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Cutaneous Angiosarcoma After Accelerated Partial Breast Irradiation: A Case Report and Review of the Literature

Fakhreddine M[1], Aoun J[2], Ayoub Z[3], Abbas J[4], Ibrahim A[4], Saghir NSE[1] and Moukadem H[1*]

[1]Department of Internal Medicine, Division of Hematology/Oncology, Lebanon

[2]Department of Pathology, Lebanon

[3]Department of Radiation Oncology, Lebanon

[4]Department of Surgery, American University of Beirut Medical Center, Lebanon

[*]Corresponding author:

Hiba Moukadem, MD,
Department of Internal Medicine, Division of Hematology/Oncology, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh, 1107 2020, Beirut – Lebanon

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1. Summary

We present a patient diagnosed with left sided early breast cancer in 2014, treated by left partial mastectomy, standard radiation therapy and adjuvant tamoxifen, and with right sided early breast cancer in 2017, treated by right partial mastectomy, accelerated partial breast irradiation [APBI] over a 2-weeks period and adjuvant aromatase inhibitor. In 2022, the patient presented with red to purple cutaneous lesions on the right breast from nipple medially toward mid chest, which is the inner quadrant that had received APBI less than five years earlier. Skin biopsy showed high grade dermal angiosarcoma. The lesions extended later to the left breast. Patient had bilateral mastectomies and anterior chest wall skin graft. She received adjuvant weekly paclitaxel chemotherapy by the end of which she had local recurrences and progression in spite of multiple chemotherapeutic regimens including doxorubicin, gemcitabine plus bevacizumab, and high dose cyclophosphamide. This is the first case of a patient who developed an aggressive high grade and refractory angiosarcoma following APBI within a short period of less than 5 years. This potential complication after APBI should be included in the discussion of side effects with patients, especially those patients who are candidates for de-escalation and omission of radiation therapy. We emphasize that medical, surgical and radiation oncologists should have a high clinical index of suspicion for this disease, and patients should be instructed to report any skin changes in order to ensure timely early diagnosis and treatment.

2. Background

Angiosarcoma is a rare type of tumors that arises from endothelial cells, either vascular or lymphatic [1]. It is an aggressive type of neoplasm, can occur in the breast secondary to treatment of breast cancer with radiotherapy, and is usually termed either radiation induced angiosarcoma [RIAS] or radiogenic angiosarcoma of breast [RASB]. RIAS of the breast constitutes less than 1% of breast malignancies overall, [2] and almost 3% of soft tissue sarcomas [3]. The absolute risk of developing breast angiosarcoma in patients who had radiation is less than 0.5% and the relative risk is 15.9% [4]. RIAS can occur as soon as 6 months post radiotherapy with an average latency of 6 years [5]. It has generally poor prognosis [6]. There hasn't been a clear prognosis, especially due to the heterogeneity of cases and higher levels of reporting in the western world, despite it being more prevalent in Asia [7]. The 5-year overall survival [OS] rate of RIAS varies between different studies depending on treatment modalities and latency period between radiation and disease appearance. In a systematic review of individual data from 222 patients with RIAS post-breast irradiation, the 5-year OS was 43% and the 5-year local recurrence free interval was 32% [8]. While the management of RIAS remains with no standardized protocol, consensus suggests surgical resection of the tumor or

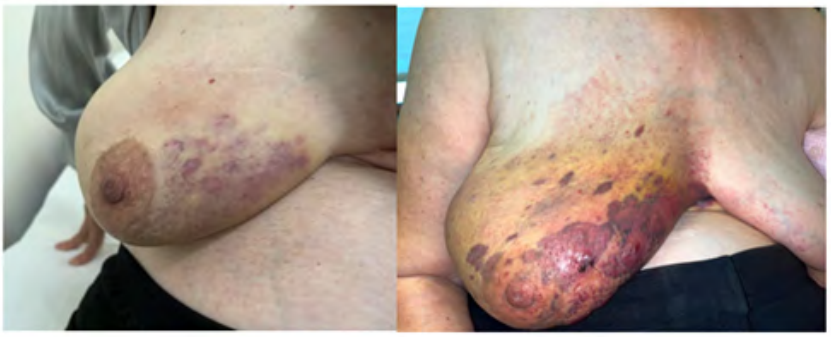
total mastectomy. We present a patient who developed cutaneous angiosarcoma following treatment for stage I breast cancer with partial mastectomy and APBI. Clinical characteristics, diagnostic work up, treatment plan and post-operative results are described in this report.

