Original Article

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Unexpectedly High Coexistence Rate of *In Situ*/Invasive Carcinoma In Phyllodes Tumors. 10-Year Retrospective and Review Study

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ABSTRACT

Objective: Phyllodes tumors (PTs) are a rare group of breast tumors. Most malignant transformations are *in situ* carcinomas that are extremely rare and are limited to individual cases in the literature. The presence of *in situ*/invasive carcinomas is important as this may alter clinical judgment and management. In this study, we aimed to determine the association of *in situ*/invasive carcinomas among PTs.

Materials and Methods: This retrospectively designed study included cases diagnosed with PTs between 2011 and 2020 in the pathology department of a tertiary level hospital. Tumors were grouped into benign, borderline and malignant, according to stromal overgrowth, stromal atypia, stromal cellularity and mitotic activity. In addition, age, location, type of operation, tumor diameter, and surgical margin information were recorded. *In situ* and/or invasive carcinoma foci accompanying the PTs were assessed.

Results: A total of 29 patients diagnosed with PTs were identified, among whom 14 (48.2%) had benign PTs, 10 (34.4%) had borderline PTs, and 5 (17.2%) had malignant PTs. Of the patients with PTs, 3 (10.3%) had coexistent invasive carcinoma and 1 (3.4%) had carcinoma *in situ*. In this cohort the incidence of coexistence of PT and carcinoma was 4/29 (13.7%), which is much higher than previously reported (1.1% and 6%). The incidence of carcinoma was 2/5 (40%) in malignant PT patients and 2/10 (20%) in borderline PT patients. The coexistence of malignant PTs and carcinoma was significantly higher than those of benign and borderline PTs (p<0.05).

Conclusion: The multidisciplinary team dealing with breast diseases has a great responsibility in both diagnosis and treatment. We anticipate that these rates will increase with an increase in the awareness and importance of this coexistence of carcinoma and PTs.

Keywords: Phyllodes tumors; breast; *in situ*; intraductal carcinoma; malignant

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Key Points

- Although the diagnosis of phyllodes tumor (PT) is not challenging, a comprehensive histopathological examination with multiple sampling when considering the coexistence with carcinoma is necessary.
- Not only full examination of the stromal component, but also meticulous microscopic examination, may be useful to detect a possible invasive focus of epithelial origin.
- The presence of ductal carcinoma in PTs is clinically significant as it may alter treatment.
- Surgeon, radiologist and pathologist should take great care in phyllodes tumors larger than 4 cm and showing sudden growth.

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Introduction

Phyllodes tumors (PTs) are a rare group of breast tumors involving a biphasic proliferation of the stroma and breast epithelium. They usually appear as a fast-growing, painless, unilateral, mobile mass with regular margins. Histologically, they display an intracanalicular growth pattern and form a typical leaf-like appearance, usually with a benign course (1).

Fibroadenoma (FA) is a frequently diagnosed lesion in clinical pathology. In the presence of increased stromal cellularity, tru-cut biopsy may be difficult to definitively distinguish FA from benign PT. In such cases, the term "fibroepithelial lesion" is used and excision is typically done for definitive classification (1, 2). Older age at diagnosis of FA, presence of radiologically synchronous masses in other regions of the breasts, and continued enlargement of the lesion are other potential "red flags" (3).

Taking sufficient amount of tru-cut biopsy pre-operatively and sampling the excision material with multiple paraffin blocks by the histopathologist will reduce the risk of missed diagnosis when PTs exhibit tumor heterogeneity and may even occur in some FAs (4).

Triple evaluation, including physical examination, radiological and histopathological evaluation, has been shown to result in increased pretest probabilities, reduced false positive and false negative results, and better identification of lesions requiring excision or further treatment (5, 6). The primary purpose of most tru-cut biopsies is to exclude malignancy. Management of malignancy is well known and continues to evolve. However, the diagnosis of benign diseases, such as FA or fibroepithelial lesions, can sometimes pose a management challenge for the breast multidisciplinary team within the current diagnostic paradigm, especially due to the lack of good evidence to guide the need for excision (6).

Based on World Health Organization (WHO) 2019 criteria (2), PTs are classified as benign, borderline, or malignant according to histological parameters, including stromal hypercellularity, cellular pleomorphism, mitotic activity, margin status, and stromal overgrowth. Malignant transformation usually occurs in the stromal part of the tumor, but the epithelial component of PTs may also transform into a malignancy (3). Most of these are *in situ* carcinomas and are extremely rare, <1% (4). Similarly, the coexistence of malignant PTs and invasive ductal carcinomas (IDC) is limited to individual cases (7-40). In this article, we investigated the rate of ductal carcinoma among PTs diagnosed in a single center.

