ANGIOSARCOMA IN PRIMARY LYMPHEDEMA OF THE LOWER EXTREMITITY — STEWART-TREVES SYNDROME
Departments of Surgery*, Pathology**, Radiology***, University of Cologne

ABSTRACT:

After a 20-year latent period an angiosarcoma developed in the edematous leg of a 74-year-old woman with primary lymphedema. A deep venous thrombosis of the leg which further exaggerated tissue swelling preceded the appearance of angiosarcoma. Histogenetic classification of the tumor as hemangiosarcoma rather than lymphangiosarcoma was favored by positive immunohistochemical staining for Factor VIII. Despite high amputation and isolated perfusion with hyperthermal cytotoxic infusion, the development led to local recurrence and distant metastases and died 16 months after operation. Patients with chronic primary or secondary lymphedema are susceptible to angiosarcoma although the overall risk is small.

The development of extremity angiosarcoma in peripheral lymphedema has been observed in over 200 patients (1,2) since Stewart and Treves published a report of 6 cases in 1948. Most commonly, this vascular malignancy develops in the lymphedematous arm of a patient after radical mastectomy for treatment of carcinoma of the breast, occurring in approximately 1% of all mastectomy patients with secondary arm lymphedema and in 0.45% of 5-year mastectomy survivors (3). The average latent period is 9 years (1).

In patients with primary or secondary chronic lymphedema without previous mastectomy, the development of angiosarcoma is much rarer (4-6). We are aware of 36 reported instances and Servelle (7) cites an incidence of angiosarcoma in lymphedematous legs of approximately 0.7% with an average latent period of 20 edema years (8). Long-standing primary or secon-
tumor locally recurred. By 14 months post-amputation, metastases were evident in the lumbar spine and the pleura. She died 2 months later in May, 1983.

PATHOANATOMIC INVESTIGATIONS

The amputated limb showed extensive livid discoloration circumferentially just below the knee and extending to the ankle. The subcutaneous tissue particularly near the ankle was edematous. Hard, tumorous subcutaneous masses with small, raised, lenticular, blackish-livid, fluctuating nodules were scattered over an area measuring 10 x 8 cm along the inner aspect of the calf. The tumor was confined to the subcutaneous region extending into the entire discolored area. Grossly, the fascia and tibia were intact. The resected inguinal lymph nodes were positive for metastasis.

Microscopically, atypical mesenchymal proliferation composed partly of spindle and partly of round cells was noted within the thickened and partially fibrosed cutis and encroaching on subcutaneous fat (Fig. 2A). Many hollow spaces lined with endotheloid or sometimes polymorphic cells were present often filled with erythrocytes (Fig. 2B). Serial sections showed progressively more solid areas composed of cells undergoing mitosis. With a malignant vascular pattern the findings were compatible with angiosarcoma.

Immunohistochemically, Factor VIII was identified in some of the neoplastic endothelial nests, suggesting that the tumor was a hemangiosarcoma rather than a lymphangiosarcoma.

DISCUSSION

Since hemangiosarcoma arose in a lymphedematous leg the diagnosis conforms to the Stewart-Treves syndrome (1,4,10,11). Two types of this disorder are recognized. In the first and larger group angiosarcoma develops in secondary lymphedema following radical mastectomy; in the second group, to which our patient belongs, in a chronic lymphedematous extremity without antecedent malignancy or radical resection. In 1951 Martorell (5) documented and classified the first example in the second group. Since the histogenesis of vascular tumors (i.e. lymphangiosarcoma, hemangiosarcoma) has not been fully clarified, the neutral term “angiosarcoma” is preferable (3). In our patient, however, identification of Factor VIII in neoplastic endothelial cells suggests an origin from blood vessels rather than lymphatics.

Angiosarcomas arising in primary or secondary lymphedematous extremities are not different clinically or morphologically from those developing after radical mastectomy for treatment of breast carcinoma. In accord with other authors, therefore, the term Stewart-Treves syndrome better designates development of angiosarcoma in chronic lymphedema irrespective of radical mastectomy (3). Based on the incidence of angiosarcoma in lower extremity lymphedema as cited by Servelle (7) and Schirger (12), the likelihood of occurrence of this malignant transformation is less than 1% with a latent period of 1.5 to 46 years (average, 20 years) (8,13). There may be, however, different latent periods for primary in contrast to secondary lymphedema (1). The incidence of other malignancies in individuals with Stewart-Treves syndrome is also higher than in the general population (13). The only known pathogenic feature is chronic lymphedema (1,9). Causal factors implicated include partial immunodeficiency and, particularly in primary lymphedema, reduced immunocompetence (1,4,10).

In animal models, focal, atypical vascular and fibroblastic proliferation has been observed in chronic lymphedematous connective tissue. Apparently, a prolonged period of capillary multiplication facilitates proliferation of malignant endothelial cells (3). Detailed structural studies, however, demonstrate a histogenetic relationship with lymphatic endothelial cells. Erythrocyte-filled hollow spaces lined with undifferentiated cells of high ribosome content have been identified by electron microscopy (14). Silberberg et al (15),
Fig. 1: Angiosarcoma of the edematous leg.

Fig. 2a: Angiosarcoma at the border of corium and subcutaneous fat. Note the narrow and dilated anastomosing spaces lined by hyperchromatic and polymorphic neoplastic endothelial cells.

Fig. 2b: Many neoplastic vascular channels are filled with erythrocytes (arrows) (HE 250x)
however, detected pericytes in the vascular proliferate, structures which lymphatics lack.

Stewart-Treves syndrome needs to be differentiated from Kaposi's sarcoma (10). This tumor differentiation with peripheral lymphedema is often difficult, because even invasive techniques such as angiography are unable to distinguish between these two angiosarcomas.

Treatment of Stewart-Treves syndrome is severely limited because of rapid growth and metastasis of the angiosarcoma; indeed in our case, metastases were already present in regional nodes at time of operation. Treatment usually entails radical limb amputation (3,8) and usually adjuvant chemotherapy (3,16). In our clinic isolated perfusion with a hyperthermal cytostatic infusion solution immediately prior to amputation has become standard for treatment of malignant soft tissue tumors including angiosarcoma.

Due to an extremely unfavorable prognosis of angiosarcoma (mean survival of 34 months) (8), regular inspection of the lymphedematous extremity in addition to prophylactic therapy and long-term treatment of lymphedema is mandatory. Frequent examination is particularly desirable when there are other complications of lymphedema such as erysipelas and superimposed deep venous thrombosis (as in our patient). Thus, angiosarcoma has seemingly been precipitated with further interference with free movement of interstitial fluid by such complications (4,16). Histologic examination of cutaneous alterations of lymphedematous extremities is also prudent to verify or exclude angiosarcomatous degeneration.

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Th. Schmitz-Rixen, Dr. med., Chirurgische Univ.-Klinik Koln, Chir. Kreislaufabtor. Altbaug, Haus 6, Josef-Stelmann- Str. 9, 5000 Koln — Lindenthal 41.

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