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## Aggressive malignant phyllodes tumor



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## ABSTRACT

**INTRODUCTION:** Originally described in 1838 by Muller, phyllodes tumor is a rare fibroepithelial neoplasm which represents roughly 0.3–0.9% of all breast cancers. Phyllodes tumor are divided into benign, borderline and malignant histologic categories. Malignant phyllodes tumor represent anywhere from 10–30% of all phyllodes tumors. This group has both the potential to recur locally and metastasize, however not all malignant phyllodes behave this way. The challenge lays in predicting which tumor will recur locally or metastasize. Distinguishing this subset of malignant phyllodes tumor is paramount.

**PRESENTATION OF CASE:** We present a case of malignant phyllodes which presented with metastatic disease. What is fascinating about this case is not only the initial presentation but also the aggressiveness of this variation of phyllodes tumor. The patient initially presented with a large mass which encompassed her whole right breast. On surgical pathology the mass measured roughly 31 cm in diameter and weighed over 10 kg. Within 5 weeks from surgery the patient had suffered brain metastases and also 6 local recurrent tumors. The patient passed roughly 11 weeks after her first visit to our office.

**CONCLUSION:** Despite biopsy proven malignant phyllodes tumor, it was near impossible to predict such a rapid course of disease progression in our patient. Our case illustrates the unpredictable nature of this disease in general and it possibly sheds light on a variant of the disease which had undergone an aggressive transformation.

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## 1. Introduction

Originally described in 1838 by Muller, phyllodes tumor is a rare fibroepithelial neoplasm. This represents roughly 0.3–0.9% of all breast cancer in women [1,2]. Characterized by a combination of hyper cellular stroma and cleft-like spaces lined by epithelium, phyllodes tumor was classically known as cystosarcoma phyllodes because of the leaf-like projections [3,4]. Renamed phyllodes tumor in the early 1980s, these tumors vary greatly in size and the histological characteristics continue to be the basis for diagnosis and sub classification. Based on established histological criteria PT are classified into three categories – benign, borderline and malignant [5]. The majority of phyllodes tumors are benign and the primary concern after surgical treatment is primarily of local recurrence vs. distant recurrence (Fig. 1a).

Malignant phyllodes represent anywhere from 10–30% of all phyllodes tumors [6]. There is an abundance of literature regarding invasive ductal carcinoma of the breast and its malignant potential however not as much research has been done on phyllodes tumors. The challenge lays in predicting which tumor will recur locally or metastasize. Phyllodes tumors which fall into histologically benign or borderline category essentially never recur [7]. Phyllodes tumors

which fall into a malignant histological category do have a recurrence potential and a metastatic potential on the other hand not all malignant phyllodes tumors recur or metastasize. Distinguishing this subset of malignant phyllodes tumors is paramount. We present a case of malignant phyllodes tumor which presented with metastatic disease, however, what was fascinating about this case was not the as much the initial presentation but the aggressiveness of this variation of phyllodes tumor (Fig. 1b).

## 2. Case report

A 50 year-old woman G3P3 presented with a right breast mass which had been there for 'several years'. A thorough history and physical exam revealed a mass localized to the right breast, which encompassed the entire breast. The mass had increased in size rapidly in the past 6 weeks and it was painful with multiple open wounds. The patient denied other lumps or mass, muscle/bone pain or headaches but complained of fatigue, night sweats and weight change. There was no significant past medical or surgical history or family history (Fig. 1c).

The physical exam, revealed a 'melon-sized' mass throughout entire right breast. There were multiple ulcerations and many engorged veins could be seen throughout breast mass as well. The mass was nodular, hard and was not fixed to the chest wall. There was no lymphadenopathy found (Fig. 2).

