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Case Report

Malignant phyllodes tumor of the breast with metastases to the lungs: A case report and literature review ☆,☆☆

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ABSTRACT

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breasts. Approximately 10%-15% of PTs are malignant, and 9%-27% of patients with malignant PTs, develop metastatic disease. The lungs are the most common target organ for distant metastasis of PT. We report a case of 44-year-old female with a malignant PT. It had recurred locally 3 times, and 3 relapses occurred 13 months after the first diagnosis, presenting multiple metastases to the lungs by CT scan. The patient underwent radiation therapy, and palliative chemotherapy with doxorubicin was initiated. Two courses of doxorubicin therapy were administered, but the patient expired 16 months after PT diagnosis. We present a rare case of malignant PT with local recurrences, lung metastases, and poor patient outcome. Although malignant breast PTs have an unfavorable prognosis, adjuvant radiotherapy combined with margin-negative resection may be associated with decreased local recurrence and distant metastasis rates. Future research should include randomized clinical trials or well-designed prospective matched studies to clarify the effectiveness of treatments of PTs.

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Introduction

Phyllodes tumors (PTs) are rare neoplastic lesions that are comprised of both stromal and epithelial components, and they account for approximately 0.3%-1% of breast tumors in women [1]. The term “phyllodes” which means leaf-like, describes the typical papillary projections that are seen on pathologic examination. They were originally called “cystosarcoma phyllodes” by Johannes Müller in 1838 [2]. World Health Organization (WHO) presented classification of tumors of the breast, introduced the term phyllodes tumors, criteria for diagnosis and grading of PT. PTs are subdivided into benign (60%-75%), borderline (15%-20%), or malignant (10%-20%),

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based on the assessment of 5 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 (ie, the presence of pure stroma devoid of epithelium); and the nature of the tumor border [3]. The average tumors size ranges from 4 to 5 cm. When PTs are larger than 10 cm in diameter, they have been classified as "giant" PTs, which account for about 20% of all PTs [4]. 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 [5]. Recent literature reports that 10%-15% of PTs are malignant and approximately 9%-27% of patients with malignant phyllodes tumor have metastasis to distant organs with spreading hematogenously to most frequent sites as lungs, bones, brain, and liver [6]. Recurrence or metastasis of breast PTs predicts a shorter survival time, less than 2 years after diagnosis [7–21].

In this report, we describe a rare case of malignant PT of the breast with local recurrences and subsequent metastases to the lungs, we provide a review of the literature, and we discuss treatment modalities.

Case report

A 44-year-old female patient from Lithuania presented to the National Cancer Institute (NCI) complaining of a mass in her left breast that had grown rapidly in the last 12 months. The patient experienced menarche at the age of 16, gave birth to 2 children. No significant signs were observed in the patient's medical or family history. On physical examination, the patient was a well-developed woman with an obvious left-sided breast mass. At the time of presentation, the left breast mass measured 11 cm × 7 cm × 8 cm in greatest dimension. Axillary, mediastinal, or clavicular lymphadenopathy was not observed. The patient's right breast was normal upon palpation. Mammography showed a high-density, smoothly contoured masses with well-circumscribed margins in the left breast measuring 7.8 × 4.3 cm, 4.5 × 2.8 cm, and 3.6 × 2.8 cm (Fig. 1). A core needle biopsy was performed on the same day. The left breast biopsy results revealed malignant neoplasms with carcinomatous and sarcomatous elements. The cells showed marked pleomorphism with >10 mitoses/10HPF. The patient underwent partial mastectomy. Detailed descriptions are shown in (Table 1). Pathological examination confirmed a malignant PT (Fig. 2). Postoperative recovery was without complications with a well-healing wound.

Three months after the surgery, the patient became aware of a soft tissue mass growing at the partial mastectomy scar. Upon physical examination, postsurgical changes consistent with a left partial mastectomy and a new parasternal 6 cm nonmobile, nontender mass fixed to the medial portion of the scar were observed. No palpable axillary lymphadenopathy was noted.

