CASE REPORT

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Early-Onset Radiation-Induced Angiosarcoma of the Breast: A Case Report and Literature Review

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ABSTRACT

Secondary breast angiosarcomas are rare tumors, and more likely to occur after breast-conserving surgery. They are commonly a late adverse event of radiation therapy that typically presents after ten years of treatment. We report a case of radiation-induced breast angiosarcoma presenting as early as 30 months following the completion of postoperative radiotherapy for breast cancer. Angiosarcoma has a potentially significant risk for local and metastatic recurrence despite total mastectomy. Therefore, a low threshold for suspicion is essential for prompt diagnosis and appropriate treatment.

Keywords: Radiation-induced angiosarcoma; breast-conserving surgery; breast cancer, radiation therapy, secondary malignancy

KEY POINTS

- Reporting an early onset of radiation-induced angiosarcoma after breast-conserving surgery.
- To raise the awareness among breast clinicians and promote early detection of radiation-induced breast angiosarcoma (RIAS).
- To emphasize the importance of early diagnosis and treatment of RAIS.

Introduction

Angiosarcoma is a rare type of cancer that has a considerable impact on patients' prognosis. It is an aggressive malignant tumor of the vascular endothelium. It accounts for less than 1% of all soft tissue breast tumors and tends to be aggressive with a high risk of local recurrence and distant metastases (1). The most common distant metastasis is to the lungs. However, multiple studies have shown metastasis to the cecum, tonsils, buttocks, oropharynx, and heart (1). While the first case of breast angiosarcoma was presented in 1907 by Borrman, the rarity of the disease has limited the assessment of prognostic factors and treatment methods (2). Multiple studies have linked histological features and growth patterns to outcomes.

Breast angiosarcoma is categorized into primary and secondary types. Primary angiosarcoma of the breast occurs de novo with no identifiable predisposing factors. It typically presents as a rapidly growing palpable mass with or without skin changes. It usually affects women between the ages of 30 and 50 years (2).

On the other hand, secondary angiosarcoma is mostly seen in elderly patients between the ages of 60 and 70 years, presenting as painless ecchymotic skin lesions with or without ulceration (1, 3).

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Secondary angiosarcoma develops secondary to underlying risk factors, most commonly, after exposure of the breast to ionizing radiation. Radiation-induced angiosarcoma (RIAS) usually develops 7–10 years following radiation therapy to the breast and/or chest wall (1, 2). It frequently appears at the edge of radiation fields where doses and tumor necrosis may be heterogeneous (1). Secondary angiosarcoma may also develop secondary to chronic lymphedema, usually after breast surgery and lymph node dissection. This condition is known as Stewart-Treves syndrome (1). There is a higher incidence of secondary angiosarcoma than primary angiosarcoma because of the availability of early detection of breast cancer and the increased use of breast conservation therapy and adjuvant radiotherapy in the past 30 years. Other predisposing factors for secondary breast angiosarcoma include pathogenic mutations, e.g., *cellular-myelocytomatosis oncogene* (*c-MYC*) amplification, which is directly associated with secondary breast angiosarcoma but to a lesser extent with primary angiosarcoma (4). Also, alterations in FLT4, HRAS, KMT2D, and CRKL are seen in RIAS (4).

Diagnosis can be established by core needle biopsy (CNB), as imaging is often equivocal. Excessive bleeding after CNB could indicate the presence of a highly vascular tumor (2). It is also recommended to perform a skin punch or incisional biopsy in case of secondary angiosarcoma (5). Histopathological analysis of the lesions shows irregular vascular formations with hyperchromatic and irregular nuclei (2). The diagnosis can be confirmed with immunohistological staining markers like CD31, VIII, Fli1, and CD34 (2).