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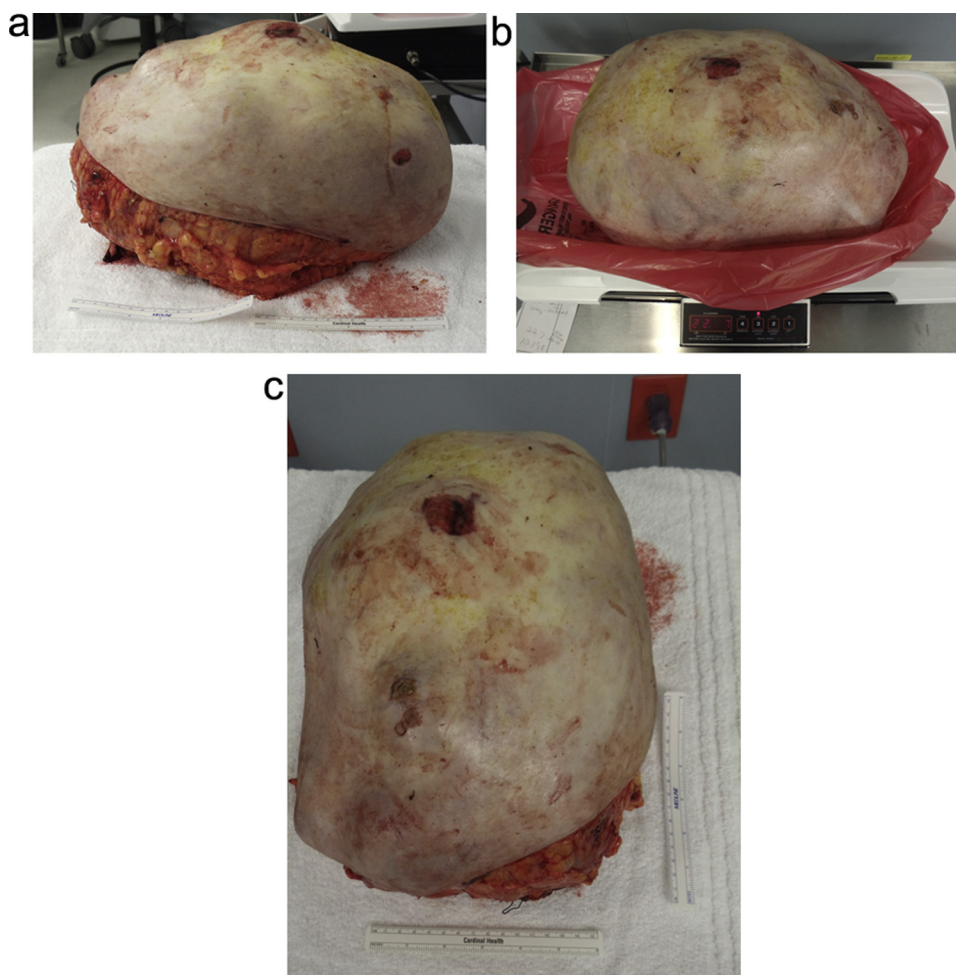


Fig. 1. Right mastectomy specimen.

A core needle biopsy was performed in office that day. The biopsy results were found to be a malignant neoplasm with carcinomatous and sarcomatous elements. The cells showed focal marked pleomorphism with  $>10$  mitoses/10HPF. Focal necrosis was seen. The biopsy was estrogen receptor negative and progesterone receptor positive. HER2 was also negative (Fig. 3).

A metastatic workup was performed; this included a CT chest, abdomen, pelvis and also PET scan. The CT of chest was positive for bilateral chest masses which were concerning for metastatic disease as well as a 30 cm mass in the right breast. The patient underwent a right simple mastectomy due to the massive size and ulcerations of the breast. The right breast mass weighed 10.3 kg at the time of excision.

