

Phyllodes Tumors and Fibroadenoma Common Beginning and Different Ending

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ABSTRACT

Phyllodes tumors and fibroadenomas are the most common benign breast tumors. They arise from intralobular fibrous tissue as a unique lesion and after a period of time they differentiate in two directions: to fibroadenoma and to phyllodes tumors. Fibroadenomas grow up to 2–3 cm and then stop growing but phyllodes tumors grow continually and sometimes are to 40 cm big. Both these lesions have two components, epithelial and stromal. Clinically fibroadenomas are well circumscribed, hard, oval, movable lesions. They can be solitary, multiple, unilateral and bilateral. They are hormone dependent changes, because they change their own consistency during menstrual cycle and gravidity. The most commonly used histological classification is in two types: pericanalicular and intracanalicular type. Phyllodes tumors make about 1% of all breast tumors. This tumor has many synonyms. It starts as fibroadenoma in intralobular stromal component. It has continuous growth and biologically it can be benign, borderline and malignant. The first description is from Miller (1838). The main goal is to find the divergence point when the developing is direct to fibroadenoma or phyllodes tumor. The second goal is to investigate the fate of epithelial and stromal component in these two lesions. Retrospective analysis is made of all fibroadenomas and phyllodes tumors in Pathology Department of Medical Center »Bežanijska kosa« in the period from 1998 to 2006. In this period, 2919 women were operated for breast changes. 343 fibroadenoma (24, 4%), were diagnosed, benign phyllodes tumor in 95 women (6.7%) and malignant phyllodes in 4 cases or 0.2%. All slides from these patients were analysed for many different histological parameters and immunohistological investigation for steroid receptors was also used, c-erbB2 (Her2/Neu), PCNA (proliferative cellular nuclear antigen) and Ki-67, androgen receptor and p53. All data were statistically investigated (Odds ratio, confidence interval, Fisher exact test, Wilcoxon sum test and Kendall test). It was concluded that fibroadenomas and phyllodes tumors arise from intralobular fibrous tissue, both changes have very close histology in the beginning and divergent growth starts later. Differences are present in stromal component. Phyllodes tumor has two component stroma. Stromal cells in phyllodes tumors are more PCNA positive than in fibroadenomas, also Ki-67 and androgen receptors are more positive in phyllodes tumors. Histologically phyllodes tumors have perforated capsule with finger like projections. These data determine surgical procedure, wide excision in phyllodes and simple excision in fibroadenomas.

Key words: fibroadenoma, Phyllodes tumors, immunohistochemistry

Introduction

Phyllodes tumors and fibroadenomas are the most common benign breast tumors. They arise from intralobular fibrous tissue as a unique lesion and after a period of time they differentiate in two directions: to fibroadenoma and to phyllodes tumors. Fibroadenomas grow up to 2–3 cm and then stop growing but phyllodes tumors grow continually and sometimes are to 40 cm big. Both these lesions have two components, epithelial and stromal^{1–3}.

Stromal cells are CD34 positive^{1,2}. CD34 positive cells are called »dendritic interstitial cells«⁴. According to Khan³, fibroadenomas are hyperplastic and phyllodes tumors neoplastic lesions.

Clinically fibroadenomas are well circumscribed, hard, oval, movable lesions. They can be solitary, multiple, unilateral and bilateral^{6,7}. They are hormone dependent changes, because they change own consistency

during menstrual cycle and gravidity. The most commonly used histological classification is in two types: pericanalicular and intracanalicular (type). This division has no clinical implication. There are some morphological changes in fibroadenomas as: focal stromal multinuclear cells, foci of mature adipose tissue, smooth muscle cells and metaplastic changes. In fibroadenomas we can sometimes see focal lactation changes, field of fibrocystic changes, apocrine changes and multifocal changes (fibroadenomatoid hyperplasia). Juvenile fibroadenoma starts earlier but histologically is not different from usual type. Fibroadenomas bigger than 10–15 cm in diameter are called giant fibroadenomas. Fibroadenomas can be multiple and can be associated with breast carcinomas. There are no genetic changes in fibroadenomas and most scientists think that there are no increased risks for subsequent breast carcinoma⁸.

