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CASE REPORT

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Loss of TSC1 in secondary angiosarcoma of the breast

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Key Clinical Message

Post-radiation angiosarcoma of the breast is a rare complication associated with a poor prognosis. This case reports the first loss of function mutation in TSC1 in breast radiation-induced angiosarcoma and illustrates the utility of evaluating these markers to identify potential therapeutic targets.

Abstract

Post-radiation angiosarcoma of the breast is rare and associated with a poor prognosis. This case presents the first loss of function mutation in TSC1 in breast radiation-induced angiosarcoma. Evaluation of these markers can aid in identifying potential therapeutic targets.

KEYWORDS

breast cancer, mTOR inhibitors, nab-sirolimus, radiation, radiation-induced angiosarcoma, TSC1 mutation

1 | INTRODUCTION

Radiation-induced angiosarcoma of the breast (RIAS) is rare and develops in only 0.2% of patients who undergo breast radiation therapy.[1] The risk of secondary breast sarcoma peaks around 7 years following completion of radiation therapy as seen with our patient.[2,3] Risk factors such as increasing doses of ionizing radiation, lymphedema and breast cancer 1 (BRCA1) or ataxia-telangiectasia mutations (ATM) increase the risk of RIAS; however, despite our knowledge of these risk factors, we are unable to currently predict which patients will develop RIAS.[4] Radiation-induced angiosarcoma has a poor prognosis with a 5-year overall survival of less than 20% due to limited therapeutic options.[5] In these rare cancers, evaluation of genomic variants to identify potential therapies is integral.

2 | CASE HISTORY/EXAMINATION

A 60-year-old female patient presented to the breast clinic with a "little bruise" for 3 months. The patient had a history of right breast cancer, stage 1A, grade 2, invasive lobular carcinoma (ILC), estrogen receptor (ER) positive (60%–70%), progesterone receptor (PR) positive (100%), human epidermal growth factor receptor 2 (HER2) negative by fluorescence in situ hybridization (FISH) in October 2014. She underwent a partial mastectomy with sentinel lymph node biopsy. Final pathology demonstrated grade 2 ILC with two foci each measuring 0.8 cm. Surgical margins were negative for malignancy, and the four lymph nodes negative for malignancy. She completed radiation therapy in January 2015 with 5000 cGy in 25 fractions to the whole right breast followed by a boost of 1400 cGy in

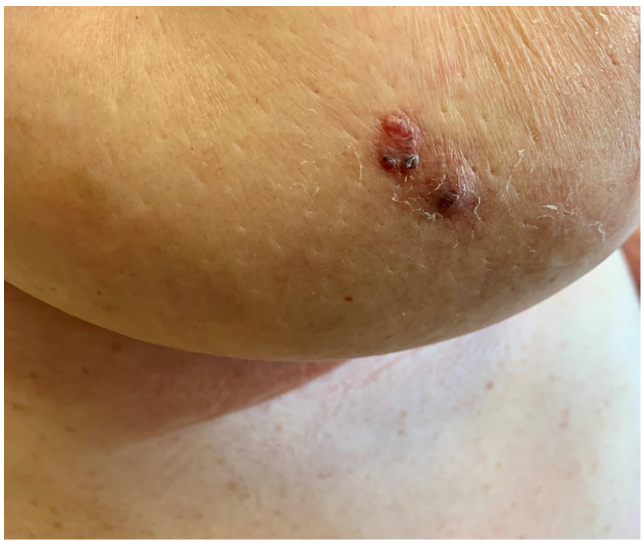

FIGURE 1 Hyperpigmentation of right breast.

seven fractions for a cumulative dose of 6400 cGy to the lumpectomy cavity. Her Oncotype Dx score of 18 with 11% risk of recurrence within 10 years with 5 years of tamoxifen. She completed 5 years of adjuvant tamoxifen. Her screening mammogram in October 2021 was breast imaging-reporting and data system (BIRADS) 2 with bilateral benign calcifications.

