Case Report

Giant Benign Mammary Phyllodes Tumor: Report of a Case and Review of the Literature

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Giant benign mammary tumor \cdot Pyllodes tumor \cdot Complete surgical excision \cdot Fibroepithelial neoplasm

Abstract  
Phyllodes tumor of the breast is an infrequently encountered fibroepithelial neoplasm, which accounts for 0.3–1% of all tumors. Few case reports have described the occurrence of giant phyllodes tumor. To our knowledge, about 20% of phyllodes tumors would be considered giant benign. Complete surgical excision is the standard of care for giant benign phyllodes tumors; axillary lymph node metastasis is rare, and dissection should be limited to patients with pathologic evidence of tumor in the lymph nodes. We report the case of a 40-year-old Mexican woman with giant mammary tumor who underwent a right total mastectomy. The pathology results showed a benign phyllodes tumor 4,857 g in weight and 40.2 × 36.3 × 15 cm in size. We do not suggest adjuvant radiation therapy for patients with benign phyllodes tumors that are widely excised. A review of the pertinent literature was performed.

Introduction  
Phyllodes tumor of the breast is a rare fibroepithelial neoplasm that accounts for less than 1% (0.3–0.5%) of all female breast neoplasms. The actual incidence of malignant phyllodes tumor is unknown [1–4].
The term "phyllodes," which means leaf-like, describes the typical papillary projections that are seen on pathologic examination. They were originally called "cystosarcoma phylloides" by Johannes Müller in 1838 [5]. The terminology has since evolved, with over 60 synonyms having been applied to this entity before the term "phyllodes tumors" was adopted by the World Health Organization [6].

Histologically, phyllodes tumors are classified as benign (60–75%), borderline (15–20%), or malignant (10–20%), based upon the assessment of five features: the degree of stromal cellular atypia; the mitotic activity per 10 high-power fields (HPFs); infiltrative or circumscribed tumor margins; the presence or absence of stromal overgrowth (i.e., the presence of pure stroma devoid of epithelium); and the nature of the tumor borders [3, 4, 7].

Tumor size is variable, ranging from 1 to 41 cm (average 4–7 cm). Giant phyllodes tumors are those larger than 10 cm in diameter, and they account for about 20% of all phyllodes tumors [3, 8, 9]. Phyllodes tumors should be completely excised; axillary lymph node dissection is not necessary. Adjuvant radiation therapy (RT) may benefit borderline or malignant, but not benign, tumors. Chemotherapy is reserved for highly selected patients with large, high-risk, or recurrent malignant phyllodes tumors [10–12].

Here, we report a case of giant benign phyllodes tumor seen at our hospital. After standard mastectomy with adequate free margins, we treated the skin defect by use of an advanced flap. The patient recovered well.
A 40-year-old Mexican woman presented to our hospital with a giant tumor in her right breast. The patient had noticed the mass 3 years earlier; 1 year later, blisters had appeared on the nipple. In the last year, the mass had presented with erythema, a venous network, a foul smell, and skin ulceration with bleeding, and it had also increased considerably in size. Due to the rapid growth, the patient consulted us for help. The family and personal history did not provide any information relevant to the case. Physical examination revealed an enlarged right breast, approximately 25 × 22 cm, with irregular margins, erythematous and hyperemic skin, ulceration of the nipple with hemorrhagic discharge, pain on palpation, and the axillary region without nodes (Fig. 1A). Laboratory tests only showed leukocytosis (12,700/μL) with neutrophilia (9,700/μL), without any other significant finding. Sonography of the breast showed a huge mass with multiple areas of cystic degeneration alternating with solid tissue, poorly defined margins, irregular vascularity, and thick hyperechogenic septa. An ultrasound-guided biopsy was performed, and the histopathology results showed a fibroepithelial neoplasm with hyalinized, myxoid, and hypercellular stromal areas, compatible with fibroadenoma, with a Ki-67 proliferation index of 2% (Fig. 1B, 2).

Subsequently, 18F-FDG PET/CT showed a right breast mass that measured 24.6 × 17.3 cm in the axial plane and 22.5 cm in the cephalocaudal plane, with loss of an interface between it and the pectoralis major muscle, with some hyperdense linear and nodular areas inside, as well as two 9-mm ipsilateral axillary lymphadenopathies (Fig. 1C–E). The patient underwent a right total mastectomy. The postoperative period was uneventful; the patient recovered well and she went home after 3 days of hospitalization. The pathology results showed a solid, multilobed, and heterogeneous tumor 4,857 g in weight and 40.2 × 36.3 × 15 cm in size. Moreover there was a skin ulceration of 8 cm in the nipple (Fig. 3A). Microscopically, the sections showed a benign mixed fibroepithelial neoplasm with areas of fibroadenoma and benign phyllodes tumor, as well as tumor-free surgical margins (Fig. 3, 4). During follow-up, there has been no evidence of local relapse or distant metastases to date.
Phyllodes tumors are an uncommon type of fibroepithelial neoplasm of the breast and present on a morphologic continuum from benign to malignant. In a study from Los Angeles county over a 17-year period, the average annual age-adjusted incidence rate of malignant cystosarcoma phyllodes was 2.1 per 1 million women. Latina whites have a higher risk of this cancer than other racial-ethnic groups (non-Latina whites, Asians, and African Americans) [7, 13].

