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Analysis of patients with phyllodes tumor of the breast

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ABSTRACT

Objective: The diagnosis and management of phyllodes tumors is challenging due to its low incidence. The treatment of these tumors is surgery, however the extent of surgery, the application of adjuvant chemotherapy and radiotherapy are still controversial. Therefore, we aimed to evaluate patients who were treated with a diagnosis of phyllodes tumor of the breast in our clinic.

Material and Methods: Patients who were treated with a diagnosis of phyllodes tumor of the breast between June 2011 and June 2013 were reviewed retrospectively. Patient demographic characteristics (age, gender), menopausal status, symptoms, radiologic and surgical methods used for diagnosis and treatment, histopathologic features of the tumor and type of adjuvant therapy were evaluated. Patients were grouped as benign or borderline/malignant according to histopathological diagnosis. Patients in these groups were compared in terms of age, menopausal status, tumor size and the number of mitosis within the tumor.

Results: The median age was 26 years (17-59), and 30 patients were female. The surgical treatment of choice was wide local excision with tumor-free surgical margins in 29 patients and mastectomy in one patient. Histopathological diagnosis after surgery was benign in 21 patients (70%), borderline in 6 patients (20%) and malignant phyllodes tumor in 3 patients (10%). Patients with borderline and malignant phyllodes tumors were significantly older ($p=0.002$) and had higher mitotic counts ($p<0.0001$). There was no significant relationship between histopathologic subtypes of phyllodes tumors and menopausal status ($p=0.06$) or tumor size ($p=0.1$).

Conclusion: Surgery is the treatment of choice for phyllodes tumors, and obtaining tumor-free margins is important. Since phyllodes tumors might recur as borderline/malignant tumors, local control with surgery and adjuvant radiotherapy should be provided when required. In this way, distant metastases and death that may arise due to possible malignant recurrences might be avoided.

Key Words: Breast, phyllodes tumor, age, menopause, mitosis, tumor size

INTRODUCTION

Phyllodes tumor was first defined by Johannes Muller in 1838 as "cystosarcoma phylloides" (1). This tumor was named as such in those years not because of its potential for metastasis, but due to its macroscopic appearance that is similar to sarcoma. The World Health Organization renamed these tumors as "phyllodes tumor" in 1982 (2). Phyllodes tumors are classified as fibro-epithelial tumors in the breast, and are rare tumors that constitute 0.3 to 0.5% of primary breast tumors. Differentiating them from fibroadenomas is difficult both clinically and radiologically, however phyllodes tumors are detected at an older age (35-55 years). They are classified as benign, borderline and malignant phyllodes tumors according to their histopathological features. The clinical course and treatment of these subtypes are quite different from each other. Difficulties in diagnosis in the preoperative period can lead to errors in treatment planning. The treatment of these tumors is surgery, however the extent of surgery, the application of adjuvant chemotherapy and radiotherapy are still controversial. Therefore, a thorough identification of phyllodes tumors and knowledge on their features are important. In this study, we aimed to evaluate patients who were treated with a diagnosis of phyllodes tumor of the breast in our clinic.

MATERIAL AND METHODS

Patients who were treated with a diagnosis of phyllodes tumor of the breast between June 2011 and June 2013 were reviewed retrospectively. Informed consent was obtained from all patients during hospitalization. Patient demographic characteristics (age, gender), menopausal status, and symptoms were extracted from patient files. In addition to these, radiologic and surgical methods used for diagnosis and treatment, histopathologic features of the tumor and type of adjuvant therapy were also evaluated. The pathology department categorized phyllodes tumors as histologically benign, borderline and malignant according to the World Health Organization classification. This classification was made according to (1) degree of stromal cellular atypia, (2) mitotic count per 10 high-power fields (hpfs), (3) degree of stromal overgrowth, and (4) infiltrative or regular bordered tumor margin. Patients were then divided into two groups according to the histopathologic diagnosis as benign or borderline/malignant cases. These two groups were compared in terms of patient age, menopausal status, tumor size and tumor mitotic count.

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Statistical Analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) 13.0 software was used for statistical analysis. Parametric data were presented as mean±standard deviation. Categorical values were compared by the chi-square or Fisher's exact chi-square tests, and Student's t test was used for comparison of continuous variables. P<0.05 was considered to be statistically significant.

