PHYLLODES TUMOR OF THE BREAST: CASE SERIES OF 40 PATIENTS

MEMENİN PHYLLOİDES TÜMÖRÜ 40 VAKALIK SERİ

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ABSTRACT

Purpose: *Cystosarcoma phyllodes is a rare, uncommon fibroepithelial tumor of the breast. In this retrospective study, we analyzed the relation of clinical situations with histopathologic findings.* ***Methods:*** *Forty patients were enrolled in the study. The types of surgery, recurrences, histopathologic diagnoses and follow-ups of the patients were studied. A histopathologic examination was performed and the results were evaluated with logistic regression analysis to determine a correlation between these clinical and pathologic parameters.* ***Results:*** *Surgery was performed in all patients as an initial treatment. In the first examination 38 cases were evaluated as benign and the remaining 2 were malignant. Recurrent tumors were seen in 9 (22.5%) cases at follow-up with a mean recurrence time of 30.1 months. Five of the recurrent cases were evaluated as malign. The total number of malignant cases was 7 (17.5%). In statistical analyses, evidence of tumor necrosis, stromal atypism, stromal cellularity, number of mitoses and stromal overgrowth were found to be significantly correlated with malignancy ($p<0.05$). Recurrences were also significantly correlated with stromal cellularity, stromal overgrowth, necrosis and malignancy ($p<0.05$).* ***Conclusion:*** *Cystosarcoma phyllodes has a high incidence of recurrence and could transform into malignant disease. Patients should be followed strictly in order to detect recurrences earlier.*

Key Words: *Cystosarcoma Phyllodes, Malignant, Recurrence, Surgery.*

ÖZET:

Amaç: *Memenin fibroepitelyal tümörlerinde cystosarcoma phylloides nadirdir. Yüksek oranda rekürrens göstermesiyle agresiv davranışa sahiptir.* ***Metod:*** *Bu retrospektif çalışmada, klinik tabloyla histopatolojik bulguların ilgisini analiz ettik. Çalışmaya 40 hasta dahil edildi. Cerrahi yaklaşım tipleri, rekürrensler, histopatolojik diagnoz ve hastaların takibi çalışıldı. Histopatolojik bir çalışma yapıldı ve sonuçların klinik ve patolojik parametre bağlantıları Logistic Regression Analise ile değerlendirildi.* ***Bulgular:*** *Tüm hastalara ilk tedavi olarak cerrahi uygulandı. İlk çalışmada 38 vaka benign geri kalan 2 vaka malign olarak değerlendirildi. Takipte rekürrens zamanı ortalama 30.1 ay olan 9 vaka (%22.5) saptandı. Rekürren vakaların 5'i malign olarak değerlendirildi. Toplam malign vaka sayısı 7'ye (%17.5) yükseldi. İstatiksel analizlerde tümör nekrozu, stromal atipizm, stromal sellularite, mitoz sayısı ve stromaya yayılım bulguları malignite ile anlamlı olarak ($p<0.05$) bağlantılı bulundu. Ayrıca, stromal sellularite, stromal yayılım, nekroz, malignite rekürrens ile anlamlı olarak ($p<0.05$) bağlantılı bulundu.* ***Sonuç:*** *Cystosarcom phylloides yüksek bir insidansta rekürrens gösterebilir ve malign hastalığa dönüşebilir. Rekürrensleri erken farkedebilmek için hastalar sıkı takip edilmelidir.*

Anahtar Kelimeler: *Cystosarcoma Phylloides, Malignite, Rekürrens,Cerrahi.*

INTRODUCTION

Cystosarcoma phyllodes is an uncommon tumor of the breast. It is a rare fibroepithelial tumor that accounts for 0.3 to 0.5% of all breast neoplasms (1). The typical presentation of these tumors is a painless, well-circumscribed large mass with an average diameter of 3 to 5 cm (2-4). The tumor is generally categorized as benign or

malignant, but in both categories it is considered to exhibit aggressive behavior. In several clinical studies it was seen that the recurrence rate is very high and is independent of its benign or malignant nature (5,6).

