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Metachronous Bilateral Angiosarcoma Post Breast Cancer Therapy: A Unique Case Report

Bekkouche Soukaina*, Najem Salma, Naciri Sarah, Mrabti Hind, Saber Boutayeb and Errihani Hassan

Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco

Abstract

Breast angiosarcoma is a severe and rare complication in the breast-preserving management of breast cancer through surgery and radiotherapy. Due to the few studies, there is no clear consensus regarding the optimal oncological management of radiation-induced angiosarcoma. However, aggressive surgical removal remains the gold standard. A 53-year-old woman had a history of medullary triple negative, metachronous bilateral breast cancer. The left tumor was treated with conservative surgery in 2000, while the right tumor was treated with radical surgery in 2004, followed in both by anthracycline-based chemotherapy, radiotherapy and brachytherapy. 21 years later after the first surgery, a locally advanced tumor appeared in her left breast. Radiation-induced angiosarcoma was impossible to diagnose with a core needle biopsy, which revealed an undifferentiated tumor. The patient received neoadjuvant chemotherapy before undergoing left mastectomy surgery and the pathological analysis yielded a diagnosis of angiosarcoma. 2 years later, a nodule appeared over the right mastectomy scar. A wide excision removing the pectoral muscle was carried out, revealing a contralateral breast angiosarcoma. Given the recurrence, the patient received adjuvant chemotherapy, despite the lack of a prospective trial study to determine whether adjuvant chemotherapy for resectable angiosarcoma should be recommended. Secondary breast angiosarcoma is a very rare and late malignant tumor induced by radiation used for the treatment of early breast cancer. Surgery is the cornerstone of therapy, however, adjuvant chemotherapy may be considered due to the risk of recurrence and distant metastasis. Prospective trials are required for more precise therapeutic strategies for this iatrogenic malignancy.

Keywords: Breast cancer • Radiation-induced angiosarcoma • Radiotherapy

Introduction

Angiosarcoma of the breast is an uncommon malignant neoplasm derived from endothelium that accounts for approximately 1% to 2% of all soft tissue sarcoma. This condition can manifest either as a primary occurrence or as a secondary result of breast tissue irradiation or chronic lymphedema following mastectomy. Characterized by polymorphic, nonspecific clinical and radiological features, angiosarcoma poses challenges in accurate diagnosis [1].

Primary angiosarcomas arise spontaneously, while secondary angiosarcomas develop in response to biological insults such as radiation therapy [2]. Although the incidence of radiation-induced breast angiosarcoma is low, with a reported cumulative incidence of 0.09% at 15 years post-diagnosis of primary breast cancer receiving radiation therapy [3], the growing use of breast conservation surgery and radiation therapy in breast cancer management may contribute to an increasing occurrence of radiation-induced breast angiosarcoma.

Surgical resection remains the preferred treatment for nonmetastatic angiosarcoma. However, despite this, there is limited understanding or consensus regarding optimal therapeutic approaches and outcomes [4].

***Address for Correspondence:** Bekkouche Soukaina, Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco; Tel: + 212642280830, E-mail: soukaina.bekkouche@gmail.com*

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Case Presentation

It's a 53-year-old woman with a history of metachronous triple-negative medullary breast cancer, who developed bilateral angiosarcoma.

Initially diagnosed in 2000 with left breast medullary triple-negative cancer, she underwent breast-conserving surgery and subsequent adjuvant anthracycline chemotherapy, radiotherapy and brachytherapy for a pT2N1M0 tumor. The external radiotherapy technique used was 3D conformal radiotherapy; the patient received 50 Gy in 25 sessions of 2 Gy each, as well as two brachytherapy sessions of 5 Gy. In 2004, she experienced a recurrence in her right breast, requiring radical surgery and similar adjuvant treatments.

Twenty-one years after her initial diagnosis, in June 2021, she showed up in consultation with a rapidly enlarging tumor in her left breast, classified as T4dN0M0. Biopsy revealed an undifferentiated, crushed tumor, with immunohistochemical analysis ruling out primary lymphoma, sarcoma, or triple-negative tumor.

