Chapter 8
Ulceration in Rheumatic Disease

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Definition

Skin breakdown results in ulceration or erosion. An **erosion** is a superficial skin breakdown that involves the epidermis only and is most often traumatic. An **ulcer** is loss of cutaneous tissue that extends into the dermis and sometimes reaches subcutaneous fat. The causes of ulceration include trauma, inflammation, vasculopathy, and vasculitis. Inflammation, vasculopathy, and vasculitis may be the result of a connective tissue disease or an adverse effect of drug use.

Cutaneous or Mucocutaneous Ulceration Due to Connective Tissue Disease (CTD)

Several CTDs are associated with characteristic patterns of skin ulceration and are listed here:

Behçet's disease (BD) is characterized by recurrent oral or genital aphthous ulcers. Oral ulcers occur on the soft palate, tongue, and gingival or buccal mucosa; have a white, fibrinous base; and heal without scarring (Fig. 8.1). Pyoderma gangrenosum (PG) is another cutaneous manifestation of BD. It has a characteristic cribriform (grate-like) appearance with undermined ulcer and purple edges (Fig. 8.2).

Reactive arthritis or Reiter's syndrome (RS) is triad of reactive arthritis and conjunctivitis following urogenital or gastrointestinal tract infection. Patients with

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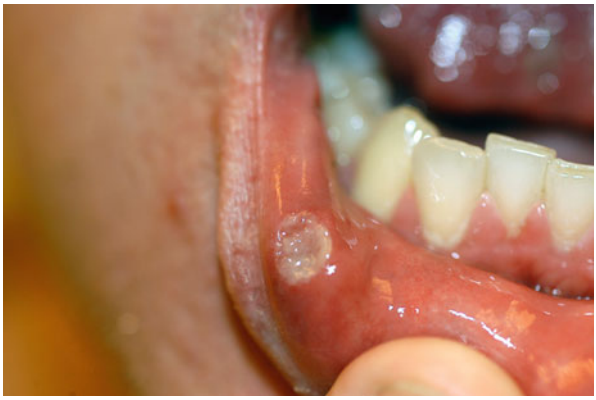

Fig. 8.1 Aphthous ulcer on the *lower lip* shows a fibrinous base

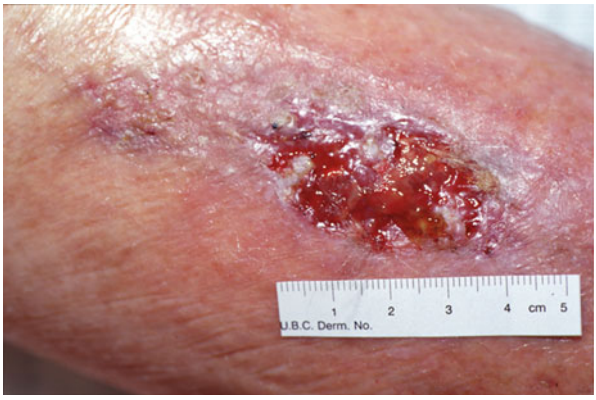

Fig. 8.2 Right leg image shows pyoderma gangrenosum with an undermined ulcer

RS may have superficial painless oral and genital ulcers. The genital ulcers in the male have a characteristic of circinate white plaques that grow centrifugally on the uncircumcised glans penis (circinate balanitis).

Systemic lupus erythematosus (SLE). Digital ulceration is a rare manifestation of SLE. It occurs most commonly in patients with disease of long duration and may be the result of vasculitis, the presence of antiphospholipid antibody, or atherosclerosis. In addition to digital ulcers, sometimes panniculitis and vasculitis can lead to ulceration. Lupus panniculitis occurs on the face, the breast, the abdomen, and thighs and is seen in 2–5 % of SLE patients. Vasculitis may cause lower leg ulceration.

Systemic sclerosis (SSc). The most common type of ulceration in SSc is the digital ischemic lesion (DIL). These ulcerations occur in up to 40 % of patients with SSc and can be extremely debilitating due to pain. The lesions come in two forms: those occurring on the digital pulp and those occurring overlying extensor joints (such as the interphalangeal joints or metacarpophalangeal joints). The digital pulp lesions usually occur on the digital tips, although they can occur at

