Stewart-Treves syndrome: a case report of lymphedema-related angiosarcoma

Agnese Di Prazza,[1] Ligia J. Dominguez,[1] Giuseppe Badalamenti,[2] Mario Barbagallo[1]

[1]Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy; [2]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy

Abstract

Stewart-Treves syndrome (STS) is an angiosarcoma associated with lymphedema deriving more often from radical mastectomy and longstanding lymphedema, first described in 1948. Irradiation is also commonly associated with chronic lymphedema of extremities. It generally occurs about 10 years after the mastectomy and/or radiotherapy. The prognosis is very poor with a mean survival of 20 months from the diagnosis especially when radical surgery is not possible. We present the case of STS in an 89-year-old female who underwent left upper outer quadrantectomy for invasive ductal carcinoma in 2009 followed by axillary lymphadenectomy, radiotherapy, and hormonal therapy until 2014. She presented swollen upper left limb associated with hemorrhagic red papular lesions. Skin biopsy revealed the presence of lymphedema-associated angiosarcoma. Radical surgery was not possible, so she underwent conservative therapy with pazopanib, a tyrosine kinase inhibitor, with benefit. Long-term follow-up of these patients is crucial to intercept this condition at an early stage.

Introduction

Soft tissue sarcomas are rare conditions accounting of 1% of adult malignant neoplasms.[1] One of these is represented by cutaneous angiosarcoma, an uncommon aggressive variant originating from blood and lymphatic vessels which includes primary/idiopathic cutaneous and secondary post-irradiation or lymphedema-associated form known as Stewart-Treves syndrome (STS). This condition was first reported in 1948 and represents a rare complication in post-mastectomy patients who underwent axillary lymphadenectomy and radiotherapy developing chronic lymphedema of the limbs.[2] Prognosis is very poor, and an early detection is critical to improve patients' outcome.

Case report

We report the case of an 89-year-old woman presenting in early September 2020 to the geriatric department for swollen upper left limb associated with papular red-purple bleeding lesions, oliguria and lower limbs swelling.

She has past medical history of hypertension, diverticulosis of sigmoid colon, gastroesophageal reflux disease, and myelodysplastic syndrome with refractory cytopenia in need of a high transfusion regimen and chemotherapy cycles with azacitidine. In 2009, she was diagnosed with left mammary carcinoma, for which upper outer quadrantectomy was performed followed by axillary lymphadenectomy. She received chemotherapy and radiotherapy followed by hormonal therapy until 2014. She developed upper left limb oedema approximately three years ago. The patient presented to the emergency department several times from July to August 2020 after noticing a worsening of upper left limb oedema and the development of multiple elevated bleeding purple and red lesions but refused hospitalizations on more occasions.

On initial evaluation the patient was in poor clinical conditions, but alert and with no abnormalities in vital signs. She presented upper left limb oedema with multiple diffused purple red haemorrhagic papules extended to the mammary region associated with a *peau d'orange* appearance of the skin. (Figure 1A). Her cardiac examination revealed normal first and second sound with grade II/VI systolic murmur and moderately severe pitting oedema in both calves. The rest of her physical examination was otherwise normal. A 2×1.2×0.4 cm biopsy was performed revealing immunohistochemical CD31+, CD34-, podoplanin+/-, CK-pan-, C-MYC+ with a high Ki67 proliferation rate (45% of total tumor cells).

Given this result, the clinical conditions, and the past medical history, the diagnosis of soft tissue angiosarcoma associated with lymphedema was made. For staging purposes, a total body contrast-enhanced computed tomography (CECT) angiography was performed, and it showed an oval polylobate lesion near the left renal vein with peripheral annular enhancement suspect for metastasis. She performed blood transfusions at first, three times a week, then almost daily due to the worsening of arm bleeding (Figure 1B).

Correspondence: Ligia J. Dominguez, Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Viale F. Scaduto 6/c, 90144 Palermo, Italy.
Tel.: +39-0916554828.
Fax: +39-0916552952.
E-mail: ligia.dominguez@unipa.it

Key words: oncogeriatrics; angiosarcoma; lymphedema; breast cancer; anemia.

