CLINICAL VIGNETTE

Radiation-Induced Angiosarcoma Post-Adjuvant Breast Cancer Therapy

Dong Ho Shin and Rena Callahan, MD

Case Presentation

A 70-year-old female with invasive ductal carcinoma presented with a progressive rash on her left breast. In 2016, the patient was diagnosed with left breast cancer and underwent left breast lumpectomy and sentinel lymph node biopsy. Pathologically, the tumor was characterized as pT2N0(i-)Mx, multifocal (2.4 cm, 0.8cm), Scarff-Bloom-Richardson grade 7/9, with high-grade ductal carcinoma in situ (DCIS). The tumor was estrogen receptor positive, progesterone receptor positive, and HER2 negative via IHC and FISH analysis. She received adjuvant chemotherapy with 4 cycles of docetaxel 75 m2/m2 and cyclophosphamide 600 mg/m2 and radiation therapy (XRT), which was completed February 2017.

In August 2020, she noticed a discolored, dime sized left breast skin lesion that was unresponsive to antibiotics and without underlying mass. MRI imaging demonstrated post-radiation skin thickening but no adenopathy or recurrent or occult malignancy. A superficial biopsy of the breast was ordered but was delayed for six months after the patient contracted COVID-19. By this time skin lesion increased to a 3-1/2-inch demarcated erythematous eruption, associated with constant pain descried as “vice grip” burning. The differential diagnosis included angiosarcoma, recurrent metastatic breast cancer, chronic radiation dermatitis, radiation induced morphea, and radiation-induced lichen sclerosus. Pathology from the biopsy was positive for CD31 immunohistochemistry, consistent with a vascular origin confirming the diagnosis of angiosarcoma. PET-CT scan demonstrated FDG avid dermal thickening of the left breast without evidence of distant metastases.

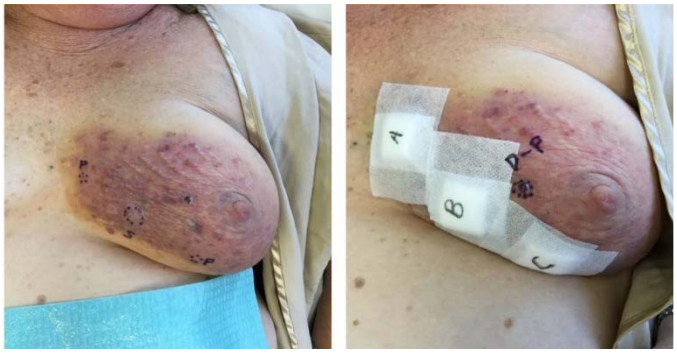

Figure 1: Skin biopsy sites for pathologic and immunohistochemical analysis.

The patient was started on neoadjuvant therapy with nab-paclitaxel/Gemcitabine and demonstrated a swift clinical response (Figure 2). Nab-paclitaxel was chosen as she had a previous infusion reaction to paclitaxel after only a few minutes of treatment on day 1 of the first cycle. After 3 cycles of treatment, she underwent an en bloc, total left breast mastectomy. Surgical pathology demonstrated a complete response to neoadjuvant chemotherapy, with no residual sarcoma in the mastectomy sample. She was then administered adjuvant chemotherapy with 3 cycles of nab-paclitaxel and gemcitabine and is doing well.

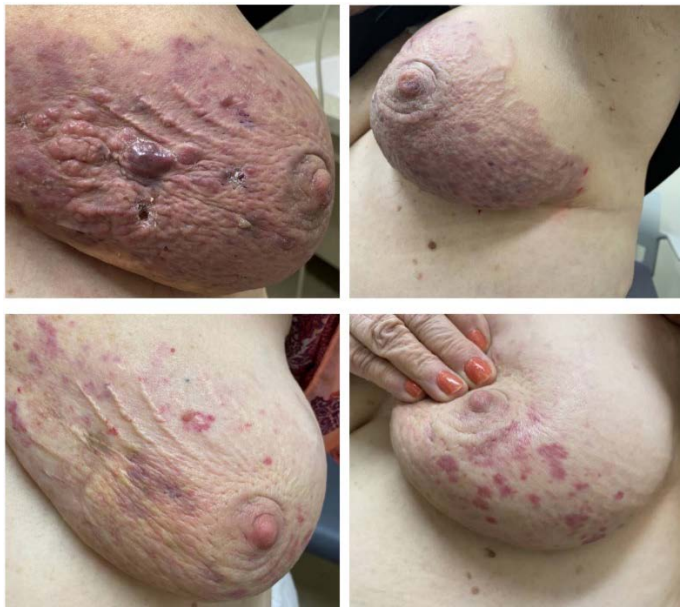

Figure 2: Left breast tissue lesions clinical presentation pre- (top) and post- (bottom) neoadjuvant therapy.

