Unusual leg ulcers: a global phenomenon

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Abstract

In this age of evidence based medicine, clinicians are encouraged to identify the ulcer type and then follow well researched clinical practice guidelines. Most lower leg ulceration is venous or mixed venous/arterial aetiology [1, 2] but there are a few ulcers that have rarer aetiologies. This article discusses some of these more unusual ulcers that the author has seen in her years as a wound consultant – skin cancers, Necrobiosis Lipoidica Diabeticorum, Pyoderma Gangrenosum, vasculitis, mycotic skin infections, Leishmaniasis, Meliodosis, Mycobacterium Ulcerans/Buruli ulcer, medication induced/related ulceration and thalassaemia related ulcers. Identification and treatment methods will be covered to assist clinicians with early diagnosis and aid a speedy recovery. As our communities become increasingly more global, aetiologies previously seen only in the developing world are being found in developed countries and clinicians in all areas will need to have some understanding of these other causes of lower leg ulcers.

Introduction

This article will address the presentation and treatment options of neoplastic ulceration, ulcers related to metabolic disorders, those related to immune disorders (including Pyoderma Gangrenosum), those related to inflammatory conditions, those related to infective conditions (including Sporotrichosis, Leishmaniasis and Melioidosis), *Mycobacterium ulcerans* or Burulii ulcer, haematological ulcers and medication derived ulcers. Table 1 represents the acronym T I M E (tissue, inflammation or infection, moisture and edge) and may assist in a quick review of some of the characteristics noted in the article.

Neoplastic ulceration

Australia has the highest rates of skin cancer in the world [3]. We must therefore always consider that a wound failing to show signs of healing may in fact be a form of skin cancer-basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma. Skin cancers do not all look the same and so careful observation of skin type and the edges of the wound are helpful.

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A BCC usually begins as a small, dome-shaped bump and is often covered by small, superficial blood vessels called telangiectases. Sometimes these lesions are described as 'pearly'. Some BCCs contain melanin pigment, making them look dark rather than shiny. BCCs grow slowly, taking months or even years to become sizable. This is the most common skin cancer. It's also the most easily treated and the least likely to spread. A SCC may begin as a small firm, red nodule on face, lips, ears, neck hands or arms. Over time this lesion begins to crust, scale, and ulcerate, becoming inflamed at the edges and painful if traumatised (Figure 1).

If the patient has had previous removal of suspicious lesions then perhaps a biopsy of the wound failing to heal would be a good suggestion. Treatment of skin cancers includes surgery (total excision or grafting), radiotherapy (to eliminate or control symptoms) or chemotherapy as well as topical or systemic treatments to eliminate or manage symptoms.

Dressings for those lesions that are unable to be managed completely by surgery are generally those that will not cause pain on removal, absorb exudate and offer some antimicrobial features as this skin is now susceptible to bacterial colonisation/infection.

Ulcers related to metabolic disorders

There are a number of wounds of metabolic origin. One important cause, given the increasing number of diabetics, is Necrobiosis Lipoidica Diabeticorum (NLD). This ulcer is usually seen on the anterior aspect of the lower limb in patients with diabetes or a strong family history of diabetes [4]. It is more common in women and there may be more than one

area involved. The wound usually commences with trauma and is not usually symptomatic apart from failure to heal.

The ulcers have distinctive yellowish depressed areas with superficial visible blood vessels traversing the wounded area and are thought to result from fat necrosis and infection although the true cause remains unknown. Histologically there is often an area of damaged collagen surrounded by inflammatory cells (Figure 2).

Treatment is with application of an appropriate product on the ulcer and application of cortico-steroid cream on the peri-wound [4]. Other authors have stated that cortisone cream works more effectively if applied to the wound and covered with an occlusive dressing [5].

Dressings for this wound type are those that aid removal of necrotic tissue and promote granulation tissue, for example Hydrogel or hydrocolloid paste. Some patients want to change the dressings too frequently – perhaps from fear of it getting worse – so constant monitoring is needed to allay their anxiety. Once the area is cleared of necrotic tissue, this author has found zinc paste bandage patches to be very effective in stimulating epithelium. The patients also find this comfortable and, as it is a cheap dressing, it can be changed daily.

Ulcers related to immune disorders

There are a number of conditions associated with poorly healing ulcers in this group. Systemic Lupus Erythematosis, Scleroederma and Pyoderma Gangrenosum are three of the most common.

