ABC of wound healing

Uncommon causes of ulceration

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This article describes some of the many rare causes of ulceration. Rare causes that are more common in developing countries—such as leprosy, fungal infections, Buruli ulcer, and ulceration resulting from Kaposi sarcoma—are not covered here.

Inflammatory disorders

Inflammatory disorders can lead to ulceration or impair healing directly or through the effect of medication used to treat the disorder; ulceration is a feature of many connective tissue diseases. For example, ulceration develops in up to 10% of patients with rheumatoid arthritis and is often painful. In addition to the underlying disease, impaired healing can result from anaemia, skin atrophy, dependent oedema, deformity, neuropathy, microvascular disease, local factors, or the toxic effects of drugs used in its treatment. Other associated conditions such as vasculitis or pyoderma gangrenosum may also lead to ulceration.

Ulceration in rheumatoid arthritis is usually of rapid onset or enlargement, associated with pain (not relieved by raising or lowering the leg), fever, malaise, arthralgia, and myalgia. The ulcer may be multifocal and/or have an atypical location, tender margin, and/or a violaceous or erythematous inflammatory border.

Connective tissue disease associated with ulceration

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Dermatomyositis
- Systemic sclerosis
- Sjögren's syndrome
- Behçet's syndrome

Pyoderma gangrenosum

Pyoderma gangrenosum is characterised by the appearance of lesions at the site of trauma (for example, venepuncture). Surgical debridement of pyoderma gangrenosum often leads to a worsening of the ulceration. The diagnosis of pyoderma gangrenosum is primarily clinical but may be associated with specific features on histology. The patient often has a history of a painful sterile pustule or nodule with surrounding erythema, which eventually ruptures and ulcerates. The ulcer has a characteristic erythematous or violaceous overhanging edge. The wound bed is often purulent and may extend to muscle. Over half of cases of pyoderma gangrenosum are associated with underlying active or quiescent systemic disease; these include inflammatory bowel disease, seronegative rheumatoid arthritis, and lymphoproliferative diseases. Treatment of pyoderma gangrenosum is usually with immunosuppressants.

Necrobiosis lipidica

Necrobiosis lipidica commonly presents as a pretibial yellowish atrophic plaque. It is often associated with diabetes mellitus and has a propensity to ulcerate, usually as a result of minor trauma. Typically, such ulceration is slow to heal, painful, and often complicated by infection. In most cases the ulceration

This is the sixth in a series of 12 articles

Causes of ulceration, according to typical clinical presentation

Rheumatoid arthritis on dorsum of foot with exposed tendon, and over medial malleolus; such ulcers have a smooth, irregular margin

Treatment of ulceration related to connective tissue disease may require immunosuppressants, including steroids and/or cytotoxic agents

Pyoderma gangrenosum over posterior gaiter area of leg (note also allergy to dressing on surrounding skin)

Necrobiosis lipidica complicated by ulceration in centre

will heal with good wound care and the use of potent topical corticosteroids to the surrounding lesion.

Skin necrosis

Skin necrosis is a manifestation of tissue death that occurs as a consequence of rapid ischaemia, often due to vessel occlusion. The pattern and extent of necrosis varies according to the size of the vessels affected. In the 1860s, Rudolf Virchow proposed that thrombus formation is attributable to a change in three components: blood flow, the vessel intima, and blood constituents. This proposal (Virchow's triad) provides a useful framework to consider the causes of skin necrosis.

Blood flow

Rapid reduction in local blood flow that may arise from an embolic event, severe chilblains, and Raynaud's phenomenon can present with dramatic digital necrosis. All patients with Raynaud's phenomenon should be advised not to smoke cigarettes and to reduce caffeine intake. Both primary and secondary Raynaud's phenomenon may respond well to conservative measures, including cold avoidance and treatment with a long acting calcium channel antagonist or another oral vasodilator. Topical vasodilators—for example, glyceryl trinitrate—may also be of benefit. In severe chronic disease, cervical sympathectomy can be done; in severe acute necrotising disease, infusions with prostaglandin E1 or epoprostenol (prostacyclin) can save digits.

