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Case report

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Local therapy for radiotherapy-associated angiosarcoma of the breast after organ-sparing treatment of primary breast cancer patients. A report of two cases and review of therapeutic options

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Radiotherapy-associated angiosarcoma of the breast in breast cancer patients is a rare, poor-prognosis malignancy. Surgical resection with mastectomy is the standard local treatment for this disease. We present two cases of localized secondary angiosarcoma of the breast following breast-conserving therapy for early breast cancer, who underwent salvage mastectomy with R0 resection, followed by chemotherapy in one case. Both patients developed thoracic wall recurrence, and received palliative radio- and chemotherapy. In 23 months after being diagnosed with angiosarcoma, they died of uncontrolled local and distant disease. Our cases confirmed the high risk of local failure after salvage mastectomy due to radiotherapy-induced angiosarcoma. Based on literature, better local control might be achieved with more aggressive surgical approach with excision of all irradiated skin and soft tissue, and with re-irradiation.

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Introduction

Radiotherapy is an essential part of breast-conserving therapy (BCT) for early breast cancer patients. It decreases loco-regional recurrence rates and improves overall survival (OS). Radiotherapy, however, has been associated with increased second cancer risk at exposed sites, including sarcomas. Five or more years after breast cancer radiotherapy, there is more than two-fold increase of second sarcomas (the estimated relative risk (RR) of 2.41). This risk was particularly evident for angiosarcoma (RR of 7.63 and of 13.7 among +1-year and +5-year survivors, respectively) [1, 2]. Post-irradiation breast angiosarcoma (AS), the most frequent second type of sarcoma after primary breast cancer, has been increasingly reported, since currently most women with breast cancer have long-term survival [3].

ASs are rare malignant tumors that arise from endothelial cells, lining vascular channels. These tumors are characterized by rapid proliferation and extensive infiltrating growth. Angiosarcomas account for 0.0005–0.05% of all malignant breast neoplasms. Secondary angiosarcoma of the breast is found in women who have undergone breast-conserving surgery (BCS) and radiotherapy or chest wall radiotherapy. There are two types of this tumor: lymhedema-associated cutaneous angiosarcoma, first described in 1948 by Stewart and Treves, and post-irradiation angiosarcoma. The first case of radiation-associated angiosarcoma (RAAS) after BCS and radiotherapy was reported in 1981 [4]. The latency of RAAS is usually 3–12 years (median 7 years), but it can be up to 30 years [1, 4, 5]. Extra chest wall metastases of RAAS including liver, lung, lymph nodes are rare, showing a spreading pattern different from that of primary angiosarcoma of the breast [6].

We present two cases of RAAS of the breast in BCT patients who underwent mastectomy and recent treatment options for such cases.

Case report

Two cases of RAAS after BCT were identified among 320 patients treated at the Medical University of Gdańsk, Poland, between 2000 and 2007 (Tab. I). In both, the primary surgery consisted of upper-outer quadrantectomy and axillary lymph node dissection. Adjuvant radiotherapy consisted of

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Table I. Characteristics and outcomes of two cases with secondary angiosarcoma of the left breast (located in another quadrant than primary breast cancer localization)

Case	Stage of breast cancer	Pathology of breast cancer	Age at BCT	Primary therapy	Latency (years)	Angiosarcoma localization	Angiosarcoma immunoprofile	Outcome/ survival (months)
1.	cT2N1	Invasive ductal carcinoma Grade II ER, PR (+)	54	Neoadjuvant CHT (6 cycles of doxorubicin and docetaxel), BCS (with re-excision due to inadequate margin), WBRT (with supraclavicular region) 50 Gy/25 fractions + boost 15 Gy [a]	6	Skin, parenchyma	CD31 (+), LCA (–), SMA (–), CK5/6 (–), CK AE1/AE3 (–), E-cadherin (–), Vimentin (+), Podolanin (+/–)	D (23)
2.	cT1N0	Invasive ductal carcinoma Grade II ER, PR (+) HER2 (–)	61	BCS, WBRT 50 Gy/25 fractions + boost 15 Gy*, adjuvant HT (tamoxifen for five years)	9	Parenchyma	CD31 (+), CD34 (+), CK AE1/AE3 (–), EMA (–), Ki67 (+)/70%	D (23)

*The boost was given with multi-catheter pulsed-dose-rate brachytherapy (1 Gy per pulse repeated every hour) performed after whole breast radiotherapy completion or preceded breast irradiation as peri-operative procedure with intra-operative tube placement

BCT — breast-conserving therapy, HT — hormone therapy, CHT — chemotherapy, BCS — breast-conserving surgery, WBRT — whole breast radiotherapy, D — death

whole breast radiotherapy (WBRT) with tangential fields and a boost dose to the tumor bed. The first patient received neoadjuvant chemotherapy, as well as irradiation to the supraclavicular region. Six years after BCT skin redness similar to an orange peel (peau d'orange) overlaid the internal quadrants of the treated breast. Pathological examination of the skin specimen revealed no malignancy. Due to the appearance of new skin nodules with a few mm diameter, the repeated biopsy was done eight months later. The breast cancer local recurrence was diagnosed. At that moment, cancer dissemination was excluded by PET CT. The patient received docetaxel/cyclophosphamide chemotherapy and then underwent salvage mastectomy. The final diagnosis of AS epithelioides type was revealed. The slides from the previously resected skin were reviewed and showed former misdiagnosed sarcoma. Two months after mastectomy RAAS in the form of red nodules progressed rapidly along both sides of the chest wall including the contralateral breast, with a metastasis in the right axillary lymph nodes. In addition to palliative thoracic radiotherapy (30 Gy in 10 fractions) including re-irradiation of the left-side chest wall, she received chemotherapy with paclitaxel and liposomal doxorubicin but no response was obtained. In the case 2., RAAS was diagnosed after mastectomy performed due to breast tumor. Postoperatively the patient was treated with 4 cycles of epidoxorubicine. Ten months later she experienced chest wall recurrence and developed bone and lung metastases. In both cases salvage mastectomy was performed with free resection margins.