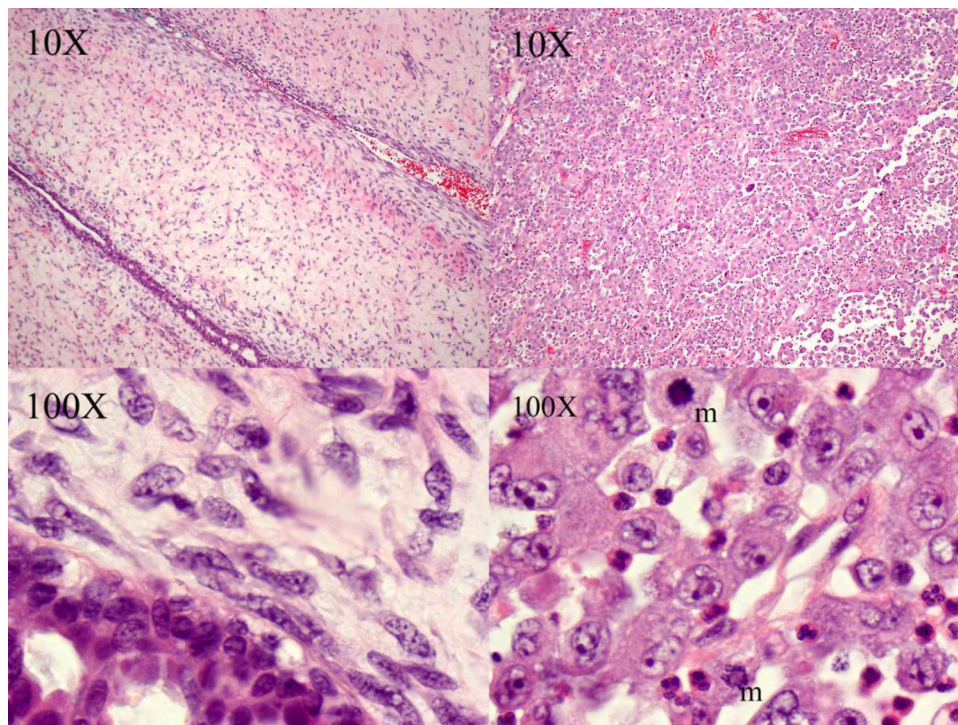
The final pathology from surgery revealed a malignant phyllodes tumor 31.5 cm length  $\times$  15.6 cm height. The tumor showed brisk mitotic activity, necrosis, and stromal overgrowth. 1 mm clear margins were attained. A minority of tumor cells in a high grade portion of round cells in the tumor are cytokeratin positive. A small portion had the appearance of myxoid sarcoma. Most of the round cell component is cytokeratin negative; however the positive cells may represent a true differentiation to an epithelial component (carcinosarcoma).

In the immediate post-operative period the patient recovered well. However, within 3 weeks of the mastectomy the patient complained of headaches and was found to have a right parietal mass. The patient underwent a right craniotomy which was positive for a right parietal tumor – metastatic malignant phyllodes tumor. Follow up in our breast clinic one week after was unremarkable and

follow up for lung masses was starting. The patient was in clinic roughly 7 weeks from her original presentation with complaints of multiple ‘new’ lumps on right post-mastectomy site. Physical exam revealed 6 new masses were found, the largest measuring 6 cm and a mass was palpated in the right axilla. A fine needle aspiration was performed. These cells were enlarged pleomorphic, epithelioid cells – identical to original tumor. Before any therapies could be initiated the patient passed shortly after.

### 3. Discussion

As stated prior, one of the challenges facing physicians for patients with phyllodes tumor is predicting which patients will develop local recurrence, metastatic disease or both. The majority of phyllodes tumors present as firm, smooth, well-circumscribed, and rarely painful masses [8]. Most phyllodes tumors occur in women between ages of 35 and 55 years old [9]. Primary treatment for phyllodes tumor is surgical. Depending on the size of the tumor; wide local excision is the treatment of choice. If margins of 1 cm cannot be attained then simple mastectomy is the next best option. Most current studies show that wide local excision with adequate margins yield equivalent results to mastectomy in terms of overall survival [10,11]. In general, borderline tumors metastasize, however this is not common. In a case review by Moffat et al. only 4% of patients with borderline tumors developed metastatic disease [12]. Malignant tumors develop metastases more commonly. In some studies metastatic disease has been reported between 9 and 32% [13–15]. Limited research and data is available regarding



**Fig. 2.** The tumor shows minimal typical ductal features of phyllodes tumor (see photomicrograph, top panel), a minority of the remainder low-grade malignant (see other photomicrograph, left half) and majority high-grade malignant 'overgrown stroma'. Mature squamous 'pearls' (see photomicrograph, lower panel) and chondroid areas (see other photomicrograph, middle panel) are obvious divergent differentiation. Foci of geographic necrosis, and broad zones of undifferentiated sarcoma with marked atypia (see other photomicrograph, right half), tumor giant cells, and numerous mitoses and karyorrhectic cells, constitute the most malignant-appearing areas.

