Sporadic Case of Breast Angiosarcoma as a Complication of Radiotherapy Following Breast-Conserving Surgery for Invasive Ductal Breast Cancer

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Established Facts

- Angiosarcomas are highly aggressive and malignant blood vessel tumors.
- Rarely, angiosarcomas develop in the breast following conservative therapy, i.e. radiotherapy, to treat breast cancer.

Novel Insights

- Immunohistochemistry of an unusual breast tumor revealed high concentrations of CD31 and D2–40 molecules as well as Ki-67, which is pathognomonic for angiosarcoma.
- The presentation of this radiation-associated angiosarcoma is non-specific, making preoperative diagnosis difficult; therefore, a biopsy of any suspicious breast skin lesion after radiotherapy is recommended.
- Although this condition is not common, it is important to take it into consideration during treatment.

Keywords

Angiosarcoma · Breast-conserving surgery · Radiotherapy

Summary

Background: Angiosarcomas are highly aggressive and malignant blood vessel tumors. Rarely, angiosarcomas develop in the breast following conservative therapy, namely radiotherapy. **Case Report:** A 70-year-old female patient presented with dark purple discoloration of the skin of the right breast. 6 years earlier, the patient had undergone conservative surgery for invasive ductal carcinoma of the right breast. According to the breast-conserving surgery protocol, the patient had been treated with radiotherapy to the residual breast tissue. The patient's annual mammograms and ultrasound findings were nor-

mal. The skin lesion was superficially localized mostly at the border between the upper and lower medial quadrants of the breast (between 2 and 4 o'clock) and above the areola. The borders were uneven; the dimensions were 7 cm × 4 cm. The mammogram was classified as Breast Imaging Report and Data System (BI-RADS) 2. Ultrasound examination showed a well-vascularized structure, although the etiology was unclear. A tissue biopsy revealed angiosarcoma. The patient underwent radical simplex mastectomy. Following surgery, the patient underwent chemotherapy. Tests excluded metastases for a follow-up period of 5 years. **Conclusion:** Angiosarcomas that develop after radiotherapy following breast-conserving surgery are sporadic, but it is important to take this possible incident into consideration during treatment.

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Introduction

Angiosarcomas are highly aggressive and malignant blood vessel tumors which usually develop on the head and neck [1]. Other, less frequent, localizations include the liver and lungs. Angiosarcomas that develop in the breast following conservative therapy, namely radiotherapy to treat breast cancer, are exceedingly rare [2]. Due to this low incidence, which is less than 1% [2, 3], radiation-associated angiosarcoma (RAAS) represents a diagnostic challenge due to its benign presentation and skin changes that are easily attributed to radiation. Therefore, it is important to take any changes of the breast seriously and to consider RAAS as a differential diagnosis [4].

Case Report

A 70-year-old female patient presented with dark purple discoloration of the skin of the right breast. 6 years earlier, the patient had undergone conservative surgery for invasive ductal carcinoma of the right breast, with sentinel lymph node biopsy of the ipsilateral axilla, resulting in negative findings. According to the breast-conserving surgery protocol, the patient had been treated with radiotherapy to the residual breast tissue. Radiotherapy was executed using a linear accelerator. The standard dose received by the patient was 50 Gy plus a booster dose of 16 Gy at the tumor site (single doses of 200 cGy: 25 single doses + 8 single doses at the tumor site). Regular follow-ups and additional testing confirmed that the disease had not spread as metastases. The annual mammograms and ultrasound findings were normal.

Regarding the above-mentioned discoloration on the breast, the skin lesion was superficially localized mostly at the border between the upper and lower medial quadrants of the breast (between 2 and 4 o'clock) and above the areola. The borders were uneven; the dimensions were 7 cm × 4 cm (fig. 1). On palpation, the lesion was solid in consistency and fixed. Breast trauma and anticoagulant therapy were excluded. The patient was referred for a mammogram, which was classified as Breast Imaging Report and Data System (BI-RADS) 2 with no suspicious lesions. Ultrasound examination showed a well-vascularized structure, although the etiology was unclear. Therefore, a tissue sample was taken

Fig. 1. Breast angiosarcoma. The visible skin lesion is superficially localized at the border between the upper and lower medial quadrants of the breast (between 2 and 4 o'clock) and above the areola. The borders are uneven; the dimensions are 7 cm × 4 cm.

