CASE REPORT

EXPERIMENTAL ONCOLOGY

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# ANGIOSARCOMA ASSOCIATED WITH RADIATION THERAPY IN PATIENTS WITH A HISTORY OF INVASIVE BREAST CARCINOMA. A CASE REPORT AND REVIEW OF THE LITERATURE

Angiosarcoma of the breast is a rare malignant tumor and accounts for 1% of all soft tissue tumors of the breast. Breast angiosarcoma caused by previous radiation therapy more frequently affects older women with a history of breast cancer. The standard treatment for such patients is radical surgery, but there are still many debatable questions regarding the treatment of these malignant tumors. The purpose of this article is to review the medical literature on angiosarcomas associated with radiotherapy and describe a case as an example.

**Keywords:** breast angiosarcoma, radiation therapy, breast carcinoma, angiosarcoma associated with radiotherapy.

Breast sarcomas constitute a heterogeneous group of rare malignant tumors, representing less than 5% of all soft tissue sarcomas and less than 1% of all malignant breast tumors [1]. Breast angiosarcoma is a highly aggressive malignant tumor of the vascular endothelium, characterized by rapid proliferation and infiltration into surrounding connective tissues, and is associated with a poor prognosis. It often tends to affect the skin and superficial soft tissue. The most common diagnoses, for which radiation was given, are breast cancer (26%), lymphoma (25%), and carcinoma of the cervix (14%). Also, the most common histologic types of sarcoma associated with radiotherapy are osteogenic (21%), malignant fibrous histiocytoma (16%), and angiosarcoma/lymphangiosarcoma (15%) [2].

Angiosarcoma associated with radiotherapy (AAWR) is a rare and severe condition, typically emerging as a late complication following breast-conserving surgery and radiotherapy for breast cancer. Interestingly, angiosarcoma is the most prevalent type of sarcoma observed after breast radiotherapy [3]. These sarcomas manifest themselves within the irradiated volume, defined as the tissue receiving a substantial dose (e.g. >50% of the specified target dose), or in the areas where irradiation is not uniform, leading to genetic mutations in surviving cells.

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The typical clinical presentation of AAWR is thickening of the skin and multifocal reddish-purple skin lesions [4]. The standard treatment for angiosarcoma is surgery. The type of operation can vary and can be either wide excision or mastectomy [5].

## Case report

In December 2022, a 92-year-old woman came to her oncologist concerned about skin and nipple lesions of the right breast. The patient had a history of invasive ductal carcinoma of the right breast diagnosed and treated 8 years before. Then, there was performed lumpectomy with regional lymphadenectomy. The pathologic examination of the lumpectomy specimen demonstrated a single 2.0 cm focus of invasive ductal carcinoma of intermediate grade (G2) with negative margins and negative lymph nodes (pT1N0M0). The immunohistochemical study showed the presence of estrogen receptors (97%), progesterone receptors (70%), and androgen receptors (90%). The tumor was HER2/neu negative. Ki-67 was expressed in 18% of cells. The surgical treatment was followed by adjuvant radiation therapy (total dose 50 Gy on residual mammary gland, 2 Gy/day, 5 days per week) and hormonal therapy (tamoxifen for five years) without complications. From that time, her mammograms had been unremarkable. The patient had a history of hypertension, took corresponding medications, and had no other serious illnesses.

During physical examination, the patient was conscious, and the body temperature was normal. On the right breast, there was a well-healed excisional scar in the upper outer quadrant. An asymmetrical pathological process of the skin of the right breast was found. The skin of the right breast exhibited a jaundiced hue and infiltration with a retracted and deformed nipple. The pathological process manifested itself by multiple evolving bluish-purple lesions, exhibiting elasticity upon palpation and clear boundaries; some lesions were ulcerated on the surface of the crust. The lesions were not injured before, became darker, and increased over the past 6 months. However, the excisional scar was not involved.

Palpation of the lesions demonstrated no areas of induration, fluctuance, or drainage. The largest lesion measured approximately 3 cm in the greatest dimension. Similar lesions of a smaller size were also noted on the nipple (Fig. 1). There were no symptoms indicating deep soft tissue involvement. The remaining physical examination, including the left breast, right and left axilla, was also unremarkable.

