Malignant phyllodes tumor of the breast: a systematic review

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Summary
Phyllodes tumors (PT) are fibroepithelial neoplasms of the breast showing a peculiar leaf-like appearance. They account for 0.3 to 1% of all primary breast tumors and 2.5% of all fibroepithelial breast tumors. PT are classified into benign, borderline and malignant based upon their stromal morphology with a distribution of 60%, 20%, and 20%, respectively. Malignant PT of the breast constitute an uncommon challenging group of fibroepithelial neoplasms. They have a relatively high tendency to recur, although distant metastasis is uncommon, and nearly exclusive to malignant PT. Adequate surgical resection remains the standard approach to achieve maximal local control. Giant malignant PT are rare and pose a diagnostic dilemma for pathologists, especially when comprised of sarcomatous elements. This review highlights the morphological features of PT detected in cytology and histology specimens and discusses diagnostic pitfalls and differential diagnosis.

Key words: fine needle aspiration, phyllodes tumor, malignant phyllodes tumor, breast disease, breast oncology, personalized medicine, pathology

Introduction
Phyllodes tumor (PT) is an uncommon breast neoplasm that exhibits variable biological behavior ranging from benign to malignant. Many PTs are characterized by rapid growth. PT have been defined as fibroepithelial neoplasms with an inherent ability to recur locally when diagnosed as borderline or malignant; metastasis is uncommon, nearly exclusive to malignant PT. PTs account for 0.3% to 1% of all primary breast tumors and 2.5% of fibroepithelial breast lesions; the remaining 97.5% are represented by fibroadenomas. The relatively high recurrence rate of PTs, despite surgical resection, remains an unresolved management problem.

PTs were first described in 1838 by Johannes Müller as cystosarcoma phyllodes, mostly due to their leaf-like (phyllodal) tumoral projections into cystic spaces and their sarcomatous stromal appearance. Nevertheless, this term is misleading because up to 70% of these tumors have a benign course and only rarely do they show cystic degeneration. In 1931, the first case of a malignant PT with metastases to the lungs was reported, which revealed that these tumors could exhibit malignant behavior.
Recent literature reports that approximately 10% to 15% of PTs are malignant. Malignant PTs have a significant potential for local recurrence (up to 30%) and the ability to metastasize. When PTs are larger than 10 cm in diameter, they have been classified as “giant” PTs, which account for about 20% of all PTs. PT is the currently accepted nomenclature according to the World Health Organization (WHO), which classifies these tumors as benign, borderline, or malignant based on a combination of histological features including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margin. The median and mean ages in which these tumors present are 45 years, which is about 15 years older than the age group for fibroadenoma. The average tumor size ranges from 4 to 5 cm, even though malignant PTs can grow to much larger sizes. PTs demonstrate a predilection for the upper outer quadrant of the breast, with only 3.4% demonstrating bilateral localization.

The distinction between PT and fibroadenoma by ultrasound (US) and mammography can be difficult. On mammography, a PT typically appears as a well circumscribed, hyperdense or isodense, round or oval mass. History of rapid growth, large size, and older age may be the only clinical findings in favor of a PT. Other features such as lobulated shape, heterogeneous internal echo pattern and absence of microcalcification are significant sonographic features used to favor PT over fibroadenomas. Of note, sonography cannot distinguish between malignant and benign PTs. Major diagnostic challenges may also be encountered with the cytological diagnosis of PT, especially those that are malignant, as well as discrimination of PT with sarcomatous overgrowth from mimics. This review focuses on the morphological features and potential pitfalls in the cytologic and histologic diagnosis of PT.

** Cytopathology **

Fine needle aspiration (FNA) has been proposed as an acceptable pre-operative modality for diagnosis of PT. Cytologically, these smears show cellular fibromyxoid stromal fragments composed of spindle cells, clusters or sheets of benign ductal epithelium without atypia, and admixed myoepithelial cells. These features are also commonly seen in fibroadenomas. PT should be suspected when the following features are encountered: i) large hypercellular stromal fragments; ii) moderate to large numbers of dyscohesive stromal cells with elongated nuclei and scant to moderate cytoplasm admixed with a fibromyxoid stromal component; iii) significant atypia in individually distributed stromal cells including nuclear enlargement, pleomorphism, and mitotic figures, especially in malignant PT; iv) a low epithelial-to-stromal ratio; v) round epithelial fragments with mild atypia; and vi) columnar epithelial cells. Despite the fact that grading is extremely difficult on FNA samples, the presence of the following should favor a malignant PT: high stromal cellularity, high degree of stromal nuclear atypia, mitotic figures, atypical single cells, multinucleated tumor cells, and heterologous differentiation of sarcomatous stroma exhibiting features of liposarcoma, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma.