Core needle biopsy of the breast mass revealed recurrent malignant PT. The patient underwent left mastectomy. The postoperative recovery was uneventful. Pathological examination revealed recurrence of malignant phyllodes tumor with atypical osteoid formation (Fig. 3). After multidisciplinary discussion among breast surgeon, medical oncologist, and radiologist, the patient underwent adjuvant radiotherapy. After adjuvant radiotherapy, the patient had routine follow-up.

Table 1 – Timeline

Time	Description	Treatment
2019.10	Diagnosis of primary malignant phyllodes tumor	Partial mastectomy
2020.01	Local recurrence	Mastectomy
2020.02		Beginning the radiotherapy
2020.10	The second local recurrence	Axillary tumor with m. pectoralis major and m. serratus anterior resection
2020.11	Detection of lung metastasis. The third local recurrence.	Beginning the chemotherapy
2021.02	The patient expired	

After approximately one month, breast ultrasound revealed 4.1 × 3.4 cm mass above the mastectomy scar and 3.8 × 2.3 cm mass subpectoral. Core needle biopsy of the breast mass revealed a recurrence of malignant PT. Computed tomography (CT) scan of the chest, abdomen, and pelvis did not reveal any pulmonary metastatic disease or any other significant findings in the abdomen. The patient underwent left side axillary tumor, m. pectoralis major, and m. serratus anterior resection. Pathological examination showed high grade (G3) malignant phyllodes tumor with sarcomatous elements and spread in the soft tissues and veins (Fig. 4). Three weeks later, the patient returned to the hospital with chest pain, dyspnea, and cough. The CT scan showed multiple lesions (Fig. 5) in both lungs and axillary recurrence. The patient received 2 courses of palliative chemotherapy (60 mg/m^2 doxorubicin hydrochloride on days 1-2). Palliative chemotherapy was stopped because of intolerable nausea, dyspnea, and grade 3 anemia with further need for blood transfusions. The patient expired 16 months after the PT diagnosis.

Discussion

Phyllodes tumors of the breast are rare fibroepithelial neoplasms and exhibit a wide range of clinical behaviors. PT and fibroadenoma (FA) are both fibroepithelial lesions, but their management differs. FA may be safely followed without further investigation, whereas PT requires surgical excision. Multidisciplinary approach is very important to distinguish PT from FA in patients with diagnosed fibroepithelial lesions. There are rare cases documented in literature of a FA transformation to a PT. There are 2 possibilities that could account for a core biopsy proven FA being rediagnosed as a PT: the first possibility is misdiagnosis at core biopsy due to their overlapping pathologic appearance, or the second possibility, more rarely, the progression of a FA into a PT [22]. There is no accurate imaging or clinical predictor of which lesion will trans-

