Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2023104340-346

An Update on Radiation-Induced Angiosarcoma of the Breast: A Diagnostic and Management Challenge

Christine Zhao*[a,b,c], Hema Mahajan[a,b,c], Phuong Dinh[a,c], Najmun Nahar[a,c], T Michael Hughes[d,e], Nicholas K Ngui[a,b,d,e]

[a]*Western Sydney Local Health District, Sydney, Australia*

[b]*Western Sydney University, Sydney, Australia.*

[c]*The University of Sydney, Sydney, Australia*

[d]*Sydney Adventist Hospital, Sydney, Australia*

[e]*Australian National University, ACT, Australia*

ARTICLE INFO

Received:
28 June 2023
Revised:
3 September 2023
Accepted:
4 September 2023

Keywords:
Angiosarcoma, radiotherapy, breast cancer

ABSTRACT

Background: Post-radiation angiosarcoma (AS) of the breast is a rare complication after breast radiotherapy. The diagnosis and management of post-radiation AS is challenging because of its non-specific but aggressive presentation. This study aims to examine the experience of a local health district with post-radiation AS to improve awareness of this condition.

Methods: A retrospective case series was performed on patients diagnosed with post-radiation AS within Western Sydney Local Health District between 2000-2021. Eligibility criteria included patients with histologically proven breast angiosarcoma and a history of past breast radiotherapy.

Results: In the study, 11 patients had post-radiation AS of the breast. The annual incidence was 1 in 18,000 of the breast radiotherapy-treated population. Descriptive analysis was performed on six patients. The median age was 67 years, with a median latency period of 5.5 years. All patients presented with non-specific skin changes. Core/punch biopsy was inconclusive in five patients. Mastectomy was the mainstay of treatment. Three patients had disease recurrence. The five-year survival rate was 68%.

Conclusion: Post-radiation AS of the breast is a rare disease associated with a poor prognosis due to its aggressive nature and high recurrence rate. Diagnosis is challenging with high false-negative rates associated with imaging and biopsy. It is important to maintain a high index of suspicion in patients treated with past breast radiotherapy.

INTRODUCTION

Post-radiation angiosarcoma (AS) of the breast, also known as radiation-associated angiosarcoma (RAAS) or radiation-induced angiosarcoma (RIAS), is a rare malignancy of vascular origin that occurs secondary to breast irradiation for the treatment of breast cancer.[1, 2] Unlike primary breast angiosarcoma which develops spontaneously in young women between 20-40 years, secondary angiosarcoma develops mainly from the dermis of the irradiated breast tissue.[2, 3] Breast angiosarcoma accounts for less than 1% of breast malignancies and post-radiation AS accounts for an even smaller percentage (<0.1%).[3] The diagnosis and management of post-radiation AS

***Address for correspondence:**
Christine Zhao,
Western Sydney Local Health District, Sydney, Australia
Tel: +610288905555
Email: czha3977@uni.sydney.edu.au

is challenging because patients usually present asymptomatically with non-specific skin changes that mimics benign skin lesions, delaying diagnosis. By the time a diagnosis is made, the disease has often metastasized to become incurable.[4, 5] Mastectomy to achieve negative margins is currently the mainstay of treatment and sentinel lymph node biopsies are not performed because of its hematogenous spread.[6] Post-radiation AS is becoming increasingly relevant to clinicians due to the rise in rates of breast conserving surgery and radiotherapy.[2] The purpose of this study is to maintain clinical awareness of post-radiation AS by reviewing the clinico-pathological characteristics, management and outcomes of patients diagnosed in the Western Sydney Local Health District (WSLHD), Sydney, Australia.

METHODS

A retrospective case series of all patients diagnosed with post-radiation AS in WSLHD over a 20-year period (2000-2021) was performed. The search term "angiosarcoma" was used to identify eligible patients from the WSLHD Pathology West Institute of Clinical Pathology and Medical Research (ICPMR) PathNet database. The ICPMR is the central pathology service for WSLHD which caters to a population of approximately 1.3 million residents.

