

Unpredictable behavior of breast phyllodes tumors

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Abstract. – OBJECTIVE: Phyllodes Tumor is a rare fibroepithelial breast tumor with variable malignant potential. These tumors that currently accepted nomenclature are benign, borderline and malignant according to the World Health Organization. It tends to behave in a benign way but it may undergo a malignant transformation. The purpose of this study was to present our Case load of phyllodes tumor, and evaluate the management and follow-up the behavior of these tumors.

PATIENTS AND METHODS: 36 patients with phyllodes tumor were treated in Bezmialem Vakif University and Okmeydani Training and Research Hospitals analyzed retrospectively. Demographics, presenting symptoms, history, local examination, preoperative clinical diagnosis, treatment, postoperative histopathology, follow-up period were evaluated retrospectively and studied.

RESULTS: A total of 36 patients treated for phyllodes tumor were analyzed. Mean age of the patients was 38 (14-79) and all were females. The presentation of the patients was breast lump in all cases, either as a primary or recurrent lump presentation. The right and left breast were affected 58% and 42% respectively. 34 of these 36 cases are briefly mentioned in this paper but the two cases, one with sarcomatous malignant transformation and the other with fatal metastatic phyllodes tumor in an adolescent female are discussed in detail. The mean duration of the symptomatic mass was 9.8 ± 7.3 months (range 0.5 to 24).

CONCLUSIONS: Phyllodes tumor is a type of tumor that may be benign or malignant. The type with malignant features may be fatal. The tumors diagnosed as benign may transform and become malignant because of unknown reasons and may be an aggressive tumor.

Key Words:

Phyllodes tumor, Malignant, Transformation.

Introduction

Phyllodes tumor (PT) of the breast is an uncommon biphasic fibroepithelial neoplasm that accounts for less than 1% of overall breast neoplasm. It has been first described by Muller in 1838 and he named Cystosarcoma phyllodes because of based on a gross pathological description of a bulky, cystic, fleshy and leafy tumor of the breast. Its incidence is 0.3-0.9% among all other breast tumors¹⁻³.

These tumors that currently accepted nomenclature are benign, borderline and malignant according to the World Health Organization (WHO)⁴. Phyllodes tumors were defined as mixed epithelial and stromal/mesenchymal proliferation of breast characterized by increased stromal cellularity and characteristic broad “leaf-like” papillae inserted into cleft-like spaces⁵. PT is a slow growing tumor for many years; alternatively onset tumors may exhibit a rapid growth from the onset of symptoms. Microscopically, they are similar to fibroadenoma. The main features differentiating from the fibroadenoma are as follows: connective tissue growth is more than epithelial tissue and cells within the tissue increased. Elements of connective tissue are pleomorphic and include mitotic areas. Myxomatous degeneration may occur within the stromal area⁶⁻⁸. Although histological criteria have been defined by several authors, these criteria are not consistently predictive of malignant tumor behavior⁹⁻¹¹.

Due to difficult preoperative diagnoses and unpredictable clinical outcomes, these tumors must be suspected in patients with rapid-growing breast lumps, to avoid inappropriate management. Surgery has become the primary role for the treatment of phyllodes tumor, with breast-

conserving therapy being the most common choice of treatment. The purpose of this study was to present our series for phyllodes tumor, and evaluate the management and follow-up the behavior of these tumors.

Patients and Methods

36 patients with PT were treated in Bezmialem Vakif University and Okmeydani Training and Research Hospitals analyzed retrospectively. Demographics, presenting symptoms, history, local examination, preoperative clinical diagnosis, treatment, postoperative histopathology, follow-up period were evaluated and studied. World Health Organization (WHO) pathological classification was followed in every case from the pathologists of concerned institutes. 34 of these 36 cases are briefly mentioned in this paper but the two cases, one with sarcomatous malignant transformation and the other with fatal metastatic PT in an adolescent female are discussed in detail under the guidance of literature.

