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Angiosarcoma of the breast: a new therapeutic approach?

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ABSTRACT

INTRODUCTION: Angiosarcomas are highly malignant endothelial cell tumors with poor prognosis. These can be due to breast cancer itself or to subsequent therapeutic modalities. No evidence-based guidelines exist concerning the ideal treatment of angiosarcomas.
PRESENTATION OF THE CASE: We report the case of a 76-year-old woman who developed an exuberant and aggressive post radiation angiosarcoma of the breast and discuss different aspects of therapy for this disease. A total left mastectomy was performed, followed by a right mastectomy. The lesions into the chest wall, and multiple abdominal skin nodules were treated with local Electrochemotherapy (ECT) with intravenous bleomicin.
DISCUSSION: No evidence-based guidelines exist concerning the ideal treatment of angiosarcomas. Electrochemotherapy (ECT) is an efficient palliative treatment of cutaneous and subcutaneous tumor nodules. It consists of the combination of a cytotoxic drug and electroporation, using appropriate electrical parameters; destabilization of the membrane is reversible, ensuring a high survival of permeabilized cells and the delivery of non-permeant molecules inside the cell.
CONCLUSION: Due to the rarity of the disease, prospective studies concerning adjuvant or neoadjuvant therapy are limited and no evidence-based guidelines exist. The response to chemotherapy seems to be poor. Treatment with ECT in addition to systemic chemotherapy achieves a complete response in all the lesions and improving patient body image perception.

1. Case report

In February 2011, we observed a 76-year-old woman with a painful, violet, multi-nodular mass occupying the entire left breast along with small nodules in right breast skin (Fig. 1). The lesion had rapidly enlarged. At the anamnesis she previously underwent breast-conservative surgery and axillary dissection for invasive ductal carcinoma of the left breast in 2003. Immunohistochemical analysis revealed estrogen and progesterone receptor positivity.

The tumor was classified as pT1 pN0 M0 G2 StageI, according to the UICC–TNM classification. She received radiotherapy as follows: 50 Gy in 25 fractions of 200 cGy/daily with boost of 10 Gy in 5 fractions of 200 cGy/daily.

No adjuvant chemotherapy was given. She received adjuvant hormone therapy (Tamoxifene 20 mg daily for two years and Anastrozole for three years). The patient did not suffer from chronic lymphedema.

In February 2007, the patient noticed a subcutaneous lesion of about 3 cm in diameter at the left breast. An excisional biopsy was performed. Histopathological examination revealed a vascular structure lined by atypical cells with hyperchromatic nuclei and eosinophilic cytoplasm.

Tumor cells were positive for CD34 and Vimentin and negative for SMA and CKP, indicating an endothelial origin. More than 90% of the cells in the solid component were positive for Ki67. The diagnosis of capillary-like grade-II angiosarcoma of the breast was made. No metastases were found at total body CT scan. Serum tumor marker levels were within normal limits. Adjuvant chemotherapy was not prescribed.

In February 2011, the cancer recurred replacing entirely the lower quadrants of the breast. It was violaceous, hemorrhagic and measured 12 × 9 cm. A total left mastectomy was performed, followed by repair of the skin defect using a dorsal skin graft. Microscopically, the lesion was composed of intricate vascular channels surrounding and invading the breast lobules. Numerous mitoses were observed. Immunohistochemistry showed CD31 and CD34 positivity. This was consistent with the diagnosis of capillary- and papillary-like grade-II angiosarcoma of the breast. A total body CT scan was repeated and showed no metastases.

The cancer was completely removed, but three months later the patient noticed a mass in her right breast with local relapse with

Abbreviations: ECT, electrochemotherapy; RIA, radiation induced angiosarcoma; RECIST, response evaluation criteria in solid tumors; ESOPE, European Standard Operating Procedures Of Electrochemotherapy.