Histopathology reports were reviewed individually to confirm that a diagnosis of breast angiosarcoma was made. Post-radiation AS is defined by histological-proven angiosarcoma with a history of previous breast irradiation.[7] Exclusion criteria included patients with primary angiosarcoma which arises de novo, or patients with inconclusive histopathology. Patient demographics (age, sex and risk factors), oncological history (surgery, chemotherapy, and radiotherapy records), and follow-up data were collected by reviewing individual patient medical records. The time of diagnosis of post-radiation AS was defined as the date of first histological diagnosis. Latency period refers to the time when the last radiotherapy was given to the time of diagnosis of post-radiation AS. Duration of follow-up was calculated from the time of diagnosis of post-radiation AS to the time of death, or until the study end date was reached, whichever was later. Disease-free survival was defined as the length of time after surgery, to the time of the last follow up or until disease recurrence.

Basic descriptive statistics were performed using IBM SPSS v26.[8] This study was approved by the Western Sydney Local Health District Human Research Ethics Committee.

RESULTS

Using the ICPMR database, twelve patients were diagnosed with breast angiosarcoma between 2000 and 2021. One patient had primary angiosarcoma and 11 patients had post-radiation AS. Five patients were excluded from descriptive analysis because they were not treated in WSLHD resulting in a total of six post-radiation AS patients for further analysis in our study. These 11 patients were diagnosed with breast post-radiation AS out of 10,060 patients who have had breast radiotherapy in WSLHD from 2000 to 2021. The annual incidence of post-radiation AS in our study population is 1 in 18,000 patients.

Patient demographics

Patient demographics and clinicopathological features are presented in Table 1. All patients were female and had a history of ipsilateral radiotherapy for primary breast cancer. The median age was 67 years (range: 55 to 86 years). Patients and their risk factors for secondary angiosarcoma are listed in Table 1. The median latency period was 5.5 years.

Table 1. Patient demographics and clinicopathological features of post-radiation AS of the breast

Patient characteristics (n=6)	
Age (years)	
Median	67
Gender	
Female	6
Risk factors for angiosarcoma	
Family history of breast cancer	2
Lymphoedema	2
Previous radiotherapy for breast cancer	6
Previous ipsilateral breast cancer	6
Time of radiation to diagnosis of angiosarcoma (years)	
<5	1
5-10	3
>10	2
Presenting symptom	
Rash	1
Skin erythema/ulceration	5
Laterality of breast angiosarcoma	
Left	6
Right	0
Size of tumour (mm)	
<50	5
>50	1
Grade	
Intermediate (Grade 2)	2
High (Grade 3)	4
Method of diagnosis	
Needle Core	1
Skin punch	1
Excisional	4

Clinico-pathological features

All patients presented with skin changes that were noticed during routine follow-up, such as a rash or

ulceration. Two patients had a history of a non-healing skin ulcer that they thought were secondary to trauma. Patient 1 presented with an ulcer presumed to be due to a cat scratch and did not seek immediate medical attention. Patient 3 presented with a 10-month history of skin lesions over her left breast first appearing as a solitary, itchy lesion (Figure 1). She had a mammogram and breast ultrasound earlier that year which did not detect any new breast lesions or abnormalities (Figure 2 and 3). She was one of the four patients who had a core needle biopsy and was diagnosed with post-radiation AS. The other three patients, however, had an inconclusive result on core biopsy and required a surgical excisional biopsy to diagnose post-radiation AS. Two patients (33.3%) had a punch biopsy as their initial form of investigation and one of them had an inconclusive result requiring surgical excision to confirm the diagnosis.

