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Clinicopathologic Features of Phyllodes Tumor in Breast

Memenin Filloides Tümörlerinin Klinikopatolojik Özellikleri

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ABSTRACT

Aim: Phyllodes tumors are rare breast neoplasms comprising less than 1% of all breast neoplasms. The objective of this study was to consider the clinicopathological features of phyllodes tumors that underwent surgery in our hospital.
Material and Methods: We retrospectively analyzed the medical records of 16 patients who had histologically diagnosed phyllodes tumors over 9 years.
Results: There were 16 female patients with a mean age of 45.6±15.3 years. Magnetic resonance imaging was performed in 5 cases for preoperative diagnosis, and 4 were reported as phyllodes tumors, all of these patients were having high-grade phyllodes tumors (borderline or malignant) histopathologically. Preoperative core biopsy was performed in 14 patients, and histopathologically phyllodes tumor was diagnosed in two patients. In six patients, differentiation between hypercellular fibroadenoma and phyllodes tumor could not be performed. Breast-conserving surgery was the most common type of operation performed in 10 (62.5%) patients, three patients with positive margins were underwent reoperation. The pathological diagnoses were benign, borderline, and malignant in seven (43.8%), five (31.3%) and four (25.0%) patients, respectively. The median diameter of the tumors was measured as 6 cm after the postoperative pathological analysis. The median follow-up time was 36 months. During this time, there was no local or systemic recurrence.
Conclusion: Wide excision with a clear margin appears to be the most important factor in the management of these tumors and in the prevention of local recurrence. The preoperative diagnosis of phyllodes tumors contributes to decreasing the necessity for secondary surgical intervention avoiding border positivity.
Keywords: Phyllodes tumor; breast; surgery.

ÖZ

Amaç: Memenin filloides tümörleri nadir görülen meme tümörleridir ve tüm meme neoplazmlarının %1'inden daha azını oluştururlar. Bu çalışmanın amacı filloides tümör nedeniyle hastanemizde opere edilen olguların klinikopatolojik özelliklerini irdelemektir.
Gereç ve Yöntemler: Histopatolojik olarak 9 yıllık süre içerisinde filloides tümör tanısı konulan 16 olgu retrospektif olarak hastane tıbbi kayıtlarından incelendi.
Bulgular: Yaş ortalaması 45,6±15,3 yıl olan 16 kadın hasta vardı. Preoperatif tanı için 5 olguya manyetik rezonans görüntüleme yapıldı ve 4'ü filloides tümör olarak raporlandı, bu hastaların tümü histopatolojik olarak yüksek gradeli filloides tümörlerdi (borderline veya malign). Preoperatif dönemde tanı amaçlı kor biyopsi 14 hastaya yapıldı ve iki hastaya histopatolojik olarak filloides tümör tanısı konuldu. Altı hastada hipersellüler fibroadenom ve filloides tümör arasında ayrım yapılamadı. Meme koruyucu cerrahi 10 (%62,5) hastada en sık yapılan operasyon tipi olup, meme koruyucu cerrahi yapılan ve cerrahi sınır pozitif gelen üç hasta tekrar ameliyat edildi. Patolojik tanı sırasıyla yedi (%43,8), beş (%31,3) ve dört (%25,0) hastada benign, borderline ve malign idi. Postoperatif patoloji sonuçlarına göre ortanca tümör çapı 6 cm olarak ölçüldü. Ortanca takip süresi 36 aydı. Bu sürede sistemik metastaz ya da lokal nüks görülmedi.
Sonuç: Sağlam cerrahi sınırla geniş eksizyon, hastalığın cerrahi yönetimi ve lokal rekürrensin önlenmesi için en önemli faktör olarak görünmektedir. Preoperatif dönemde tanı koymak sınır pozitifliğini önleyerek sekonder cerrahi müdahale ihtiyacını azaltmaya katkıda bulunur.
Anahtar kelimeler: Filloides tümör; meme; cerrahi.

INTRODUCTION

Phyllodes tumor of the breast is rare fibro epithelial breast tumor, comprising less than 1% of all breast neoplasms (1,2). Phyllodes tumors can occur at all ages, but the mean age is 37-52 (3,4). Based on histological criteria, phyllodes tumors are classified as benign, borderline, and malignant. These are including the degree of stromal cellularity, stromal cytologic atypia, mitotic activity, stromal overgrowth, and status of tumor margins; permeative/circumscribed (5).