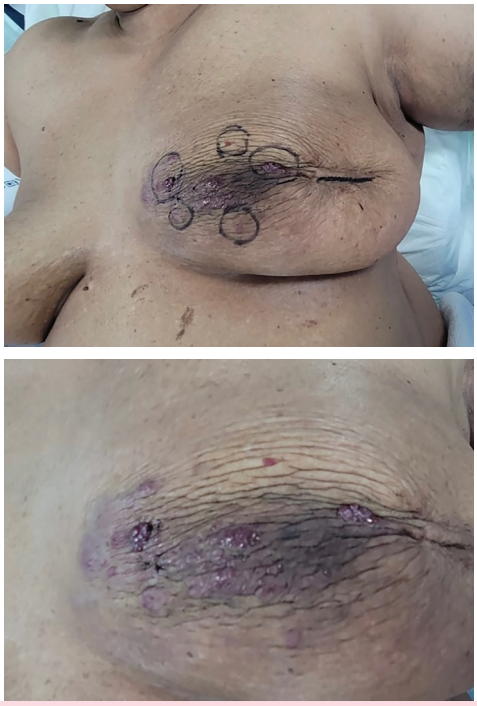

Figure 1. Left breast showing multiple purplish skin lesions (angiosarcoma)

The purpose of reporting this rare case of early-onset RIAS of the breast is to raise the awareness among breast surgeons and oncologists, promote early detection, and discuss the latest guidelines for managing secondary angiosarcoma of the breast.

Case Presentation

Our patient is a 72-year-old female with multiple medical comorbidities and a past medical history of left breast cancer, that was treated with wide local excision and axillary lymph node dissection followed by adjuvant whole breast irradiation. Radiotherapy was in the form of 40.05 Gy in 15 fractions encompassing the whole left breast and regional lymphatics with deep inspiration breath hold technique. It was delivered between February and March 2021. The patient was placed on aromatase inhibition therapy thereafter.

In September 2023, the patient attended the breast surgical oncology clinic with a complaint of left breast skin changes. The left breast examination (Figure 1) revealed a healed radial lumpectomy scar at 3:00 position with no underlying palpable masses. Skin hyperpigmentation was observed at 9:00, associated with multiple cherry-like, small, purple skin nodules around the areola, with no underlying masses. There was no axillary or supraclavicular lymphadenopathy. There was no evidence of breast or upper limb lymphedema. The rest of the examination was unremarkable.

Diagnostic Work Up

Bilateral Breast Mammogram

Mammography revealed bilateral nipple retraction. Left breast showed skin thickening. A lesion with lucent center was identified in the left breast upper outer quadrant (UOQ). Left retro-areolar suspicious calcifications were of note. There was no suspicious axillary lymphadenopathy. The left breast was labelled as Breast Imaging Reporting and Data System (BIRADS 4) (Figure 2).

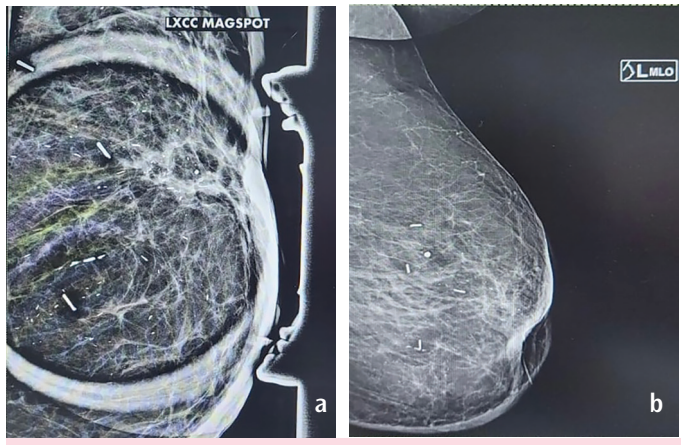

Figure 2. Mammogram of the left breast craniocaudal magnification view (a) showing central microcalcifications, and mediolateral oblique view (b) showing skin thickening

Bilateral Breast Ultrasound

The ultrasound showed evidence of left skin thickening and mild subcutaneous edema, more prominent in the area of skin nodules. A thick wall, poorly defined area of fat necrosis measuring about 17x14 mm was observed in the UOQ, corresponding to the mammographic finding. No significantly enlarged axillary lymph nodes were noted. The left breast was reported as BIRADS 4.

