian tumors

based on the origin	No. of patients	Percentage
Surface epithelial tumors	187	91.66
Sex cord -stromal tumor	10	4.9
Germ cell tumor	4	1.96
Lymphoma	1	0.5
Metastatic carcinoma	2	0.9
Based on histopathology		
Serous carcinoma	86	42.15
Mucinous carcinoma	36	17.64
Endometroid carcinoma	42	20.6
Clear cell carcinoma	17	8.33
Granulosa cell tumour	8	3.92
Seromucinous carcinoma	5	2.45
Dysgerminoma	4	1.96
Malignant steroid cell tumour	2	0.98
Metastatic carcinoma	2	0.98
Malignant Brenner tumour	1	0.49
Lymphoma	1	0.49
Stage		
Stage- I	97	48
Stage- II	87	43
Stage- III	18	9
Stage- IV	0	0

Table 3: Distribution of surface epithelial tumors taken for CD44 study

Diagnosis	No. of cases	Percentage
Serous carcinoma	17	48.57
Mucinous carcinoma	5	14.28
Endometroid carcinoma	7	20
Clear cell carcinoma	4	11.42
Seromucinous carcinoma	2	5.71

Table 4: Expression of CD44 in surface epithelial carcinomas

CD44 status	No. of cases	Percentage
Negative	4	11.42
Weak	7	20.00
Moderate	9	25.57
Strong	15	42.85

Table 5: CD44 expression with menstrual status of the patient

	CD44 expression (No of cases)				
Menstrual status	Negative	Weak	Moderate	Strong	p-value
Premenopausal	0	2	0	1	0.031
Perimenopausal	2	4	2	2	
Postmenopausal	2	1	7	12	

Table 6: CD44 expression with tumor stage

	CD44 expression					Stage
	Negative	Weak	Moderate	Strong	Total	p-value
Stage-I	4	4	1	1	10	0.038
Stage-II	0	3	7	10	20	
Stage-III	0	0	1	4	5.0	

In our study it was found that moderate-strong positivity for CD44 was seen predominantly in postmenopausal women. Majority of the cases of premenopausal and perimenopausal patients showed weak positivity.

Out of 35 cases, 20 cases were of grade II, among which 10 cases showed strong CD44 positivity and 7 cases showed moderate positivity. In grade III tumours 4 out of 5 cases showed strong positivity and 1 case showed moderate positivity. Negative staining for CD44 was seen only in stage I tumors.

In our study grade I tumors showed negative as well as weak staining of CD44 while majority of the grade-II tumors showed moderate positivity. Out of 18 grade-III cases, 14 showed strong positivity.

In present study, tumor grade was significantly associated with CD44 expression (p-0.0361).

DISCUSSION

Ovarian cancer is the sixth most common cause of death from cancer in women[7]. The high mortality rate is because >70% of the ovarian carcinomas present at an advanced stage[8]. The biology of ovarian carcinoma is different from that of hematogenously metastasizing tumors because ovarian cancer cells primarily disseminate within the peritoneal cavity and are only superficially invasive[2].

During the 5-year study period, 1,909 cases of ovarian tumors were received in our department. Among them, 204 (10.68%) cases were malignant. Major part of the malignant cases was occupied by surface epithelial carcinomas (91.17%), out of which serous carcinoma (42.15%) constituted the most common type followed by endometroid carcinoma (20.6%).

In the study conducted by Ameena *et al.*[9] and Mondal *et al.*[10] most common type of ovarian carcinoma was surface epithelial tumors [75.5%] among which serous carcinoma was the most common type. The second common type of ovarian cancer were sex cord stromal tumors followed by germ cell tumors. These findings were similar to that seen in the present study. Ovarian cancer rates increase with age. It is considered as an independent prognostic factor. In patients less than 45 years of age, about one of eight ovarian tumors is malignant. On the other hand, in older women the proportion is about one of three[3].

In the present study, age at the presentation ranged from 11-80 years. The mean age was 55 years. Approximately 66% of the patients are above the age of 55 years. Majority of the patients with surface epithelial carcinomas belong to the age group between 51-60 years.

Jing *et al.*[11] found out a mean age of incidence of ovarian carcinoma to be 59 years which was comparable with the present study. Study conducted by Ameena Ashraf *et al.*[9] showed a mean age of 35.6 years , which was lower than our study. In the study conducted by Mondal *et al.*[10] the highest frequency of ovarian carcinoma was seen in the age group of 41-50 years (44.36 %) while in our study, it was 51-60 years (38.23%).

