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Case Report

Radiation-associated breast angiosarcoma after strut-adjusted volume implant brachytherapy ☆,☆☆

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ABSTRACT

Angiosarcoma is a rare malignancy that may classically occur in the post-treatment breast. Radiation and post-treatment edema have been identified in the literature as causative risk factors. Modern treatment innovations have provided patients with more targeted radiation therapy and more conservative surgical options, which may individually limit exposure to these risk factors. Advanced treatment options are also able to provide superior cosmetic outcomes that can positively impact patient quality of life. Despite the ability for modern treatment options to mitigate post-treatment morbidities, there is still long-term risk to the patient of developing treatment-related pathologies, such as breast angiosarcoma. Here we present a patient who underwent lumpectomy and received targeted brachytherapy through a strut-adjusted volume implant device to her lumpectomy site. Her initial post-treatment course was mildly complicated by localized breast lymphedema, which resolved and left the patient with favorable cosmetic results. She developed treatment-associated breast angiosarcoma after initial breast conservation therapy was completed approximately 6 and a half years prior. Her presenting physical exam and imaging findings are portrayed with a comprehensive discussion of the commonly described presenting clinical features and imaging findings of breast angiosarcoma. Factors related to radiation treatment planning and use of the strut-adjusted volume implant device are also discussed. Comparisons between primary and secondary breast angiosarcoma are made, and a review of treatment options is given.

Introduction

Angiosarcoma is a rare vascular soft tissue tumor originating from vascular endothelium and reflecting less than 1% of breast malignancies [1,2]. Primary and secondary angiosarcomas can occur within the breast with secondary breast angiosarcoma more classically associated with radiation, edema, poor prognostic outcomes, and recurrence. In applicable post-treatment settings, secondary breast angiosarcoma may be

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referred to as radiation-associated breast angiosarcoma. Advancements in the diagnosis and treatment of primary breast malignancy have expanded the characteristically older patient base more commonly provided with treatment options, including breast conservation therapy, which increases the population at-risk for post-treatment-induced pathologies. Popular innovations in radiation therapy, such as accelerated partial breast irradiation (APBI), have sought to enhance post-treatment cosmesis while minimizing post-treatment risks in contrast to whole breast irradiation (WBI), by allowing higher dose treatment to smaller breast tissue volumes over a shorter treatment regimen period. APBI can be delivered through application of a strut-adjusted volume implant (SAVI) brachytherapy device to target the treatment dose to the excisional site. Here we present a patient who developed secondary breast angiosarcoma after undergoing APBI administered via SAVI to her lumpectomy site. Awareness of the increasing application of these contemporary techniques in the expanded treatment of primary breast malignancy calls to recognition the probable associated risks of radiation-induced sarcoma.

Case

Patient presentation

The patient initially presented for treatment of invasive ductal carcinoma of the left breast. The primary tumor was discovered upon diagnostic characterization of an inner left breast asymmetry noted on an outside facility screening mammogram. The initial primary tumor was highly estrogen and progesterone receptor positive and HER-2/Neu negative without angiolymphatic invasion. Excisional margins were negative. Adjuvant high-dose radiation brachytherapy was initiated soon after diagnosis, and treatment planning actively minimized skin dose. The patient completed a regimen of 3 fractions that were delivered with the SAVI mini device. The initial post-treatment course was mildly complicated by asymptomatic left breast lymphedema for which a compression brassiere was recommended. Early post-treatment diagnostic imaging demonstrated expected post-treatment edema. Favorable symmetry, healing, and overall cosmesis were reported by the patient during post-treatment follow up visits with radiation oncology.

Approximately 6 and half years after initial treatment and presentation, the patient reported progressive left breast “bruising” and discomfort, worsening over the course of months. Diagnostic breast imaging demonstrated skin thickening and edema (Fig. 1). Biopsy was performed at an outside facility and pathology was designated as benign and reflective of fibrosis and lymphohistiocytic infiltrate. Left breast skin punch biopsy was soon after performed, and pathologic findings were consistent with high-grade angiosarcoma. PET/CT and breast MRI were performed for further assessment of local and possible distant disease. MRI assessment depicted enhancing left breast skin thickening with nodular enhancement just deep to the skin findings, and mild non-mass enhancement extending to the site of prior lumpectomy (Fig. 2).