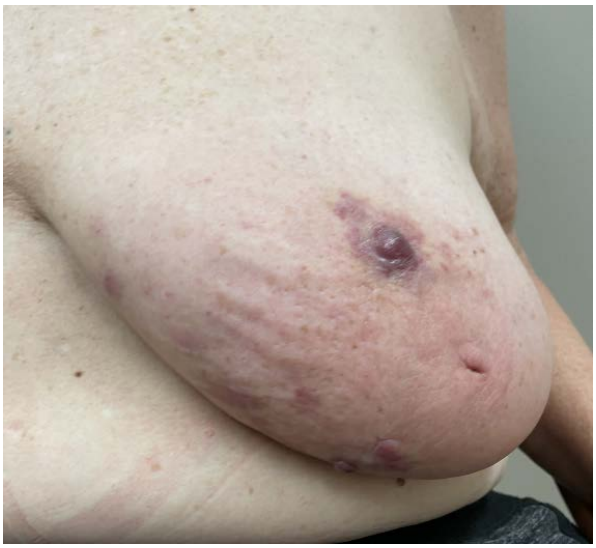

Figure 1. Photo of patient 3 who was diagnosed with post-radiation AS of the breast, who initially presented with skin erythema and cutaneous nodules

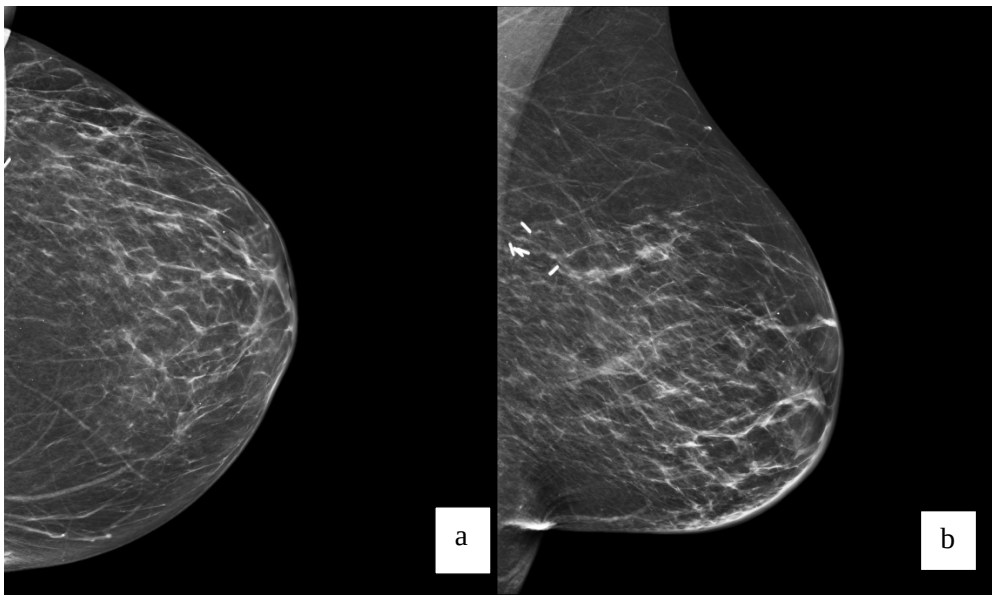

Figure 2. Left breast mammogram (CC and MLO views, a & b respectively) of patient 3 both showing no abnormal findings

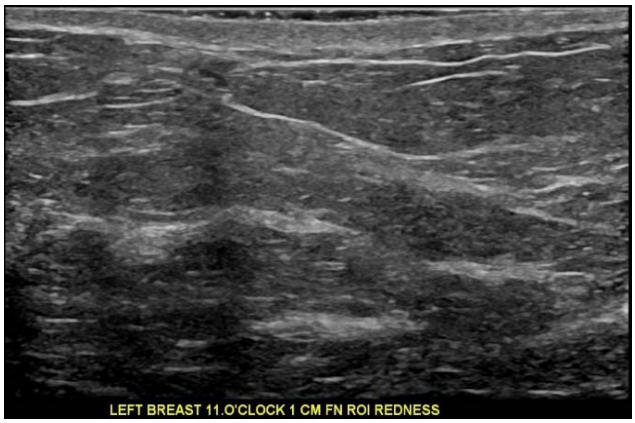

Figure 3. Left breast ultrasound of patient 3 adjacent to new skin lesions showing no abnormal lesions

Histopathology

The tumor size of angiosarcoma ranged from 7mm to 155mm. Two patients had an intermediate grade angiosarcoma whilst the remaining patients had features of high grade angiosarcoma on histopathology. Four patients had multifocal angiosarcoma. Immunohistochemical stains such as CD31, CD34, ERG and c-Myc were used in some cases to confirm the diagnosis of angiosarcoma. No molecular tests were done. Figure 4 shows the features of a low grade angiosarcoma on histology, in contrast to Figure 5 which has the features of a high grade angiosarcoma of the breast.

