

Malignant Phyllodes Tumor of the Breast. Case Report and Literature Review

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Abstract

Background: Phyllodes tumor accounts for less than 1% of all primary breast tumors and only 8% to 20% of cases are malignant; due to their rarity most treatments are based on retrospective studies. **Aim:** Describing the current recommendations for the diagnostic approach and treatment of these neoplasms. **Case Presentation:** A 59-year-old woman with a progressively and rapidly growing phyllodes tumor of the breast treated by total mastectomy classified as malignant on the final histopathological report. **Conclusion:** Current recommendations for the treatment of phyllodes tumor are not standardized. The treatment of choice is surgical resection either by lumpectomy or total mastectomy achieving a negative resection margin. With regard to adjuvant therapy, radiotherapy is most beneficial for malignant subtype.

Keywords

Phyllodes Tumor, Malignant Phyllodes Tumor, Breast Sarcoma, Fibroepithelial Lesion with Increased Stromal Cellularity, Fibroadenoma

1. Introduction

Phyllodes tumor (PT) was first described in 1774 as a giant fibroadenoma and was

later named “cystosarcoma phyllodes” by Johannes Müller in 1838 due to its leaf-like (phyllodal) tumoral projections into cystic spaces and its sarcomatous stromal appearance [1]-[5]. In the beginning, PT was initially considered a benign tumor until Virchow reported in 1867 that it was capable of generating metastases, then in 1931 the first case of a metastatic malignant phyllodes tumor in the lung was reported, and in 1943, Cooper and Ackerman confirmed their malignant potential [2] [6]. In 1982, the World Health Organization (WHO) designated it as a “phyllodes tumor” and in 2003 it was classified as benign, borderline, and malignant based on the mitotic rate, the stromal cellularity, and the tumoral borders [1]-[4] [7]. Currently the PT is described as a biphasic fibroepithelial neoplasm characterized by its distinctive leaf-like (phyllodal) epithelial pattern and a prominent stromal proliferation [1], its name is derived from the greek words *phyllos* (leaf) and *eidos* (form) [4], and the terms “cystosarcoma phyllodes” and “periductal stromal sarcoma” are historical synonyms [4]. We present the case of a patient diagnosed with MPT who was treated with surgery and adjuvant radiation therapy describing the current recommendations for the diagnostic approach and treatment of these neoplasms.

2. Case Presentation

A 59-year-old woman with no relevant medical history presented with a progressively and rapidly growing tumor in her right breast of 8 months of evolution. She was evaluated by gynecology department who ordered a contrast-enhanced computed tomography (CT scan) of the chest, abdomen, and pelvis which revealed a large tumor in the right breast (145 mm in longest axis) involving all quadrants, solid with lobulated edges, with heterogeneous enhancement at contrast and some hypodense areas consistent with necrosis, and with skin thickening (**Figure 1**); so she was referred to surgical oncology. On initial physical examination, she presented a multilobulated mobile tumor that encompassed the entire breast distorting its entire contour measuring approximately 18 cm in diameter with no palpable axillary lymphadenopathy. Given the clinical findings and the tumor characteristics observed on CT scan, a guided core needle biopsy was performed by interventional radiology which revealed a biphasic tumor with both epithelial and stromal components consistent with a PT. Considering the tumor size, the feasibility of achieving a negative resection margin, and the absence of metastatic disease, in a multidisciplinary meeting with the reconstructive plastic surgery department, we decided a surgical treatment by a total mastectomy and reconstruction of the defect using a bilateral transverse rectus abdominis musculocutaneous (TRAM) flap (**Figures 2(A)-(C)**). During surgery two macroscopic axillary lymphadenopathies were detected and underwent to histopathological examination by frozen section discarding the presence of neoplastic cells in them, so an axillary lymph node dissection was not necessary. The histopathology report confirmed a PT measuring $15 \times 8 \times 12$ cm with negative resection margins of 1 cm, with diffusely infiltrative tumor borders, high diffusely stromal cellularity, high stromal

pleomorphism, with 9 mitoses per mm², and with high stromal overgrowth. The tumor was classified as a MPT (**Figures 3(A)-(C)**). Based on this result and taking into account the malignant subtype, the diffusely infiltrative border pattern and the tumor size, it was decided during a multidisciplinary meeting to continue an adjuvant treatment with radiotherapy using a conventional fractionation schedule of 50 Gy in 25 sessions to the whole breast. Currently our patient is on surveillance without clinical or radiological evidence of tumor recurrence.