The patient noticed the bruise in May 2022, 7 years and 7 months after her initial breast cancer. Over the next few months, she noted deepening of pigmentation and increased firmness in the area. On examination, hyperpigmented lesions were found on the lower inner and outer quadrants of her right breast (Figure 1).

3 | INVESTIGATION AND TREATMENT

Ultrasound revealed skin thickening and hyperemia of the areas of concern. Mammogram confirmed skin thickening but did not identify any concerning masses, calcifications or areas of distortion. Punch biopsies of the two sites demonstrated angiosarcoma. On immunohistochemical stains, the cells expressed CD31, CD34, ERG, and D2-40 while lacking AE1/AE3 and GATA3 (Figures 2–4). In addition, PD-L1 was positive with tumor proportion score (TPS) > 1% on immunohistochemistry (IHC) while DNA mismatch repair protein nuclear expression was present. Given that mammographic evaluation did not identify any intramammary abnormalities, magnetic resonance imaging (MRI) was performed to further evaluate for any intraparenchymal disease. MRI breast showed diffuse right breast skin thickening with numerous dermal/subdermal masses as well as patchy nodular dermal enhancement

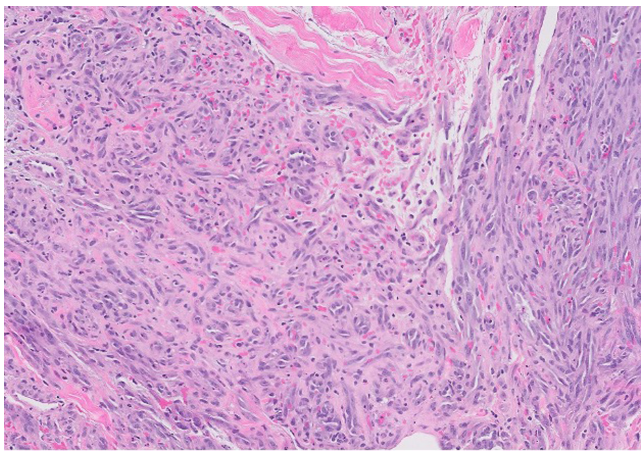

FIGURE 2 Differentiated area with slit-like vascular spaces and relatively bland cytology (hematoxylin and eosin, 10×).

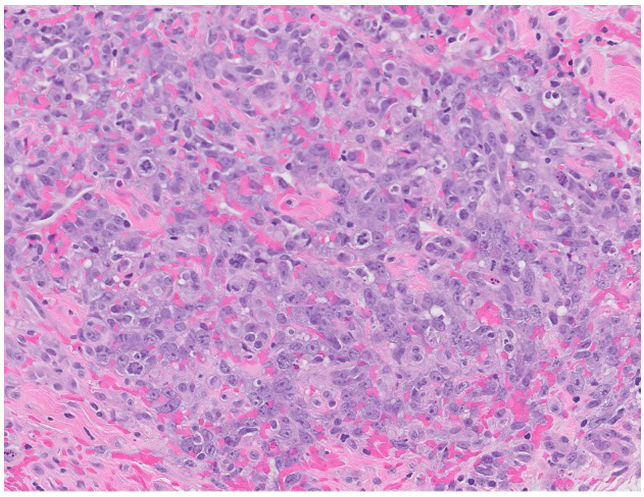

FIGURE 3 Anaplastic area with solid growth of high-grade epithelioid cells; note mitotic figures (hematoxylin & eosin, 20×).

reflective of known angiosarcoma (Figure 5). Staging chest computed tomography (CT) and positron emission tomography (PET) scan were without evidence of metastatic disease.

The patient had a significant family history of breast cancer. Her mother and sister both were diagnosed with recurrent breast cancers. Her sister was found to have a pathogenic CHEK2 mutation. As a result, Tempus next generation deoxyribonucleic acid (DNA) sequencing was performed on her skin biopsy specimen, which demonstrated copy number gains of MYC and a loss of function mutations of tuberous sclerosis complex 1 (TSC1) due to frameshift mutation c.1383del.

