Radiation-Induced Breast Angiosarcoma: A Case Report
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Abstract
Angiosarcoma is a rare, aggressive sarcoma of endothelial derivation that represents 1% to 2% of all soft tissue sarcomas. Radiation-induced breast angiosarcoma, a rare adverse sequela of treatment of primary tumors, may be growing in incidence due to an increased use of breast-conservation therapy. We report the case of an 81-year-old female found to have a high-grade angiosarcoma that was previously misdiagnosed. The presenting signs of post-irradiation angiosarcomas are skin findings, so it is essential that health care providers have a high index of suspicion for this entity.

Introduction
Angiosarcoma is a rare, aggressive sarcoma of endothelial derivation that represents 1% to 2% of all soft tissue sarcomas. Angiosarcoma of the breast can be classified into primary and secondary forms. Primary lesions of the breast most commonly present in middle-aged females as a painless, palpable mass with areas of dyspigmentation. Secondary angiosarcomas of the breast can arise in the setting of chronic lymphedema or in association with congenital, filarial, traumatic and idiopathic etiologies. Greater than 90% of these cases are seen post mastectomy, a condition known as Stewart-Treves syndrome. Secondary angiosarcomas spread to parenchyma, while primary forms arise in parenchyma. Other forms of secondary angiosarcoma of the breast include post radiation-induced angiosarcoma, the prevalence of which has increased with the use of breast-conservation therapy (partial mastectomy with adjuvant breast radiation therapy), although the incidence still remains low (.03% to .20% of patients treated). Women who receive radiation therapy in treatment of breast cancer have a 9-fold to 16-fold increase in the relative risk of developing angiosarcoma compared to those treated with other modalities.

Therapy-related angiosarcomas of the breast may present differently from primary tumors. The average age of occurrence for radiation-induced angiosarcomas is older (median 64 years, range 44 years to 84 years) compared to primary angiosarcomas, which is found in patients under 40 years of age. They may exhibit rapid growth, presenting as infiltrative plaques, nodules or echymotic papules. The latency period from completion of irradiation of primary breast carcinoma to the diagnosis of angiosarcoma ranges from 18 months to 204 months, with a median latency period of 71 months.

Radiation-induced angiosarcomas may carry a worse clinical outcome than sporadic primary breast sarcomas. There is usually a delay in diagnosis, which attributes to the poor prognosis. Even after primary surgical resection, patients are more prone to local and distant recurrence as well as death from disease. In one series with 31 patients with radiation-associated angiosarcomas, nearly two-thirds of patients treated with surgical resection developed local recurrence despite clear margins. In another retrospective series of 55 women with breast angiosarcomas (23 radiation-associated, 32 primary), patients with radiation-naive angiosarcomas appeared to have a more favorable disease-free and overall survival in the first three years compared to those with radiation-associated angiosarcomas; however, differences in overall survival curves between the two groups were not significant.

Case Report
An 81-year-old Caucasian female presented to our outpatient clinic on November 2015 for an indurated, erythematous rash on her left breast for approximately two months. The patient’s medical history included a T1b N0M0 infiltrating ductal carcinoma, 8 mm in diameter, that was treated with lumpectomy and sentinel lymph node biopsy in July 2008. She was found to have a total of four negative nodes and negative margins. Her tumor was estrogen/progesterone-receptor positive and HER-2/neu negative by FISH. Operatively, she underwent adjuvant radiation therapy (34 treatments) to the left breast (dosimetry records unavailable), as well as adjuvant letrozole for five years, completing the treatment regimen in 2013. The patient had undergone mammogram and ultrasound of bilateral breasts in 2014, demonstrating BI-RADS 2 with no evidence of disease recurrence.

Prior to the consultation in our office, the patient was seen by her dermatologist in September 2015. At that time, a skin biopsy of the lesion was performed, demonstrating subtle interface alteration with superficial chronic inflammation, consistent with drug reaction. The patient was treated with a medium-potency topical steroid without resolution. Upon evaluation in November 2015, the patient presented with an erythematous, indurated, pruritic plaque on the lower medial aspect of the left breast measuring approximately 2 cm x 5 cm (Figure 1a). Two punch biopsies were taken (Figure 1b), showing atypical vascular proliferation with dilated vascular structures at the superficial dermis, along with atypical cells intersecting collagen bundles and invading the reticular dermis and subcutaneous tissues (Figures 2a, 2b). Immunohistochemical studies showed a phenotype positive for CD31, D2-40 (strong), and p53 (nuclear, faint); CD34 staining was only focal. Correlation of the clinical features and microscopic findings were consistent with the diagnosis of lymphangiosarcoma.