Phyllodes tumors can vary in size but are frequently large, with a median size of 4–5 cm. Few case reports have described the occurrence of giant phyllodes tumors, which are phyllodes tumors of a size greater than 10 cm. Sizes described range from 15 to 50 cm. The tumor described here is one of the largest reported in the literature. 73% of benign phyllodes tumors are smaller than 5 cm, and those that are larger than 7 cm are associated with malignancy. About 20% of phyllodes tumors would be considered giant benign. Phyllodes tumor occurs mainly in women, although there are reports of some cases in men. They can occur in women of a median age at presentation of 42–45 years (range 10–82), about 15–20 years later than fibroadenomas. In men, phyllodes tumors usually occur in association with gynecomastia. Higher-grade tumors are more common in older patients [3, 8, 9, 14–38].

Genetic risk factors for phyllodes tumors are largely unknown, but the literature describes phyllodes tumors in Li-Fraumeni syndrome patients and a mother-daughter pair [39, 40]. Stromal induction of phyllodes tumors can occur due to growth factors produced by the breast epithelium and stromal expression of endothelin-1, insulin-like growth factors (IGF-I and II), and epithelial overexpression of Wnt5a in benign/borderline phyllodes tumors.

**Discussion**

**Fig. 3.** A Surgical specimen. Grossly, the nipple area was extensively ulcerated. The tumor measured 40.2 cm in the greatest diameter. The cut surface presented whitish and yellowish areas. Its heterogeneous consistency was distinguished by prominent firm areas, with other friable and mucoid-like zones. Deeper cystic degeneration was identified. It should be noted that the tumor was entirely lobed, with pushing edges. B Microscopically, the tumor had mixed features. In some areas, the classic pattern of fibroadenoma was evident: ductal epithelial-lined clefts with variable hyperplasia immersed in a paucicellular stroma with a myxoid and collagenized matrix with a lobulated architecture. C These sites alternated with larger leaf-like projections, remarkably hyalinized and with a bland ductal epithelium, consistent with benign phyllodes tumor.
Trauma, pregnancy, increased estrogen activity, and lactation occasionally have been implicated as factors stimulating tumor growth [41–43].

Phyllodes tumors may grow slowly or rapidly or exhibit a biphasic growth pattern. As they grow larger, phyllodes tumors can form a visible mass that distorts the contour of the breast or even cause pressure necrosis of the overlying skin. Unlike breast carcinomas, phyllodes tumors start outside of the lobules and ducts, in the breast’s connective tissue, called the stroma, which includes the ligaments and fatty tissue that surround the lobules, ducts, and lymph and blood vessels in the breast. Phyllodes tumors can also contain stromal cells [44, 45]. They most likely develop de novo, although there have been reports of progression of fibroadenoma to phyllodes tumor [45, 46].

Recent studies have focused on defining a molecular classification of phyllodes tumor. Comparative genomic hybridization studies showed recurrent chromosome imbalances, including +1q, −6q, −13q, −9p, −10p, and +5p. Although to date no chromosomal aberrations...
have been found to be specific to phyllodes tumor, Laé et al. [47] reported that low-grade (benign) and high-grade (borderline/malignant) phyllodes tumors segregate into two genetic groups based on genomic alterations, with high-grade phyllodes tumor consistently showing 1q gain and 13q loss and low-grade phyllodes tumor showing few or no alterations [47, 48]. Preliminary data from array comparative genomic hybridization demonstrate interstitial deletion 9p21 involving the CDKN2A locus and 9p deletion in malignant and some borderline phyllodes tumors [49]. Recurrent mediator complex subunit 12 (MED12) somatic mutations, frequently (50–70%) in uterine leiomyomas, have recently been identified in fibroadenomas (59–67%) and phyllodes tumors (45–67%). In addition, MED12 is frequently mutated in all phyllodes tumors. These findings suggest that both entities may share a genetic etiology, and MDM2 mutation is an early event of fibroadenoma and phyllodes tumor pathogenesis [47, 50].