Materials and Methods

A retrospective review to identify phyllodes cases between 2011-2020 was conducted in the Department of Medical Pathology at the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The study was approved by the clinical trials ethics committee of the referred hospital (PN 381/2020). Clinical data were retrieved from the database for analysis. All patients who underwent core biopsy followed by complete surgical excision and were subsequently diagnosed with PT by histopathology were included in the study. Tumors were reviewed according to WHO criteria by two pathologists (S.A., Ö.G.), one of whom is board certified (S.A.). To illustrate, a phyllodes tumor was diagnosed when the tissue showed an exaggerated intracanalicular pattern of leaf-like protrusions into cystically enlarged spaces accompanied by fibroepithelial architecture and stromal hypercellularity. A benign phyllodes tumor differed from a fibroadenoma by showing slightly increased stromal cellularity, minimal nuclear atypia and pushing borders, mitoses in ≤5/10 high magnification field (HPFs) compared to a fibroadenoma. In stromal overgrowth; the criterion of epithelial-free stroma was based on at least one low magnification field with the x4 microscope objective.

Malignant phyllodes tumor, on the other side of the histopathological spectrum, was generally recognized by easily defined stromal overgrowth, prominent stromal cellularity and atypia, permeative borders, and mitotic activity of at least 10/10 HPF. Phyllodes tumors with intermediate features were included in the borderline category.

Ducts that appeared to be entrapped within the phyllodes tumor and were suspicious for tumor were evaluated with p63 immunohistochemistry for the presence/absence of myoepithelial cells.

In addition, age, location, type of operation, tumor maximum diameter, and surgical margin information were recorded. The occurrence of concomitant *in situ* and/or invasive foci was investigated.

SPSS, version 22.0, was used in the analysis of data (IBM Inc., Armonk, NY, USA). Comparative analysis of the groups was made with Fisher's Exact test.

Results

A total of 29 patients diagnosed with PTs were identified from the database (Table 1). All patients were female, with an age range of 17-81 years, with a mean age of 42.8±16.2 years. Core biopsy revealed fibroepithelial lesions in 21 patients and it was noted that core biopsy in 12 of these patients could be PTs. All patients underwent surgical resection. Three patients underwent total mastectomy due to the tumor/breast tissue ratio, one patient underwent modified radical mastectomy, nine patients underwent breast-conserving surgery, while wide local excisions (WLEs) were performed in 15 patients. Benign PTs were identified in 14 patients (48.2%), borderline PTs were found in 10 patients (34.4%) while malignant PTs were detected in five patients (17.2%) (Table 2). The incidence of carcinoma (both *in situ* or invasive carcinoma) was 40% (2/5) in malignant PT patients and 20% (2/10) in borderline PT patients. The coexistence of malignant PTs and carcinoma was significantly higher than in patients with benign and borderline PTs (p<0.05). There were three patients (10.3%) in whom invasive carcinoma also revealed a PT and one patient (3.4%) had carcinoma *in situ* with PT. These case are briefly presented below to provide a better understanding of the series (Table 3).

Case No. 20: A 25x25 mm mass was detected at the 10 o'clock position in the right breast of a 45-year-old patient in 2018. The tru-cut biopsy performed in the outer center was reported as FA. This mass, which was excised locally, was diagnosed as borderline PT. In the post-op breast US performed at our center in the same year, a new mass of 41x20 mm was detected at the 3 o'clock position in the left breast, and a tru-cut biopsy was performed. Left WLE was carried out upon detection of an IDC focus in this biopsy. A grade 2 IDC with a size of 30x20 mm was detected in the WLE material. In the immunohistochemical assay performed on this subject, estrogen receptor (ER) was detected as 100% positive, progesterone receptor (PR) was 90% positive, while the c-erbB2 score was 1 negative. No relapse and/or metastasis was detected during the 22-month follow-up period after treatment.

Case No. 23: A 50x35 mm mass at the 3 o'clock position was detected in the left breast of a 69-year-old patient in 2014. Fibroadenomatoid-phillodes like changes were detected via a tru-cut biopsy, and WLE was performed. A 45x35 mm borderline PT was detected in the WLE material, but the lesion persisted within surgical margins. Therefore, re-excision was performed with clear margins and a solid type ductal carcinoma *in situ* (DCIS) was identified in the re-excision material. The patient could not be followed up after treatment.

Case No. 28: A 60x55 mm mass was detected at the 1 o'clock position of the left breast in the US performed in 2019 on a 45-year-old patient with a history of excision of FA in the left breast in 2018. PT was diagnosed in the tru-cut biopsy while a benign PT diagnosis was made in the WLE performed afterward. A mass with a size of 120x110 mm was detected in the left breast at 3 o'clock position in the follow-up US and a malignant PT was diagnosed in the re-performed segmentary mastectomy, but the tumor was observed in the CSs in the surgical

Table 1. Summary of the clinicopathologic characteristics of the 29 patients described in the current series

