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# Lymphedema-related angiogenic tumors and other malignancies

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**Abstract** Chronic lymphedema has a permissive effect with certain types of malignancies, particularly angiosarcomas, in what is known as Stewart-Treves syndrome. The presumed mechanism of this effect is an immunocompromised district of the affected area. Most other cutaneous malignancies have also been described in lymphedematous areas, including basal cell carcinoma, squamous cell carcinoma, melanoma, Kaposi sarcoma, Merkel cell carcinoma, and several cutaneous lymphomas. The occurrence of such malignancies suggests a more general immunosuppression within the skin. The formation of collateral lymphatic and vascular vessels in response to lymphedema produces an environment rich in growth factors, which may also play a role. In addition to infection and other general skin care issues, regions affected by lymphedema should be monitored for malignant changes not limited to angiosarcomas.


## Introduction

The role of lymphedema in cutaneous malignancy is best explained by the local immunosuppression caused by the inability to circulate lymphatic fluid, as well as the rich medium of growth factors induced by lymphatic stasis.[1] Immunosuppression secondary to acquired immunodeficiency syndrome (AIDS), immunosuppressive agents, and chemotherapeutics has long been associated with various malignancies. The immunocompromised district is susceptible to many of the same complications seen in systemic immunosuppression.[2]

Lymphedema is classified into primary and secondary forms. Primary lymphedema may be further subdivided by age of clinical onset: (a) congenital lymphedema (before age 2 years), (b) lymphedema praecox (between age 2 and 35 years), and (c) lymphedema tarda (after age 35 years). Milroy disease (hereditary lymphedema type 1A) is the congenital familial form of primary lymphedema. It can also be seen in Turner syndrome and Noonan syndrome. Different types of lymphedema praecox include Meige disease (hereditary lymphedema type 2), lymphedema-distichiasis syndrome, yellow nail syndrome, and hypotrichosis-lymphedema-telangiectasia syndrome.

Classic causes of secondary lymphedema include chronic bacterial infections, iatrogenic causes (including radical mastectomy and vein harvesting), radiation, trauma, lymphoma, and filariasis. Lymphedema is commonly seen as a complication of breast cancer and affects approximately 14% of patients who undergo complete axillary lymph node dissection during their treatment.[3] Massive localized lymphedema (MLL) secondary to obesity has emerged and is a challenging pathologic diagnosis,[4] with cancers reported in these regions as well.[5] The incidence of MLL is expected to rise with the global obesity epidemic[6]; the malignancies associated with lymphedema may accompany it. Microscopic lymphatic dysfunction in rhinophyma may give rise to occult malignancy; therefore, resected specimens should be sent to preclude the possibility of cancer.[7,8] Venous obstruction from other diseases can lead to phlebolymphedema, another form of

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the immunocompromised district caused by venous stasis, and one that also may give rise to cancers.[9] There may be overlap between the etiologies of lymphedema and risk factors for skin cancer such as local irradiation, chemotherapy, and malnutrition. Numerous case reports of skin cancers, including rare types of cancer, in lymphedematous areas exist. Clinicians should be vigilant in monitoring patients with lymphedema for the development of cutaneous malignancy.[10]

## Lymphedema and neoplasia

A seminal work on the lymphatic system and cancer in 1973[11] was the first convincing piece of evidence for enhanced neoplasia in lymphatic dysfunction. In that experiment, alymphatic pedicles of skin from guinea pigs were inoculated with liposarcoma cells and were compared with controls that received the same inocula to normal pedicled skin. The normal skin showed complete clearance of the tumor cells, whereas the alymphatic pedicles showed tumor progression in most cases. Others built on this principle by suggesting that fibrosis, infection, and immunosuppression may be underlying initial neoplasia in lymphedema.[12] Cell-mediated immunity (CMI) plays an important role in the recognition and destruction of tumor cells in the human body. Immune impairment in lymphedema was first reported in 1960[13], when researchers noted increased survival of skin homografts after surgical destruction of regional lymph nodes. Impaired cell-mediated immunity in lymphedematous extremities was also suggested[14] based on a dysfunctional response to induce contact dermatitis with dinitrochlorobenzene. The skin is rich in antigen-presenting dendritic cells (DCs), which use lymphatics to migrate[15] and participate in antigen presentation with cytotoxic T-lymphocytes (CTLs). The role of newly described killer DCs in direct cytotoxic responses has been recently delineated; they may serve as powerful tools for the development of cancer immunotherapies.[16]