Breast Biopsy

The temporary unavailability of the stereotactic mammogram biopsy at that time precluded the ability to biopsy the left breast BIRADS 4 microcalcification. However, a skin biopsy was determined appropriate to obtain a histological assessment of those skin lesions. Left breast multiple skin punch biopsy showed infiltrative vasoformative nodular growth with focal vasoformative differentiation and solid spindle cell irregular nodules with nuclear atypia and frequent mitosis. The immunohistochemical (IHC) stains showed strong CD34, CD31, and VIMENTIN positivity. In addition, SMA was positive in focal areas. The Ki-67 was 40%. The other IHC stains were all negative, including Caldesmon, Pankeratine Desmin, Calponin, EMA, S100, and CK AE1/AE3. The histopathological examination confirmed the diagnosis of angiosarcoma (Figure 3).

Metastatic Work Up

PET-CT scan was performed to rule out nodal or distal metastasis. It showed fluorodeoxyglucose avid skin enhancement of the medial aspect of the left breast, with no underlying parenchymal enhancement. There was no evidence of nodal or distal metastasis (Figure 4).

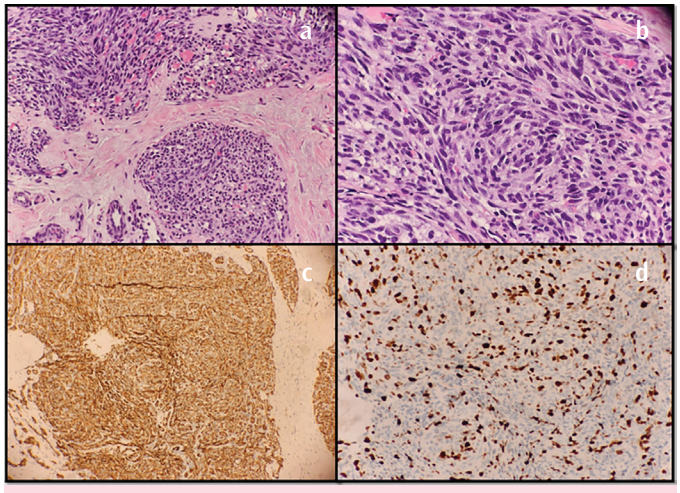

Figure 3. Post-radiation angiosarcoma; intermediate grade. (a) Hematoxylin and eosin shows infiltrating vasoformative spindle cell growth in the deep dermis, (b) High power field shows intermediate-grade solid areas of spindle cell growth, (c) Immunohistochemistry shows diffusely positive CD31. (d) High proliferative activity confirmed through high Ki-67 staining

Course of Management

The case was discussed in both breast and sarcoma multi-disciplinary tumor boards as a radiation-induced secondary angiosarcoma of the breast with no evidence of distal metastasis and no evidence of breast cancer recurrence. Genetic testing was recommended due to the very early onset of disease occurrence. The tumor boards recommended mastectomy as the primary treatment. Axillary surgery was not recommended due to the lack of clinical evidence of nodal metastasis and the previous history of axillary dissection for breast cancer. In the absence of distal metastasis, National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology guidelines recommend adjuvant chemotherapy if the final pathological size of the tumor is more than 5 cm (6, 7). The patient underwent simple skin-reducing mastectomy, with no reconstruction, in an attempt to excise most of the radiated skin and reduce the risk of recurrence.

The final pathology examination reported post-radiation angiosarcoma involving the skin, 4 cm in maximum dimension, intermediate grade (stage 2A). No necrosis was identified. All surgical margins were negative for tumor cells. Histological examination of the breast tissue showed post-surgical scarring, with no evidence of mammary invasive carcinoma, ductal carcinoma *in situ*, or atypia.

Based on the final diagnosis, no adjuvant treatment was offered for the sarcoma. The patient continued receiving adjuvant aromatase inhibitor for the breast cancer.