Vessel intima

Calciophylaxis is characterised by painful, haemorrhagic skin necrosis with a reticulate edge. Skin histology shows vessel intramural hyperplasia, intravascular calcification, and thrombosis. Calciophylaxis most often occurs in patients with renal failure who are having dialysis or patients with hyperparathyroidism, or idiopathically. Treatment consists of analgesia, removal of calcium deposits at the site of any ulceration, and control of predisposing factors.

Almost all types of vasculitis can present with skin necrosis. In some cases, such as Wegener's granulomatosis and classic polyarteritis nodosa, they can be a cause of chronic ulceration. Vasculitis is classified according to the size of vessel affected. Medium sized vessel vasculitis presents with painful nodules that may ulcerate. Small vessel vasculitis typically presents with palpable purpura.

Blood constituents

Several coagulation factors are associated with skin necrosis and are due either to genetic or acquired alteration in function. Some syndromes are also associated with hypercoagulability.

Antiphospholipid syndrome is a heterogeneous group of disorders characterised by the presence of autoantibodies against various phospholipids, including lupus anticoagulant and anticardiolipin. The disorder affects mostly females and may be associated with systemic lupus erythematosus. Antiphospholipid syndrome may present as a cause of multiple arterial and venous thrombotic episodes, recurrent spontaneous abortions, and the presence of livedo reticularis. Antiphospholipid syndrome is a cause of livedoid vasculopathy, a disorder characterised by painful ulceration in association with livedo reticularis and atrophie blanche. Livedoid vasculopathy has also been described as being associated with factor V Leiden mutation. This progressive, painful, and debilitating disease requires anticoagulation, plus drugs to treat the underlying disease.

Topical PUVA (psoralens and ultraviolet A) therapy may also have a role in necrobiosis lipoidica

Ulcerations due to Raynaud's phenomenon over proximal interphalangeal joint of index finger (associated with infection) and over distal interphalangeal joint of middle finger

Left: Calciophylaxis showing calcium deposits in base of ulcer. Right: X ray of same patient showing extensive subcutaneous calcification

Causes of vasculitis, classified according to size of vessel affected*

Large vessel	Medium vessel	Small vessel
Giant cell (temporal) arteritis	Classic polyarteritis nodosa	Wegener's granulomatosis; Churg-Strauss syndrome; microscopic polyangiitis
Takayasu's arteritis	Kawasaki disease	Henoch-Schönlein purpura; essential cryoglobulinaemic vasculitis; cutaneous leukocytoclastic angiitis

*Chapel Hill consensus conference, 1992.

Abnormalities of coagulation factors associated with skin necrosis

- Protein C deficiency
- Protein S deficiency
- Antithrombin 3 deficiency
- Heparin cofactor 2 deficiency
- Homocystinaemia
- Raised prothrombin concentrations
- Factor 12 deficiency
- Factor V Leiden mutation

Warfarin necrosis is an uncommon transient phenomenon, which occurs at the start of warfarin treatment in the absence of heparin. The condition affects mostly females, and individuals are usually in their 50s or 60s. It typically involves sites abundant in subcutaneous fat, such as breasts, hip, buttock, and thigh. The use of warfarin results in a transient decrease of vitamin K sensitive factors, including protein C, resulting in a temporary hypercoagulable state, which spontaneously corrects itself. Warfarin should therefore be continued.

Heparin necrosis is rare and may be caused by both unfractionated and low molecular weight heparin. It is associated with the formation of antibodies, leading to platelet clumping. The continued use of heparin leads to greater platelet clumping and emboli affecting both cutaneous and internal organs. Skin necrosis occurs at injection and distant sites. Heparin aggravates the condition, with potentially fatal consequences, so it should be stopped immediately.