RESULTS

The study included 30 female patients with a median age of 26 (17-59) years. Twenty-eight patients (93.3%) were premenopausal and 2 (6.7%) were postmenopausal. All patients presented with a breast mass. The phyllodes tumor was located in the right breast in 17 patients (56.7%), and in the left breast in 13 patients (43.3%). All patients underwent bilateral breast ultrasonography, and 6 patients (20%) received additional bilateral mammography. Magnetic resonance imaging was not used in any patient. Image-guided core needle biopsy was performed in all patients and all lesions were reported as benign. The imaging and histopathological examinations of these lesions were benign, nevertheless, since the greatest dimension of these masses was larger than 2 cm they were discussed with the patient and it was decided to perform an excision upon their preferences. As surgical treatment, wide local excision with at least 1 cm macroscopic tumor-free surgical margins was performed in 29 patients, and one patient underwent mastectomy. Histopathological diagnosis after surgery was reported as benign phyllodes tumor in 21 patients (70%), as borderline phyllodes tumor in 6 patients (20%) and as malignant phyllodes tumor in 3 patients (10%). The mean size of the tumors removed surgically was 3.8±1.6 cm, and the mean mitotic count was 3.2±1.2/10 hpfs. The patient who received mastectomy was diagnosed with malignant phyllodes tumor, and despite two additional re-excisions a tumor-free surgical margin could not be achieved, and a simple mastectomy was performed. A sentinel lymph node biopsy was performed during the mastectomy, since technically it would not be possible to perform postoperatively and because of the possibility of diagnosis of malignancy in the pathologic evaluation. Axillary lymph node metastasis was not detected by sentinel lymph node biopsy. Histopathological tumor-free surgical margins were achieved in all patients except the patient who underwent mastectomy. Patients with malignant phyllodes tumor received adjuvant chemotherapy containing doxorubicin and iphosphamide. Two patients who underwent breast-conserving surgery for malignant phyllodes tumor received adjuvant radiotherapy in addition. The median postoperative follow-up was 18 months (range 6-32 months). Any local-regional recurrence or distant metastases were not detected during the follow-up period.

In addition, patients with borderline and malignant phyllodes tumors were compared to patients with benign phyllodes tumors in terms of age, menopausal status, tumor size and mitotic count. Patients with borderline and malignant phyllodes tumors had more advanced age (p=0.002) and a higher mitotic count (p<0.0001). On the other hand, there was no statistically significant relationship between phyllodes tumor subtypes and menopausal status (p=0.06) or tumor size (p=0.1).

DISCUSSION

Phyllodes tumor of the breast is a rare entity, and it is important to know its clinical presentation and histopathological subtypes. The treatment of these tumors should be applied according to the histological subtype. There are different proposals for the histopathologic classification of phyllodes tumors. The use of different classification systems in studies conducted in this regard makes it difficult to compare the results. The classifications used currently are not always compatible with the clinical course of phyllodes tumors. New classifications that use different features of the tumor are required. On categorization of phyllodes tumors according to the commonly used classification system, benign phyllodes tumors show stromal cellular increase, mild-to-moderate atypia, mitosis <4/10 hpfs, and the tumor has regular borders without stromal overgrowth. Borderline phyllodes tumors have more stromal cellular proliferation and atypia, with infiltrating borders, a mitotic count of 4-9/10 hpfs, but without stromal overgrowth. In malignant phyllodes tumors, there is significant stromal cellular proliferation and atypia, mitotic count is ≥10/10 hpfs, with infiltrating margins and stromal overgrowth (2). In this study, patients were diagnosed histopathologically according to this classification.

The diagnosis of phyllodes tumors might be challenging in daily clinical practice. The lack of preoperative diagnosis of malignant phyllodes tumors may lead to recurrence and even distant metastases in the short term due to inadequate excision. On the other hand, since the radiological and histopathological findings of phyllodes tumors are often similar to fibroadenoma, clinical suspicion is essential for diagnosis. Phyllodes tumor should be kept in mind even in lesions that are considered as benign such as breast fibroadenoma, and appropriate diagnostic and treatment strategies should be determined. Follow-up of phyllodes tumors that are considered as benign is risky due to the possibility of malignant transformation. Patient age >35 and rapid growth should be considered as indicators of phyllodes tumors in clinically and radiologically benign-looking breast masses. The compression of phyllodes tumor may lead to dilation of veins on breast skin, blue discoloration and nipple-areola complex changes like necrosis and these findings suggest phyllodes tumors.

Age may play an important role in the differential diagnosis of breast lesions with benign features. Although phyllodes tumors are similar to fibroadenomas in many ways, they appear later in life. The phyllodes tumor patients enrolled in this study were younger than expected. In previous studies, it has been reported that patients with borderline/malignant phyllodes tumors were older than those with benign phyllodes tumors (3, 4). In this study, it was detected that the borderline/malignant phyllodes tumor patients also had more advanced age. In contrast, there are also studies indicating that there was no relationship between age and phyllodes tumor subtype (5). The reason for this relationship is not clear, although some theories have been suggested. According to this, all phyllodes tumors appear in the same age group and those that remain undetected until advanced ages undergo malignant transformation due to the influence of the changing hormonal milieu. The opposing theory states that benign and malignant phyllodes tumors arise in different ages and are tumors with different biological properties. The assumption that phyllodes tumors may be affected by hormonal milieu suggest a relationship between these types of tumors and menopausal status. However, in both previous reports and the current study

a significant association was not detected between the histopathological subtype of phyllodes tumor and menopausal status (3). Phyllodes tumors, similar to breast cancer, are often seen in women. All of the patients included in this study were female.

