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Original Research Article

ROLE OF p53 AND KI-67 IN HISTOPATHOLOGICAL GRADING OF PHYLLODES TUMOUR: A PROSPECTIVE STUDY

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Abstract

Background: Phyllodes tumours are divided into benign, borderline, and malignant based on histologic features, but these divisions are arbitrary, and they lie along a histologic continuum. p53 is a tumour suppressor gene whose mutation and increased expression is reported in almost all malignancies. Ki 67 is a non-histone nuclear protein associated with cell proliferation. On this background the objective of the study was to evaluate the expression of p53 and K-i67 in different grades of phyllodes tumour. **Materials and Methods:** This study was conducted in the department of pathology, Government Medical College. 26 phyllodes tumour specimens were received for analysis. All the cases demographic and clinical data was recorded. The specimens were subjected to histopathological evaluation and expression of p53 and Ki-67 markers. The data was analysed with SPSS (20.0 version) and expressed in number and percentage. **Results:** A total of 26 samples were included in the study. 5 malignant, 7 border line and 14 benign. Maximum number of patients are age between 21-40 years. P53 and Ki-67 expression was more in malignant cases compared to others. Ki-67 expression is more in benign compared to other tumors. **Conclusion:** P53 and Ki 67 expression does not have a significant correlation with grade of phyllodes tumour and more over cannot be used as reliable markers to differentiate phyllodes tumours.

INTRODUCTION

Phyllodes tumour is an uncommon stromal epithelial neoplasm of breast. Reported incidence is less than 1%. It is seen in middle aged women (mean age 45 years).[1,2] Phyllodes tumours are histologically graded into benign, borderline and malignant on the basis of histological features, like, mitotic count, cellularity and pleomorphism of stromal cells, and stromal overgrowth, infiltration.[3,4] But this division is essentially arbitrary because they lie along a histologic continuum rather than discrete histological categories. Mutations of p53 gene are among the commonest detected in human malignancies. p53 is a tumour suppressor gene, ie, its activity is to stop formation of tumour. It is located on chromosome 17p13.[5] it encodes for a 53kDa nuclear phosphoproteins that is expressed in all normal cells at low levels. Mutant p53 protein acquire oncogenic properties enabling them to promote invasion, metastasis, proliferation and cell survival.[6] As half-life of wild p53 is short, immunohistochemistry is believed to highlight the expression of mutant p53 protein that is more stable with a longer half-life. p53 protein expression in phyllodes tumour has been reported in several studies. In studies that correlates grade of phyllodes tumour to p53 protein expression, it was suggested that malignant phyllodes tumour have strong staining that allowed distinction of malignant from benign and borderline phyllodes and so immunostaining for p53 protein expression can be utilized in the diagnosis of malignant ones.[7,8] Similar results have been obtained in case of Ki-67 expression, that is, malignant phyllodes tumour shows positive Ki-67 expression compared to benign tumours. Ki-67 is a nuclear protein that is associated with cellular proliferation and so increased expression show increased cellular proliferation.[9,10]

Considering all these facts, the aim is to study variable expression of p53 and Ki-67 in phyllodes tumour.

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MATERIALS AND METHODS

Study Settings

The study was conducted in the department of pathology, Government Medical College, Thiruvanthapuram, Kerala.

Study Period

This descriptive study was conducted for the period of 2 years.

Procedure

All phyllodes tumor cases were included in the study during the study period. Gross features like size of the tumor, margin of the tumor was assessed. Representative formalin fixed paraffine embedded sections of the tumour will be stained with H & E and microscopy was studied based on stromal cellularity, mitosis, stromal overgrowth, stromal atypia, infiltrative margins and histological typing was done according to WHO criteria to classify them as benign, borderline, malignant phyllode tumour. Sections were immunostained with IHC markers p53 and Ki67 antibodies to study their expression in each of the specimen. The p53 expression and Ki-67 antigen (MIB-1 index) were defined as the percentage of positive nuclear staining after counting five hundred neoplastic stromal cells. We separate the percentage of p53 and Ki-67 into four groups as follows: 0-10%, 11-30%, 31-50% and 51- 100%. Fisher's exact probability test was performed to compare results of p53 and Ki-67 antigens with the morphological benign and malignant groups of phyllodes tumour.