Phyllodes tumors makes about 1% of all breast tumors. This tumor has many synonyms⁹. It starts as fibroadenoma in intralobular stromal component. It has continuous growth and biologically it can be benign, borderline and malignant. The first description is from Miller (1838). Tumor phyllodes arise about ten years after fibroadenomas. The current opinion is that phyllodes tumors smaller than 4 cm in diameter are benign, between 4 and 8 cm are borderline, and bigger than 8 cm are malignant. It has papillary projection on outside surface and this projection can be the reason for recurrence after surgery. The histological picture is sometimes different from that in fibroadenomas (Figures 2, 3, 4, 5).

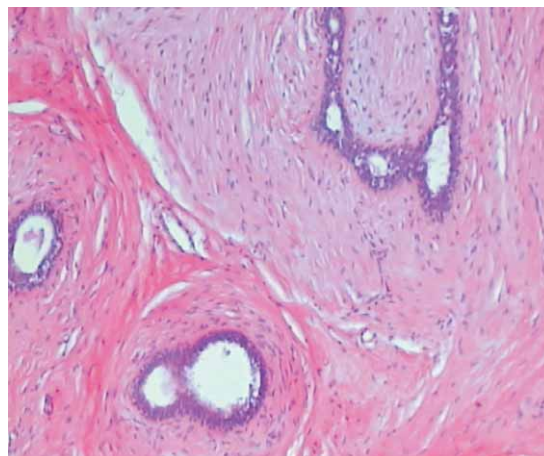


Fig. 2. (HE, 100x) Mixed picture of fibroadenoma (lower left) and tumor phyllodes (upper right).

There are three biologically different categories: benign (0–4 mitoses per 10HPF), borderline (5–9 mitoses per 10HPF) and malignant (more than 9 mitoses per 10HPF). Malignant phyllodes tumors metastasize in lung (66%), bones (28%), heart (9, 8%) and liver (5, 6%). There are described metastases also in omentum, stomach, pancreas, mesenterium, kidneys, adrenals, and so on.

Therapy depends on histological diagnosis^{10,11}. In fibroadenomas, surgical excision is the therapy of choice¹². The cut resection can be close to tumor but in phyllodes tumor the cut resection has to be about 2 cm away of the edge of tumor, because some rest of finger like protrusions can be the reason of recurrence. In metastases we can see only stromal cell component and this look like sarcomatous metastasis^{13,14}.

Material and Methods

The main goal is to find the divergence point when the developing is direct to fibroadenoma or phyllodes tumor. The second goal is to investigate the fate of epithelial and stromal component in these two lesions.

We made retrospective analysis of all fibroadenomas and phyllodes tumors in Pathology Department of »Bežanijska kosa« Medical Center in the period from 1989 to 2006 (Table 1, Figure 1). In this period, 2919 women were operated for breast changes. 343 fibroadenomas were diagnosed (24, 4%), benign phyllodes tumor in 95 women (6, 7%) and malignant phyllodes in 4 cases or 0,2%.

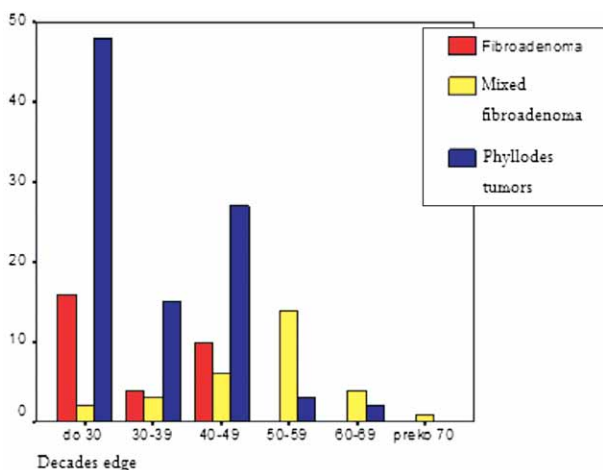


Fig. 1. The frequency of fibroadenoma and phyllodes tumors.

