
**Stewart-Treves Syndrome Involving Chronic Lymphedema Postmastectomy:
a Case Report and Review of the Literature.**

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Abstract

Stewart-Treves syndrome (STS) is a rare and fatal entity, defined as the cutaneous angiosarcoma that arises in the context of long-standing chronic lymphedema. It usually occurs in women who develop lymphedema in the upper limb secondary to treatment for breast cancer (BC). It occurs in approximately 0.5% of patients who survive at least 5 years after radical mastectomy. Here, we present the case of an 84-year-old woman with chronic lymphedema secondary to BC surgery. She developed a purple macule over the area with chronic lymphedema 7 and a half years after BC diagnosis. Pathological results from biopsies of the lesion were consistent with angiosarcoma (STS). She received chemotherapy treatment followed by amputation of the affected limb. She died 18 months after diagnosis, due to local and distant spread of the disease. Despite the treatment, the prognosis remains severe with poor survival.

Keywords: Stewart-Treves syndrome; Angiosarcoma; Chronic Lymphedema; Lymphangiosarcoma; Postmastectomy Angiosarcoma; Breast Cancer; Extremity Swelling.

Acronyms

STS	Stewart-Treves syndrome
BC	Breast cancer

Introduction

The nomenclature of malignant neoplasms showing endothelial differentiation of blood vessels includes the terms hemangiosarcoma, malignant angioendothelioma, and malignant hemangioendothelioma. The distinction between malignant tumors showing differentiation of blood vessels (angiosarcoma) and those with lymphatic differentiation (lymphangiosarcoma) is often confusing, reason why both types are considered jointly.

Basically there are three clinicopathological subtypes associated with the breast: primary angiosarcoma of the breast, radiation-induced breast angiosarcoma and angiosarcoma in upper limbs with chronic lymphedema. In this last entity, since the tumor originates from an extremity with lymphedema, the term lymphangiosarcoma is frequently used, although it is histopathologically indistinguishable from angiosarcoma. The pathogenesis of angiosarcoma (lymphangiosarcoma) arising in areas with chronic lymphedema is unknown. Irradiation is unlikely to contribute directly to this process because the lesion develops in the absence of radiation therapy and in irradiated patients it originates outside the radiation field.

Angiosarcoma arising in an arm with chronic lymphema is not a primary neoplasm of the breast, although in most cases it develops as a complication of treatment for breast cancer (BC). In 1948, Stewart and Treves published 6 cases of lymphangiosarcoma arising in the upper limb with postmastectomy lymphedema [1]. They found that lymphangiosarcoma was an association of these tumors with severe and prolonged lymphedema as a result of surgery and it was not a metastasis from BC. This condition was named Stewart-Treves syndrome (STS) in 1952 [2]. Currently, STS is considered to be an angiosarcoma arising in the context of chronic lymphedema, either primary or secondary, and at any location [3, 4]. Classic STS is when it occurs in patients with a history of BC, in the ipsilateral upper limb with chronic lymphedema. But it can also arise from congenital lymphedema or from lymphedema caused by parasitic infestation [5, 6].

Lymphangiosarcoma, or STS, is a highly malignant vascular tumor. It occurs in approximately 0.45% of patients undergoing mastectomy with axillary dissection after at least 5 years [3, 7, 8]. With the increase in breast conserving surgery as well as new radiotherapy techniques, the prevalence of STS has decreased. Early amputation offers better survival. As treatment options, chemotherapy and radiation therapy may be used, but the prognosis is limited.

We present an unusual case of an 84-year-old woman with STS in the context of chronic lymphedema of the upper limb secondary to BC treatment. She died 18 months after diagnosis, due to local and distant spread of the disease.

Case Report

Our patient is a 76-year-old woman with no relevant medical history but a family history of cancer (a sister with bilateral BC). She consulted for a lump in her left breast associated with breast retraction. Imaging tests showed a nodule highly suspicious for malignancy. The malignancy was confirmed by a core needle biopsy: invasive breast carcinoma non-special type (NST). A modified radical mastectomy with axillary dissection was performed. The surgical specimen exam confirm the diagnosis of invasive breast carcinoma NST, grade III, with a maximum diameter of 2.5 cm and negative surgical margins; metastatic involvement in 6 of the 12 dissected axillary nodes. The immunohistochemical study showed that the tumor cells were positive for hormone receptors (estrogens and progesterone) and negative for HER2 and p53, with high proliferation marker (Ki67 > 20%). TNM stage IIB: pT4 (skin extension) pN2a M0. Surgical treatment was followed by radiotherapy and adjuvant chemotherapy (6 cycles of FAC: 5-Fluorouracil, Adriamycin and Cyclophosphamide). Completing the treatment with hormone therapy (Tamoxifen) for 5 years.

