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A STUDY ON IMMUNOHISTOCHEMICAL EXPRESSION OF KI67 IN SURFACE EPITHELIAL OVARIAN CARCINOMAS

Pathology

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ABSTRACT

Surface epithelial tumors are the most common type of ovarian neoplasm, and their malignant variants account for approximately 90% of ovarian cancers. Ki67 is a prognostic marker that indicates the growth fraction of a tumor; its overexpression is linked to malignancy, tumor aggressiveness, poor prognosis, and metastasis. Among the 35 surface epithelial ovarian carcinomas studied, high-grade serous carcinomas were the most common. High Ki67 index was associated with high grade serous carcinomas. The study also depicted a statistically significant correlation of Ki67 between age, CA-125 levels, necrosis, papillary projections and mitotic figures .

KEYWORDS

Immunohistochemistry; Ki67; Ovarian tumors.

INTRODUCTION

Thirty percent of tumors of the female genital tract are ovarian cancers, making them one of the most prevalent gynecological malignancies. It is currently the seventh most prevalent cancer in women of reproductive age and older women, and the fifth most common cause of cancer-related deaths in these populations. More than 90% of ovarian cancers are surface epithelial ovarian tumors (SEOT), which are also the most deadly type.[1]

Even with the introduction of more advanced diagnostic and chemotherapeutic techniques, the overall 5-year survival rate remains low, at approximately 40%. At the time of diagnosis, more than 70% of the women diagnosed with ovarian carcinoma have advanced disease due to its asymptomatic nature and lack of reliable markers for early diagnosis. Several prognostic factors which are known to influence survival of ovarian cancer include age at diagnosis, histological type and grade, ploidy, International Federation of Gynecology and Obstetrics (FIGO) stage, CA-125 levels and the amount of residual tumor after primary surgery.[1]

An important factor influencing the aggressiveness and clinical behavior of ovarian tumors is cellular proliferation. This can be evaluated by measuring the tumor's proliferative activity, which has been shown to have diagnostic and prognostic significance. A good immunohistochemistry marker to identify the tumor's proliferating cells is Ki-67.

Except for quiescent cells in the G0 phase, which are in resting state, it is expressed throughout all active phases of the cell cycle (G1, S, G2, and M phase). The nuclear Ki-67 antigen expressed in cells that are proliferating responds with the monoclonal Ki-67/MIB-1 antibody. In many human malignancies, including connective tissue tumors, breast tumors, lymphoproliferative diseases, meningiomas, and tumors of the central nervous system, its expression is known to predict the course of the disease and to reflect tumor proliferation. It has also been found to indicate tumor aggression and metastasis.[1]

The goal of the current study is to evaluate the proliferative marker Ki 67's value in Surface Epithelial Ovarian carcinomas and how it can improve our understanding of the tumor's biological behavior and guide the modification of treatment plans.[1]

OBJECTIVES

1. To assess the expression of proliferative marker Ki-67 in Surface epithelial Ovarian carcinomas.
2. To correlate the level of expression of Ki-67 with clinico-pathological parameters including the International Federation of Gynaecology and Obstetrics (FIGO) staging and pre-operative CA 125 levels for diagnostic and prognostic purpose.

MATERIALS AND METHODS

This was a prospective study conducted over a period of one and a half years (July 2022 - December 2023) in the department of Pathology, KIMS, Hubli, Karnataka. The study included 35 cases of surface epithelial ovarian carcinomas. Immunohistochemistry was done on formalin fixed paraffin embedded tissue blocks using the heat induced antigen retrievel method with specific murine monoclonal antibody MIB1 and KI 67 labelling index and scoring was done. Labelling index is measured as per-centage of MIB-1 positive cells in a 1000 randomly selected tumor cells. Only nuclear staining was regarded as positive, weak nuclear or cytoplasmic staining is regarded as negative.

Ki-67 Scoring

Ki-67 immunopositivity was observed as brown granular nuclear staining.

For Ki-67 scoring, the most immunopositive area of the tumor was selected avoiding foci of inflammation. The number of immuno-positive nuclei is counted in 1000 tumor cells in at least 10 high power fields in 40x.

The percentage of immunopositive cells is referred to as labelling index(LI)/ proliferative index. The average of three counts of Ki-67 immunopositive cells over the same slide was taken and expressed as the percentage of Ki-67 immunopositive cells in the tumor.

Ki-67 overexpression was quantitatively assessed as negative (<1% cells), 1+ (1-10% positive cells), 2+ (10-20 % positive cells), 3+ (>20% cells) based on previous studies .

The staining pattern was interpreted as:

a) focal pattern : a small number of positively stained cells;
b) diffuse pattern: uniform diffuse positively stained cells ; and
c) heterogenous pattern: areas of strong positively stained cells alternating with areas of low positively stained cells.