Statistical Analysis

The data was expressed in number, percentage, mean and standard deviation. Statistical Package for Social Sciences (SPSS 20.0) version used for analysis. Microsoft excel 2003 version used for analysis.

RESULTS

A total of 26 samples were analyzed in this study. Maximum number of tumors were benign (n=14), Borderline (n=7) followed by malignant (Table-1). 3 in malignant and 7 in benign had age between 21-40 years. In borderline maximum number of patients had age between 41-60 years. One in benign had age above 60 years. It was observed that malignant and benign tumors are common in age group between 21-40 years. 4 in malignant had tumor size more than 10 cm. 5 in borderline had tumor size between 5-10 cm. Maximum number (n=10) in benign showed tumor size between 2-5 cm. Maximum number of cases in borderline and benign not showed gross infiltration but 4 in malignant showed gross infiltration. 11 in benign, absent of mitosis. 5 in malignant had more than 10.10hps followed by 6 in borderline had 5-9/10 hpf and 3 in benign 1-5/10 hpf. 5 in malignant and 1 in borderline showed microscopic infiltration. 5 in malignant, 7 in borderline and 14 in benign showed increase in stromal cellularity. 7 in borderline and 5 in malignant had stromal overgrowth (Table-2). 4 in malignant, 6 in borderline and 14 in benign showed less than 10% of P53 and Ki-67 expression. 1 in malignant showed 51-100 % P53 expression. 2 in benign and 1 in borderline showed 11-30% of Ki-67 expression (Table-3).

Table 1: Distribution of tumours

Histopathological diagnosis	Number	Percentage (%)
Malignant phyllodes tumour	5	19.23
Borderline phyllodes tumour	7	26.92
Begin phyllodes tumour	14	53.85
Total	26	100.00

Table 2: Demographic data

Observations		Malignant		Borderline		Benign	
		n	%	n	%	n	%
Age (Years)	<20	0	0.00	1	14.30	2	14.30
	21-40	3	60.00	1	14.30	7	50.00
	41-60	2	40.00	5	71.40	4	28.60
	>61	0	0.00	0	0.00	1	7.10
Size in diameters (cm)	<2	0	0.00	0	0.00	3	21.40
	2-5	0	0.00	1	14.30	10	71.50
	5-10	1	20.00	5	71.40	1	7.10
	>10	4	80.00	1	14.30	0	0.00
Gross infiltration	Present	4	80.00	0	0.00	0	0.00
	Absent	1	20.00	7	100.00	14	100.00
Mitosis	Absent	0	0.00	0	0.00	11	78.60
	1-5/10hpf	0	0.00	0	0.00	3	21.40
	5-9/10hpf	0	0.00	6	85.70	0	0.00
	>10/10hps	5	100.00	1	14.30	0	0.00
Microscopic infiltration	Present	5	100.00	1	14.30	0	0.00
	Absent	0	0.00	6	85.70	14	100.00
Increased stromal cellularity	Present	5	100.00	7	100.00	14	100.00
	Absent	0	0.00	0	0.00	0	0.00
Stromal overgrowth	Present	5	100.00	7	100.00	0	0.00

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	Absent	0	0.00	0	0.00	14	100.00

