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Case Report

Radiation-Associated Angiosarcoma of the Breast: A Case Report and Literature Review

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Radiation-associated angiosarcoma · Breast conservation therapy · Recurrent breast neoplasms

Abstract
In the last couple of decades, breast conservation therapy, which utilizes a combination of surgery, radiotherapy, and endocrine or chemotherapy, has become the standard of care for treating early-stage breast cancer. This practice has been greatly beneficial in the improvement of the patient's quality of life but has also led to the increased use of radiotherapy and associated soft-tissue sarcomas, with angiosarcoma being the most common malignancy. Radiation-associated angiosarcoma (RAS) of the breast is a rare phenomenon, which has been reported to occur in approximately 0.9 out of 1,000 cases, with a reported onset as late as 23 years following radiotherapy. Here we report 2 cases of RAS that occurred within 6 and 13 years following radiotherapy of their primary breast lesion. We discuss the diagnostic and therapeutic challenges regarding this disease and review the current literature. This case report serves as cautionary lessons on the importance of considering RAS of the breast in the differential diagnosis during evaluation for recurrent breast neoplasms. Ongoing clinical trials using combinations of vascular endothelial growth factor inhibitors and chemotherapy may provide future avenues of treatment for this difficult-to-treat disease.

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Introduction

In the last 20 years, breast conservation therapy, which utilizes a combination of surgery, radiotherapy, and endocrine or chemotherapy, has become the standard of care for treating early-stage breast cancer. This practice has been greatly beneficial in the improvement of the patient's quality of life but has also led to the increased use of radiotherapy. Unfortunately, this has also led to a reported increase in radiotherapy-associated soft-tissue sarcomas, with angiosarcoma being the most common malignancy [1, 2]. Radiation-associated angiosarcoma (RAS) of the breast is a rare phenomenon, which has been reported to occur in approximately 0.9 out of 1,000 cases, with a reported onset as late as 23 years following radiotherapy [1–5]. Here we report 2 cases of RAS that occurred within 6 and 13 years following radiotherapy of their primary breast lesion. We discuss the diagnostic and therapeutic challenges regarding this disease and review the current literature. This case report serves as cautionary lessons on the importance of considering RAS of the breast in the differential diagnosis during evaluation for recurrent breast neoplasms.

Case Report

Case 1

A 68-year-old female was diagnosed with stage II (T1N1M0) invasive ductal carcinoma, which was estrogen receptor (ER) and progesterone receptor (PR) positive. She was treated with a right breast partial mastectomy followed by adjuvant radiotherapy and 5 years of endocrine therapy with an aromatase inhibitor as the patient refused chemotherapy. Six years after initial diagnosis, the patient developed multiple red papules on the inferior portion of her right breast with an initial biopsy showing atypical postradiation cells. Due to concern for possible recurrence of her breast cancer (especially since she had refused adjuvant chemotherapy), a bilateral mastectomy was performed. To our surprise, the surgical pathology results showed low-grade multifocal angiosarcoma centered in the dermis and extending up to 1.1 cm, with multiple nodules of vascular proliferation throughout the dermis and perineural invasion and focal infiltration into the subdermal adipose tissue (Fig. 1a). Two months after mastectomy, a follow-up positron emission tomography and computed tomography scan showed no evidence of residual or active hypermetabolic foci indicative of metastatic disease. After a long discussion with the patient, a decision was made for close surveillance as her poor performance status and multiple medical comorbidities made her an inadequate candidate for adjuvant chemotherapy with various anthracyclines or vascular endothelial growth factor (VEGF) inhibitors.

Case 2

A 44-year-old female was diagnosed with stage II (T1N1M0) invasive ductal carcinoma of the left breast, which was ER/PR negative. She was treated with neoadjuvant chemotherapy, which was followed by left breast mastectomy, sentinel lymph node dissection, and adjuvant radiotherapy. On surgical pathology, the patient had complete response with only residual ER/PR-negative ductal carcinoma in situ with no residual nodal disease. Of note, genetic testing for *BRCA1* and *2* genes did not show any known driver mutations but did show some single nucleotide polymorphisms which were consistent with variation of unknown significance. She received yearly diagnostic mammograms for surveillance which showed only benign disease for 12 years. Then in the 13th year, the patient developed a pal-

pable left breast mass at the mastectomy and radiation site. Ultrasound-guided biopsy was performed, and the pathology showed low-grade angiosarcoma with interanastomosing vascular channels, nuclear atypia, and hyperchromasia (Fig. 1b). The patient then underwent radical excision of the left breast and left chest wall angiosarcoma. As of the time of submission, the patient's follow-up computed tomography scans have shown no evidence of recurrent disease.

Discussion

Angiosarcoma following the treatment of breast cancer was first described more than 50 years ago in 1948 as a surgical complication from radical mastectomy and axillary lymph node dissection [3]. More recently, radiotherapy has been found to be a significant risk factor associated with secondary soft tissue sarcomas and in particular angiosarcoma [1, 2]. Not only is RAS of the breast rare, but it remains a challenge to diagnose and treat [1, 2]. Mery et al. [6] reviewed the National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER) database of early-stage breast cancer patients (approx. 560,000 cases) with up to 15-year follow-up data and estimated that RAS of the breast occurred in 0.9 out of 1,000 cases. Furthermore, they estimated that adjuvant radiotherapy increased the risk of RAS of the breast by 9-fold compared to those who had received no radiation therapy [6]. It was also found that RAS of the breast has a poor prognosis with an overall 5-year survival of 38% [6].