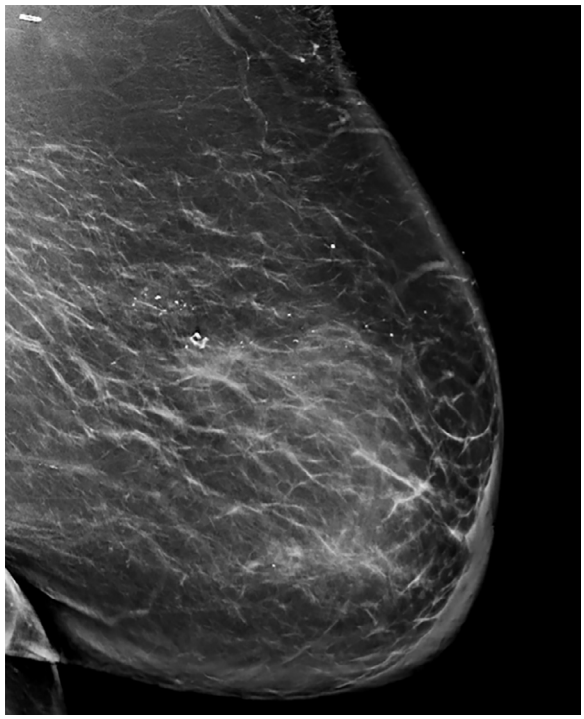

Fig. 1 – Mammogram mediolateral oblique (MLO) view of the left breast. Study was performed for assessment of skin changes noted years after initial breast conservation therapy. Note trabecular thickening and overall increased breast density. Skin thickening predominantly distributed over the anterior breast.

PET/CT demonstrated avid uptake within the thickened left breast skin (Fig. 3). The patient resumed multidisciplinary care with a treatment plan consisting of chemotherapy followed by radiation and subsequent surgery.

Discussion

Background

Though more common than primary, secondary breast angiosarcoma occurs rarely after breast conservation therapy (BCT) as a result of treatment-associated radiation and lymphedema; however, increasing frequency has been reported as a consequence of increasing incidence of BCT utilization for management of primary breast malignancy [3–6]. In contrast though, the frequency of lymphangiosarcoma in the setting of chronic lymphedema, also known as Stewart-Treves syndrome, after axillary dissection and radical mastectomy has declined because of rising implementation of BCT [7].

As primary breast malignancies treated with breast conservation more commonly occur in older women, they are also the more common demographic for developing secondary breast angiosarcoma [1,5,8]. And with increasing early detection, more patients are diagnosed with primary breast malignancy and undergo BCT, leading to increased radiation exposure and instances of post-treatment edema [8]. This logic has