At 84 years of age (7 and a half years after the diagnosis of breast cancer), our patient presented significant chronic lymphedema in the left upper limb. On this lymphedema, on the inner side of the arm, a purple-colored macular lesion of about 3 cm appeared. Biopsy of this lesion was reported as poorly differentiated skin angiosarcoma. Therefore, it was a cutaneous angiosarcoma in an upper limb with lymphedema secondary to BC treatment, consistent with a STS.

Chemotherapy treatment with Taxol was started. Four months after the initial diagnosis of angiosarcoma, it was decided to perform surgery due to local spread; so the left upper limb was amputated. The pathology report showed histological changes of chronic lymphedema and multifocal malignant transformation of low-grade angiosarcoma.

Ten months after the amputation, our patient presented an extensive ulcerated lesion on the skin of the anterior chest and lung metastases. She died four months later, at the age of 85, due to the local and distant extension (pulmonary and pleural) of the disease.

Discussion

Angiosarcoma, or malignant angioendothelioma, is a rare soft tissue sarcoma originating from vascular endothelial cells. They can arise anywhere on the body, being its most important location the head and scalp of elderly white men [9]. Angiosarcoma is an aggressive subtype, with rapid proliferation and infiltration of surrounding tissues; generally associated with a poor prognosis. They can be caused by therapeutic radiation or chronic lymphedema, and therefore secondary angiosarcomas of the breast are an important subgroup.

Based on their aetiology, angiosarcomas of the breast can be classified as primary (de novo) and secondary (related to a treatment for BC: after radiotherapy, or due to lymphedema in the arm or breast after the treatment) [10-12].

Lymphedema is the result of an accumulation of protein-rich interstitial fluid, caused by a failure in normal lymphatic drainage. The origin of this oedema can be congenital or acquired (secondary to infection, trauma, radiation or surgery) [13].

STS or secondary lymphangiosarcoma is a complication developed in the soft tissues of the upper extremities as a consequence of chronic lymphedema after radical mastectomy, or exceptionally after conservative surgery. Currently, they are rare since BC therapies manage to avoid the appearance of chronic lymphedema, and when it appears it rarely reaches the severity of times past. However, another type of iatrogenic angiosarcoma has replaced it: angiosarcoma induced by radiotherapy.

STS or angiosarcoma secondary to chronic lymphatic obstruction is a very rare and fatal disease. It is defined as the association between chronic lymphedema and angiosarcoma [9]. The presence of this syndrome significantly worsens the outcome of patients with BC [3, 9]. It is most commonly seen in the upper arm of patients who have undergone a mastectomy and axillary lymph node excision as a treatment for BC [3]. In addition to chronic lymphedema, additional factors such as radiation therapy can increase the risk. The use of radiation therapy contributes to the development of the syndrome, directly affecting the DNA and indirectly causing a lymphatic blockage. The incidence of STS has decreased with the improvement of surgical and radiotherapy techniques.

STS generally develops many years after mastectomy, most commonly 5-15 years after surgery. In the original series, Stewart and Treves reported that the earliest angiosarcoma appeared at 6 years and the latest at 24 years [1]. Tomita et al. demonstrated that the most common interval between mastectomy and development of lymphangiosarcoma was 5 to 14 years [14]. Cohen-Hallaleh et al. suggested two groups of patients: those treated for BC with radical mastectomy and radiotherapy, who developed STS in the ipsilateral arm with lymphedema after a median of 11 years; and those treated with conservative surgery and radiation therapy, who developed radiation-induced angiosarcomas in the radiated field after a mean of 7.3 years [15].

Although the pathogenesis is not well established, current theories highlight that when lymphedema develops, regardless of the cause (radiation, surgery or any other), an angiogenic stimulus is produced in the oedema territory; which leads to the neoformation of collateral lymphatic and blood vessels [13]. As early as 1959, McConnel and Haslam [16] outlined the development of lymphangiosarcoma in three stages: 1) long-term lymphedema, 2) premalignant or angiomatosis phase, and 3) established angiosarcoma.

