Original Article

Breast Phyllodes Tumor: A 6-year Retrospective Series Analysis at Mayo Hospital/King Edward Medical University, Lahore, Pakistan

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ABSTRACT

Objective: This study was conducted to determine the frequency and salient pathological features of the different subtypes of phyllodes tumors (PT) at Mayo Hospital/King Edward Medical University, Lahore, Pakistan.

Methodology: It was a cross-sectional study conducted at the Histopathology Section of the Pathology Department of Mayo Hospital/King Edward Medical University, Lahore, Pakistan. The study was approved by the ethical committee of the institution. The histopathological records of 30 patients with a diagnosis of PT reported in 6 years from 1st January 2013 to 31st December 2018 were reviewed. The tumors were categorized into benign, borderline and malignant subtypes based on the World Health Organization (WHO) criteria. Other parameters analyzed were the age at the time of presentation, tumor size, tumor laterality, the type of surgical specimens received, the status of surgical margins and recurrence of the tumor. The Statistical Package for the Social Sciences (SPSS) version 24 was used for analyzing the data.

Results: Out of 30 cases, there were 15(50%) cases of benign PT, 6(20%) cases were classified as borderline and 9(30%) cases were placed in the malignant category. The age of the patients ranged from 25 to 80 years with a mean of 41.07±11.13 years. The size of the tumors ranged from 4-22 cm with a mean of 10.53±4.13 cm. The surgical specimens comprised of 2(6.67%) wedge biopsy samples, 20(66.67%) lumpectomy specimens, 4(13.33%) simple mastectomy and 4(13.33%) cases of modified radical mastectomy specimens. These specimens included 4(13.33%) recurrent cases of phyllodes tumor.

Conclusion: Our study concluded that benign phyllodes tumor was the most common type (50%) of phyllodes tumor followed by malignant category (30%). Recurrence of the tumor was reported in 4(13.33%) cases. All 3 subtypes of phyllodes tumors are prone to recurrences so wide surgical excision is the preferred therapy.

Keywords: *Phyllodes tumor. Breast tumor. Lumpectomy. Mastectomy. Wide surgical excision.*

INTRODUCTION

Phyllodes tumor (PT) is an uncommon breast tumor that accounts for less than 1% of all primary tumors of the breast and 2.5% of all tumors in the fibroepithelial group.[1] The tumor originates from the neoplastic proliferation of the mesenchymal stromal cells.[2] These tumors can occur at any age but are more common in women over the fourth decade of life with early onset in Asian countries.[1] The histological hallmark is a leaf-like pattern produced due to a predominantly intracanalicular ductal architecture and elongated cleft-like spaces lined by epithelial & myoepithelial cells within a hypercellular spindle cell stroma which is more accentuated around the lactiferous ducts.[3] Johannes Muller was the first to describe this tumor in 1838 and he called it Cystosarcoma Phyllodes (the word *phyllodes* is the Greek term for "leaf-like").[4] In the year 1981, the World Health Organization (WHO) introduced the new terminology of phyllodes tumor for this pathological breast entity and later in 2003, WHO International Histological Classification group proposed its subdivision into 3 categories: benign, borderline and malignant on the basis of 4 microscopic features. These features included stromal atypia & hypercellularity, stromal overgrowth over the epithelial component, number of mitotic figures and infiltration into the tumor margins.[5] Heterologous malignant elements with areas resembling a liposarcoma, osteogenic sarcoma and chondrosarcoma categorize the tumor into the malignant category irrespective of other histological characteristics.[3,6] Stromal over growth is histologically defined as the "presence of stroma without the epithelium in at least one low power field as observed with a 4X microscope objective". Stromal mitosis is seen in the mitotically active areas of the tumor and counted per 10 HPF.[6]

Grossly, PTs are large with a firm tan white cut surface with cleft-like spaces resembling a leaf. Hemorrhage and necrosis may also be seen. Patients with PTs usually present with painless, palpable and fast-growing tumor nodules.[3] Phyllodes tumor is locally aggressive & infiltrative and usually does not metastasize to the regional axillary lymph nodes. Axillary dissection is therefore not recommended.[2] The route of tumor metastases is usually bloodstream. It may metastasize to the lungs, bones & pleura.[7,8] The overall metastatic rate reported by WHO is 0% for benign PT, 4% for borderline and 22% for malignant PT.[5] Phyllodes tumor exhibits a very high recurrence rate for which a wide margin of surgical excision is