under local anesthesia due to the superficial localization of the lesion. Histopathologic examination of the sample found the peripheral zone around the lesion to be negative. Due to rapid superficial spreading of the lesion, the biopsy was repeated. A sample was taken from the central area of the lesion; hemostasis was achieved by electrocoagulation after profuse bleeding. Histopathological analysis showed pathological blood vessels, abnormal and abundant vascularization, and malignant mesenchymal cells. An additional immunohistochemical analysis showed significant levels of vascular endothelium markers, namely CD31 molecules as well as D2-40 and Ki-67 (69%). All test results indicated a diagnosis of angiosarcoma. The patient underwent radical surgery or, more precisely, right-sided simplex mastectomy (fig. 2). Macroscopically, the removed breast measured 38 cm × 30 cm × 8 cm and the section of skin amounted to 34 cm × 19 cm. The purple discoloration of the breast skin measured 8.5 cm × 7 cm, which corresponded to the size of the tumor on the transverse section of the breast. Radical removal of the tumor was confirmed by clean surgical margins. Histologically, the tumor was located directly below the epidermis, infiltrating the dermis and subcutaneous adipose tissue. The postoperative course ran smoothly with no complications and the wound healed normally. The surgical drain was removed on the 10th postoperative day due to prolonged drainage from the wound. The stitches were removed on the same day. After surgery, the patient underwent chemotherapy. All test results were negative, and metastasis was excluded. A thoracic radiogram and other systemic evaluations (positron emission tomography combined with computed tomography (PET-CT)) for distal metastases did not show any suspicious lesions in the lungs or other organs for a follow-up period of 5 years.

Discussion

The etiology of breast angiosarcomas remains controversial, with some scientists supporting the theory that many of the previously presented cases are actually metaplastic variants of a primary cancer [5]. Angiosarcoma of the breast occurs in both a primary form without a known precursor and a secondary form that has been associated with a history of irradiated breast tissue [6], as it has been shown in this case report.

The radiation dose of 50 Gy plus a booster dose of 16 Gy to the tumor received by the patient correlates with the increased inci-

Fig. 2. Breast specimen. The patient underwent simplex mastectomy, and the breast specimen is shown. Pathohistological examination confirmed that the tumor was radically removed.

dence of angiosarcoma induced by irradiation [7]. Clinically, angiosarcomas typically manifest as subcutaneous or cutaneous lesions, often painful when palpated, with uneven borders and purple discoloration that may be mistaken for hematoma, atypical telangiectasis, or a benign variant of blood vessel tumor [4, 8]. Based on clinical presentation, mammography was indicated to exclude relapse of the primary disease. The mammogram was classified as BI-RADS 2 and did not suggest a tumor, and this is typical of angiosarcoma [4] due to its superficial localization. After breast trauma or another benign form of the disease was excluded, the patient underwent further diagnostic evaluation including a biopsy of the lesion. In the biopsy material, atypical tumor cells were not found due to inadequate sampling [4]. The purple discoloration on the breast increased rapidly [9], and a few weeks later, another biopsy was performed from the center of the lesion. In this biopsy material, pathological vascularization was found, along with characteristic malignant mesenchymal cells, pathological mitoses, and inflammatory cells, which is typical of malignant blood vessel tumors [3]. From the same tissue sample, immunohistochemical analysis showed high concentrations of CD31 and D2-40 molecules as well as Ki-67, which is highly specific for angiosarcoma [6, 10, 11]. After confirmation of the diagnosis, the patient underwent a simplex mastectomy, which is the primary treatment of these tumors [12]. Pathohistological analysis confirmed clean surgical margins. Still, due to the aggressive nature of the tumor, this may not firmly indicate successful treatment. Therefore, the patient underwent an additional chemotherapy [13]. Due to the size of the tumor, the high recurrence rate, and the great metastatic potential

[14], regular follow-ups were recommended every 6 months after surgery. There were no signs of relapse during a period of 5 years.

All things considered, although RAASs are rare tumors, a higher incidence of this type of tumor can be expected in the future due to the increasing popularity of breast-conserving surgery of malignant glandular tissue breast tumors followed by mandatory high-dose radiation therapy, which is a direct trigger for the development of angiosarcoma. Regardless of normal test results, a successful outcome was unclear in this case due to the high malignancy of this type of tumor. Nevertheless, further test results did not show any lesions or metastases during the 5-year postoperative period. This is a tremendous length of time considering the fact that the mean survival time is 2 years [14].

In conclusion, angiosarcomas that develop after radiotherapy following breast-conserving surgery for invasive breast carcinoma are highly sporadic cases. They present as a non-specific breast skin lesion, making preoperative diagnosis difficult. Therefore, a biopsy of any suspicious breast skin lesion after radiotherapy is recommended, even in cases where the radiological diagnostic evaluation does not concur with the physical examination (as in this case where the mammogram was classified as BI-RADS 2). Although this condition is not common, it is important to take it into consideration during treatment.

Disclosure Statement

All of the authors declare that there is no conflict of the interest.

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