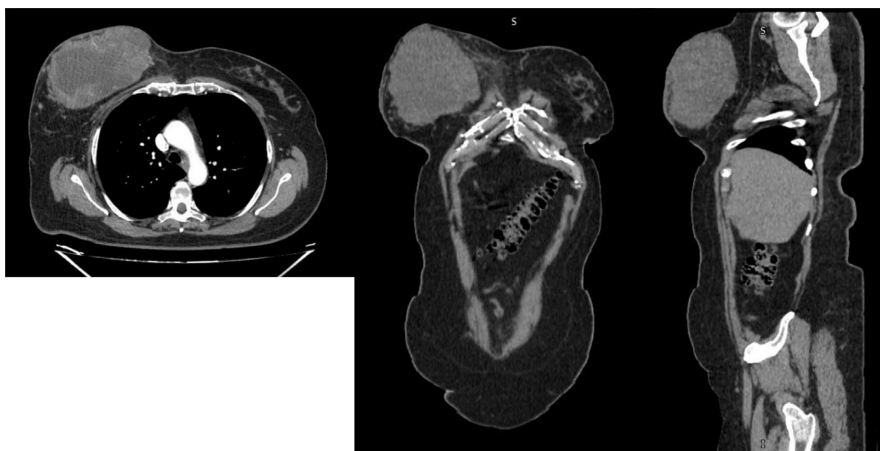


Figure 1. CT scan revealing a large tumor in the right breast involving all quadrants, solid with lobulated edges, with heterogeneous enhancement at contrast and some hypodense areas consistent with necrosis, and with skin thickening.



Figure 2. Total Mastectomy. (A) Multilobulated mobile PT that encompassed the entire breast distorting its entire contour measuring approximately 18 cm in diameter. (B) Resection site without suspicious axillary lymphadenopathy. (C) Resection site with donor site marking and a TRAM flap.

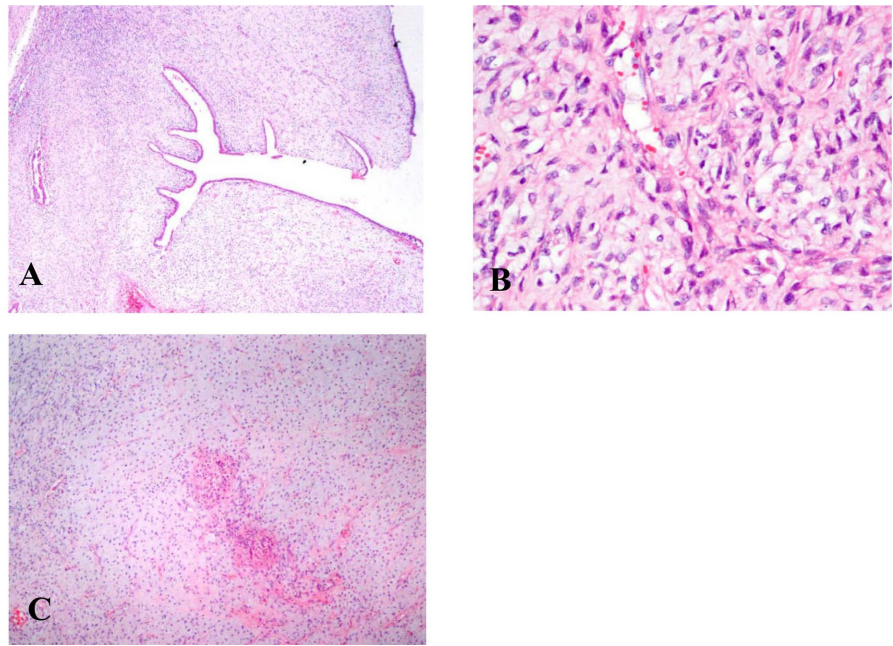


Figure 3. (A) Biphasic lesion with an epithelial component showing a leaf-like pattern and a high stromal overgrowth with diffusely infiltrative tumor borders. (B) Stromal component with a high stromal pleomorphism and an increased mitotic activity ($\geq 5/\text{mm}^2$). (C) Marked stromal nuclear pleomorphism and high diffusely stromal cellularity.