Patient no	Age	PT Type	Localization	PT size (cm)	Margins	Operation	Axillary Surgery
1	46	Benign	Left	10x10	Clear	WLE	(-)
2	17	Benign	Right	2.5x2.3	Clear	WLE	(-)
3	45	Benign	Right	3.5x3.5	Clear	WLE	(-)
4	55	Benign	Right	5x4	Clear	WLE	(-)
5	29	Benign	Right	6x5.5	Clear	WLE	(-)
6	42	Benign	Left	9x7	Clear	WLE	(-)
7	23	Benign	Right	7x6	Clear	WLE	(-)
8	48	Benign	Right	13x9.5	Clear	WLE	(-)
9	26	Benign	Right	5x4	Clear	WLE	(-)
10	41	Benign	Right	4x4	Clear	WLE	(-)
11	35	Benign	Right	4.5x4	Clear	WLE	(-)
12	20	Benign	Right	6.5x3.5 3x2.5	Clear	WLE	(-)
13	57	Benign	Left	5x2.2	Clear	WLE	(-)
14	22	Benign	Right	5x4.5	Clear	WLE	(-)
15	30	Borderline	Right	NA	Clear	WLE	(-)
16	81	Borderline	Left	8x6	Clear	WLE	(-)
17	49	Borderline	Right	11x0.5	Clear	TM	(-)
18	73	Borderline	Right	2x2	+	WLE	(-)
19	45	Borderline	Left	7x5	Clear	WLE	(-)
20*	45	Borderline	Right	2.5x2.5	Clear	WLE	(-)
21	57	Borderline	Right	3.5x3.5	Clear	WLE	(-)
22	39	Borderline	Left	5.5x4.5	Clear	WLE	(-)
23*	69	Borderline	Left	4.5x3.5	Clear	WLE	(-)
24	25	Borderline	Left	1.3x1.3	Clear	WLE	(-)
25	31	Malign	Left	24.5	Clear	MRM	(-)
26	39	Malign	Right	5x4	Clear	WLE	(-)
27	45	Malign	Right	5.5x5.5	Clear	TM	(-)
28*	45	Malign	Left	12x11	Clear	WLE	(-)
29*	63	Malign	Left	20x16	Clear	TM	(-)

PT: phyllodes tumor; WLE: wide local excision; MRM: modified radical mastectomy; TM: total mastectomy, *coexisting with carcinoma

Table 2. Histological type and age distribution of the 29 patients described in the current series

n (%)	PT type	Median age (Range)	Coexisting with carcinoma n (%)	*p*-value
14 (48.2)	Benign	36.1 (17–57)	0 (0)	
10 (34.4)	Borderline	51.3 (25–81)	2 (20)	
5 (17.2)	Malign	44.6 (31–63)	2 (40)	0.038

PT: phyllodes tumor

Table 3. Summary of the pathologic characteristics of the four patients described with PT coexistent with *in situ*/invasive carcinoma)

Patient no	Pre- op core bx	PT type	Carcinoma	Carcinoma size (cm)	Mitotic rate	ER (%)	PR (%)	HER2
20	FEL	Borderline	IDC (G2)	3X2	5/10 HPF	100 +	90 +	Score 1 (Negative)
23	FEL	Borderline	LCIS, DCIS	0.5X0.5 and 0.4x0.3	5/10 HPF	90 +	70 +	Score 1 (Negative)
28	Likely PT	Malign	IDC (G2)	0.8X0.8	>20/10 HPF	90 +	90 +	Score 2 (FISH negative)
29	FEL	Malign	IDC (G1)	0.8X0.8	>10/10 HPF	100 +	70 +	Score 2 (FISH negative)

PT: phyllodes tumor; ER: estrogen receptor; PR: progesterone receptor; FEL: fibroepithelial lesion; IDC: invasive ductal carcinoma; DCIS: ductal carcinoma *in situ*; LCIS: lobular carcinoma *in situ*; NA: not available; HPF: high powered field; FISH: fluorescent *in situ* hybridization; HER2: human epidermal growth factor receptor 2

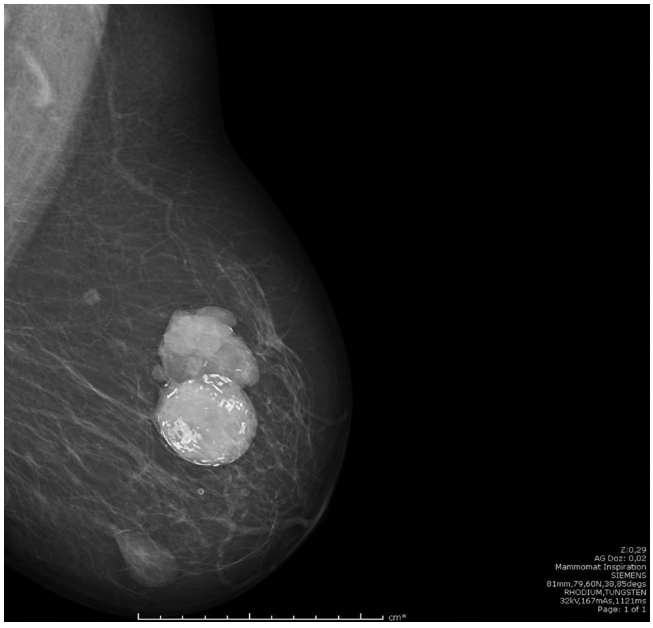

Figure 1. LMLO mammogram. In the upper-outer quadrant of the left breast, there is a 51 mm diameter, well-defined, radio-dense lesion in which extensive, coarse calcifications are superposed, and two radio-dense lesions 25 mm and 22 mm in diameter are located adjacent to it

margins. Therefore, in addition to a malignant PT, a grade 2 IDC with a diameter of 8 mm was detected on re-excision, and no lesions were observed in CSs. Immunohistochemical assay showed ER 90% positive, PR 90% positive, and the c-erbB2 score was 0 negative. No relapse and/or metastasis was detected during the 10-month follow-up period after treatment.