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crucial to control its recurrence and relapse.[9] A 1 cm margin of excision is therefore recommended for all the three subtypes of phyllodes tumors.[10] The differential diagnosis of malignant PT is any high-grade sarcoma and metaplastic carcinoma.[6,8]

This study was planned to determine the salient pathological features of phyllodes tumor and categorize it into benign, borderline & malignant subtypes. Meticulous histopathological examination of surgical specimens is considered the gold standard for this categorization.[1] Like all morphological grading systems, this grading system is also subject to interobserver variability especially at the interphase between the 3 grades. Many PTs show focal areas with benign, borderline and malignant characteristics intermixed within the same tumor which necessitates careful gross examination and histological assessment as a crucial component for accurate categorization.[6]

METHODOLOGY

It was a cross-sectional study conducted at the Histopathology Section of the Pathology Department of Mayo Hospital/King Edward Medical University, Lahore, Pakistan. The study was approved by the ethical committee of the institution. The histo-pathological records of 30 patients with a diagnosis of PT reported in 6 years from 1st January 2013 to 31st December 2018 were reviewed. The histopathology reports and blocks were retrieved. Fresh slides were prepared & reviewed to reconfirm the previous diagnosis and classify the tumors into benign, borderline and malignant categories based on the 4 histological parameters proposed by the WHO (Table 1).[5] Other parameters noted were the age at the time of presentation, types of surgical samples received, tumor size, tumor laterality, the status of the surgical resection margins and axillary lymph nodes in cases of the modified radical mastectomy specimens. All information was retrieved from the computer records of these patients. Retrospective records were also studied to see whether the patient had presented with a recurrent tumor or with an initial tumor mass.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 24 was used for analyzing the data. The results were compiled and tabulated as frequencies & percentages. Quantitative variables like age & size of the tumors were expressed as mean values±SD.

RESULTS

Our study comprised of 30 female patients with histologically diagnosed phyllodes tumor of the breast. The age of the patients ranged from 25 to 80 years with a mean of 41.07±11.13 years. All females in the benign & borderline category were in the age range of 25-55 years. In the malignant group which comprised of 9 cases, 2 patients were 25 years old & one was 80 years old. The remaining 6 cases were in the age range of 40-55 years. Phyllodes tumors were categorized according to the WHO criteria into 3 groups as benign, borderline and malignant. Out of 30 cases, there were 15(50%) cases of benign PT, 6(20%) cases were classified as borderline and 9(30%) cases were placed in the malignant category (Table 2). The histopathological photographs of benign, borderline and malignant tumors are shown in Figure 1-6.

Table 1: "Three-Tiered Grading System for Phyllodes Tumors Based on 2012 WHO Classification of Tumors of the Breast"[5]

Criteria	Benign	Borderline	Malignant
Stromal Cellularity and Atypia	Minimal	Moderate	Marked
Stromal Overgrowth	Minimal	Moderate	Marked
Mitosis/10 High Power Fields	0-4	5-9	≥10
Tumor Margins	Well circumscribed with pushing tumor margins	Zone of microscopic invasion around tumor margins	Infiltrative tumor margins

Table 2: Frequency Distribution of Phyllodes Tumor into Benign, Borderline and Malignant Category

Tumor Type	Frequency (n=30)	Percentage
Benign	15	50%
Borderline	6	20%
Malignant	9	30%
Total	**30**	**100%**

Figure 1: Benign Phyllodes Tumor: Low Power Microscopic Images Demonstrating the Typical Leafy Stromal Fronds Capped by Epithelium, Increased Stromal Cellularity & Overgrowth

