

# Is there a role for adjuvant therapy in radiation-induced angiosarcoma of the breast? A case report and review of the literature

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**Abstract. – BACKGROUND:** Angiosarcoma (AS) of the breast is very rare, accounting for 1% of all soft tissue breast tumors. AS may present as primary tumors of the breast or as secondary lesions usually associated with previous radiotherapy. Commonly, secondary AS affects older women (median age 67-71 years) with a clinical history of breast cancer. The preferred site of onset of RIAS is the edge of radiation fields, where radiation doses and tumor necrosis may be heterogeneous, resulting in a DNA damage and instability. Radical surgery is the treatment of choice, but no clear consensus exists on surgical management of breast AS.

**CASE REPORT:** We describe an atypical case of relapsed RIAS after radical mastectomy, treated with new surgery and, considering the higher risk of recurrence, subsequent adjuvant chemotherapy with weekly paclitaxel.

**CONCLUSIONS:** The frequency of radiation-induced angiosarcomas (RIAS) after breast-conserving surgery and radiotherapy has been increased to 0.14-0.5% among long survivors. Nevertheless, even if RIAS continues to be prognostically an extremely unfavorable cancer due to a high rate of recurrence, distant spread, and median overall survival (OS) of about 60 months, the benefits of loco-regional breast radiotherapy are clearly higher than the risk in developing angiosarcoma.

*Key Words:*

Angiosarcoma, Breast cancer, Radiation-induced angiosarcoma.

## Abbreviations

AS: angiosarcoma; BRCA: breast cancer-related tumor-suppressor; CD: cluster of differentiation; CNB: core-needle biopsy; CT: computed tomography; DFS: disease-free survival; EMA: epithelial membrane antigen; FL1: follicular lymphoma, Susceptibility to, 1; FLT4: Fms-related tyrosine kinase 4; FNA: fine needle aspiration; FNCLCC: Fédération Nationale des Centres de Lutte Contre Le Cancer; KDR: kinase insert domain receptor; MRI: magnetic resonance imaging;

MSI: micro-satellite instability; MYC: myelocytomatosis; NCCN: National Comprehensive Cancer Network; NOTCH1: notch homolog 1, translocation-associated; OS: overall survival; RIAS: radiation induces angiosarcoma. ROS: reactive oxygen species; RT: radiotherapy; TIA: transient ischemic attack; VEGFR: Vascular Endothelial Growth Factor Receptor.

## Introduction

Angiosarcoma (AS) of the breast is very rare, accounting for 1% of all soft tissue breast tumors. AS may present as primary tumors of the breast or as secondary lesions usually associated with previous radiotherapy. They should be considered as two separate clinical entities, with aggressive behavior and poor prognosis<sup>1</sup>.

Primary ASs account for <0.04% of malignant neoplasms and has been observed in younger women, usually aged between 30 and 50 years; the most frequent clinical presentation is a poorly defined mass of the breast, which typically originates from the parenchyma and grows rapidly. Unlike secondary AS, skin involvement is mostly occasional, with purple discoloration of the overlying skin and apparent bruising. Due to its non-specific clinical and imaging manifestations, and different histopathological manifestations, it is difficult to accurately diagnose it before surgery, often resulting in missed diagnosis or misdiagnosis<sup>2</sup>.

Secondary AS affects older women (median age 67-71 years) with history of breast cancer. It frequently arises in the dermal and subdermal layers and may not necessarily involve the parenchyma, presenting as painless bruising that is frequently multifocal, purplish discoloration, eczematous rash, hematoma-like swelling, diffuse breast swelling or less commonly as single or multifocal cutaneous

mass. This clinical presentation may be easily mistaken for bruising or benign skin changes, leading to delayed diagnosis. Secondary ASs may occur in the context of long-standing chronic lymphedema after total mastectomy and axillary dissection (Stewart-Treves syndrome), usually between 5 and 15 years after the surgery, or after breast radiotherapy [radiation-induced angiosarcoma (RIAS)]<sup>1,3,4</sup>. In scientific literature the median time of RIAS presentation is from 5 to 10 years after radiotherapy, with case series reporting latency over 20 years<sup>5</sup>. The preferential site of onset of RIAS is the edge of radiation fields, where radiation doses and tumor necrosis may be heterogeneous, resulting in DNA damage and instability<sup>1</sup>. Both primary and secondary ASs may lead to platelet sequestration, hemorrhagic manifestations, and several cases of disseminated intravascular coagulation by consumption coagulopathy (Kasabach-Merrit syndrome) have been reported in scientific literature<sup>6-9</sup>.