Case No. 29: A 63-year-old patient had been operated for endometrial adenocarcinoma in 2015. During the follow-up in 2017, a mass was detected in the left breast. On LMLO (left mediolateral oblique view) mammography, there was a 51 mm diameter, well-circumscribed radio-dense lesion in which dense, coarse calcifications overlapped and there were adjacent radio-dense lesions 25 mm and 22 mm in diameter in the upper-outer quadrant of the left breast (Figure 1). The patient, whose

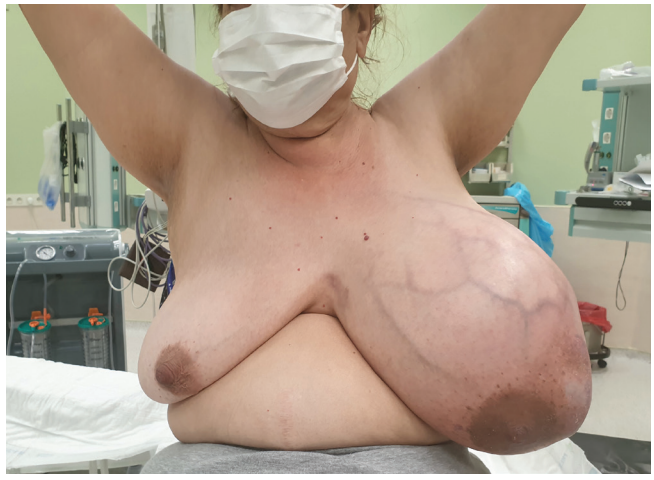

Figure 2. Preoperative picture of patient. Red, hard, fluctuating mass covering more than 50% of the left breast

breast tru-cut biopsy could not be performed in February 2017, was admitted in March 2020 with a mass that filled the entire breast. She had a red, hard, fluctuating mass covering more than 50% of the breast in her left breast (Figure 2). The preoperative magnetic resonance imaging (MRI) revealed a cystic-solid mass of 160x120 mm with an irregular, lobular contour and intense contrast enhancement in the solid component after the left breast was filled with intravenous contrast media almost completely and was evaluated as BI-RADS category 4C (Figure 3). Mammogram in 2017 and preoperative MRI in 2020 and US examination did not suggest the presence of ductal carcinoma. On the cut surface of the mastectomy specimen a dirty yellow-white tumoral lesion with cystic-solid appearance, which was hemorrhagic-necrotic and filled almost the entire breast was seen (Figure 4). In the samples prepared from the mastectomy specimen, a tumor with infiltrative margins, prominent stromal cellularity and stromal cellular atypia, characterized by necrosis and mitosis (>10/10HPF) was observed (Figures 5,6). Total mastectomy revealed a malignant PT of 20x16 cm and grade 1 IDC with a diameter of 0.8 cm in a focus (Figure 7). On p63 immunohistochemical staining, ducts that do not show immunoreactivity were observed in myoepithelial cells (Figure 8). The axillary staging was N0 via sentinel lymph node

biopsy. Immunohistochemical assay showed ER 100% positive, PR 70% positive, while the c-erbB2 score was suspicious positive 2. Fluorescence in situ hybridization-negative adjuvant radiotherapy (RT) was performed. No relapse and/or metastasis was detected during the 9-month follow-up period after treatment.

Discussion and Conclusion

The term "Philodes" comes from the latin root "Philodes" meaning leaf-like, describing the appearance of "Phyllodium" on microscopic examination (1). Johannes Müller, a German physician, first described PTs as cystosarcoma phyllodes in 1838, despite the rare cystic component of these tumors and the rarity of malignancy (1, 2). PTs, which make up 0.5-1% of all breast tumors, have a younger age at diagnosis than breast carcinoma, which occurs at an average age of 40 years (1, 41). Although typically diagnosed after palpation of a breast mass on physical examination, 20 percent of patients are initially detected by radiographic imaging, such as mammography (41). In our series, the mean age was 36.1 years which is somewhat younger than