Pyoderma Gangrenosum

Pyoderma Gangrenosum (caution – the name can upset patients) is an acute necrotising cutaneous ulceration, often

Table 1. Characteristics of ulcers discussed in the article.

Ulcer type	Tissue	Infection/inflammation	Moisture	Edge
Neoplastic ulceration				
• BCC	Fibrotic, sloughy base	Can be colonised and crusty, bleed easily when traumatised	Minimal	Raised with epithelium creeping up side
• SCC	Ulcerated, sloughy, rapid growth in size	Can be colonised, painful and bleed easily when traumatised	Minimal-moderate	Scaly, crusty
Ulcers related to metabolic disorders				
• Necrobiosis Lipoidica Diabeticorum	Yellow, visualise blood vessels within tissue	Not usually infected but can become secondarily infected with too wet dressings	Moderate-heavy	Yellow/brown peri-wound discolouration
Ulcers related to immune disorders				
• Pyoderma Gangrenosum	Granulation, soft, friable, soft slough	Secondary infection possible, very painful, inflamed peri-wound early in disease	Minimal-moderate	Violaceous blue, scalloped edge
Ulcers related to inflammatory conditions				
• Vasculitis	Initially a dark dry scab which then ulcerates – granulation or soft slough	Inflamed, very, very painful	Minimal-moderate	Purple, blue
Ulcers related to infective conditions				
• Mycotic skin infections	Nodules, ulcerate look like volcanoes, necrotic tissue deep down	Not painful, not usually inflamed	Minimal	Papular, cliff like
• Leishmaniasis	Sandfly bites – sloughy develops a crusty cap	Mild inflammation, pain not excessive	Minimal	Erythematous raised edge
Mycobacterium ulcerans				
• *M. ulcerans*/ Buruli ulcer	Papule, ulcerates	Minimal pain, oedema, cellulitis	Minimal-moderate	Undermined, cavitated beneath skin surface

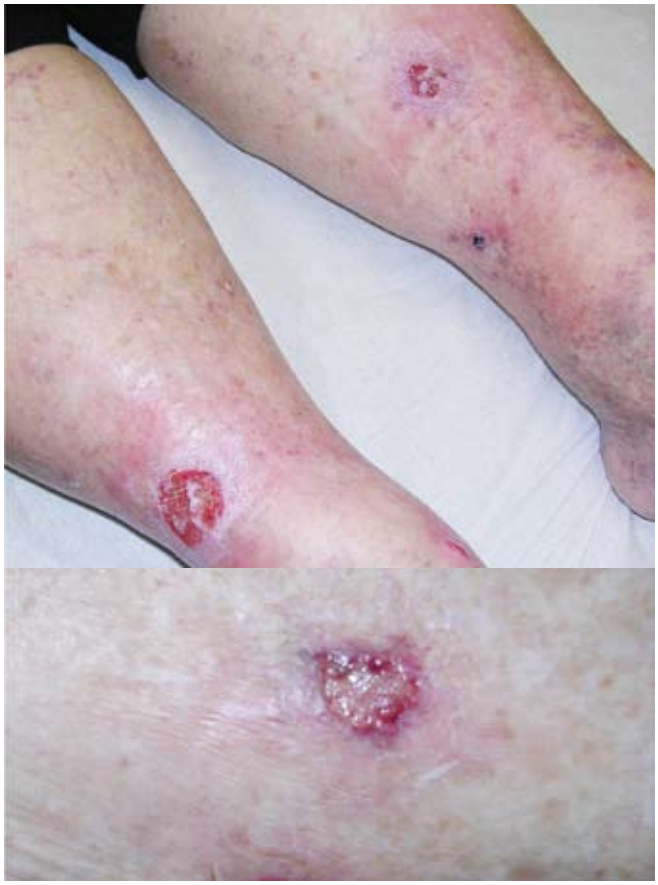

Figure 1. Wounds that will not heal and begin to show signs of healing then break down are a characteristic feature of a skin cancer. They are not generally painful but may be itchy.