On examination, most patients have a smooth, multinodular, well-defined, firm mass that is mobile and painless. Shiny, stretched, and attenuated skin may be seen overlying a large tumor. Nipple retraction, ulceration, chest wall fixation, and bilateral diseases are rare (33%), but have been described for phyllodes tumors. The most frequent location is in the right breast, being multicentric in a third of cases; 35% are in the upper external quadrant, 15% in the upper internal quadrant, 10–25% in the lower external quadrant, and fewer than 10% in the lower internal quadrant [3, 10, 16, 44, 51, 52]. Although palpable axillary lymphadenopathy can be identified in up to 20% of patients, most cases are reactive; metastatic involvement of lymph nodes with phyllodes tumor is rare [51–53].

Phyllodes tumors should be suspected when a patient presents with a large (>3-cm), rapidly growing breast mass that is usually palpable. Although imaging features of a phyllodes tumor can be suggestive of fibroadenoma, the large size and history of rapid growth indicate otherwise. Approximately 20% of phyllodes tumors present as a nonpalpable mass identified on screening mammography. The typical appearance of a phyllodes tumor on mammography is a smooth, polylabeled mass resembling a fibroadenoma; calcifications within the mass are rare, but they can be large [52–54]. On ultrasound, phyllodes tumors present as a hypoechoic, solid, partially indistinct or partially circumscribed mass with frequent posterior enhancement. A cystic component is more typical in malignant phyllodes tumors. Frequently, phyllodes tumors will show increased vascularity on color or power Doppler [55]. Breast MRI may help determine the extent of disease and resectability in selected cases. The characteristics on MRI are seen as well-circumscribed tumors with irregular walls, high signal intensity on T1-weighted images, and low signal intensity on T2-weighted images. Cystic change may be seen as well. A rapid enhancement pattern is seen more commonly with benign rather than with malignant phyllodes tumors, which is the opposite of the pattern seen with adenocarcinomas of the breast [54–57]. 18F-FDG PET/CT therefore is useful in imaging recurrent phyllodes tumors, since it can display rare unexpected sites of metastasis [57].

Breast lesions suspicious for phyllodes tumors should undergo core biopsy, which is typically diagnostic. Compared with core biopsy, fine needle aspiration is less accurate. Grossly, phyllodes tumors may be indistinguishable from fibroadenomas. They are round-to-oval multinodular masses with a grayish-white appearance that resemble the head of a cauliflower. Phyllodes tumors grow radially, creating a pseudocapsule through which tongues of stroma may protrude and grow into adjacent breast tissue. Necrosis and hemorrhage can occur in larger tumors. Microscopically, the characteristic leaf-like architecture consists of elongated cleft-like spaces that contain papillary projections of epithelial-lined stroma with varying degrees of hyperplasia and atypia. The stromal elements are a key component in differentiating phyllodes tumors from fibroadenomas and in differentiating a benign tumor from a malignant one [16, 47, 54, 58]. Phyllodes tumor is classified as benign, borderline, or malignant according to the WHO classification of 2012 [59] (Table 1).
Multiple immunohistochemistry markers have undergone study in an attempt to improve the classification of phyllodes tumors and to predict their outcomes. Studies have demonstrated that p53, Ki67, CD117, EGFR, p16, and VEGF (being lowest in benign phyllodes tumors and highest in malignant phyllodes tumors) are associated with the histologic grade of phyllodes tumors, but none has been proven to be clinically useful [60–63]. Differential diagnoses are fibroadenoma, sarcoma, periductal stromal tumor, and metaplastic carcinoma [64–67].

Regarding treatment, complete surgical excision is the standard of care for phyllodes tumors, and with greater than 1-cm margins is often curative and reduces the risk of local recurrence [11]. Mastectomy is generally not indicated for benign phyllodes tumor, unless negative margins cannot be achieved and/or if a tumor is so large that breast-conserving surgery would result in suboptimal cosmetic outcomes. A 2019 meta-analysis of 54 observational studies also found that a positive margin only correlated with a higher local recurrence risk of malignant, but not of benign and borderline, phyllodes tumors [68]. Surgical margins of greater than or equal to 1 cm have been associated with a lower local recurrence rate in borderline and malignant phyllodes [3, 69].

When adequate surgical margins cannot be achieved because of tumor location, adjuvant RT should be administered, even after mastectomy. However, if adequate surgical margins can be achieved, there is less agreement about the need for adjuvant RT. We base our decision about adjuvant RT on tumor grade; thus, we do not suggest adjuvant RT for patients with benign phyllodes tumors that are widely excised, whereas we suggest adjuvant RT for patients with borderline or malignant phyllodes tumors following surgical excision [69–73].