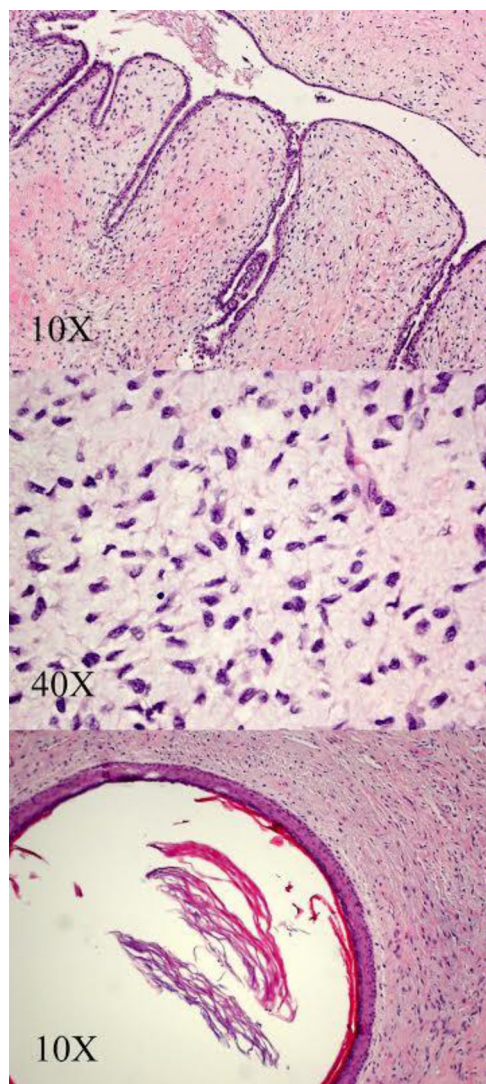
patients like ours; those which present with metastatic disease and very aggressive tumors as far as treatment after primary surgical resection. The overall metastatic rate of phyllodes tumor in general has been reported at <5% [16].

The histological classification adopted by the World Health Organization in the early 1980s allowed pathologist to classify phyllodes tumor into benign, borderline, and malignant categories [17,18]. This classification is currently the best method at trying to predict the likelihood of developing local recurrence, metastatic disease or both. The system does have its limitations; not all malignant tumors recur or metastasize and some borderline tumors do. Traditionally predictors of malignant behavior include tumor size, cytological atypia, mitotic rate [19,20], and stromal overgrowth. Various studies have reported the local recurrence rate at roughly 20% regardless of histological classification [21,22]. Some studies report recurrence rates of malignant phyllodes in a range of 20–65% [23,24]. Some of the factors which have shown an increase in the change of local recurrence (LR) are tumor size, positive surgical margins, stromal overgrowth, high mitotic count, and necrosis. From Oktar et al., stromal overgrowth increased the probability of LR by 7-fold whereas surgical margin of <1 cm, the risk was increased by 5-fold and if the tumor size was >10 cm, then the prevalence of LR was 4x greater than smaller tumors [25]. Of note, the mean time of LR in their study was 26 months. Similar reports have also shown a mean time of LR of around 2 years [26]. In the previously cited report they had one patient which presented with a 30 cm tumor who within 2 months of a radical mastectomy developed a 2 cm chest wall recurrence, which was excised. 2 months later this patient presented with metastatic disease of the contralateral breast which was found to invade the chest wall and sternum. The mass was found to be inoperable and the patient died of the disease. Geisler et al. had 3 patients which presented with metastatic disease, one patient had low-grade tumor with metastatic disease to the lung and thoracic vertebrae who died 14 months after pre-

sentation. The other 2 patients presented with high-grade MPT with metastatic disease – the first died 37 months following mastectomy with metastatic disease to the brain and the second patient was treated with partial mastectomy and died one month later with metastasis to the right sacral wing [27].