Table 3: Gross morphology of phyllodes tumour

Observations		Malignant		Borderline		Benign	
		n	%	n	%	n	%
P53 expression	<10%	4	80.00	6	85.70	14	100.00
	11-30%	0	0.00	1	14.30	0	0.00
	31-50%	0	0.00	0	0.00	0	0.00
	51-100%	1	20.00	0	0.00	0	0.00
Ki-67 expression	<10%	4	60.00	6	85.70	14	100.00
	11-30%	2	40.00	1	14.30	0	0.00
	31-50%	0	0.00	0	0.00	0	0.00
	51-100%	0	0.00	0	0.00	0	0.00
	Absent	0	0.00	0	0.00	0	0.00

DISCUSSION

PT is further subdivided into malignant, borderline, benign and therefore more elaborate surgical management is needed in malignant and borderline phyllodes Studies prove that PT have a common origin, i.e., arise from intralobular fibrous tissue as a unique lesion and after a period they differentiate in two directions. Phyllodes tumour is a rare tumour which constitute <1 % of tumours of breast and is seen predominantly in middle aged female. Since there is histological continuum and a grey zone in the diagnosis of various grades of PTs, which can be proved with immunohistochemical analysis of these tumours.[11] Two main immunohistochemical stains used for this purpose were p53 and Ki67 various studies conducted by Yu-Jan Chan.[12] et al, Ulku Kucuk et al, B.R.[13] Vani et al concluded that p53 and Ki67 expression is strong in cases of malignant and borderline PTs compared to benign PT. Present study conducted focused on the expression of both Ki67 and p53 expression on phyllodes tumour including malignant, borderline and benign PT. Study included 120 samples which included 5 malignant PT, 7 borderline PT, 14 benign PT. In the present study, age of presentation of phyllodes tumour ranged from 19 to 68 years, with malignant PT ranging from 28-58 years with a mean of 41.6 years, borderline PT ranging from 19-53 years with a mean age of 41.7 years, benign PT ranging from 17-68 years with a mean age of 38.7 years. This was similar to age distribution in study conducted by Yoshihisa Umekita.[14] In the present study majority of malignant PT had tumour size >10 cm diameter while majority of borderline phyllodes and all cases of benign phyllodes. All malignant PT showed mitosis > 10/10 hpf, while majority borderline PTs (6/7) showed mitosis between 5-9/10 hpf and all benign PT. In the present study only one 1/5 cases of malignant PTs showed a high Ki 67 expression of >10 while all other cases of malignant PTs showed an expression >10 % which can be considered low or insignificant according to studies conducted by Vani et al and Yu-Jan Chan et al.[12] Similarly, in case of borderline phyllodes tumour only one case out of 7 showed Ki 67 expression >10 % which can be considered strong, while all other six cases showed expression < 10 %. All cases of benign PTs showed a weak Ki 67 i.e., < 10 %. Since the positive or strong expression of Ki 67 was very low i.e., only 2 cases from the entire 120 samples showed strong reaction there is no role for p value in this case. Present study could not show any significant relationship between grade of phyllodes tumour and Ki 67 expression and also, we could not find any significant difference in the expression of Ki 67 in phyllodes tumour. This was in contrary to other studies which showed a significant relation between grade of phyllodes tumour and Ki 67 index i.e., as the grade of tumour increased Ki 67 expression also increased.

This dissimilarity in the present study with earlier conducted study could be due to wide difference in the sample size of cases included in our study, i.e., only 5 and 7 cases of malignant and borderline phyllodes tumour were obtained for the study. But since in our study on 2 among the total 120 sample showed a positive value, the finding is in significant and there is no significance in calculating the p value. So, from the present study it has to be concluded that there is no significant relation between grade of phyllodes tumour and p53 expression and also, we could not find any significant difference in the expression of Ki 67 in phyllodes tumour.

CONCLUSION

The study results concluded that p53 and ki 67 cannot be considered as immunohistochemical markers for grading phyllodes tumour or differentiating phyllodes tumour from other cancers.

Conflict of interest: Nil

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Ethical Clearance

This study was approved by Institutional Human Ethics committee with approved number IEC.No.02/52/2014/MCT.

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