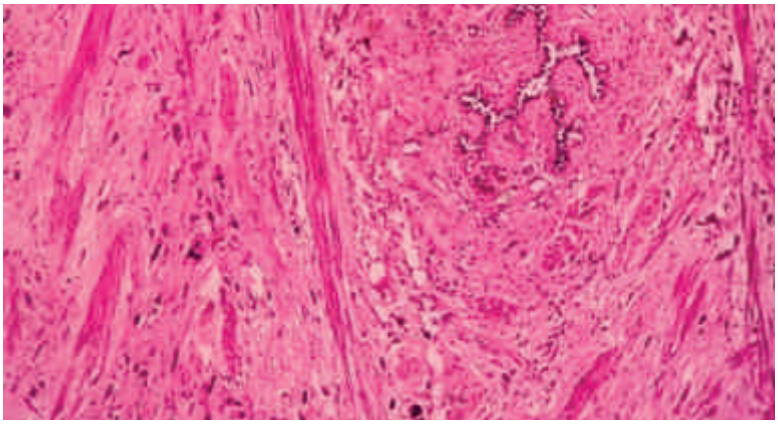

Figure 2: Borderline PT: Low Power View Showing Increased Stromal Cellularity & Overgrowth and the Benign Appearing Ductal Component on the Upper Right Hand Side of the Field. Moderate Degree of Pleomorphism can be Appreciated in the Stromal Component

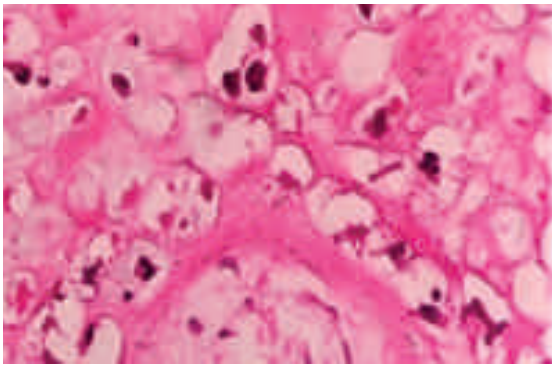

Figure 3: High Power View Microscopic Image Showing Lipomatous Heterologous Sarcomatous Component in a Case of Malignant PT

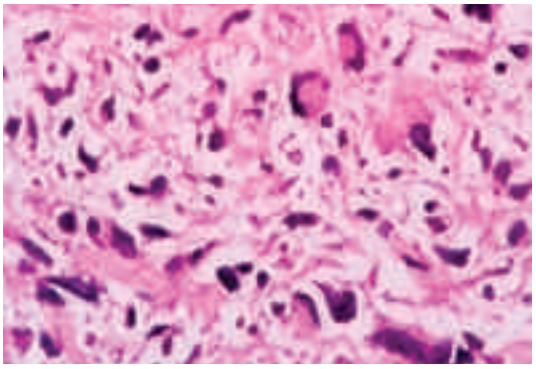

Figure 4: High Power View of Malignant PT Showing Marked Atypia, Pleomorphism & Rhabdoid Cells in the Stromal Component

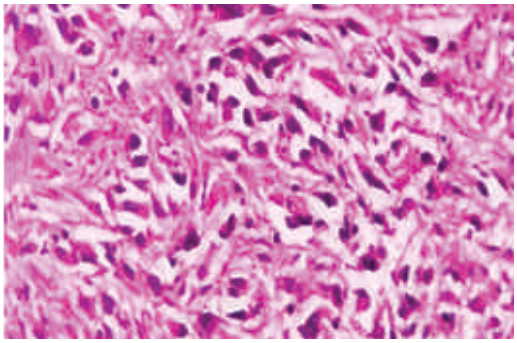

Figure 5: Malignant PT Showing a High-Grade Sarcoma Like Pattern in the Stromal Component

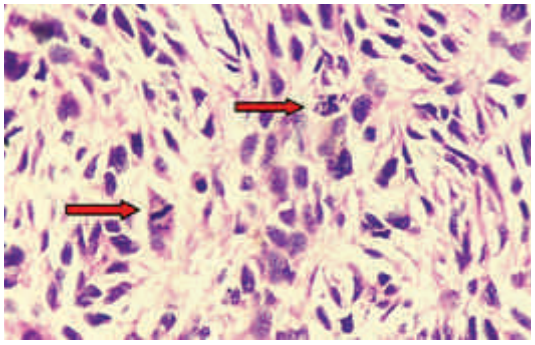

Figure 6: High Power View of Malignant PT Showing Marked Nuclear Atypia, Bizarre Appearing Cells & Mitotic Figures (Arrows) in the Stromal Component Resembling a High-Grade Sarcoma

Table 3: Clinical and Pathological Features of Phyllodes Tumor (n=30)