Surgical resection is still the primary treatment modality for these lesions. However, which patients will benefit from adjuvant radiotherapy and which type of surgery should be performed, are unclear (6). Also patients' outcomes were affected by clinical factors such as age, delay in diagnosis or misdiagnosis and inappropriate and inadequate management. We aimed to present patient and tumor characteristics, the clinicopathological findings, preoperative diagnostic modalities and to evaluate treatment outcomes of the patients diagnosed with phyllodes tumors.

MATERIAL AND METHODS

This study was approved by the clinical research ethics committee of Erciyes University Faculty of Medicine with the number of 2019/880 and dated 25.12.2019. Sixteen patients with pathological diagnosis of phyllodes tumors who underwent surgery at Kayseri City Hospital and Kayseri Training and Research Hospital between 2010 and 2019 were included in the study and clinicopathologic properties, the treatment modality, and radiological and pathological diagnoses were retrospectively analyzed. Patients who were diagnosed as having phyllodes tumor by radiological modalities or core biopsy but not operated in our hospital were not included in the study.

Statistical Analysis

To summarize data obtained in the study, descriptive statistics were given as mean±standard deviation or median with the interquartile range (IQR), minimum maximum [min-max] depending on the distribution of the continuous variables, while categorical variables were summarized as numbers and percentages. The normality test of the numerical variables was controlled by the Sahapiro-Wilk test. In a comparison of more than two independent groups, the Kruskal Wallis H test was used for the numerical variables without normal distribution, and the Dwass-Steel-Critchlow-Fligner test was applied for the differences between the groups.In a comparison of categorical variables in the groups, Fisher-Freeman-Halton test was used for RxC tables. For statistical analysis and figures, Jamovi Project (2020), Jamovi (Version 1.1.9.0), [Computer Software] (Retrieved from https://www.jamovi.org) and JASP Team (2019), JASP (Version 0.11.1) programs were used, and the significance level was taken into account as 0.05 in statistical analysis.

RESULTS

The demographic and clinical features of the patients with phyllodes tumors are given in Table 1. There were 16 female patients with a mean age of 45.6±15.3 (range, 17-74) years. The median diameter of the tumors was 7 (range, 2-22) cm using imaging findings. Most (n=7, 43.8%) of the lesions were located at the central locations.

Table 1. Demographic and clinical features of the patients with phylloides tumor (n=16)

Variables	
Age (year)¶	45.6±15.3 [17-74]
Radiological tumor size (cm)‡	8.5±6.2 / 7 (6.5) [2-22]
Site†	
Right	9 (56.3)
Left	7 (43.8)
Quadrant†	
Upper outer	2 (12.5)
Upper inner	1 (6.3)
Lower outer	2 (12.5)
Lower inner	4 (25.0)
Central	7 (43.8)
Preoperative diagnostic modality†	
US	3 (18.8)
MG+US	8 (50.0)
US+MRI	1 (6.3)
MRI+MG+US	4 (25.0)
Clinical/radiological diagnosis*†	
Fibroadenoma	2 (16.7)
Phylloides tumor	4 (33.3)
Breast cancer	1 (8.3)
None	5 (41.7)
Preoperative pathological diagnosis*†	
Fibroadenoma	2 (14.3)
Phylloides tumor	2 (14.3)
Benign	3 (21.4)
Mesenchymal tumor	1 (7.1)
Hypercellular fibroadenoma / phylloides tumor	6 (42.9)
BIRADS category*†	
3	2 (25.0)
4	4 (50.0)
5	2 (25.0)
Surgery†	
BCS	10 (62.5)
Simple mastectomy	2 (12.5)
NSM	1 (6.3)
MRM	3 (18.8)
Pathological tumor size (cm)‡	7.8±4.5 / 6 (7) [3-18]
Surgical margin (cm)‡	2.3±1.5 / 2 (3) [1-4]
Pathological diagnosis†	
Benign	7 (43.8)
Borderline	5 (31.3)
Malignant	4 (25.0)
Positive surgical margins*†	
Posterior	1 (33.3)
Anterior	1 (33.3)
More than one side	1 (33.3)
Coexisting diagnosis*†	
Cystic disease of the breast	1 (6.7)
In-situ ductal carsinoma	1 (6.7)
Simple ductal hyperplasia	1 (6.7)
Chondorsarcoma-osteosarcoma	1 (6.7)
None	11 (73.3)
Local recurrence†	0 (0.0)
Systemic recurrence†	0 (0.0)
Postoperative radiotherapy†	1 (6.3)
Length of follow-up (month)‡	42.9±29.1 / 36 (38) [4-110]

