

**Case Report**

Complete Pathologic Response Following Multimodality Therapy for a Recurrent, High-Grade Phyllodes Tumor

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Abstract

Introduction: Phyllodes tumor is a rare mesenchymal tumor of the breast for which surgical resection is the primary therapy. Despite adequate surgical resection, local recurrence rates of up to 40% are observed in patients with high-grade tumors. The role of adjuvant radiation therapy and chemotherapy for phyllodes tumor to improve local and systemic control is not well established. However, several small studies have shown improvements in local control rates with adjuvant radiation therapy. The management of aggressive local phyllodes tumor recurrences can be a clinical challenge and multimodality therapy should be considered in these cases for optimal results.

Case presentation: We present the case of a high-grade phyllodes tumor that recurred in the radiation field after adjuvant radiation therapy. The patient was treated with neoadjuvant hyperfractionated, accelerated radiotherapy in combination with hyperthermia and chemotherapy followed by radical surgical resection. A completed pathologic response was observed.

Conclusion: This multimodality approach may be a successful treatment algorithm for high-grade tumors that reoccur in a prior radiation field.

Keywords: Phyllodes tumor; hyperfractionated accelerated radiotherapy; hyperthermia; sarcoma

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Introduction

Phyllodes tumor (PT) is a rare tumor of the breast which develops from the intralobular stroma and accounts for less than 1% of all breast cancers.[1] Phyllodes tumors have variable tumor biology, ranging from benign (low-grade) tumors which cause local problems to malignant (high-grade) tumors which have a substantial risk of local recurrence and the potential to metastasize. Standard treatment for PT is complete surgical resection with wide margins. However, even with adequate surgical excision, local recurrence as high as 40% are observed in patients with high-grade tumors.[2, 3] Due to the rarity of this malignancy, the role of adjuvant radiation and chemotherapy to improve local and systemic control is not well established. We present a case report of a 49 year old female with a recurrent, high-grade PT with stromal overgrowth, which progressed during conventional radiation therapy and recurred as pure high-grade sarcoma.

Case Report

The patient is a 49 year old Caucasian female who presented to an outside institution with a palpable mass in the upper outer quadrant of the left breast in June 2013. A biopsy was performed which showed a high-grade spindle cell proliferation interpreted as metaplastic carcinoma. Based on the initial pathology, the patient underwent a total mastectomy with sentinel lymph node biopsy and placement of a tissue expander in July 2013. The final pathology showed a 5 cm high-grade spindle cell tumor consistent with high-grade PT with stromal overgrowth (Fig. 1) with 2 negative lymph nodes. No adjuvant radiation was given at that time. The patient underwent reoperation in September 2013 for tissue expander removal and placement of a permanent implant.

In October 2013 (3 months after her initial operation), the patient presented with a palpable mass on the lateral aspect of her mastectomy incision. A biopsy was performed which was consistent with recurrent PT. The patient was treated with wide excision and removal of her breast implant in November 2013. The pathology showed a 4 cm tumor which focally extended to within less than 0.1 cm of the deep resection margin. She then received radiation therapy to the entire left chest wall and supraclavicular fossa to 50.4 Gy and 48.6 Gy respectively, followed by a boost of 10 Gy to the site of the recurrence. Radiation therapy was completed in February 2014.

During radiation the patient noted an area of thickening on the medial aspect of her mastectomy incision near the sternum in the radiation field. A chest computed tomography (CT) performed in early February 2014 showed 2 small nodules on the medial aspect of the mastectomy incision. After completing radiation, a biopsy of this area was performed at an outside institution and the pathology showed no evidence of malignancy. The patient was referred to the Breast Surgery Clinic at the University of Maryland in March 2014 for continued follow up. On exam, the patient had a small area of thickening on the medial aspect of her mastectomy incision with no palpable mass. After reviewing the patient's chest CT from February 2014, a repeat biopsy of the 2 nodules on the left chest wall was recommended because of concern for discordant imaging and pathology results. The biopsy showed high-grade sarcoma, consistent with a recurrence of the patient's high-grade PT with stromal overgrowth. (Fig. 2)