3. Case Presentation

A 77-year-old female patient was diagnosed with an early stage left breast cancer treated in 2014 with partial mastectomy, sentinel lymph node biopsy, hypo fractionated radiation therapy [15 fractions of 2.67 Gy to a total of 40 Gy] and tamoxifen. In 2017, patient presented again with new right breast cancer while on tamoxifen, for which she underwent right sentinel lymph node biopsy and partial mastectomy. On pathology, tumor was invasive ductal carcinoma, grade 1, T1aN0M0, ER positive, PR negative and HER2/neu not overexpressed. She received accelerated partial breast irradiation using external beam radiotherapy in 10 sessions over 2 weeks [38.5 Gy total in 3.85 Gy per fraction] and given adjuvant aromatase inhibitor planned for a total of 5 years. In 2022, patient presented with a new onset of painless red spots with bluish discoloration of the skin over the inner quadrant of the right breast. Cutaneous changes were apparent with ecchymotic-like areas, progressed to dark red and black-purple violaceous satellite patches located over the previously APBI-irradiated area of the right breast and extending to the axillary line as well as to the inferior medial aspect of the left breast. It was associated with skin thickening [pictures 1.a and 1.b]. No palpable axillary lymph nodes bilaterally.

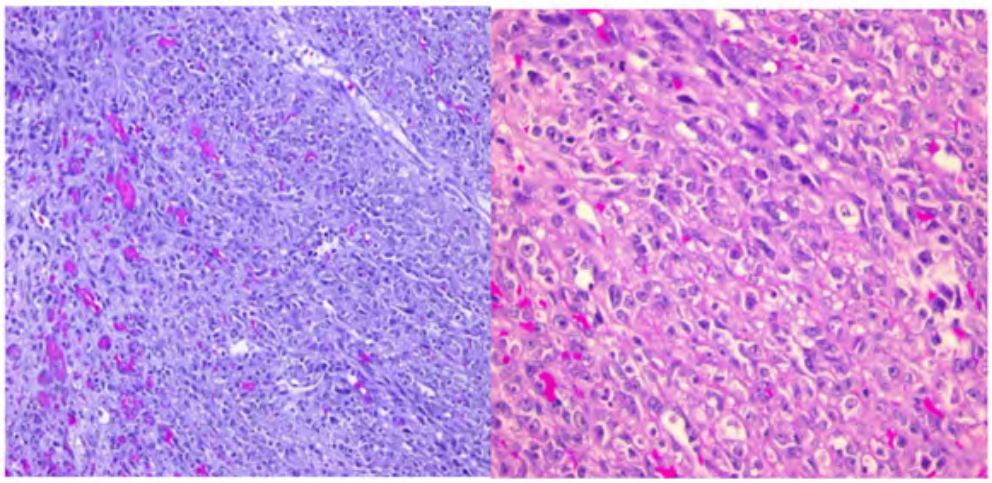
Mammography of the right breast revealed right breast diffuse skin and trabecular thickening. Sonography of the right breast showed skin thickening and mild edema mainly along the inner peri-areolar region at the site of skin discoloration. There were no enlarged lymph nodes in the axilla. MRI of the breasts showed diffuse skin and trabecular thickening of the right breast with new associated enhancement more significant in the inner aspect of the right breast. A skin punch biopsy showed irregularly shaped anastomosing vascular channels and sheet-like highly infiltrative poorly-demarcated dermal growth of atypical cells with nuclear atypia and scattered mitoses consistent with angiosarcoma [pictures 2.a and 2.b]. Patient was referred for surgery. She had bilateral mastectomies on October 22, 2022 with local tissue rearrangement and split thickness skin graft for coverage of open chest wound post bilateral total mastectomies [pictures 3.a, 3.b, and 3.c]. Post-operative surgical pathology report confirmed the diagnosis of high grade angiosarcoma involving the right breast and extending focally to the left breast over a range of at least 20 cm with predominantly dermal involvement and negative margins. The tumor cells were positive for CD31 and CD34 and showed patchy positivity for c-MYC. Complete healing was noted at 7 weeks after surgery [picture 3.d].