***Fig. 1.*** Right breast with multifocal skin lesions

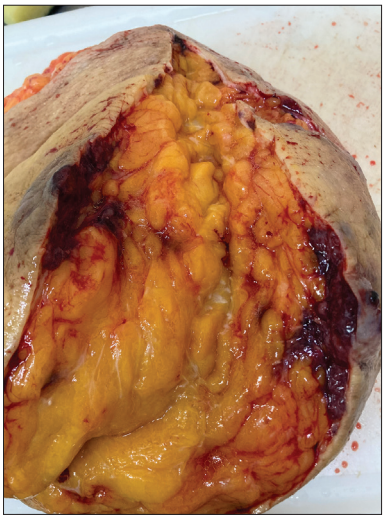
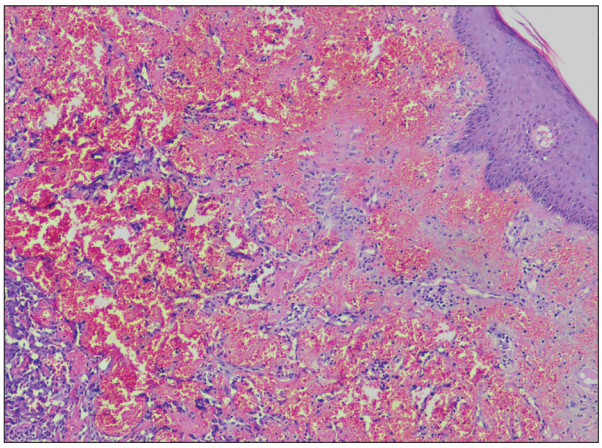


***Fig. 2.*** Gross pathologic image of the right breast simple mastectomy specimen

Based on the computed tomography results for the chest, abdominal cavities, and pelvis, there were no signs of a metastatic process.

A punch biopsy was performed for a lesion on the patient's right breast. The oncology council decided to perform a mastectomy for the patient, as the pathology report showed angiosarcoma with invasion into the derma and ulceration (Fig. 2).

A neoplasm with poorly defined margins is located within the dermis and underlying the stroma of the breast. It is composed of irregularly shaped, anastomosing vascular channels of varying calibers, lined by atypical endothelial cells. The stroma reveals the presence of blood lakes, representing accumulations of extravasated erythrocytes (Fig. 1). In certain areas, papillary structures and bundles of endothelial cells are observed (Fig. 2). Additionally, small foci of solid tumor cell growth are identified (Figs. 3 and 4). The endothelial cells exhibit moderate cytologic atypia (Figs. 5—7), with polygonal and



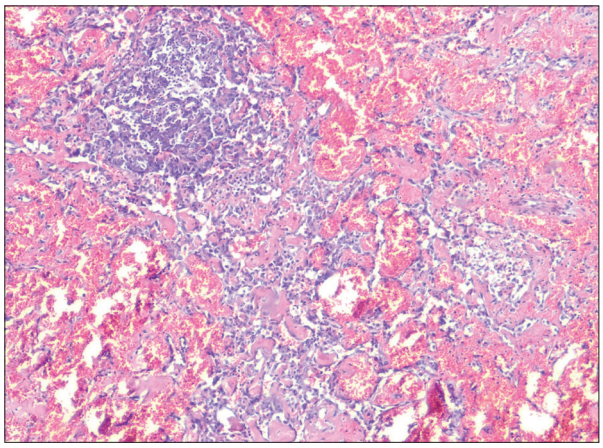
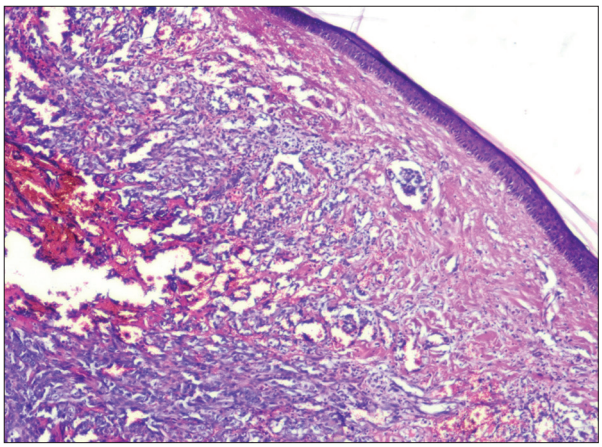