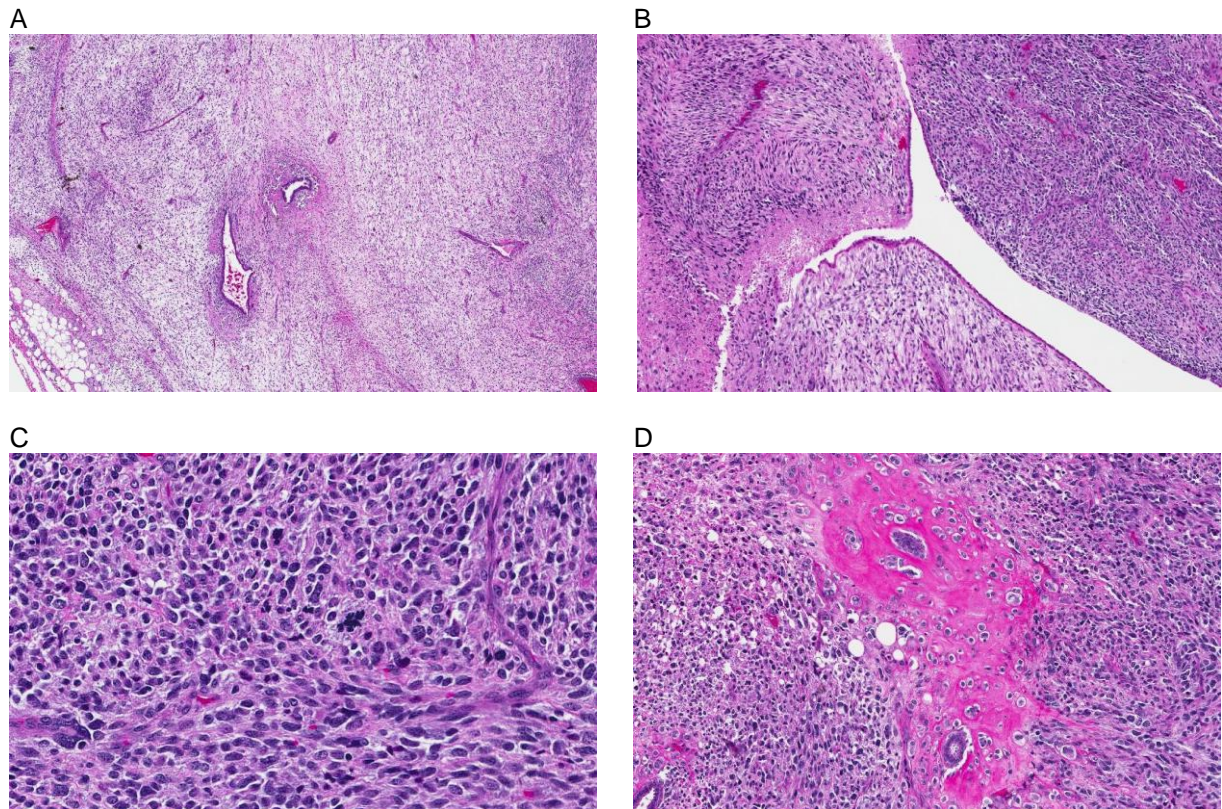


Figure 1 Initial phyllodes tumor biopsy. A, stromal heterogeneity with periductal condensation, stromal overgrowth and an infiltrative border (H&E stain, 20x magnification). B, prominent leaflike architecture, stromal hypercellularity and focal tumor cell necrosis (H&E stain, 40x magnification). C, tumor stroma with marked hypercellularity, pleomorphism and atypical mitotic figures (H&E stain, 400x magnification). D, malignant osteoid (heterologous osteosarcoma) in the periductal area (H&E stain, 200x magnification).