Contributions: ADP, LJD, GB, MB, were involved in patient care; ADP, was involved in the literature search, data collection, figures, and writing of the report; ADP, LJD, GB, MB, were involved in the interpretation and critical review of the report.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Informed consent: written informed consent to publication was obtained.

Availability of data and materials: data and materials are available by the authors.

Received for publication: 5 December 2022.
Accepted for publication: 3 March 2023.

Licensee PAGEPress, Italy
Geriatric Care 2022; 8:11065
doi:10.4081/gc.2022.11065

According to the oncologist, the patient was not eligible for surgery, and a palliative approach was preferred instead. The patient started immunotherapy with pazopanib 800 mg/day *per os*, a multitargeted tyrosine kinase inhibitor for metastatic soft tissue sarcoma,[3] after excluding chemotherapy with gemcitabine given the history of myelodysplastic syndrome and the higher risk of myelotoxicity. After one month of treatment lesions were significantly improved and bleeding diminished (Figure 1C) and the patient was in better clinical conditions with an interval time of 2 weeks between blood transfusions. By December 2020, the appear-

ance of the lesions definitely improved, and the patient was able to walk and did not require blood transfusions.

Discussion

Angiosarcoma is a malignant neoplasm of blood and lymphatic vessels, it is a rare aggressive variant of sarcoma. Angiosarcoma counts two variants which are primary/idiopathic cutaneous and secondary post-irradiation or lymphedema-associated (STS). STS was first described in 1948 by Fred W. Stewart, Professor of Pathology and Norman Treves, Associate Professor of Surgery at Cornell University Medical College of New York; they described six patients who developed angiosarcoma after radical mastectomy. All patients had lymphedema, with an average interval between surgery and angiosarcoma onset of 12 years.[2] This type of sarcoma has been described also in congenital and others secondary causes of lymphedema such as trauma, filariasis, venous stasis, leg ulceration, obesity, and surgical treatment of penile cancer.[4-6] More than 400 cases have been documented in the literature; in the 1960s, the incidence was 0.7% to 0.45% among patients who underwent radical mastectomy and survived for at least five years.[7] Today, it occurs in 0.03% of patients who survive 10 years after radical mastectomy.[8] The peak age is 65-70 years corresponding to breast cancer occurrence. Lymphedema after radical mastectomy and axillary lymphadenectomy has been reduced from 40 to 4% related to breast conservation therapy. The mechanism for the development of STS is unclear; however, Ruocco *et al.* hypothesized a state of local immunodeficiency due to lymphedema.[9] Another hypothesis is that chronic lymphedema leads to the accumulation of fluid rich in protein and growth factors which contribute to the formation of blood and lymphatic vessels and then of the malignancy.[10] The initial lesions present as subcutaneous mass or eschar with recurrent bleeding, then macular purple or red nodules, while in the advanced stage necrosis may be present.[11] In 1959, McConnel and Haslam developed a stage system with three stages: i) prolonged lymphedema causing fat and collagen degeneration, especially in the reticular dermis; ii) premalignant lymphangiomatosis with a diameter of 100µm-2cm, multiple foci of small, proliferative channels in dermis and subcutis with hyperplastic endothelial cells, superficial areas with bruises or vesicles, and deeper areas with induration or haemorrhage; iii) malignant lymphangiosarcoma.[12] The differential diagnosis includes benign and malignant diseases, the most important being kaposi sarcoma (KS). The difference is that usually, KS does not require the presence of lymphedema to develop, although it may be a predisposing factor.[13] Histology and immunohistochemistry are mandatory for the diagnosis. Cases were considered positive for CD34, CD31, D2-40, CK-pan, FVIII, β-catenin or vimentin with membrane or cytoplasmic immunoreaction, nuclear immunoreaction for ERG and c-MYC, and immunoreactivity for Ki67. Histologic grade is not used for staging given that angiosarcoma is a high-grade neoplasm by definition; CECT angiography, magnetic resonance, radiography, and fluorodeoxyglucose-positron emission tomographyare used for grading and for treatment planning.[14,15] There is still no standard treatment for STS due to its rarity. Although local excision is always followed by recurrence, it is the most frequently applied treatment; early amputation has a superior efficacy. Other options are chemotherapy with 5-fluorouracil, methotrexate, bleomycin, and/or a combination of actinomycin D, vincristine, doxorubicin, cyclophosphamide, and/or dacarbazine or radiotherapy with no superiority between the two techniques.[16,17] Immunotherapy is an alternative for metastatic cases with pleural effusion.[13] In particular, pazopanib is a multitarget tyrosine kinase inhibitor with activity against vascular endothelial growth factor 1, 2 and 3 and platelet-derived growth factor, this molecule was first registered as a treatment of renal cells cancer and then also for non-adipocytic soft-tissue sarcomas.[3] It is well tolerated in patients with relapsed, advanced non-adipocytic soft tissue sarcomas with good performance status. Common adverse effects are fatigue, anorexia, weight loss, nausea, hypertension, and liver disorders.[18] There are only two cases described in literature with the use of pazopanib for STS. In the first one, tumor progression was prevented with a low dose of pazopanib; a quarter of the usual dose (200 mg/day) was enough to prevent disease progression and to control its adverse events (hypertension and thyroid dysfunction).[19] In the second case, treatment was effective for both local and lung metastases, but when the patient had to discontinue pazopanib for gastrointestinal bleeding, the metastases worsened, and the patient died two months after discontinuation.[20] The present case is the third one of STS treated with pazopanib with clinical response. Prognosis is very poor due to the aggressive nature of the condition, high rate of recurrence and early multiple metastasis, especially pulmonary and pleural lesions. There are no long-term survivors reported in literature, with a median survival of 2.5 years after the diagnosis and two years for metastatic disease. If untreated, patients have a mean survival of 5 to 8 months.[11]