Multiple case reports describe the first signs of RAS of the breast as skin changes including discoloration, dimpling, and thickening [2, 7]. In our first case, the patient presented with multiple red papules; however, in the second case, the presenting sign was a palpable breast mass which is unusual in the setting of RAS of the breast. RAS of the breast can be difficult to find on mammogram and may only appear as skin thickening. Rarely, angiosarcoma appears as an ill-defined or lobulated mass without calcifications [2]. The lack of radiographic findings was seen with our second patient who had routine yearly mammograms which demonstrated only benign findings. All patients with breast cancer, particularly those who have undergone radiation therapy, require routine follow-up as local recurrence rates can be high. The risk of radiation-induced angiosarcoma is highest 10 years after treatment and remains high for the following 10 years [8]. The prognosis of radiation-induced angiosarcoma is poor and correlates with the time of onset, the age of the patient, and depth of tumor invasion. However, tumor grade is not a prognostic indicator [9, 10].

Treatment for radiation-induced angiosarcoma primarily involves an aggressive surgical approach as this represents the only potential for a cure [10]. In a study which looked at 33 patients, Morgan et al. [5] found that even a standard mastectomy may be inadequate for treatment. They found that complete resection of all radiated tissue as opposed to resection of only the tumor provided a better prognosis and decreased the incidence of recurrence. Additional radiation therapy has been shown to provide little benefit as most radiation-induced angiosarcomas are resistant to any additional radiation therapy [11]. Unfortunately, chemotherapy with anthracyclines/taxanes or surgery has been found to be only minimally effective in angiosarcomas with a reported response rate ranging from 17 to 34% [12, 13].

Another approach currently being investigated is the use of molecularly targeted agents such as VEGF inhibitors. It has been suggested that since angiosarcomas overexpress VEGF at high levels, the use of VEGF inhibitors may be another effective strategy [14, 15]. Agulnik et al. [15] conducted a phase II study of 30 patients to study the efficacy of the VEGF inhibi-

tor bevacizumab for the treatment of metastatic or locally advanced angiosarcoma and epithelioid hemangioendothelioma. They found that 17% of the patients (2 angiosarcoma and 2 epithelioid hemangioendothelioma) had a partial response with 50% of the patients (11 angiosarcoma and 4 epithelioid hemangioendothelioma) showing stable disease with a mean time to progression of 26 weeks [15]. These findings are encouraging and there are several ongoing clinical trials investigating the use of combination therapy with a VEGF inhibitor and other chemotherapy agents (NCT02979899, NCT01462630, NCT02048722).

In conclusion, radiation-induced angiosarcoma is a rare and aggressive disease which presents a potential challenge to the treating physician. Diagnosis can be challenging as it is often missed on mammography and often presents with dermatologic findings. Our patient's presentation with a palpable breast mass represents a unique and potentially challenging presentation of radiation-induced angiosarcoma of the breast. Although RAS of the breast can be potentially life-threatening, studies have shown that the overall risk of angiosarcoma following radiation therapy does not outweigh the benefits of radiation therapy in the treatment of primary breast cancer [8, 10]. Ongoing clinical trials using combinations of VEGF inhibitors and chemotherapy may provide future avenues of treatment for this difficult-to-treat disease.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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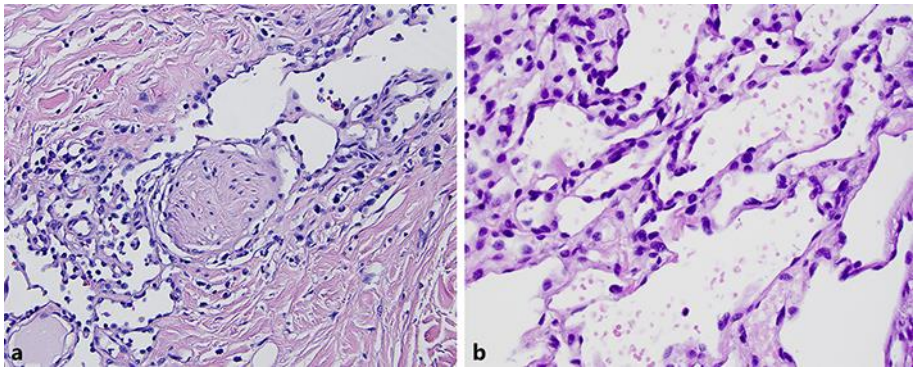

Fig. 1. Radiation-associated angiosarcoma of the breast. **a** Case 1 (H&E stain). Low-grade angiosarcoma surrounding an area of perineural invasion with small variable endothelial cells of mild atypia and hyperchromasia. **b** Case 2 (H&E stain). Vascular spaces are lined by enlarged and hyperchromatic endothelial cells. Specimen is absent of necrotic or mitotic cells, which is consistent with low-grade angiosarcoma.