Giant malignant phyllodes tumor with metastasis to the brain

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ABSTRACT

We present the case of a 32-year-old African American woman with a giant malignant phyllodes tumor that metastasized to the lungs and subsequently the brain. Her treatment included six cycles of adjuvant therapy with AIM (Adriamycin[®], ifosfamide, and mesna) followed by therapy with gemcitabine and docetaxel. A grand mal seizure led to discovery of a 6 × 5 × 5 cm brain mass which was resected. After resection, the patient developed pulmonary edema, repeat seizure activity, and massive intra-thoracic progression before succumbing to her disease. This is an unpredictable and understudied neoplasm that can be aggressive and fatal in rare cases.

KEYWORDS Brain metastasis; breast cancer; phyllodes tumor

Phyllodes tumors (PTs) of the breast are rare fibro-epithelial neoplasms that comprise <1% of all breast cancers and display diverse biological behaviors. Metastatic disease with PT is uncommon, and spread to the central nervous system is even more atypical. We found 10 reports of central nervous system metastasis of PT.^{1–10} However, the possibility of aggressive disease should not be overlooked, especially in patients with malignant PTs, which are more likely to metastasize than benign or borderline tumor types.¹¹ Patients who develop metastasis have an average survival time of <2 years, and spread to the brain often predicts a worse prognosis.⁶ Research has shown that the incidence of PTs is highest in Latina women from Mexico, Central America, and South America, whereas a lower incidence is reported for Caucasians, Asians, and African Americans.^{12,13} However, as highlighted in this case report, African American women are thought to have a more aggressive presentation and greater morbidity.¹⁴

CASE REPORT

A 32-year-old African American woman with known heterogeneously dense breast tissue and multiple fibroadenomas presented with asymmetric enlargement of the left breast.

Ultrasound and computed tomography confirmed the presence of a large solid mass occupying the entire left breast; a radical mastectomy with split thickness skin grafting was performed. The tumor measured 32 × 32 × 17 cm and weighed 6 kg. Histopathological analysis revealed an epithelial component with broad “leaf-like” papillae within cleft-like spaces and a cellular stromal component. Most stroma contained low-grade spindled cells in a relatively loose background (*Figure 1a*), but multiple areas demonstrated overgrowth by high-grade sarcomatous stroma with increased cellularity, atypical malignant nuclei, and many mitoses (>10 per 10 high-powered fields [HPFs]) (*Figure 1b*). Borders were focally infiltrative, consistent with a malignant PT diagnosis.

Two months after surgery, a computed tomography scan showed pulmonary nodules and a biopsy confirmed metastatic disease. AIM (Adriamycin[®], ifosfamide, and mesna) chemotherapy was started, and six cycles were completed. During cycle 5, another scan showed that pulmonary nodules had decreased in size, which indicated partial response to treatment. Repeat imaging 4 months after chemotherapy revealed pulmonary nodule progression. Four cycles of second-line therapy with gemcitabine and docetaxel were completed, but disease progression continued. The patient developed recurrent headaches and had a grand mal seizure.

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Received June 14, 2018; Revised August 30, 2018; Accepted September 4, 2018.

Figure 1. Histology of the primary breast tumor. **(a)** The tumor has an epithelial component with broad “leaf-like” papillae within cleft-like spaces, as well as a cellular stromal component with low-grade spindled cells in a relatively loose background (200 $\times$). **(b)** This is one of multiple areas demonstrating stromal overgrowth by high-grade sarcomatous stroma with increased cellularity of markedly atypical, malignant nuclei and numerous mitoses (>10/10 high-powered fields; 400 $\times$).

Figure 2. Histology of the brain metastasis. **(a)** The tumor is a malignant spindled cell neoplasm with areas of varying cellularity (20 $\times$). **(b, c)** There are less cellular areas with atypical spindled cells (200 $\times$ each). **(d)** Other areas demonstrate high-grade sarcomatous stromal overgrowth with increased cellularity of mitotically active, markedly atypical, malignant nuclei (200 $\times$).

Her clinical workup revealed a 6 $\times$ 5 $\times$ 5 cm cerebral mass. Upon resection, the mass was determined to be a malignant spindled cell neoplasm with varying cellularity (*Figure 2a*); some areas were less cellular with atypical spindled cells (*Figures 2b and 2c*), and others demonstrated high-grade sarcomatous stromal overgrowth (*Figure 2d*). These sarcomatous regions were morphologically similar to those in the original breast lesion; however, no epithelial component was seen.

Postoperatively, the patient underwent rapid decompensation with progressive dyspnea. She was admitted and found to have massive intrathoracic progression. Just days later, she developed seizures and ultimately succumbed to her disease 20 months following diagnosis.

DISCUSSION

PTs are heterogeneous fibroepithelial neoplasms marked by a distinct, leaf-like architecture.¹⁵ The World Health Organization classifies PTs as either benign, borderline, or malignant based on stromal characteristics such as atypia, cellularity, and overgrowth, mitosis per HPF, and tumor margins. Malignant PTs have a higher risk of metastatic disease, whereas benign and borderline tumors demonstrate a proclivity for local recurrence and rarely metastasize.¹⁶ Approximately 10% to 15% of PTs are malignant, and in patients with malignant PTs, 1.7% to 27% develop metastatic disease.^{1,15,16} Malignant PTs demonstrate intracanalicular growth, stromal overgrowth, >10 mitoses per 10 HPFs,

nuclear pleomorphism, and infiltrative margins.¹⁵ Stromal overgrowth is the most important prognostic indicator for distant metastasis and overall survival.¹⁷ Additionally, necrosis within the surgical specimen and prior history of fibroadenoma increase the risk of local recurrence and metastasis, both of which were present in this case.¹

Treatment for large PT typically involves a total mastectomy without axillary dissection and nodal sampling unless metastasis is confirmed by intraoperative biopsy due to presumed hematogenous spread.¹³ Adjuvant radiotherapy is associated with decreased local recurrence and may be considered if further surgery would cause considerable morbidity, but it has not been shown to impact overall survival.¹⁸ Due to the paucity of metastatic malignant PT cases, there are no randomized controlled trials specifically assessing the benefit of chemotherapy. However, in a retrospective single institution study of 37 patients with metastatic PTs, patients receiving a doxorubicin-based polychemotherapy had an improved mean survival of 9 months compared to those treated with endocrine therapies (mean survival of 2 months) versus single-agent chemotherapies (mean survivals ranging from 5 to 7 months).⁶ The National Comprehensive Cancer Network currently recommends that cases of recurrent metastatic PT follow treatment guidelines for metastatic soft tissue sarcomas.¹⁹

The 5-year survival rate for malignant PT patients is 54% to 82%, and patients with metastases often do not respond to standard therapies.^{15,17} In a study of 293 PT patients, 5 developed metastatic disease by 1.2 years. These five patients were out of seven with aggressive pathologic features, and their median survival was 4.2 months.¹ Another study reported a 12.5% rate of metastatic disease with a mean survival of 2.8 months for four patients with brain metastases.⁶

Our patient had massive disease at presentation and rapid distant recurrence culminating in brain metastasis. According to the literature, a malignant PT in an African American patient is uncommon, but African American women may experience greater morbidity and be more advanced at presentation than other PT patients.^{1,14} This case highlights the aggressive potential of an often underestimated disease that is typically regarded as relatively benign.¹

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