Phyllodes Tumors of the Breast

25

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Introduction

Phyllodes tumors are rare fibroepithelial neoplasms of the breast that comprise <1% of all breast malignancies and 2–3% of fibroepithelial neoplasms [1, 2]. Müller first described phyllodes tumors in 1838 as a mass with leaflike projections and cysts [3]. The clinical course for phyllodes tumors can be unpredictable, but these neoplasms are typically benign, unlike their namesake. In the past, these neoplasms have had various names; however, the World Health Organization (WHO) has designated "phyllodes tumors" as the standard nomenclature, with its histological types classified as benign, borderline, and malignant [4]. The malignant form of phyllodes tumors can have an aggressive clinical course with local recurrence and metastatic spread, whereas the benign form is clinically nearly indistinguishable from a benign breast lump. It is important to differentiate a phyllodes tumor from fibroadenomas, which are treated differently. Diagnostic evaluations remain challenging because these tumors have few characteristic findings on most imaging modalities. The surgical management of phyllodes tumors typically consists of wide excisions with adequate surgical margins or simple mastectomies.

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Epidemiology and Risk Factors

Because of the rarity of these tumors, well-defined risk factors have not been identified. There is some evidence suggesting that there is increased risk for East Asians and for Latina women born in Central or South America but living in the United States [5–7]. For women in the United States, the incidence rate for malignant phyllodes tumors is 2.1 cases per million [5]. In addition, these tumors are clearly more frequent in women, with only a few cases reported in men, which have invariably been associated with gynecomastia [8, 9].

Clinical Presentation and Diagnosis

According to the current literature, the median age of patients diagnosed with phyllodes tumors is 45 years, with an age range of 9–93 years [2, 5, 10, 11]. Although phyllodes tumors can be observed in all ages, the majority of patients are over 40 years old [1, 2, 5]. The most common symptom leading to diagnosis is a rapidly growing mass in the breast (Fig. 25.1). Dilated veins and a blue discoloration can also be observed with large tumors (Fig. 25.2); however, nipple retraction and skin ulcerations are uncommon. Bilateral cases are very rare, with an occurrence rate of 1.6% [8]. The mean tumor size ranges between 5.2 and 7.3 cm [8, 12, 13]. Tumors up to 50 cm in size have been reported in the literature [14, 15]; however, tumor size and growth rates are not often associated with histopathology. Clinical, radiological, and histopathological evaluations of suspected breast lumps are mandatory. Ultrasound imaging typically shows a smooth, lobulated border, a radiolucent halo, and coarse microcalcification, but malignant calcifications are rare. Intramural cysts and an absence of posterior acoustic enhancement can be present. On mammographic imaging, phyllodes tumors typically appear as nonspecific, large, round, or oval masses with well-circumscribed lesions (Fig. 25.3). There is no indicator of malignancy or any characteristic findings on ultrasounds

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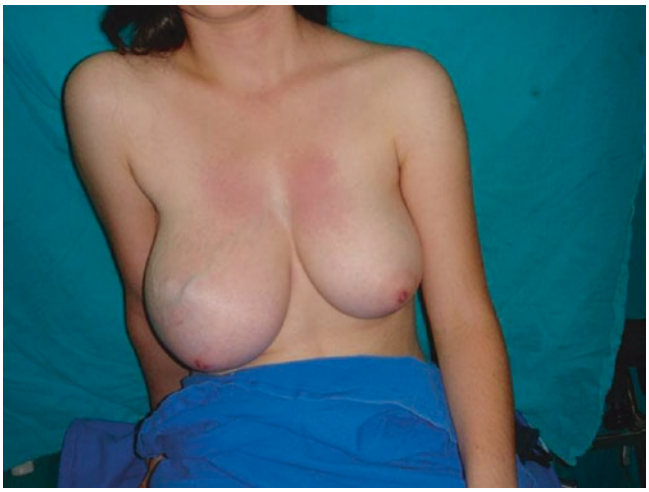