| Table I. Cytological and histological features of fibroadenoma and phyllodes tumors. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Tumor border**                | **Fibroadenoma**                | **Phyllodes Tumor**             | **Phyllodes Tumor**             | **Phyllodes Tumor**             |
| **Stromal cellularity**         | Variable                        | Mild                            | Moderately increased, can be focal | Diffuse and marked |
| **Stromal atypia**              | Absent                          | Present-mild                     | Moderate                         | Present-severe |
| **Mitotic figures**             | Absent                          | Present-low                     | Present-moderate                 | Present-high |
| **Stromal overgrowth**          | Absent                          | Absent                           | Absent or very focal             | Present |
| **Patterns (cytology)**         | Solid and isolated cells        | Solid-sheets and few isolated cells | Solid sheet-few-moderate isolated cells | Solid sheets and increased atypical isolated cells |
| **Background (cytology)**       | Clean                           | Cellular                         | Moderately cellular              | Highly cellular |
| **Ductal hyperplasia (cytology)** | Present                       | Absent                           | Absent                           | Absent |
| **Nuclei (cytology)**           | Mild atypia                      | Mild atypia                      | Moderate atypia                  | Moderate-severe atypia |
| **Bipolar nuclei in the background (cytology)** | Present                       | Absent                           | Absent                           | Absent |
The most important differential diagnoses include fibroadenoma with a prominent intracanalicular growth pattern and cellular stroma, spindle cell/metaplastic carcinoma, and primary or metastatic sarcomas. Given the overlap of cytological features for a benign PT and cellular fibroadenoma, these two biphasic fibroepithelial lesions cannot be reliably distinguished on FNA. Increased stromal cellularity favors a PT diagnosis. The diagnosis of a malignant PT depends on the amount of the epithelial component obtained by FNA. In challenging cases a core needle biopsy may be necessary to render a more definite diagnosis to guide subsequent patient management. The correct diagnosis can be supported by using immunohistochemistry. For example, the spindle cells in metaplastic carcinoma usually show positivity for keratins and p63, unlike the spindle cells of malignant PT where keratins are negative and p63 is positive in only 20% of tumors.

**Histopathology**

PT resemble intracanalicular fibroadenomas (i.e. double-layered epithelial component) arranged in leaf-like clefts surrounded by a hypercellular stromal component. As mentioned, the WHO classifies PT into benign, borderline and malignant neoplasms. The difference is based on a combination of histological features (Tab. I) including the degree of stromal hypercellularity, overgrowth and atypia, numbers of mitoses, tumor border/margins, and the presence of malignant heterologous elements. Although the majority of PTs are benign, recurrences are not uncommon. Moreover, hematogenous metastases can occur with malignant PT, although this is uncommon. A PT with a bland stromal component can mimic a fibroadenoma whereas a PT with stroma that appears overtly sarcomatous can be challenging to differentiate from a sarcoma. The main features in favor of a benign PT over fibroadenoma are the presence of more cellular stroma characterized by monomorphic spindle-cell nuclei and rare mitotic figures (< 5 mitoses per 10 high-power fields, HPF). Stromal cellularity is often higher in the areas immediately adjacent to epithelium. There may be stromal hyalinization or myxoid change. The presence of necrosis can be seen in large PTs, along with occasional bizarre large stromal cells. Benign lipomatous, cartilaginous, and osseous metaplasia can been seen in PT; such features should not lead to a diagnosis of malignancy. Benign PTs are usu-
ally characterized by pushing, well-defined margins that only exhibit a small protruding component into the surrounding tissues.\(^1\) Borderline PT is diagnosed when a PT shows some (but not all) of the features typically associated with a malignant PT.\(^1\) Similar to benign PT, borderline PT may recur locally, but they do not metastasize. Malignant PT is defined by the combination of marked nuclear pleomorphism of stromal cells, stromal overgrowth (defined by the absence of epithelial component in one low-power microscopic field), diffuse stromal cellularity with increased mitotic activity (> 10 per 10 HPF) and infiltrative borders.\(^1\) A diagnosis of malignant PT can also be made when malignant heterologous elements are present in the absence of other features. Distant metastases have been reported in up to 10% of malignant PTs with involvement in nearly all organs, especially the lung and skeleton.\(^6\)-\(^10\). (Fig. 3-4). Local axillary lymph node metastases are rare; hence, wide local excision or mastectomy with appropriate margins is the preferred clinical intervention.\(^43\)-\(^46\). Axillary node staging is not required because of rare lymph node involvement.\(^3\),\(^21\). Data regarding sentinel lymph node biopsy in PTs are lacking, since metastatic spread of these tumors is primarily hematogenous. Patients with a giant PT may have clinically enlarged axillary lymph nodes suspicious for metastatic disease.\(^3\),\(^10\),\(^16\),\(^22\).