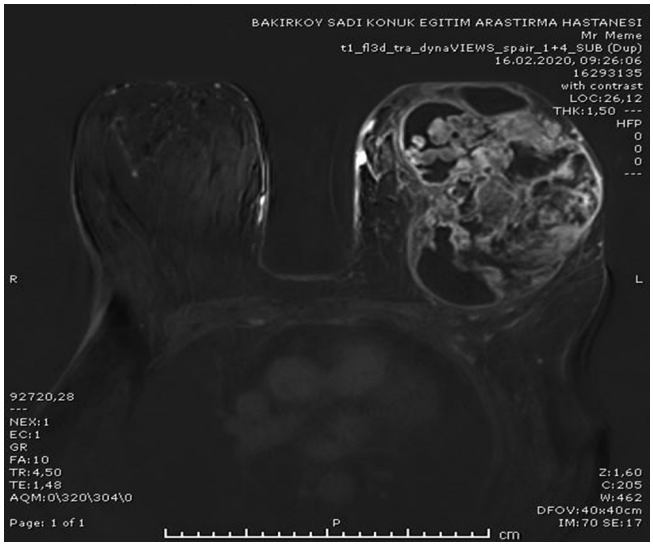

Figure 3. T1-weighted dynamic magnetic resonance imaging. It is seen that the volume of the left breast is increased compared to the right. A 16x12 cm sized, irregular lobule-contoured, cystic-solid mass that almost completely fills the left breast is notable, with intense contrast enhancement in its solid component after intravenous contrast material

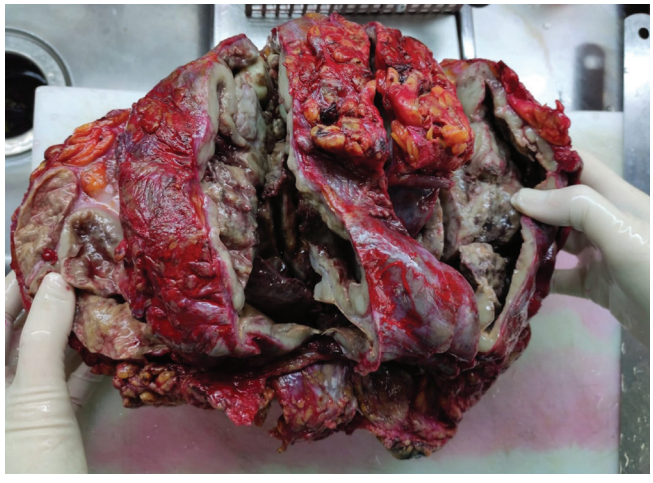

Figure 4. Postoperative macroscopic picture. On the cut surface, a dirty yellow-white tumoral lesion with cystic-solid appearance and hemorrhage-necrosis is seen

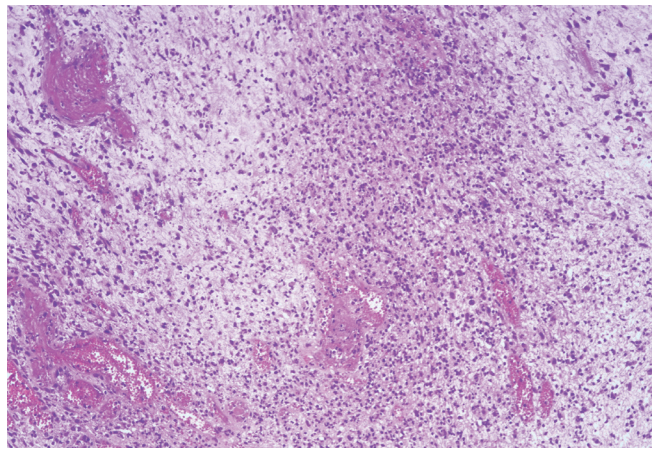

Figure 5. Microscopic evaluation reveals atypical spindle cells with stromal cellularity within large areas of necrosis (H&E, x100)

H&E: hematoxylin and eosin stain

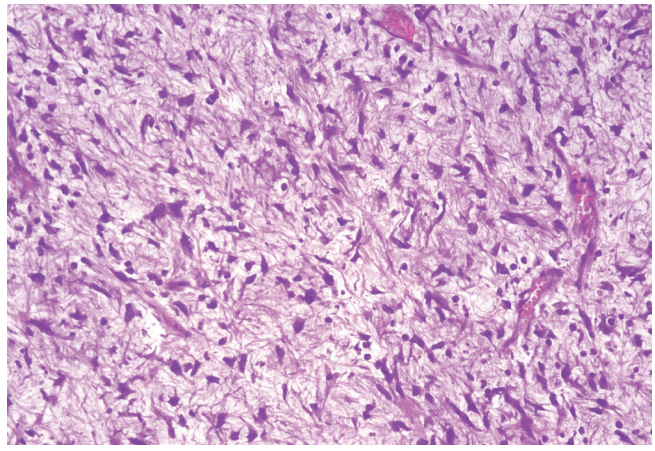

Figure 6. The picture shows cellular tumor tissue characterized by mitotic figures formed by prominent cellular atypia (H&E, x200)