Abdominal, pelvic and thoracic CT-Scan revealed two sizable masses in the left breast invading the skin with homolateral axillary lymphadenopathy. However, no distant metastases were observed on bone scintigraphy.

She underwent 6 cycles of neoadjuvant chemotherapy with PACLITAXEL CARBOPLATIN followed by a left mastectomy with Patey procedure and axillary lymph node dissection. Histopathological analysis revealed high-grade angiosarcoma, with immunohistochemistry showing positive anti-CD31 and negative anti-CKAE1/AE3 antibodies.

In July 2023, the patient presented with a mass at the scar site of her right mastectomy. Clinically, the skin appeared bluish and adherent to the firm mass. Breast ultrasound identified a 16 × 15 mm pre pectoral lesion, categorized as BI-RADS 5. PET scan confirmed nodular hypermetabolism in the right pre pectoral area, with no distant metastasis (Figure 1). Subsequently, she underwent wide excision (parietectomy), with negative surgical margins.

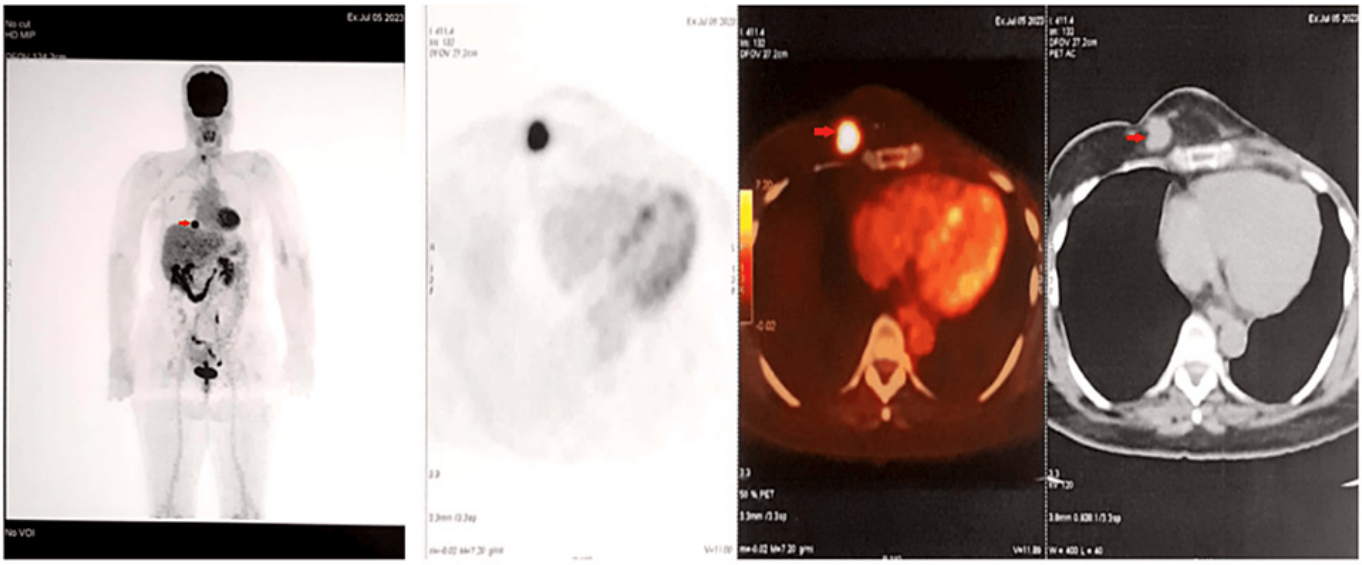

Figure 1. Pet scan showing prepectoral nodular hypermetabolism located in the right prepectoral region (SUV max 12,94), with no evidence of distant metastasis.