Patient received adjuvant therapy with weekly paclitaxel at a dose of 80 mg/m2. Treatment was interrupted due to herpes virus encephalitis. One month later, two new dark colored skin lesions appeared at the engrafted skin. New biopsy from the new lesions showed recurrent angiosarcoma. PET CT scan showed hyperactive foci representing the 2 cutaneous chest wall lesions; additional axillary lymph nodes were noted. After a short 2 months treatment with doxorubicin, the patient presented with symptomatic local disease progression involving chest wall and extending to the right axilla. A new trial of gemcitabine with anti-angiogenic bevacizumab failed within 2 cycles. A trial of high dose cyclophosphamide 1200/m2 was also unsuccessful. Palliative surgery with excision of the exophytic oozing and painful chest mass and closure with reverse abdominal flap was done in February 2024. Wound dehiscence and tumor regrowth recurred [pictures 4.a and 4.b]. A trial of immunotherapy with nivolumab 480 mg monthly dose and cabozantinib 40 mg orally daily was initiated.



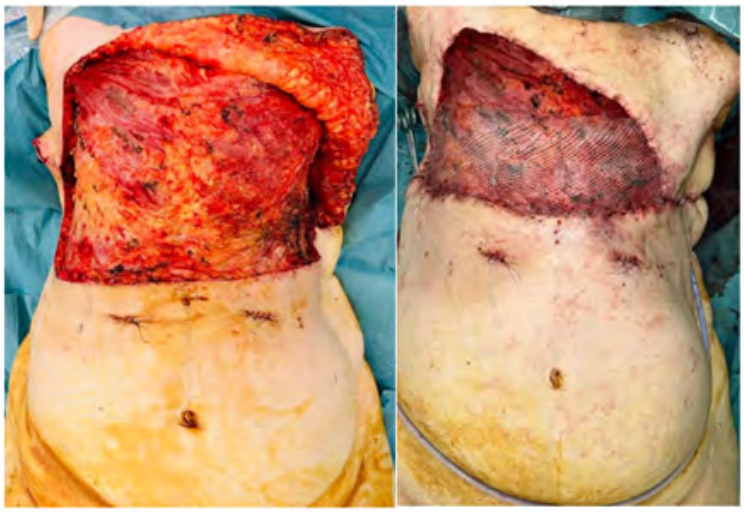
Picture 1.a **Picture 1.b**

Pictures 1.a and 1.b: Picture 1.a shows breast skin changes at the initial clinic presentation in June 2022; picture 1.b was taken in September 2022 at the time of diagnosis of cutaneous radiation inducted angiosarcoma of the breast.

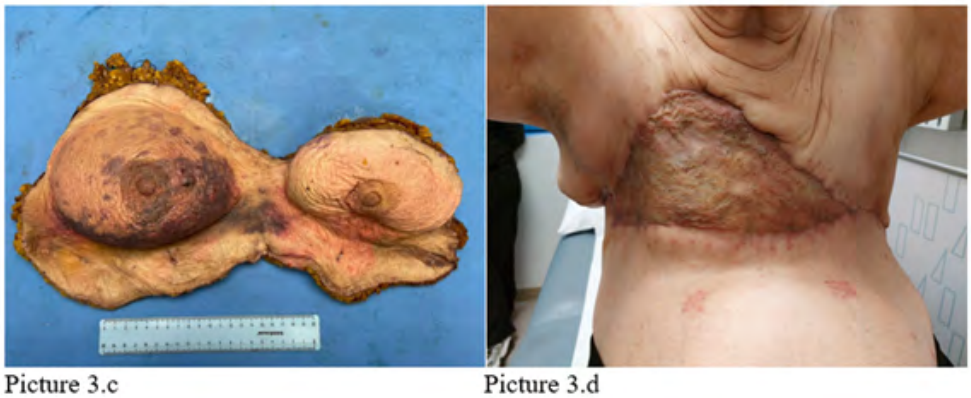


Picture 2.a Picture 2.b

Pictures 2.a and 2.b: At 20x (2.a) and 40x (2.b) magnification, presence of cells with high-grade morphology attempting to form anastomosing vascular channels.