Our patient had all the common factors for high probability of LR. With a tumor size of >30 cm, surgical margins of <1 mm, high mitotic rate of >10, focal tumor necrosis, marked pleomorphism, and stromal overgrowth. However, we do not think we could have predicted such a rapid course. Our patient and a few of the prior patients perhaps fall into a subcategory of rapidly aggressive malignant phyllodes tumors. Even in that, there are limited reports and data on patients like ours. Our patient had this mass of 'many years' however, it 'rapidly' enlarged in the prior weeks to presentation. Perhaps there was a malignant transformation at the genetic level which accelerated the rate of spread of her disease in those prior weeks. In all likelihood presenting with metastatic disease is likely a risk factor for local recurrence at the original site.

A question for our patient would have been continued treatment had she not had such aggressive disease. Is there a benefit of radiation therapy or systemic therapy in malignant phyllodes tumors? Also, would the patient have been a candidate for future surgery for her pulmonary metastases? The benefit or role of adjuvant therapy is not well established. This is secondary to the lack of randomized trials and rarity of this tumor. Currently there is no consensus regarding radiotherapy. Most studies have involved those treated with wide local excision and not necessarily those treated with mastectomy [28,29]. Belkacemi et al. reported that radiotherapy was associated with superior local control rate at 10 years, from 59% to 86% for both borderline and malignant phyllodes tumors [30]. Also, in a prospective multi-institutional study of adjuvant radiotherapy (RT) on 46 patients with borderline or malignant phyllodes tumors treated with wide local excision followed by RT, there were no local recurrences with a median follow up of 56



**Fig. 3.** The upper panel shows the most typical phyllodes sampled (10×), the middle panel chondroid differentiation (40×), and the lower panel squamous 'pearls' (10×).

months [31]. Two patients with malignant phyllodes tumor died of metastatic disease. Due to the fact that our patient was treated with simple mastectomy and had surgical margins at roughly 1 mm adjuvant radiotherapy might have decreased her rate of local recurrence, however there are no data we found where a patient with metastatic disease was treated with RT. Our patient would have had to have her metastatic disease dealt with likely before the subject of radiation therapy could have been approached.

Systemic chemotherapy and hormonal therapy is debatable in phyllodes tumor. To date there is no double blinded, multicenter study on this topic. There was an observational study over a 10 year period with patients treated with doxorubicin plus dacarbazine or observation alone after surgical resection [32]. Based on the limited data available on systemic therapy of soft tissue sarcoma, adjuvant chemotherapy could possibly be offered to patients with large (>5 cm), high-risk or recurrent malignant tumors. This would be better understood through an evaluation of adjuvant and neo-adjuvant chemotherapy for soft tissue sarcoma which is not within the scope of this case report. Turalba et al. showed that doxorubicin and ifosfamide-based chemotherapies have some efficacy in women with metastatic phyllodes tumors [33]. Hormonal therapy is not effective in phyllodes tumor. This is despite the presence of positive hormone receptors. The hormone receptors are com-

ponent of the epithelial aspect of the tumor whereas the stromal aspect of the tumor is responsible for the metastatic behavior of the tumor [34]. The receptor from the stromal component expresses estrogen receptor beta, not alpha as with adenocarcinoma [35,36]. To date, there is no established role for adjuvant chemotherapy or hormonal therapy in phyllodes tumor. Had our patient presented earlier and despite limited data, she might have been a candidate for systemic therapy.

#### 4. Conclusion

In conclusion our patient presented with an aggressive metastatic form of phyllodes tumor. Based on physical exam alone the case is extraordinary. Through physical examination and biopsy data alone, in accordance with prognostic criteria, she was at an elevated risk for local recurrence and further metastatic disease. Even with this understanding, it would have been near impossible to predict such a rapid course of disease progression as she displayed due to the limitations of our knowledge of this disease. Our case illustrates the unpredictable nature of this disease in general and it likely sheds light on a variant of the phyllodes tumor which had undergone an aggressive transformation.

#### Conflict of interest

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#### Consent

Consent obtained from next of kin.

#### Author contribution

Nathan Roberts- data, writing.

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