Ultrasound and mammography are non-specific, and primary AS can be mistaken for a breast carcinoma or a benign lesion. In both primary and secondary AS, magnetic resonance imaging (MRI) scan is helpful in determining the malignancy of the lesion. Necrosis or bleeding areas affect the appearance in T1-weighted and T2-weighted images of MRI, while contrastographic behavior shows significant heterogeneous enhancement in the early phase and varying degrees of concentric enhancement in the delayed phase. The dynamic contrast enhancement curves may show plateau pattern or washout pattern<sup>10</sup>.

Fine needle aspiration (FNA) or Core-needle biopsy (CNB) are required for diagnosis of primary AS, while secondary AS generally needs an excisional biopsy or skin punch. Biopsy methods may be complicated by post-procedural bleeding. Prognosis is poor in both types due to the high rate of recurrence. Although data are controversial, high-grade tumors seem to have lower disease-free survival (DFS) and OS compared to low and intermediate grade tumors. The role of tumor size is unclear, while infiltration of surgical margins is associated with increased risk of local and distant recurrence and worse prognosis.

Local and distant recurrence is frequent, especially in high grade tumors and R1 excisions. Angiosarcoma preferentially spreads by the hematogenous route, although lymphatic spread has been more rarely documented. The lung is the most frequent site of metastasis, although irregular patterns of metastasizing (intestine, tonsils, heart, buttock) have been reported in scientific literature.

Radical surgery is the standard care, but no clear consensus exists on surgical management of breast AS. Axillary nodes excision is usually performed, but its role is debated because lymphatic spread is uncommon; analogously, also adjuvant chemotherapy is controversial<sup>11,11</sup>.

## Case Report

The patient is a 58-years old woman. In her clinical history, she presented high blood pressure, iatrogenic hypothyroidism as a result of post thyroidectomy due to goiter, lower limbs venous insufficiency and a previous transient ischemic attack (TIA) in 2014. No family history of cancer.

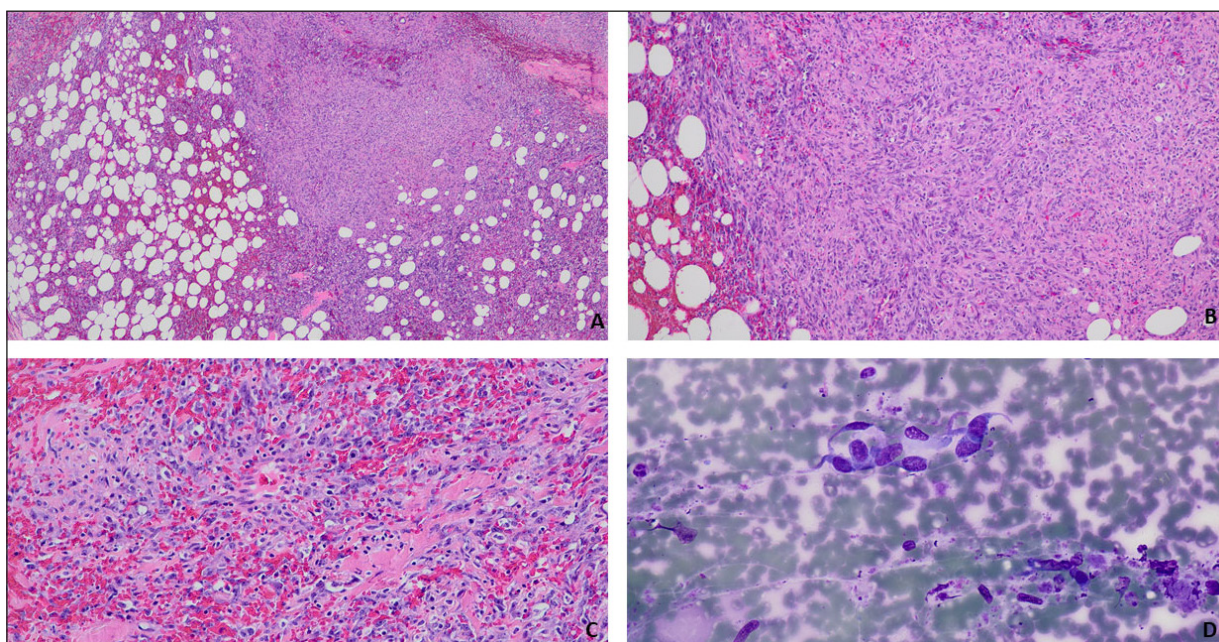
In October 2011, patient underwent surgery for supero-external quadrantectomy of right breast and homolateral lymph nodes dissection for intraductal breast cancer, stage pT1mic pN0, estrogen receptor (ER) 80%, progesterone receptor (PgR) negative, ki67 70% and HER2 negative. After surgery, she was treated with adjuvant radiotherapy for a total dose of 60 Gy: 50 Gy on residual right mammary gland (2 Gy/day, 5 days/week) and 10 Gy on tumor bed (2 Gy/day, 5 days/week). Radiotherapy was followed by 5 years hormone-therapy (tamoxifen for two years and letrozole for three years).