Anatomopathological examination of the specimen revealed a malignant spindle cell tumor with an immunohistochemical profile consistent with high-grade angiosarcoma, positive for CD31, CD34 and ERG antibodies, potentially indicating malignancy secondary to radiation therapy. Adjuvant chemotherapy with IFOSFAMIDE ETOPOSIDE was administered due to the recurrence.

Discussion

Radiation-induced sarcoma after breast cancer is a rare oncological complication, occurring in 0.2% of all irradiated breast cancers. The development of this malignancy has been reported to have a latency period ranging from three to twenty years [5,6].In a comprehensive study involving 13,472 patients, Kirova YM, et al. revealed that the cumulative occurrence of breast radiation-induced angiosarcoma was 0.07% at 5 years, 0.27% at 10 years and 0.48% at 15 years. This underscores the necessity for extended monitoring of breast cancer survivors after radiation therapy [7].

Secondary angiosarcoma typically manifests in patients with an average age of 67.5 years, contrasting with primary (*de novo*) angiosarcoma, which predominantly affects younger women with an average age of 40 years [8,9].

Metastasis in radiation-induced breast angiosarcoma commonly occurs in the lungs and liver, often concomitant with or shortly after local recurrences [10]. Tumor size at diagnosis is a major prognostic factor [11].

The diagnosis from fine needle aspiration cytology or the core needle biopsy is very difficult, requiring often excisional biopsy [4]. That was the case in our patient at her first relapse, diagnosis of angiosarcoma was made only after surgery.

Immunohistochemistry analysis typically reveals angiosarcomas as positive for antigens associated with CD31, CD34 and occasionally podoplanin, aiding in diagnosing less-differentiated tumors [12]. While the expression and amplification of c-MYC is demonstrated in radiogenic angiosarcoma of the breast [13].

Currently, there is still no definitive agreement on the most effective approach to oncological management of breast radiation-induced angiosarcoma.

The preferred treatment is surgery involving the removal of the lesion with an adequate safety margin. Mastectomy is the preferred surgical procedure, as it is more likely to achieve R0 status, defined as a free margin greater than 2 cm. The necessity of axillary dissection remains debatable, given the infrequent occurrence of nodal involvement [5].

Due to the absence of randomized controlled trials and prospective clinical studies assessing the effectiveness of chemotherapy or radiotherapy, the efficacy of these treatment modalities remains uncertain. In cases of inoperable or advanced disease, chemotherapy is recommended. Some studies propose that anthracycline-based chemotherapy, utilizing either doxorubicin or epirubicin with ifosfamide, could improve both Disease-Free Survival (DFS) and overall survival [14]. Other studies suggest that angiosarcomas are particularly sensitive to taxanes and liposomal doxorubicin, making their weekly administration an alternative to traditional anthracycline treatment with ifosfamide [15].

Although the risk of radiation-induced sarcoma after breast cancer cannot be eliminated, careful planning of radiation therapy to minimize exposure to surrounding healthy tissues and continuous monitoring of patients post-treatment is crucial. Proton therapy has been shown to precisely target tumors, thereby protecting the function of surrounding normal tissues and reducing side effects and secondary cancers [16].

One study indicated that proton therapy reduces soft tissue exposure outside the CTV and compared to 3DCRT and IMRT, the risk of soft tissue sarcoma post-breast cancer proton therapy is lower [17].

A systematic review conducted by Depla AL, et al. involving 222 patients, demonstrated improved local control when re-irradiation was administered after surgery. However, no observed benefit in terms of overall survival was noted after radiotherapy [18].

Conclusion

Radiation-induced breast angiosarcoma is an uncommon malignant tumor, with a poor prognosis and presents therapeutic management difficulties due to the lack of definite standardized treatment. It is anticipated to rise as a result of the expanded utilization of radiation therapy and the extended survival of individuals with breast cancer, hence the need for prolonged monitoring.

Disclosures

Conflict of interest

No disclosures or conflicts of interest will be reported.

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Human subjects

Consent was obtained or waived by the participant in this study.

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