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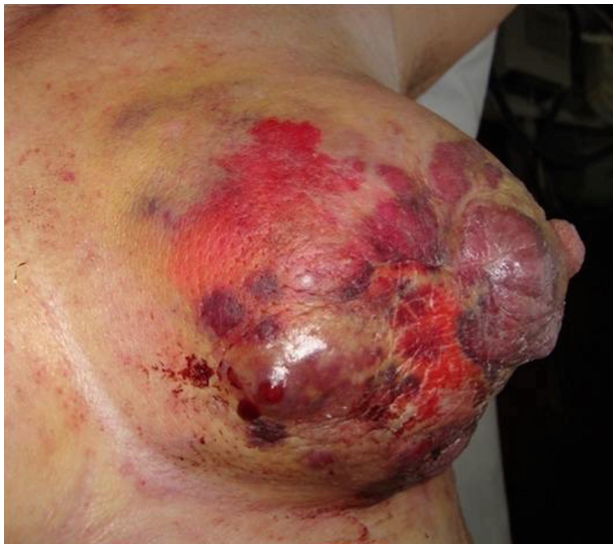

Fig. 1. Multi-nodular mass occupying the entire left breast.

multifocal nodes in her left chest wall. A right mastectomy was performed. The lesions into the chest wall were not amenable for surgery.

The left chest wall was treated with local ECT with intravenous bleomicin (Fig. 2). Treatment was performed according to the standard operating procedures for ECT (ESOPE – European Standard Operating Procedures of Electrochemotherapy) [9] under general anesthesia. Bleomycin 15000 IU/m^2 was injected intravenously. Pulses were delivered 8–30 min after injection [10]. Electric pulses were delivered using a square wave electroporator (IGEA, Carpi, Italy). The applied voltage was 1.0 kV/cm for needle electrodes, and pulses were applied at 5 kHz.

Six months later the patient developed multiple abdominal skin nodules not suitable for surgical treatment. Another treatment with ECT was performed (Fig. 3). Response rate was evaluated similarly to the response evaluation criteria in solid tumors (RECIST version 1.0) [11]. Overall, 51 lesion were treated at first and second therapeutic session of ECT with median (range) diameter of 15 (10–25) mm. Considering all treated nodules (N = 51), 51(100%) had complete response, as assessed atphysical examination (Fig. 4).

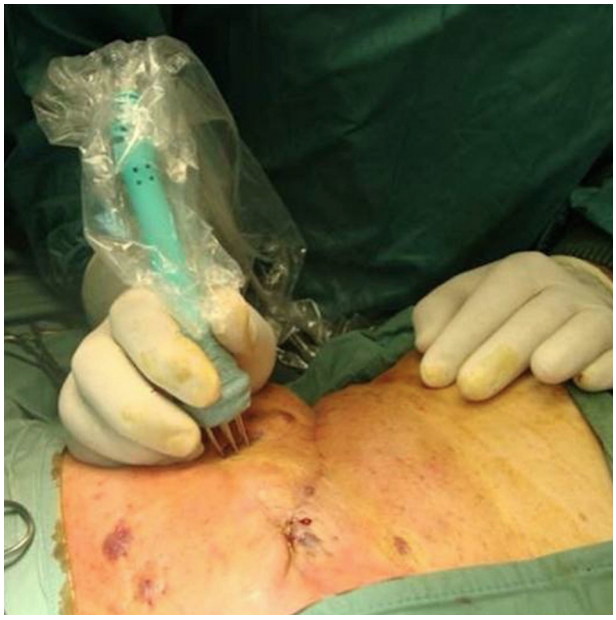

Fig. 2. Electrochemoterapy of multiple thoracic skin nodules, the needles are inserted into the lesion and electric pulses are delivered after intravenous injection of bleomycin.

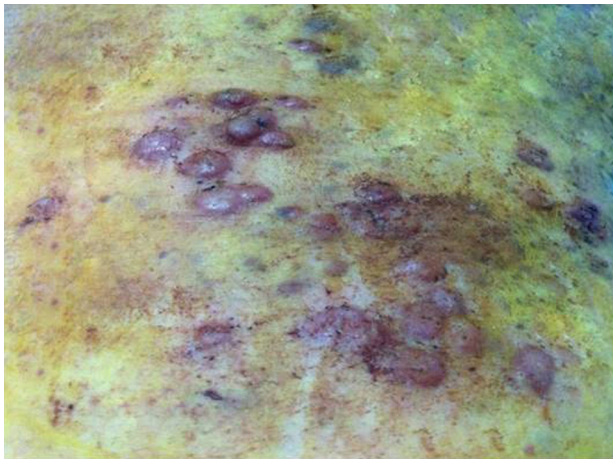

Fig. 3. Multiple neoplastic abdominal skin nodules.

No detectable metastatic disease was found. Adjuvant chemotherapy with Doxorubicine(40 mg/m^2) was prescribed, repeated every 4 weeks for 6 cycles aiming to prevent distant recurrences. The patient is currently well with no recurrence 18 months after the operation.

