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

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Conflict of interest: None declared

Patient: Female, 67
Final Diagnosis: Breast angiosarcoma
Symptoms: Skin lesion
Medication: —
Clinical Procedure: Surgery
Specialty: Oncology

Objective: Unusual clinical course

Background: Radiation-associated breast angiosarcoma is a rare clinical entity that is thought to be increasing in incidence.

Case Report: Here we present the case of a 67-year-old female with a history of left breast invasive ductal carcinoma who received breast conserving surgery and radiation therapy eight years ago. She then presented with a painless mild skin discoloration of the left breast that had been present for over one year. Mammograms and ultrasounds were normal. A punch biopsy and a subsequent excisional biopsy revealed the diagnosis of angiosarcoma. The patient was treated with mastectomy and had no subsequent recurrences.

Conclusions: The long-term clinical surveillance for all patients who receive breast conservation surgery is recommended and a high degree of suspicion should be exercised in view of potential atypical presentations of this disease.

MeSH Keywords: Breast Neoplasms • Heavy Ion Radiotherapy • Hemangiosarcoma • Mastectomy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905157

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Background

Angiosarcoma is a rare vascular malignancy originating from endothelial cells (endoderm tumor) and can arise spontaneously or in association with factors like chronic lymphedema and radiation therapy. Most angiosarcomas develop in the skin or superficial soft tissue, while only 20% are in the deep soft tissues. Typical immunohistochemical expression profiles for angiosarcomas include upregulation of certain vascular-specific thyroxin kinase receptors, including, *TIE1-2* and *VEGFR1(FLT1)*, *VEGFR2 (KDR)*, and downregulation of *VEGFR* ligand expression [1,2]. Interestingly, recent studies have shown that *de novo* angiosarcomas have distinct genetic profile compared to radiation-induced or lymphedema-associated angiosarcomas. As an example, a high level of amplification of *MYC* on 8q24.21 is found in most radiation-induced angiosarcomas while it is extremely rare in *de novo* angiosarcomas [3]. Prognosis has been historically poor especially for radiation-induced and large deep soft tissue angiosarcomas with a median survival of less than years [4]. Surgical resection is rarely curative, and there is only a modest sensitivity of angiosarcoma to taxanes or anthracycline-based chemotherapy [5,6]. However early detection and radical surgical treatment is potentially curative [7] hence the importance of increased awareness and knowledge about presenting symptoms.

Case Report

A 67-year-old Hispanic female with a past medical history of left breast invasive ductal carcinoma treated with lumpectomy, axillary lymph node dissection, and standard radiation therapy to the breast eight years ago, presented with a well circumscribed red skin discoloration with no additional skin changes or nodules in the left breast. Examination of the left breast revealed a flat 1 cm area of mild skin redness in the left lower quadrant of the breast without any palpable mass, warmth, or tenderness. The lesion was not associated with any edema, lesions, or blisters. Subsequent mammogram and ultrasound were negative for malignancy (BI-RADS-2). A punch biopsy demonstrated a vascular neoplasm with malignant cytological and histologic features (including nuclear pleomorphism, irregular nuclear contours, and invasion). Confirmatory immunohistochemistry stains were positive for endothelial marker (CD31, CD34, factor VIII), negative for pancytokeratin, ER, PR, HER2 and HHV8. A *c-MYC* immunohistochemical stain was equivocally positive, but was verified with a positive FISH study for *MYC* amplification (MYC/CEP8 ratio of 3.3). The patient was referred to surgery and underwent a left excisional biopsy in September 2016. The lesion from the excision was suspicious for angiosarcoma, positive for immunohistochemical endothelial markers CD31 (Figure 1) and CD34 (Figure 2) as well a positive c-MYC (Figure 3), however, with low Ki-67 at 5%. To further confirm the diagnosis, this case was sent to an outside consulting institution, and a consensus diagnosis of angiosarcoma of the breast involving the superficial dermis was established (Figures 4, 5). As margins of the biopsy were focally positive for angiosarcoma, the excisional biopsy was considered inadequate for treatment purposes and the patient underwent a left mastectomy in February 2017 with immediate reconstruction with tissue expanders and latissimus dorsi musculocutaneous flap. Pathology following this final surgery confirmed the absence of residual angiosarcoma. The patient was discharged home after surgery and currently is disease free and continues with routinely visits at our University Breast Clinic.