RESULTS

Of the 35 surface epithelial carcinomas, majority of cases were observed in patients over 50 years of age (62.9%).

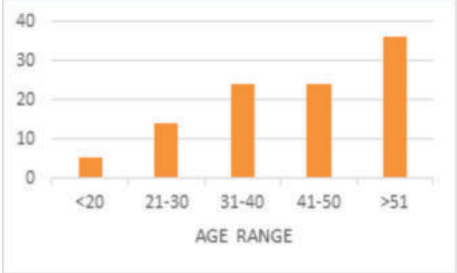

Figure no:1. Age Distribution of the Surface Epithelial Ovarian Cancers.

Out of the 35 cases, 14 (40%) were bilateral. 11 out of 21 bilateral tumours were serous carcinomas.

Among the histopathological subtypes, serous carcinomas were the

most common, accounting for 24 of the 35 cases. Of these, 19 were high-grade serous carcinomas, and 5 were low-grade serous carcinomas.

The remaining cases included 7 mucinous carcinomas, 3 endometrioid carcinomas, and one malignant Brenner tumor.

The mean Ki 67 index of all the tumors were 35.94. High grade serous carcinoma showed the highest mean ki67 index of 46.63 with a standard deviation of 23.88, followed by mucinous carcinoma (31.57) and low grade serous carcinoma (23.60).

Table no:1 Mean ki 67 Index in Histopathological Subtypes

Histolopathological subtypes	KI67%		
	Count	Mean	SD
Low grade serous carcinoma	5	23.60	15.19
High grade serous carcinoma	19	46.63	23.88
Mucinous carcinoma	7	31.57	18.86
Endometrioid carcinoma	3	10.33	15.31
Malignant Brenner tumour	1	2.00	.00

A higher mean ki67 labelling index is seen in more than 50 years of age (25.12) and in less than 20 years of age (23.85).

Majority of the cases were in stage IA and stage IB (60%), followed by stage IIIC. None of the tumours were in stage IV. Stage IIIB showed a higher mean Ki 67 index of 54.80 followed by stage IB which showed a mean KI 67 index of 51.11.

Elevated CA 125 levels above 35 IU/ml were observed in 27 cases. The highest CA 125 levels were observed in high-grade serous carcinoma. Higher ki 67 mean index is seen with higher CA 125 levels when compared with patients having normal CA125 levels.

Out of 35 cases 15 cases showed heterogenous pattern,10 cases each in diffuse and focal pattern.

65.7 percent of the tumours were in score 3 group. The high proliferation groups (score 2 and score 3) showed predominantly solid and cystic appearance (50% and 79.25 % respectively). Papillary projections were present in 50 percent of cases of score 3 group and 16.7 percent of score 2 group. Necrosis was present in 33.33% of cases of score 3 and score 2 group.

29 cases showed mitotic figures in >5/10hpf which is statistically significant (P value <0.001). All cases with >5/10 hpf mitotic figures showed a higher mean ki 67 labelling index.

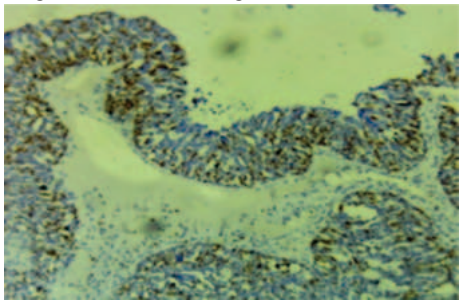

Fig no: 2. Ki 67 Expression Showing Heterogenous Pattern in Low Grade Serous Carcinoma (10x)

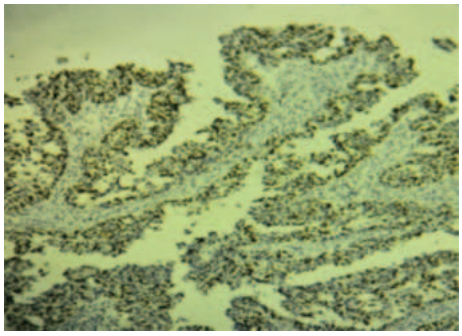

Fig no:3. Ki 67 Expression Showing Diffuse Pattern in High Grade Serous Carcinoma (10x)

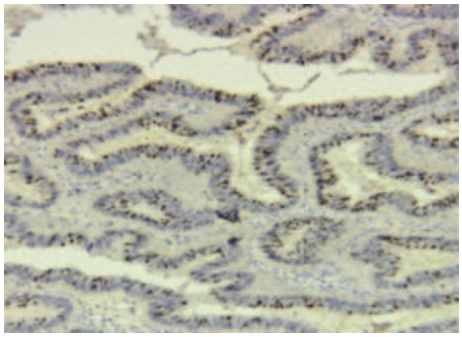

Figure no:4 Ki 67 Expression Showing Heterogenous Pattern in Mucinous Carcinoma (10x)

