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Multidisciplinary Management of Radiation-Induced Breast Angiosarcoma: A Two-Case Series

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Background	Radiation-induced angiosarcoma (RIAS) is a rare, aggressive malignancy with a poor prognosis, typically arising years after adjuvant radiotherapy for breast cancer. Due to its low incidence, standardized treatment regimens are lacking.
Summary	We present two cases of RIAS managed with a multidisciplinary approach, highlighting the importance of coordinated care throughout the disease course. Both patients developed RIAS years after initial treatment and required complex surgical management. These cases provide a framework for navigating the complexities of RIAS treatment and emphasize the need for ongoing research to optimize outcomes for this challenging disease.
Conclusion	RIAS presents significant therapeutic challenges due to its rarity, variable presentation, and aggressive behavior. Optimal management necessitates a multidisciplinary approach involving surgical oncology, plastic surgery, pathology, and medical oncology, emphasizing preoperative planning for wound closure and adjuvant therapy considerations.
Key Words	radiation-induced angiosarcoma; breast cancer; breast radiation

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Case Description

Case 1

A 65-year-old postmenopausal female with a history of right breast cancer (diagnosed in 2001, treated with breast-conserving therapy, adjuvant cyclophosphamide/methotrexate/fluorouracil, and 5 years of anastrozole) presented to an outside clinic in 2015 with purple discoloration of the right nipple, raising initial concern for Paget's disease. Core needle biopsy revealed a "deep dermal infiltrate of atypical epithelioid cells" but was diagnostically inconclusive. Mammography demonstrated peri-areolar skin thickening (BI-RADS 4). Due to progressive skin changes over the following month, she was referred to our clinic. Excisional biopsy performed by the breast surgery team confirmed angiosarcoma, with immunohistochemical staining positive for CD31 and CD34. Staging CT of the chest, abdomen, and pelvis (CT C/A/P) showed no evidence of metastatic disease. Right mastectomy with primary closure was subsequently performed. Final pathology identified a 3.5 × 2.0 × 1.4 cm intermediate-grade angiosarcoma with negative margins (>2 cm). Postoperatively, the patient was referred to medical oncology for follow-up, including physical examination and chest CT every three months.

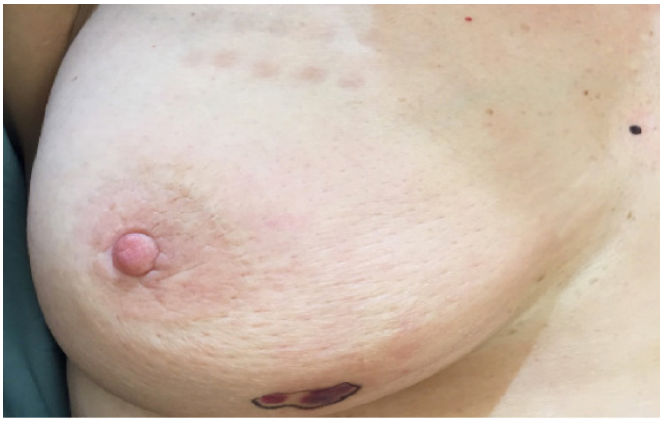
Approximately two years post-mastectomy, the patient presented with a progressively enlarging, non-mobile, subcutaneous nodule near the mastectomy scar, concerning for recurrence. Biopsy confirmed recurrent angiosarcoma. While CT C/A/P showed skin changes of the right chest, it was otherwise negative for distant metastases. Chest MRI also showed no evidence of metastatic disease. Preoperative planning for chest wall resection was conducted by breast and plastic surgery. The planned resection area was marked preoperatively, incorporating prior radiation tattoos and excision scars with a 2 cm gross margin.

Following wide excision of the right chest wall skin and subcutaneous tissue, plastics partially closed the wound with an abdominal tissue advancement flap and application of a negative pressure system, with plans for definitive closure pending final margin status. Pathology revealed an 8 × 9 cm area of scattered foci of disease with negative margins. At the patient's request, reconstruction was declined, and the right chest wall was closed with a split-thickness skin graft. In consultation with medical oncology, a decision was made to continue surveillance every three months without adjuvant therapy. At last follow-up, the patient remained disease-free, 57 months after the initial RIAS diagnosis and 33 months after local recurrence.

