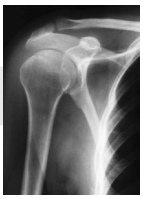

Lower Extremity Ulcers in Connective Tissue Disease

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Key words: connective tissue disease, livedoid vasculopathy; atrophie blanche, lower extremity ulcer

Abstract

Lower extremity ulcers are a late complication of connective tissue diseases and occur more commonly in patients with these diseases than in the general population. Although these lesions have historically been attributed to vasculitis, it is now recognized that inflammatory vessel injury accounts for fewer than 20% of ulcers in connective tissue disease. The pathogenesis of these lesions is complex, and often several processes act synergistically to initiate and perpetuate tissue injury. We review the evidence for antiphospholipid antibodies and prothrombotic states contributing to a vasculopathy in patients with connective tissue disease, precipitating ulceration and impairing healing.

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Lower extremity ulcers are considerably more common in patients with connective tissue disease than in the general population. Of first-time visits to a multidisciplinary limb preservation clinic, 6.6% were found to have leg ulcerations in association with a systemic autoimmune disease [1]. Similarly, in a survey of outpatients with rheumatoid arthritis, 9% reported leg ulcers [2], and, in systemic lupus erythematosus, ulcers were seen in 5.6% of patients [3]. Although the incidence of leg ulcers in patients with other connective tissue diseases has not been documented, they are also described in mixed connective tissue disease, scleroderma, and primary antiphospholipid syndrome.

One of the clinical manifestations of connective tissue disease-associated lower extremity ulcers is livedoid vasculopathy, a condition previously known as atrophie blanche [4]. This is a clinical diagnosis based on lesions that develop as purpuric macules, undergo painful ulceration, and heal to form stellate porcelain white scars with surrounding telangiectasia. The characteristic histological finding in these lesions is a fibrin-occlusive vasculopathy [Figure 1], and it is now recognized that this pattern of tissue injury represents a final common pathway in a variety of inflammatory diseases and prothrombotic states [Table 1].

Vasculitis accounts for the presence of lower extremity ulcers in fewer than 20% of patients

Etiology of leg ulcers

The etiology of non-healing lower extremity ulcers in patients with connective tissue diseases is often multifactorial [5-7]. Although some lesions may have an antecedent history of

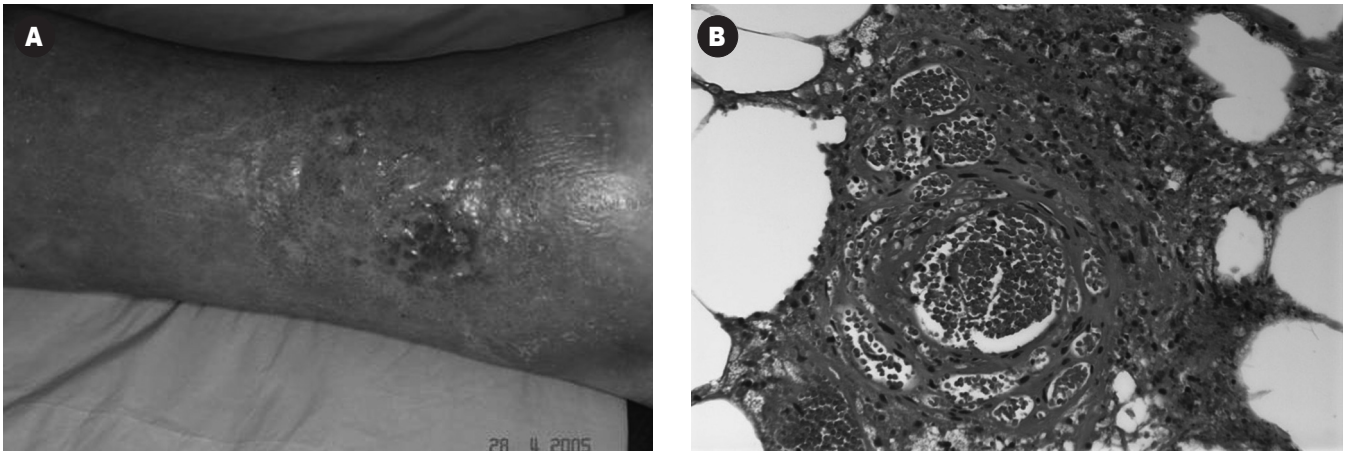

Figure 1. Livedoid vasculopathy skin ulcer. **[A]** Typical skin lesion with stellate porcelain white scars and surrounding telangiectasia. **[B]** Characteristic pathology showing fibrin occlusive vasculopathy.