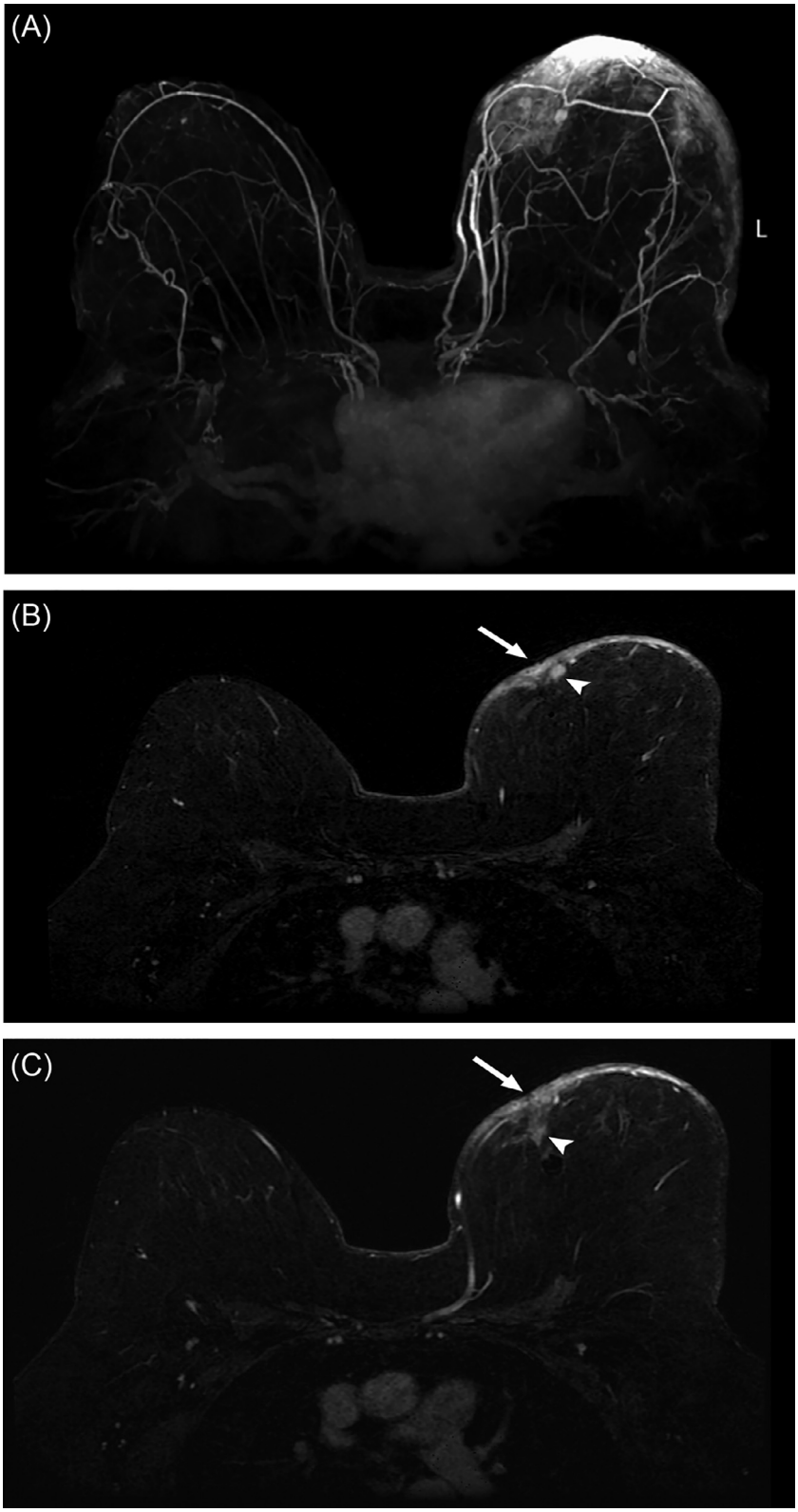

Fig. 2 – Bilateral breast MRI post-contrast subtraction Maximum Intensity Projection (MIP) (A). Axial post-contrast subtraction MRI images (B and C). Images depict asymmetric peripheral left breast enhancement with nodular enhancement just deep to thickened skin (arrows and B arrowhead). Note non-mass enhancement extending from the thickened, enhancing skin to the site of prior lumpectomy (C arrowhead).