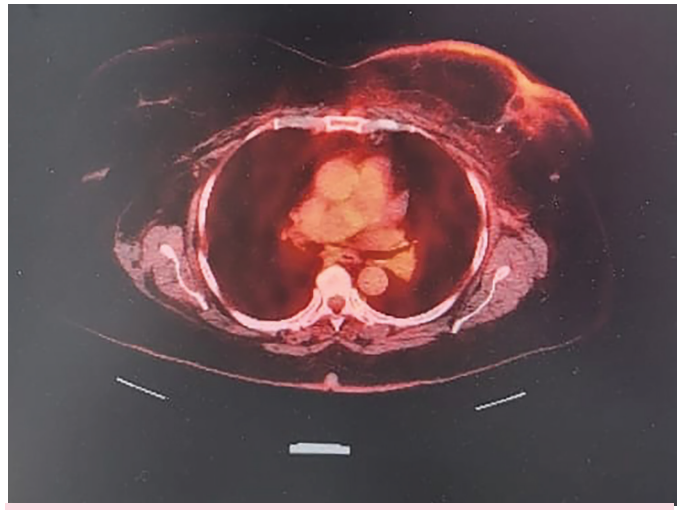

Figure 4. Positron emission tomography-computed tomography of left breast showing fluorodeoxyglucose-avid skin enhancement of the medial aspect of the left breast

Follow-Up

The patient is under surveillance and she remains disease free of both RIAS and breast cancer to date.

Genetic Testing

A hereditary cancer comprehensive panel of 158 genes test was performed for this patient. It showed no pathogenic variants that may explain the clinical phenotype.

Ethical Considerations

A written informed consent was obtained from the patient for publication of this case report and any accompanying images. This was done in accordance with institutional guidelines, the patient's information/identity was kept anonymized and confidential to ensure privacy.

Discussion and Conclusion

In this case, we report the earliest onset of radiation-induced secondary angiosarcoma of the breast described in the literature, occurring approximately 2.5 years after adjuvant whole-breast radiotherapy. To our knowledge, the shortest latency period previously reported was three years following radiation, with a median latency period of 6.5 years (5).

We conducted a literature review in MEDLINE and PubMed to identify papers published in English over the past 10 years (between 2015 to 2025), about radiation- induced secondary angiosarcoma of the breast, which are summarized in Table 1 (1, 3, 8-15). In all reported series, similar to our case, RIAS developed after whole-breast radiation therapy. Most patients were postmenopausal and diagnosed with RIAS between 50

Table 1. Previously reported RIAS

Study	Age (Y)	Breast cancer surgery	Radiation therapy	Radiation type	Onset of RIAS (years)*	RIAS grade	Surgical treatments	Systemic treatments	Prognosis
Wyer et al. (12) (2025)	56	BCS	WBR	CFRT	5	NA	Mastectomy+extensive skin resection+portions of pectoralis major muscle+SLNB	None	NA
Parisi et al. (10) (2024)	57	BCS	WBR	CFRT	5	Intermediate	Mastectomy	None	Recurrence at 18 months; received chemotherapy+ radiation. Died 6 months later
Kawata et al. (13) (2024)	70	BCS	WBR	HFRT	6	NA	Skin tumor resection	Chemotherapy	No recurrence
Caterino et al. (1) (2023)	58	BCS	WBR	CFRT	7	High	Mastectomy and ipsilateral node sampling	None	Recurrence after 2 years; underwent excision +adjuvant chemotherapy
Yoshino et al. (3) (2023)	70	BCS	WBR	CFRT	10	Intermediate	Mastectomy	Chemotherapy	NA
Rhoul et al. (9) (2023)	52	BCS	WBR	CFRT	3	NA	Mastectomy	Chemotherapy	No recurrence
Retter et al. (11) (2022)	67	BCS	WBR	CFRT	10	High	Mastectomy	None	No recurrence
Layton et al. (15) (2022)	68	BCS	WBR	HFRT	3	NA	Mastectomy	Radiotherapy	NA
Kacen et al. (14) (2021)	60	BCS	WBR	HFRT	4	NA	Mastectomy	Chemotherapy	NA
Shiraki et al. (8) (2020)	72	BCS	WBR	CFRT	5	High	Mastectomy+extensive skin resection+skin graft	None	Recurrence after 1 year; underwent excision +chemotherapy. Died 32 months after surgery