Cystosarcoma phyllodes remains a challenge to pathologists. There are some difficulties including the histologic diagnosis, classification and correlation of clinical and histopathologic parameters.

The tumor is composed of an epithelial and a cellular stromal component. The determination of the tumor as benign or malignant is mainly based on the histologic assessment such as stromal overgrowth, hypercellularity and an increase in the mitotic rate (6). It seems that this designation is independent of its size, presentation form and behavior. Therefore, in this retrospective study we tried to analyze the relation of clinical situations with histopathologic findings.

MATERIALS AND METHODS

Between 1980 and 1997 at Ankara Oncology Hospital 40 patients with cystosarcoma phyllodes were enrolled in the study and were retrospectively analyzed. The mean age of the patients was 37.5 (18-74) years. The localization of the tumor was left-sided in 17 and right-sided in 23 cases. In 20 cases the largest diameter of the

Table-1: Characteristics of patients.

No.	Age	Side	Size (cm)	Surgery	Diagnoses	Recurrences	Follow-up (month)	Status
1	74	L	13	SMAD	B	2 (Malign)	115	AED
2	45	R	3	TE	B	-	124	OF
3	27	R	4	TE	B	-	25	OF
4	23	R	2.5	TE	B	-	6	OF
5	40	R	12.5	SM	B	-	10	OF
6	45	L	8.5	TE	B	-	15	OF
7	44	L	3	TE	B	-	26	OF
8	52	L	11	TE	B	2 (Malign)	54	AED
9	22	L	2.5	TE	B	-	32	AED
10	30	R	4.5	TE	B	-	47	AED
11	56	R	6.5	TE	B	-	36	AED
12	35	L	5	TE	B	-	80	AED
13	32	L	10	TE	B	5 (Malign)	26	DDD
14	35	R	4	TE	B	-	11	OF
15	27	R	9	TE	B	1 (Benign)	81	OF
16	44	R	9.5	SM	B	-	27	OF
17	60	L	8	SMAD	M	2 (Malign)	28	DDD
18	47	R	2	TE	B	2 (Benign)	41	AED
19	29	R	3.5	TE	B	-	19	OF
20	24	R	7	TE	B	-	9	OF
21	38	R	4	TE	B	-	33	OF
22	48	R	12.5	SM	B	-	15	AED
23	35	R	15	SM	B	-	17	AED
24	46	R	4	TE	B	-	25	OF
25	19	L	11.5	SM	B	-	13	OF
26	21	L	3	TE	B	-	27	OF
27	40	L	4	TE	B	-	11	OF
28	39	R	9	TE	B	-	3	OF
29	31	R	4	TE	B	1 (Malign)	28	DDD
30	30	L	3.5	TE	B	-	21	OF
31	18	L	3	TE	B	-	15	OF
32	25	L	13	SM	B	-	21	OF
33	39	L	8	TE	B	-	13	OF
34	30	R	4	TE	B	1 (Benign)	19	OF
35	48	R	7.5	TE	B	1 (Malign)	35	AED
36	45	L	7.5	TE	B	-	1	OF
37	25	R	8	SM	M	-	1	OF
38	40	L	4.5	TE	B	-	16	AED
39	59	R	13.5	SM	B	-	33	AED
40	35	R	4.5	TE	B	-	25	AED

L: left, R: right, SMAD: simple mastectomy+axillary dissection, TE: total excision, SM: simple mastectomy, B: benign, M: malign, AED: alive without evidence of disease, OF: out of follow-up, DDD: death because of distant disease

tumor size was <5 cm, 5< - <10 cm in 12 cases and ≥10 cm in 8 cases with a mean of 6.8 cm (2-15 cm) (Table 1). All of these patients underwent surgery. The types of surgery, recurrences, histopathologic diagnoses and follow-ups of these patients were studied. With these clinical findings a histopathologic examination was performed by a specialist pathologist and the results were evaluated to determine a correlation between these clinical and pathologic results. Stromal cellularity, stromal cellular atypism, mitosis number, stromal overgrowth, tumor necrosis, components other than myxoid changes in stroma and border of the tumor were evaluated in a categorical manner (Table 2). Logistic regression analysis was also performed to determine a significant correlation between malignant diagnosis and the mentioned histopathologic parameters, as well as which factors have an effect on recurrence rates.