3. Discussion

PT accounts for 0.3% to 1% of all primary breast tumors and 2.5% of all fibroepithelial breast lesions (the remainder being fibroadenomas) [1]-[3] [6]; it has an annual incidence of 2.1 cases per million in women and tends to occur most frequently in the upper outer quadrant of the breast [3] [4] [6] [8] [9]. The most common age at presentation is between 40 and 50 years (15 years later than the age of presentation for fibroadenomas) [1]-[4] [6], up to 3.4% of cases may occur bilaterally [3] [6], and there have been reports of some cases in men in which it appears to be associated with gynecomastia and an estrogen-androgen imbalance [2] [4].

In terms of prevalence, the benign subtype predominates (60% - 75%) followed by the borderline subtype (15% - 26%) and MPT (8% - 20%) [1] [4] [10] [11]; generally the benign subtype predominates in young women, while the median age at presentation for MPT is 50 years consistent with our patient's age [1] [5]. In 80% of cases, MPT presents as localized disease, in 8.2% as regional disease, and in 1.5% as metastatic disease [5].

The etiology of PT has not yet been established [2]; Li-Fraumeni syndrome has been considered a genetic risk factor, and therefore TP53 germline mutations may play a role in tumor development [2] [12]. It is believed that the induction of PT stromal tissue is secondary to growth factors produced in the mammary epithelium, which may be stimulated by factors such as trauma, pregnancy, estrogenic activity, and lactation [2].

PT presents as a well-defined, fast-growing, painless, palpable, lobulated, mobile tumor, sometimes accompanied by changes in the adjacent skin and/or distortion of the breast contour, reaching an average size of 1.9 to 10.9 cm at the time of diagnosis [1] [2] [4]; likewise in some patients the tumor may remain stable for prolonged periods and subsequently exhibit an accelerated growth [2].

Certain factors such as a fast growth, a large initial size, and a history of a fibroadenoma or a benign PT, may be associated with the borderline subtype or MPT; however, this correlation is not always present [1]. Other findings secondary to a fast growth that do not necessarily imply malignancy include ulceration, dilation of dermal vessels, changes and discharge from the areola-nipple complex, and axillary lymphadenopathy, which may be secondary to tumor necrosis and/or local infection [2]. In our literature review, the clinical findings most strongly associated with the malignant subtype were rapid tumor growth and large tumor size, both of which were present in our patient.

Unlike carcinoma, PT originates in the intralobular and periductal stroma of the breast and includes a combination of epithelial and stromal components, the presence of which is necessary to confirm the histopathological diagnosis; in the absence of an epithelial component, the diagnosis is breast sarcoma [2]. The stromal component consisting of hyperproliferative fibroblasts arranged in abnormal patterns, constitutes the neoplastic component [2] [13].

Histologically, PT exhibits a prominent leaf-like architecture that distinguishes it from fibroadenoma and is characterized by a biphasic architecture consisting of an epithelial component and a stromal component [1] [4]. The diagnostic criteria of the WHO classification system for phyllodes tumors include stromal cellularity, mitotic activity, pleomorphism (stromal cell atypia), stromal overgrowth, and tumor margins; based on these criteria, the tumor is classified as benign, borderline, or malignant [1] [2] [4] [7] [10]; to be classified as malignant the tumor must exhibit marked stromal nuclear pleomorphism, stromal overgrowth, increased mitotic activity ($\geq 10/10$ HPF or $\geq 5/\text{mm}^2$), diffuse stromal hypercellularity, and infiltrative tumor borders [12] [14]. Based on these criteria, our patient's PT was classified as malignant (**Figures 3(A)-(C)**).

The presence of sarcomatous elements such as liposarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, rhabdomyosarcoma, chondrosarcoma, or osteosarcoma classifies PT as malignant regardless of other histopathological criteria [2] [5] [6]. Likewise coexisting breast carcinomas have been reported in PT, including ductal carcinoma in situ, tubular carcinoma, lobular carcinoma, invasive ductal carcinoma, squamous cell carcinoma, and atypical ductal hyperplasia [2] [14].

