Journal of Tissue Viability (2013) 22, 92–102

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JOURNAL OF tissueviability

www.elsevier.com/locate/jtv

Review

Connective tissue ulcers

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KEYWORDS
Ulcers;
Connective tissue disease;
Vasculitis;
Connective tissue ulcers

Abstract Connective tissue disorders (CTD), which are often also termed collagen vascular diseases, include a number of related inflammatory conditions. Some of these diseases include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma), localized scleroderma (morphea variants localized to the skin), Sjogren's syndrome, dermatomyositis, polymyositis, and mixed connective tissue disease. In addition to the systemic manifestations of these diseases, there are a number of cutaneous features that make these conditions recognizable on physical exam. Lower extremity ulcers and digital ulcers are an infrequent but disabling complication of long-standing connective tissue disease. The exact frequency with which these ulcers occur is not known, and the cause of the ulcerations is often multifactorial. Moreover, a challenging component of CTD ulcerations is that there are still no established guidelines for their diagnosis and treatment. The morbidity associated with these ulcerations and their underlying conditions is very substantial. Indeed, these less common but intractable ulcers represent a major medical and economic problem for patients, physicians and nurses, and even well organized multidisciplinary wound healing centers.

Introduction

Connective tissue disorders (CTD), which are often also termed collagen vascular diseases, (will go forward referring to them as connective tissue disorders (CTD)), include a number of related inflammatory conditions. Some of these diseases include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma), localized scleroderma (morphea variants localized to the skin), Sjogren's syndrome, dermatomyositis, polymyositis, and mixed connective tissue disease. The various CTD are distinct entities but they have features that are common, notably they share autoantibodies, but each disease also has their own specific autoantibody (Table 1). Despite the hallmark physical exam findings that lead

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0965-206X/$36
http://dx.doi.org/10.1016/j.jtv.2013.04.003

clinicians to a diagnosis or narrow differential diagnosis (Table 2), one cannot make a diagnosis of a CTD based on the presence of ulceration alone. The ulcerations that occur in CTD are late-onset and due to a variety of factors, most notably inflammatory vasculitis and thrombotic nonvasculitic causes [1]. Vasculitides are not only associated with autoimmune forms of CTD but they themselves can be classified as a CTD.

When patients present with an ulceration, it becomes imperative to establish the primary cause of the ulceration. Cutaneous ulcers of CTD often have unusual shapes and can be mistakenly thought of as factitial (Fig. 1a) [2]. This is why a complete history and physical exam including extensive review of systems, family history, and current and relevant past medications is imperative for diagnosis and management [3]. Having a CTD does not mean that a patient cannot have other concomitant vascular/neuropathic insufficiency like venous or pressure ulcers. This causes confusion because there is overlap. Here we review the main autoimmune connective tissue ulcers, their presentation, pathology, pathogenesis, and treatment and management.

Connective tissue disorders

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disorder expressed most commonly as a symmetrical, deforming arthropathy. Physical exam findings include symmetric swelling of the small joints of the hand and feet, ulnar deviation, swan neck, and boutonniere deformity [2]. Although RA primarily affects the joints, extraarticular manifestations are frequent, such as rheumatoid nodules and skin ulcerations. The cause of leg ulcerations in RA is multifactorial, including, vasculitis, paraproteinemias, anticardiolipin antibodies, venous insufficiency, toxic effects of medications, superficial ulcerating rheumatoid necrobiosis, pressure ulcers, neuropathic ulcers, and pyoderma gangrenosum [1,2]. The ulcers as seen on physical exam have an angular configuration or an undulating border (Fig. 1b) [2].

Venous insufficiency can be a complication of impaired movement of the ankle joint as a result of RA because of poor muscle pump action [1,3]. Toxic effects of medications include use of corticosteroids that cause skin atrophy where minor trauma leads to ulceration [2]. RA patients can be debilitated from their disease and bedridden making them prone to pressure ulcers [2]. Superficial ulcerating rheumatoid necrobiosis (SURN) lesions are bilateral over pretibial areas and are refractory to treatment. They are characterized by yellow-red plaques that ulcerate [4]. A well-known cause of ulceration in RA is vasculitis. Vessels of different sizes may be affected. These include small to medium sized muscular arteries, arterioles, and venules. Small to medium size vessels, when involved, can mimic polyarteritis nodosa and can be a severe rheumatoid vasculitis. These patients will require systemic therapy because mortality can be high [5]. Milder vasculitic disease also occurs in RA patients, where postcapillary venules are affected. These patients present with palpable purpura [6].

Workup for the patients should include complete history and thorough physical exam,

Table 1 Serum markers associated with connective tissue disorders.

	Serum markers
Rheumatoid arthritis	Rheumatoid factor, anti-CCP (cyclic citrullinated peptide)
Scleroderma (localized)	Anti-ssDNA, peripheral blood eosinophilia, anti-histone
Scleroderma (generalized)	Anti-Scl-70, anti-centromere
Systemic lupus erythematosus	ANA, anti-dsDNA, anti-Smith, anti-histone (drug induced SLE)
Sjogren's syndrome	Anti-SSB(anti-La), anti-SS-A (anti-Ro)
Dermatomyositis	CPK, aldolase, anti-Jo1
Mixed connective tissue	Anti-nRNP

Table 2 Distinctive clues observed away from the ulcer location. (Copyrighted V. Falanga, 2010).

Clinical clues	Conditions
Hard fingers, face	Scleroderma
Facial butterfly rash	Lupus erythematosus
Muscle weakness, eyelid rash	Dermatomyositis
Ear redness with sparing of ear lobe	Relapsing polychondritis
Livedo reticularis of microlivedo	Occlusion of small blood vessels, from vasculitis, coagulopathy, cryoglobulin, cryofibrinogen
Rheumatoid hands	Rheumatoid ulcers
Swelling of face, posterior neck	Cushingoid appearance (steroids)