RESULTS

As a first-line treatment, surgery was performed in all patients: a wide local excision in 30, simple mastectomy in 8, and simple mastectomy+axillary dissection in 2 cases were performed. In the first examination 38 cases were evaluated as benign and the remaining 2 (5%) as malignant. In the malignant cases, after a diagnostic procedure with a core biopsy, a simple mastectomy was performed with axillary dissection because of palpable axillary lymph nodes. Recurrent tumors were seen in 9 (22.5%) cases in follow-up with a mean recurrence time of 30.1 months (5-110). In these 9 cases 17 recurrences were developed with 5 recurrences in one case. All of the recurrent cases were treated with surgery (12 total excisions, 4 simple mastectomy+axillary dissections and a simple mastectomy) (Table 1). As in the other 2 cases whose initial treatment was axillary dissection and simple mastectomy, there were clinically palpable lymph nodes in 4 of the recurrent cases. However, during pathologic examination no axillary metastases were detected. The total number of malignant cases was 7 (17.5%). Two of them were diagnosed in the first evaluation and the other 5 were regarded as malignant after recurrences occurred. The mean follow-up time for all patients was 29.4 months (1-124). There were 12 patients who were alive without disease at the time this study was performed and 3 patients who were dead because of metastatic disease; the other 25 patients discontinued follow-ups at different times. In those that died because of metastatic disease it was observed that they were diagnosed with a benign disease at the initial operation. After the recurrence of the disease, their pathologies were considered malignant and simple mastectomy+axillary

Table-2: Histopathologic parameters and results.

		Benign	Malign
Stromal cellularity			
	Slight to moderate	26	-
	Prominent	10	9
Stromal cellular atypism			
	None to moderate	29	2
	Prominent	7	7
Mitotic activity (No. of mitoses per 10 High Power Fields)	0	1	1
	≤3	26	4
	4-9	4	1
	10-20	2	2
Stromal overgrowth			
	None	24	2
	Evident	12	7
Tumor necrosis			
	None	34	6
	Evident	2	3
Components other than myxoid changes	None	34	7
	Evident	2	2
Border of the tumor			
	Not evaluated	7	5
	Pushing	25	2
	Infiltrative	4	2

dissections were performed. Pulmonary metastases were developed in follow-up. In all of these cases, chemotherapy was applied after metastatic disease was detected (FAC protocol: 5 Fluorouracil, Adriablastin, Cyclophosphamide), but no response was achieved.

In pathologic examinations the specimens of 37 cases were available for re-examination. There were 45 different tumor specimens including recurrences for examination. Microscopic slides were evaluated as mentioned in the previous section and the results are shown in Table 2.

In statistical analyses with linear regression evidence of tumor necrosis, stromal atypism, stromal cellularity, mitosis and stromal overgrowth were found to be significantly correlated with malignant diagnoses (Table 3) (Fig. 1). During analyses for occurrence of recurrence it was observed that stromal cellularity, stromal overgrowth, necrosis and malignant diagnoses were significantly important for recurrences ($p<0.05$) (Table 3) (Fig. 2).

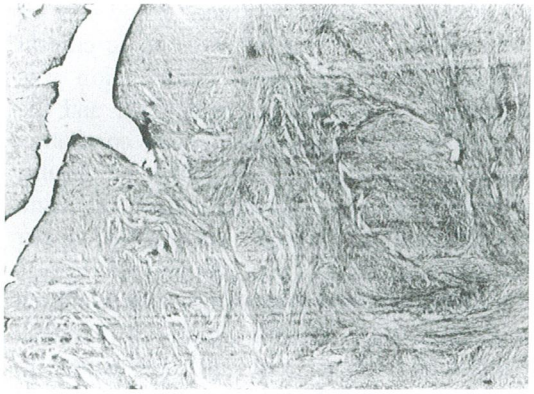

Fig. 1: Area of stromal overgrowth abutting ducts in a border (Hematoxylin-eosin, x20).