The patient was presented at multidisciplinary tumor board and neoadjuvant gemcitabine/docetaxel for 4 cycles followed by total mastectomy and then six cycles of adjuvant gemcitabine/docetaxel was recommended.

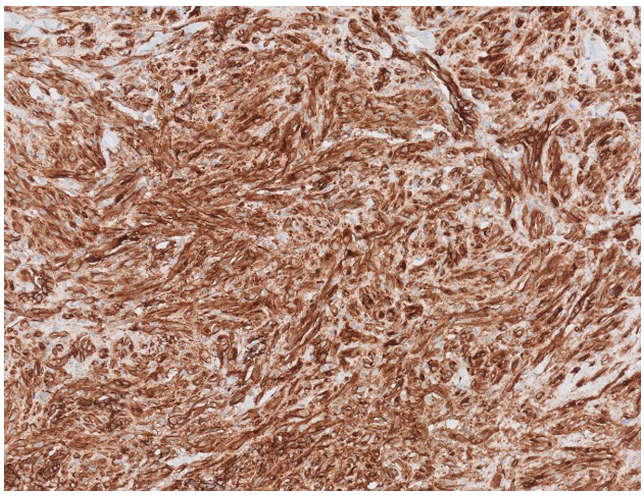

FIGURE 4 Strong staining with immunohistochemical stain for CD31, a marker of endothelial cells; a similar pattern was seen for CD34 (10×).

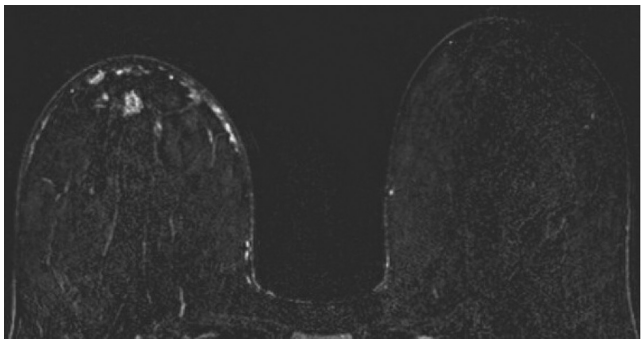

FIGURE 5 MRI breast showing diffuse right breast skin thickening with numerous dermal/subdermal masses and patchy nodular dermal enhancement.

4 | OUTCOME

The patient is currently undergoing her neoadjuvant chemotherapy.

5 | DISCUSSION

MYC amplifications have been described in breast RIAS; however, loss of function mutations in TSC1 have not.[6] TSC1 is a tumor suppressor gene in the mammalian target of rapamycin (mTOR) pathway, and alterations of TSC1 are found in 2.15% of all cancers including breast invasive ductal carcinoma.[7,8] mTOR is a promising target for these rare cancers, and some inhibitors have already been approved with many more being evaluated in clinical trials. Targeting mTOR with *nab*-sirolimus in advanced malignant perivascular epithelioid cell neoplasm patients with TSC1/TSC2 mutations demonstrated a response rate of 39% in the Advanced Malignant PEComa (AMPECT) trial.[9] Five patients within the study had TSC1-mutated sarcomas. One patient had a partial response with nab-sirolimus while three patients had stable disease. These results identify TSC1 as a marker for potential targeted therapy and suggest there may be a role for nab-sirolimus in treatment or breast of RIAS. This case reports the first loss of function mutation in TSC1 to our knowledge in breast radiation-induced angiosarcoma and illustrates the utility of evaluating these markers to stratify patients for future clinical trials and therapeutic options. Despite increasing incidence of RIAS given widespread use of breast conserving therapy for breast cancer, it remains rare, and as such, identification of these markers may become essential for management of radiation-associated angiosarcoma.[10]

AUTHOR CONTRIBUTIONS

Lucy Rose: Writing – original draft. **Nicci Owusu-Brackett:** Writing – original draft; writing – review and editing. **Stephen Moore:** Resources; visualization. **Bridget Oppong:** Conceptualization; resources; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this article are available from the corresponding author on reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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