TABLE 1
THE DISTRIBUTION OF FIBROADENOMAS AND PHYILLODES TUMORS

	Frequency	Percentage	Valid percentage	Cumulative percentage
Fibroadenoma pure	30	19.4	19.4	19.4
Fibroadenoma mixed	30	19.4	19.4	38.7
Phyllodes tumours	95	61.3	61.3	100.0
Total	155	100.0	100.0	

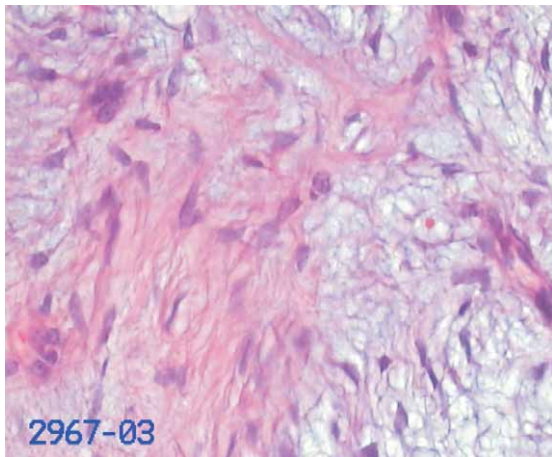


Fig. 3. (HE,200x). Two types of stromal cells in tumor phyllodes.

We took 30 fibroadenomas (15 without other proliferative changes and 15 with some proliferative changes) and 90 phyllodes tumors. All slides from these patients were analysed for many different histological parameters and we also used immunohistological investigation for steroid receptors, c-erbB2 (Her2/Neu), PCNA (proliferative cellular nuclear antigen) and Ki-67, androgen receptor and p53. All data were statistically investigated (Odds ratio, confidence interval, Fisher exact test, Wilcoxon sum test and Kendall test).

The mean age of operated women from fibroadenoma was 31. The youngest patient was seventeen years old and the oldest 49 years old, SD 10.866.

In the mixed group (fibroadenoma and other proliferative changes), the mean age was 59, 97, the youngest was 21 years old, the oldest 71 years old with SD 10.788. The mean age in the group with phyllodes tumor was 32, the youngest was 14, the oldest 63 and SD was 11.741.

In our series of patients, the mean ages with fibroadenoma and phyllodes tumors were very close, 31 and 32. The reasons for this are non-adequate clinical crite-

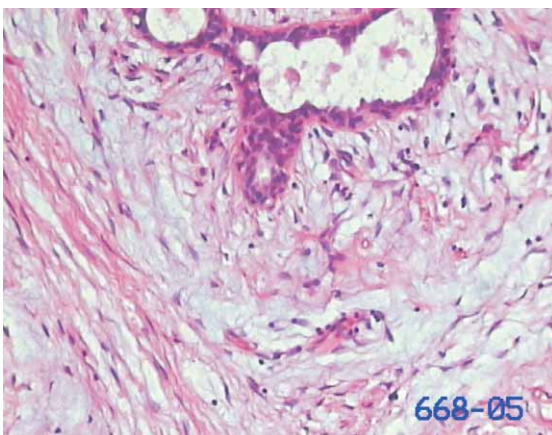


Fig. 4. (HE, 100x). Two cellular components of stroma in phyllodes tumor, and fascicle of smooth muscle cells.

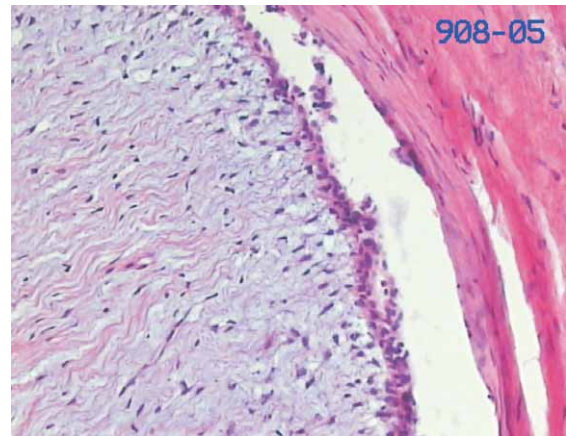


Fig. 5. (HE,100x). Perpendicular position of subepithelial stroma cells in phyllodes tumor.

ria. The mean age of patients in the group with other proliferative changes was 50.097. The patient was operated for other reason.