H&E: hematoxylin and eosin stain

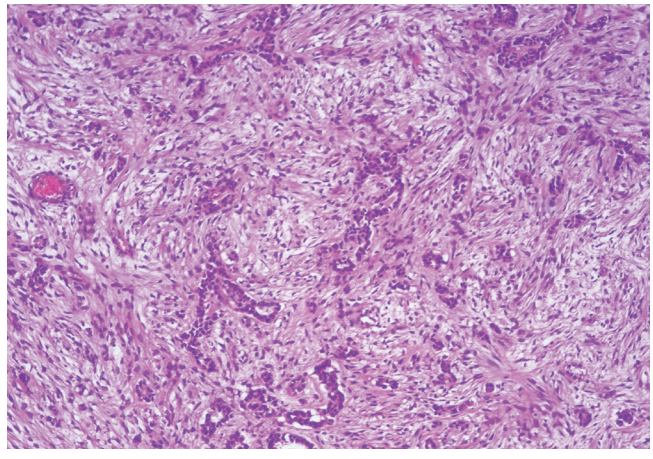

Figure 7. The picture shows areas of invasive carcinoma, some of which forms a well-formed tubule in the stroma (H&E, x100)

H&E: hematoxylin and eosin stain

the reported 40 years in benign PTs, while it was over 40 years in borderline and malignant PTs (51.3 and 44.6 years, respectively).

Diagnosing these lesions as malignant or benign by fine-needle aspiration remains difficult preoperatively, with an accuracy of 63% (5). Although high sensitivity rates have been reported, diagnostic difficulties may also be experienced with core needle biopsy (41).

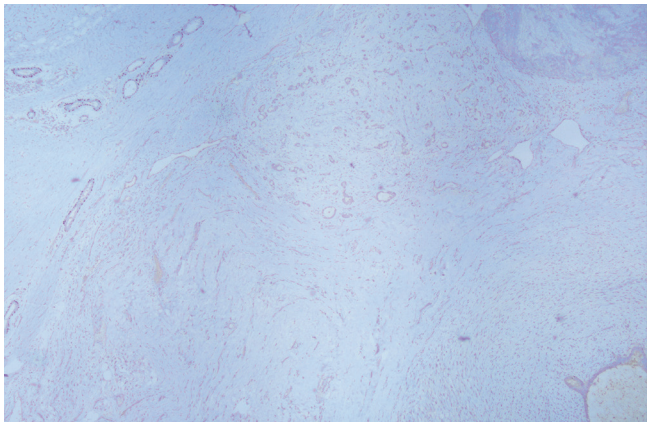

Figure 8. On p63 immunohistochemical staining, ducts that do not show immunoreactivity are observed in myoepithelial cells. Please compare with normal breast tissue in the upper left corner (x40)

However, since surgical excision provides the most definitive diagnosis, if there are findings that may raise clinical suspicion for phyllodes, such as rapid growth, excisional biopsy should be performed regardless of the results of core needle biopsy. Tru-cut biopsy was performed in case 20 for rapidly growing mass in the same year, and a focal invasive ductal carcinoma was detected in the WLE performed subsequently.

It is noted in the WHO breast tumor classification that PTs may include *in situ* and/or invasive carcinoma due to the presence of epithelial components (2). Although their mechanism of development is not fully understood, when carcinoma is detected within the PT it is believed that the epithelial component, stimulated by systemic growth factors, is responsible for this (3). Some investigators believe that the carcinoma begins in the breast parenchyma adjacent to the PT (4). In the cases in our study, the coexistence was detected in the ipsilateral breast. However, since there are reports of carcinoma in the contralateral breast, we suggest that mechanisms other than stimulation of the epithelial component must also be present.

Breast ductal carcinomas arise from the terminal lobular unit, while PTs arise from the stroma (1, 2). However, there is no evidence that when these two tumors coexist, stromal genetic changes lead to the neoplastic transformation of the epithelium, although this mechanism is plausible (4). It is unclear whether malignant transformation of the epithelium is due to stroma-epithelial interactions within the PT or whether it represents cancerization of a PT by carcinoma arising in

Table 4. Malign PTs coexisting with *in situ* carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Seemayer et al. (8)	DCIS	27	60	Ipsilateral	NA
Huntrakoon (9)	DCIS	31	90	Ipsilateral	AW at 24 months
Christensen et al. (10)	LCIS	42-58	NA	Ipsilateral	DA 12 months from metastatic PT
Schwickerath et al. (11)	DCIS	47	20	Ipsilateral	NA
Morimoto et al. (12)	LCIS	49	110	Contralateral	AW at 132 months
Powell and Rosen (13)	DCIS	17–71	8–100	Ipsilateral	NA
Powell and Rosen (13)	LCIS	17–71	8–100	Contralateral	NA
Padmanabhan et al. (14)	LCIS	47	75	Ipsilateral	AW at 6 months
Nishimura et al. (16)	DCIS	80	105	Ipsilateral	DA 3 months from metastases
Lim and Tan (19)	DCIS	45	120	Ipsilateral	DA 108 months from unrelated cause
Tan et al. (20)	DCIS	NA	NA	Ipsilateral	NA
Nomura et al. (22)	DCIS	75	35	Ipsilateral	AW at 32 months
Korula et al. (25)	DCIS	51	210	Ipsilateral	AW at 11 months
Sin et al. (31)	DCIS	45	120	Ipsilateral	AW at 43 months
Sin et al. (31)	LCIS	48	50	Ipsilateral	AW at 43 months
Widya et al. (34)	DCIS	75	50	Ipsilateral	AW at 53 months
Widya et al. (34)	DCIS	49	40	Ipsilateral	AW at 53 months
Widya et al. (34)	LCIS	53	10	Ipsilateral	AW at 53 months
Co et al. (35)	DCIS	52	10	Ipsilateral	AW at 70 months
Co et al. (35)	DCIS	48	5	Ipsilateral	AW at 70 months
Hasdemir et al. (39)	DCIS	15–75	1.5–12	Ipsilateral	NA
Nistor-Ciurba et al. (40)	DCIS	45	60	Ipsilateral	NA