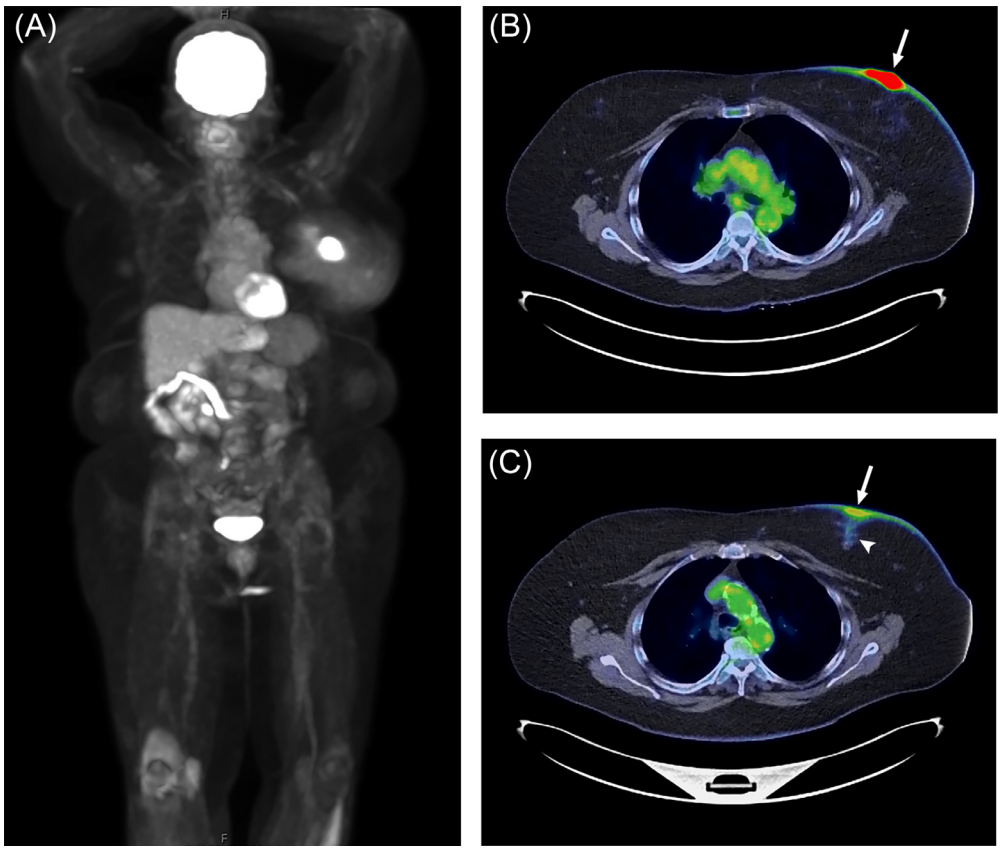

Fig. 3 – PET/CT 3D Maximum Intensity Projection (MIP) (A). Axial PET/CT (B and C). Images depict asymmetric left breast uptake and focal inner left breast avidity better appreciated on 3D MIP. Fluorodeoxyglucose (FDG)-avid left breast skin thickening (arrows) and mild avidity extending to the site of prior lumpectomy (C arrowhead).

been used to explain the rising incidence of this still rare tumor, which continues to compose less than 1% of breast malignancies [1,2]. A retrospective clinicopathologic review performed by Fodor et al. assessing patients of mean age 72, previously diagnosed with and conservatively treated for primary breast malignancy, demonstrated a mean post-BCT latency period of 6 to 7 years prior to clinical onset of post-treatment angiosarcoma with an estimated incidence of 0.14% [4]. A systematic review performed by Soto et al. found a median age at diagnosis of 71 with a latency period ranging from 0.5 to 14.9 years and a median latency of 6.0 years [8].

Although angiosarcoma has been reported in patients treated with surgical management alone without radiation, radiation-induced parenchymal change has been proposed as a pathogenic contributor given the co-occurrence of angiosarcoma in patients given radiotherapy [3,4]. It has been hypothesized that multifactorial post-treatment contributors to breast edema and fibrosis occurring with either surgery or radiotherapy create lymphangiogenic microenvironments which foment tumor development and progression [3,4,9]. Radiation treatment and chronic lymphedema are accepted independent factors reported to contribute to the development of secondary angiosarcoma [3,5,8,7]. Increased risk has been described in patients with genetic mutations associated with increased risk of primary breast malignancy, providing additional factors for treatment consideration and patient discussion [10].

