Stewart-Treves syndrome: Pathogenesis and management

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Stewart-Treves syndrome is a malignancy that arises within chronic lymphedema. Although classically described as a consequence of radical mastectomy, this lymphangiosarcoma has been documented to occur in cases of congenital and other causes of chronic secondary lymphedema. The development of this aggressive lymphangiosarcoma at sites of chronic lymphedema renders it a possible model for Kaposi sarcoma. Because of the increase in conservative treatment for breast carcinoma and improvement of operative and radiation therapy techniques, the prevalence of Stewart-Treves syndrome has decreased. Regardless, this malignancy significantly worsens patients' outcomes and needs to be diagnosed and treated early. Chemotherapy and radiation therapy have not improved survivorship significantly. Early amputation or wide local excision offers the best chance for long-term survival. Yet, overall prognosis remains dismal. Untreated patients usually live 5 to 8 months after diagnosis. (J Am Acad Dermatol 2012;67:1342-8.)

Key words: breast cancer; Kaposi sarcoma; lymphangiosarcoma; lymphedema; postmastectomy angiosarcoma; Stewart-Treves syndrome.

Stewart-Treves syndrome is a rare and deadly disease. It is described as a cutaneous lymphangiosarcoma arising within chronic lymphedema as a consequence of mastectomy and axillary lymph node dissection. Although the patient with breast cancer may be cured with surgery and adjuvant therapies, this secondary malignancy significantly worsens patient outcomes. Classically associated with mastectomy, the term "Stewart-Treves syndrome" can be broadly applied to lymphangiosarcoma that develops from chronic lymphatic obstruction both congenital and acquired. Originally considered to be a lymphangiosarcoma, this cancer, through electron microscopic and immunohistologic evidence, was later believed to have a blood vessel rather than lymphatic endothelium origin, changing its classification to a hemangiosarcoma. Recent immunohistochemical studies, however, confirm that Stewart and Treves' original description of the cancer as a lymphangiosarcoma to be correct. Stewart-Treves syndrome shares similarities to Kaposi sarcoma, an angiosarcoma that may arise in the setting of lymphedema. Although less prevalent, usually more aggressive, and not presently linked with a viral cause, Stewart-Treves syndrome represents a pivotal model for cancers related to lymphedema, especially Kaposi sarcoma.

HISTORICAL ASPECT

In 1906, Loewenstein[1] described angiosarcoma in a patient's arm that had been affected by severe posttraumatic lymphedema for 5 years. The first description written in the English language is credited to Kettle,[2] who, in his 1918 paper, detailed an angiosarcoma of the leg in a 44-year-old woman with elephantiasis since childhood. In 1948, Fred W. Stewart, Professor of Pathology, and Norman Treves,[3] Associate Professor of Surgery, both at Cornell University Medical College, New York, NY, reported 6 cases of angiosarcoma arising from sites of postmastectomy lymphedema, "elephantiasis chirurgica." They recognized that chronic lymphedema, without recurrent cancer, may produce "a heretofore unrecognized and unreported sequel… long after the malignant breast neoplasm has apparently been arrested… a new specific tumor."[3] They also explained why this cancer was not previously observed, stating, "That they were erroneously

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considered as diffusely recurrent, inoperable, cutaneous manifestations of mammary cancer seems probable."[3] Stewart and Treves[3] thought the cancer to have a lymphatic vessel origin, titling their article *Lymphangiosarcoma in postmastectomy lymphedema*.

EPIDEMIOLOGY

There are more than 400 cases of Stewart-Treves syndrome reported in the literature. The incidence of this disease is between 0.07% and 0.45% in patients who survive at least 5 years after radical mastectomy.[4] No racial predominance has been shown for Stewart-Treves syndrome. Most patients given the diagnosis of the disease are women with a history of breast cancer treated with the Halsted radical mastectomy. Unlike Kaposi sarcoma, Stewart-Treves syndrome has not been shown to be more prevalent in patients with AIDS or other immunodeficiency disorders. The peak age for developing Stewart-Treves syndrome is 65 to 70 years, corresponding to trends in breast cancer occurrence with additional years for the development of chronic lymphedema.[5] One study reported an average patient age of 68.8 years at the onset of disease with a range of ages at diagnosis of 44 to 84 years.[6]

Because of the popularity of breast conservation therapy, improvement of operative and radiation therapy techniques, and development of novel chemotherapeutic agents, the incidence of Stewart-Treves syndrome has significantly decreased.[7] Moreover, as most radiotherapists abstain from routinely irradiating the axillae after lymphadenectomy, the incidence of chronic lymphedema after breast cancer treatment has been reduced from 40% to 4%.[8]

PATHOPHYSIOLOGY

The most important causative linkage in Stewart-Treves syndromes is chronic lymphedema.[9] Although the disease mainly develops in patients who have lymphedema secondary to radical mastectomy, it may arise in forms of congenital and acquired lymphedema that result from trauma, filariasis, idiopathic acquired lymphoma, venous stasis, morbid obesity, leg ulcerations, and surgical invasion of the groin for treatment of cervical or penile cancer.[6,10-15] Edema that accompanies cardiac or renal disease is not associated with Stewart-Treves syndrome.

The pathophysiology of Stewart-Treves syndrome is a matter of controversy. Although it is widely acknowledged that lymphedema can induce angiosarcoma, the mechanism by which such transformation takes places is unknown. Stewart and Treves[3] speculated that a systemic carcinogenic factor was the causative agent, given findings of a high incidence of a third malignancy in patients with postmastectomy lymphangiosarcoma. This hypothetical factor has yet to be isolated.

Local immunodeficiency may be involved in disease development. In 1960, it was demonstrated that homograft skin transplanted on a lymphedematous arm survived much longer than homograft skin transplanted to healthy arms. It was thus postulated that lymphedema may cause some degree of local immunodeficiency that is conducive toward oncogenesis.[16,17] Mallon et al[18] showed that in a region of lymphedema there was impairment of the afferent and efferent loops of the allergic contact dermatitis reaction, adding evidence for suppression of immune competence that may facilitate oncogenesis. Malignant transformation of lymphangioma circumscriptum is rare.[19] However, there is no evidence for a benign precursor for Stewart-Treves syndrome. Ruocco's immunocompromised district might be recalled as linking lymphedema with this sarcoma,[16,20,21] as should other potential triggering factors.[21]

Radiation therapy may cause axillary node sclerosis,[22] leading to local lymphedema and, thus, an immunocompromised state. We postulate that, in accordance to Ruocco immunocompromised district, this may contribute to the development of Stewart-Treves syndrome. A correlation was made that patients with the shortest interval between radical mastectomy and disease diagnosis received both preoperative radiation therapy of involved breast and axillary lymph nodes followed by fractionated radiation in these areas.[14] Among patients receiving radiation therapy, the relative risk of developing angiosarcoma is 15.9.[23]

Kaposi sarcoma, particularly in its classic form, usually appears on acral sites accompanied or preceded by lympedema.[24] Similar to Stewart-Treves

CAPSULE SUMMARY

- Stewart-Treves syndrome is a rare and aggressive lymphangiosarcoma linked with chronic lymphedema after radical mastectomy for breast cancer.
- Lymphostasis, in Stewart-Treves syndrome and other angiosarcomas, may produce local immunodeficiency, which could promote vascular oncogenesis.
- Stewart-Treves syndrome has a poor prognosis and, thus, preventative measures and early diagnosis are important.