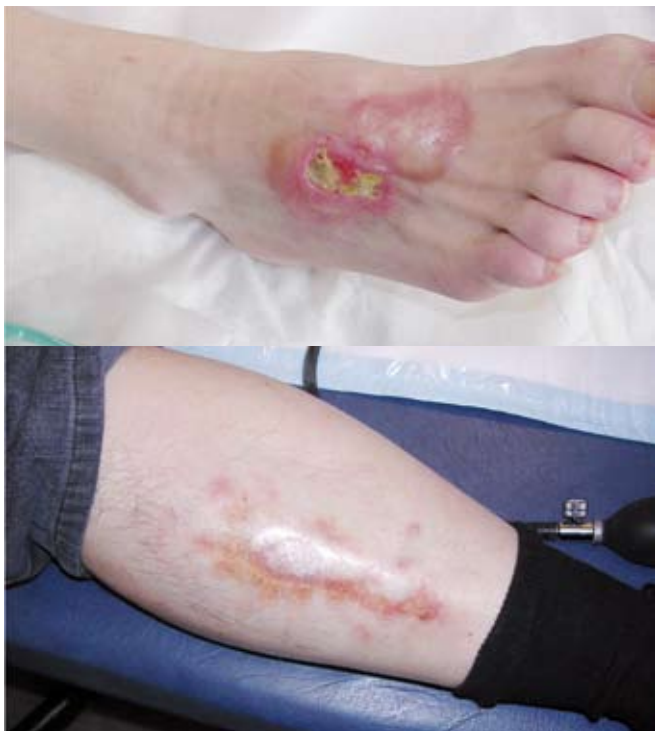

Figure 2. Necrobiosis lipoidica diabeticorum – with wound and healed area with characteristic yellow markings.

associated with other disorders such as rheumatoid arthritis, myeloma or some gastrointestinal diseases[1]. The ulcer usually commences with small pustules or fluctuant nodules and rapidly deteriorates into a necrotic, purulent open wound with sharply circumscribed violaceous edges[6] and severe pain. These wounds are confined not only to the lower legs but may be found on the trunk or areas of trauma. There are four types described – ulcerative, pustular, bullous and vegetative[7] (Figure 3).