Table 1. Associations of livedoid vasculopathy

Antiphospholipid syndrome
Dysproteinemias
Cryoglobulinemia
Macroglobulinemia
Hyperglobulinemia
Cryofibrinogenemia
Systemic necrotizing vasculitis
Microscopic polyangitis
Polyarteritis nodosa
Granulomatous vasculitis
Connective tissue diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Systemic sclerosis
Hematologic malignancy
Venous insufficiency
In some cases associated with Factor V Leiden mutation
Peripheral vascular disease
Especially abdominal aortic aneurysm
Prothrombotic disorders
Factor V Leiden mutation
Protein C or S deficiency
Hyperhomocysteinemia
Prothrombin gene mutation (G20210A)
Methylenetetrahydrofolate reductase (C677T)
PAI-1 (4G) mutation
Solid organ malignancies
Colon
Pancreas
Prostate

trauma, it is postulated that impaired vascular supply or drainage – such as due to large vessel arterial or venous disease, vasculitis of small perforating arteries, or small vessel vasculopathy – may contribute to tissue loss and poor wound healing.

It has long been recognized that several factors may contribute to vessel occlusion, including abnormal vessel flow (due to the reduced ankle pump function in rheumatoid arthritis), abnormalities of the vessel wall or endothelium (for example, due to inflammatory vasculitis or the vasculopathy associated with many autoimmune diseases), and propensity of the blood to clot or inability to lyse clots when they occur.

For the purposes of this review, we will concentrate on the role of vasculitis, vasculopathy and hypercoagulable states contributing to chronic non-healing leg ulcers in connective tissue diseases.

Vasculitis

In rheumatoid arthritis patients fulfilling clinical criteria for systemic vasculitis, only 50% have vasculitis confirmed on biopsy, and it is now thought that vasculitis accounts for less than 20% of ulcers in these patients [6,8]. Biopsies of ulcers in connective tissue diseases are of limited clinical importance since inflammatory changes may be reactive. Although biopsy of intact skin may have a higher diagnostic yield, it is frequently not obtained due to concerns about wound healing [4].

Leg ulcers may be a manifestation of systemic vasculitis in other connective tissue diseases including systemic lupus erythematosus, Sjögren's syndrome and Wegener's granulomatosis. However, although inflammatory vasculitis may initiate the tissue injury, it does not always account for the delayed wound healing in these patients, and unlike inflammatory tissue injury in other sites, these lesions are poorly responsive to traditional immunosuppressant therapies.

Livedoid vasculopathy

The original description of livedoid vasculopathy by Milian in 1923 noted the presence of positive syphilis serologies in these patients, and drew the conclusion that these lesions were infectious in nature. The association between false positive syphilis serologies and circulating antiphospholipid antibodies is now well recognized, and several authors have reported the association of livedoid vasculopathy with antiphospholipid antibodies [9,10]. The pathological finding in these lesions is a fibrin-occlusive vasculopathy; and prothrombotic states and impaired fibrinolysis may have a pathogenic role in the development or persistence of these lesions [Table 1] [9,11].

The role of antiphospholipid antibodies

Antiphospholipid antibodies are also reported to contribute to leg ulceration in primary antiphospholipid syndrome [12], and in other connective tissue diseases including systemic lupus erhythematosus and rheumatoid arthritis. The association of antiphospholipid antibodies with thrombosis is well recognized and postulated mechanisms include direct effects of the antibodies on endothelial cells, inhibition of the natural anticoagulant system or impaired fibrinolysis [13].

The role of prothrombotic states

The contribution of prothrombotic states to lower extremity ulcers in connective tissue diseases has also not been formally evaluated, but in livedoid vasculopathy an association with prothrombotic states has been suspected for some time. The female predominance in livedoid vasculopathy was previously attributed to the lower venous fibrinolytic activity in women [14], and enhancement of fibrinolysis using phenformin and ethylestranol was successful in the treatment of a small number of patients [14,15]. McCalmont et al. [16] found elevated levels of the thrombin cleavage protein fibrinopeptide A in patients with this disease [16], and several groups have demonstrated defective release of vascular plasminogen activator [17,18]. More recently,

tissue plasminogen activator has been effective in treating some recalcitrant lesions [18,19].

Thrombomodulin, a transmembrane glycoprotein that accelerates activation of protein C, was also reduced in several patients [20], and the prostacylcin analog beraprost sodium used in combination with aspirin was found to be beneficial. Finally, heparin is a profibrinolytic agent that has been used with some benefit in a few small case series for livedoid vasculopathy [21-23].

Lower extremity ulcers are associated with antiphospholipid antibodies, either as a manifestation of the primary antiphospholipid syndrome or secondary to the underlying connective tissue disease.

Conclusions

Lower extremity ulcers are an infrequent but disabling complication of long-standing connective tissue disease. Previously, these lesions were attributed to vasculitis, but the pathology is complex, often with several processes acting in synergy. In some cases, prothrombotic states may contribute to a vasculopathy that precipitates ulceration and impairs healing. To better understand the contribution of procoagulant states to ulceration in connective tissue diseases and livedoid vasculopathy, focused research is necessary to move from largely empiric treatments to targeted evidence-based therapeutic interventions.

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The trouble with the world is that the stupid are cocksure and the intelligent are full of doubt

Bertrand Russell (1872-1970), British philosopher, historian, logician, mathematician, advocate for social reform, and pacifist