N: Number of cases reported; RIAS: Radiation-induced angiosarcoma; BCS: Breast conserving surgery; RT: Radiotherapy; WBR: Whole breast radiation; HFRT: Hypofractionated radiotherapy; CFRT: Conventionally fractionated radiation therapy; SLNB: Sentinel lymph node biopsy; N/A: Not available; *: Since radiotherapy

and 70 years of age, a similar age group to our patient. The typical latency period ranges from 3 to 10 years after irradiation. Our patient had the shortest latency period of 2.5 years, compared to reported cases. Mastectomy was the treatment of choice in almost all reported cases, as well as in our case, to achieve a wide surgical margin. In the studies that reported follow-up, recurrence of angiosarcoma was observed within 2 years of surgery and was associated with a poor outcome. After 30 months of follow up, our patient remains disease-free despite not receiving adjuvant chemotherapy or radiation therapy. This could be attributed to detection at an early stage, when the lesion was small in size and of low grade.

There have been multiple suggested theories regarding the mechanism of radiation-induced angiosarcoma. Some studies suggest that ionizing radiation alters DNA structure, damaging the genome and leading to instability and cancer-related gene mutations, thereby promoting tumorigenesis (16). Multiple studies have reported many genetic alterations associated with angiosarcoma, including amplification of the chromosome 8q24 mapping, *TP53* gene expression, MYC oncogene inactivation, and alteration in *POT1, RAS, ATM, APC*, and many more (16). The MYC oncogene is subdivided into *c-MYC*, L-MYC, and N-MYC (16). They are essential in regulating cell growth, maturation, and cell death (16). Many studies have shown that MYC amplification is more likely to be present in secondary angiosarcoma than primary angiosarcoma (16). This may aid in distinguishing the primary cause of angiosarcoma. In our case, the patient's genetic test showed no pathogenic variants that may explain the clinical phenotype.

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant disorder that affects the TP53 (17). It was reported in 1969 by Li and Fraumeni as a remarkable cancer predisposition syndrome (17). It is known to highly predispose patients to leukemia, breast cancer, soft tissue sarcoma, brain tumors, and adrenocortical cancer (17). RIAS risk increases by 16-fold in patients with LFS, through radiogenetic mutations. The *p53* gene is crucial in DNA repair, cell differentiation, apoptosis, and cell cycle arrest (17). Moreover, it was noted that prominent expression of p53 and MDM-2 proteins correlates with increased vascular endothelial growth factor (VEGF) expression, which is observed in approximately 80% of angiosarcomas. Alterations in the VEGF receptors, either by mutation or amplification, can lead to the development of angiosarcoma and is associated with worse overall survival (16). *CHEK2* gene mutation has also been reported in LFS (16). Therefore, for patients with LFS who develop breast cancer, many physicians recommend mastectomy over breast conservative surgery to avoid radiation exposure and risk of secondary malignancies such as angiosarcoma.

The diagnosis of breast angiosarcoma can be challenging as imaging is deemed to be nonspecific. It has been reported that 33% of mammary angiosarcomas present with normal mammograms (18). On magnetic resonance imaging, angiosarcoma appears as a low T1 signal and prominently high T2 signal lesion, and the dynamic phase shows early staining followed by persistent staining. Approximately 37% of FNA and CNB results can be false-negative (18). Tumor histological grade is classified into three groups: a) low-grade, vascular channels that anastomose to invade the surrounding breast tissue; b) intermediate-grade, characterized by increased mitotic rate and solid neoplastic vascular growth; c) high-grade lesions that are composed of necrosis, sarcomatous areas, infarction, and hemorrhage (18). The tumor in our patient did not demonstrate any necrosis or infarction, and was labeled as intermediate grade. Certain immunohistochemistry markers may be used to confirm the diagnosis, such as CD31, VIII, Fli1, and CD34, or to differentiate between primary and secondary angiosarcoma in the absence of known risk factors. For example, MYC amplification can be identified in 55% of primary angiosarcoma and up to 100% in secondary angiosarcoma. The loss of H3K27me3, an epigenomic chemical marker, has been reported as a valuable tool in the diagnoses of secondary angiosarcoma (3). In this case report, the IHC stains were strong for CD34, CD31, and VIMENTIN positivity, which confirmed the diagnosis of RIAS.