PT: phyllodes tumor; DCIS: ductal carcinoma *in situ;* LCIS: lobular carcinoma *in situ;* AW: alive and well; NA: not available; DA: died after

Table 5. Malign PTs coexisting with invasive carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Powell and Rosen (13)	ILC	17–71	8–100	Ipsilateral, Contralateral	NA
Kasami et al. (15)	ILC	47	NA	Contralateral	NA
Gebrim et al. (17)	ILC	58	300	Contralateral	AW at 84 months
Auerbach (18)	IDC	69	NA	Ipsilateral	DA 51 months from metastases
Tokudome et al. (21)	Undifferentiated	59	35	Ipsilateral	AW at 5 months
Merck et al. (23)	IDC	NA	NA	Contralateral	AW at 32 months
Kefeli et al. (26)	IDC	26	45	Ipsilateral	DA 12 months
Choi et al. (29)	ICC	62	165	Ipsilateral	AW at 24 months
Shin et al. (30)	Invasive carcinoma, NOS and MC	45	240	Ipsilateral (Invasive), Contralateral (MC)	NA
Zhao et al. (32)	IDC	44	100	Contralateral	NA
Muthusamy et al. (36)	Invasive carcinoma, NOS	51	155	Ipsilateral	NA
Co et al. (35)	IDC	45	4,8	Ipsilateral	AW at 70 months
Kaur et al. (38)	NEC	26	90	Ipsilateral	NA
Hasdemir et al. (39)	IDC	15–75	1.5–12	Ipsilateral	NA
Hasdemir et al. (39)	IDC	15–75	1.5–12	Contralateral	NA
Nistor-Ciurba et al. (40)	IDC	71	50	Ipsilateral	AW at 39 months
Current study (Case no: 20)	IDC	45	NA	Contralateral	AW at 22 months
Current study (Case no: 28)	IDC	45	120	Ipsilateral	AW at 10 months
Current study (Case no: 29)	IDC	63	200	Ipsilateral	DA 2 months from unrelated cause

PT: phyllodes tumor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; NEC: neuroendocrine carcinoma; ICC: invasive cribriform carcinoma; MC: metaplastic carcinoma; AW: alive and well; NA: not available; DA: died after

Table 6. Malign PTs coexisting with *in situ* and invasive carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Widya et al. (34)	DCIS	75	2	Ipsilateral	AW at 53 months
Widya et al. (34)	DCIS	49	40	Ipsilateral	AW at 53 months
Widya et al. (34)	LCIS	53	3	Ipsilateral	AW at 53 months
Sugie et al. (24)	IDC, DCIS	54	60	Ipsilateral	DA 40 months from metastatic PT
Abdul Aziz et al. (27)	IDC, DCIS, LCIS	43	35	Ipsilateral	AW at 12 months
Macher-Goeppinger et al. (28)	IDC, DCIS	70	60	Ipsilateral	NA
Warrier et al. (33)	ILC, DCIS	50	110	Contralateral (ILC), Ipsilateral (DCIS)	AW at 24 months
To et al. (37)	ILC, LCIS	48	65	Ipsilateral	NA
Nistor-Ciurba et al. (40)	IDC, DCIS	50	110	Ipsilateral	AW at 132 months
Nistor-Ciurba et al. (40)	IDC, DCIS	75	40	Ipsilateral	DA 1 months from metastases

PT: phyllodes tumor; DCIS: ductal carcinoma *in situ;* LCIS: lobular carcinoma *in situ;* IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; AW: alive and well; NA: not available; DA: died after

the immediately adjacent breast tissue (39). This coexistence is usually found incidentally as it is often unnoticed in the limited evaluations provided by tru-cut biopsies and preoperative radiological evaluations. Therefore, although the diagnosis of PT is not challenging, we believe that a comprehensive histopathological examination with multiple sampling upon considering the coexistence with carcinoma is critical. The presence of ductal carcinoma in combination with PT is clinically important because it can alter the diagnostic process and the management of the patient.