Secondary breast angiosarcoma usually originates within the dermis, rarely developing within the breast parenchyma proper [3]. Systematic low, intermediate, and high grading can be applied to pathologic findings with reported prognostic implications most unfavorable for high-grade tumors, which occurs with higher frequency in cases of secondary breast angiosarcoma [1,7]. Pathologic findings of low-grade angiosarcoma may resemble atypical post-radiation vascular lesions and may result in a dilemma of pathologic concordance [7].

Clinical presentation

Initial concerning findings suggesting tumor proliferation usually originate within the dermis, as opposed to primary breast angiosarcoma, which more frequently originates within the breast parenchyma proper [5,11]. Commonly reported presenting findings consist of blue, black, purple, or red skin nodules or ulcerations, though patients may display concomitant progressive edema and skin thickening [3,4,12]. Ecchymosis, erythema, and violaceous macules and papules have been described as presenting findings [11,13]. Skin changes and discoloration may be mistaken for bruising or hematoma, so careful correlation for recent trauma

is necessary, though trauma may in turn call attention to skin findings consistent with intradermal tumor [5-7,14,15]. Concerning early findings can also occur in the chest wall within the radiation field [7].

The presence of multiple skin lesions at presentation is associated with lower 2-year survival rates, and the overall number of lesions has been a reported predictor of overall survival [4]. To mitigate these risks post-BCT skin surveillance is a recommended component of patient management [4]. In the presence of questionable persistent skin changes, the clinical history of BCT may be the deciding factor inciting further follow-up and performance of cutaneous punch biopsy to acquire confirmatory histology, even prior to imaging acquisition [13–15]. After surgical excisional biopsy, data supports cutaneous punch biopsy as a slightly superior mechanism for pathologic diagnosis over core needle biopsy [14].

Importantly, additional pathologies which may confound the diagnosis of post-treatment angiosarcoma should be recognized. Perioperative breast cellulitis, presenting as erythema and edema, may occur prior to radiation therapy and may also demonstrate post-radiation relapse or develop after seroma aspiration [4]. Radiodermatitis is a commonly encountered acute to subacute progressive prodrome of radiation-induced skin toxicity usually encountered within weeks to months of radiotherapy, following an expected progression that conforms to established grading paradigms. Primary angiosarcoma is overall extremely rare but may present within the breast, more commonly originating from the breast parenchyma and usually affecting younger patients with dense breasts, possibly presenting as a palpable mass [3,5]. Atypical vascular lesions are benign lymphovascular tumors that may appear after radiation treatment and may resemble low-grade angiosarcoma clinically and pathologically [7].

Imaging

Mammography may display asymmetries or trabecular and skin thickening as accompanying imaging findings consistent with edema; nonspecific findings may be misinterpreted as expected post-treatment changes [5,6,11]. Skin and trabecular thickening producing increased breast density should diminish within 2 years post-radiation so that reappearance of these findings or findings within a site separate from lumpectomy but still within the radiation field should raise concern for interval pathology [11]. In younger patients presenting with dense fibroglandular tissue, sonography may be a fruitful supplement to indicate an underlying intraparenchymal mass. Sonographic presentation may range from hypervascular circumscribed or indistinct hyperechoic to hypoechoic masses, with cases of mixed echogenicity and lack of a discrete mass described [3,5]. Intradermal disease may only reveal skin thickening, which may generally be expected in post-treatment patients [5]. Contrast-enhanced mammography may similarly depict skin and trabecular thickening with mass or non-mass enhancement, though skin enhancement may prompt concern for underlying vasoformative neoplasm [16]. Initial diagnosis can be challenging in spite of appropriate imaging [8].

