Stewart-Treves syndrome: cutaneous angiosarcoma developing in chronic lymphedema

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Summary

Cutaneous Angiosarcoma (CAS) is an uncommon, highly malignant, endotelial-derived tumor with a poor prognosis that may develop on chronic lymphedema as in Stewart-Treves Syndrome (STS). We report the case of a 82-year-old female affected by chronic lower limbs lymphedema, worsened after 2 pregnancies, and she was affected by diabetes, chronic heart disease, hypertension, peripheral arterial disease and slight vascular dementia. The patient referred a previous 2-month history of purpura. Two punch biopsies were performed and histology showed, in the superficial and deep dermis, extravasated erythrocytes, lymphocytes infiltrate, irregular vascular spaces involving inguinal and pelvic lymph nodes, liver and lungs. The patient died shortly after.

Our case highlights the poor prognosis of STS, the difficult management in old patients and confirm that chronic lymphedema is an “immunocompromised district” and a predisposing factor for the development of cutaneous neoplasias.

Case report

A 82-year-old woman referred to us because of red-violaceous ulcerated nodules of the right leg, measuring 13 x 7 centimeters (Figure 1). She suffered from chronic lower limbs lymphedema, worsened after 2 pregnancies, and she was affected by diabetes, chronic heart disease, hypertension, peripheral arterial disease and slight vascular dementia. The patient referred a previous 2-month history of purpura. Two punch biopsies were performed and histology showed, in the superficial and deep dermis, extravasated erythrocytes, lymphocytes infiltrate, irregular vascular spaces with anastomosis, lined by atypically endothelial cells, presenting mitoses on dissecting collagen bundels (Figure 2). Immunohistochemistry was performed and the atypical endothelial cells were positive for CD31 and CD34 stainings. Human Herpes Virus (HHV) 8 staining was negative. A diagnosis of CAS on chronic lymphedema, also called STS, was made.

Arterial and venous ecocolordoppler of the legs

KEY WORDS: chronic lymphedema; cutaneous angiosarcoma; immunocompromised district; lower limb; Stewart-Treves syndrome.

Introduction

Cutaneous Angiosarcoma (CAS) is a rare highly aggressive tumor, typical of elderly people, with a peak in the 7th-8th decade of life. Men are more frequently affected (1). CAS occurring on chronic lymphoedema are a minority of the cases of CAS and were first reported by Halsted under the term “elephantiasis chirurgica” (2). Stewart and Treves in 1948 well described CAS associated with chronic lymphedema due to breast cancer surgery, so this entity was called Stewart-Treves Syndrome (STS) (3). STS is clinically characterized by raised purplish lesions that may rapidly grow, leading to red-violaceous nodules and ulcerations (4). STS is more frequently described in the upper limbs after mastectomy and axillary lymph nodes dissection, complicated by chronic lymphedema of the omolateral arm, but may also occur in the legs (4). Lymphedema associated to STS can be congenital, idiopathic, traumatic, filarial, postsurgical and obesity-related (5-7). To the best of our knowledge, only a few cases of CAS have occurred in lower limbs lymphedema (8) as in the case here reported.
Stewart-Treves syndrome

Figure 1 - Red-violaceous ulcerated nodules of the right leg, measuring 13 x 7 centimeters.

Figure 2 - In the superficial and deep dermis, extravasated erythrocytes, lymphocytes infiltrate, irregular vascular spaces with anastomosis, lined by atypically endothelial cells, mitoses, dissecting collagen bundles (H&E 20x).

showed venous insufficiency, lymphedema and atherosclerotic disease of the femoro-popliteal arteries, even though without significant stenosis. Thoracic-abdominal-pelvic Computer Tomography (CT) did not reveal abnormalities.