Results

Estrogen receptors

In 63.3% of cases, solitary fibroadenomas were estrogen negative, in 16.7% of cases, 30% of fibroadenoma cells were estrogen positive, in 56.7% mixed fibroadenoma were estrogen negative, 30% were estrogen positive. About 42, 5% of phyllodes tumors were estrogen negative, in 55% of cases, about 30% of cells were estrogen positive.

16, 7% of fibroadenomas showed about 30% stromal cells with estrogen receptors but this percentage in phyllodes tumor was present in 55% of cases.

There is no normal distribution according to estrogen positive cells in all three analyzed groups. (One Sample Kolmogorov-Smirnov $Z=1.962$ $p=0.001$ for solitary fibroadenoma, $Z=1.777$ $p=0.004$ for mixed fibroadenomas and $Z=1.715$ $p=0.006$ for phyllodes phyllodes tumors. There is no statistical difference in the number of estrogen positive cells in the three analysed groups (Kruskal Wallis test $\chi^2=1.481$ $p=0.484$).

The presence of estrogen receptors in stromal cells can explain higher proliferative activity as a reason of bigger growth. Phyllodes tumor accompanies growth of fibrous component neither in the epithelial component nor in fibroadenomas.

The receptors for estrogen were analyzed in epithelial and stromal cells (Figure 6). The positivity in epithelial cells can be a normal characteristic of these cells. Stromal cells in fibroadenomas are always negative. The positivity for estrogen receptors in epithelial cells in fibroadenomas is greater if these cells are hyperplastic.

The positivity of estrogen receptors in epithelial cells in phyllodes tumors is higher and uniformed in intensity but in phyllodes tumor we can see the positive reaction in

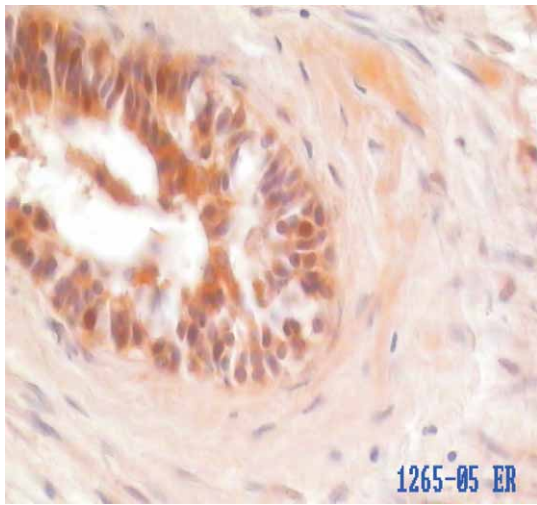


Fig. 6. (ER,100x). Strong positivity in epithelial cells and feeble in stromal cells.

stromal cells, especially in the cells close to ducts. Sometimes around ducts, we can see myoepithelial cells which are always negative for ER and PR.

Progesteron receptors

In the group of solitary fibroadenomas, progesteron receptors were negative in 43, 3% vs. mixed fibroadenoma which were negative in 53,% for PR.

The positivity for PR in phyllodes tumors was higher than in fibroadenomas which can explain its higher growth (Figure 7).

There is no normal distribution of progesteron receptor positive cells in all the three analysed groups. (One Sample Kolmogorov-Smirnov $Z=1.582$ $p=0.013$ for solitary fibroadenomas, $Z=1.956$ $p=0.001$ for mixed fibroadenomas and $Z=1.521$ $p=0.02$ for phyllodes tumors. There is no statistical significance in the number of progesteron positive cells in all the three group. (Kruskal Wallis test $\chi^2=4.180$ $p=0.124$).