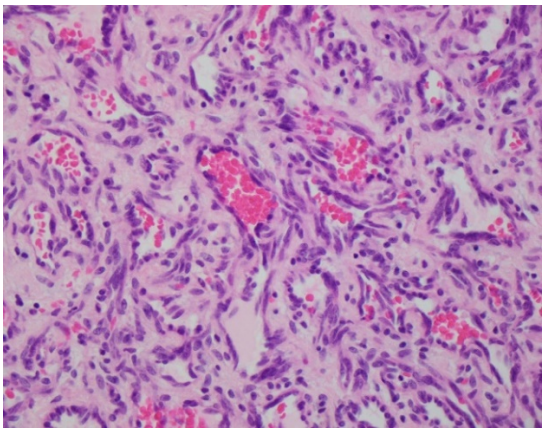

Figure 4. Low grade angiosarcoma, anastomosing/branching, vascular channels lined by minimally atypical endothelial cells with plump, hyperchromatic nuclei. H&E, x40

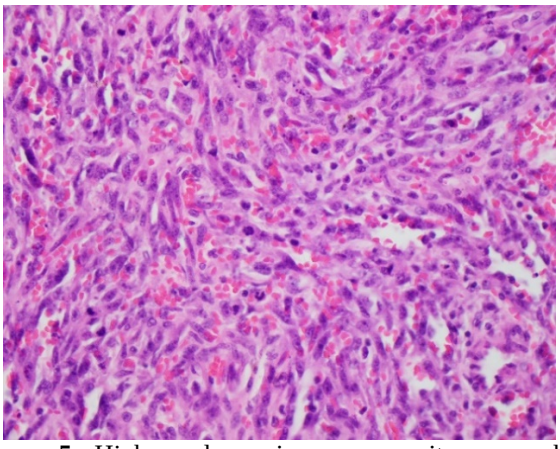

Figure 5. High grade angiosarcoma, mitoses, marked pleomorphism and solid growth with extravasation of blood. H&E, x40

Treatment

Computed tomography (CT) was performed in all patients for staging and all but one patient had no evidence of metastasis. Table 2 summarizes the treatment and management of patients in our cohort. Four out of six patients (66.7%) were treated with simple mastectomy. Sentinel lymph node biopsy was not performed in this cohort. One patient (16.7%), who initially declined a mastectomy, had a wide local excision but subsequently had a mastectomy for positive margins. One patient had a wide local excision because she already had a mastectomy previously for primary breast cancer. Only one patient with evidence of bone metastasis on CT received adjuvant chemotherapy. No patients received adjuvant radiotherapy.

Follow-up and treatment for recurrence

The median follow-up was 55 months (Range: 4.5 to 177.0 months). Three out of six patients (3/6, 50.0%) had evidence of disease recurrence. The median disease-free survival was 98 months. One patient had locoregional recurrence to the ipsilateral chest wall and lung that was treated with aggressive surgical resections. Two patients had distant metastasis. Figure 6 shows a PET-CT of patient 3 demonstrating extensive metastases eight months post-surgery. She later received taxol-based chemotherapy and radiotherapy but died from her disease progression. The other patient unfortunately died before any treatment could commence. The 5-year survival rate was 66.7% (4/6). Both patients who died within 5 years had distant metastatic disease.