***Fig. 3.*** The dermis exhibits anastomosing vascular structures of variable calibers, accompanied by prominent erythrocyte extravasation. Hematoxylin and eosin, ×200.

***Fig. 4.*** Atypical endothelial lining of the anastomosing vessels gives rise to the formation of cellular bundles and papillary structures. Hematoxylin and eosin, ×400



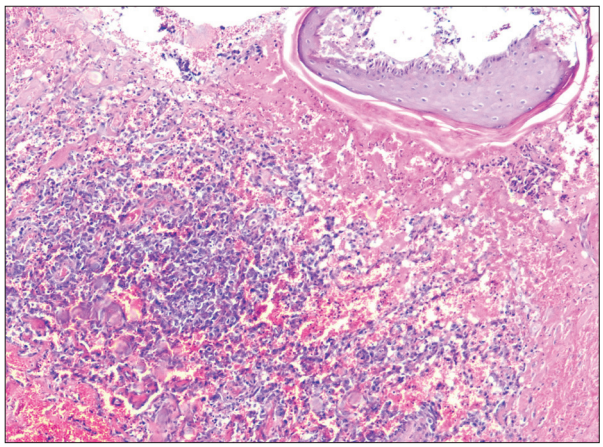


***Fig. 5.*** Blood lakes are present in the dermis, alongside foci of solid tumor growth composed of atypical endothelial cells. Hematoxylin and eosin, ×200

***Fig. 6.*** Tumor cells give rise to small papillary formations, as well as solid and spindle-shaped foci. Hematoxylin and eosin, ×200

spindle-shaped morphology, moderate amounts of eosinophilic or pale cytoplasm, and ovoid, vesicular, hyperchromatic nuclei containing small but conspicuous nucleoli, alongside occasional mitotic figures.

After counseling and discussing with the patient, a decision was made to apply a watch-and-wait strategy as her age and multiple comorbidities made her an unlikely candidate for systemic adjuvant therapy. The patient is currently in follow-up.

## Discussion

There is a clear difference between primary breast sarcomas and secondary breast sarcomas developed after radiation therapy; however, both are rare. Altogether, data on the annual incidence of breast sarcoma vary, which mostly depends on the histologic type of sarcoma. A population-based case-control Swedish study by Karlsson et al. [6] reported about 1.52—2.04 cases of breast sarcoma per million per year. Wang et al. [7] identified 11 cases of sarcoma among more than 5000 cases of breast cancer over 10 years. 3 cases of primary angiosarcoma and 8 of angiosarcoma had history of radiotherapy for breast cancer. Yapp et al. [8] reported about 3.2 sarcomas per 1000 cases of breast cancer when patients received radiotherapy and 2.3 sarcomas per 1000 cases without radiotherapy.

It is believed that the first report on angiosarcomas in patients after mastectomy was published by Stewart and Treves in 1948 [9]. Later, radiotherapy was found to be a risk factor associated with sarco-