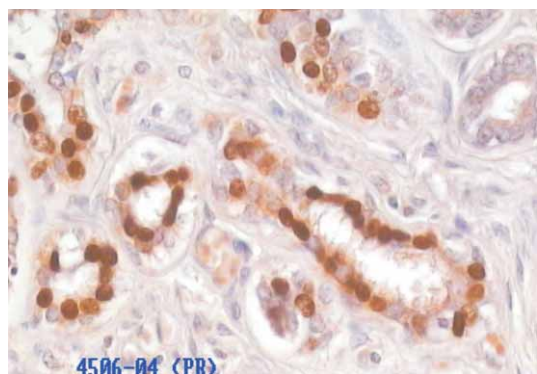


Fig. 7. (PR,100x). The positive reaction in epithelial and some stromal cells.

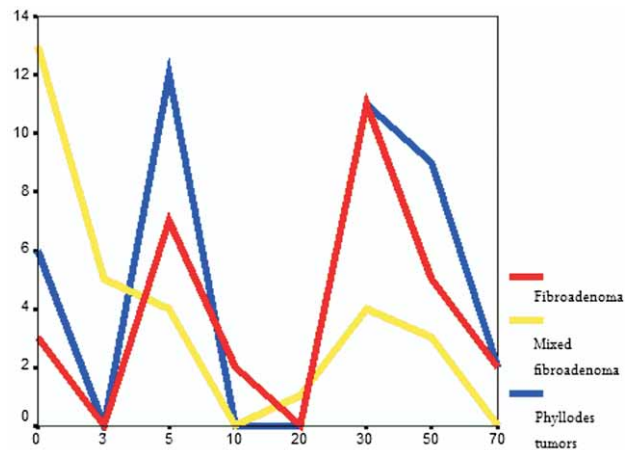


Fig. 8. The distribution of PCNA positive cells in fibroadenomas, mixed fibroadenomas and phyllodes tumors.

P-53

P-53 was negative in all fibroadenomas and in 82, 5% of phyllodes tumors. In some cases of phyllodes tumor the positivity was present in stromal cells^{15,16}.

Ki-67

In 83, 3% of solitary fibroadenomas, Ki-67 was negative, in the rest of cases, the finding was positive. In 73, 3% of mixed fibroadenomas, Ki-67 was negative and in 30%, it was positive. In 55% of phyllodes tumors, the finding of Ki 67 was negative, but in the rest of the cases, the finding was positive.

In cytoplasm of stromal cells in phyllodes tumors, spotty positivity of Ki 67 was present. The same finding was in some stromal cells^{17,18}.

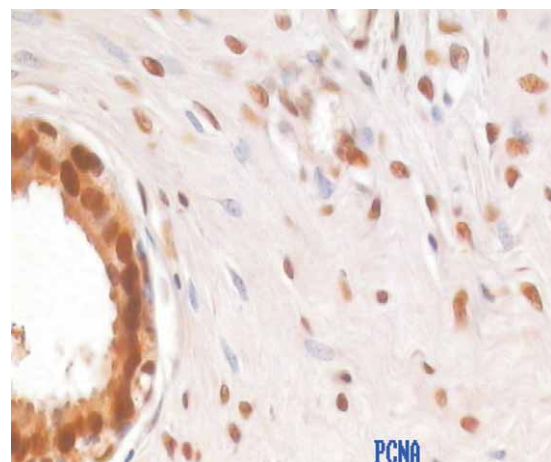


Fig. 9. (PCNA,200x). Ductal epithelial cells and most of the stromal cells are positive.

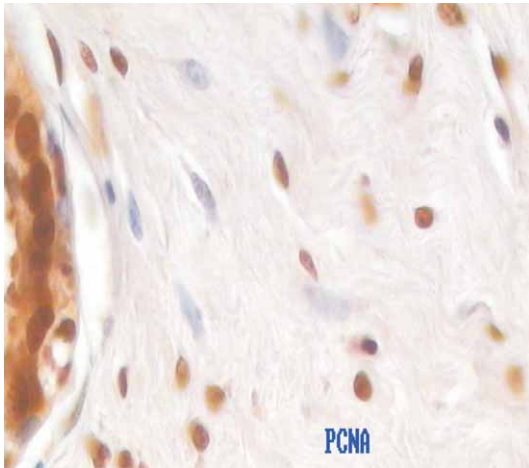


Fig. 10. (PCNA,200x). There are two types of stromal cells (positive and negative).

