Original Article

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Phyllodes Tumors of the Breast: A Single-Center Experience

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ABSTRACT

Objective: We aimed to analyze the clinicopathological findings, treatment approach, and treatmen outcomes in patients diagnosed with phyllodes tumor (PT).

Materials and Methods: The clinicopathological data of 26 patients with PT, who were treated between 2008 and 2019, were retrospectively analyzed.

Results: Mean age was 35.07±13.95 years (range: 14–71), while mean tumor size was 54.76±29.24 mm (range: 25–135). Benign, borderline, and malignant PT were detected in 18 (69.2%), 3 (11.5%), and 5 (19.2%) patients, respectively. Marginless excision was performed in 20 patients (76.9%), while six (23.1%) patients underwent mastectomy. A statistically significant correlation of tumor type with mean tumor size and mean age was observed (p=0.041 and p=0.013, respectively). Margin positivity on first excision was more frequent in the malignant tumors (p=0.02). No statistically significant correlation of PT type with presence of breast cancer in the family history, and tumor localization was observed (p=0.79 and p=0.13, respectively). Mean postoperative follow-up duration was 56 months (range: 6–147). Local recurrence was not observed in any of the patients. Lung and left vastus lateralis muscle metastases were encountered. The patient with lung metastasis became exitus because of the same reason 6 months after detection of the metastasis.

Conclusion: PT is a rare fibroepithelial tumor of the breast that is characterized by a mixed histology seen in younger ages when compared to the classical breast tumors. The probability of PT should be considered in the presence of a rapid-growing mass in the breast. In addition, it should also be considered that the contribution of imaging techniques may be limited.

Keywords: Breast, fibroepithelial lesion, phyllodes tumor

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Introduction

Phyllodes tumors (PTs) of the breast are rare fibroepithelial tumors that constitute 0.3%–0.5% and 2%–3% of primary breast tumors and fibroepithelial tumors, respectively (1). They may be observed in all ages; nevertheless, they are mostly observed in the age range of 35–55 years (2). They are radiologically and clinically similar to fibroadenomas (FAs); however, they are differentiated from FAs with increased cellularity and metastatic invasion capacity of the local recurrence and malignant types. Although it was previously termed "cystosarcoma phyllodes" by Müller because of its macroscopically similar appearance with sarcoma, it is now termed PT by World Helath Organization (3, 4). PTs are classified as benign, borderline, and malignant phyllodes based on histological features such as cellular atypia, mitotic count, tumor necrosis, stromal overgrowth, and tumor margins. Approximately 60%–75% of all PT cases are benign (5).

The essential treatment modality is by surgical intervention. Although the National Comprehensive Cancer Network (NCCN) guidelines recommend large local excision with a least surgical margin of 1 cm, recent studies have reported the application of excisions with narrower surgical margins. Tumor size, surgical therapeutic technique, and tumor-related histopathological features have been found to be associated with recurrences, as well as surgical margin status in literature (6). In the present study, we aimed to analyze the clinicopathological findings, our treatment approach, and treatment outcomes in patients diagnosed with PT, who applied to our clinic.

Materials and Methods

The hospital records of 26 patients, who were treated for PT of the breast between January 2008 and December 2019 in the Clinic of General Surgery Department of Pamukkale University Medical Faculty, were retrospectively analyzed, following approval of the study by The Clinical

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Demographic data, clinical findings, diagnostic imaging techniques, surgical technique and dates, pathological examination results, and follow-up patient records were evaluated. Patients with a follow-up duration of at least 6 months were included for this study. Tumors were classified as benign, borderline, and malignant tumors. The patients were compared in terms of age, tumor size and type, margin status on the first excision, presence of breast cancer in family history, surgical therapeutic modality, metastasis, and mean follow-up duration.

Statistical analysis

All the statistical analysis was performed using SPSS Statistics for Windows Version 25.0 (SPSS, IBM, Chicago, IL, USA). Essential features of the patients were represented by descriptive statistics. One-way analysis of variance was used in compare the tumor types in terms of variables such as age, tumor size, and follow-up duration. Categorical variables were compared using Fisher's Exact test. We obtained some categorical data that do not meet 25% of cells > n=5 rule, according to the Fisher's Exact test. This study could not be carried out with an "n" number of patient population indicating sample size not exceeding 25% of cells, since a rarely seen tumor type was investigated.