Reported local recurrence rates in large patient cohorts were 11.2%, 15.9%, and 24.5% for benign, borderline, and malignant PT subtypes.\(^1\)-\(^3\). The reported rates of distant metastases are 0%, < 2%, and 16% respectively for benign, borderline and malignant PT.\(^1\)-\(^3\). Most patients with distant metastases also experience local recurrence.\(^7\),\(^12\),\(^13\). Malignant PTs have a high risk of metastasis ranging from 1.7 to 16%; patients with metastases rarely respond to chemotherapy and typically die within 3 years of initial treatment. Histological factors associated with the development of distant disease are: tumor size larger than 7 cm, infiltrative borders, marked stromal overgrowth, marked stromal cellularity, > 5 mitoses per 10 HPF, and necrosis.\(^9\)-\(^11\),\(^16\). Heterologous elements do not appear to influence prognosis in malignant PT.\(^11\).
Figure 3. Morphological features of a malignant phyllodes tumor (on VABB and surgical sample). (A, B, C) A biopsy sample of a fibro-epithelial biphasic neoplasm constituted by increase stromal cellularity (an overview; A, HE x4). For moderate-severe nuclear atypia (B, HE x20) and presence of elevated mitotic index (C, HE x40), a diagnosis of malignant phyllodes tumor was made. (D) Breast surgical sample with the malignant phyllodes tumor diagnosed on the VABB observed and commented in A-B-C. We can note the following features: permeative margins into the surrounding breast parenchyma (D, HE x4), increased stromal cellularity, being usually diffuse (E, HE x20), with areas of stromal overgrowth and marked stromal nuclear pleomorphism (F, HE 40X), with scattered fields with brisk mitotic activity (up to 18 mitoses/10 HPF of 0.5 mm²). No malignant heterologous elements were observed.

Figure 4. Vertebral metastasis of a malignant phyllodes tumor: histological and immunohistochemical findings. (A-B) After 1 year from histological diagnosis, the patient (affected from the malignant phyllodes tumor shown in Figure 1), experienced a vertebral metastases (on D3), constituted by a proliferation of spindle atypical cells (A, HE x10; B, HE x20), morphological resembling the primitive breast tumor, with a significant proliferative index (Ki-67: 20%, LSAB-HRP, x20; insert on the right top in image B).
Immunohistochemistry and genetic alterations

The correlation between genetic alterations and histological features has not been entirely clarified. Sawyer et al. suggested a possible pathogenesis of PT in the epithelial-stromal interaction with stromal expression of β-catenin and insulin-like growth factors (IGF-I and II) and the epithelial overexpression of Wnt5a in benign/borderline PT, which might promote stromal overgrowth. The immunohistochemical pattern is characterized by the expression of p53, Ki-67, CD117, EGFR, p16, and VEGF, which show the lowest positivity in benign PT and the highest in malignant PT.

Some recent studies have attempted to define a molecular classification for PT. Lae et al. reported that high-grade (malignant) PTs had 1q gain and 13q loss while low-grade (benign/borderline) PTs had few or no alterations. Nevertheless, these results have not been confirmed by other authors. The loss of 13q in PT suggests that the RB1 gene could be relevant to PT oncogenesis or progression. Other authors have reported deletions of 9p21 associated with mutations in RB1, mutations in NF1, and PIK3CA. Some authors have studied breast cancer-related genes in fibroepithelial lesions, concluding that the profile of benign PTs is similar to fibroadenomas, whereas malignant PT was identified as claudin-low and basal-like. Recent studies have demonstrated that recurrent mediator complex subunit 12 (MED12) somatic mutations are frequently identified in both fibroadenomas (50-67%) and PTs (45-67%). In addition, MDM2 and RARA mutations may be early events in the pathogenesis of fibroadenoma and PT, whereas mutations in FLNA, SETD2, and KMT2 have been observed only in malignant PT.

Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have suggested that CNB is an effective tool for diagnosing PT. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma. Some authors have deliberated over the role of core-needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma.
useful in personalizing management, thereby reducing the need for additional interventional procedures. This high concordance rate was not totally confirmed when Choi and Koo compared CNB and surgical excisions in 129 cases with histologically proven PT.32 Their series included 90 benign PT, 30 borderline PT and 9 malignant PT. The benign PT group had 74.4% concordant diagnoses on CNB. The concordant rate for borderline PTs and malignant PTs was 26.6% and 44.4%, respectively on CNBs. The discordant diagnoses were underestimated in matched CNBs, especially in their stromal cellularity and mitotic counts. They concluded that CNB has some limitations in grading of PT, despite the fact that they reported a concordance rate for diagnosis between CNB and surgical excision of about 60%32.

Management

Although PT is mainly treated by surgical excision, there is reported evidence that all PTs can recur regardless of their histology, with the lowest incidences of recurrence observed in benign tumors and higher rates reported in borderline and malignant tumors.8,13,15,17,18,22,76-78 Local recurrence rates range from 15% to 40% among different types of PT.3,15 Nevertheless, surgical excision with breast conserving surgery (BCS) can offer adequate management, without causing significant cosmetic deformity.9-11 The National Comprehensive Cancer Network (NCCN) guidelines recommend at least a 1 cm excision margin or more as the best approach for conservative surgery.12 Cases with positive margins have a far higher local recurrence (LR) rates when compared to those with negative margins, highlighting the importance of achieving negative surgical margins at the initial surgical attempt regardless of PT histotype, and obviating the need for future mastectomy.8,13,15,17,18,22,76-78 The most common factors associated with local failure include not only positive margins, but also the presence of necrosis, stromal overgrowth, and larger tumor size. No difference was found in terms of LR between patients treated with BCS and mastectomy.9-11 A multicenter, large retrospective study on malignant PT management reported that a 3 mm margin threshold was adequate, with no impact of wider margins on overall survival (OS), while they recommended reexcision to obtain wider margins in cases with 0-1-2 mm margins.13 The role of radiation therapy and chemotherapy remains undefined in the management of PT, which is further confounded due to a lack of randomized controlled data.24 Adjuvant radiotherapy may be beneficial to reduce local recurrence and is sometimes considered for high risk malignant PT including those that are greater than 5 cm, have high stromal overgrowth, or more than 10 mitoses per HPF. Overall, radiotherapy has demonstrated a positive effect on local disease control, but without prolonging survival. The benefit of radiotherapy seems to be strongest for patients treated by BCS, especially when employed in patients with worse prognostic factors such as large tumor size or tumor necrosis. Further prospective studies are needed to demonstrate the efficacy of adjuvant therapy, since most data thus far have been retrospective.13,25-26 Chemotherapy has been used for recurrent and metastatic disease, without clear survival benefit. Patients with recurrent or metastatic PT are often treated in accordance with the guidelines for metastatic soft tissue sarcomas, as recommended by the NCCN.46 Prior studies reporting adjuvant chemotherapy did not improve metastasis-free survival.9,13,27 The potential role of endocrine therapy in this clinical setting is limited, as stromal cells constitute the neoplastic cell population in PTs and only exhibit low stromal expression of hormone receptors (ER, PR).1 The reported 5-year survival rate for malignant PTs ranges from 54% to 82%, sometimes even up to 95.7%.9,15

Conclusion

PT is a rare biphasic neoplasm of the breast, which belongs to the group of non-epithelial tumors. Malignant PT of the breast is a very rare disease. Although most PTs are benign, careful attention to worrisome clinical and radiological features is critical. Furthermore, reliable pre-surgical diagnosis on CNB can be difficult. The identification of PT based solely on their cytological features in FNA samples is controversial. More studies on histologic features and molecular correlations are needed to reach more accurate pre-surgical diagnosis. The role of genetic alterations in the acquisition of malignant characteristics and aggressive biologic behavior in PT is under investigation. Clearly, while much is known about the pathology and biology of PTs, more research is needed to refine diagnosis and improve treatment.

Abbreviations:
Malignant phyllodes tumor (MPT), Phyllodes tumor (PT), Multidisciplinary Meeting (MDM), Breast conserving surgery (BCS), Local recurrence (LR), Overall survival (OS).

Conflict of interest
The Authors declare no conflict of interest.
References