PCNA (Proliferative Cell Nuclear Antigen)

In 10% of solitary fibroadenoma, PCNA was negative, in 23.3%, there was 5 % of positive cells, in 6.7%, there was 10% of positive cells, in 36.7%, there was 30% of positive cells, in 16.7%, there was 50% of positive cells, and in 6.7 %, there was 70 % of positive cells.

In 43.4%, mixed fibroadenoma PCNA was negative, but in the rest of the cases, it was positive up to 50 %. In 15% of phyllodes tumors, PCNA was negative, in 30%, there was 5% of positive cells, and in the rest of the cases, it was positive up to 70%. (Figure 10).

In fibroadenomas and in phyllodes tumors, PCNA was positive in high percentage (90:85%). This indicates that both lesion have proliferative potential¹⁹.

There is normal distribution of PCNA positive cells in solitary fibroadenoma (One Sample Kolmogorov Smirnov $Z=1.026$ $p=0.243$) (Figure 8), but there is not normal distribution in mixed fibroadenomas (One Sample Kolmogorov Smirnov $Z=2.024$ $p=0.01$), nor in phyllodes tumors (One Sample Kolmogorov Smirnov $Z=1.674$ $p=0.007$). There is important difference in the number of PCNA positive cells in the three analyzed groups (Kruskal Wallis test $\chi^2=15.0861$ $p=0.001$). There is important statistical difference between solitary fibroadenoma and mixed fibroadenomas (Man Whitney $U=219.000$ $p<0.001$). There is important statistical difference between mixed fibroadenomas and phyllodes tumors (Man Whitney $U=329.500$ $p=0.001$). There is not important statistical difference between solitary fibroadenomas and phyllodes tumors (Man Whitney $U=567.000$ $p=0.686$). Solitary fibroadenomas and phyllodes tumors have remarkable number of PCNA positive cells²⁰.

In very cellular lesions, positive reaction on PCNA is present in epithelial and stromal cells (Figures 9, 10, 11, 12). This indicates that both components are active and their cells are normally or intensively divided. In the lesions where the growth is stopped, only some epithelial cells are positive.

Androgen

In 60% of solitary fibroadenomas, androgen was negative but in the rest of the cases, it was positive up to 50%. In mixed fibroadenomas, androgen was negative in 76.7% of the cases, and in the rest, it was positive up to 10%. In 47.5% of phyllodes tumors, androgen was negative, in 37, 55, it was positive up to 20%, and in the rest of the cases, it was positive up to 30%.

In the cases of phyllodes tumors, androgen was positive in more than half of the cases, which shows us the possible influence on proliferation of these cases^{21–23}.

In the normal distribution of the number of androgen, there are not any positive cells in the three investigated groups (One Sample Kolmogorov-Smirnov $Z=1.872$ $p=0.02$ for solitary fibroadenomas $Z=2.516$ $p<0.001$; for mixed fibroadenomas and $Z=1.955$ $p=0.01$ for phyllodes tumors).

There is important statistical difference in relation to androgen positive cells in the three analysed groups (Kruskal Wallis test $\chi^2=8.678$ $p=0.013$). There is important statistical difference between solitary and mixed fibroadenomas (Man Whitney $U=340.500$ $p=0.049$), between mixed fibroadenomas and phyllodes tumors (Man Whitney $U=371.000$ $p=0.002$), but not between solitary fi-

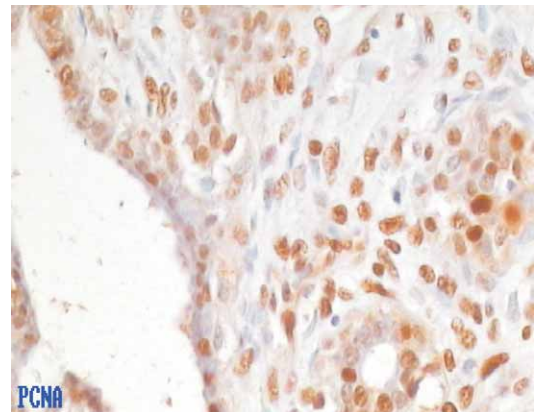


Fig. 11. (PCNA, 100x). Intensive positivity of stromal cells.