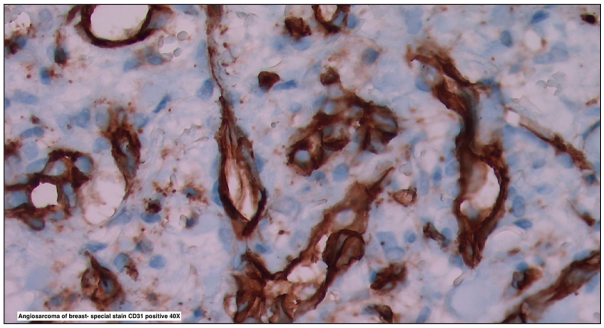

Figure 1. Angiosarcoma of breast: special stain CD31 positive 40×.

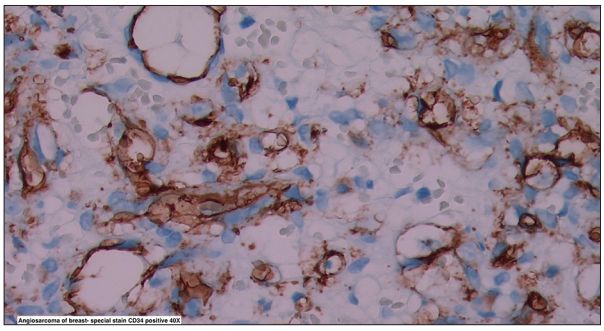

Figure 2. Angiosarcoma of breast: special stain CD34 positive 40×.

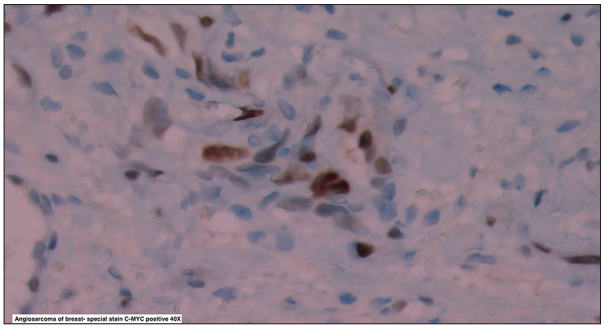

Figure 3. Angiosarcoma of breast: special stain C-MYC positive 40×.

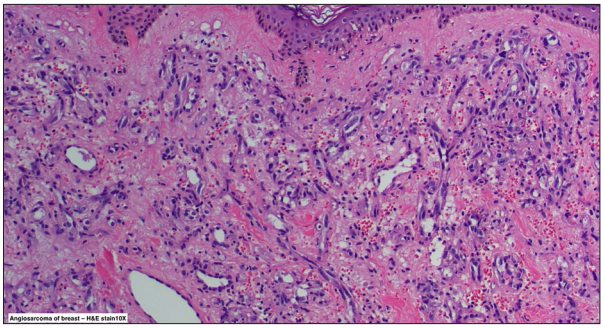

Figure 4. Angiosarcoma of breast: H&E stain 10×.

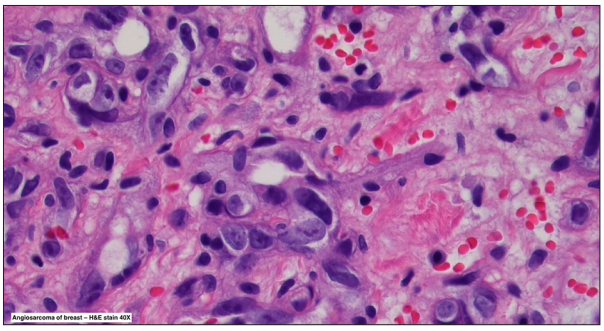

Figure 5. Angiosarcoma of breast: H&E stain 40×.

Discussion

The incidence of radiation-induced angiosarcoma is low, ranging from 0.09 to 0.16% [7,8]. However, an increasing number of case reports are showing secondary angiosarcomas following radiation therapy, suggesting that the incidence is possibly on the rise [9]. In comparison, primary angiosarcomas account for 0.04% of all malignant breast tumors [10] constituting approximately 1 in 2,000 of primary breast cancers and typically occurring in young women in the third and fourth decades of life [11]. In contrast, secondary angiosarcomas are found in older women with a history of breast conservation therapy and radiation therapy since breast carcinoma commonly occurs in women between the ages of 55 and 69 years [11]. The average latency of secondary angiosarcoma of the breast following radiation therapy is around six years, with some studies reporting the occurrence of angiosarcoma as soon as 1–2 years after radiation and as late as 41 years after radiation [12–14]. Overall, the occurrence of breast angiosarcoma post-radiation appears to be shorter compared to radiation-induced sarcomas in general, which typically have a latency period of 10–12 years [14]. The odds ratio for women with a history of breast cancer for developing angiosarcoma in the chest or breast was found to be 11.6 in a retrospective case control study [15]. In one study, the relative risk of developing angiosarcoma following radiation therapy was found to be increased at a relative risk of 15.9, compared with a non-radiotherapy cohort and the largest increase in risk of angiosarcoma was noted in the chest wall and breast [16].