Case 2

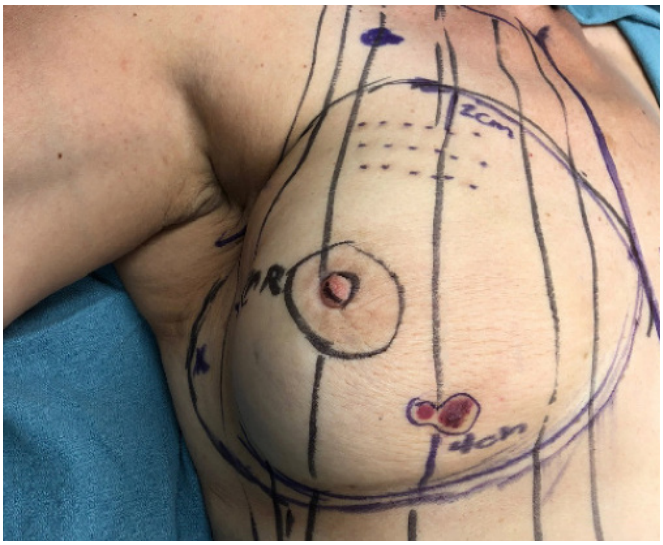
A 60-year-old female with a history of right breast cancer (diagnosed in 2015 and treated with breast-conserving therapy and tamoxifen) presented in 2018 with multiple violaceous lesions on her inferior right breast (Figure 1).

Figure 1. Initial Presentation of RIAS. Published with Permission



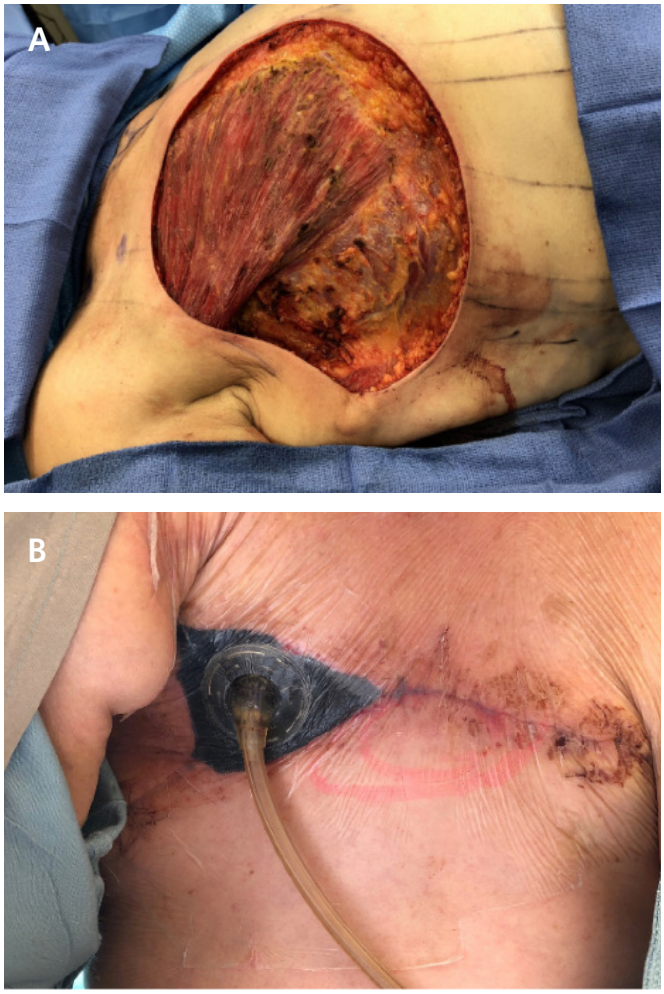
Biopsy confirmed an atypical vascular proliferation consistent with RIAS, with positive staining for c-Myc and CD31. Following referral, she was evaluated by a multidisciplinary team, including breast, plastic, and medical oncology surgeons. Staging CT revealed a 1.5 cm soft tissue nodule in the right breast but no evidence of distant metastasis. Preoperative marking encompassed all radiation tattoos and skin lesions with at least a 2 cm margin (Figure 2). A right mastectomy with extensive resection of the right chest wall skin and subcutaneous tissue was per-

Figure 2. Preoperative Marking. Published with Permission



formed, followed by abdominal tissue advancement flap and negative pressure wound therapy (Figure 3). A dedicated breast pathologist was present in the operating room to assist with specimen orientation by the breast surgeon.