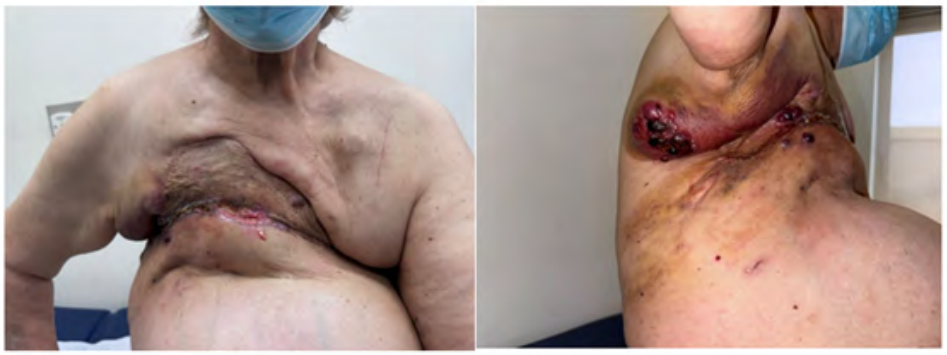


Picture 3.a Picture 3.b



Picture 3.c Picture 3.d

Pictures 3.a, 3.b, 3.c and 3.d: 3.a: Bilateral mastectomies with anterior chest wound left open for plastic care. 3.b: Skin graft application. 3.c: Total bilateral mastectomies tissue raised. 3.d: 7 weeks post-operative surgical result (day 49).



Pictures 4.a and 4.b: (March 20, 2024): 16 days post-operative palliative surgery.

4. Discussion

We report a case of a patient with secondary dermal angiosarcoma that occurred within 5 years after stage I breast cancer treated by breast conservation surgery [BCS] and APBI. The disease presented as red to purple raised cutaneous spots within the previous site of irradiation, was resected, recurred shortly after resection, and responses to systemic therapy were short-lived. Only two other cases of RIAS after APBI were reported in the literature and had occurred 8 years after radiotherapy. Our patient had received external beam APBI at a dose of 38.5 Gy total in 3.85 Gy per fraction in 10 sessions over a period of 2 weeks; while the other two reported cases had received a dose of 38.5 Gy in 10 fractions administered twice daily for a shorter period of 5 days [9]. Of the two-patient reported in the literature, one patient developed peri-cicatricial angiosarcoma in the irradiated skin, while the other developed parenchymal disease away from the high-dose field of radiotherapy that quickly spread to involve all breast quadrants and eventually the overlying skin. RIAS was also reported in 5 cases as secondary to mammosite based intra-cavitary brachytherapy at a latency period of 4, 6, 7, 8 and 9 years respectively [10-14]. It consists of placing a catheter with a balloon at its tip into the tumor bed then sending radioactive seeds through the catheter,

RIAS usually manifests itself as painless patches, plaques, or nodules on the previously irradiated skin. The median time from breast irradiation to the development of breast angiosarcoma is 8.9 years [15]. Our present case occurred earlier than 5 years. The prognosis of RIAS is generally poor, and affected by multiple variants, including age of patient, [8, 16] tumor size, [8, 17-21] histological grade [17, 19, 21-23] and difference in clinical image of patients which eventually leads to diagnosis delay [24]. RIAS is managed by a multidisciplinary team. For localized tumors, surgery with negative margin, usually 3 cm for RIAS, is the standard of care, with/without radiotherapy to reduce local recurrence [25, 26]. The standard recommendation for RIAS is total mastectomy with radical excision of all radiated skin even outside the breast margin. Tumor in our present case recurred soon after complete resection and even within the skin graft.

The value of chemotherapy in the treatment of RIAS is limited and survival is poor. Trials of taxane based chemotherapy reported responses up to 54% with overall survival rates up to 19.5 months [28]. The tumor in our reported case was refractory to several lines of chemotherapeutic agents including taxanes, anthracylices, ifosphamide and a combination of gemcitabine with antiangiogenic bevacizumab therapy. A trial of cabozantinib with nivolumab has not shown any tumor regression over the last month. Supportive care, including narcotics for chest wall pain was required and continued throughout the management. Treatment with hyperthermia and re-irradiation with or without surgery were reported in a study to show a complete response rate of 56 %, with a local control rates of 46% at 3 years [29]. In conclusion, we report the first case of a RIAS that occurred within 5 years after treatment with BCS and external beam APBI. Patients should always be well informed of this potential, though rare, life-threatening complication, especially in patients who are candidates for omission of radiation therapy [30-33]. This case report emphasizes raising awareness among physicians and patients who should be instructed to report and present for any discolored cutaneous changes that they may notice in the irradiated area of their breast. Early histological diagnosis and surgical resection with wide margins offer the best results. A high clinical index of suspicion, early diagnosis and multidisciplinary management are most important.

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