Clinical and Pathological Features		Frequency	Percentage
Surgical Specimens	Wedge biopsy	2	6.67%
	Lumpectomy	20	66.67%
	Simple Mastectomy	4	13.33%
	Modified Radical Mastectomy	4	13.33%
Laterality	Right Sided	13	43.33%
	Left Sided	17	56.67%
No. of Mitosis/10 HPF	0-4 (Benign)	15	50%
	5-9 (Borderline)	6	20%
	10 or ≥10 (Malignant)	9	30%
Status of Resection Surgical Margins	Involved	8	26.67%
	Not involved	17	56.67%
	Not Assessed/Indeterminate Status	5	16.67%
Recurrent Cases		4	13.33%
Lymph Node Status in 4 Modified Radical Mastectomy Specimens Cases		None Involved	0%
Size of the Tumor		**Range**	**Mean±SD**
	Benign Phyllodes Tumor	4-12 cm	8.87±3.34 cm
	Borderline Phyllodes Tumor	8-12 cm	10.67±3.25 cm
	Malignant Phyllodes Tumor	8-22 cm	13.22±4.39 cm
Age of the Patients	Benign Phyllodes Tumor	25-55 years	38.93±8.04 years
	Borderline Phyllodes Tumor	25-55 years	41.83±8.90 years
	Malignant Phyllodes Tumor	25-80 years	44.11±15.34 years

The size of the tumors ranged from 4-22 cm with a mean of 10.53±4.13 cm. The tumor size varied according to the categorization as benign, borderline & malignant with the largest sized tumor masses observed in the malignant category as compared to the benign and borderline categories of PT. The surgical specimens comprised of 2(6.67%) wedge biopsy samples, 20(66.67%) lumpectomy specimens, 4(13.33%) simple mastectomy and 4(13.33%) cases of modified radical mastectomy specimens. These specimens included 4(13.33%) recurrent cases of phyllodes tumor. Out of a total of 8 mastectomies, 6 mastectomies were performed for malignant PTs and 2 were performed for borderline PTs. No axillary lymph node involvement by tumor deposits was reported in any of the 4 radical mastectomy specimens. The clinical and pathological features of phyllodes tumor are shown in table 3.

DISCUSSION

Phyllodes tumors show a variety of histological changes.[5] Benign PTs show a slight increase in stromal cellularity, a mild degree of cellular atypia and 0-4 mitosis/10 HPF with pushing borders. Borderline PTs show a moderate increase in stromal cellularity, atypia & stromal overgrowth over the epithelial components with mitosis ranging from 5-9 mitosis/10 HPF and areas of microscopic invasion into the tumor margins. Malignant PTs show marked stromal cellularity, an extreme degree of cellular atypia & pleomorphism and stromal overgrowth with >10 mitosis/10 HPF with grossly visible infiltrative tumor margins.[3,5,11]

In our study, the mean age of the patients was 41.07±11.13 years with the age range of 25 to 80 years. In the malignant group which comprised of 9 cases, 2 patients were 25 years old & one was 80 years old. The remaining 6 cases were in the age range of 40-55 years. All females in the benign & borderline category were in the age range of 25-55 years. The left-sided breast was involved in 17 patients and the right-sided breast in 13 patients. In the present study, no significant correlation between laterality and phyllodes tumor was appreciated. In a study carried out at Jinnah

Postgraduate Medical Centre, Karachi, the age of patients ranged between 19 to 66 years with the mean age of 40 years. Similarly, they reported 12 cases involving the left breast and 16 cases involving the right breast.[12] A study carried out on 26 patients of PTs in Farhat Hached Hospital, Tunisia reported the mean age of 40 years.[8]

In the present study, there were 15(50%) cases of benign PT, 6(20%) cases of borderline PT and 9(30%) cases were classified as malignant. A retrospective study carried out in Fudan University, Shanghai Cancer Centre classified 168(41.6%) cases into benign PT, 184(45.5%) cases as having borderline PT and 52(12.9%) cases were placed in the malignant group.[11] In another study carried out over a period of 10 years at the Cancer Hospital Chinese Academy of Medical Sciences, there were 125(55%) cases of benign phyllodes, 55(24%) cases of borderline phyllodes and 47(21%) cases of malignant PT.[13] In a study conducted by Karim et al., 65 PT were analyzed. Out of these, 34(52.3%) cases were classified as benign, 23(35.3%) cases as borderline and 8(12.3%) cases were placed in the malignant category.[14] Two malignant phyllodes tumors in the present study showed osteogenic sarcoma, chondroid & liposarcoma-like stromal areas along with benign glandular elements.