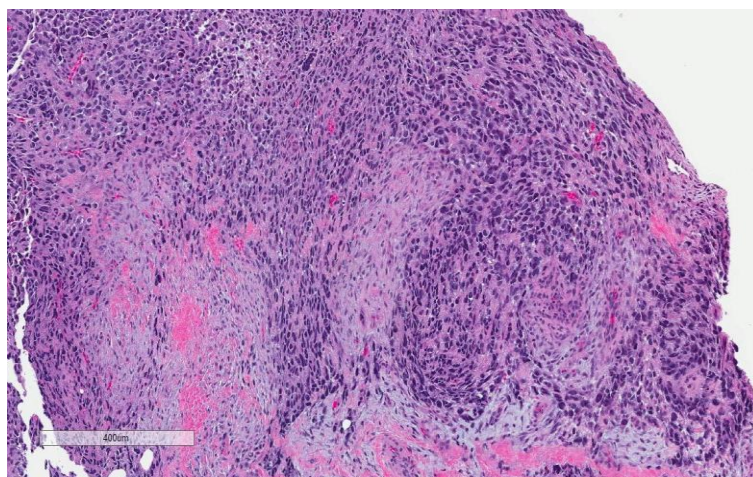


Figure 2 Local recurrence showing stroma only, without accompanying epithelial elements. Monophasic high-grade sarcoma with areas of necrosis. H&E stain, 40x magnification

Three weeks after initial evaluation at the University of Maryland, the patient presented with a rapidly enlarging mass on the left chest wall that on physical exam measured 6 x 5 cm. Positron Emission

Testing and Computed Tomography (PET/CT) was performed which showed a hypermetabolic mass on the medial left chest wall extending to the edge of the sternum that measured 4.6 x 2.8 cm with a maximum SUV of 24.5. (Fig. 3A) The patient also had a separate 1 cm nodule adjacent to the sternum near the second rib that was also hypermetabolic with a maximum SUV of 4.6. (Fig. 3B) There was no evidence of metastatic disease.