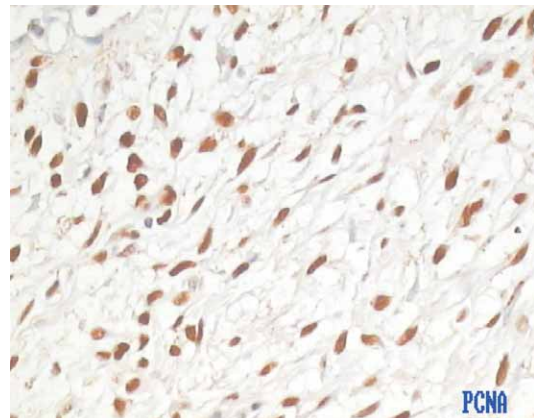


Fig. 12. (PCNA, 100x). Intensive positivity of stromal cells.

broadenomas and phyllodes tumors (Man Whitney U= 576.500 p=0.760). More androgen positive cells were present in solitary fibroadenomas and phyllodes tumors.

Discussion

Fibroadenomas and phyllodes tumors are fibroepithelial tumors which arise from intralobular fibrous tissue^{23,24}. In the very beginning, both of these tumors are very similar in composition but histological divergency starts later²¹. Fibroadenomas can be solitary or associated with other breast changes, most commonly with fibrocystic dysplasia²² or with malignant tumor in the opposite breast. The histological criteria are not strong for small lesions. It is very important to differentiate small fibroadenomas from fibrous foci in other malignant tumors. In our series, there were 343 fibroadenomas and 95 phyllodes tumors (343:95 or 11, 8:3, 3%). We divided fibroadenomas in »pure« group and in mixed group where they are associated with other proliferative changes. Quite common association with fibrocystic dysplasia, adenosis and carcinoma indicates hormonal dysregulation. In fibroadenomas the stromal component, there is some type of collagenisation or very different types of metaplasia. The proliferative process can stop when the lesion grows up to 2–3 cm and the stromal component also stops with proliferation. In phyllodes tumor, stromal component continues to grow and some finger like projections are made. These projections are blamed for recurrent disease^{24,25}. In proliferative stroma in phyllodes tumors, we can see two types of cells: periductal cells and the cells located deeper²⁶. Phyllodes tumors can be malignant and they metastasize in lung not in auxiliary lymph nodes²⁷. There are no cases of fibroadenomas which had malignant stroma but carcinomas can develop from ductal epithelial cells. We analyzed steroid receptors in fibroadenomas and phyllodes tumors²⁸. Many investigators believed that estrogen and progesteron receptors are important for growth^{29–32}. We also analyzed p53 and Ki-67 in both lesions. In our cases p53 was negative in all fibroadenomas and in 80% of phyllodes tumors. In 155 of phyllodes tumors stromal cells showed p53 expression. Ki-67 was negative in 80% of fibroadenomas and positive in 45% of phyllodes tumors. The grade of proliferation

correlates with the growth of changes in the breast³³. PCNA was positive in fibroadenomas and phyllodes tumors. The positivity was greater in phyllodes tumors. In phyllodes tumors, the positivity of PCNA is present in stromal cells and in epithelial cells. The presence of PCNA positivity is in early fibroadenomas and phyllodes tumor. In later stages, the PCNA positivity is higher in phyllodes tumors. This explains the continuous growth of phyllodes tumors. Myoepithelial cells in phyllodes tumors are never positive for PCNA. In phyllodes tumors, androgen receptors are also positive. Androgen was positive in myoepithelial and stromal cells.