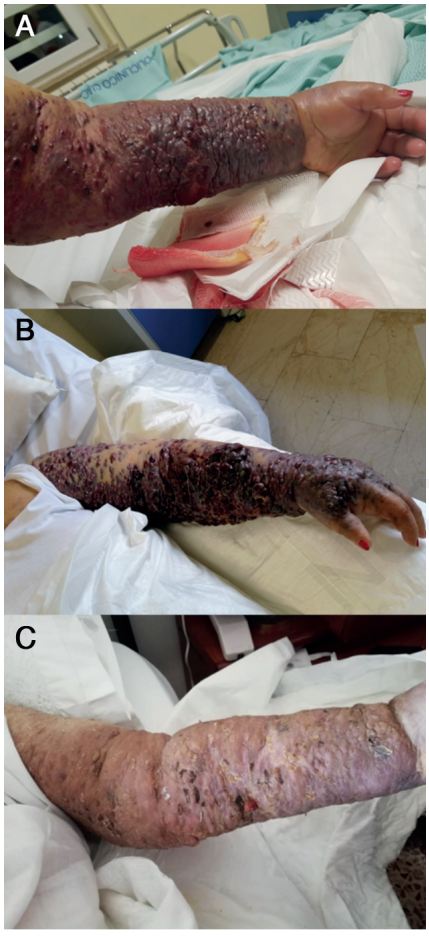

Figure 1. A) Clinical picture of the upper left limb with angiosarcoma at admission; B) Clinical picture of the upper left limb with angiosarcoma at 20 days after admission; C) Clinical picture of the upper left limb with angiosarcoma after 70 days of treatment with pazopanib.

Conclusions

STS is an aggressive angiosarcoma that develops on chronic lymphedema often after a radical mastectomy for breast cancer. The literature does not report any case of STS after quadrantectomy, as it occurs in the patient described here. Given the scarcity of data on this condition, a standard treatment is not yet available. At present, preventive measures are the most promising strategy. These measures consist of prompt treatment of cellulitis to prevent lymphatic vessels blockage, treatment of lymphedema with pressure gradient techniques, and avoiding unnecessary interruption of lymphatic vessels during surgery. A multidisciplinary approach is crucial for early detection; every

suspicious lesion in a patient with post-mastectomy lymphedema should be biopsied so that a radical treatment can be feasible at the time of diagnosis with a more favorable prognosis. In advanced disease, as in the case of our patient and the other two cases described in literature,[16,17] treatments with pazopanib may be initiated, provided collateral effects allow this course of action. We need further studies to better understand this condition and develop a standard of care.