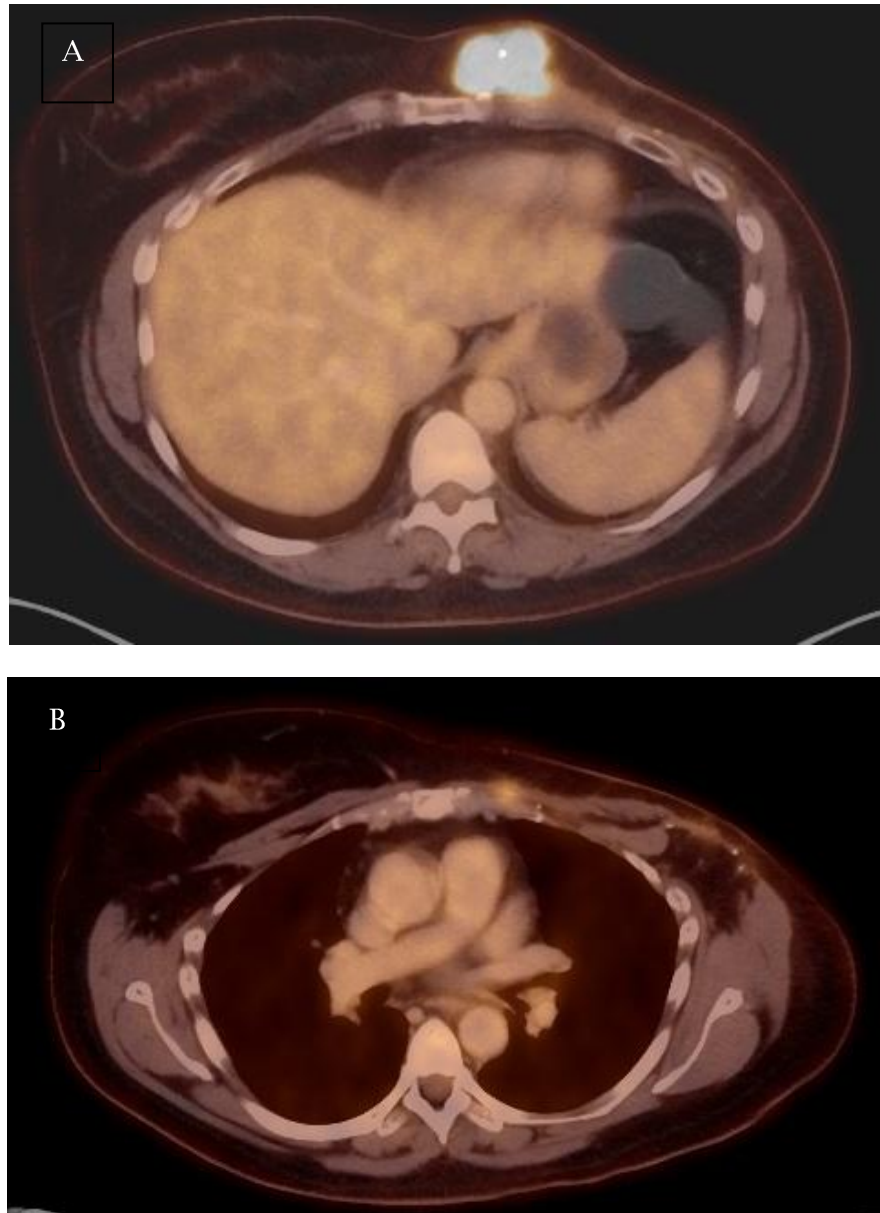


Figure 3 Positron emission tomography-computed tomography of the chest. A, large hypermetabolic mass of the medial left chest wall. B, smaller hypermetabolic mass of the superior left chest wall.

The patient's case was reviewed in the Breast Multidisciplinary Clinic at the University of Maryland Marlene and Stewart Greenebaum Cancer Center. Based on the rapid growth rate in the absence of distant metastatic disease, the decision was made to treat the patient aggressively with multimodality therapy. It was recommended that the patient receive hyperfractionated, accelerated radiotherapy (HART), similar to treatment described for radiation induced angiosarcoma.[4, 5] The patient received external beam radiation therapy to the 2 sites of recurrence using electrons with a 3 cm blocked margin, at 1.5 Gy per fraction delivered 2 times per day with 6 hours between fractions to a total of 57 Gy. In addition, the patient received concomitant treatment with hyperthermia and chemotherapy.[6-8] Hyperthermia was administered with a maximum temperature of 43 degree Celsius for 60 minutes using interstitial thermometry 3 times per week. Similar to the sarcoma literature, the patient received 2 cycles of ifosfamide 1500 mg/m² with mesna on day 1-5 every 21 days concurrently during radiation therapy.[6] Local side effects noted during treatment included erythema and dry desquamation of the skin of the chest wall which was treated with topical agents.

Six weeks after the completion of multimodality therapy, the patient underwent a repeat chest CT which showed stable masses on the left chest wall with imaging findings consistent with central necrosis. The patient was taken for surgical resection. An en bloc resection of the left chest wall and the 2 sites of tumor recurrence was performed and included the overlying skin and soft tissue, ribs 2-6, and part of the sternum. The patient's chest wall was reconstructed with gortex mesh and the soft tissue defect was closed with a combination of a latissimus dorsi myocutaneous rotational flap and a rhomboid rotational soft tissue flap.

The final pathology from the surgery showed a complete pathological response with no residual viable tumor in the specimen. The patient underwent follow up imaging 12 months after surgery which showed no evidence of local regional recurrence or metastatic disease.

Discussion

Phyllodes tumor is a rare mesenchymal tumor of the breast that accounts for less than 1% of all breast malignancies. Standard treatment for this malignancy is wide local excision. Risk factors for local recurrence include tumor size, grade, margin status, and stromal overgrowth.[2, 9, 10] Patients with high-grade, malignant tumors have local recurrence rates that range from 10-40% even when negative margins are achieved at surgery.[3] The role of adjuvant radiation therapy in patients with high-grade tumors is controversial, although several small studies have shown that adjuvant radiation therapy reduces local recurrence rates in patients with borderline and malignant PT.[11-13] In addition, radiation therapy may be beneficial in patients with more aggressive tumor features, such as a high mitotic index.[14] While chemotherapy has been utilized in the metastatic setting to decrease tumor burden and improve clinical symptoms,[15, 16] it has not been shown to prevent local recurrence in the adjuvant setting.[17]