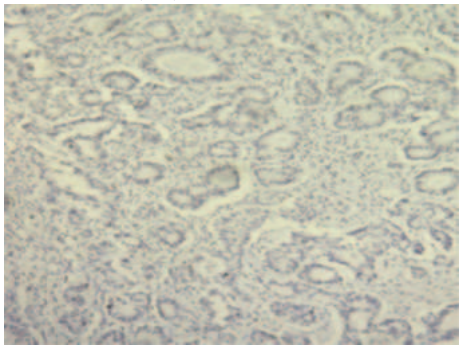

Fig no: 5. Negative Ki 67 Expression in Endometrioid Carcinoma (10x)

DISCUSSION

Tumours malignant in nature are more highly invasive as compared to benign and borderline tumours. Due to this, malignant tumours show high Ki-67 levels, while the latter shows little to no Ki-67 via immunostaining. Ovarian tumours are heterogeneous with variable degrees of disease progression. Early detection of tumours is critical for the prevention of spread in ovaries as well as timely application of chemotherapy for malignant tumours. Ki-67 being reliable, cost-effective and a new technique helps in evaluating the proliferative index of neoplastic lesions. Ki-67 expression marker should be preferred over other immunohistochemistry markers (oestrogen receptors, progesterone receptors, p53 gene, etc.) because of its strong correlation with the histological staging/ grading as per a study by Verma et al.[2]

The study comprised 35 cases. Maximum number of cases were present above 50 years of age. In the study done by Verma et al[2] 60.53% of cases above 40 years showed malignancy. Higher mean ki67 labelling index is seen in more than 50 years of age and in less than 20 years of age. There is a statistically significant association with age of the patient and ki 67 expression (P value =0.03, Kruskal Wallis test). Singh et al[3] showed a significant correlation between ki67 and age.

Fourteen out of 35 (40.0%) malignant tumours presented bilaterally. This finding was similar to a study done by Jha R et al[4] who encountered only 6.7% benign tumours and 42.3 % malignant tumours presenting bilaterally.

High-grade serous carcinoma was the most common malignant tumor encountered in our study as in another study by Jha R etal.[4] High mean ki 67 is observed in high grade serous carcinomas with a mean ki 67 LI of 46.63%, and the highest value of ki 67 LI observed was 75%. Whereas low grade serous carcinomas showed a mean ki67 LI of 23.60 %. These findings were similar to the study done Asha Mahadevappa et al [5] where among the serous group, the Ki 67 LI was higher in high grade serous carcinoma (65.34%) as compared to the lowgrade serous carcinoma (37.96%).

In another study by Singh et al,[3] the median ki67 index in high grade serous carcinomas was 45% and ki67 LI of LGSC was 24%. In Kobel et al,[6] the median Ki67 LI of LGSC was 2.5 % and that of HGSC was 22.4 %.

Papillary projections were seen more in serous carcinomas. In the study by Singh et al,[3] among the negative group, 72.7% of the tumours

had a cystic appearance. Whereas low and high proliferation groups showed solid with cystic appearance of 48.1% and 94.1% respectively. These findings were similar to findings of the present study. In the present study papillary projections were present in 50 percent of cases of score 3 group and 16.7 percent of score 2 group. Necrosis is present in 33.33% of cases of score 3 and score 2 group which is significant. Thus the papillary projections can be linked to high Ki67 expression. A study by Ramlingam P et al [7] reported that high-grade serous carcinoma with a papillary pattern is associated with elevated Ki-67 expression.

The study showed association of CA 125 levels with Ki 67 is statistically significant (P<0.001, Mann Whitney test). Higher ki 67 mean index is seen with CA 125 levels >35 U/ ml when compared with patients having normal Ca 125 levels. This has indicated that higher the CA 125 levels, there are higher chances of malignancy. Similar results were observed by Laishram et al[1] and Singh et al[3] which signifies a positive co-relation of CA125 levels with Ki 67 expression levels.

In the present study 29 tumours with mitosis of > 5/10 hpf showed a higher mean ki67 index of 40.63. A positive association was seen between ki67 expression and mitotic rate (p value- <0.0001). Guro Aune et al [8] and Dr U Bharathi et al [9] also showed similar findings in their study.

Overall, the study demonstrated a statistically significant relationship between Ki67 expression and the nature of the tumor, age, necrosis, papillary projections, mitotic figures, and CA-125 levels.

CONCLUSIONS

The study concludes that Ki67 expression can aid in the clinicopathological diagnosis of SEOT. As an economical and reliable marker, Ki67 could be useful in determining tumor behavior, progression, prognosis, and in evaluating therapeutic responses.

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