Proliferating activity in the epithelial and stromal component of fibroadenomas and phyllodes tumours of the breast

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Abstract

The aim of the study was an evaluation of PCNA and Ki-67 expression in the epithelial and stromal component of fibroepithelial tumours (FT) of the breast in correlation with morphological parameters. A series of 11 fibroadenomas (FA), including 8 cases of the cellular type (FAC), 19 benign phyllodes tumours (PTLGM), 8 bordeline (PTBM) and 6 malignant phyllodes tumours were assessed, using immunohistochemistry. The expressions of Ki-67 and PCNA in the epithelial component were significantly higher in PTLGM, when compared with FA and PTBM. A significant increase of Ki-67 and PCNA stromal expressions was associated with the progression from PTLGM to PTHGM. Our results show that Ki-67 and PCNA may be useful in the evaluation of stromal proliferation in phyllodes tumours (PT), which play an integral part in the progression from PTLGM through PTBM to PTHGM.

Key words: Ki-67, PCNA, fibroadenoma, phyllodes tumour

Introduction

Phyllodes tumour (PT) is a rare fibroepithelial neoplasm of the breast, composed of epithelial and stromal elements. Based on the stromal cellularity and overgrowth, nuclear pleomorphism, mitotic activity and the type of border PTs are classified as benign, borderline and malignant [1]. FA is the most common benign fibroepithelial neoplasm of the breast in young adult women. A rare variant of FA is that of the cellular type, what poses some problem in the diagnosis on FNA [2]. Attempts have been made to identify markers which may be useful in the differential diagnosis of FT and in predicting prognosis in patients with PT [1, 3, 4, 5]. Ki-67 and PCNA antigens have been shown to be useful in the analysis of cellular proliferation [1, 6, 7]. The aim of this study was to evaluate Ki-67 and PCNA expressions in epithelial and stromal elements of fibroepithelial tumours from 44 patients in correlation with morphological features.

Material and methods

The examined group included 11 cases of FA - Group I, 19 cases of PTLGM - Group II, 8 cases of PTBM - Group III and 6 cases of PTHGM - Group IV. In the series of FA, there were 8 cases of cellular type. All the PTs were histologically classified, taking into account stromal overgrowth, cellularity, mitotic activity and atypia, using the 1-3 scale. Immunostaining was performed with PCNA (PC - 10, Dako) and Ki-67 (Ki-67, Dako) monoclonal antibodies, using an LSAB KIT with DAB as a chromogen. Scores in the examined groups were based on the following scale: (-) below 10 % of the cells with positive reaction for PCNA and Ki-67 proteins, (+) between 10 % - 50 % and (++), when above 50 % cells were immunopositive. The obtained values were subjected to statistical analysis with the use of the chi-squared and Mann - Whitney tests. The correlation between the scores and pathological variables was evaluated, using Pearson and Spermans correlation analysis. Values of $p<0.05$ were considered as statistically significant.

Results and discussion

FA and mammary PT are biphasic lesions with epithelial and stromal elements. FA of a conventional type is a benign neoplasm. A cellular variant of FA shows a rapid growth and may

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Table 1. Ki-67 and PCNA expression in the epithelial component of fibroepithelial tumours

Groups	Ki-67				PCNA			
	(-)		(+)		(-)		(+)	
	No	%	No	%	No	%	No	%
I	4	*36.4*	7	*63.6*	2	*18.2*	9	*81,8*
II	0	*0*	19	*100*	0	*0*	19	*100*
III	8	*100*	0	*0*	8	*100*	0	*100*

Table 1. Ki-67 and PCNA expression in the stromal component of fibroepithelial tumours