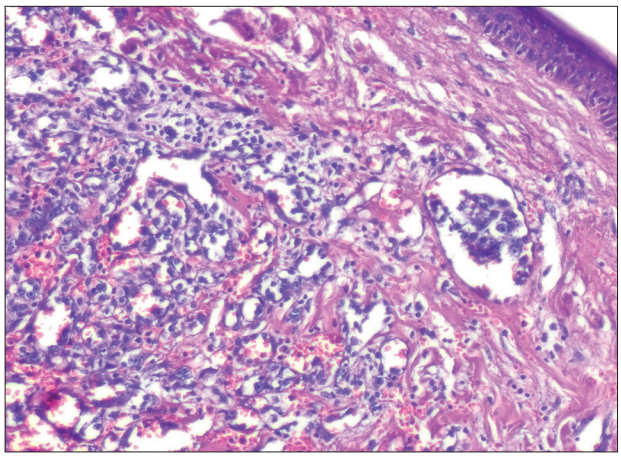


***Fig. 7.*** Atypical endothelial cells, characterized by polygonal and spindle-shaped forms, possess moderate eosinophilic and pale cytoplasm and vesicular hyperchromatic nuclei. Small, conspicuous nucleoli are seen in a subset of tumor cells. Hematoxylin and eosin, ×400

mas and especially angiosarcomas. AAWRs are prognostically unfavorable type of malignant tumor due to the high rate of recurrence and medium overall survival of about 60 months [10, 11].

Treatment options depend on the stage of the disease (localized or metastatic process). The standard treatment for localized angiosarcoma as sarcoma in general is surgery with margin-negative resection. Patients in whom margin-negative resection was not achieved (R1, R2) have a lower survival rate [12]. The issue of the optimal safe margins of the resection margins remains debatable; some authors consider safe surgical margins to be more than 3 cm [13—15]. A reduction in size after neoadjuvant chemotherapy makes resection with negative margins more attainable [16].

There are conflicting data regarding the effectiveness of systemic chemotherapy for angiosarcomas. In a retrospective study, Lagrange et al. [17] reported no significant difference in survival rates between patients treated with surgery alone and with surgery and chemotherapy. A study by Rosen et al. [18] showed better survival rates after using adjuvant chemotherapy. Some studies showed better results of adjuvant chemotherapy after surgery with margin-negative resection [19, 20]. The ANGIOTAX study by Penel et al. [21] demonstrated that weekly paclitaxel has a good impact on the overall survival in the first line setting of patients with angiosarcoma. The National Comprehensive Cancer Network guidelines recommend that preferred treatments for the soft-tissue sarcoma subtypes with non-specific histologies are paclitaxel and anthracycline- or gemcitabine-based regimens. However, for chemotherapy of metastatic angiosarcoma docetaxel, paclitaxel, and vinorelbine are used. For cutaneous angiosarcoma. pembrolizumab can also be useful.

Despite radiation therapy being the cause of AAWRs, there are some data on the improving effect of hyperfractioned radiotherapy on the local control and disease-free and overall survivals [22].

AAWRs are tumors with limited options of treatment and high rates of relapse and mortality. Due to the rarity of this disease and the limited research on the topic, uniform standards of treatment have yet to be established. The primary method of treatment continues to be surgical, with a focus on achieving resection margins R0. It is essential to aggregate patients with this pathology for treatment within the context of large-scale studies. This approach will help identify and refine effective options for systemic therapy to improve the survival of such patients. However, the benefits of radiotherapy for patients with breast cancer are higher than the risk of developing angiosarcoma.

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## АНГІОСАРКОМА, АСОЦІЙОВАНА З ПРОМЕНЕВОЮ ТЕРАПІЄЮ, У ПАЦІЄНТОК З ІНВАЗИВНИМ РАКОМ МОЛОЧНОЇ ЗАЛОЗИ В АНАМНЕЗІ: КЛІНІЧНИЙ ВИПАДОК ТА ОГЛЯД ЛІТЕРАТУРИ

Ангіосаркома молочної залози — це рідкісна злоякісна пухлина, що становить близько 1% всіх пухлин м'яких тканин молочної залози. Часто ангіосаркома молочної залози, спричинена попередньою променевою терапією, уражає жінок старшого віку з анамнезом раку молочної залози. Стандартним методом лікування таких пацієнток є радикальне хірургічне втручання, однак у лікуванні цих злоякісних пухлин досі існує багато дискусійних питань. Метою цієї статті є огляд медичної літератури щодо ангіосарком, асоційованих із променевою терапією, а також опис клінічного випадку як прикладу.

**Ключові слова:** ангіосаркома молочної залози, променева терапія, рак молочної залози, ангіосаркома, асоційована з променевою терапією.