Lymphangiosarcomas are more frequently located in the upper limb (90%), on the ipsilateral side where the mastectomy was performed [3]. Haagensen [17] in his classic book *Diseases of the breast* describes the clinical picture of this entity: "In the thickened skin of the edematous arm, faint reddish macules appear. The regions that are involved first in most patients are the anterior and inner side of the arm. These macules converge, their color intensifies and induration appears. At this stage the injury tends to be confused with an ecchymosis. Shortly afterwards, purple nodules develop on the affected skin, which ulcerates". Around the nodules, there may be small

satellite areas, which can become confluent. In advanced disease, necrosis may be evident [18]. Eventually, extensive skin nodules appear and metastatic disease develops [3].

SST dissemination occurs in the subcutaneous tissue, following the subcutaneous veins and extending beyond the proximal region of the affected limb [19]. The lesions progress: generally developing first on the arm and antecubital region, then on the forearm and back of the hand, and finally on the adjacent skin of the chest [20]. Metastases can affect any organ by hematogenous dissemination, most often affecting lungs and bones.

For diagnosis, a histopathological examination of the lesions should be performed. Histological findings of angiosarcoma in STS show an irregular proliferation of vascular channels that dissect dermal collagen [3]. The malignant endothelial cells lining these channels are hyperchromatic and pleomorphic, with frequent macronucleoli and mitoses. Tumor cells are round or oval with an epithelioid cytomorphology and often project into the lumen of the vessels [21,22]. The overlying epidermis can be acanthotic, hyperkeratotic, or atrophic, with or without proliferation of reticular fibers in the dermis. Interestingly, angiosarcomas in STS present a heterogeneous morphology with areas dominated by hemangiosarcoma and lymphangiosarcoma structures [23].

Immunohistochemical confirmation is essential for diagnosis. Useful markers for diagnosis include: CD31, CD34, FLI-1 and factor VIII [3,22]. In addition, numerous associated lymphatic antibodies have been developed as an aid in the diagnosis: podoplanin (D2-40), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), prospero homeobox protein 1 (PROX1) and vascular endothelial growth factor receptor 3 (VEGFR -3) [9, 22].

Given the rapid growth of lymphangiosarcomas and their high metastatic potential, especially to the lung and the pleural cavity, treatment is usually very aggressive. This aggressive treatment generally involves amputation of the affected limb, as in our case, or wide resections in some selected cases. However, despite radical treatment, the prognosis is poor. Anecdotally, promising results have been published with other less aggressive therapies, such as that reported by Breidenbach et al. [24] with intra-arterial mitoxantrone and paclitaxel and limb-sparing surgery. The efficacy of other adjuvant treatments such as radiotherapy or chemotherapy is poorly documented, although most authors give them little value. Thus, Grobmyer et al. [25] found no significant difference in survival for patients treated with postoperative chemotherapy or radiation. With respect to adjuvant chemotherapy, it has shown benefit in poorly differentiated angiosarcomas, but not in well-differentiated ones [26]. Long-term survivorship after chemotherapy/radiation is reported in case reports, but the overall results are poor. Even with these treatment therapies, local recurrence and metastasis is high.

The prognosis of STS is poor due to the high rate of local recurrence and metastatic disease. Its survival rate is approximately 15 to 30 months, and 5 to 8 months without treatment [3, 9, 21, 27]. Five-year survival has been reported to be between 8.5% and 13.6% [3, 28]. Median survival is 2.5 years after diagnosis, and most patients die from metastatic disease within 2 years. Long-term survival is rare. Our patient died 15 months after diagnosis, mainly due to lung metastatic disease.

In relation to the aggressiveness of this disease and its low survival, it is necessary to make an early diagnosis. We must perform a biopsy in patients who present new skin lesions after radiotherapy or surgery for BC. Given the disappointing results of treatment despite early diagnosis, we must also encourage and optimize lymphedema preventive measures.

Conclusion

Although it is a rare disease, the diagnosis of STS is extremely important due to its morbidity and especially its mortality. It can cause disability and impairment of the quality of life, as well as cause death in a short period of time. Emphasizing the importance of lymphedema prevention is of vital interest given the poor prognosis of STS, so existing medical measures must be optimized to achieve this goal. If chronic lymphedema is established, it is important to carry out a regular clinical examination of all affected patients and to biopsy any unusual skin lesions, in order to make an early diagnosis of this disease.

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