Statistical Analysis

Statistical analysis was done using Student's *t* test and analysis using SPSS version 11 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

A total of 36 patients treated for phyllodes tumor were analyzed. Mean age of the patients was 38 years (14-79) and all were females. The presentation of the patients was breast lump in all cases, either as a primary or recurrent lump presentation. The mean duration of the symptomatic mass was 9.8 ± 7.3 months (range 0.5 to 24). The right and left breast were affected 58% and 42%, respectively. The mean size of the presenting breast lump was 6.4 cm (range 1.5 to 25 cm). Preoperative diagnoses were 8 cases fibroadenoma, 17 cases pyhllodes tumor, 4 cases malign tumor, 4 cases unknown tumor, 1 case pyhllodes tumor or breast sarcoma and 2 cases malign pyhllodes tumor that diagnosed by pathology and imaging methods. Wide local excision of the tumor was performed for 24 patients that take care to keep a sufficient margin of healthy tissues, which reduces the risk of local recurrence. One of these 24 patients was diagnosed as a fibroade-

noma preoperatively and performed local excision. In consequence of the malignant histopathologic character of phyllodes tumor and tumor positive borderline result in this current case, quadraneotomy was performed within 2 weeks. Otherwise, simple mastectomy was performed for 9 patients. Mastectomy with level 1 clearance and latissimus dorsi myocutaneous flap reconstruction was performed for the patient with recurrence malignant phyllodes tumor. Modified radical mastectomy was performed for the patient with preoperative carcinoma diagnosed and breast conserving surgery for the patient with recurrence borderline phyllodes tumor. Histologic classification revealed 15 benign (41.6%), 5 borderline (14%) and 16 malignant (44.4%) (including 6 malignant transformation that previously diagnosed as benign or borderline) phyllodes tumor. Multifocal lesions were detected in 2 (5.5%) cases in the same breast, and the histologic characteristics of the lesion in each case were malignant phyllodes tumor. One of these two cases had a togetherness of malignant phyllodes tumor and lobular carcinoma in situ.

Adjuvant radiotherapy and chemotherapy (two cycles of trial of mesna 2 g/m², ifosfamide 2 g/m², epirubicin 50 mg/m², decarbazine 300 mg/m² each divided over 2 days) were used in one case and only chemotherapy was administered to one case. There were no response in both of two cases and they were died within 1 year because of distant metastases. Patient characteristics are shown in Table I.

Case 1

A 16-year old female was admitted with complaints of an ulcerated and bleeding mass at the

Table I. Patient characteristics and clinical situation before operation.

Patients (n: 36)	
Age (years)	38 (14-79)
Tumour localization	
Right breast	21 (58%)
Left breast	15 (42%)
Preoperative diagnosed	
Fibroadenoma	8
Pyhllodes tumor	17
Unknown tumor	4
Phyllodes tumor or breast sarcoma	1
Malign Phyllodes tumor	2
Malign tumor	4

Table II. Tumor characteristics of patients and follow-up time.

Patients (n: 36)	
Tumor Size (cm)	6.4 (1.5-25)
Single Tumor	35
Multiple Tumor	1
Recurrence	5
Recurrence Tumor Size (cm)	6 (3-12)
Died	2
Follow-up Time (months)	29.5 (4-80)

left thoracic wall. The tumor had been noticed one year before, and she underwent simple mastectomy 8 months ago in another hospital. The histological examination revealed malignant PT but there were no relevant information about surgical borders of tumor. The diagnosis was established by reexamination of paraffin slices. Two months after the operation, the recurrence was noted in the lateral portion of the previous incision. On clinical examination; painful, partially mobile, lobulated tumor was found occupying the whole upper left lateral thoracic wall and axillary fossa. In the lower lateral part of the mass, there was an area of pressure necrosis. Ultrasound showed an irregular mass consisting of solid and cystic components. CT showed a mass occupying left axillary fossa and infiltrating thoracic wall and axillary vascular components. The tumor was 19 × 15 × 15 cm size with heterogeneous low density, and there were two pulmonary metastatic lesions in the left lung. Because of massive hemorrhage in the lesion, local tumor excision was performed immediately. Defect was repaired with latissimus dorsi musculocutaneous pedicled flap. Histopathology was consistent with the initial operation (Figures 1 and 2). On postoperative 27th day, she complained of a non-productive cough and dispnea. Chest radiogram and CT showed opacification of left hemithorax and mediastinal shifting toward the right side. Closed tube drainage performed for 8 days. The patient died of progressive disease 1 year after the initial operation.

Table III. Patients histopathological classification.