During the following seven years, the patient practiced regular follow-up with blood tests, tumor markers, breast ultrasounds, mammograms, and computed tomography (CT) scans. All exams were negative until October 2018 when patient noted the appearance of a millimetric nodule around the areola of right breast, near the scar from the previous surgery. This lesion grew fast and in February 2019 excision was performed. Histological report showed evidence of high-grade angiosarcoma, caused by previous radiotherapy (RT).

In March 2019 patient underwent right mastectomy with removal of pectoralis major muscle fascia and ipsilateral node sampling; after that, patient started follow-up.

In July 2021 during a follow-up visit, the physician saw a reddish-brown lump on right chest skin.

In September 2021 patient underwent FNA of this lump, but the result of the procedure was not conclusive to formulate a diagnosis. For this reason, the following month the patient underwent surgery once again and the nodule was removed; histology was compatible with relapse of high grade angiosarcoma, associated with previous RT, as seen in Figure 1.



**Figure 1.** A, Histology, Haematoxylin-Eosin (HE), 4x lens: solid and infiltrating growth pattern. B, Histology, HE, 10x: solid growth pattern with spindled cytology and increased mitosis. C, Histology, HE, 20x: markedly atypical cells with blood lakes. D, Cytology, May Grunwald-Giemsa (MGG), 40x: spindled and polygonal cells with high grade atypia.

Considering the recurrent disease, adjuvant chemotherapy was proposed to the patient with weekly paclitaxel 80 mg/sqm on day 1, 8 and 15 on a every 28 days schedule, for five cycles.

In January 2022 patients started chemotherapy. The first two cycles were well tolerated; by the third cycle patient had grade 1 acroparesthesia on her fingers as collateral effects so 25 mg of pregabalin in therapy was added. For hematological toxicities (grade 2 neutropenia) patient continued treatment, for last two cycle, with dosage reduced to 80%. The patients is currently in follow-up.

## Discussion

Nowadays the frequency of RIAS after breast-conserving surgery and radiotherapy has increased to 0.14-0.5% among long survivors. Nevertheless, even if RIAS continues to be prognostically an extremely unfavorable cancer due to the high rate of recurrence, distant spread and median overall survival of about 60 months, the benefits of loco-regional breast radiotherapy are clearly higher than the risk of developing angiosarcoma<sup>12</sup>.

The association between ionizing radiation exposure and secondary malignancies has been extensively described in the epidemiologic literature, even if pathogenesis of RIAS is still un-

known, nor it is explained whether it is a dose-dependent radiation-induced cancer<sup>13</sup>. It may be that photons directly damage DNA structure inducing DNA double-strand breaks, generating reactive oxygen species (ROS) that oxidize the double-layered cellular membrane and DNA too<sup>14</sup>. The direct oncogenic effects of ionizing radiation lead to genomic instability and mutations of specific oncogenes, some of which specifically used to differentiate radiation-induced from sporadic sarcomas: among these, the most frequent are the inactivation of *p53* gene and amplification of the 8q24 region containing myelocytomatosis (*MYC*) proto-oncogene<sup>15,16</sup>. An association between breast cancer-related tumor-suppressor (*BRCA*) 1-2 genes and RIAS is under investigation, considering the well-known parallelism with radiation-induced genome instability: in this way investigating micro-satellite instability (*MSI*) status would be useful to understand AS carcinogenesis<sup>17,18</sup>. Moreover, it could be hypothesized that radiation-induced chronic lymphedema may interfere with repair mechanisms, promoting uncontrolled neoangiogenesis through gene amplification of Fms-related tyrosine kinase 4 (*FLT4*), that encode vascular endothelial growth factor receptor (*VEGFR*) 3, and kinase insert domain receptor (*KDR*) gene mutations, encoding *VEGFR* 2: the former reported in 25% of secondary AS

and always in association with *MYC* amplification, the latter described in 10% of patients with AS. Specifically, this mutation seems to clearly identify AS of the breast, regardless of a previous exposure to radiotherapy<sup>19</sup>.