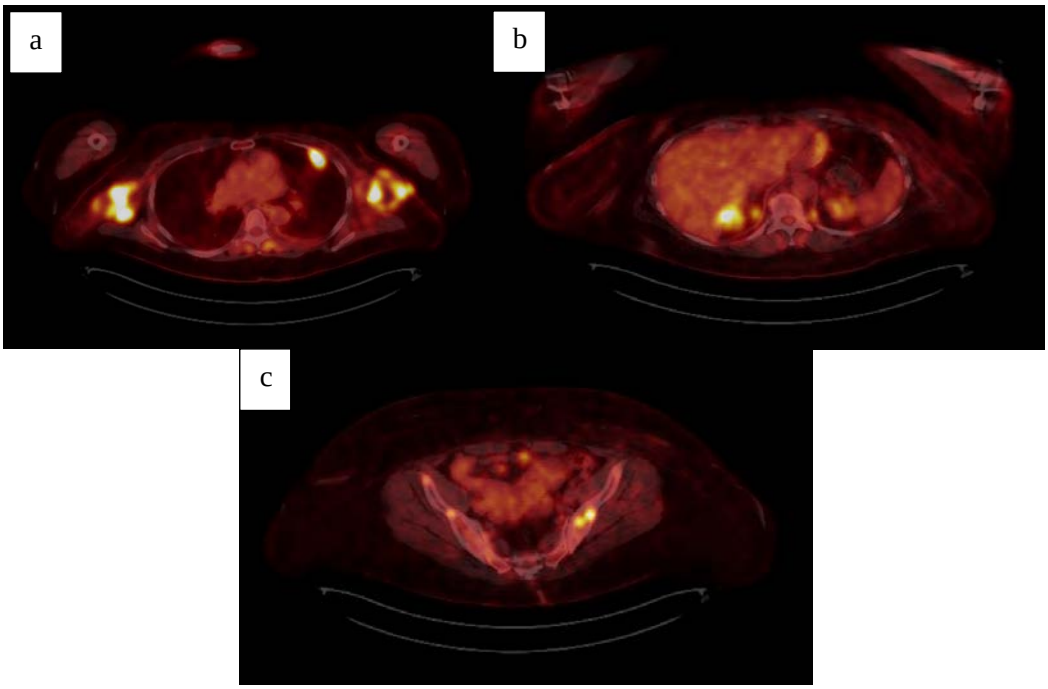

Figure 6. PET-CT of patient 3 showing extensive metastatic disease to axillae & lung (a), right suprarenal gland (b) and pelvis (c).

Table 2. Patient treatment characteristics and outcomes

Case	Age of primary breast cancer diagnosis	Previous breast surgery and type	Latency period (years)	Histology	Multifocal at presentation	Grade	Size (mm)	Treatment	Disease recurrence	Disease free survival (months)	Treatment for recurrence	Follow up duration (months)	Survival status	Cause of death
1	36	Left WLE, axillary clearance and sentinel LN biopsy	5	Punch: Atypical vascular lesion Final tissue specimen: Intermediate grade angiosarcoma	Yes	2	7	1. Left WLE + skin graft 2. Completion mastectomy due to positive margins	Locoregional, chest wall and lung	26	Surgery	168	Alive	-
2	47	NA	4	Punch biopsy: Poorly differentiated angiosarcoma, positive CD31 & ERG Final tissue specimen: poorly differentiated angiosarcoma	No	3	35	Left mastectomy	No	97	NA	97	Alive	-
3	50	Left WLE and sentinel LN biopsy	4	Core biopsy: Poorly differentiated angiosarcoma Final tissue specimen: Multifocal dermal angiosarcoma, positive forCD31, CD34, ERG, c-MYC.	Yes	3	20	Left mastectomy	Distant, suprarenal glands and peritoneum	7	Chemotherapy followed by radiotherapy	13	Died	Progression of angiosarcoma
4	45	Left WLE and axillary clearance	6	Core biopsy: No evidence of malignancy Final tissue specimen: Radiation induced angiosarcoma	No	2	23	Left mastectomy	No	177	NA	177.5	Died	Metastatic neuroendocrine lung cancer unknown primary
5	61	Left WLE and axillary clearance	11	Core biopsy: Angiosarcoma Final tissue specimen: High grade Angiosarcoma	Yes	3	25	Left mastectomy	No	165	NA	165	Alive	-
6	34	Left modified radical mastectomy	7	Core: No evidence of malignancy Excisional biopsy: Multifocal high grade angiosarcoma, positive for CD31	Yes	3	155	1. Excisional biopsy 2. Palliative thalidomide	Distant, spine	4	NA	4.5	Died	Progression of angiosarcoma

