

Stewart–Treves syndrome in a spinal cord injury patient with *MYC* amplification



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Angiosarcoma is a rare, aggressive vascular malignancy with a poor prognosis. Primary cutaneous angiosarcoma arises de novo on the head and neck of the elderly, whereas secondary angiosarcoma arises in the setting of known risk factors, including chronic lymphedema or previous irradiation. When associated with chronic lymphedema, it is eponymously referred to as Stewart–Treves syndrome. The pathophysiology of tumorigenesis in these cases is not fully understood, but may be related to ongoing angiogenesis and impaired cellular immunity induced by lymphedema.¹ This is supported by recent research showing that these tumors feature a characteristic *MYC* amplification, a nuclear transcription factor crucial for vascular endothelial growth factor–dependent angiogenesis.^{2–5}

We report a case of angiosarcoma arising in a chronically edematous limb of a patient with a spinal cord injury (SCI). We report this unusual case to highlight angiosarcoma as a potential complication of lymphedema in the SCI population. With the number of traumatic SCIs on the rise,⁶ these patients represent a subset of the population who are uniquely susceptible to developing lymphedema and its complications. Management of these patients is complex, often requiring a multidisciplinary approach.

CASE REPORT

A 42-year-old male veteran with C6 motor/C4 sensory complete tetraplegia was referred to the

dermatology clinic for a bothersome lesion on the lateral aspect of his right lower leg. He had long-standing lower extremity edema since his cervical spine injury during military service in the mid-1990s. He was otherwise in his normal state of health with active full-time employment when a bruise-like lesion had appeared 1 month earlier with no history of trauma. Over the ensuing weeks, the patient described it as a “blood blister,” with constant spontaneous bleeding and without pain, itch, or a history of similar lesions. There was no history of malignancy, pelvic surgery, radiation, or long-standing infection.

On examination, he was wheelchair bound with bilateral lower extremity–dependent 2+ pitting edema and overlying stasis changes (Fig 1). On the lateral surface of his right lower leg was a 3.5 × 3.4 cm erythematous to violaceous, spongy, nontender nodule with overlying serum crust (Fig 1). There was no surrounding erythema or purulent discharge.

A biopsy specimen was obtained and revealed a mitotically active, atypical spindle cell proliferation in the dermis with extravasated red blood cells (Supplemental Fig 1). The lesional cells showed nuclear positivity for erythroblast transformation-specific related gene (Supplemental Fig 2) and were negative for human herpesvirus-8 and glucose transporter 1. Fluorescence in situ hybridization showed marked *c-MYC* amplification with an increased ratio of *c-MYC*/CEP-8

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Fig 1. Rapidly growing and bleeding lesion above the ankle on the right lower leg.

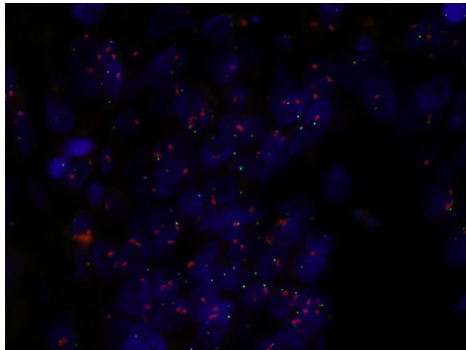


Fig 2. The initial biopsy specimen reveals *c-MYC* amplification (8q24 probe red, centromere of chromosome 8 probe green) via fluorescence in situ hybridization, supporting the diagnosis of secondary angiosarcoma.

(Fig 2). Taken together, the diagnosis was that of high-grade angiosarcoma, and complete removal was recommended.

After a staging full-body computed tomography scan confirmed the absence of metastatic disease, a wide local excision with 2-cm clinical margins was performed. The excisional specimen confirmed the diagnosis of a 7-cm, high-grade angiosarcoma with subcutaneous/suprafascial extent in discontinuous lobules (Fig 3), areas of necrosis, and with multiple positive margins (Fig 4), bringing the final American Joint Committee on Cancer staging to IIIa. A 1-cm complete re-excision was performed with clusters of large atypical tumor cells seen again in a margin. A second targeted 1-cm margin re-excision was performed and was negative for tumor cells. The post-operative wound was initially closed with a skin graft, which failed after the patient completed 6000 cGy radiation therapy. A biologic dressing was then placed with increasing wound closure upon last examination, approximately 14 months from the original excision.

DISCUSSION

Lymphedema-associated angiosarcoma typically presents as a red-blue papulonodule that may

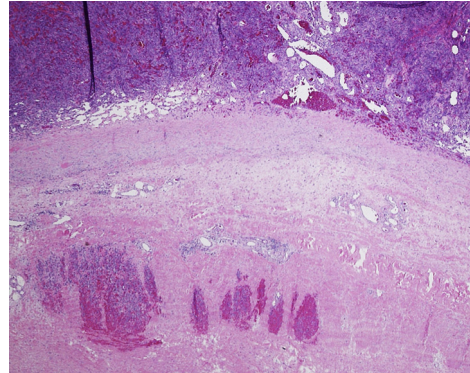


Fig 3. Primary excision shows an invasive tumor with discontinuous lobules extending to the deep soft tissue. (Hematoxylin–eosin stain; original magnification: $\times 4$.)