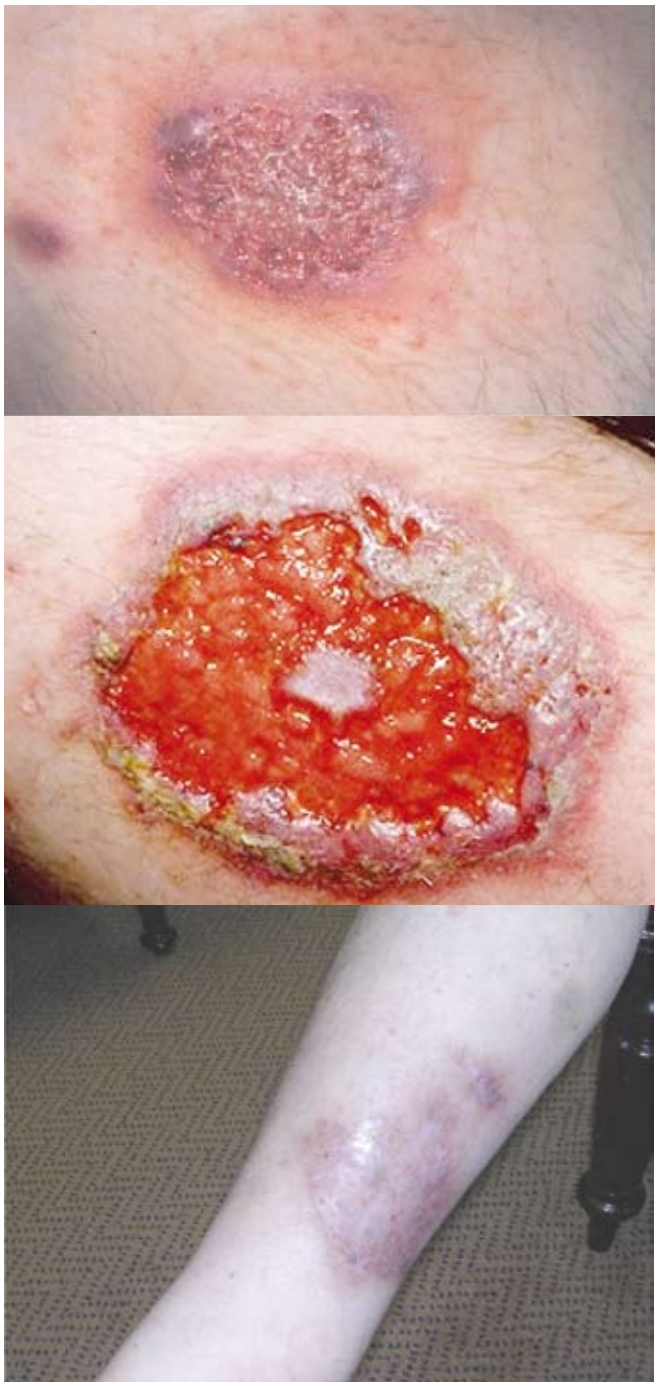

Figure 3. Pyoderma Gangrenosum – wound and then area once healed revealing characteristic severe scarring.

Diagnosis is made especially difficult as it tends to be by exclusion rather than a histological biopsy. Having said this, a biopsy is necessary to exclude other pathologies. It is always important to look at the patient as immune system disorders often become apparent under times of great stress. An enquiry into their lives and the possibility of stress and the offer of counselling or advice does help. This author has identified that some of the cases she has treated are also vitamin or trace element deficient – vitamin C, vitamin B, magnesium and most commonly zinc. Any systemic disease must also be addressed.

Systemic corticosteroids are usually the first line of treatment, for example 40-120mg of prednisolone daily until healing begins. At these doses very close observation must be maintained by the physician commencing the treatment as side effects are frequent and include mood changes, elevated blood glucose and fluid retention. Cyclosporin (6mg/kg) may also be used either alone or in combination with steroids if steroids alone are unsuccessful [8]. Other agents used include mycophenolate and topical immunosuppressants such as steroids and pimicrolimus. More recently intravenous immunoglobulin has been reported as being efficacious when other treatments have failed [8].

In dressing this wound, the clinician will have to consider pain, often excruciating, so less frequent dressings would be an aim. The newer colloidal or silicone meshes with or without silver (silver can add antibacterial and anti-inflammatory properties) have been well accepted by patients. Absorbent padding can act as a protective secondary dressing and, if on lower extremities, a supportive graduated sock assists in alleviating the inflammatory oedema. Due to pain it is strongly advised to utilise a stocking applicator when applying these garments.

Ulcers related to inflammatory conditions

The relationship between inflammatory illnesses and ulceration or impaired healing may be mediated by high levels of antineutrophil cytoplasmic antibodies (ANCA) [9]. These antibodies lead to inflammation of arterioles, venules and capillary blood vessels, which produces vascular obstruction, tissue ischaemia and infarction.

Vasculitic ulcers are often triggered by infection, malignancy, medication or other connective tissue diseases and are more commonly seen in women than in men. The ulcer often commences as a ruptured blood vessel, skin infarction or a dark spot. There is severe pain, sometimes even before the lesion appears, and the lesion is surrounded by erythema (Figure 4).

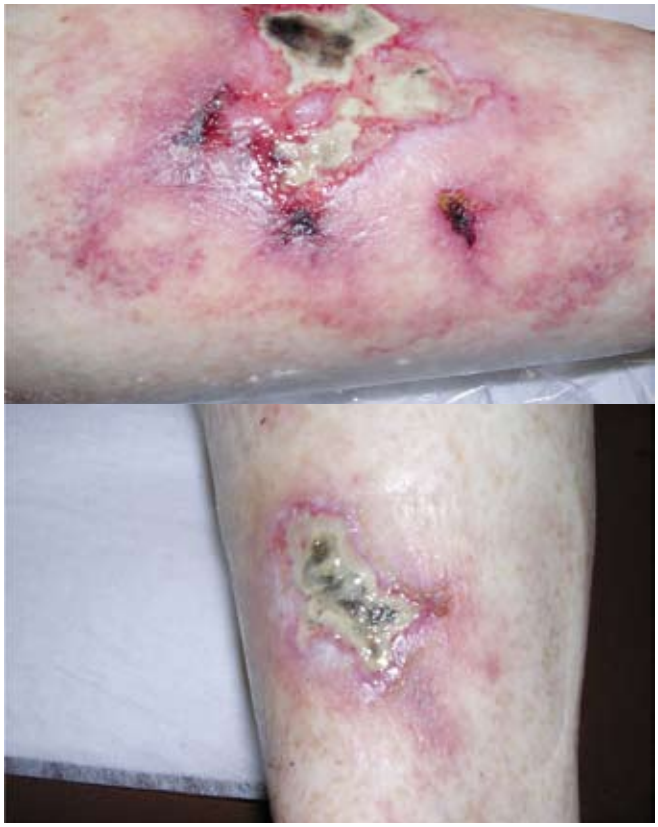

Figure 4. Vasculitic ulcers – superficial necrotic tissue, purple/red edge, severe pain.