In the present case, a multimodality approach based on treatment algorithms for high-grade sarcoma was utilized because the tumor recurred as pure high-grade sarcoma and progressed during conventional radiation therapy. Local control of high-grade sarcoma continues to be a challenge and multiple combined therapy approaches have been evaluated. Our review of the published literature indicates that treatment approaches which combine hyperthermia, radiotherapy and chemotherapy are more effective than single modality therapy in providing local control.[6-8]

Hyperthermia has been shown to enhance the effects of radiotherapy and chemotherapy in multiple tumor types.[18-21] This is due to a combination of factors which include the direct cytotoxic effects of heat on tumor cells, increased tumor perfusion which increases tissue oxygenation and intratumoral drug

concentrations, and inhibition of cellular DNA-repair proteins.[22] One of the largest studies to evaluate combined radiotherapy and hyperthermia for high-grade soft tissue sarcoma was conducted by Prosnitz et al. at Duke University.[7] A total of 97 patients were treated on protocol from 1984-1996. Patients received preoperative radiation therapy to a total a 50-50.4 Gy, 1.8-2 Gy per fraction and generally received 2 treatments of regional hyperthermia per week. The 10-year local control rate was 95% for extremity sarcoma and 63% for non-extremity sarcoma which is significantly higher than historical controls. As expected, the treatment did not impact the rate of distant metastases.

In a recent phase III trial comparing perioperative chemotherapy and hyperthermia to perioperative chemotherapy alone (Etoposide, Ifosfamide and Doxorubicin) in the treatment of high risk soft tissue sarcoma, patients who received combined therapy had a better overall response rate (28.8% vs. 12.7%), an increase in R0 resection at the time of surgery (51% vs. 41.6%), improvement in local progression-free survival at 2 years (76% vs. 61%), and a longer disease-free survival (median 32 months vs. 18 months; relative hazard = 0.70 for combined therapy, 95% CI 0.54-0.92, $p = 0.011$) compared to chemotherapy alone.[8] At a median follow up of 34 months, 132 patients developed local progression, 56 patients treated with combined therapy and 76 patients treated with chemotherapy alone. The local progression-free survival benefit was more significant in patients with non-extremity tumors. Patients who received combined therapy were also less likely to develop disease progression during preoperative treatment (6.8% vs. 20.6%). Although the overall survival was not statistically different between the groups due to the development of metastatic disease, in those patients who were able to complete the entire perioperative regimen, an improvement in overall survival was observed in patients in the combined therapy group (HR 0.66, 95% CI 0.45-0.98, $p=0.038$).

The rationale for using HART in the present case is based on reports using this technique for angiosarcoma after breast conserving therapy for epithelial breast cancer.[4, 5] Radiation has typically not been utilized in this setting, since it was felt that these tumors were radioresistant. However, outcomes with surgical resection alone for angiosarcoma are quite poor, with rapid recurrence of tumor observed in the majority of patients. A review of 14 patients who were treated for angiosarcoma using HART, demonstrated that neoadjuvant treatment followed by surgical resection appeared to be the most successful treatment algorithm.[5] The preoperative approach was also preferred so that the twice irradiated tissue would be removed at surgery to minimize the risk of late radiation effects. Of the 9 patients treated using this approach, 7 underwent surgical resection and pathology showed a complete response in all 7 patients. For all 14 patients, the progression-free survival rates at 2 years and 5 years were 71% and 64%, respectively, and the overall and cause-specific survival rates at 2 years and 5 years were 86% and 79%, respectively.

Conclusion

The management of aggressive local recurrences from solid tumors can be a clinical challenge which requires a coordinated multidisciplinary approach. Our patient presented with a high-grade PT, and despite adequate surgical resection and adjuvant radiation therapy, an aggressive chest wall recurrence developed. The patient was treated with combined modality therapy using HART with hyperthermia and chemotherapy with ifosfamide, followed by en bloc chest wall resection and reconstruction. A complete pathologic response was achieved, and the patient currently remains without evidence of disease. This combined modality therapy appears to be a promising approach for the local treatment of high-grade tumors that reoccur in a prior radiation field.

Consent

Consent was obtained from the patient for publication of this case report and is available on request.

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