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Angiosarcoma after radiotherapy for male breast cancer: A rare clinical case

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Introduction

Soft tissue sarcomas are a heterogeneous group of malignant neoplasms derived from mesenchymal cells. Breast sarcomas are rare, representing less than 1% of all breast cancers and less than 5% of all soft tissue sarcomas [1,2]. The subtype of sarcoma strongly linked to the breast is the angiosarcoma, originating in the endothelial vascular or lymphatic cells. It is usually aggressive, with rapid proliferation and infiltration into the surrounding tissues. Based on their etiology, it can be classified as primary (de novo) and secondary (related to a treatment for breast cancer, after radiotherapy, or due to lymphedema in the arm or breast after the treatment). Despite its rare incidence, its long latency and high mortality rate justify the need for long-term follow-ups.

In this report, we present the case of a man with an angiosarcoma in the arm with lymphedema at the age of 91, after having been treated eleven years earlier for breast cancer, with surgery, radiation, chemotherapy (6 cycles of CMF-cyclophosphamide + methotrexate + 5-fluorouracil) and hormone therapy (Tamoxifen for 5 years and Letrozol for another 4 years).

This clinical case is important to discuss as it is extremely rare for two reasons: First, the low incidence rate of breast cancer in males, and secondly, because secondary angiosarcomas are infrequent as a consequence of breast cancer treatments.

Clinical case

We present the case of a male patient diagnosed with breast cancer at the age of 79. This man had a personal history with a diagnosis of a prostatic adenocarcinoma treated seven years earlier with hormonal therapy, and a family history of a first degree relative (mother) diagnosed with breast cancer at the age of 60. The intervention for breast cancer in this male included a radical mastectomy in the right side, with ipsilateral axillary lymphadenectomy. He also received adjuvant treatment with radiation therapy, chemotherapy (6 cycles of CMF-Cyclophosphamide + Methotrexate + 5-Fluorouracil) and hormonal therapy (Tamoxifen for 5 years and Letrozol for another 4 years).

The primary mammary adenocarcinoma that he presented was an invasive ductal carcinoma known as not other wis-



pecified (NOS), with a size of 1.6 cm, histologically classified as grade 2, with vascular infiltration and positive for axillary test, pT2N1M0, stage IIA, luminal B subtype (luminal B-Like, HER2 negative: Estrogen receptors positive, progesterone receptors negative, HER2 negative, Ki67 with moderate rate of proliferation).

A physical examination of this patient at the age of 90 (11 years and 2 months after the breast cancer treatment) revealed a purplish/reddish nodule (**Figure 1**) on the right arm, ipsilateral to the previously radiated breast, with chronic lymphedema (secondary to the axillary lymphadenectomy performed also at the time of the intervention for breast cancer). A biopsy of the lesion was performed, confirming the histology of an angiosarcoma poorly differentiated. The magnetic resonance imaging confirmed that the disease was locally advanced. The treatment included chemotherapy for palliative care, passing the patient away seven months later, due to the already advanced stage of the disease.



Figure 1: Radiation-associated angiosarcoma of the breast. Reddish-violaceous nodule on an radiated arm with lymphedema secondary to breast cancer surgery.

Discussion

Primary angiosarcomas of the male breast are extremely rare [3-8], with very poor prognosis and a treatment that consists in the surgical removal of the tumor with clean margins and without axillary lymphadenectomy. Out of the secondary angiosarcomas, those radiation-induced follow Cahan's criteria: A location in the previously irradiated fields, a latency period of at least 4 years between the initial irradiation and the induced malignancy, a histological discordance between the primary and the secondary tumors [9]. Specifically, those tumors associated to chronic lymphedema seem to appear after a variable period of 4-27 years, frequently in an extremity with lymphedema as a secondary consequence of a mastectomy with removal of axillary lymph nodes (Syndrome of Stewart-Treves) [10].

In the majority of the secondary cases, there is evidence of tislular lesions induced by radiation and lymphedema. Generally, radiation therapy is considered the most important etiological factor. Numerous cases have been described in the literature of radiation-induced ipsilateral angiosarcomas that appear in the breast, thoracic cavity or arm, after a long latency period of 4-15 years, [11]. Mery et al [12] reported an estimated incidence of 0.9 per every 1000 cases of breast cancer treated in an early stage. Other authors have described cases of angiosarcomas af-

ter radiation therapy without evidence of lymphedema [13,14] as well as cases of angiosarcomas on lymphedema regions without any history of radiation therapy [15]. These variations suggest that lymphedema also plays an important role, and it is present in the majority (almost 95%) of the described cases of angiosarcomas in the extremities [16]. The clinical case we describe here presented both risk factors, chronic lymphedema and previous history of radiation therapy.

