Skin Biopsy Evaluation of Lower Leg Ulcers

Chronic ulcers of the lower extremities occur in 2% or more of people, increasing in frequency with patient age. Venous ulcers account for 70% and have been the attributed cause of 2 million lost days of work and $3 billion treatment cost per year in the USA. Other causes of leg ulcers include thrombotic disorders, arterial disease, autoimmune disease, inflammatory conditions, infections and neoplasia.

The clinical characteristics of ulcers, medical history and vascular studies will allow for the etiologic classification of leg ulcers in many patients. In cases of unusual ulcer morphology, complicated patients with multiple comorbidities and poor response to therapy, skin biopsy may provide information to better understand the pathophysiology of a leg ulcer.

VASCULAR DISEASE

Venous insufficiency: Chronic venous insufficiency is the most common cause of lower leg ulcers. Venous hypertension in the skin causes proliferation of capillaries in the papillary dermis, dilatation and thickening of veins in the dermis and subcutis, fibrosis, edema and hemosiderin deposition. These structural changes are evident in a skin biopsy, and are sometimes accompanied by eczematous changes in the epidermis with variable amounts of inflammation. The ulcerations related to venous disease are typically at the level of the dermis, have fibrin exudate but show little inflammation unless complicated by surface bacterial infection.

Procoagulant disorders: A subset of patients with chronic ulcers related to venous disease have an underlying coagulopathy. Antiphospholipid antibodies and lupus anticoagulant promote venous thrombosis. In skin biopsies from leg ulcers, fibrinoid change in capillary walls and luminal thrombi are clues to an underlying coagulopathy. However, these microscopic observations are sometimes made in patients without a detectable coagulopathy. Livedoid vasculopathy is now considered an idiopathic thrombotic condition that may lead to scarring (atrophie blanche) and ulceration. Thrombophilia, a predisposition to form clots, may also be due to inherited abnormalities in coagulation such as antithrombin or protein C deficiency.

Arterial disease: Arteriosclerosis causes inadequate perfusion of oxygenated blood and chronic ischemia may promote cutaneous leg ulcers. Diabetes mellitus often has associated arterio- and arteriolosclerosis with coexisting peripheral nerve disease. Skin biopsies from ulcers related to chronic ischemia typically show thickening of walls of small arteries and arterioles with narrowing of lumens. Cutaneous fibrosis is present with atrophy of epidermis and cutaneous appendages. The vessels and tissues are not typically inflamed, unless there is complicating bacterial infection that will manifest with suppurative inflammation with or without necrosis.

Acute and subacute vascular lesions with ulceration: There are rare causes of leg ulcers that present with lesions that have only been present for days or a few weeks. These relate to vascular occlusive events due to thrombosis or embolism. It is possible for these to occur in a background of chronic venous insufficiency or peripheral arterial disease, and careful clinical history and biopsy may be necessary to identify the process correctly. Calciphylaxis shows interstitial calcification in adipose and calcification in the walls of capillaries and arterioles, typically with luminal thrombus formation. There may be attendant changes of ischemic necrosis. Careful scrutiny of histopathology and clinical findings are important as calcification may occur in the tissue in other settings and in arterial vessels in Monckeberg’s medial calcific sclerosis. Cocaine use, especially cocaine adulterated with levamisole, can sometimes promote a thrombotic vasculopathic condition with retiform purpura and cutaneous necrosis and ulceration. Cholesterol emboli and atheroemboli may result in vascular occlusion and ulceration. Arterial catheterization or invasive arterial procedures may precede such events.

Other disorders with vasculopathy: Scleroderma and radiation injury are associated with cutaneous sclerosis and microvascular compromise that may lead to ulceration. Hematologic disorders such as sickle cell anemia and thalassemia may be complicated by leg ulcers.
mon infections that may manifest with acute, subacute and chronic conditions. Chronic skin ulcers related to burns and radiation are also known to sometimes develop carcinomas within them. Lymphomas, sarcomas and metastatic malignancies may sometimes have ulceration. Skin biopsy is necessary to identify and classify ulcerated malignant tumors on the leg.

**Benign neoplasms:** Primary benign skin tumors of the leg may sometimes ulcerate due to large size or trauma. Keratoses, sweat gland tumors and dermal fibromas are examples of benign tumors that may have ulceration. Skin biopsy is helpful to identify and classify benign tumors of the skin and differentiate them from malignant neoplasms and inflammatory conditions.

- Paul G. Goode, MD

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**References:**

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**Causes of Lower Leg Ulcers**

- **Vascular diseases**
  - Chronic venous insufficiency/venous stasis disease
  - Vasculopathies, thrombophilia
  - Idiopathic (hereditary, obesity, other risk factors)
  - Venous malformation
  - Phacoacanthosis
  - Anti-phospholipid antibodies, lupus anticoagulant
  - Idiopathic/livedoid vasculopathy

- **Arterial diseases**
  - Arteriosclerosis/arteriosclerosis
  - Heredity, smoking, hyperlipidemia, hypertension
  - Diabetes mellitus
  - Sickle cell disease, thalassemia

- **Mixed vascular lesions**
  - Calcinosis
  - Coccaine/livosamide
  - Sclerodema
  - Radiation injury

- **Inflammatory diseases**
  - Autoimmune vasculitis
  - Lupus erythematosus, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa
  - Neutrophic dermatoses
  - Pyoderma gangrenosum
  - Granulomatous disorders
  - Necrobiosis lipoidica
  - Sarcoidosis

- **Infections**
  - Bacteria
  - Pyogenic bacteria, staph, strep, “man-eating”, necrotizing cellulitis/fasciitis
  - Non-tuberculous mycobacteria

- **Fungus**
  - Primary cutaneous infection
  - Systemic infection

- **Virus**
  - Herpes Simplex, Herpes Zoster

- **Neoplasia**
  - Basal cell carcinoma, squamous cell carcinoma, melanoma
  - Lymphoma
  - Sarcoma
  - Metastatic malignancy

- **Benign**
  - Sweat gland tumors
  - Dermatofibroma

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**LABORATORY NOTES:**
1. Skin biopsy may not be necessary or indicated in patients with leg ulcers in cases when clinical findings, medical history and vascular studies are diagnostic.
2. Skin biopsy of leg ulcers should be considered in patients with uncertain diagnosis or unexpected response to treatment.
3. Skin biopsy of leg ulcer is indicated when there is suspicion of malignancy.
4. Communication of clinical findings and medical history is imperative when submitting skin biopsy from a leg ulcer.
5. Skin biopsy from a leg ulcer should include tissue at edge of wound including epidermis, dermis and subcutaneous fat.
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Paul B. Googe, M.D., Founder and Laboratory Director of KDL, is board certified in dermatopathology and anatomic pathology. A native of Knoxville, TN, he completed his post-graduate training in pathology and dermatopathology at Massachusetts General Hospital in Boston, MA following medical school and an internal medicine internship at The University of Tennessee College of Medicine. Dr. Googe has practiced dermatopathology for over 20 years and holds volunteer faculty appointments as Clinical Professor of Pathology at The University of Tennessee Graduate School of Medicine and Vanderbilt University.

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