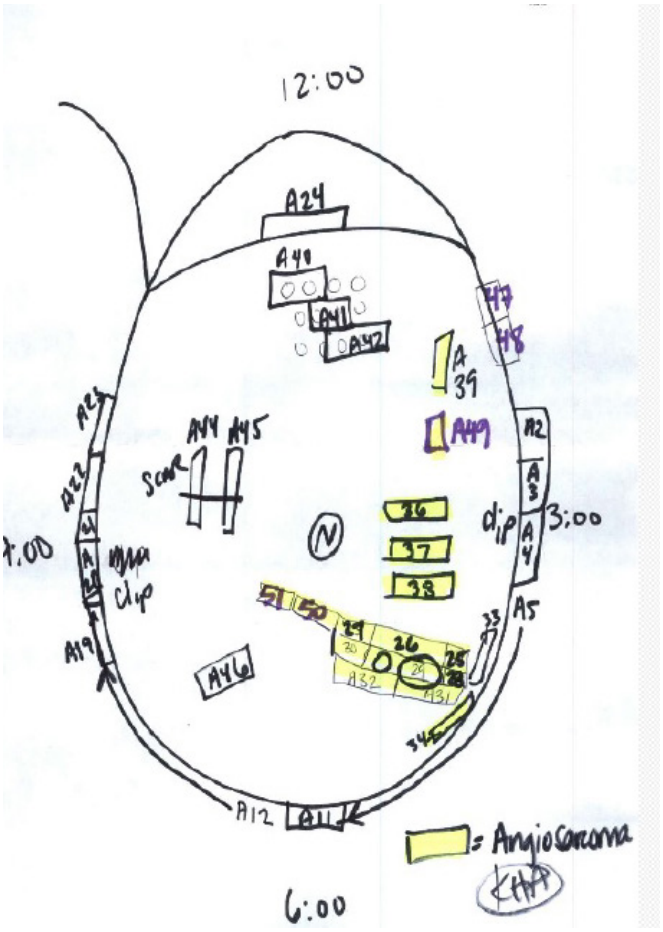
Figure 3. Post-Mastectomy Chest Wall Defect and Temporary Closure. Published with Permission



A) *Large tissue defect following total mastectomy.* ***B)*** *Temporary closure with reverse abdominoplasty/abdominal tissue advancement flap and negative pressure wound therapy.*

A dedicated breast pathologist was present in the operating room to assist with specimen orientation by the breast surgeon. Final pathology revealed an 11.2 × 9.5 cm area of disease with clear margins (closest margin 3 mm). The pathologist provided a detailed specimen diagram for the surgical team (Figure 4).

Figure 4. Intraoperative Specimen Diagram. Published with Permission



After confirmation of negative margins, the right chest defect was closed with a split-thickness skin graft. The patient is undergoing close surveillance with CT every six months and remains disease-free nearly two years after initial RIAS diagnosis. This case further demonstrates the positive impact of multidisciplinary management.

Discussion

Radiation-induced angiosarcoma (RIAS) is a rare and aggressive malignancy with challenging diagnostic and therapeutic considerations. While typically presenting in the sixth or seventh decade of life (50s-60s)[1,2] with a latency period of 4-10 years post-radiation, some cases, as in this report, occur earlier (within 6 months to 2 years).[2–4]

RIAS presents with diverse cutaneous manifestations, ranging from violaceous skin changes and blisters to induration. This variability can lead to diagnostic delays, with

RIAS being misdiagnosed as bruising, infection, or benign post-radiation changes. Therefore, a high index of suspicion is crucial in any patient with a history of breast radiation presenting with new skin changes, warranting prompt referral to a breast surgeon for biopsy.

Definitive diagnosis requires adequate tissue sampling (core needle, punch, or incisional biopsy are preferred over fine-needle aspiration) and expert pathologic evaluation.[3] The histologic hallmark is the presence of abnormal, pleomorphic endothelial cells,[2] often with atypical vascular proliferation and positive immunohistochemical staining for endothelial markers such as CD31 and CD34.[5] Following diagnosis, a multidisciplinary approach involving medical oncology, breast surgery, and plastic surgery is essential for a coordinated plan of care.