Patients (n: 36)	
Benign	15 (41.6%)
Borderline	5 (14%)
Malignant	16 (44.4%)
Malignant transformation	6 (16.6%)

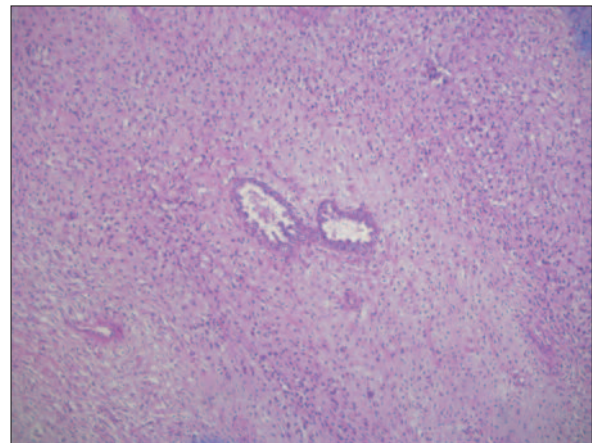


Figure 1. Sarcomatous overgrowth in pyhllodes tumor. Epithelial component was identified only after extensive search. (H&E × 40).

Case 2

A 56 years old female patient was admitted to our clinic by complaining from a mass in right breast. Physical examination revealed a 6x6 cm palpable mass at upper outer quadrant of the right breast which is mobile, soft and distinguishable from the surrounding tissues by its lobulated contours. The result of the fine needle aspiration biopsy of the mass was consistent with fibroadenoma. By mammography, two masses with a diameter of 3 cm were seen in right breast upper outer quadrant; their contours were regular and they were superimposed onto each other. The mass was removed by total excision. Histopathological diagnosis was PT with mitotic activity under two and sufficient margin of healthy borders. The patient was lost to follow-up during 1 year after surgery.

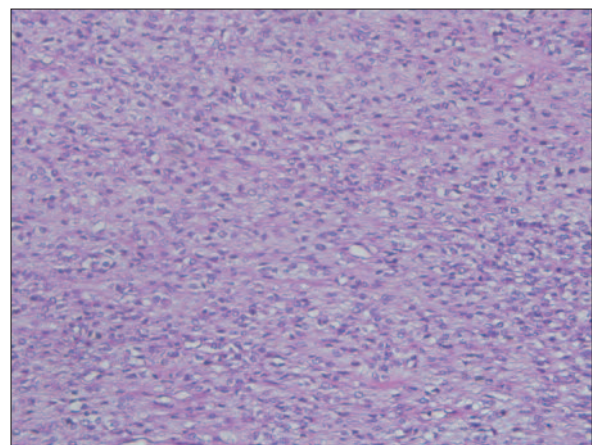


Figure 2. A cellular spindle cell stroma with moderate degree dysplasia. (H&E × 200).

She was referred to our clinic once again by complaining of a mass at the same breast. Physical examination revealed a 10 × 5 cm palpable mass with prominent contours at upper outer quadrant of the right breast which is hard, mobile and painless with no palpable axillary lymph node. By mammography, at right breast upper outer quadrant there was a 9 × 9 cm space occupying lesion was seen with relatively readily distinguishable lobulated contours and homogenous density. Based on these findings the diagnosis was considered as PT and quadrantectomy was performed. Histopathologically, overgrowth of the sarcomatous component occurred and a cellular spindle cell stroma with mitotic figures were detected in our case (Figure 3). Histopathological examination has revealed monophasic sarcomatous tumor originated from the background of PT but simple mastectomy was performed because of suspicious surgical borders.

Discussion

Phyllodes tumors are rare breast fibroepithelial neoplasms with an incidence of less than 1% of all breast tumors that are sometimes difficult to preoperative diagnoses and can be potentially aggressive. Phyllodes tumor classification was proposed as benign, borderline and malignant categories according to cellular atypia, mitotic activity, tumor margin status, stromal cellularity and overgrowth^{12,13}. In consequence of unpredictable clinic outcomes, these tumors must be suspected in patients with rapid-growing breast lumps.