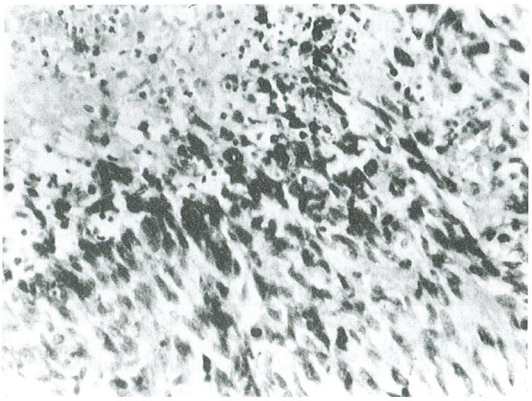

Fig. 2: Stromal cells showing increased cellularity, mitotic figures and necrosis in the upper-left corner of the field (Hematoxylin-eosin, x20).

DISCUSSION

The appropriate surgical treatment for cystosarcoma is still under debate. The preference for breast conserving therapy, wide local excision or simple mastectomy remains unclear. There is insufficient data to make a healthy choice that balances the risk of malignity or recurrence. Recurrence rates of the tumor are between 17 and 28.1% in some series (1,5-12), as was the case in our study. Salvadori et al. (8) mentioned in their study that the choice of surgery did not affect the prognosis and they added that all phyllodes tumors can recur regardless of their histology and the risk of local recurrence is very low for benign phyllodes and much higher for borderline and malignant tumors. Our findings were similar in this regard. From 40 patients recurrences were seen in 9 cases and in these 9 patients malignant tumors developed in 6. These cases were diagnosed as benign in previous pathologic examinations. It may be thought that the tumor has transformed from benign to malignant. Lu et al. (13) indicated that an increased copy number of 1q material in chromosomes was associated with recurrence and might therefore be considered an indicator of local aggressiveness requiring more radical

Table-3: Results of logistic regression analyses.

Factors affecting malignancy	
	Significance
Stromal cellularity	0.0041
Stromal atypism	0.046
Number of mitoses	0.019
Tumor necrosis	0.0016
Stromal overgrowth	0.015
Factors affecting recurrence	
	Significance
Stromal cellularity	0.038
Stromal overgrowth	0.001
Tumor necrosis	0.007
Malignity	0.000

treatment. We found that stromal cellularity, stromal overgrowth, necrosis and malignant diagnoses were significantly important factors for recurrences.

Biologically, all phyllodes tumors are considered to be potentially malignant. The reported incidence of malignant phyllodes tumors ranges from 12 to 54% (5,6,8-11,14). These rates are high for a tumor that is generally considered benign. These tumors could transform from benign to malignant over time along with their recurrence, as shown previously (1,9,14). Several authors analyzed the histopathologic factors, which are considered important in malignant diagnoses. Cedermark et al. (6) found that tumor necrosis and the presence of stromal elements other than fibromyxoid tissue were important, while Kario et al. (7) and Richard et al. (9) claimed that stromal overgrowth is an important factor in malignancy. Azzopardi (15) has established that mitoses exceeding 3 per 10 HPF is a potential indicator of malignancy. Kocova et al. (16) found a significant correlation with the expression of the Ki-67 antigen and malignant disease. In our study we found tumor necrosis, stromal atypism, stromal cellularity number of mitoses and stromal overgrowth to be significantly correlated with malignancy. We believe that to make a risk analysis for the prediction malignancy is quite difficult because of the small sample sizes of previous studies.

There is insufficient data for the adjuvant treatment of cystosarcoma phyllodes. Only sporadic reports of a few cases that receive radiotherapy could be found (17). In metastatic cases chemotherapy was generally found to be ineffective. In a study of Contarini et al. (18), only 1 of 17 patients with metastatic disease responded to combination chemotherapy.

The choice of surgical treatment for phyllodes tumor depends on the size of the tumor and the breast. If an adequate margin can be achieved, wide local excision can be performed, otherwise total mastectomy should be the proper treatment modality, while axillary dissection is not recommended (5,8,14,19). It should be remembered that these tumors have a high incidence of recurrence and can transform into the malignant disease. Patients should be strictly followed in order to detect recurrences earlier.

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