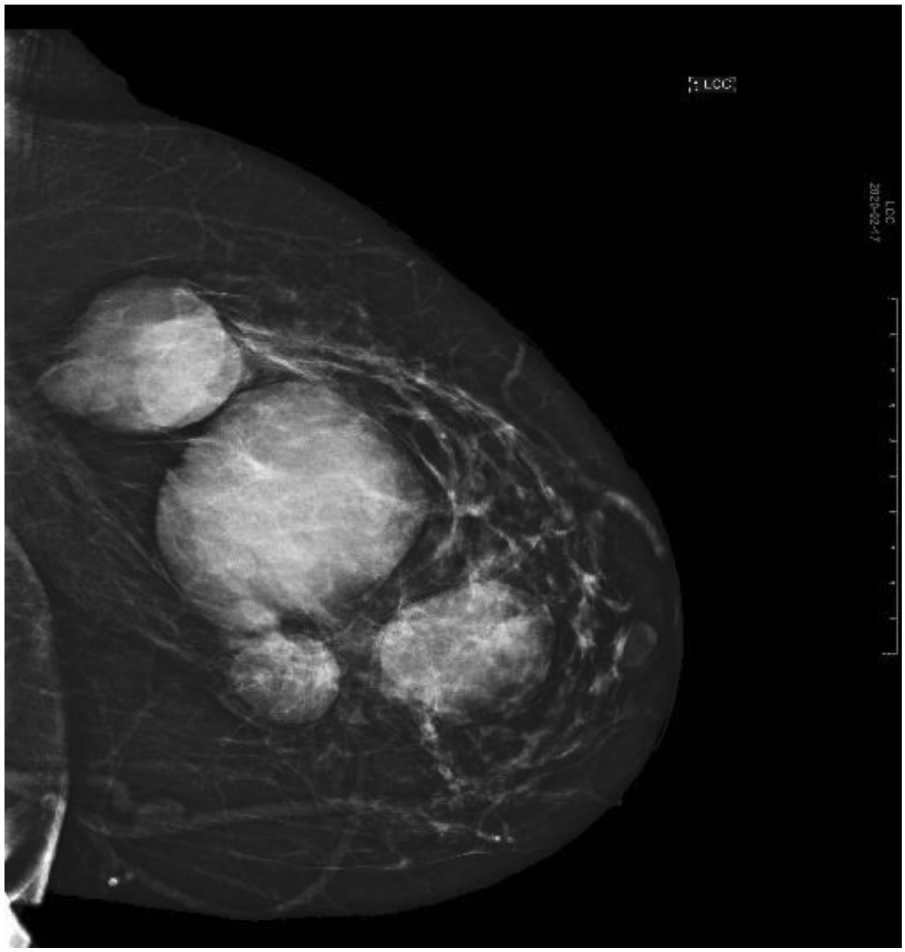

Fig. 1 – Mammogram of the left breast. There is a high-density, smoothly contoured formations (7.8 x 4.3 cm, 4.5 x 2.8 cm, and 3.6 x 2.8 cm), with circumscribed margins in left region of the breast.

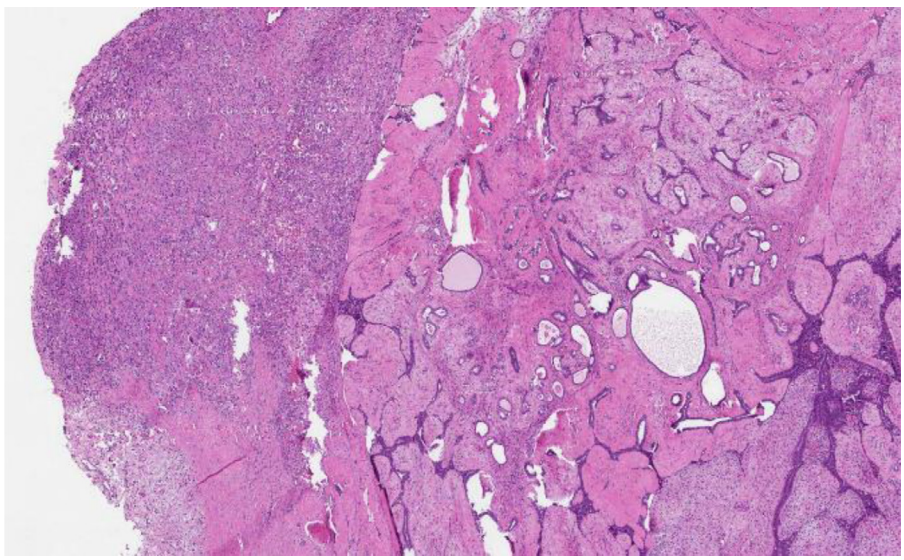

Fig. 2 – Malignant phylloid tumor with 2 distinct components: on the right side classical phylloid tumor with overgrowth of cellular stroma and intraductal leaf-like structures; on the left side diffuse sarcoma-type growth of highly atypical cells (HE staining).