¶: mean±standard deviation [minimum-maximum], ‡: mean±standard deviation / median (interquartile range) [minimum-maximum], †: n (%), *: less than 16 patients, US: Ultrasound, MG: Mammography, MRI: Magnetic Resonance Imaging, BIRADS: Breast Imaging And Reporting Data System, BCS: Breast Conserving Surgery, NSM: Nipple Sparing Mastectomy, MRM: Modified Radical Mastectomy

Phyllodes tumor was diagnosed preoperatively in four of 12 patients (33.3%) using clinical and imaging findings. However, there were two (16.7%) fibroadenomas and one (8.3%) breast cancer diagnosis. Preoperative core biopsy was performed in 14 (87.5%) patients. In six (42.9%) patients, differentiation between hypercellular fibroadenoma and phyllodes tumor could not be performed. Fibroadenoma and phyllodes tumor was diagnosed in two (14.3% for both) patients. Core biopsy results of 4 patients did not reach in patients' records.

Breast-conserving surgery was the most common type of operation performed in 10 (62.5%) patients. The median diameter of the tumors was measured as 6 (range, 3-18) cm after the postoperative pathological analysis. The pathologically negative margins after the surgery were recorded in 13 (81.3%) patients. Three patients who underwent breast-conserving surgery with positive margins were reoperated; in two patients mastectomy was performed and one performed re-excision. The final margin status is clear. The pathological diagnoses were benign, borderline, and malignant in seven (43.8%), five (31.3%) and four (25.0%) patients, respectively. Although the median diameter of the tumors was found to be statistically higher in the borderline group, most of the tumors were >5 cm in size, both in malignant and borderline groups (Table 2).

In terms of histopathological features of phyllodes tumors, mild stromal atypia and moderate stromal hyperplasia were seen in 11 (67.5%) and seven (43.5%) patients, respectively. Stromal overgrowth was absent in 11 (68.8%) patients. Although the mitotic counts were between 0 and 4 in seven (43.8%) patients, ≥10 mitoses were detected in four (25.0%). In general, diffuse involvement of the margins (p=0.008), marked stromal atypia (p<0.001) and hyperplasia (p<0.001), presence of stromal overgrowth (p=0.001), and more mitoses (p<0.001) were more likely to be associated with malignant phyllodes tumors (Table 2). There was a significant association between ≥10 mitosis and malignant phyllodes tumor (p<0.001). All counts of ≥10 were seen only in patients with malignant pathology.

The median follow-up time was 36 (range, 4-110) months. During this time, there was no local or systemic recurrence. Postoperative radiotherapy was needed in one patient who underwent breast conserving surgery, because of pathological diagnosis also includes ductal carcinoma in situ.

DISCUSSION

Phyllodes tumors are rare fibroepithelial lesions, and the mean age is 37-52 in different studies with high patient numbers (3,4,7). In our series, the mean age was 45.6±15.3 (range, 17-74), two cases were 17 years old; all others were older than 38 years old. Fibroadenomas are widely accepted as the most common tumors in young ages (8). Clinically to differentiate fibroadenoma from phyllodes tumor is difficult without histological confirmation. Juvenile fibroadenoma often has a size larger than 5 cm, but that can reach giant sizes; therefore, the size of the lesion is important for differentiation, but it is not a clear parameter (9,10). In literature, borderline and malignant phyllodes tumor is uncommon in adolescent girls and young women but seems to be occurring with increased frequency (11). One of our 17 years old patients was

