Histopathologic analysis of dermal lymphatic alterations in chronic venous insufficiency ulcers using D2-40

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Background: Chronic venous insufficiency (CVI) ulcers represent a major medical problem worldwide. Current theories concerning the pathogenesis of CVI ulcers focus on abnormalities in the blood vascular system. Other abnormalities, such as chronic leg edema, may also play pathogenic roles in CVI ulcer development and further understanding of such alterations may lead to better treatments.

Objective: To gain insight into lymphatic abnormalities occurring in CVI, we compared dermal lymphatics in histologic sections from CVI ulcers and normal controls.

Methods: We compared global and architectural features of dermal lymphatics in D2-40–stained histologic sections from CVI ulcer tissue and from normal controls. D2-40 recognizes podoplanin, a transmembrane glycoprotein that is constitutively expressed in lymphatic endothelial cells, allowing us to distinguish dermal blood vessels from lymphatic vessels.

Results: Our analyses reveal that CVI ulcer specimens have more dermal lymphatic vessels per unit area than controls (5.71 vs 4.08 per mm^2, respectively; $P = .0281$); a higher percentage of lymphatic vessels with collapsed lumina compared with controls (30.5% vs 8.1%, respectively; $P < .0001$); and a higher percentage of competent lymphatic vessels displaying open inter-endothelial junctions compared with controls (5.7% vs 2.9%, respectively; $P < .0369$).

Limitations: Our study is limited by its retrospective nature and relatively small sample size.

Conclusions: Lymphatic vessels in CVI ulcer specimens display global and architectural differences compared with lymphatic vessels in control specimens. These findings further implicate lymphatic dysfunction in the pathogenesis of CVI ulcers and allow for the formulation of a hypothesis concerning lymphatic changes that may be tested in future studies. (J Am Acad Dermatol 2011;64:1123.e1-12.)

Key words: chronic venous insufficiency; dermal lymphatics; D2-40; edema; light microscopy; ulcer.

INTRODUCTION

Chronic venous insufficiency (CVI) ulcers represent a common and important medical problem worldwide. They account for more than half of all leg ulcers, are notoriously difficult to treat, and often recur even after complete healing is achieved.[1,2]

Abbreviations used:

BCC: basal cell carcinoma
CVI: chronic venous insufficiency
SCC: squamous cell carcinoma
TEM: transmission electron microscopy

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These characteristics translate into a significant impairment in quality of life for affected patients and a tremendous burden on healthcare spending, with estimates for costs of treating CVI ulcers in the United States alone reaching $1.5 to $2.5 billion annually.[1]

The pathogenesis of CVI ulcers is complex and there are numerous theories concerning their formation.[2] Presently the most popular theory implicates increased dermal capillary luminal pressure in the eventual formation of perivascular fibrin cuffs, growth factor trapping in the perivascular space, and the release of proteolytic enzymes by extravasated leukocytes.[1] With time, these events are thought to disrupt local tissue homeostasis and lead to an environment in which tissue breakdown overwhelms tissue repair, eventually resulting in ulcer formation.

This theory, however, only describes processes attributed to blood vascular system derangements and therefore likely does not account for all of the pathogenic steps leading to formation of CVI ulcers. For example, failure to treat CVI adequately is known to result in long-term skin changes, which can lead to recurrent infections that promote tissue breakdown and ulceration. Additionally, chronic leg edema is a common problem in patients with CVI and can disrupt local tissue metabolism and immunologic responses, further promoting tissue breakdown and eventual ulceration. Understanding the roles these extravascular processes play in the formation of CVI ulcers will not only further our understanding of CVI ulcer pathogenesis, but may also lead to improved or novel treatments for these common leg ulcerations.

We are particularly interested in the roles of chronic edema and lymphatic system dysfunction in the pathogenesis of CVI ulcers. Under normal circumstances, accumulation of extravasated fluid and proteins in the interstitial space is prevented by the lymphatic system, a one-way vascular system that is mostly distinct from the blood vascular system (Fig 1). Damage to dermal lymphatic vessels not only leads to chronic edema, but also to an inability to perform other important roles critical to maintaining local tissue homeostasis, such as providing a route for immune cell trafficking to local lymph nodes for antigen delivery, eliminating toxic cellular by-products and mutant cells, and removing foreign and inorganic materials.[3-6]

Analysis of histopathologic characteristics of dermal lymphatic vessels in CVI ulcers offers the opportunity to gain further insight into both lymphatic alterations occurring in CVI and the pathogenesis of CVI ulcer formation. However, the ability to examine dermal lymphatics using light microscopy has previously been limited due to the difficulty of identifying lymphatic lumina in histologic specimens.[7-9] In particular, it has been difficult to distinguish between lymphatic and blood vessel lumina.[8] Recently, the introduction of D2-40 as an immunohistochemical tool has provided a means to circumvent these obstacles. D2-40 is a murine monoclonal antibody that recognizes podoplanin, a 40-kd transmembrane glycoprotein that is both highly and constitutively expressed in lymphatic endothelial cells.[10-12] Although D2-40 is expressed in other cutaneous structures, such as sebaceous glands, it does not react with blood vessel endothelial cells and therefore can serve as a powerful tool to allow one to distinguish them from lymphatic endothelial cells.

CAPSULE SUMMARY

- Improved understanding of CVI ulcer pathogenesis may lead to improved treatment options.
- Previous studies have implicated lymphatic dysfunction in the pathogenesis of CVI ulcers, but understanding of this dysfunction is limited.
- We have used D2-40 to stain histologic specimens to study CVI ulcer lymphatic abnormalities on a cellular level.
- Our observations further implicate lymphatic dysfunction in CVI ulcer pathogenesis and provide a basis for the design of future research.

In this study we utilized D2-40 to analyze dermal lymphatics in biopsy specimens obtained from patients with CVI ulcers and compare them to dermal lymphatics in tissue specimens from patients without CVI. Our hypothesis was that the dermal lymphatics would be damaged in patients with CVI ulcers and would exhibit both global and architectural alterations.

METHODS

We performed a search of the University of Miami Dermatopathology archives for punch biopsy specimens or small incisional biopsy specimens given a diagnosis of "chronic venous ulcer" between Jan 1, 2008 and Feb 1, 2009. Anatomic location was limited to either "right leg" or "left leg." Hematoxylin-eosin–stained (H&E) specimens meeting these criteria were examined with light microscopy to assess adequacy for inclusion in our study. Exclusion criteria included lack of tissue extension to subcutaneous fat and evidence of another significant pathologic process (eg, malignancy, infection, vasculitis) that could potentially compromise the integrity of dermal lymphatic vessels.

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