Fig. 25.1 Presentation of a giant primary phyllodes tumor

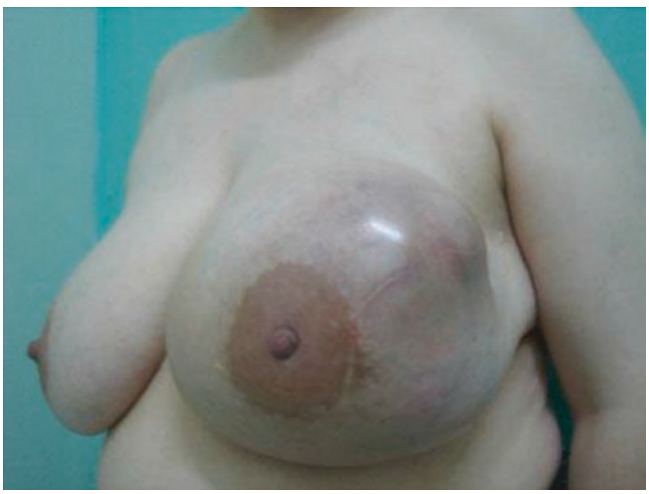

Fig. 25.2 Presentation of a giant recurrent malign phyllodes tumor

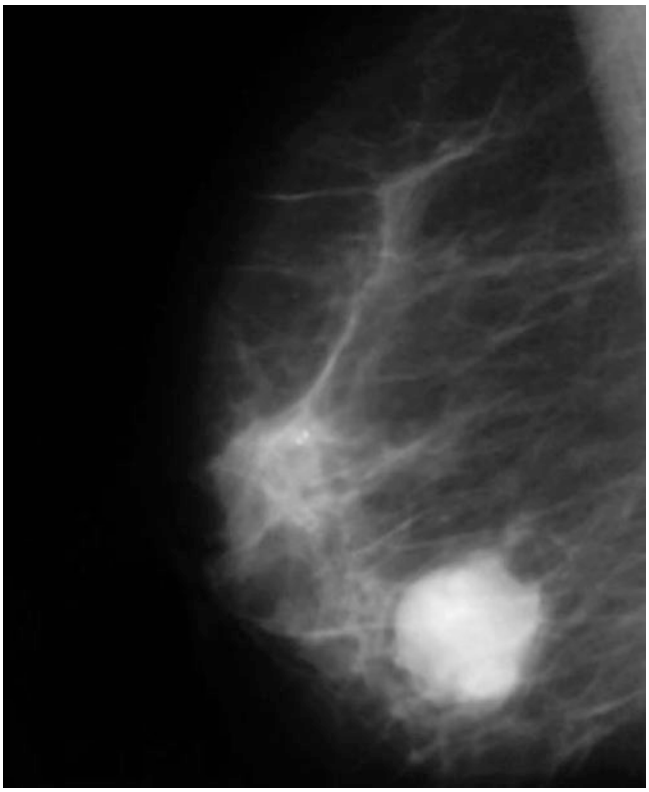

Fig. 25.3 Mediolateral oblique mammography view demonstrating a circumscribed round mass

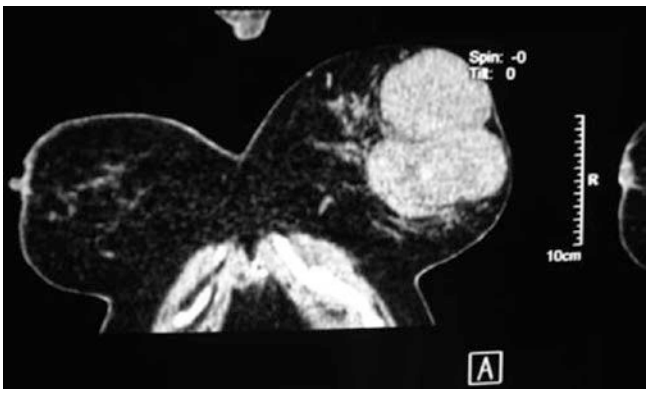

Fig. 25.4 Magnetic resonance imaging of a phyllodes tumor

or mammography. Phyllodes tumors have higher signal intensities than normal breast parenchyma on T1-weighted images and lower or equal signal intensity on T2-weighted images (Fig. 25.4). The role of magnetic resonance imaging (MRI) in this setting remains under debate, but some authors have found evidence suggesting that MRIs may correlate with histopathology [2, 16]. A fine-needle aspiration (FNA) biopsy is often inadequate for a clear, differential diagnosis. Ultrasound-guided Tru-Cut biopsies can be a useful method but can be insufficient in some cases. Differentiating between fibroadenomas and benign phyllodes tumors is more difficult than differentiating between benign and malignant phyllodes tumors. The accuracy of clinical, radiological, and histopathological diagnoses is poor; all three have low specificity. Both epithelioid and stromal components must be visible to confirm a pathological diagnosis, but only the stromal component determines the biological behavior [17] of phyllodes tumors. Generally, there are no masses in the axillary region. Axillary palpable nodes, which are observed in 20% of patients, are often reactive in nature [13, 18]. Phyllodes tumors metastasize hematogenously rather than through the lymphatic system; therefore, routine axillary dissection is not recommended [2, 8, 13].