Axillary lymph node involvement by phyllodes tumors is rarely reported, even when tumors are malignant. In the SEER database study, only 8 of 498 women with known lymph node status had involved nodes [72]. Thus, axillary surgery is rarely indicated in patients diagnosed with phyllodes tumors.

Due to scarce data, the role of systemic chemotherapy in phyllodes tumors is limited. Patients with benign or borderline phyllodes tumors are usually cured with surgery and should not be offered chemotherapy unless they develop unresectable metastases. Based on

| Type               | Characteristics                                                                 | Histologic features                                                                 |
|--------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Benign phyllodes tumors | This variety comprises 60–75% of all phyllodes tumors. The stroma is usually more cellular than in fibroadenomas | Mild, non-uniform or diffuse. 0–4/10 HPF. Mild or none/absent. Circumscribed, pushing. Absent |
| Borderline phyllodes tumors | This variety comprises 15–20% of all phyllodes tumors. These tumors are diagnosed if the mass does not possess all the adverse histological characteristics found in malignant phyllodes tumors | Moderate, non-uniform or diffuse. 5–9/10 HPF. Mild or moderate/may be focal. Circumscribed or focally infiltrative. Absent |
| Malignant phyllodes tumors | This variety comprises 10–20% of all phyllodes tumors | Marked, usually diffuse. ≥10/10 HPF. Marked usually present, may be diffuse. Infiltrative. Present |
experience and limited data, we recommend adjuvant chemotherapy only to a small minority of patients with high-risk (>10-cm) or recurrent malignant phyllodes tumors who have excellent functional status and minimal comorbidities, and only after a thorough discussion about the risks, benefits, and controversial nature of such treatment. When systemic chemotherapy is indicated, malignant phyllodes tumors should be treated according to protocols designed for soft tissue sarcoma rather than breast cancers [74]. Hormone therapy is not effective against phyllodes tumors [51, 75].

When phyllodes tumors recur, they typically recur locally within 2 years of the initial excision [3, 51]. Some series have found that the time to local recurrence was shorter for malignant than for benign or borderline tumors. Although recurrences typically have the same grade as the original tumors, there have been several case reports of benign tumors transforming into malignant ones upon recurrence [9, 72, 76, 77]. Despite the best surgical efforts, phyllodes tumors are known to recur locally at rates that vary with tumor grade. As an example, a 2019 meta-analysis of 54 retrospective studies reported an overall local recurrence rate of 12% (95% CI 10–14), as well as pooled local recurrence rates of 8, 13, and 18% for benign, borderline, and malignant tumors, respectively [68]. Local recurrences generally develop within 2–3 years.

Most clinically malignant/metastatic phyllodes tumors have had overgrowth of one or several sarcomatous elements (4–7%). These elements include liposarcoma (7%), rhabdomyosarcoma, chondrosarcoma, osteosarcoma (1.3%), and undifferentiated/unclassified sarcoma [78, 79]. Distant metastases are almost exclusively a feature of malignant phyllodes tumors. The lungs (66%), the bones (28%), and the brain (9%) are the most common sites of spread [54]. Rarely, metastases can involve the liver and heart (<5%). Tumors that metastasize are typically large (≥5 cm) or have malignant histologic features (benign: 0.13–3.2%; borderline: 1.6–11%; malignant: 16.7–28.6%) [79].

The impact of histology on survival was explored in the SArcoma and PHYllode Retrospective (SAPHYR) study. The overall 3-year survival rate for combined benign and borderline tumors was 100% [79]. The overall 3-year survival rate for malignant phyllodes tumors was 54%, similar to that for non-angiosarcoma primary breast sarcomas (60%). Also, the 5-year overall survival rate for patients with benign/borderline and those with malignant tumors was 91 and 82%, respectively [76].

Conclusions

Phyllodes tumors are uncommon fibroepithelial breast tumors that are capable of a diverse range of biologic behaviors. Giant phyllodes tumors account for about 20% of all phyllodes tumors. Given the rarity of the disease, treatment principles are based mainly on retrospective series and case reports. Mastectomy is the standard of care for giant benign phyllodes tumors.

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Statement of Ethics

The patient gave informed written consent to publish her case (including the publication of images).
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The authors contributed to the conception of the case report, to the analysis and critical revision of the content, and to the final approval of the version to be published. A. Arroyave-Ramírez, D. Motola-Kuba, G. Alvarado-Luna, and I. Mackinney-Novelo contributed to critical revision of the content, as well as to the final approval of the version to be published. R. Segura-Rivera carried out the exhaustive review of the histopathological characteristics of phyllodes tumor and analysis of the article. All authors agree to be responsible for all aspects of the work to ensure that questions related to the accuracy or completeness of any part of the work are properly investigated and resolved.

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