Results

The study included 26 patients (all female) treated for PT of the breast between year 2008 and 2019 (Table 1).

Demographic structure

Mean age of the patients was 35.07±13.95 years (range: 14–71), while mean tumor size at diagnosis was 54.76±29.24 mm (range: 25–135). Of the patients diagnosed with PT, 22 (84.6%) and four (15.4%) were premenopausal and postmenopausal, respectively. In addition, Of the total 26 patients, 12 (46.2%) and 14 (53.8%) were below and over 30 years of age, respectively.

Diagnosis

Patients were diagnosed based on clinical findings, radiological imagings, and histopathological examination.

Of the patients diagnosed, 24 (92.3%) patients applied due to complaint of mass, which was localized in the left breast in 65.4% of the patients. Mass was detected by routine control examinations

Table 1. Comparison between clinicopathological features and tumor types

Characteristic	Benign	Borderline	Malignant	p-value
	n (%) or mean (standard deviation)			
Age	29.50 (10.52)	49.66 (9.29)	46.40 (15.58)	0.013
Tumour size mean (mm)	46.33 (22.32)	48.33 (12.58)	89.00 (36.46)	0.041
Initial margin status				
Negative	17 (94.4%)	2 (66.7%)	2 (40.0%)	0.022
Positive	1 (5.6%)	1 (33.3%)	3 (60.0%)	
Family history of breast cancer				
No	15 (83.3%)	2 (66.7%)	4 (80.0%)	0.794
Yes	3 (16.7%)	1 (33.3%)	1 (20.0%)	
Operation				
Lumpectomy	18 (100.0%)	2 (66.7%)	0 (0.0%)	<0.001
Mastectomy	0 (0.0%)	1 (33.3%)	5 (83.3%)	
Location				
Right	4 (22.2%)	2 (66.7%)	3 (60.0%)	0.135
Left	14 (77.8%)	1 (33.3%)	2 (40.0%)	
Distant metastasis				
No	18 (100.0%)	3 (100.0%)	3 (60.0%)	0.011
Yes	0 (0.0%)	0 (0.0%)	2 (40.0%)	
Axilla				
Without axillary surgery	18 (100.0%)	2 (66.7%)	0 (0.0%)	
SLNB	0 (0.0%)	1 (33.3%)	3 (60.0%)	<0.001
AD	0 (0.0%)	0 (0.0%)	2 (40.0%)	
Follow-up (year)	5.43 (4.24)	4.53 (3.18)	2.86 (3.22)	0.451

p<0.05 was accepted as statistically significant
SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; n: Number

of the patients. Findings from the examinations included masses with moderate stiffness, smooth surface, and partial mobility. As expected, higher stiffness and less mobility were determined in the masses assessed according to histopathological examination; however, no additional findings, such as irregular edges or cutaneous changes and nipple discharges similar with those of typical breast cancers, was encountered despite the large tumor size. Multiple masses in unilateral breast and/or single masses in bilateral breasts were initially identified as FAs in the baseline examination and/or ultrasonography in twelve (46.15%) of the patients (all below 30 years of age). Masses that demonstrated rapid growth during the follow-up period were excised and diagnosed with benign PT according to histopathological examination. In addition, six of the 12 patients with comorbidity of PT and FAs had undergone at least one surgical operation for FAs in their medical history. FAs was determined in only one (7.1%) of the 14 patients (over 30 years of age) diagnosed with PT.

Diagnostic ultrasonography was performed in all the patients. Hypoechoic solid mass lesions with regular margin were detected in 18 patients, while eight patients were found to have lobulated contour masses with heterogeneous appearance and increased vascularity. Patients with borderline and malignant PT were included in this group. Mean tumor sizes were calculated as 46.3±22.32 mm, 48.3±12.58 mm, and 89.0±36.46 mm for benign, borderline, and malignant PTs, respectively.