Malignancy

Many types of cancers, including metastases, present with skin ulceration, including the commonest forms of skin cancer, basal cell carcinoma, and squamous cell carcinoma. Although the incidence of squamous cell carcinoma increases with age, it may present in younger individuals with a genetic predisposition or with a history of excessive exposure to ultraviolet light, of organ transplantation, or of immunosuppressants (such as ciclosporin).

Squamous cell carcinoma may also develop in longstanding chronic ulceration associated with burns, scalds, radiotherapy, or venous disease (Marjolin's ulcer). Features indicative of malignancy include rapid enlargement of the lesion despite conventional treatment; pain; bleeding; and often a rolled edge. Squamous cell carcinoma arising in longstanding chronic ulcers can exhibit a more aggressive phenotype, with a greater potential to metastasise. In most cases of lower leg skin cancer the preferred treatment is surgical excision. However, in cases of substantial comorbidity or disseminated metastatic disease, palliative treatment (radiotherapy and local wound care) may be more appropriate.

Drug and iatrogenic causes

Hydroxycarbamide (hydroxyurea), used to treat myeloproliferative diseases, may cause a painful, shallow, lower leg ulcer, usually over the medial malleolus, up to 15 years after start of treatment. Healing is normally only achieved when hydroxycarbamide is discontinued.

Radiotherapy, used to treat benign and malignant diseases, is associated with an endarteritis that may result in ulceration and impair wound healing. Furthermore, after radiotherapy the skin is at risk of ulceration as a result of chronic radiation dermatitis, allergic contact dermatitis, squamous cell carcinoma, and angiosarcoma.

Factitious

Factitious wounds and non-accidental injury can also present as atypical wounds. Often the patient's history is incongruent with the clinical appearance of the wound. Further clues can be gained from the pattern of the lesion and from a skin biopsy (useful for excluding disease and for identifying the presence of foreign material). Occasionally, admission to hospital is necessary to verify the diagnosis. The management of such cases invariably relies on a multidisciplinary approach involving a liaison psychiatrist.

***Purpura fulminans* includes three different syndromes (neonatal; associated with sepsis; and postinfective) associated with widespread capillary and venule thrombosis that present as purpura and skin necrosis. Skin necrosis favours the extremities, particularly the digits. *Purpura fulminans* is a complication of either hereditary or acquired protein C or protein S deficiency**

Infection

- β -haemolytic *Streptococcus pyogenes* and *Staphylococcus aureus* are responsible for many of the infections that can complicate existing ulceration
- They may also in certain circumstances be the cause of ulceration. β -haemolytic streptococcus may lead to erysipelas, bullous cellulitis, punched out ulceration (ecthyma) and necrotising fasciitis
- When the patient has a history of foreign travel, then *Leishmania*, atypical mycobacterium, and deep mycotic infection should also be considered as causes of ulceration
- In patients with AIDS or other immunosuppressive states, ulceration may indicate infection with syphilis, tuberculosis, bacillary angiomatosis, herpes simplex, or cytomegalovirus infection

Left: Basal cell carcinoma presenting over medial aspect of knee; note evidence of biopsy of centre of lesion and orange coloration (due to dressing containing iodine). Right: Florid, ulcerating, necrotic squamous cell carcinoma of lower leg

Marjolin's ulcer—a squamous cell carcinoma arising as a complication of longstanding venous leg ulceration

Further reading

- Enoch S, Kupitz S, Miller DR, Harding KG. Dystrophic calcification as a cause for non-healing leg ulcers. *Int Wound J* 2005;2:142-7.
- Enoch S, Miller DR, Harding KG, Price PE. Early diagnosis is vital in the management of squamous cell carcinomas associated with chronic non-healing ulcers: a case series and review of the literature. *Int Wound J* 2004;1:165-75.
- Rovee DT, Maibach HI. *The epidermis in wound healing*. Boca Raton, FL: CRC Press, 2003.
- Falanga V, ed. *Cutaneous wound healing*. London: Martin Dunitz, 2001.
- Leaper DJ, Harding KG, eds. *Wound: biology and management*. Oxford: Oxford Medical, 1998.

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