Discussion

Angiosarcoma (AS) is a rare, malignant tumor that originates from blood or lymphatic vessels. Cutaneous AS can be seen clinically as: Stewart-Treves syndrome (lymphangiosarcoma secondary to chronic lymphedema); idiopathic age-related AS, and radiation-induced angiosarcoma (RIAS).[1] AS represents 0.05% of all malignant breast malignancies and is classified as primary or secondary.[2-4] In patients with lumpectomy and combination radiotherapy (XRT), secondary breast AS has been primarily associated with radiation compared to patients with mastectomy and axillary lymph node dissection who develop Stewart-Treves syndrome.[2,3] The incidence of RIAS in

breast-conserving therapy varies from 0.14% to 0.5%.[1,3] A retrospective study of 49 patients with RIAS of the breast reported median diagnosis age at 72 years (range 51-93 years) and median time from XRT completion to diagnosis of 7.5 years.[5] Another study reported latency of RIAS development ranged from 6 months to 41 years and averaged 6 years after completion of radiation therapy.[1,2,6] The prognosis of RIAS is poor with a review of 222 patients reporting 43%, overall survival and 5-years local recurrence-free survival at 32%.[7]

There are several proposed mechanisms of pathogenesis of radiation-induced angiosarcoma. Ionizing radiation promotes several cancer-related genomic alterations, specifically p53 inactivation,[8,9] *MYC* amplification at 8q24 region,[8-10] FLT4 amplification (resulting in *myc* amplification),[6] and KDR mutation.[6] In addition to its direct oncogenic effects, radiation therapy could cause ischemia with resulting cellular repair defects[11] and promote malignancy/lymphedema from pre-existing benign lesions.[12]

RIAS presents with ill-defined nodular purpura, dermal thickening, edema, ulcerations, or dimpling.[2] These features can distinguish RIAS from hemangioma, which produces well-circumscribed, smaller lesions,[13] and atypical vascular lesions (AVLs), which present with pink, erythematous papules in comparison to the RIAS's purpura plaque.[1] Pathologically, RIAS is described by endothelial cells with scarce cytoplasm and nuclear atypia[14] which are usually high-grade with infiltrative growth.[1] Angiosarcoma can be diagnosed with immunohistochemical staining of vascular antigens CD31, CD34, factor VIII-related antigen, FLI1, and ERG, among which CD31 is most specific to the endothelial cell and most sensitive.[3,15]

RIAS of the breast has been studied in small retrospective studies and case reports, and, does not have standardized, evidence-based treatments. Current treatment typically involves mastectomy.[2] A review of 76 patients compared half who underwent "radical" mastectomy including all irradiated skin vs. partial "conservative" skin resection. Those with mastectomy had improved 5-year recurrence rate (23% vs. 76%, $p<0.01$) and 5-year disease-specific survival (86% vs. 46%, $p<0.01$).[16] However, even with R0 resections, several studies reported high rates of local recurrence, ranging from 65% to 73%,[15,17,18] which may be attributed to tumor multifocality and microsatellite lesions.[15]

With high recurrences, adjuvant therapy may be of therapeutic benefit.[19] However, there are no prospective studies to date demonstrating improved survival with adjuvant chemotherapy in nonmetastatic, resected RIAS. A retrospective study of RIAS patients who received surgery and adjuvant chemotherapy vs. surgery alone reported lower local recurrence rate but no impact on distant recurrence or OS.[20] In addition, several retrospective studies reported adjuvant chemotherapy was not a significant prognostic factor for disease-free survival.[21-23] RIAS case reports have shown possible therapeutic benefits with paclitaxel chemotherapy (PTX). Suzuki et al[19] and Nakamura et al[24] reported weekly PTX resulted in freedom from recurrence for 8 months and 15 months. Regardless, without prospective clinical studies, the survival benefit of adjuvant therapy remains unclear.

Conclusion

We present a patient with radiation-induced angiosarcoma (RIAS), which has a poor prognosis. Our patient's clinical presentation and the immunohistochemistry of the skin biopsy allowed us to diagnose RIAS, versus other benign skin conditions, such as hemangioma. Although total mastectomy is the current standard treatment, both neoadjuvant and adjuvant therapy potential to improve disease-free survival requires further study.

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