The association between radiation and angiosarcoma of the breast has been reported in the literature in various cohort studies [17]. Breast angiosarcoma is typically seen affecting the dermis within the radiation field making these angiosarcomas cutaneous in origin [7–12]. Cases of angiosarcoma developing in the breast parenchyma, arising from parenchymal vascular endothelial cells, have also been reported [8–11]. Radiation-associated angiosarcomas have distinct biological features. A study comparing the histopathology of sporadic angiosarcoma and radiation-associated angiosarcoma showed that radiation-associated angiosarcoma does not have overexpression of p53 and does not have a mutation in *ATM* [12]. High Ki-67, a marker associated with increased rates of metastasis, was found in 44% of radiation-associated angiosarcomas and *hTERT* expression was found in both radiation-associated and sporadic angiosarcomas [12]. Another study found *MYC* gene amplification in 90% of angiosarcomas cases associated with radiation for breast cancer [18,19]. Proposed mechanisms for the development of radiation-induced angiosarcoma link lymphedema as a causative factor, as chronic lymphedema may result in an increase of vascular growth factors and thus, enable the transformation to malignant tumors, or impair the repair of genetic mutations [17]. Radiation therapy itself may be a cause as it results in similar genetic damage.

Typically, a patient with angiosarcoma of the breast will present with a painless cutaneous lesion and blue-red skin discoloration resembling a hematoma [1,17]. It may be multifocal, typically involves a significant part of the breast, and is often associated with swelling, skin dimpling and thickening. The tumor size may vary and has been reported to range between 0.4 and 20 cm, with a mean tumor size of 7.5 cm [8]. In this case report, the clinical presentation was somewhat atypical as the tumor was small, not associated with edema or purple skin discoloration and showed low proliferation. However, despite being a low grade tumor, the characteristic *MYC* gene amplification was detected in this patient's tumor.

The diagnostic work-up for radiation-induced angiosarcoma includes imaging and biopsy. Imaging modalities include mammogram and ultrasound, but lesions can be occult on mammography, as was the case in this patient. MRIs are useful in defining disease extent but have low diagnostic sensitivity [10,11]. Incisional biopsy of the discolored skin and underlying mass is the most accurate and fastest way to obtain a diagnosis [10]. The hallmark findings of angiosarcoma microscopically are abnormal, pleomorphic, malignant endothelial cells. There may be well-differentiated areas, in which the endothelial cells form functioning vascular sinusoids that have areas of monocyte infiltration. In poorly differentiated areas, malignant endothelial cells form sheets of cells and have areas of hemorrhage and necrosis [20]. *MYC* amplification can be used as a prognostic indicator, as it was found to be associated

with an adverse prognosis. However, it is a highly specific but poorly sensitive marker for angiosarcoma, and a negative result would not exclude the diagnosis [21].

The treatment for angiosarcomas is surgical resection with mastectomy aiming at obtaining negative margins. Obtaining negative surgical margins is more important than the type of surgery, and the standard surgical procedure is mastectomy with negative margins [22]. However, studies following patients treated with radical surgery have noted that extensive recurrences can occur as soon as two months of surgery, and might occur in the chest wall flap [14].

The role of chemotherapy has not been clearly established. Most data came from retrospective case series studies or even case reports suggesting that angiosarcomas are relatively sensitive to taxanes and anthracyclines with initial overall response rate from 20% to 60% [23–26]. However, the relapse rate is high and overall survival is between 5 and 48 months [6,25]. A small study using hyperfractionated accelerated re-irradiation (HART) found that 79% of patients achieved disease control beyond the typical intervals to recurrence, suggesting that this treatment method may be more favorable than chemotherapy, however, it would be best to avoided in radiation-induced angiosarcomas [15].

Conclusions

In conclusion, this case illustrates an atypical presentation of radiation-associated secondary angiosarcoma, presenting with a small flat skin discoloration in the radiation field, not associated with a mass, edema, or other skin changes. Also, the tumor was low grade and was not detected on mammogram. A high level of suspicion should be exercised when patients who receive breast conservation surgery and radiation present with any skin discoloration. Continuous long-term surveillance and increasing both patient and physician awareness is also indicated.

Conflicts of interest

None.

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