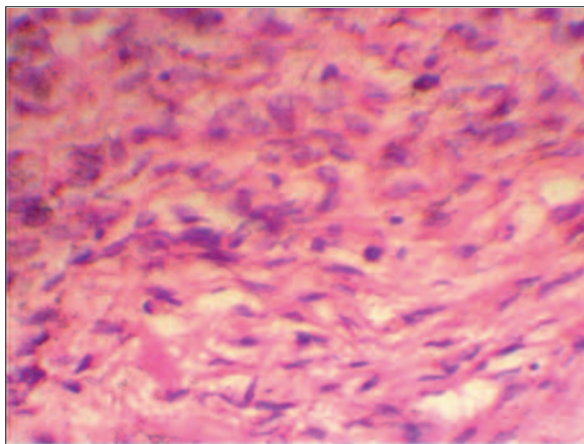


Figure 3. A cellular spindle cell stroma with 0-2 mitotic figures per 10 HP these tumors have a potential for local recurrence but are very unlikely to metastasize. (H&E × 400).

Although the relationship to fibroadenoma was estimated, the cause of phyllodes tumors was not clearly understood. The curious question is whether a phyllodes tumor originates from fibroadenoma and other benign breast disease or is caused by to completely different process. In histopathological examination, microscopic findings of phyllodes tumors are different from those of fibroadenoma. PT that are determined as biphasic neoplasms consist of epithelial cells and fibrose connective tissue with more stromal proliferation than fibroadenoma^{14,15}. Contrary to phyllodes tumors, fibroadenoma shows low stromal cellularity, true capsule and no evidence of mitoses or pleomorphism in most cases. There are studies suggesting that the disease stems from background of fibroadenoma¹⁶. Noguchi et al¹⁷ suggested that fibroadenoma should be regarded as a hyperplastic lesion rather than a neoplasm because of the polyclonal components. In one of our two cases, histopathological examination of the one year ago excised mass at the same breast was found to be fibrocystic disease and in the other one there was history of fibroadenoma excision from the left breast 15 years ago. Features of these two patients appear to be supportive of the above mentioned literature.

According to the 2003 WHO tumor classification phyllodes tumors were commented into three categories as benign, borderline and malignant¹⁸. Others have subdivided phyllodes tumors into benign and malignant and further categorized the malignant group into low and high grades, essentially still resulting in a 3-tiered classification, with low-grade malignant and borderline lesions being synonymous¹⁹⁻²¹. PT is mostly benign but 10 to 30% of cases may reveal histologically malignant features²². Malignant forms are reported in the literature as 23-54%²³. In our cases we obtained 15 benign (41.6%), 5 borderline (14%) and 16 malignant (44.4%) (including 6 malignant transformation that previously diagnosed as benign or borderline) phyllodes tumor. Predominant findings of the malignant forms are pleomorphic cells, increased mitotic activity and abnormal mitosis and presence of necrotic areas. There are a lot of prognostic factors in PT including diameter of the tumor, stromal growth strength, tumor necrosis, mitosis rate, stromal cell structure and size of the nucleus and pleomorphism²⁴⁻²⁶. Also Ki67 index that indicator of the proliferative activity and expression of the p53 protein in tumor cells could be useful as a predictive indicator^{2,27,28}. Age, duration of

symptoms, clinical tumor size and type of surgery aren't considered as prognostic factors²². 16 of our cases (including 6 malignant transformation that previously diagnosed as benign or borderline) were malignant PT. The presence of infarction or tumor necrosis were correlated with grade and recurrence²⁹. We observed that our malignant PT patients had a large high-grade tumor with increased mitotic activity and it was associated with areas of necrosis. The concomitance of these tumors with ductal or lobular malignant neoplasm is rare. The literature reported the association of phyllodes tumors with malignant epithelial components mainly in the form of ductal or lobular in situ lesions and less often in the invasive form³⁰. One case in our series that had three separate masses, togetherness of malignant phyllodes tumor and lobular carcinoma in situ was seen.

There are no any pathognomonic signs that are evaluated via mammography and ultrasonography. These lesions commonly present as voluminous isodense mass to breast parenchyma, a sharply defined round or oval mass with lobulation, usually greater than 5 cm, in mammography images¹. In ultrasound, they are generally characterized as heterogeneous internal echoes and intramural cysts signs³¹. We had only three cases that had well-defined mass lesions correlated with postoperative histopathology.

Foxcroft et al³² reported that FNAC and core biopsy have difficulties with diagnosis of PT. In cases where core biopsy and FNAC were done at the visits, they found correct diagnosed 65% and 23% of PTs, respectively. In our study, 60% PT diagnosis was made preoperatively on the basis of core biopsy only which is consistent with other studies.