Pathology

Fibroepithelial neoplasms mostly originate from the stroma in the terminal ducto-lobular unit. Phyllodes tumors are evaluated in fibroepithelial neoplasms, and their microscopic appearance is widely variable, often mimicking fibroade-

noma or sarcoma (Fig. 25.5). The established histological types—benign, borderline, and malignant—are determined by the tumor margin, stromal cellularity, stromal overgrowth, tumor necrosis, cellular atypia, and number of mitoses per 10 high-power fields (hpf), as defined by Azzopardi and Salvadori [10, 19] (Table 25.1). A phyllodes tumor is not a pure sarcomatoid lesion. If there are no epithelial components observed during a histological examination, tissue sarcomas [20] should be considered. The clinical appearances of malignant and benign phyllodes tumors are more alike than different; however, tumors of the malignant type often show a more aggressive course. Today, it is widely accepted that fibroadenomas should be treated conservatively; therefore, it is critical to differentiate between benign phyllodes tumors and fibroadenomas, which display similar clinical, radiological, and cytological findings. Benign phyllodes tumors constitute between 35% and 64% of known cases, whereas the malignant form constitutes approximately 25% of cases [13, 15]. Fibroadenomas and phyllodes tumors can appear synchronously or metasynchronously. Noguchi et al. showed that phyllodes tumors can arise from monoclonal proliferation caused by somatic mutations in a portion of a fibroadenoma [21]. Because of the rarity of this phenomenon, there are no well-described risk factors; however, the expression levels of some genetic factors, such as Ki-67, p53, c-myc, c-kit, CD117, and actin, may be helpful in distinguishing between the malignant and benign forms [22–24].

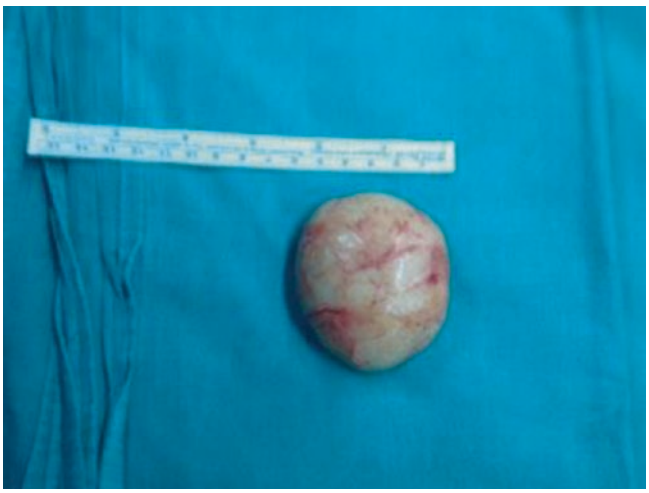

Fig. 25.5 Gross specimen of a phyllodes tumor

Table 25.1 Histological features used in the classification of phyllodes tumor subtypes

Histological features	Benign	Borderline	Malignant
Tumor margins	Pushing	↔	Infiltrative
Stromal cellular atypia	Mild	Marked	Marked
Mitotic activity	<4 per 10 high-power fields	4–9 per 10 high-power fields	≧10 per 10 high-power fields
Stromal overgrowth	Absent	Absent	Present

Treatment

Surgery is the mainstay treatment of phyllodes tumors [25]. Wide excision with at least 10 mm tumor-free margins should be performed for recurrent and malignant forms of the tumor [26]. However, due to the lack of an accurate preoperative diagnosis, these tumors are treated as fibroadenomas with enucleation [27]. Wide excision tends to be preferred for all phyllodes tumors, but recent data have revealed that there is no direct relationship between the margin status or width of negative margins and recurrence [26, 28]. Additionally, re-excision may cause poor cosmetic results. A consensus review for phyllodes tumors of the breast recommended that the conservative approach be used for benign phyllodes tumors that have been initially enucleated without margins [26]. Mastectomy is preferred for patients with a giant lesion. The management for phyllodes tumors is shown in the algorithm presented in Fig. 25.6. Axillary lymphadenopathy is clinically positive in 10% of patients, but metastases occur in <1% of patients [2, 29]. Adjuvant radiotherapy after breast-conserving surgery should be considered for malignant phyllodes tumors larger than 2 cm in diameter [30–32]. There are no prospective randomized data supporting the use of radiation treatment with phyllodes tumors. However, in settings in which additional recurrences would create significant morbidity (e.g., chest wall recurrence following mastectomy), radiation therapy may be considered following the same principles that are applied for the treatment of soft tissue sarcoma. Adesoye et al. noted increasing utilization of adjuvant radiotherapy in patients diagnosed with phyllodes tumors of the breast based on the Surveillance, Epidemiology, and End Results Program (SEER) database [33].

The use of adjuvant chemotherapy is more controversial and is generally not recommended. There is no evidence that adjuvant cytotoxic chemotherapy provides benefits in reducing recurrences or death. Although the epithelial component of most phyllodes tumors contains estrogen receptor (58%) and/or progesterone receptor (75%), endocrine therapy has no proven role in the treatment of phyllodes tumors [34].