Conclusions

1. Fibroadenomas and phyllodes tumors arise from intralobular fibrous tissue.
2. In early phases of evolution we can see elements of both tumors.
3. Fibroadenomas grow up to 2–3 cm and then stop but phyllodes tumors grow farther.
4. Both tumors have two components, epithelial and fibrous.
5. Epithelial cells can be positive for ER, PR and androgen sometimes.
6. Stroma in fibroadenomas is less cellular than in phyllodes tumors.
7. PCNA and Ki-67 are more often positive in stromal cells of phyllodes tumors than in fibroadenomas.
8. Expression of androgen receptors is more often in phyllodes tumors.
9. Evolution of fibroadenoma is directed to calcification and collagenisation but evolution of phyllodes tumors is directed to cystic degeneration.
10. Phyllodes tumors can be benign, borderline and malignant.
11. Fibroadenomas almost never undergo malignant transformation.
12. Capsule in fibroadenoma is pseudocapsule but in phyllodes tumors is perforated with fingerlike projections.
13. All these changes are caused by growth factors.

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FILOIDNI TUMORI I FIBROADENOMI. ISTI POČETAK, RAZLIČIT ZAVRŠETAK

SAŽETAK

Filoidni tumori i fibroadenomi najčešći su benigni tumori dojke. Nastaju od intralobularnoga fibroznog tkiva kao jedinstvena promjena, a kasnije se diferenciraju u dva smjera: fibroadenom ili filoidni tumor. Fibroadenomi dostižu veličinu 2 do 3 cm i tada obično prestaju rasti, a filoidni tumori nastavljaju rasti i mogu dostići veličinu do 40 cm. Obje lezije sastoje se iz dvije komponente: epitelne i stromalne. Klinički fibroadenomi dobro su ograničene, čvrste, ovalne i pokretne lezije. Mogu biti solitarne, multiple, unilateralne i bilateralne. To su hormonalno ovisne promjene jer mijenjaju svoju konzistenciju tijekom menstrualnoga ciklusa i trudnoće. Histološki dijele se na dva tipa: perikanalikularni i intrakanalikularni tip. Filoidni tumori čine 1% svih tumora dojke. Ova vrsta tumora ima puno sinonima. Javlja se kao fibroadenom u intralobularnoj stromalnoj komponenti. Ima kontinuirani rast i biološki se dijeli na benigni, granični i maligni. Prvi ga je opisao Miler (1838.). Glavni je cilj ovoga rada bio je odrediti točku divergencije u tijeku razvoja koja tumor usmjerava ili k fibroadenom ili k filoidnom tumoru dojke. Drugi je cilj bio utvrditi ulogu epitelne i stromalne komponente u ove dvije lezije. Retrospektivnom analizom obuhvaćeni su svi fibroadenomi i filoidni tumori Službe za patologiju KBC »Bežanijska kosa« u periodu od 1998. do 2006. godine. U navedenom vremenskom periodu promjene u dojci operiralo je 2919 žena, dijagnosticirano je 343 fibroadenoma, 95 benignih filoidnih tumora i 4 maligna filoidna tumora. Svi uzorci ovih pacijentica analizirani su različitim histološkim parametrima i obrađeni imunohistokemijski na steroidne receptore, c-erbB2(Her2/Neu), PCNA, Ki-67, androgene receptore i p53. Svi podatci statistički su obrađeni. Zaključak je da fibroadenomi i filoidni tumori nastaju iz intralobularnog fibroznog tkiva. Obje su promjene na početku histološki veoma slične, a divergentni rast javlja se kasnije. Razlike se javljaju u stromalnoj komponenti. Filoidni tumor ima dvokomponentnu stromu. Stromalne stanice kod filoidnog tumora više su PCNA pozitivne nego kod fibroadenoma, kao i Ki-67 i androgeni receptori. Histološki filoidni tumori perforiraju kapsulu s »finger like« projekcijama. Ovaj podatak značajan je za kirurške zahvate jer se zbog toga kod filoidnih tumora radi široka ekcizija, a kod fibroadenoma obična ekcizija.