Table 2. Comparison of histopathological features of phylloids tumor

Variable	Overall (n=16)	Benign (n=7)	Borderline (n=5)	Malignant (n=4)	p
Pathological size‡	7.8±4.5 6 (7) [3-18]	4.8±1.4 5 (2.5) [3-7]	11.2±4.5 12 (3) [5-18]	9.3±1.4 7 (9) [6-15]	**0.027**
Pathological size group†					
≤5 cm	6 (37.5)	5 (71.4)	1 (20.0)	0 (0.0)	0.058
>5 cm	10 (62.5)	2 (28.6)	4 (80.0)	4 (100)	
Margin status†					
Not-involved	11 (68.8)	5 (71.4)	5 (100)	1 (25.0)	
Focal involvement	2 (12.5)	2 (28.6)	0 (0.0)	0 (0.0)	**0.008**
Diffuse involvement	3 (18.8)	0 (0.0)	0 (0.0)	3 (75.0)	
Stromal atypia†					
Mild	11 (68.8)	7 (100)	4 (80.0)	0 (0.0)	
Moderate	2 (12.5)	0 (0.0)	1 (20.0)	1 (25.0)	**<0.001**
Marked	3 (18.8)	0 (0.0)	0 (0.0)	3 (75.0)	
Stromal hyperplasia†					
Mild	5 (31.3)	5 (71.4)	0 (0.0)	0 (0.0)	
Moderate	7 (43.8)	2 (28.6)	5 (100)	0 (0.0)	**<0.001**
Marked	4 (25.0)	0 (0.0)	0 (0.0)	4 (100)	
Stromal overgrowth†					
Absent	11 (68.8)	7 (100)	4 (80.0)	0 (0.0)	**0.001**
Present	5 (31.3)	0 (0.0)	1 (20.0)	4 (100)	
Microscopic border†					
Circumscribed	8 (50.0)	6 (85.7)	2 (40.0)	0 (0.0)	**0.024**
Permeative/infiltrative	8 (50.0)	1 (14.3)	3 (60.0)	4 (100)	
Mitotic activity†*					
0-4	7 (43.8)	6 (85.7)	1 (20.0)	0 (0.0)	
5-10	5 (31.3)	1 (14.3)	4 (80.0)	0 (0.0)	**<0.001**
≥10	4 (25.0)	0 (0.0)	0 (0.0)	4 (100)	

‡: mean±standard deviation / median (interquartile range) [minimum-maximum], †: n (%), *: 10 high power fields, IQR: interquartile range

having borderline phyllodes tumor with a size of 12 cm, and the other one was having benign phyllodes tumor and with a 5 cm lesion.

The primary approach in the treatment of phyllodes tumors is surgery, and as a result of the high recurrence rate, it requires at least 1 cm intact surgical margin in all cases (12). Therefore, preoperative diagnosis of the cases is important to determine the surgical approach. However, in clinical practice, fibroadenoma-phyllodes tumor differentiation is not always possible with preoperative pathological diagnostic methods. Therefore, it is important for patients to have a preoperative suspicion of phyllodes tumor, to plan surgery to provide a wide surgical margin and to reduce the local recurrence rates.

The median follow-up time was 36 (range, 4-110) months. Three cases were followed up with the diagnosis of fibroadenoma for 1.5 years, 6 months, and 3 years. In one of the cases, the cystic component was observed in the US, which was performed due to the sudden increase in size, contained hemorrhagic fluid in aspiration and was operated on for cellular fibroadenoma/phyllodes after the tru-cut biopsy performed 6 months later. If heterogeneous hypoechoic internal echoes and lobulation are present, and calcifications are absent, a diagnosis of phyllodes tumors should be considered (13). However, sonography cannot distinguish among malignant, borderline, and benign phyllodes tumors. Among the ultrasonography findings of phyllodes tumors, in a study examining 84 cases, the presence of macrocysts was reported as the most common finding of 5 malignant cases (14). In mammography, they are seen as hyperdense, large, round/lobulated, well-circumscribed masses, and it is difficult to distinguish these tumors from fibroadenoma with similar mammography findings (14,15). Recently, magnetic resonance imaging uses for phyllodes tumors have been shown to determine for benign and malignant, especially silt-like patterns in enhanced images and signal changes from T2-weighted to enhanced images correlated significantly with the histologic grade (15). Magnetic resonance imaging was done in five patients, and 4 were reported as phyllodes tumor, and all of them were high-grade phyllodes tumor (borderline or malignant) as histopathologically. These patients had a clear surgical margin and there was no need for a secondary operation.