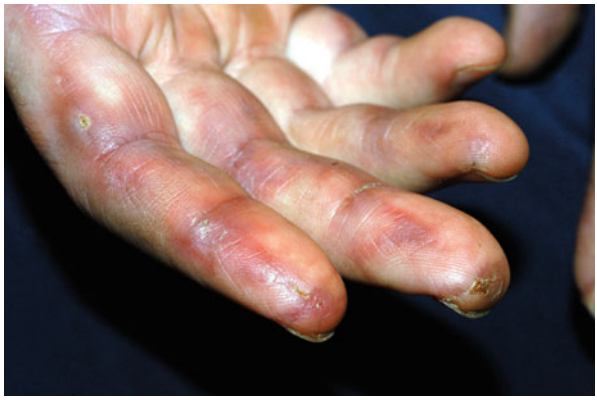

Fig. 8.3 Right hand in dermatomyositis patient. Note the ulceration on the digit pulp and the lateral erythema

the hyponychium (the junction of the free edge of the nail plate and the fingertip) or on the lateral tips of the digit. They present as punctate ulcerations filled with a hyperkeratotic inclusion without surrounding erythema and are usually quite tender. They resolve with a pitted scar. The other type of lesion overlying the extensor joints typically presents as true ulcerations, which can often be associated with some crust and/or eschar. They often heal with lacy telangiectasias. In addition to being found on the hands, they are also seen overlying the elbows, knees, and malleoli. These lesions are likely the result of a combination of trauma and poor blood supply.

Another cause of ulceration in the SSc patient is pyoderma gangrenosum. These commonly present as ulcers on the leg with a rolled, inflammatory border and they can change in size quickly.

Dermatomyositis (DM). An ulcer in DM can be the result of calcinosis or vasculopathy. In general, ulcers can indicate one of three scenarios: first, necrotic skin ulceration, especially in non-acral regions and regions without surrounding rash, is considered a predictive factor for the presence of underlying cancer; second, ulceration of Gottron's papules can occur following DMARD therapy, especially methotrexate or mycophenolate mofetil; and third, patients with melanoma differentiation-associated gene 5 antibodies (MDA5) have a higher incidence of ulcerative cutaneous lesions on the digital pulp and periungual areas, within Gottron's papules, and over the elbows (Fig. 8.3) [1]. In addition diffuse punched-out ulcerations and ischemic digital necrosis have been described in literature. These patients may be at higher risk of interstitial lung disease. It should be noted that ulcers can also occur in areas of intense inflammation and may be of no particular prognostic significance.

Rheumatoid arthritis (RA): Pyoderma gangrenosum (PG), rheumatoid vasculitis, venous insufficiency, peripheral arterial disease, peripheral neuropathy, and Felty's syndrome are causes of skin ulcers in RA. The most common location of ulceration is on the lower leg. Leg ulcers in RA patients usually are chronic and occur in patients with seropositive and erosive disease. PG presents as a painful necrotic

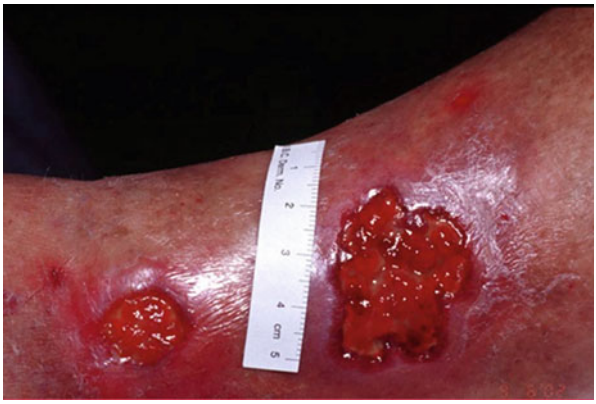

Fig. 8.4 Left leg with ulcers in a patient with rheumatoid arthritis

ulcer with undermined border. Felty's syndrome is characterized by RA, splenomegaly, leg ulcers, and granulocytopenia. Leg ulcers secondary to rheumatoid vasculitis are usually painful, deep, and punched-out in appearance (Fig. 8.4) [2].

Superficial ulcerating rheumatoid necrobiosis is a chronic, superficial ulceration, commonly on the limbs and most frequently on the lower legs, that histologically shows features of necrobiotic palisading granulomas. It occurs in association with RA but also other CTDs.

Ulceration of the psoriatic plaques secondary to methotrexate toxicity is rare. It can occur within psoriatic plaques during the first month of starting therapy. The psoriatic plaques become red and painful and then develop a superficial ulceration [3].

Ulcers in vasculitis/vasculopathy can be seen in **granulomatous vasculitis** like Wegener's granulomatosis (WG) and Churg–Strauss syndrome (CSS) where they tend to occur on the elbows. In **necrotizing inflammation** of small to medium arteries in polyarteritis nodosa (PAN), leg ulceration is more common. Vasculopathic diseases include livedoid vasculopathy, thrombophilic disorders, and cryoglobulinemia.