Considering the size of the tumor, the age of the patient, comorbidities and general conditions, wide surgery was not performed. We started a chemotherapeutic regimen with liposomal doxorubicin local radiotherapy but after 5 months worsening of CAS occurred, and thoracic-abdominal-pelvic CT revealed metastases in the liver, lungs, pelvic and abdominal lymph nodes. Shortly after the patient died.

Discussion

Angiosarcomas are rare malignant tumors (1-2% of all sarcomas), derived by endothelial cells. There are two types, the haemangiosarcoma and the lymphangiosarcoma. Persistent lymphoedema, radiation and av-shunts are the main risk factors. The lymphedema-associated angiosarcoma (Stewart-Treves-Syndrome) is extremely rare (0.45% of lymphoedemata), and develops late up to 27 years after lymphoedema-onset (9, 10). The most of patients affected by STS are women (peak age 65-70 years) with a history of radical mastectomy due to breast cancer (8). STS of the lower limbs is rare and the duration of the lymphoedema before the development of CAS is about 5 to 15 years (7, 8).

The diagnosis of STS is made on the basis of clinical features, anamnesis of chronic lymphedema, histological findings, usually completed with immunohistochemistry (11). Immunostainings for CD31, Ki67 (7), UEA-1, CD34, and VIII-related antigen markers have been used for the diagnosis of CAS. Recently, endoglin (CD105) and claudin-5 have been studied and may be new useful markers for CAS (11).

The management of STS is difficult, because the tumor is aggressive, poor responding to therapies, usually affects elderly people and because diagnosis is frequently made at advanced stages. There is no treatment of choice but case reports suggest that large or radical resections, usually amputation or disarticulation, might provide improved survival (4). Surgical treatment can be preceded or followed by local radiotherapy. Monochemotherapy or polychemotherapy may also be curative or palliative purpose for locally advanced or metastatic STS (7). Drugs that may be used are doxorubicin, paclitaxel, docetaxel, ciclophosamide, high-dose methotrexate, vincristine and paclitaxel plus sorafenib. Electrochemotherapy could theoretically be another palliative therapeutic option (7).

Because of bleak outcomes, researchers are looking for target therapies and recently it has been demon-
strated that breast harbor Kinase Insert Domain Receptor (KDR) mutations might occur in about 10% of patients affected by CAS. KDR inhibitors could be a valid specific target therapy of primary and radiation-induced CAS (12). Besides it may be useful to implement prevention measures, such as the use of elastic compression stockings and lymphatic drainage, that has shown to improve cell-mediated immunity (13). However, further efforts are focused in understanding the pathogenesis of STS, that as of today is still unknown. It seems to be related to impaired immune surveillance and loss control of endothelial proliferation (14). The most likely hypothesis is that the immune response is altered because the chronic hindrance to lymph flow, that causes the storage of interstitial fluid, impairment of local immune surveillance due to the difficulty of the immunocompetent cells trading, encouragement of lymphangiogenesis in the damage district. The area with lymph flow dysfunction becomes an immunologically vulnerable area, (because of the continual angiogenetic stimulus and opportunistic oncogenesis) predisposed to malignancies, mostly those of vascular origin, as STS (15). Differential diagnosis includes both benign and malignant vascular diseases, particularly Kaposi Sarcoma. However Kaposi Sarcoma has positive immunohistochemistry for HHV 8 (16). Kaposi Sarcoma and STS may be different responses to abnormalities in lymph drainage and immune control, in fact they may share clinical and histological features and there might be a “gray zone” as in borderline cases (16). Also a recently described entity, called “massive localized lymphedema”, is caused by the obstruction of lymphatic drainage by adipose tissue in obese patients, and it is not known if is a differential diagnosis or may be associated to CAS (5). The case of STS here reported can be considered as an example of malignancy occurred in an “immunocompromised district”, an area of regional destabilization were the compromised immune surveillance is the cause of the development of malignancies (14, 15). Further studies are required to completely understand the mechanisms that can lead to the development of a tumor in a specific body area affected by alterations of lymphatic or venous systems.

References