Groups	Ki-67						PCNA					
	(-)		(+)		(++)		(-)		(+)		(++)	
	No	%	No	%	No	%	No	%	No	%	No	%
II	19	*100*	0	*0*	0	*0*	19	*100*	0	*0*	0	*0*
III	0	*0*	8	*100*	0	*0*	0	*0*	8	*100*	0	*0*
IV	0	*0*	0	*0*	6	*100*	0	*0*	0	*0*	6	*100*

attain large size in the breast [4]. The classification of PT as benign, borderline malignant and malignant tumour, reflects the probable clinical course, based on the histological appearance of the tumour [1]. The diagnosis of FTs in our series depended on the careful assessment of morphological features in numerous specimens. The group of FAs included 8 cases of those with stromal cellularity. The microscopic picture revealed enlarged ductules with hyperplastic epithelium and superimposed small papillations. The stroma was focally or diffusely hypercellular with considerable pleomorphism. Benign PT had bland, sometimes cellular spindle cells or myxoid stroma with low mitotic rate, minimal atypia and pushing borders. PTBM had an increased mitotic activity, cellularity, stromal overgrowth, nuclear pleomorphism and either pushing or infiltrative borders. Malignant tumours revealed a greatly increased cellularity, high mitotic rate, marked nuclear pleomorphism and an overgrowth of stromal elements. Most of them had also necrosis. The structural variability among PTs creates a substantial difficulty in the proper diagnosis of some lesions, sampled by FNA [2]. Many PTs exhibits epithelial hyperplasia, often represented by a variable increase in the thickness of the cuboidal or columnar epithelium, lining the glandular spaces. The epithelial component of PTs contains much higher concentrations of endothelin - 1 (ET - 1), when compared with FAs. Yomashita et al. suggest a possible paracrine role of endothelin 1 in stimulating the proliferation of stromal cells in PTs [8]. Sawhney et al. suggest that there is an interdependence of growth between the epithelial and stromal elements in PTs [9]. In our series, Ki-67 and PCNA protein expressions in the epithelial component were assessed as positive in 28, out of 44 cases (63,6%) and in 30, out of 44 (68,2%). There were statistically significant differences in Ki-67 and PCNA epithelial expression between Groups I - II and Groups II - III. In Group I, 63.6% and 81.8% were (+) positive for Ki-67 and PCNA respectively. In Group II, 100% of examined cases were (+) positive for Ki-67 and PCNA. In Group III, all the cases were immunonegative for Ki-67 and PCNA (Table 1). The epithelial elements of PTBM and PTHGM were not distinctive, when compared with PTLGM. Sawhney et al. suggest that stromal dependence on epithelium, which may become atrophic, is lost with increasing malignancy of PTs [9]. In our series, PCNA and Ki-67 positive reaction in the stromal component was observed in 14, out of 44 cases (31.7%). Statistical analysis revealed significant differences in Ki-67 and PCNA stromal expressions between Groups II -III and Groups III-IV. In Group II, all the cases were negative for Ki-67 and PCNA. In Group III, 100% were (+) positive for Ki-67 and PCNA. In Group IV, all the cases were (++) positive for Ki-67 and PCNA (Table 2). In the examined group, Ki-67 and PCNA protein expressions correlated significantly with stromal overgrowth, cellularity, mitotic count and atypia in PT. Our results support those from previous reports which showed that Ki-67 stromal expression correlated with the degree of malignancy in PT [6,

10]. In the examined group, we did not find any significant difference in Ki-67 and PCNA expressions between FAC and PTLGM. The findings are in agreement with those, obtained by Kaya et al, who observed proliferating activity almost at the same level in both of these entities [4]. Examinations, concerning the expression of the high molecular form of tenascin (HMT) in FA revealed 2 groups of lesions - the first and the second - which were above represented in 60% and in 20%, respectively. Tenascin is a glycoprotein, produced mainly by stromal cells, and its expressions correlates with cell proliferations. Borsi et al. revealed a significant presence of HMT in the stromal cells of benign PT and some FA with an evident proliferation of stromal elements [11]. Surgery is the treatment of choice in patients with FT of the breast. Accepted treatment of FA is surgical enucleation of the tumour mass. In women with a small PTLGM, PTBM and PTHGM, a local excision, with wide margins to prevent recurrence, or simple and radical mastectomy in case of larger tumour size has been recommended [3,5]. Based on the obtained results, the optimal therapy for patients with cellular FA should be a complete excision of the tumour, together with adequate margins of the breast tissue. In conclusion, Ki-67 and PCNA immunohistochemistry may be useful in the evaluation of the stromal proliferation in PTs, which plays an integral part in the progression from PTLGM to PTHGM.

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