Although fine-needle aspiration biopsy is not preferred among the pre-operative pathological diagnostic methods of phyllodes tumors due to high false negativity, tru-cut biopsy results are more reliable in diagnosis. In the series including ninety-one patients, they have shown the sensitivity of fine-needle aspiration cytology, tru-cut biopsy, and imaging for diagnosing phyllodes tumors to be 40%, 63% and 65% respectively (16). Preoperative diagnosis is important for extensive excision planning; local recurrence rates range from 3-15% (7,17) for benign phyllodes tumors and 3-50% (7,12) in malignant cases. The differences between the rates may be related to the surgical margin positivity rates in different series. In addition, delay in diagnosis and increase in size may result in increased mastectomy rates. In our series, core biopsy was performed in 14 patients, and phyllodes tumor was diagnosed in two patients. In six (42.9%) patients, differentiation between hypercellular fibroadenoma and phyllodes tumor could not be performed. Our patients with delayed diagnosis and treatment did not have a tru-cut biopsy or were not compatible with phyllodes.

Preoperative core biopsy was performed in 14 (87.5%) patients. In six (42.9%) patients, differentiation between hypercellular fibroadenoma and phyllodes tumor could not be performed. Phyllodes tumor was diagnosed in two (16.7% for both) patients. Core biopsy results of 4 patients did not reach in patients' records.

Malignant phyllodes tumors mostly spread by the hematogenous way, and therefore axillary dissection is not recommended in most of the cases (3). Chen et al. (3), in their series of 172 cases, performed modified radical mastectomy in 42 patients due to recurrence of primary phyllodes tumors; no patients had lymph node metastasis. In our series, one patient underwent modified radical mastectomy six years ago, and it seems related to surgeons' experience and choice. The other two patients had suspected metastatic axillary lymph nodes. None of these patients had axillary node metastases.

The treatment is completely surgical in cases with benign phyllodes. The role of adequate postoperative adjuvant therapy in high-risk patients diagnosed with malignant phyllodes is controversial. Radiotherapy is only recommended for selected patients whose surgical margins are positive or that close and advanced surgery cannot be applied (18). In cases where the tumor is removed with wide excision, there is no consensus about whether radiotherapy provides additional benefit and whether it offers additional survival advantage. In our series, all patients had a clear surgical margin at the final pathological examination (including pathological examination of the second operation); none of these patients received radiotherapy except for ductal carcinoma in a patient having breast conserving surgery with in situ focus.

Pathologically, phyllodes tumors are classified as benign, borderline, and malignant according to the degree of stromal cellularity and atypia, mitotic count, stromal overgrowth, and the nature of their tumor borders (19). A benign phyllodes tumor shows mildly increased stromal cellularity and has minimal nuclear atypia, pushing borders, and mitoses of ≤4/10 high-power fields (HPFs). A malignant phyllodes tumor has marked stromal cellularity and atypia, has permeative margins, and has the mitotic activity of at least 10/10 HPFs. Stromal overgrowth is usually easily identified. Phyllodes tumors with intermediate properties are accepted as to be involved in the border category. In our series, there was a significant association between ≥10 mitosis and malignant phyllodes tumor; all counts ≥10 were seen only in patients with malignant pathology. Malignant phyllodes tumors may be confused with primary or metastatic sarcomas and metaplastic carcinoma. In such cases, the diagnosis of phyllodes tumor hinges on finding residual epithelial structures in the first and immunohistochemical demonstration of diffuse epithelial differentiation in the latter help to confirm the diagnosis (20). Three patients with malignant phyllodes tumor who had diffuse involvement were undergone the second operation, and a robust surgical margin was achieved over 1 cm.

Limitations of this study, in addition to its retrospective design, include the low number of patients and no events (recurrences and deaths) observed and also no patient

received radiotherapy for phyllodes tumor. This situation limited the ability to evaluation of treatment approaches.

CONCLUSION

As a result, phyllodes tumors are generally clinically and pathologically benign, and it is important to ensure that the surgical margin is negative in all patients. There was no recurrence in our series, all patients had clear margins, especially patients with a positive margin and malignant histology should undergo further surgery to obtain clear margins. Preoperative diagnosis and careful management are important because of the high local recurrence rate and their malignant potential. Magnetic resonance imaging can be used to contribute to the diagnosis. The preoperative diagnosis of phyllodes tumor contributes to decreasing the necessity for secondary surgical intervention avoiding border positivity.

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