Mammography was performed in 10 patients over 40 years of age. Macrolobulated lesions with regular contours (BI-RADS 2), BI-RADS 0 appearance and necessity of an additional examination, and BI-RADS 4 lesion were encountered in five, three and two patients, respectively.

Dynamic contrast-enhanced breast MRI was performed in seven (26.9%) patients suspected with malignancy according to examinations and other imaging techniques; four (57.1%) patients had Type 1 lesion, while Type 3 contrast-enhanced lesion, which indicates suspicion of malignancy, was detected in 3 (42.9%) patients. All patients encountered with Type 3 contrast enhancement were diagnosed with malignant PT after excision. Radiological images of other patients diagnosed with malignant tumors were not different from those of benign tumors.

Tru-cut biopsy was performed in four patients with clinically and radiologically suspected malignancy; however, malignant PTs were reported in only two (50%) of these four patients.

Treatment modality

Mass excision was primarily preferred in all the patients; however, mastectomy was suggested for patients with confirmed malignancy and a ratio of tumor size to breast tissue that may pose a cosmetic problem after excision. Unfortunately, none of the patients accepted this suggestion. The tumors technically considered to be benign were excised close to the margin, remaining no residual tumor tissue (20 patients, 76.9%). On the other hand, macroscopically, a margin-free excision of 2 cm was performed in the tumors identified to be malignant according to tru-cut biopsy result or tumors considered to be clinically malignant. Mastectomy was suggested for patients diagnosed with malignant PT according to the pathological examination report and margin positivity or close margin. Mastectomy was performed in patients who accepted this suggestion (six patients, 23.1%). Sentinel lymph node biopsy was performed in patients with tumor size >5 cm, outer quadrant localization, and high histological grade (four patients). Axillary dissection without sentinel lymph node biopsy was performed in only two patients, since no histopathological diagnosis, except "malignant mass", could be established by preoperative tests and intraoperative frozen procedure; as well as due to the fact that enlarged axillary lymph nodes were detected.

Adjuvant chemotherapy and radiotherapy were implemented in three of the patients diagnosed with malignant PT.

Histopathological evaluation

Postoperative histopathological examination revealed 18 benign PTs (69.2%), three borderline PTs (11.5%), and five malignant PTs (19.2%). One of the malignant patients was 17-week pregnant (20%). Mastectomy was performed for 5 malignant and 1 borderline PT patient. Tumor was close to the surgical margin according to the histopathological examination of the first surgery in all the patients. No metastasis was detected in patients who underwent axillary dissection or sentinel lymph node biopsy.

The results of statistical analysis

Malignant PTs had statistically significantly larger diameter (p=0.041).

It was determined that tumor types and age distribution are statistically significantly correlated and that benign phyllodes tumors are encountered in younger ages (mean patients ages were 29.50±10.52 and 49.66±9.26 years in the benign and malignant tumors, respectively) (p=0.013).

The correlation between margin status of the patients on first excision and tumor type were analyzed and margin positivity was found to be significantly higher in the malignant tumor as estimated (p=0.02).

The tumor type was not significantly correlated with presence of breast cancer in the family history and tumor location (p=0.79 and p=0.13, respectively).

Mean postoperative follow-up duration was 56 months (range: 6–147months). Local recurrence was determined in none of the patients. Lung and left vastus lateralis muscle metastases were encountered in one patient each diagnosed with malignant PT (Table 2). The patient with metastasis to lung became exitus due to a similar reason 6 months after detection of the metastasis.

Discussion and Conclusion

PTs are group of tumors that require early diagnosis, given their malignancy potential and probability to reach larger sizes even though they are rarely seen.

The etiology of PTs and their relationship with FAs are still not clear. Noguchi et al. (7) showed that a major part of the FAs contain polyclonal elements and should be accepted as hyperplastic lesions. It thas been proposed that monoclonal proliferation may develop from polyclonal element due to somatic mutation. Also, growth factors produced by breast epithelium and stimulated by trauma, breastfeeding, pregnancy, and hyperestrogenism are considered to be responsible in the etiology of PT (4, 7). In our case series, FAs were clinically and/or ultrasonographically present in 12 (46.1%) of the patients below 30 years of age and previous excision of FAs was experienced in half of these patients. Chen et al. (8) reported a previous FAs excision in the history of 22 patients in their cases series of 172 patients.