2. Discussion

Angiosarcomas are rare malignant tumors which arise from endothelial cells lining vascular channels. Breast angiosarcomas can be either observed as primary neoplasms or, more commonly, in upper limb lymphedema as a result of breast conservative surgery and radiotherapy for breast carcinoma [1–10]. Radiation-induced angiosarcoma (RIA) was first reported in the literature in 1929 [11], and is a common form of angiosarcoma. The diagnostic criteria for RIA include: a previous history of radiotherapy, peak incidence between 5 and 10 years, development of sarcoma within a previous irradiated field, histology confirmation .RIAs are charac-

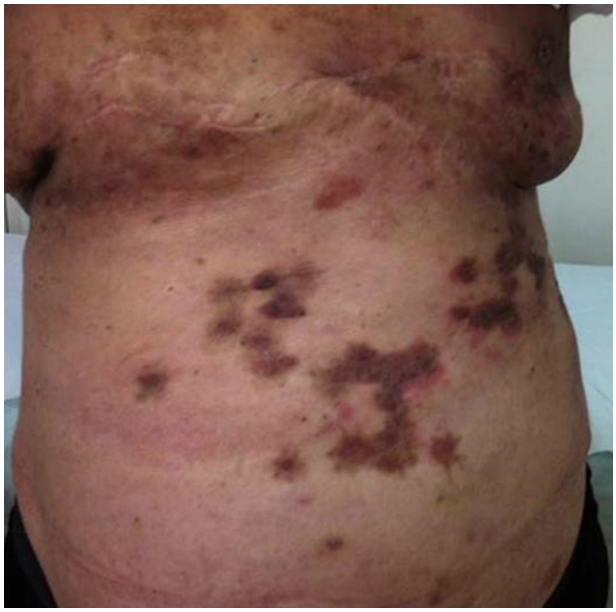

Fig. 4. Complete response and no relapses is observed 18 months after Eletrochemoterapy.

terized by their aggressive nature and most of them are high-grade tumors. The prognosis is poor and local recurrence rates reaches 70% after mastectomy [11–13]. RIAs often present as cutaneous or subcutaneous painless, flat or nodular, bluish or purplish lesion/s, similar to benign angiomas, small hematomas, or atypical telangiectasia [10].

Due to the rarity of the disease, prospective studies with regard to adjuvant therapy are limited and no evidence-based treatment guidelines exist [12,13]. Skin metastases from solid tumors behave in a similar fashion, irrespective of the tumor entity [14]. The lesions may be distressing for the patient, due to their visibility or symptoms such as weeping, bleeding, and pain.

ECT has emerged as an effective local treatment for patients with cutaneous and subcutaneous tumor nodules. It combines the effects of a cytotoxic intravenous drug and electroporation by means of electric fields, which temporarily increase the permeability of cell membrane allowing the direct diffusion of the drug within malignant cells [4,17–19].

ECT has recently been proposed as a novel, complementary therapeutic option for the control of superficial disease. This therapeutic approach is a feasible alternative in case of inoperable tumors, located in pre-irradiated areas and in areas resistant to chemotherapy [7,17,18,20]. Since recurrence and survival rate of angiosarcomas mainly depend on wide excision margins, safety histological margins of at least 5 cm are recommended, but may require extended excisions, which are not always possible. Due to the rarity of the disease, prospective studies concerning adjuvant or neoadjuvant therapy are limited and no evidence-based guidelines exist. The response to chemotherapy seems to be poor. However, anthracyclines are effective agents for soft tissue sarcomas and are mainly used as first-line therapy. In this case local treatment was combined with doxorubicine [15,16].

In our patient, presenting with unresectable and extended angiosarcomas, treatment with ECT in addition to systemic chemotherapy was likely to have significantly boosted the efficacy of the intravenous drug at the sites of angiosarcomas, achieving a complete response in all the lesions and improving patient body image perception. Neither symptomatic nor asymptomatic recurrences were observed at 18-months follow-up, suggesting that ECT is a promising tool in the palliative care of patients presenting with angiosarcomas after breast surgery.

Conflicts of interest

None.

Sources of funding

None.

Ethical approval

Our research is based on clinical notes of an individual patient and does not require research ethical approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Nine authors have contributed to this study:

(1) All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data.

(2) All authors participated in drafting the article or revising it critically for important intellectual content.

(3) All authors gave final approval of the version to be submitted.

Guarantor

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