The treatment for phyllodes tumors remains surgical removal of this tumor. There were controversies regarding extent of the surgery performed for this disease. Breast-conserving surgery appears to be appropriate primary therapy for patients with PT of the breast. The most favorite treatment approach is local excision. The relation between surgical approach and recurrence is still being debated but the preferred opinion is such that local recurrence is not related with the type of surgical treatment. However insufficient clearance of surgical borders was accepted as effective factor for local recurrence. Local recurrence usually occurs within the first two years after the surgery. A recurrent lesion is often more aggressive histologically than prima-

ry tumor. The incidence ranges between 7.5-58.8% in various manuscripts^{23,33-34}. Recurrent cases are treated by simple mastectomy and the treatment of choice is radical mastectomy in patients with pectoral muscle infiltration. Axillary dissection should be performed only in patients whom axillary spread is present^{35,36}. The role of adjuvant treatments is unproven and must be considered on a case-by-case basis. We observed local recurrence in our seven cases (19.4%) within first two years after operations. The nearest healthy surgical margin was 1-2 cm in histological study for these seven cases. Haagensen was reported that the healthy border in order to prevent local recurrence was 1-2 cm³⁷. Local recurrence of benign PT is suggestive of an aggressive tumor or malignant transformation. Stromal overgrowth, larger tumor size and involved margin were all significantly correlated with local recurrence.

The presence of exclusively sarcomatous elements within the tumor, without epithelial phylloid structures, along with the small size of tumor established the diagnosis of a pure sarcoma, and not a malignant phyllodes tumor³⁸. The stromal components may contain liposarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, angiosarcoma, chondrosarcoma and osteosarcoma. Malignant PT must be differentiated from primary stromal breast sarcomas. For this reason it is important to adequately sample the neoplasm to determine whether ductal elements are present. In the absence of epithelial cells the neoplasm is classified as primary stromal sarcoma of the breast which is generally more aggressive than PT¹⁰. In various publications the rate of malignant transformation differs^{3,39}. Local recurrence occurred in 7 of our cases. One of this case's recurrence material came out to be sarcomatous malignant transformation. Histologically PT is composed of a benign epithelial component and cellular spindle-cell stroma; the tumor is characterized by formation of leaf-like processes protruding into cystic spaces. The epithelial elements lining the ducts and slit-like spaces and covering the leaf like processes consist of the two cell type's characteristic of the mammary duct system. As a rule the stroma is more cellular than that of fibroadenomas and it is generally fibrosarcomatous in appearance, spindle-shaped fibroblastic cells generally constitute the stroma but highly atypical and multinucleated cells also occur. Clinically most of these tumors tend to

behave in a benign fashion, but they can recur locally and can undergo malignant progression to sarcoma⁴⁰. As in our case the overgrowth of the sarcomatous component occurs in some cases, but this feature has been quantities only recently^{41,24,38}. Sarcomatous overgrowth may severely diminish the epithelial elements to a very few minuscule foci.

Benign phyllodes tumors rarely spread (metastasis) to other parts of the body, while borderline phyllodes tumors metastasize in about 4% of patients (1 of 25) and malignant phyllodes tumors metastasize in 22% of patients (about 1 in 5)⁴². There may be distance metastasis in malign cases with or without local recurrence after the surgical therapy. Metastasis usually spreads by blood stream. The prevalence ranges between 8-21%⁴³. In consequence of primarily hematogenous spread of these tumors, axillary lymph nodes are not palpable at presentation in most patients. Metastasis to axillary lymph nodes occurred in only 2%⁴⁴. We could not find any axillary metastasis in our case series. Optimal therapy for metastatic disease hasn't been determined yet. It's usually resistant to chemotherapy and radiotherapy. In several publications phosphamide, doxorubicin combination and cisplatin, etoposide combination were found to be effective^{23,36}. We used chemotherapy for 2 malignant PT cases but it was found to be ineffective and these two cases were died within 1 year.

Conclusions

Patients with phyllodes tumor must be followed carefully, since the clinical course is not predictable and whatever the histological type is initial surgical approach must be widely debated. Phyllodes tumor is a type of tumor that may be benign or malignant. The type with malignant features may be fatal. The tumors diagnosed as benign may transform and become malignant because of unknown reasons and may behave as an aggressive tumor. Therefore, extensive excision of the benign tumors and total removal may eliminate one of the most important factors in this malignant transformation.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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