Table 2. Characteristics of the metastatic patients

Tumor subtype	Operation	Tumor size (mm)	Margin status	Mitoses per 10xHpf	Stromal hypercellularity	Cytologic atypia	Stromal overgrowth	Necrosis	Time of metastasis (months)	Sarcomatous heterologous differentiation	Metastasis site
Malignant	Mastectomy	50	-	20	Marked	Yes	Yes	Yes	21	No	Lung
Malignant	Mastectomy	70	+	17	Marked	Yes	Yes	Yes	23	No	Muscle

Hpf: High power field

PTs are detected in younger ages (averagely 42–45 years) when compared to classical adenocarcinomas of the breast (1, 9, 10). Mean age of our case series was 35 years, which is similar with that of the case series of Ditsatham and Chongruksut (11). As stated in our study, borderline and malignant PTs were determined in more advanced ages than benign tumors.

The essential application complaint of the patients is a palpable mass in the breast in all the age groups. Particularly, rapidly progressive painless mass should be a warning against PT (12). It may be a single mass and may present bilateral and multifocal localization (13). In our case series, 92.3% of the patients applied due to the complaint of mass and the tumor was localized in the upper outer quadrant of the breast in more than half of the patients.

PTs are hardly differentiated from the FAs using imaging techniques because they are macroscopically smooth-surfaced and multilobulated masses (14). Recent studies have reported that well-contoured tumors with rapid contrast enhancement and high signal intensity in T2-weighted images of gadolinium-enhanced dynamic MRI of the breast were compatible with benign PTs (15). Tumor size is important in differentiation of PTs from the FAs and in classification between the phyllodes types. Many studies have reported a correlation between the tumor size and risk for malignancy (2, 4, 10). In literature, mean diameter of the PTs and FAs were reported to be 4-7 and 2 cm, respectively (2, 4, 10). Mean tumor size was 5.47 cm in our case series and there was a correlation between tumor size and tumor type. PTs are classifed as benign, borderline, and malignant based on histopathological characteristics such as mitotic count detected in x10 high power fields, stromal cellularity, atypia, and stromal overgrowth beside surgical margin status (5). In literature, benign, borderline, and malignant tumors were determined in 72.7%, 18.4%, and 8.9% of the 605 patients in a large case series, respectively; whereas another study reported benign, borderline, and malignant PTs in 60%, 20%, and 20% of the patients, respectively (16, 17). In our study, the rates of the benign, borderline, and malignant tumors were found to be 69.2%, 11.5%, and 19.2%, respectively.

The treatment option for PT is surgery; however, there is no consensus yet on the width of the surgery that should be performed (8). NCCN guidelines recommends a large local excision with a margin-free incision of at least 1 cm (18). Tumor type, tumor size, breast size, breast/tumor ratio, and localization of the tumor are critical for the selection of the surgical technique. In literature, some studies have stated that local recurrence indicates a low rate such as 0%–13% in bening PTs and that positive surgical margin is not correlated with local recurrence. Therefore, local excision and close monitoring are adequate for such cases (11, 17, 19). On the other hand, larger excision and further mastectomy are recommended for patients with borderline and malignant PTs, taking the probability of inadequate surgical margin or sequelae of deformity into consideration, since these tumor types demonstrate higher local recurrence rates (20, 21). Surgical margin status is the essential parameter that affects the probability of local recurrence and higher local recurrence rates have been reported in patients with positive surgical margin (3, 20, 21). In our study, surgical margin positivity after the initial excision was 23.1%, while malignant and borderline PTs were detected in 80% (four patients) and 20% (one patient) of these cases. Mastectomy was recommended and performed for these patients. Local recurrence was encountered in none of these patients.

PTs spread hematogenously. The rate of axillary metastasis is low (0%–2%) and therefore routine axillary examination is not recommended (8, 22). However, axillary examination can be performed in aggressive tumors with a diameter greater than 5 cm and high mitotic activity. We encountered no lymph node metastasis in the patients that we subjected to axillary examination.