Wound-healing studies in mice have showed that lymphatic dysfunction causes increased levels of interleukin 10 (IL-10).[17] IL-10 prevents DC maturation, which may inactivate the DCs that are commonly found in the tumor microenvironment.[18] Pathologically, lymphangiectases are usually noted in benign and malignant skin changes, including warts and nonmelanoma skin cancer,[19] suggesting that even microscopic lymphatic disease caused by common skin conditions may compromise immune trafficking.[20]

Ongoing inflammation, as evidenced by erythrocytes in lymphatic fluid collected from lymphedematous areas,[21] may also contribute to local neoplasia by chronic irritation. Congenital lymphedema is not rare (Figure 1). Filariasis is a common cause of lymphedema worldwide. When caused by *Wuchereria bancrofti* and *Brugia* species, it is known to induce production of vascular endothelial growth factor (VEGF),[22] which may promote aberrant blood vessel growth and neoplasia. VEGF receptor 3 (VEGFR-3) has been identified as an important marker of lymphatic endothelial cells, and its

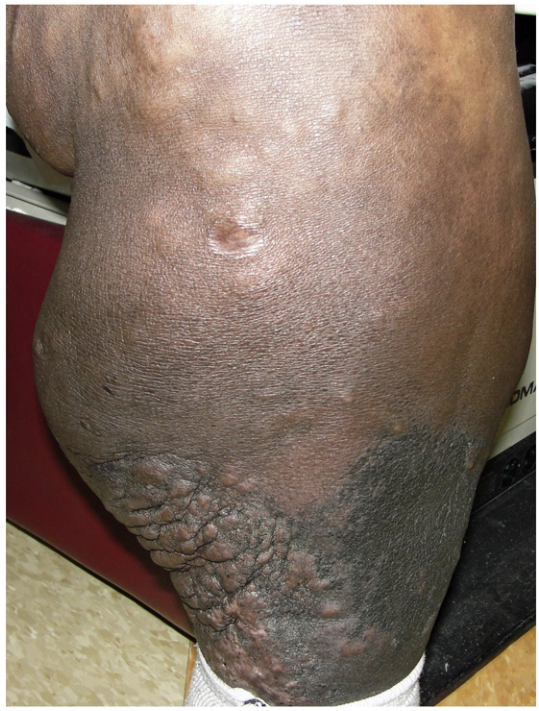

**Fig. 1** Congenital lymphedema of the leg.

expression has been documented in tumor neovascularization and wound granulation tissue.[23] Tumor lymphangiogenesis is part of a complex and poorly understood sequence of events that allows for metastasis.[24,25] The natural history of lymphedema is progressive until a steady state is reached without any functional return of lymphatic flow.[26,27] VEGF-C has been identified as a potential agent for the treatment of lymphedema, and studies in animals are promising.[28]

## Angiosarcomas and Stewart-Treves syndrome

Angiosarcoma/lymphangiosarcoma arising in the setting of lymphedema was first described in 1906.[29] Other researchers[30] then reported six patients who developed angiosarcoma at sites of postmastectomy lymphedema. Since then, at least 400 cases of angiosarcomas developing in the context of chronic lymphedema have been reported, many of which historically were associated with the Halstead radical mastectomy. The development of upper extremity angiosarcoma after breast cancer treatment carries an adjusted odds ratio as high as 59. Lymphedema plays a role in the pathogenesis of angiosarcomas, but other factors such as radiation therapy may also increase risk.[31] The onset of angiosarcoma after mastectomy ranges from 5 to 25 years in some case series. Clinically, angiosarcomas appear as multiple reddish blue macules or nodules that may become polypoid and coalesce. Most potential causes of chronic lymphedema have been linked to the development of lymphangiosarcomas.[32] Lymphangiosarcomas arising in hereditary lymphedema,[33] recurrent erysipelas,[34] and filariasis[35] are well documented, and lymphedema from other malignancies