Breast MRI may depict tumor extent and assist in surgical planning for resection of local disease but rarely demonstrates a distinct mass [4,5]. If a mass is evident, then characteristic features involve gross signal heterogeneity encompassing predominant T1 hypointensity and T2 hyperintensity, though hemorrhage and venous lake formation in higher-grade tumors may confer areas of T1 hyperintensity; higher grade tumors also more aptly display rapid enhancement and washout kinetics [5,11]. MRI signal characteristics may also be attributed to necrosis and cystic degeneration, and intermittent hemorrhage may result in a visualized hemosiderin ring [6]. Cross-sectional imaging may demonstrate enhancing skin nodules within the thickened, enhancing dermis consistent with dermally based disease [5,14]. Nodular dermal enhancement alone may be the only pertinent MRI finding with suspected presence of neoplasia confirmed after surgical excision [17]. Multicentric disease with relatively large tumors is also commonly encountered and can be further characterized with cross-sectional imaging [5]. FDG avidity has been demonstrated with angiosarcomas, allowing for supplemental staging with ^{18}F-FDG PET [5].

Radiotherapy considerations

Radiotherapy techniques have evolved to deliver high doses more accurately to targeted volumes; however, proposed dose-related risks including post-treatment radiation-induced sarcoma have been described [18]. Volumetric modulation arc therapy (VMAT) in the administration of radiotherapy can increase radiation exposure to surrounding normal tissue by increasing the dose per delivered fraction, though this advanced technique of intensity-modulated radiation therapy (IMRT) may allow for specific volumetric tumor targeting in an effort to reduce surrounding dose [19,18]. APBI, which may be performed via a SAVI brachytherapy device (a form of air-filled single-entry brachytherapy delivery) may be delivered utilizing VMAT techniques of IMRT delivery with shorter overall treatment regimens when compared with WBI. The goal of APBI is focused exposure to the target site and a relatively narrow margin of bordering tissue as opposed to the whole breast in WBI, which allows for higher dose delivery to the target volume over a shorter time period.

APBI is a common option for radiotherapy in patients with early local malignancy amenable to conservative resection and may be delivered via three primary brachytherapy methods: interstitial implants, liquid-filled single-entry devices, or air-filled single entry devices [20]. The SAVI brachytherapy device can be directly inserted into an excisional site, such as the lumpectomy bed, for direct radiotherapy administration at exact points within the operative site in an effort to further reduce dose to site adjacent normal tissue [21,22]. Superior cosmesis and quality of life compared to WBI, with minimal to no instances of fat necrosis or other persistent breast changes, have been recounted with SAVI usage [19,22].

Treatment criteria and dosimetric guidelines for SAVI delivery of APBI, such as limits to maximum acceptable skin dose, can vary by institution, and dose to the excisional site may be necessarily sacrificed to reduce skin dose [23]. Treatment planning considerations, including small breast volume, small excisional sites with small treatment target volumes, and short target to skin distance, may act as exclusionary criteria when considering treatment strategies [24]. Breast

mobility between treatments may also contribute to dose exposure to variable volumes of normal surrounding tissue, but favorable non-target organ doses have been reported [24]. It has been proposed that these techniques slightly increase the risk of secondary malignancy in treated patients with specific consideration for radiation-induced sarcoma development at 15 to 20 years within areas receiving doses of 10 to 15 Gy [18].

Management and treatment

The high-grade propensity of post-BCT secondary breast angiosarcoma contributes to a habitually poorer prognosis compared to primary breast angiosarcoma [2,18]. Current treatment options for radiation-induced breast angiosarcomas are limited, as these tumors commonly are not amenable to surgical or chemotherapeutic management or further radiotherapy [4].

Axillary-sparing total mastectomy is a proposed primary management option, unless evident pathologic lymphadenopathy is present [3,25]. Axillary nodes are usually nonpathologic in appearance, as distant hematogenous metastasis is more characteristic, but lymph node metastasis may occur in a few patients [6,26–28]. Unfavorable axillary status has been described as a primary poor prognostic indicator and is considered stage IV disease by the American Joint Committee On Cancer, warranting axillary assessment [27]. Sentinel lymph node biopsy and axillary dissection combined with mastectomy have been reported as surgical management components of treatment planning [29].