Before 1970, mastectomy was the treatment of choice, regardless of PT subtypes (5, 43). Since then the type of operation to be selected in the surgical treatment of PTs varies depending on whether the tumor is benign, borderline, or malignant. While the absence of a tumor at the surgical margin is sufficient in benign tumors, a wide excision and >1 cm surgical margin is recommended in borderline and malignant tumors (41, 43). *National Comprehensive Cancer Network* guideline therapy recommends complete surgical excision with 1 cm margins without sentinel lymph node biopsy for or malignant phyllodes tumor (43). Axillary dissection is not routinely recommended because lymph node involvement is very rare, occurring in <1% of patients (43-45). However, the prognosis of patients with lymph node metastasis tends to be poor (46). The general surgical approach for giant PTs is simple mastectomy (44).

The coexistence of invasive carcinoma and PTs in patients undergoing breast-conserving surgery, adjuvant RT, chemotherapy, and targeted therapy may be performed in addition to surgical treatment, depending on immunohistochemical findings. However, this coexistence is quite rare and limited to individual cases in the literature (8-40). In our study, the incidence of the coexistence of PTs and carcinoma was 13.7% (4/29). This rate was higher than the previously reported incidence rates (Tables 4,5,6). In a multicenter study the rate of coexistence of PT and carcinoma was 1.07% (6/557) (35). In another single-center study (34), the rate of *in situ*/ invasive carcinoma was 6.01% (11/183) among all phyllodes. The largest study on this subject was performed by Co et al. (35) and their series consisted of 557 PTs. In the study, which included a large population (Hong Kong and Southern China) and included five hospitals over a period of 20 years, only 6 cases show the coexistence of phyllodes tumor and ductal carcinoma. In our tertiary center, the number of PTs over 10 years was only 29, and the association with ductal carcinoma was found in 4 (4/29=13.7%). This high rate of association may be due to small study numbers. However, considering that the association of phyllodes and ductal carcinoma reported from our country is limited to case reports (26, 39), there will not be a significant decrease. Perhaps more importantly, breast cancer incidences differ by ethnicity and are about four-fold higher in Western Europeans (90.7) compared to South Central Asia (26.2), possibly due to Western lifestyle and diet (47). Another reason may be that we oversampled tumor tissues for resident training.

In our study, the incidence of carcinoma, both *in situ* and invasive carcinoma, was 40% (2/5) in malignant PT patients and 20% (2/10) in borderline PT patients. The coexistence of benign PT and carcinoma was not detected. The coexistence of malignant PTs and carcinoma was significantly higher than those of benign and borderline PTs (p<0.05). In the series of Co et al. (35) and Widya et al. (34) the rate of carcinoma in malignant PT patients was 4.6% (3/64) and 27.2% (3/11) while this rate was 0.7% (1/130) and 45.4% (5/11) in borderline and 0.5% (2/363) and 27.2% (3/11) in benign PT patients, respectively. This coexistence was detected in the same breast in all cases in the study of Co et al. (35), while PT and carcinoma were found in the same breast in 3 of the 4 cases (75%) with PT coexistent with carcinoma in our study and one case (25%) had contralateral breast tumor. IDC was detected in 0.1% (1/557) of patients with concomitant PT, and DCIS was detected in 0.8% (5/557) of patients, while these rates were 3.4% (1/29) for DCIS, 3.4% (1/29) for LCIS and 10.3% (3/29) for IDC in our study. Human epidermal growth factor receptor 2 (HER2) was negative in all patients and ER positivity was detected in 50% (3/6) of the patients in the study by Co et al. (35), while HER2 was 50% (2/4) positive and ER was 75% (3/4) positive in our study. In the present series and in those of Co et al. (35) and Widya et al. (34) all PT diameters were >4 cm, with the exception of one patient in each.

There is a general lack of standardization in the treatment of PT, although there are rare cases of malignant epithelial transformation. As the association of PT with carcinoma influences patient management decisions, a multidisciplinary approach is needed with data from breast cancer surgeons, histopathologists, medical oncologists, and radiation oncologists to personalize treatment. In the adjuvant systemic and local treatment decision-making process, axillary nodal staging, pathological stage, borderline status and careful pathological examination are important.

We present a series that has found the highest rate of this rare association in the literature, to the best of our knowledge. However, a weakness of the present study is the low number of cases. Further limitations include the retrospective and single center nature of the study. However, we anticipate that the rate of coexistence of PT and breast carcinoma will increase as the importance of this assocaition is recognized. The multidisciplinary team dealing with breast diseases has a great responsibility in both diagnosis and treatment stages. Future studies with larger case numbers and patients with long-term follow-up data will provide better evidence concerning optimal management of this patient group.

Ethics Committee Approval: The study was approved by the clinical trials ethics committee of the referred hospital (PN 381/2020).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: Ö.D.G., S.A.; Design: Ö.D.G., S.A.; Data Collection and/or Processing: Ö.D.G., S.A., R.İ.T., S.F.; Analysis and/or Interpretation: Ö.D.G., S.A., R.İ.T., S.F.; Literature Search: Ö.D.G., S.A.; Writing: Ö.D.G., S.A.

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