In this regard histological diagnosis, fundamental in the therapeutic algorithm, always requires an excisional biopsy that allows a careful microscopic and above all immunohistochemical analysis<sup>20</sup>. In fact, a critical point is to morphologically differentiate healthy vascular and endothelial cells from neoplastic ones, considering that the two components could also coexist surrounded by abundant inflammatory infiltrate, which contributes to making diagnosis more complex. Differential diagnosis includes hemangiomas, Massons's tumor and atypical vascular proliferation; typical vascular markers include clusters of differentiation (CD) CD31, CD34, Follicular Lymphoma Susceptibility to 1 (FL1) and factor VIII related antigen, often co-expressing epithelial antigens such as epithelial membrane antigen (EMA), Cam 5.2 and pankeratin AE1/3<sup>18</sup>. *MYC* immunohistochemical positivity is regarded as a specific marker, present in more than 67% secondary angiosarcomas and completely negative in primary angiosarcoma and secondary atypical vascular lesions; moreover, its amplification seems to be a marker of worse prognosis<sup>18,21</sup>. However a negative result does not entirely rule out secondary angiosarcoma. In addition, Notch homolog 1, translocation-associated (NOTCH 1) immunoreactivity, a signaling pathway regulating mesenchymal transition, has been observed especially in moderately- or well-differentiated cancer according to Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading system<sup>21</sup>. So, it appears clear that a simple fine-needle aspiration biopsy may not be sufficient in formulating the right diagnosis.

Cahan et al<sup>13</sup> assessed the four criteria for the diagnosis of RIAS: history of RT, asymptomatic latency period of several years (5 or more), occurrence of sarcoma within a previously irradiated field, and histologic confirmation of the sarcomatous nature. In the literature it was later described that RIAS could develop either less than 6 months or more than 40 years after radiotherapy, with an average latency of about 6 years.

The cornerstone of the treatment is surgery with negative margins (R0). There are no randomized trials comparing a conservative approach to mastectomy. Total mastectomy alone or with axillary node dissection is the preferred

surgical treatment, with conservative surgery used only in smaller lesions when a R0 resection is considered possible. No clear data on axillary nodal dissection are available as nodal metastases are not common. Adjuvant radiotherapy should only be considered for close soft tissue margins, also considering that angiosarcoma is believed to be radioresistant and refractory to radical doses<sup>22</sup>. In a systematic review Depla et al<sup>23</sup> reported a 57% of 5-year local control rate with post-operative irradiation compared to 37% of surgery alone, although with no significant difference in OS. However, in case of inoperable lesion, widely infiltrated to the skin and the muscle layer, RIAS should be treated with three-dimensional conformal radiotherapy, as described by Ikenohira et al<sup>24</sup>. Re-irradiation of the breast after previous surgery and RT may be well-tolerated, as pointed out by RTOG 1014 trial<sup>25</sup> and some retrospective experiences<sup>26</sup>, with tissue fibrosis less than 2% and skin necrosis of 1%.

Current indications for the choice of systemic treatment for RIAS are borrowed from angiosarcomas trials, regardless of site. Penel et al<sup>28</sup> had previously reported in ANGIOTAX study<sup>27</sup> that weekly paclitaxel administration was well-tolerated and has a significant impact on OS in the first line setting, while PALETTE trial<sup>28</sup> assessed a benefit in PFS for Pazopanib in a second-line treatment. Specifically, in the Phase II ANGIOTAX study 3<sup>27</sup>, patients with locally advanced breast AS were converted to resectable after a treatment with Paclitaxel; 2 of them obtained a complete response to the histological examination.

National Comprehensive Cancer Network (NCCN) guidelines recommend docetaxel, paclitaxel and vinorelbine for metastatic AS, highlighting that the role of adjuvant therapy is still debated, and a decision should be made case by case because the majority of the data is based on small retrospective studies<sup>22</sup>, lacking strong conclusions and coming to conflicting findings. Nakamura et al<sup>29</sup> reported a breast RIAS without metastasis who underwent mastectomy and adjuvant chemotherapy with weekly paclitaxel with absence of recurrence for 15 months. Moreover, Suzuki et al<sup>20</sup> described a radiation-induced angiosarcoma of the breast, surgically excised with a mastectomy, that recurred one month after surgery with a nodule on the surgical scar. Their choice has been to propose a re-surgery and adjuvant chemotherapy with paclitaxel considering the higher risk of recurrence<sup>20</sup>.

## Conclusions

RIAS represents a rare and challenging diagnosis, which could negatively impact patients' prognosis and quality of life; its intrinsic clinical features, however, favor expert clinicians to undertake the right therapeutic procedures.

Our clinical experience reflects what has already been previously reported by Suzuki et al<sup>20</sup>. In view of the rapid recurrence of the disease despite a first radical treatment, it was preferred to proceed with a new oncological radical surgery and subsequent adjuvant treatment with weekly paclitaxel considering an important risk of loco-regional and systemic progression. In case of inoperable disease, we would have carried out a radical radiotherapy treatment (with the limits related to the pathology in exam), also confirming the chosen adjuvant treatment.

## Authors' Contributions

All authors contributed equally.

## Conflict of Interest

The authors declare no conflict of interest.

## Informed Consent

Written informed consent has been obtained from the patient to publish this paper.

## Ethics Approval

Ethical approval is not required for this case report in accordance with local or national guidelines.

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