Imaging studies are not accurate enough to distinguish between fibroadenomas, PT, and breast cancer [4]. Although PT may appear similar to fibroadenomas, the characteristics that distinguish them from the latter include the presence of lobulations, heterogeneous internal texture, cystic components, the absence of calcifications, the presence of fluid-filled spaces, hyperechoic septa, and larger dimensions [1]-[3] [5] [10]; the reported sensitivity of mammography for distin-

guishing between the two tumors ranges from 31% to 70% [1].

On magnetic resonance imaging (MRI) PT generally shows heterogeneous enhancement, areas of thickening at the edges, cystic spaces, necrosis, and irregular septa with intense enhancement [4] [14], and CT scan show clearly defined dense or clustered soft-tissue masses with varying degrees of enhancement [4]. Because the tumor characteristics on CT scan (**Figure 1**) and our patient's clinical course were suggestive of a nonmetastatic PT, we did not consider it necessary to perform any additional imaging studies.

Fine-needle aspiration (FNA) is generally insufficient for diagnosis [2] [3]. A PT may be suspected in the presence of large hypercellular stromal fragments, moderate to large numbers of dyscohesive stromal cells with elongated nuclei and scant to moderate cytoplasm admixed with a fibromyxoid stromal component, significant atypia in individually distributed stromal cells including nuclear enlargement, pleomorphism and mitotic figures, a low epithelial-to-stromal ratio, round epithelial fragments with mild atypia, and columnar epithelial cells [3] [6].

The diagnostic accuracy of core needle biopsy ranges from 13% to 84% and has a false-negative and underestimation rates of 25% - 30% and 18.8% - 37.5%, respectively due to possible overlapping histological features and tumor heterogeneity [1] [2]. In fact, because the result may be inconclusive, it has been suggested that in this scenario the histopathological diagnosis be reported as "fibroepithelial lesion with increased stromal cellularity" to perform a complete resection of the lesion [1] [2] [10]. For this reason, it is recommended to always consider PT as a possible diagnosis when clinical findings are suggestive of it (a large, rapidly growing tumor in an elderly patient) [6] [11].

Regarding immunohistochemistry, the three subtypes of PT generally express Estrogen Receptor (ER) and Progesterone Receptor (PR) at low percentages, and there appears to be a relationship between the expression of these receptors and the degree of malignancy, as expression is higher in benign tumors [4] [5]. An elevated Ki-67 proliferation index is considered indicative of a malignant phenotype, making it particularly useful in predicting the behavior of borderline PT, and aberrant p53 expression has been linked to malignant transformation; therefore, it could serve as a prognostic marker for aggressive behavior, including the risk of recurrence and distant metastasis [4].

Other stromal markers that may be useful in distinguishing PT from other breast lesions include vimentin and smooth muscle actin (SMA), which are generally associated with greater invasive potential and myofibroblastic differentiation [4], CD44 which appears to be expressed at higher levels in borderline and malignant PT compared with benign PT [12], and the homeoproteins SIX1 and PAX3 whose expression correlates with histological grade and prognosis [12].

Guidelines and large-scale clinical trials for the therapeutic management of PT, particularly MPT, both localized and metastatic, are limited due to the rarity of the condition; therefore, most treatments are based on retrospective studies and patient series [12] [14] [15]. The primary treatment is surgical resection [2] [10],

however the optimal resection margin remains a matter of debate, and recommended margins range from 1 cm to 2 cm [1] [2] [4] [10] [16]. The National Comprehensive Cancer Network (NCCN) guidelines recommend a margin of ≥ 1 cm for all three subtypes regardless of tumor size [1]-[4] [14] [17], however many studies have reported that grossly complete excision is sufficient for the benign subtype since even with positive margins approximately 87% of patients with this subtype do not experience recurrence [7] [10] [17]. For MPT and borderline tumors local recurrence rates of up to 55.6% have been reported when margins are <10 mm and also a lack of benefit in disease-free survival (DFS) and overall survival (OS) with margins greater than 1 cm [2] [5] [16] [17], and some authors have reported that margins of various sizes including “tumor not touching the ink,” ≥ 1.0 mm, 3 mm, and ≥ 5.0 mm have not influenced on DFS or local recurrence rates [2] [11] [17].