The benefit of mastectomy over conservative breast surgical management has been questioned, as a lack of statistically significant comparative prognostic benefit has been shown [1]. Nevertheless, surgical management with the goal of resecting the entire irradiated field with wide margins has been advocated [10,14,17,29]. High incidences of recurrence after radical mastectomy have been reported with short post-mastectomy latency periods ranging from 1 to 5 months [4]. In spite of local treatment efforts, skin graft recurrence has also been reported within 1 year of attempted curative mastectomy [30]. Multiple recurrences have been characteristic in contributing to the overall high recurrence rate [2]. A multidisciplinary treatment review of cases of radiation-associated breast angiosarcoma performed by Guram et al. reported reduced recurrence in patients treated with a sarcoma-targeted multidisciplinary team effort, with more patients attaining 3-year local recurrence-free survival periods, suggesting additional factors may assist in prolonging a recurrence-free treatment course [12].

The ability to perform complete surgical resection with negative margins remains an important prognostic factor in attempting to mitigate recurrence, though prognosis remains poor [1,5,9,10,28]. Higher grade tumor, delayed diagnosis, larger size, and incomplete resection are reported poor survival indictors [7,29]. Presence of distant metastasis has been correlated with larger lesion size at presentation and higher mortality, compelling ^{18}F-FDG PET staging [11,28].

Prior radiation to the affected site may limit treatment planning and role of repeat radiotherapy, though successful prognoses have been reported with the use of hyperfractionated radiotherapy in patients presenting with secondary post-radiation breast angiosarcoma [4,5]. Electrochemotherapy as an adjunct has been reported to produce a favorable response [3]. Hyperthermia utilization as a radiosensitizing mechanism has been combined with accelerated radiotherapy techniques with reported favorable results [29]. Antiangiogenic agents which inhibit the effects of factors such as vascular endothelial growth factor (VEGF) are also utilized for treatment, though more data regarding pathogenesis is necessary to refine more targeted therapies, as VEGF expression is more commonly associated with lower grade tumors [3,10].

Conclusion

Secondary breast angiosarcoma is a rare malignancy presenting in older post-treatment patients with more likely higher grade and locally advanced tumor at the time of presentation. As components of radiation treatment planning, APBI delivered through a SAVI brachytherapy device can multifactorially augment radiation exposure post-surgery through its ability to deliver higher, more focused doses to less breast tissue volume than WBI, though more information on outcomes would be beneficial. APBI techniques are capable of superior cosmesis and patient quality of life compared to WBI; however, our case may demonstrate persistent post-radiation risks, including radiation-induced angiosarcoma.

Poor prognosis can be mitigated to a degree by early recognition, prompt tissue diagnosis, and complete resection, though recurrence is likely. The high risk of recurrence and mortality in addition to the morbidity risk associated with attempted tumor burden control accentuate the necessity of early prodrome recognition and patient diagnosis. Imaging observations in patients presenting with clinical findings of concern may be ambiguous and nonspecific and should not hinder attempted tissue diagnosis through cutaneous punch biopsy. Clinical surveillance of post-BCT patients is a critical component allowing for early diagnosis. Addressing post-treatment lymphedema is also of note and is not only important for patient quality of life but also relevant to mitigating associated comorbidities.

In patients with intraparenchymal secondary breast angiosarcoma, initial imaging may more aptly demonstrate a distinct breast mass or localized parenchymal pathology. Local staging with dedicated breast MRI is central to treatment planning by characterizing regional extent of disease ^{18}F-FDG PET assists in characterizing locoregional disease and identifying distant metastasis, which may be particularly characteristic of locally extensive disease. Imaging contributions play a vital role in characterizing disease extent for further treatment planning, assisting in the feasibility of complete resection.

Patient consent

The patient in this case report signed a consent form to allow for her de-identified imaging and history to be used for research purposes, including publication. She also has

Minnesota Research Authorization consent to use her de-identified information.

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