The patients diagnosed with malignant PT may manifest distant metastasis at a rate of 2.4%–7.5%. We detected distant metastasis in two (7.7%) patients (2, 23). Metastases to soft tissue, lung, and bone are the most common types of metastasis of PTs. It has been reported that metastases may rarely spread to the liver and heart (3). Borderline and malignant PTs are metastatic. It has been stated that metastatic tumors have histopathologically stromal components more than epithelial components (24). In our case series, metastases to lung and left vastus lateralis muscle were encountered in two patients diagnosed with PT. Furthermore, the patient with lung metastasis in our study became exitus 6 months later due to this reason. These patients had histopathologically remarkable stromal hypercellularity, cytological atypia, stromal overgrowth, and necrosis.

The role of adjuvant therapies such as radiotherapy and chemotherapy is controversial (25). Chaney et al. (26) reported that a surgical margin closer than 0.5 cm or surgical margin positivity, presence of the tumor larger than 10 cm in diameter, or recurrence tumor are the risk factors for local recurrence and suggested radiotherapy. There is no routine chemotherapy protocol established for the treatment

of PTs. Patients with malignant PTs that manifest high recurrence risk are the candidates for chemotherapy protocols including doxorubicin, dacarbazine, and iphosphomid (27). In our case series, radiotherapy and chemotherapy were administered in 2 patients diagnosed with metastatic malignant PT and one patient diagnosed with malignant PT larger than 10 cm in diameter.

Five-year overall survival rates have been reported to be 91%–100% and 53.4%–91% in cases with benign and malignant PTs, respectively (27, 28). In our case series, overall survival rates at the end of the 56-month follow-up process were 100% and 20%, respectively.

As a consequence, PTs are rare fibroepithelial tumors of the breast (with a mixed histology) more commonly observed between 35–45 years of age and have a tendency to develop large-size masses in the breast without axillary metastasis of the benign types. However, the malignant types have the potential for local recurrence and metastasis. The primary treatment option is surgery; nevertheless, there is no consensus yet on the adjuvant treatment modalities such as radiotherapy and chemotherapy. The number of the patients in our case series is inadequate for the recommendation an adjuvant therapy. However, we conclude that sharing our experience would be crucial for the diagnostic approach in the practical course. From this point of view, considering PT of the breast may not be possible in the initial examination of all the cases, since it is a rarely seen and may lead to delays in accurate diagnosis. The detection of FAs with a rate of 10%–15%, particularly in females aged below 30 years of age in the community and inability to easily differentiate these cases from the phyllodes tumor of the breast by clinical examination and radiological imaging techniques may lead to delays in accurate diagnosis (29). Our clinical experience suggests that close and meticulous follow-up is required in patients aged below 30 years of age, particularly in the patients with multiple FAs-like masses, because of technical and cosmetic difficulties, as well as the non-necessity of excision of all these masses. We recommend the arrangements of more frequent follow-up examinations with short intervals, application of tru-cut biopsy in the masses with rapid growth, and performance of excision in the cases with a definite result without waiting longer. It is obvious that every mass should be approached with suspicion in females over 30 years of age, among which classical breast cancer is frequently seen. However, the probability of PT of the breast should be considered in partially mobile masses with rapid growth and moderate stiffness rather than the well-known clinical symptoms of the breast cancer. It should also be considered that the contribution of the imaging techniques may be limited. In the light of our clinical experience, occasionally ignoring mass, omitting control examinations, or directing the physician subjectively to consider the mass as a benign tumor by stating that "the mass was located here for many years" are the possible reasons for the delay in the process of diagnosis. Therefore, excision of the mass without delay may provide both diagnostic and therapeutic benefits in this group of patients, especially when tru-cut biopsy indicates no definite result.

Key Points

- Phyllodes tumors are rare tumors.
- Rapidly and painless progression of the mass should be a warning against phyllodes tumor.
- The contribution of imaging techniques is limited and biopsy is necessary, particularly in patients over 30 years of age.

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Authorship Contributions

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