The patient was referred to Oncology, and it was determined she should undergo surgical resection and radiation therapy as soon as possible. A simple left-breast mastectomy followed by reconstructive surgery with a rectus abdominis myocutaneous flap for wound closure was performed in December 2015. Pathology showed a high-grade angiosarcoma measuring 4.5 cm in greatest dimension involving the nipple, skin, and breast parenchyma. The margins were clear.

Figure 1a. Erythematous, indurated, ill-defined dermal plaque, seven years post radiation therapy.
Figure 1b. Marks demonstrating sites of two 4-mm punch biopsies.

Figure 2a

Figure 2b

Figures 2a, 2b. Punch biopsies showing atypical vascular proliferation with dilated vascular structures at superficial dermis and atypical cells intersecting collagen bundles and invading reticular dermis and subcutaneous tissues.
Conclusion
Early diagnosis of radiation-induced angiosarcoma is essential for a positive prognosis. Median time of survival ranges from 18 months to 40 months, and the overall survival rate at five years is up to 20%. A delay or misdiagnosis may occur if a health care provider is not aware of this potential side effect of radiation. We present this case due to the interesting clinical presentation as well as the two-month delay in diagnosis secondary to poor tissue sampling. To ensure accurate, prompt diagnosis and prevent the possibility of false negatives, we advise performing multiple punch biopsies when a patient presents with a breast lesion and history of breast carcinoma. Our patient underwent mastectomy with a complex flap repair as well as adjuvant radiotherapy at single daily fractions with successful results.

Discussion
Over the past few decades, breast-conservation therapy (conserving surgery) followed by moderate-dose radiation therapy has replaced conventional radical mastectomy as the preferred method of treating breast cancer. Prospective, randomized clinical trials have found little difference between the two in 15-year breast cancer mortality rates. As more patients elect for breast-conservation therapy, the incidence of angiosarcomas may increase. As the presenting sign of post-irradiation angiosarcomas are skin findings, it is essential that health care providers have a high index of suspicion for this entity.

Angiosarcomas have been described in an array of clinical presentations, including bruise-like patches of skin, blue painless nodules, erythematous patches and, at advanced stages, as red, violaceous plaques with ill-defined, nodular appearances. Less common presenting findings include eczematoid changes, ulcerations, bloody nipple discharge and non-pigmented macules. Lesions should be differentiated from recurrent breast carcinomas, atypical hemangiomas, and radiation dermatitides. The latency intervals of angiosarcomas may differ depending on etiology: 72 months for radiation-induced angiosarcomas compared to 10 years to 15 years for those associated with chronic lymphedema. An accurate diagnosis of angiosarcomas may be made with simple skin tissue sampling, such as punch biopsy. Of note, it has been documented that the edge of an angiosarcoma may have low-grade changes that are indistinguishable from post-radiation transformation. Thus, we recommend that multiple biopsies be taken at different areas of the lesion to prevent false-negative reports. If multiple punch biopsies do not provide adequate information, performing a more generous open biopsy should be considered.

The standard treatment for post-radiation angiosarcomas is total mastectomy. Regional lymph node metastasis is rare, and axillary node dissection is not indicated in the absence of clinically evident metastatic disease. For radiation-induced angiosarcomas treated with surgery alone, recurrence rates may be as high as 50% to 70%, so patients may benefit from adjuvant treatments including chemotherapy and radiotherapy. The role of adjuvant radiotherapy in radiation-induced breast angiosarcoma remains controversial. Recent reports show success with the use of reirradiation with a hyperfractionated schedule of administration; in a study of 14 patients treated with the regimen, the five-year survival rate was found to be 86 percent. Other treatment options include adjuvant chemotherapy; however, results are limited, and its use is not clearly defined. Sorafenib, brivanib, sirolimus and docetaxel have been administered in addition to combination therapy in case studies. For patients who cannot undergo surgery, palliative chemotherapy can extend survival rates, with taxane and anthracycline agents used most commonly.

References

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