Twenty percent of phyllodes tumors lead to metastases in distant organs. In most of these cases, the affected organs are the lungs and pleura. Chemotherapy, radiotherapy, and hormonal therapies are all used to treat metastatic disease, but their role and efficacy are unclear.

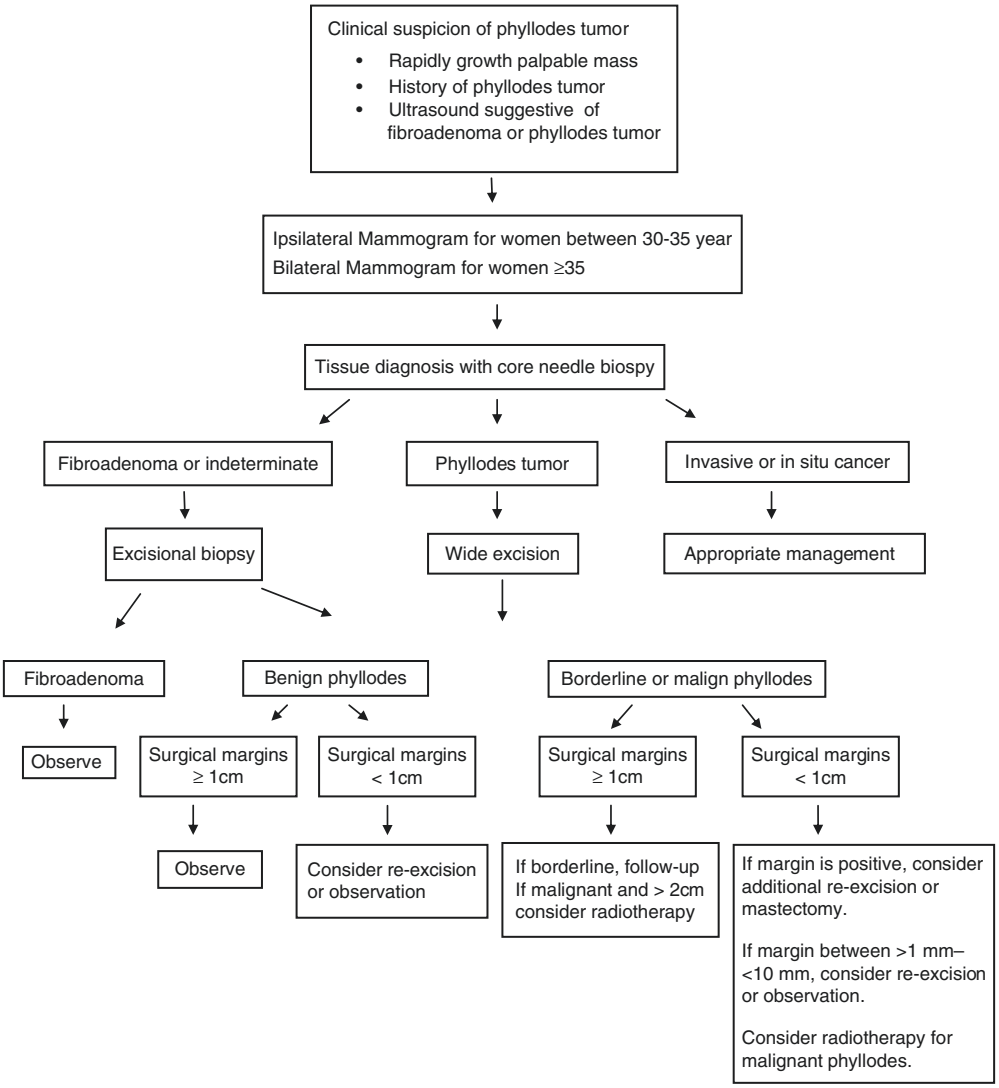

Fig. 25.6 Management algorithm for a phyllodes tumor

Local Recurrence and Metastatic Disease

Local recurrence rates ranging between 0% and 60% have been previously reported [26, 31]. Local recurrence usually occurs within the first 2 years [35]. For patients with positive surgical margins, the local recurrence rates are as high as 32% [8]. Distant metastases are very unusual in the benign form, but it has been reported that borderline tumors can metastasize to distant organs [13].

Follow-Up

The most important mode for detecting recurrent disease is clinical evaluation. After treatment for a phyllodes tumor, a clinical assessment should be performed every 6 months. In the vast majority of recurrences, breast phyllodes tumors develop in the excision bed. The 5-year survival rates are approximately 96%, 74%, and 66% for benign, borderline, and malignant types, respectively [2, 35].

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