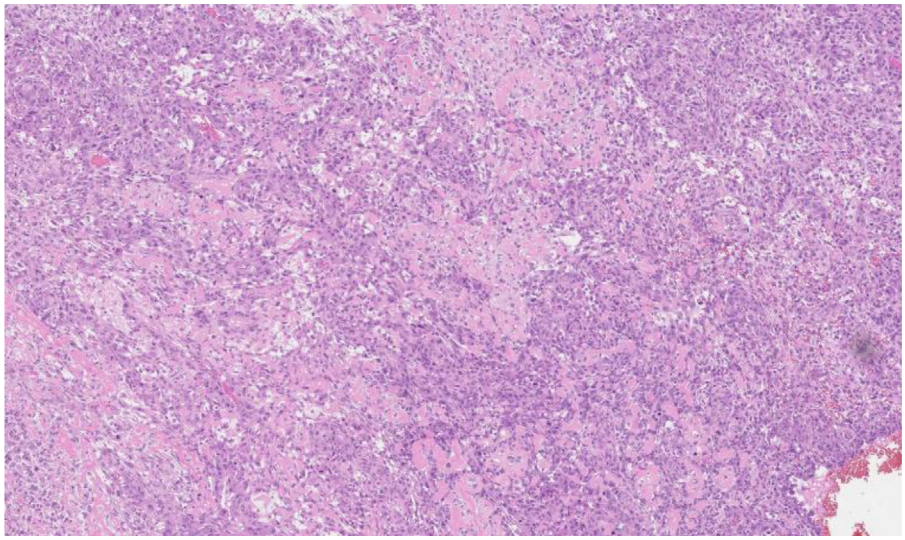

Fig. 3 – Diffuse sarcoma-like growth of highly atypical spindle cells, foci of atypical osteoid formation (HE staining).

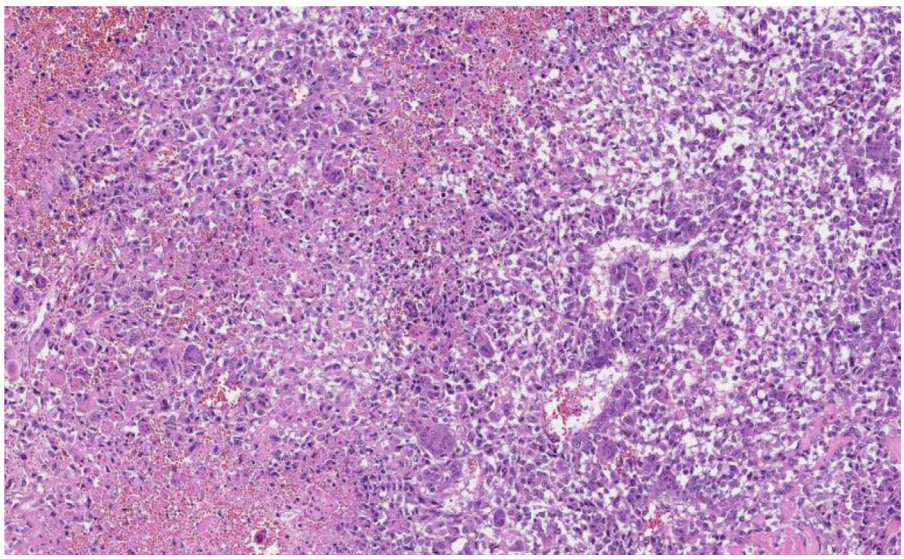

Fig. 4 – The histological picture with higher degree of atypia, giant cell component of the tumor (HE staining).

form. The majority of PT occur in women between the ages of 35 and 55 years, whereas a FA is the most common solid breast mass in a woman under the age of 30 but can be seen in older women as well [22]. In men, phyllodes tumors usually occur in association with gynecomastia. PT is reported rarely in men [23]. PTs can be caused by genetic syndromes, such as Li-Fraumeni syndrome (germline TP53 mutation), which is related to breast cancers, brain tumors, soft tissue sarcomas, and rarely other types of tumors [24]. Malignant PTs have a higher risk of metastatic disease, whereas benign and borderline tumors demonstrate a proclivity for local recurrence and rarely metastasize [25]. Koh et al. [26] showed that a combination of large tumor size (≥90 mm) ant the presence of malignant heterologous elements had a statistically significant association with the development of distant metastasis. Most frequently, malignant PTs metastasize to the lung, bones, brain, and liver [7–21]. Few rare distant metastatic sites are the adrenal glands [20], kidney [13], skin [27], ovary [28], heart [29], pleura [30], oral cavity [31], duodenum [32], pancreas [33], tonsillar [12], and para-aortic nodes [34]. Once patients with malignant PT develop metastasis, their prognosis is extremely poor. The median survival ranged from 5 to 30 months [35]. Our patient expired 16 months after the diagnosis of PT.