A systematic review and meta-analysis which investigated the association between local recurrence and the status of resection margins in 34 studies involving a total of 6431 patients, reported that in benign PT there was no significant difference in the local recurrence rate between margins <1 and ≥ 1 cm and nor between breast-conserving surgery (BCS) and mastectomy; however in the presence of a positive margin there was a significant correlation with the risk of local recurrence leading to a recommendation for re-excision, although due to its low rate (12.9%) in this scenario, close monitoring might be chosen, particularly due to the patient’s psychological distress and secondary cosmetic damage [17]. For the borderline subtype and MPT the results regarding the relationships between margin width, the type of surgery performed (BCS versus mastectomy) and the risk of local recurrence were similar leading to the conclusion that a margin of less than 1 cm might be feasible and re-excision would only be required in the event of a positive margin; however, for the MPT most studies continue to recommend a margin of ≥ 1 cm [17].

Despite the varying results, the consensus in the literature is to achieve a negative margin, as this is associated with a higher survival rate, and the National Comprehensive Cancer Network (NCCN) guidelines recommends lumpectomy or partial mastectomy as the preferred surgical therapy [2]; our resection margin was 1 cm which is the most commonly recommended margin for MPT. Finally, although it has been reported that extending a positive margin improves recurrence-free survival since the reported rate of residual disease in margin extensions is 16.7% [1] [11] [18], its role in cases of narrow negative margins remains undefined, and only one multicenter retrospective study of MPT has recommended a margin re-excision when the negative margin is 1 to 2 mm [2] [6].

Until 1970 total mastectomy was the surgery of choice regardless of tumor grade or size due to the known risk of recurrence [2] [16]. Currently BCS is being performed with increasing frequency, but although similar outcomes have been reported between BCS and total mastectomy in the three subtypes of PT provided that negative margins are achieved [6] [10] [11] [16], total mastectomy is still per-

formed in at least 50% of cases, likely due to tumor size and the required resection margin, as these factors may make breast conservation difficult in some patients [5] [10]. Some studies comparing the two surgical procedures have reported higher OS and DFS with BCS; however the difference was not statistically significant likely because these survival benefits may be due to tumor characteristics and patient selection since mastectomy is generally performed for larger and high-grade tumors [15] [16]. In our patient, BCS was not feasible due to the size of the tumor and its spread to all four quadrants.

Although up to 10% to 15% of patients with MPT may present with clinically suspicious axillary lymphadenopathy [1] [2] [5], metastases to axillary lymph nodes have been reported in only 1% to 3.8% of cases. However, the reported rate of axillary dissections performed is 17% likely because regional lymph node enlargement is a common finding that may raise suspicion of metastatic lymph node involvement [1] [2] [10]. Currently due to the well-known tendency of PT to spread via the hematogenous route rather than the lymphatic route [8] [18], a histopathological examination to confirm malignancy is recommended only in the presence of suspicious axillary lymphadenopathy prior to performing an axillary lymph node dissection, and sentinel lymph node biopsy is not considered useful [2] [6] [8] [10]. In our case the intraoperative histopathological examination ruled out the presence of neoplastic cells in the macroscopically examined lymph nodes therefore, it was not necessary to complete the axillary lymph node dissection.

Due to the low incidence there are currently no prospective trials evaluating the role of radiation therapy as an adjuvant treatment [2]; most reported studies conclude that while it may reduce the risk of local recurrence in borderline and malignant subtypes [1] [2] [4] [6] [7] [9] [10] [14], it does not appear to have a significant impact on distant metastasis-free survival or OS and therefore its impact on long-term survival remains inconclusive [1] [3]-[6] [10] [14] [16] [18]. It is not currently recommended for benign PTs [8] and it may be considered in borderline tumors and MPT with high-risk features such as a size greater than 5 cm, infiltrative tumoral borders, positive or close margins (generally < 5 mm, although some studies consider 3 mm to be the threshold), and in cases of local recurrence following surgical resection [3]-[5] [8] [9] [15]. Given our patient's histological subtype and tumor characteristics (infiltrative margins and a tumor size greater than 10 cm), we decided to complete her treatment with adjuvant radiation therapy. Finally, although some studies have reported a greater benefit in local recurrence-free survival with adjuvant radiation therapy in patients treated with BCS [9] [10], these findings may be due to the fact that tumors treated with BCS are generally smaller, which is one of the main prognostic factors for recurrence.