A study done by Amajoud et al. in 2018 [17] presented a retrospective data analysis of 10 women diagnosed with radiation-induced angiosarcomas. The women' age ranged 64-80 years old (mean: 65 years) at the time of their first diagnose of breast cancer, nine of them with invasive ductal carcinoma and one with ductal carcinoma in situ. They were primarily treated surgically and all patients received adjuvant radiation therapy. At the time of their diagnosis of radiation-induced angiosarcoma, the women were 64-86 years old (mean: 73 years), and the latency period between the radiation and the diagnosis of the sarcoma ranged from 4.1 to 14.9 years (average of 7.3 years). All tumors, although showing various clinical presentations and varying in size from 1 to 10 cm, were located within the radiation fields, and most importantly, the overall 5-year survival rate was only 46%. These authors concluded that because radiation-induced angiosarcomas can occur beyond the conventional 5-year oncological follow-up, long-term evaluations are necessary, with close attention particularly to post radiation skin lesions, to ensure early detection, prompt intervention and increase the survival rate of the patients. Surgery continues to be the mainstay treatment for these secondary malignancies at this time, and the role of chemotherapy and more radiation therapy is still unclear, mostly due to lack of research studies.

Angiosarcomas often appear at a slow rate, as changes in the skin (lesions, ulcerations, nodules) purplish or reddish, and that can be confused easily with hematomas, bruises or benign changes in the skin, delaying the appropriate clinical diagnosis. Early detection and rapid identification can potentially reduce the number of patients that present unresectable tumors and can improve the localized and distal control of the disease [18].

Clinically, these malignancies can affect the skin, the mammary parenchyma or both, although the cutaneous subtype is more common. Initially they can appear as multifocal nodules or similar to a reddish eczema, like in the case of our patient (**Figure 1**). As the lesions grow in size, ulcerations and edema can appear [19], but symptoms such as pain are infrequent. The growth is more explosive in high-grade tumors and insidious in low-grade tumors. The differential diagnosis includes the carcinoma erysipeloides (cutaneous metastasis of breast cancer similar to erysipelas) and atypical vascular lesions that appear after radiation therapy for breast cancer.

The clinical diagnosis of these malignancies is difficult. Mammograms and ultrasounds might show unspecific findings, but ultrasounds are a little more specific and could show suspicious lesions clearly. For lesions in upper limbs, ultrasounds and Computed Tomography (CT scans) seem not to be able to define the lesions, classifying them as "subcutaneous edemas". In these cases, Magnetic Resonance Imaging (MRI) is more informative and has a higher reliability to identify the tumor. However, the definitive diagnosis is performed by biopsy and a histological study with immunohistochemical techniques, to confirm the endothelial nature of the tumor. Since metastases of angiosarcomas occur via hematogenous dissemination (blood vessels),

the armpit biopsy of the lymph nodes is usually negative.

Due to the rare frequency of secondary angiosarcomas in patients with breast cancer, there is no consensus to date on the best approach. Complete tumor resection with negative margins is the base treatment, via conservative surgery or mastectomy for mammary lesions. Elective axillary lymphadenectomy is not justified considering the low frequency of regional lymph node metastasis (11-20%), and it is only recommended if the armpit is positive. In the case of upper extremities, a wide local excision could be done, an amputation included. The selection of adjuvant therapy is even more unclear. Radiation therapy seems to produce an additional benefit in these types of tumors, especially those with positive margins nearby. However, the role of adjuvant chemotherapy is questionable, except in high grade tumors, where it seems to be beneficial [20], constituting the chosen treatment for locally advanced unresectable (no capable of being surgically removed) tumors.

Angiosarcoma is an aggressive tumor, easily infiltrative and with a high rate of local recurrence and metastasis [21,22]. Local relapses are frequent (45-64%) despite the performance of a wide tumor resection. In a 25-year retrospective study of 81 patients, done by Buehler et al., it was found that 26% of these patients presented metastases, varying in their incidence from 16% (breast) to 42 % (soft tissues), with a survival rate of 6-16 months [23]. Based on a study done by Mery et al. [12] the 5-year overall and disease-free survival rate for patients with radiation-induced angiosarcoma is in the 25-50% range.

The risk of developing a secondary angiosarcoma is still rare and does not supersede the benefit of receiving radiation for breast cancer [24]. Therefore, radiation continues to be the choice to treat patients with breast cancer.

Conclusion

Cutaneous angiosarcomas are extremely rare and one of the cutaneous neoplasias with the lowest prognosis. They are very aggressive and with a high degree of local relapse, limiting the survival rate to 5 years in less than 35% of the patients [25,26]. In comparison to other sarcomas, the grade of differentiation of these types of angiosarcomas is not indicative of their prognosis. Requena et al. [27] observed that a larger tumor size and an advanced age in the patient were both associated with a poor prognosis, but a less evident association was observed when the following histological features were present: Necrosis, predominance of epithelioid cells, invasion of deeper layers and a larger number of mitoses.

Post-radiation angiosarcomas are also very aggressive, rare and characterized by a high rate of local recurrence and poor survival prognosis. Not only is this type of tumor very rare, but its proper diagnosis and therapeutic approach continues to be a challenge.

At the present time, the diagnosis is fundamentally clinic, and considering that it cannot be clearly distinguished from other lesions, it is fundamental to suspect that it is a possible angiosarcoma and perform a biopsy of any vascular lesions located in an area of the skin previously irradiated or with lymphedema. This measure allows an early diagnosis and an early aggressive surgical treatment, with the purpose of increasing the patient's prognosis and survival. In this regard, it is crucial for the doctors and for the patients to be aware during physical examinations in consultations and follow-ups of the early signs and symptoms of these types of tumors.

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