A major diagnostic dilemma is the distinction between a cellular fibroadenoma and benign PT. Both entities show many overlapping features and areas resembling a fibroadenoma are frequently observed histologically in some PTs although the incidence of such occurrence has not been documented.[3] In the present study, such areas were observed as a focal finding in 3 cases which included 2 cases of benign PTs and 1 case of borderline PT. It is important to differentiate the two entities since both have different surgical implications.[6] According to a study published in the American Journal of Clinical Pathology, it was established that presence of any of the following three histological findings like stromal fragmentation, stromal hypercellularity & overgrowth, infiltration into the surrounding fat, stromal heterogeneity, subepithelial stromal condensation and nuclear atypia favour the diagnosis of a benign PT rather than a cellular fibroadenoma.[15]

Repeated local recurrence is the most important prognostic feature of this tumor having an estimated recurrence rate of 40% collectively for the 3 subtypes of PTs.[9,10] Most recurrences of PTs occur within 2 years after diagnosis. These recurrences are more common in the malignant and borderline PTs.[1,13] Even benign PTs can show repeated recurrences and are prone to rapid growth.[9] In the present study, 4 patients presented with tumor recurrences. Two patients had malignant PT & both presented with recurrences in the first 2 years of clinical diagnosis. The 3rd case was a borderline PT & presented within 6 months with recurrence which was reported as malignant. The 4th case with 5 times recurrences had no previous record available but the present diagnosis was malignant PT.

Wide local excision of the tumor is the standard recommended surgical treatment of any type of PT and mastectomy is recommended for the recurrent & overtly malignant tumors.[11] Therefore, all patients of PT, whether benign, borderline or malignant must be kept on close follow-up for tumor regrowth & recurrence.[9,10] An excision margin of 1 cm is therefore considered essential to prevent tumor recurrence.[10,16]

The tumor size in the present study varied depending on the types of PTs. All malignant tumors were huge, protuberant nodular masses measuring in the range of 8 cm to 22 cm (mean=13.22 cm). In another study, the mean tumor size was 8.3 cm (Range 1.5-25 cm).[17] Abdelkrim et al. reported the tumor size between 1.5-40 cm (mean=7.8 cm).[8] The larger the size, the greater the chances of the tumor being malignant.[13] Tumors more than 10 cm qualify as giant phyllodes tumor.[18] Most patients with malignant PTs present with a rapid increase in tumor size.[7]

In the present study, a modified radical mastectomy with axillary dissection was performed in 4 malignant PTs, none of which exhibited axillary involvement which is according to the well known biological feature of this tumor. Borderline and malignant phyllodes tumors show a rare potential for (although very rare) distant metastatic spread.[8] It is only the stromal component that metastasizes. To prevent recurrence and distant metastasis of malignant phyllodes tumor, negative surgical margins should be obtained.[11]

The role of radiotherapy and chemotherapy in the treatment & management of PT has not been clearly defined due to the rarity of the tumor.[19] Molecular and genetic studies reveal the expression of β-catenin and insulin-like growth factors I and II in the stromal component of PT. Several immunohistochemical stains p53, Ki67, CD117, epidermal growth factor receptor (EGFR), p16 and vascular endothelial growth factor (VEGF) are positive in the stromal cells.[6,18] Alterations in chromosome 3p and 1q are common in recurrent

PTs.[20] Recently MED12 mutations have also been discovered in these tumors associated with aberrantly activated estrogen signaling.[3] Due to a lack of resources and high cost, molecular studies and immuno-histochemical stains were not performed in the present study.

CONCLUSION

Our study concluded that benign phyllodes tumor was the most common type (50%) of phyllodes tumor followed by malignant category (30%). Recurrence of the tumor was reported in 4(13.33%) cases. Phyllodes tumor of the breast requires correct histopathological categorization based on tumor margin, stromal atypia and overgrowth, stromal hypercellularity and mitosis. Proper diagnosis, categorization and management are crucial because of its ability to recur and causing considerable morbidity & distress to the patient. Complete surgical removal of the tumor with a 1 cm grossly uninvolved margin is essential to prevent local recurrences & relapse. Mastectomy is recommended for the recurrent & overtly malignant PTs but axillary lymph node dissection is not required. The accurate histological categorization of PTs into benign, borderline and malignant categories remains a challenging task even with the most experienced breast pathologists.

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