Preoperative staging with CT of the chest, abdomen, and pelvis or PET/CT is performed to exclude metastatic disease. Imaging findings in RIAS are often nonspecific, demonstrating normal findings, skin thickening, or post-treatment changes.[5,6] Some studies suggest breast MRI may offer superior delineation of disease extent compared to mammography or ultrasound.[5]

Based on our experience, preoperative consultation with plastic surgery is strongly recommended to facilitate planning for reconstruction options and the potential use of negative pressure wound therapy as a temporizing measure pending final pathology. If flap or graft closure is anticipated, negative pressure therapy is preferred, with definitive closure deferred until negative margins are confirmed.

Surgery remains the primary curative modality, aiming for R0 resection with removal of all irradiated tissue. Given that radiation-induced sarcomas often arise at the periphery of the radiation field (where the dose may be suboptimal for tumor eradication), producing survivable mutations that progress to tumor development,[7,8] thus wider margins are typically pursued. While no formal guidelines exist, many surgeons aim for 2-3 cm margins.[9] Our practice involves preoperative marking incorporating a 2 cm margin from all radiation tattoos and skin lesions. While completion mastectomy is our standard approach, wide local excision has also been reported. The extent of RIAS often exceeds the initial clinical impression. Given the low incidence of axillary metastasis, sentinel lymph node biopsy and axillary dissection are generally not indicated.[3,10] Early involvement of an experienced breast pathologist is crucial for thorough specimen examination and proper orientation of the specimen if margins are positive and additional resection is required.

The role of adjuvant therapy remains debated. In a review of 95 patients with RIAS, Torres et al. reported a statistically significant reduction in local recurrence with chemotherapy.[10] The combination of propranolol with chemotherapy has shown promise,[11] with beta-blockade demonstrating a "suppressive" effect against angiosarcomas leading to a decrease in angiosarcoma tumor cell viability, decreased tumor growth in mice, and decreased tumor cell proliferation rates.[12] Propranolol may potentiate the anti-proliferative and anti-angiogenic properties of certain chemotherapy agents, with a suggested regimen including propranolol 40mg BID plus a weekly chemotherapy agent.[12]

Unfortunately, patients with RIAS frequently have local recurrence. While positive margins are associated with a significantly increased risk of recurrence,[3,13] the incidence remains high even with negative margins, likely due to the often multifocal nature of RIAS, with discontinuous foci of disease throughout the specimen. Monroe et al. reported a 73% recurrence rate in their review of 75 surgically treated patients.[5] However, margin width appears to correlate with recurrence risk; Cohen-Hallaleh et al. found significantly narrower resection margins in a series of 49 patients who developed local recurrence compared to those who remained disease-free (median clearance of 1.0 cm vs. 2.5 cm).[9] In a cohort analysis of 79 patients, D'Angelo et al. identified resection margin status as the most significant prognostic factor for distant recurrence-free survival.[14]

Our institutional protocol involves clinical examination and CT C/A/P every 3–6 months for surveillance. While most recurrences (84%) occur within one year of initial surgery,[5] late recurrence is also possible, as demonstrated in Case 1.

Reported overall five-year survival rates for RIAS range from 15–48%.[3,5,9] Dogan et al.'s literature review reported a mean recurrence-free survival of 15.9 months and overall survival of 27.4 months.[15] Jallali et al. reported a median survival of 42 months for patients with complete excision, compared to a maximum survival of 15 months when complete excision was not achieved.[7]

Several factors are associated with worse outcomes, including higher tumor grade, presence of metastatic disease, and incomplete resection.[3,13] The number of skin lesions is also a significant prognostic indicator; patients with multiple lesions have a 0% two-year survival rate compared to 50% for those with single lesions.[3,16] Tumor size is also prognostic, with mean survival times of 80 months and 20 months for tumors <2 cm and >5 cm, respectively.[3,13]

Conclusion

The rarity, variable presentation, and aggressive nature of RIAS presents significant therapeutic challenges. A multidisciplinary approach involving breast and plastic surgeons, specialized pathologists, and medical oncologists is essential for optimal management.

Lessons Learned

While surgical resection remains the mainstay of RIAS treatment, multidisciplinary collaboration is crucial for achieving optimal outcomes. Our experience underscores the importance of a multidisciplinary team, including breast and plastic surgeons, medical and radiation oncologists (when applicable), and a specialized pathologist, in managing these complex cases. Preoperative consultation with plastic surgery is mandatory for wound closure planning and reconstruction discussions. Similarly, preoperative medical oncology consultation is necessary to evaluate the potential role of adjuvant therapies. This case highlights a valuable framework for RIAS management, from initial presentation through follow-up.

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