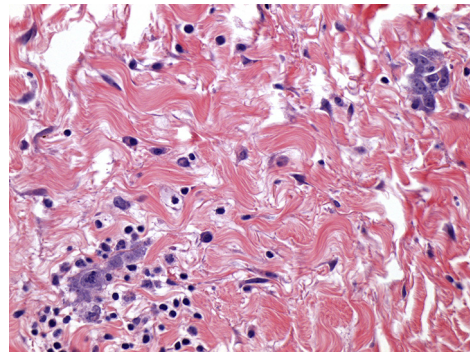


Fig 4. Clusters of atypical tumor cells were noted at the margin of the primary excision (upper right and lower left). (Hematoxylin–eosin stain; original magnification: $\times 40$.)

ulcerate, leading to recurrent episodes of bleeding, infection, and even necrosis. These aggressive tumors have a propensity to metastasize to the lung, liver, bone marrow, and brain. The high-grade lesion in our patient demonstrated a predominantly spindle cell pattern with deep invasion, numerous mitotic figures, and extravasated red blood cells. The tumor demonstrated strong erythroblast transformation-specific related gene nuclear positivity, which is highly specific for vascular tumors and highly sensitive for angiosarcoma.⁷ Surgical excision followed by radiation remains the mainstay of treatment. As evidenced by our case, there is often a diffuse infiltrative growth pattern extending far beyond the clinically apparent lesion underscoring the need for wide local excision and careful histopathologic margin examination.

The mechanism by which lymphedema induces tumorigenesis is not fully understood, but may be caused by impaired lymphatic drainage that disrupts immune cell trafficking and creates an environment inept at recognizing and destroying tumor cells.¹

Simultaneously, lymphatic stasis stimulates vigorous angiogenesis via growth factors used for the production of new, collateral lymphatic and vascular channels.¹ Recent studies have shown that overexpression of *MYC*, which is key for angiogenesis, seems to be highly associated with secondary angiosarcoma.²⁻⁵ For this reason, *MYC* amplification by fluorescence in situ hybridization or anti-*MYC* immunohistochemical studies can be used to support the diagnosis. Only a minority of cases with *MYC* amplification have been associated with lymphedema, as opposed to radiation. Of these, the causes of lymphedema were morbid obesity, deep venous thrombosis syndrome, or were unspecified.^{2,3,8}

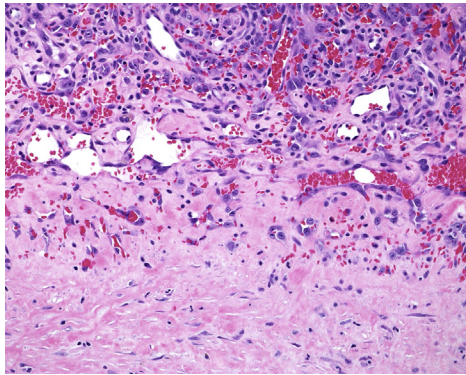
With the number of SCIs on the rise, these patients represent an important, and vulnerable, subset of the population.⁶ The combination of muscle paralysis and limited mobility makes them especially susceptible to developing lymphedema. Even with the best management, lymphedema may progress and can be complicated by infection, cutaneous ulceration, and malignancy, as shown in this case. Unfortunately, there remains a paucity of high-quality evidence to support specific therapeutic modalities for lymphedema because none have undergone satisfactory metaanalysis or large, randomized clinical trials.⁹ The International Society of Lymphology recommends monitoring the affected limb for changes in size or appearance, maintenance of an ideal body weight, limb elevation, prevention of infection, and the avoidance of limb constriction.⁹ Further therapy emphasizes techniques to move excess fluid into circulation, including compression bandages, manual lymphatic drainage, complete decongestive therapy, and intermittent pneumatic compression.¹⁰ In general, there is a limited role for pharmacotherapy, including diuretics, with the exception of antibiotics for recurrent infection.⁹

The veteran population is a subset of patients with SCI that remains at increased risk for unique disease

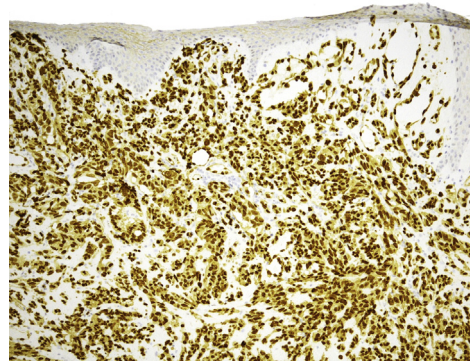
presentation and complications. We present this case of angiosarcoma arising in the lower extremity of a veteran with SCI to underscore the need for physicians caring for this population to be vigilant of such unusual presentations and their complications.

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Supplemental Figure 1. Invasive angiosarcoma forming vessels with leading edge single tumor cells and extravasated red blood cells in the initial biopsy specimen. (Hematoxylin–eosin stain; original magnification: $\times 20$.)



Supplemental Figure 2. Tumor cell nuclear reactivity with erythroblast transformation-specific related gene by immunohistochemical analysis, supporting the diagnosis of angiosarcoma. (Original magnification: $\times 10$.)