Differential Diagnosis of Ulcers in the Setting of CTD

Cutaneous Ulcers

From the discussion above, it is clear that ulcer location is an important factor in determining etiology – involvement of the nose and ears is suggestive of vasculopathy, often in the setting of cryoproteins, although forms of vasculitis (such as Wegener's) should be considered. In general, extreme pain and/or the presence of necrosis often indicates a vasculopathy of some kind – here, the clinician should be considering vasculopathy related to certain known CTDs (systemic sclerosis, dermatomyositis,

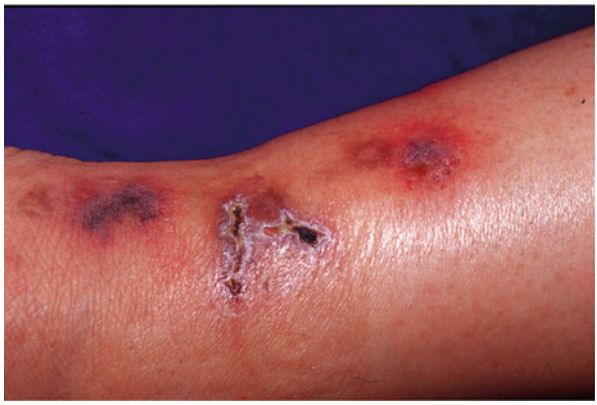

Fig. 8.5 Left leg ulcers in a patient with medium-vessel vasculitis; note the irregularity of the ulcer and the retiform purpura

lupus) versus other vasculopathies mentioned above. Irregular borders, angulation in ulcers, and presence of livedo reticularis are suggestive of underlying vasculitis or vasculopathy (Fig. 8.5). Violaceous, elevated, and undermined borders that follow minor trauma are often indicative of pyoderma gangrenosum, which can occur most often in the setting of rheumatoid arthritis, Behçet's disease, and systemic sclerosis.

In addition to ulcers secondary to CTD, common causes of skin ulceration should be excluded. These include arterial ischemia (clues include persistent pain, claudication, diminished pulses, and capillary refill), venous stasis (edema and varicosities), and neuropathy (decreased sensation). A diagnosis of PG is a diagnosis of exclusion that requires clinicopathologic correlation. Biopsy is required for histology, special stains, and culture to exclude other infectious causes such as ecthyma gangrenosum, ecthyma, chronic herpes simplex, sporotrichosis, and mycobacterial, parasitic, or deep fungal infections. Finally, one should consider the possibility of neoplasm or factitial causes of ulceration.

Mucosal Ulcers

Aphthous ulcers can be differentiated from intraoral herpes simplex by location as herpetic ulcers affect the hard palate and attached gingiva, while aphthous ulcers affect nonkeratinized mucosa only. Varicella is characterized by widespread cutaneous vesicular eruption with fever. Hand–foot–mouth disease, caused by coxsackievirus, presents with elliptical vesicles surrounded by an erythematous halo on hands, feet, and buttocks. In herpangina the ulcers affect soft palate and tonsillar pillar areas with lymphadenopathy. Oral ulcerations secondary to inflammatory bowel disease are associated with recurrent bloody or mucous diarrhea and oral ulcerations due to cyclic neutropenia present with fever, cervical lymphadenopathy, and neutropenia [4].

Drugs That Have Been Associated with Ulceration

Methotrexate, hydroxyurea, penicillamine, and cocaine/levamisole have all been associated with skin ulceration. NSAIDs may induce aphthous stomatitis.

Biopsy

A biopsy is useful to confirm the diagnosis histologically, to obtain tissue for culture, and to rule out malignancy. Generally any ulcer that does not heal over 4 months requires a biopsy to exclude underlying malignant changes either primary or secondary, e.g., Marjolin's ulcer (squamous cell carcinoma arising in a preexisting chronic ulcer). The specimen should include subcutaneous tissue from the periphery of the ulcer and the area near the ulcer center. This is achieved by incisional biopsy perpendicular to ulcer edge or multiple punch biopsies. The ulcer tissue specimen needs to be stained with hematoxylin and eosin (routine histology), PAS or silver for fungi, Ziehl–Neelsen for mycobacteria, and Giemsa for leishmaniasis.

Common causes of Leg Ulcer
Arterial disease
Look for abnormal arterial pulse, cold skin with hair loss
Neuropathy
Look for abnormal sensation
Venous insufficiency
Look for
Lipodermatosclerosis
(Hardening of the skin
& increased Pigmentation)
Arterial Ulcer
Located on distal extremities such as the tips of toes or fingers
Painful punched out ulcer
Neuropathic Ulcer
Located mainly on pressure areas
Painless punched out ulcer
Venous Ulcer
Located on medial malleolus
Painless with irregular border ulscer
• Behcet disease.
• SLE (painless).
• Venous Ulcer.
• Arterial Ulcer.
• Neuropathic Ulcer.
• Inflammatory Diseases: RA,PG,PAN,CSS and WG.
• Cryoglobulinemia.
• Thrombophilias.
• Scleroderma.
• SLE.
• DM.

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