Surgery is the mainstay of treatment for breast PTs. Lu et al. [36] showed in a recent meta-analysis of 54 retrospective studies with 9234 patients that a positive surgical margins increased the risk of local recurrence: 8% for benign, 13% for borderline, and 18% for malignant PTs. Jang et al. [37] retrospectively reviewed 164 patients with PTs and found that the main prognostic factor for local recurrence of PTs was the presence of tumor cells on the resection margin. They also found, that the width of the resection margin did not confer

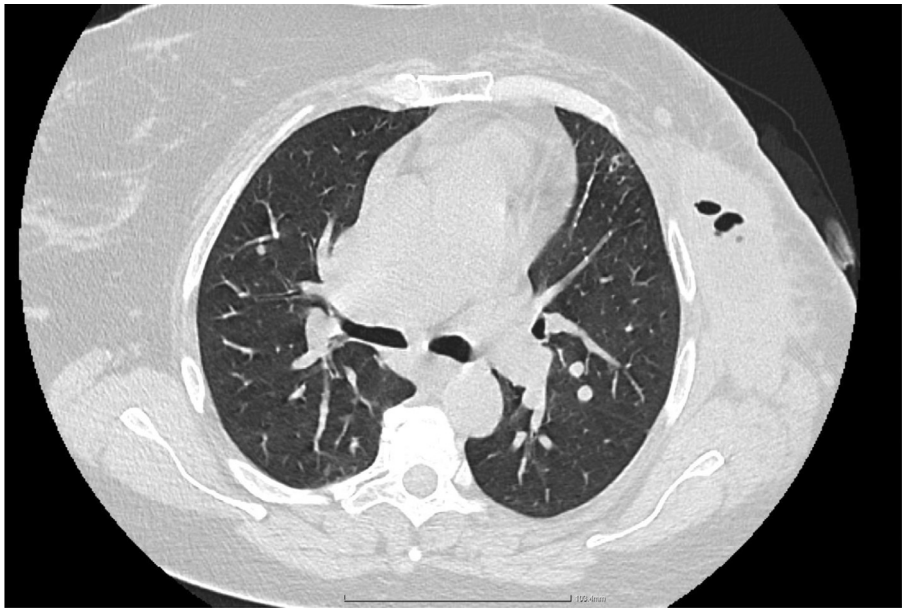

Fig. 5 – Contrast-enhanced CT of the chest. (A) Lung windows demonstrate a multiple well-defined pulmonary nodules on both sides of the lungs.

Table 2 – Study characteristics, adjuvant treatment, and follow-up of 16 patients with PT and distant metastasis to the lungs

Author, year, country	Age[a] (years)	Tumor size (cm)	Distant metastasis	Adjuvant treatment	Mean survival (Month)
Basto et al. [7] 2021, Portugal	57	25.8	Lungs	Radiotherapy, chemotherapy	14+
Wang et al. [8] 2021, China	26	19	Lungs	Radiotherapy	13+
Koukourakis et al. [9] 2021, Greece	62	7.4	Lungs	Radiotherapy, chemotherapy	24+
Moon et al. [10] 2019, Korea	48	15	Lungs	Chemotherapy	36+
Le et al. [11] 2021, Vietnam	57	8	Lungs	Chemotherapy	N/A
Sera et al. [12] 2017, Japan	57	10	Lungs, tonsillar	/	8
Borowska et al. [13] 2015, Poland	41	4	Lungs, kidney, bones, liver	Radiotherapy, chemotherapy	17
Nakamura et al. [14] 2020, Japan	71	15	Lungs	/	13+
Johnson et al. [15] 2016, USA	66	16	Lungs, bones, brain	Radiotherapy	14
Augustyn et al. [16] 2015, USA	56	22	Lungs	Radiotherapy	N/A
Gregston et al. [17] 2019, USA	32	32	Lungs, brain	Chemotherapy	20
Abe et al. [18] 2020, Japan	44	20	Lungs	Chemotherapy	4
Ganesh et al. [19] 2017, Canada	43	3.5	Lungs	Radiotherapy, chemotherapy	30
Khanal et al. [20] 2018, Nepal	37	15	Lungs, adrenal, brain	/	N/A
Singer et al. [21] 2013, USA	43	19	Lungs, bones	Radiotherapy, chemotherapy	N/A
Our case, 2022, Lithuania	44	11	Lungs	Radiotherapy, chemotherapy	16