The size of phyllodes tumors is quite variable. Giant phyllodes tumors larger than 10 cm are frequent. This variability in tumor size depends on late diagnosis due to diagnostic difficulties and the tumor's benign or malignant nature. Generally, tumor size varies between benign and borderline/malignant phyllodes tumors (5, 6). Rapid growth can be detected especially in malignant phyllodes tumors. In this study, there was no significant relationship between phyllodes tumor size and histopathological sub-groups. This can be explained by the fact that patients who were generally considered as having benign masses had benign phyllodes tumor on histopathologic examination. Similarly, previous studies also stated that no significant relationship between tumor size and histological sub-groups was identified (4, 7).

The first method to be used in the histopathological diagnosis of breast masses is image guided core needle biopsy. This approach is required to technically facilitate possible/future breast-conserving surgery and sentinel lymph node biopsy, especially in lesions considered as malignant. Core needle biopsy can also be applied to exclude malignancy in lesions that are thought to be benign. Image-guided biopsies can be misleading in phyllodes tumors because they have a heterogeneous structure consisting of both epithelial and stromal components. Therefore, the distinction between benign phyllodes tumor and fibroadenoma is difficult by fine-needle or tru-cut biopsy. During fine-needle or tru-cut biopsy of phyllodes tumors, if the sampling consists of benign cells it can be diagnosed as fibroadenoma, or if malignant stromal cells were sampled a diagnosis of sarcoma is likely. For the diagnosis of phyllodes tumor, the sensitivity of fine-needle biopsy ranges between 23-40%, and the sensitivity of tru-cut biopsy ranges from 63-65% (8, 9). The lesions of study patients were radiologically benign and they were excised due to their large size. In our daily clinical practice, even masses that are considered to be benign are excised together with normal surrounding tissue, and in this series only one patient who was diagnosed with malignant phyllodes tumor required re-excision and eventually underwent mastectomy. In addition, if tumor size/breast size ratio or the location of the tumor is not suitable for breast conserving surgery, patients with benign phyllodes tumor also may require mastectomy.

Local recurrence rates during follow-up of patients with phyllodes tumor have been reported between 10-40% in different studies (10). The 5-year disease-free survival has been reported as 81% in patients with longer follow-up (4). Local recurrences are often detected within the breast tissue, but rarely local-regional recurrence involving the chest wall can be identified. Local recurrence rates are higher in malignant phyllodes tumors, nevertheless, there is a risk of recurrence in patients with benign phyllodes tumor. Malignant recurrence can be detected in 15-20% of benign or borderline phyllodes tumor recurrences (6, 11). The principal factor affecting the risk of local recurrence in phyllodes tumors is attaining tumor-free surgical margins during surgery (6, 12, 13). Especially in borderline and malignant phyllodes tumors, the probability of local recurrence was reported as 21% even when surgical margins were tumor-free (14). Therefore, adjuvant radiotherapy should be applied following breast conserving surgery for borderline and malignant phyllodes tumors. Application of breast radiotherapy significantly reduces the rate of local recurrence (11, 12, 14). In our study, tumor-free surgical margins were achieved in all patients. There was no local recurrence during follow-up of patients, but there is the possibility of local recurrence in the coming years due to the short follow-up (median 18 months). That is why, patients with phyllodes tumor should be closely followed-up especially during the first two years when recurrence and metastasis are more frequent, at intervals of 3-6 months. Patients then can be followed-up on an annual basis.

In general, phyllodes tumors cause distant metastasis with hematogenous spread without metastasizing to regional lymph nodes, in contrast to breast adenocarcinomas. The rate of axillary lymph node metastasis was reported as 0-2% (3, 13). In this study, sentinel lymph node biopsy was performed in the patient who underwent mastectomy, and metastasis was not detected. The most common distant metastases sites of phyllodes tumors are soft tissue, lungs and bones. Liver and heart metastases have rarely been reported. Distant metastases are observed in malignant phyllodes tumors. Systemic therapy is recommended in this group of patients. Although the number of studies on the effectiveness of adjuvant chemotherapy in borderline or malignant phyllodes tumors is insufficient, protocols containing doxorubicin, dacarbazine and iphosphamide are being used (15). That is why in our study, patients with a diagnosis of malignant phyllodes tumor received chemotherapy after surgery. In this study, distant metastases was not detected during the short follow-up period.

The results obtained in this study are similar to those reported in previous studies. The number of patients included in the study is sufficient considering the time period (2 years), nevertheless, the retrospective design of the study and short follow-up (median 18 months) are limitations of the study.

CONCLUSION

Surgery is the mainstay treatment of phyllodes tumors and it is important to obtain tumor-free surgical margins during surgery. Phyllodes tumor recurrence can present as histopathological borderline/malignant tumors, therefore local control must be provided with surgery and adjuvant radiotherapy if necessary. In this way, distant metastases and deaths related to phyllodes tumors due to the possible malignant recurrences may be reduced.

Ethics Committee Approval: Local Review Board decision was not obtained due to the retrospective nature of the study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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