Chemotherapy is only recommended for metastatic, unresectable, and/or recurrent unresectable disease since it has not been shown to provide any benefit in terms of OS or in reducing the risk of distant recurrence as an adjuvant treatment [3] [5] [6] [8] [12] [14]. When necessary, the regimens used are similar to those

for soft tissue sarcomas which generally include as first-line agents (as monotherapy or in combination) doxorubicin, ifosfamide, gemcitabine, docetaxel, trabectedin, and dacarbazine, and as second-line agents eribulin and pazopanib [5] [12] [14]. Likewise in the rare case of an isolated metastasis, surgical treatment may be indicated [2] [15].

The therapeutic role of endocrine therapy is limited because the malignant component is the stromal one and hormone receptor expression on it is low [6]; however, molecular and genomic research on MPT has been conducted characterizing apparent molecular subtypes with actionable genomic modifications that could be useful for treatments, including molecular targets such as EGFR, VEGFR/PDGFR, BRAF V600E, NF1, and PDL1 mutations, as well as alterations in the PI3K/Akt/mTOR pathway [13].

PT is known for its potential for local recurrence, and tumor grade is currently considered the primary risk factor for this [2]. The WHO reports an overall local recurrence (LR) rate of 10% to 17% for benign PT, 14% to 25% for borderline PT, and 23% to 30% for MPT [1] [3] [4] [10]. 9% to 27% of MPT may metastasize even with a history of negative surgical margins and/or may develop without a prior local recurrence [1] [10] [13], and the most commonly affected sites include lung, bone, and brain (66%, 28%, and 9%, respectively), although metastases have been reported in muscle, soft tissues, liver, peritoneum, mediastinal lymph nodes, oral cavity, kidney, pleura, pancreas, and adrenal glands [1] [15] [18]. Furthermore, it is not uncommon for recurrent PT to progress to a higher histological grade (16% to 31.5% of cases) [1] [2] [7] [8], and up to 30% of patients may experience re-recurrence [1].

Factors associated with local and distant recurrence rates include tumor grade, tumor size (>10 cm), surgical margin status (especially for borderline and malignant tumors), pathological features (infiltrative borders, stromal atypia, mitosis, and overgrowth), tumor necrosis, and age (higher risk in young women) [1]-[4] [6] [10]. Although it has been noted that another factor is the type of surgery, this does not appear to influence the risk of recurrence and is significant only in relation to the final margin status [16].

The median time interval between the diagnosis of the primary tumor and that of metastatic disease ranges from 13 to 60.5 months, and histopathologically, these metastatic foci lack an epithelial component and consist solely of a malignant stromal component [2]. Unfortunately, the prognosis in this scenario is poor due to the limited response of these neoplasms to conventional chemotherapy [1] [6] [14], and although resection of the primary tumor offers no survival benefit, palliative resection may be performed on a case-by-case basis [10]. Finally, some authors have reported a certain metastatic potential for borderline tumors (<2%) [2] [6].

4. Conclusion

MPT is a rare tumor and as a result current recommendations for its treatment at

various stages of the disease are not standardized, the treatment of choice and the one with the highest probability of eradicating the disease is surgical resection either by total mastectomy or BCS as long as a negative resection margin is achieved. Although the optimal margin width has not been conclusively established, most retrospective studies on this topic agree that it should be 1 cm and that it may be smaller in borderline and benign subtypes; however it should be noted that it is sometimes difficult to accurately determine the PT subtype preoperatively and therefore wider margins may be necessary, especially in borderline and malignant subtypes. With regard to adjuvant radiotherapy most retrospective studies recommend it only for MPT because evidence suggests that it improves local control in this patients and/or in selected high-risk MPT cases, however no clear benefit in overall survival has been reported.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

Phyllodes tumor (PT)

Malignant phyllodes tumor (MPT)

Computed tomography (CT scan)

Disease-free survival (DFS)

Overall survival (OS)

Breast conserving surgery (BCS)