Based on histopathology most common type was serous carcinoma (42.15 %), followed by mucinous carcinoma (17.64%), endometroid carcinoma (20.6%), clear cell carcinoma (8.33%), granulosa cell tumour (3.92%), seromucinous carcinoma (2.45%) and dysgerminoma (1.96%). On comparing our study with the study conducted by Mondal *et al.*[10] a similar pattern of frequency was noted in the surface epithelial The ratio of benign to malignant tumors in the study by Ameena *et al.*[9] was 2:1 which was significantly low when compared to the ratio 6:1 obtained in our study. However, the ratio obtained in the study by Mondal *et al.*[10] (4:1) was comparable with ours. Majority of the patients presented at stage I, closely followed by patients at stage II which comes

Table 7: CD44 expression in different grade of tumors

	CD44 positivity				grade Tumor
	Negative	Weak	Moderate	Strong	Total
Serous carcinoma					
Grade-I	3	1	0	0	4
Grade-II	0	1	4	0	5
Grade-III	0	1	1	6	8
Mucinous carcinoma					
Grade-I	0	0	0	0	0
Grade-II	0	0	2	0	2
Grade-III	0	0	1	2	3
Endometroid carcinoma					
Grade-I	0	2	0	0	2
Grade-II	1	2	0	0	3
Grade-III	0	0	1	1	2
Clear cell carcinoma					
Grade-I	0	0	0	0	0
Grade-II	0	0	0	0	0
Grade-III	0	0	0	4	4
Seromucinous carcinoma					
Grade-I	0	0	0	0	0
Grade-II	0	0	0	1	1
Grade-III	0	0	0	1	1

Table 8: Relationship of tumor grade with CD44 expression

	CD44 expression				Tumor
grade	Negative	Weak	Moderate	Strong	p-value
Grade I	3	3	0	0	0.0361
Grade II	1	3	6	1	
Grade III	0	1	3	14	

to around 48-43% respectively. Around 9% of the patients presented at stage III and none presented at stage IV. This pattern of presentation may be because of the new diagnostic and treatment modalities available in the medical field. In the study by Mondal *et al.*[10] most of the carcinomas presented as stage III (60%) but in our study stage I tumors predominated (48%).

In our study moderate-strong positivity for CD44 was mainly seen in cases of stage II and stage III, while negative or weak staining was seen mainly in stage I cases. A significant *p-value* of 0.038 was obtained. A similar increase in CD44 positivity with tumor stage is noticed in the study by Jing *et al.*[11].

The significance of the immunohistochemical expression of the CD44 family in ovarian malignancies especially epithelial carcinomas has been investigated during recent years. In the study done by Jing *et al.*[11] CD44 expression was seen in only 12% of low-grade carcinomas, compared with 39% of high-grade carcinomas[62]. There was a significant association between CD44 -positive expression and high-grade carcinomas (p = 0.037) which is similar to the present study(*p = 0.0361)*. However, no association was seen between the histological type of carcinoma and CD44 positivity.

There has been an outstanding advance in the diagnosis and management of ovarian carcinoma over the past few decades. This has improved the quality of life and has reduced the morbidity and mortality of women with ovarian cancer. Still epithelial cancer of the ovary remains a highly lethal neoplasm due to its propensity to form widespread tumor implants. There is increasing evidence to suggest that CD44, a cell surface glycoprotein play a major role in peritoneal implantation of ovarian cancer cells[13,14].

Recently, CD44 has been identified as a biomarker of cancer stem cells in many malignancies, including ovarian carcinoma. CD44 can be considered as an adverse prognostic factor the expression of which increases with tumor grade and stage[15,16]. Such a positive relation may contribute to anti-tumor therapy and prevention of metastasis in ovarian epithelial cancers by CD44 inhibition therapy. The newer diagnostic modalities for early detection of cancer combined with CD44 inhibition therapy can impede the onslaught of ovarian cancer. A positive relation if present may contribute to anti-tumor therapy and prevention of metastasis in ovarian epithelial cancers by CD44 inhibition therapy.

CONCLUSION

From our study we conclude that the surface epithelial carcinomas constituted the major part of ovarian malignancies the second being sex cord stromal tumors, followed by germ cell tumors. Among the malignant surface epithelial tumors, serous carcinomas were the most common type.

We also noticed a positive correlation between tumor grade and CD44 positivity. Strong positivity was seen in most of the grade III tumors and moderate positivity was seen in grade II tumors. An increase in CD44 staining was also noted with an increase in tumor stage. However, no association was found between the histological type of ovarian cancer and CD44 positivity.

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