[a] – Age at diagnosis of primary phyllodes tumor. + – No information of death upon last follow up; N/A – not available.

a local recurrence risk. According to the newest 3.2022 guidelines of the Nation Comprehensive Cancer Network (NCCN), the recommendation for the treatment of PT is local surgical excision with tumor-free margins of 1 cm or greater for malignant and borderline PT. Narrow surgical margins are not an absolute indication for mastectomy when partial mastectomy fails to achieve a margin width ≥1 cm. Total mastectomy is only necessary if negative margins cannot be obtained by lumpectomy or partial mastectomy. While for benign PT excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins. Since phyllodes tumors rarely metastasize to the ALNs, surgical axillary staging or ALN dissection is not necessary unless the lymph nodes are pathologic on clinical examination [24].

Currently, there is no consensus regarding the role of radiotherapy in malignant PT. Comprehensive Cancer Network (NCCN) 3.2022 guidelines recommend consideration of radiotherapy for malignant PTs only in the setting of local

recurrence (level 2 B evidence) [24]. However, Barth et al. [38] in a prospective, multi-institutional study, revealed that margin-negative resection combined with adjuvant radiotherapy is very effective for local control of borderline and malignant phyllodes tumors. [39]According to Chao et al. [39] meta-analysis of 17 retrospective studies with 696 patients, found that radiotherapy is effective in achieving local disease control and preventing metastasis. Belkacemi et al. [40] reported that in 159 patients with malignant and borderline phyllodes tumors, radiotherapy significantly decreased local recurrence rate ($P = .02$). Accordingly, margin-negative resection combined with adjuvant radiotherapy could be the new gold standard for borderline and malignant PT's.

Adjuvant chemotherapy effects in PTs treatment are lacking because of insufficient data from large prospective studies. In our literature review of patient with distant metastasis to the lungs, the most frequent chemotherapy was with Doxorubicin and ifosfamide [7,10,17–19]. In 6 studies [8,12,14–16,20] adjuvant chemotherapy was not given due to controversial effects or patient's request, detailed descriptions are shown in (Table 2). Moon et al. [10] showed complete remission of lung metastasis and no evidence of locoregional or distant metastasis 3 years after mastectomy with axillary lymph node dissection and adjuvant chemotherapy with doxorubicin and ifosfamide. Koukourakis et al. [9] revealed that the combination of cisplatina with nab-paclitaxel and liposomal doxorubicin chemotherapy had acceptable toxicity and was highly effective in eradicating metastatic lesions. Within 2 years of follow-up, the patients were free of disease and treatment-related toxicities. The Comprehensive Cancer Network (NCCN) guidelines recommend that treatment of distant metastasis with PT following the NCNN Soft Tissue Sarcoma Clinical Practice Guidelines version 2.2022. Preferred regimens: (doxorubicin, ifosfamide, mesna/ifosfamide, epirubicin, mesna) [24].

Conclusion

We present a rare case of malignant PT with local recurrences, lung metastases and poor patient outcome. Although malignant breast PTs have an unfavorable prognosis, adjuvant radiotherapy combined with margin-negative resection may be associated with decreased local recurrence and distant metastasis rates. Future research should include randomized clinical trials or well-designed prospective matched studies to clarify the effectiveness of treatments of PTs.

Author contribution

Drs E.O. and V.O. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: E.O. and A.O. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: E.O. and A.O. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: V.O. and A.B.

Ethical approval

Ethical approval was not required for this study.

Data availability

The data used to support the findings of this study are included within the article.

Patient consent

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

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