There is no standard staging or grading system for angiosarcoma, due to the different subtypes, locations and organs of origin. The American Joint Committee on Cancer (AJCC) Staging Manual uses a complex system that includes tumor size (T), regional lymph node involvement (N), distant metastasis (M), and histological grade (G), then further divides the primary tumor according to the tumor depth in relation to deep fascia; "a" for superficial tumors and "b" for deep tumors, then categorizes it into anatomic stage or prognostic group. The AJCC TNM system is difficult to apply in staging soft tissue angiosarcoma, because of the different subtypes and the dispersed anatomical locations. The Fédération Nationale des Centres de Lutte Contre le Cancer is a French grading system that looks into tumor differentiation score, mitotic score, and necrosis score (19). Based on the French system, the sarcoma stage in our patient was 2A.

There are no specific guidelines for the management of breast angiosarcoma. However, there are two management guidelines for other soft-tissue sarcomas that are published by the European Society for Medical Oncology and the NCCN (6, 7). Both guidelines for soft tissue sarcoma are comparably similar, and categorize the recommendations based on the AJCC stage.

The mainstay of treatment of breast angiosarcoma is surgical resection. It is essential to ensure a negative margin of at least 2–4 cm (5). Residual tumors after resection may reduce survival.

Our patient underwent a simple mastectomy to enable wide margin excision at the skin level. However, a 54–92% recurrence rate has been reported after negative-margin resection (5). Lymph node metastasis is rare. As a result, axillary surgery is not necessary (2). A prospective study showed that high-grade tumors less than 5 cm have a low recurrence rate with surgery alone (7). This finding supports the NCCN guideline recommendation to omit chemotherapy in tumors <5 cm if widely respected (7). Therefore, our patient did not receive adjuvant chemotherapy. The role of adjuvant treatment in breast angiosarcoma is not well established. It is, however, reported that chemotherapy may play a role in high-grade tumors and metastatic tumors (14). The most commonly used chemotherapies are paclitaxel, docetaxel, and doxorubicin. Paclitaxel is usually recommended in unresectable and metastatic angiosarcoma, as studies have shown good outcomes with its use (8). Also, bevacizumab (anti-VEGF antibody) and pazopanib (tyrosine kinase inhibitor) are used as second-line therapies (8).

The prognosis of RIAS is generally poor. Angiosarcoma, in general, shows a five-year recurrence-free survival rate of only 33% and the median survival is usually two years (16). Multiple factors contribute to the poor prognosis of angiosarcoma, such as tumor size (>5 cm), older age (>60 years), histological grade of the tumor, positive surgical margins, multiple skin lesions, and distant metastasis (5). The early recognition of the disease in our patient ensured the diagnosis at an early stage and favorable disease characteristics that are likely to improve her prognosis.

Radiation-induced secondary angiosarcoma of the breast is a rare malignant tumor with a very poor prognosis. This case study showed that the disease can onset as early as within the first three years after radiotherapy. Therefore, physicians should have a low suspicion index for skin lesions in women with a prior history of radiotherapy, as prompt diagnosis at earlier stage may improve prognosis.

Ethics

Informed Consent: A written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., K.A., F.A., A.D., J.A.; Concept: S.A., J.A.; Design: S.A., J.A.; Data Collection or Processing: S.A., J.A.; Analysis or Interpretation: S.A., K.A., F.A., A.D., J.A.; Literature Search: S.A., J.A.; Writing: S.A., K.A., F.A., A.D., J.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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