Discussion

RAAS of the breast is a rare and difficult-to-treat disease. There are no established risk factors for RAAS. Apart from radiotherapy, partial mastectomies and lymph node dissections were found to be independent risk factors for the development of breast RAAS [2]. The increasing use of newer techniques, i.e. intensity-modulated radiotherapy (IMRT) might be associated with a higher risk of mutagenesis. Due to the higher number of fields and monitor units IMRT has been shown to have greater out-of-beam doses including higher low-dose exposure of the normal structures. The addition of chemotherapy, including preoperative, an increasingly applied strategy, might have also contributed to secondary malignancy. It is not clear whether AS is induced by radiation or persistent edema, or has a multifactorial origin. In most reported RAAS cases clinical lymphedema was not identified. Both our patients underwent axillary dissection and one received supraclavicular region irradiation. Hence, in spite of lack of clinical lymphedema, they might have had some minimal subclinical lymph stasis involving the breast.

ASs grow in a multifocal pattern. Various changes in the irradiated breast have been described, with or without a palpable mass in the breast. Typically, patients present with a rapidly growing, painless breast mass within the radiation field. The overlying skin may have blue or purple discoloration. The appearance of such lesions on the irradiated breast may be confused with skin sequelae after radiotherapy, as was in our case leading to delayed diagnosis [7]. Moreover, epithelioides type, a rare subtype, can be more difficult to diagnose and must be distinguished from several diseases, including carcinoma and other sarcomas, as well as "atypical vascular lesions", which may occur after radiotherapy.

The overall prognosis for patients with RAAS is quite dismal with high rates of recurrences approaching 70–73% and poor median OS, ranging from 1.5–3 years with a 5-year OS of 15% [4]. The systematic review of 222 RAAS patients demonstrated OS of 43% at 5 years and the overall 5-year local recurrence free survival of 32% [8]. Tumor size and age were found to be independent predictors of adverse outcomes [4, 5, 8].

Surgical resection with salvage mastectomy is the standard treatment for RAAS. The patients with completely resected tumors had improved median survival compared to patients with incomplete excision [9, 10]. Long-term survival in five of six patients with breast RAAS after BCT treated with resection of all irradiated skin and associated extra-thoracic soft tissue was reported [11]. The surgical treatment was planned using radiotherapy coordination tattoos and the patient's radiation dose planning charts. Pre-operative MRI was used to determine the resection depth needed to achieve wide surgical margins in relation to the thoracic wall. The latter varied from including the deep fascia and superficial muscle tissue to include all extra-thoracic muscles and sometimes periosteal stripping of the ribs. Reconstructions were performed using pedicled m. latissimus dorsi or m. rectus abdominis flaps, and split thickness skin grafts.

A high, mostly local, recurrence rate after surgery suggests that adding re-irradiation to surgery improves the local control of RAAS [8]. There are reports of good results when hyperfractionated and accelerated radiotherapy (HART) are used, which reduces cell repopulation in these rapidly growing tumors [12, 13]. HART was given either before or after surgery [12]. With HART, patients received three radiation treatments each day, with a minimum interfraction interval of four hours, five days a week, at 1 Gy per fraction, to the total doses of 45 Gy, 60 Gy, and 75 Gy for areas with a moderate and high risk for subclinical, and gross disease, respectively [13]. After the median follow-up of 7 years five- and 10-year OS rates of 79% and 63%, respectively with HART, were achieved.

The role of adjuvant chemotherapy is unclear. In the largest retrospective review on 95 patients with RAAS adjuvant chemotherapy reduced the risk of local recurrence [5]. Chemotherapy for RAAS consisted of combining anth-

racyclines, dacarbazine, and ifosfamide, as well as taxanes and gemcitabine. Two cases with locally relapsed RAAS who achieved complete remission following treatment with weekly paclitaxel were reported [14].

The roles of anti-angiogenic agents and tyrosine kinase inhibitors that target c-KIT, including bevacizumab, pazopanib, sorafenib, and apatinib, are worthy of investigation given the possible importance of the VEGF signaling pathway and the expression of CD117 in these tumors. The response rate to sorafenib of 33.3% (1 complete and 2 partial response) among 9 tumors [15], but no objective response in another series of 5 RAAS were reported [6].

Conclusion

RAAS of the breast is a rare, and late severe complication of BCT, which presents a potential challenge to the treating physician. Diagnosis can be challenging, as it may be misdiagnosed with both breast cancer recurrence and dermatologic findings. Salvage mastectomy, even with R0 resection, for localized RAAS of the breast in BCT patients is associated with the high risk of local failure. Achieving better local control is possible by using more aggressive surgical approaches. Adding re-irradiation including HART to surgery might be beneficial for the local control of the RAAS. Ongoing clinical trials using combination of VEGF inhibitors and chemotherapy may provide future avenues of treatment for this difficult-to-treat disease. In long term BCT survivors the secondary AS should be kept in mind in the case of patients who developed changes of the irradiated breast.

Conflict of interest: none declared

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