References

1. Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. New Engl J Med 2005;353:701-11.
2. Stewart FW, Treves N. Lymphangio-sarcoma in postmastectomy lymphedema: a report of six cases in elephantiasis chirurgica. Cancer 1948;1:64-81.
3. Van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (palette): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-86.
4. Woodward A, Ivins JC, Soule EH. Lymphangiosarcoma arising in chronic lymphedematous extremities. Cancer 1972;30:562-72.
5. Al-Najjar AA, Harrington CI, Slater DN. Angiosarcoma: a complication of varicose leg ulceration. Acta Derm Venereol 1986;66:167-70.
6. Krause KI, Hebert AA, Sanchez RL, Solomon Jr AR. Anterior abdominal wall angiosarcoma in a morbidly obese woman. J Am Acad Dermatol 1986;15: 327-30.
7. Fitzpatrick PJ. Lymphangiosarcoma and breast cancer. Can J Surg 1969;12:172-7.
8. Wierzbicka-Hainaut E, Guillet G. Stewart-Treves syndrome (angiosarcoma on lyphoedema): a rare complication of lymphoedema [Article in French]. Presse Med 2010;39:1305-8.
9. Ruocco V, Schwartz RA, Ruocco E. Lymphedema: an immunologically vulnerable site for development of neoplasms. J Am Acad Dermatol 2002;47:124-7.
10. Shon W, Ida CM, Boland-Froemming JM, Rose PS, Folpe A. Cutaneous angiosarcoma arising in massive localized lymphedema of the morbidly obese: a report of five cases and review of the literature. J Cutan Pathol 2011;38:560-4.
11. Schwartz RA. Stewart-Treves syndrome. In: Demis DJ, ed. Clinical dermatology. 16th ed. Philadelphia, PA: Harper and Row Inc; 1989. pp. 1-6.
12. McConnell EM, Haslam P. Angiosarcoma in post-mastectomy lymphedema; a report of five cases and review of the literature. Br J Surg 1959;46:322-32.
13. Sharma A, Schwartz RA. Stewart-Treves syndrome: pathogenesis and management. J Am Acad Dermatol 2012;67:1342-8.
14. Jensen MR, Friberg L, Karlsmark T, Bulow J. (18)F-FDG PET/CT in a rare case of Stewart-Treves syndrome: future implications and diagnostic considerations. Lymphat Res Biol 2011;9:61-4.
15. Wang LL, Cui LF, Gao Y, Jiang ZC. Clinicopathologic features of Stewart-Treves syndrome. Int J Clin Exp Pathol 2019;12:680-8.
16. Grobmyer SR, Daly JM, Glotzbach RE, Grobmyer AJ. Role of surgery in the management of postmastectomy extremity angiosarcoma (Stewart-Treves syndrome). J Surg Oncol 2000;73:182-8.
17. Malhaire JP, Labat JP, Simon H, et al. One case of Stewart-Treves syndrome successfully treated at two years by chemotherapy and radiation therapy in a 73-year-old woman. Acta Oncol 1997; 36:442-3.
18. Koca S, Beşiroğlu M, Özçelik M, et al. Pazopanib for metastatic soft-tissue sarcoma: a multicenter retrospective study. J Oncol Pharm Pract 2020;27:541-6.
19. Yamada M, Osada SI, Toyoshima A, et al. Prevention of tumor progression in Stewart-Treves syndrome with a low dose of pazopanib. J Dermatol 2019;46:e 263-5.
20. Hayashi M, Makino T, Mori N, et al. Effectiveness of pazopanib for local and lung metastases in Stewart-Treves syndrome. Eur J Dermatol 2020;30:68-9.