DISCUSSION

Post-radiation AS is a rare complication after breast radiotherapy. The rarity of post-radiation AS is reflected in our study, with an annual incidence of approximately 1 in 18,000 of the breast radiotherapy-treated population. Post-radiation AS commonly affects older women with a median age of 67.5 years in our study, and this is comparable to what was reported in the literature of 70 years.[9] The median latency period observed in our study was 5.5 years, also comparable to literature of 6 years.[9] Post-radiation AS often presents asymptomatically; skin changes may be difficult to differentiate from irradiated skin changes and skin lesions can appear benign, which can contribute to a delayed diagnosis.[10]

Post-radiation AS is diagnostically challenging because radiological findings are often normal or non-specific.[11] Mammogram may reveal skin thickening, calcifications, or an ill-defined mass; and the ultrasound appearance can appear hypo or hyper-echoic.[9, 12] One study reported that approximately 33% of mammograms appear normal, resulting in a delayed diagnosis.[13] Punch or core biopsies can also give a false negative or an inconclusive result, as seen in our study. One study reported a false negative rate of 37%[14].

Post-radiation AS is an aggressive malignancy with a poor prognosis. In our study, we report a recurrence rate of 50% and a 5-year survival of 66.7%. Surgery is the standard of care and usually involves a mastectomy and excision of all irradiated tissue with wide clear margins.[10] There have been variable data published about the effectiveness of adjuvant treatment. Lahat *et al.* showed that taxol-based chemotherapy was a positive predictor of disease-specific survival, although this was not statistically significant (HR 0.67, p 0.06).[15] In a retrospective study of ten patients, Johnstone *et al.* showed that all patients treated with adjuvant radiotherapy had a 5-year disease-free survival of 68% and an overall survival of 66%.[16] In addition, seven out of ten patients were alive and free of disease at 11.8 years, suggesting that adjuvant radiotherapy can potentially achieve excellent local control. Another meta-analysis showed that patients treated with surgery and adjuvant radiotherapy had significantly better recurrence-free survival compared to surgery alone (HR 0.48, 95%CI 0.27-0.86, p<0.05).[17] In our retrospective study, no patients received adjuvant radiotherapy, possibly due to the lack of data on its efficacy. If radiotherapy is shown to have good outcomes, perhaps clinicians should consider using it as adjuvant therapy. More research is warranted in this area to provide robust evidence-based recommendations for patients.

Breast conserving surgery followed by radiotherapy has been shown to be equivalent to mastectomy in terms of oncologic outcomes in early breast cancer and as a result, most patients receive breast conserving therapy with local surgery and radiotherapy.[18] Clinicians should be aware of the subtle presentation of post-radiation AS, its tendency for multifocality and have a high index of suspicion. Prompt diagnosis with excisional or generous incisional biopsy and subsequent treatment with radical surgical excision should improve outcomes. Due to the rarity of this disease, it is difficult to make treatment recommendations from this study. Our study does reinforce published literature and serves as a reminder to clinicians about the subtle presentation, diagnostic pitfalls, aggressive clinical behavior, and treatment patterns for this rare disease.

CONCLUSION

Post-radiation AS of the breast is a rare disease associated with a poor prognosis due to its aggressive nature and high recurrence rate. Diagnosis is challenging with high false-negative rates associated with breast imaging and skin punch or core needle biopsy. Prompt diagnosis is required to improve patient outcomes, including careful physical examination, appropriate investigations and maintaining a high index of suspicion in patients treated with past breast radiotherapy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

None.

ACKNOWLEDGMENTS

None.

DATA AVAILABILITY

Not Applicable.

ETHICAL CONSIDERATIONS

All patients whose medical records were used in this study singed an informed consent to present the detail of her pathology and medical findings in this medical journal.

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How to Cite This Article

Zhao C, Mahajan H, Dinh P, Nahar N, Hughes TM, Ngui NK. An Update on Radiation-Induced Angiosarcoma of the Breast: A Diagnostic and Management Challenge. Arch Breast Cancer. 2023; 10(4):340-6.

Available from: https://www.archbreastcancer.com/index.php/abc/article/view/758