The characteristic raised purpuric, palpable edge to the ulcer assists in diagnosis but a biopsy is usually required to ensure correct diagnosis and determine which form of vasculitis is present [10]. Other tests to assist in diagnosing this condition include:

- Urinalysis for proteinuria, haematuria.
- Erythrocyte sedimentation rate, standard blood profiles, haemoglobin, liver function tests, renal function tests.
- Antinuclear antibodies, rheumatoid factor, Compliment C4.
- ANCA, paraproteins, immunoglobulin fractions [10].

Dressings need to provide comfort and prevent further inflammation. Hydrogels are often useful, particularly sheet hydrogels, if the clinician is sure there is no infection present. Silvazine™ was previously the most useful dressing for these ulcers as it provided soothing to the inflamed area and was relatively easy to remove. With the emergence of modern and easier to use silver dressings, clinicians are beginning to prefer these in managing the pain (inflammatory), and exudate of these ulcers. Examples of these dressings include Acticoat Moisture Control™, AQUACEL Ag™, Contreet™ and Polymem Silver™. The use of cadexomer iodine in these cases appears to have further deleterious effects on the ulcer, questionably

due to a stimulatory effect. Additionally, the author would like to highlight the need for clinicians to listen to patients as pain can affect their whole life. Associated depression should be sought and if necessary treated.

Ulcers related to infective conditions

Whether bacterial, viral, parasitic or fungal, diagnosis of some infective causes of ulcers can prove difficult, given that some pathology laboratories are not set up to test for some of the rarer forms of parasites or fungi.

Mycotic skin infections are increasingly seen in Australia, possibly due to the increase in world travel and also to an increased number of immunosuppressed patients [11]. The clinician who is requested to consult on a patient who has a lesion that looks unusual and where the patient has recently been in central parts of USA, Asia, Africa, South America or northern Australia should take a fungal culture, or use direct fluorescent antibody testing on the tissue itself. The laboratory should be alerted to the possibility of an unusual organism.

Sporotrichosis

Sporotrichosis is one such condition, acquired from sphagnum moss, animal claws, thorns, soil and decaying vegetation. It can present many weeks to months after the infection [11]. The painless hard nodules follow the lymphatic tract of the region. The lesions can ulcerate, looking like a volcano with high sides and a deep central crater. Perhaps the best diagnostic tool is a fungal culture married with a high level of suspicion in a person who may have frequent contact with the aforementioned material (gardeners, florists, farmers). There are other forms of mycotic skin infections which are becoming more frequently seen with increased travel.

Treatment of sporotrichosis is with potassium iodide 1ml three times per day, slowly increasing until a maximum of 18mg/day is reached [11]. Heat therapy can also be a useful adjunctive therapy as the fungi do not tolerate temperatures above 38.5°C, but care must be taken not to cause further thermal damage to the wound and surrounding skin.

Dressings may be cleansing dressings which can be applied daily after showering. A hydrocolloid paste with a secondary dressing of a non-adherent pad is generally enough. The resultant scars may benefit from silicone dressings.

Leishmaniasis

Leishmaniasis is another infective ulceration that is endemic in 88 countries on five continents with approximately 12 million people infected [2]. The Leishmania parasites are transmitted by sandflies. When the sandfly bites after becoming infected it regurgitates the promastigotes into the victim and so distribution occurs. With increasing acceptance of refugees and resettlement programmes, these unusual lesions are seen increasingly in developed countries. They may take up to 1 year to manifest as ulcerations and so clinicians need to be vigilant on questioning patients about their past activities or travels. Most of these lesions occur on the face but approximately 20% are on the lower extremities [2].

Diagnosis is made by microscopic identification of amasigotes in biopsies of the base of the ulcer. The use of polymerase chain reaction is more sensitive, but is usually not available in developing countries [2]. The ulcerated lesion has an erythematous raised edge and develops a crusty cap (Figure 5).

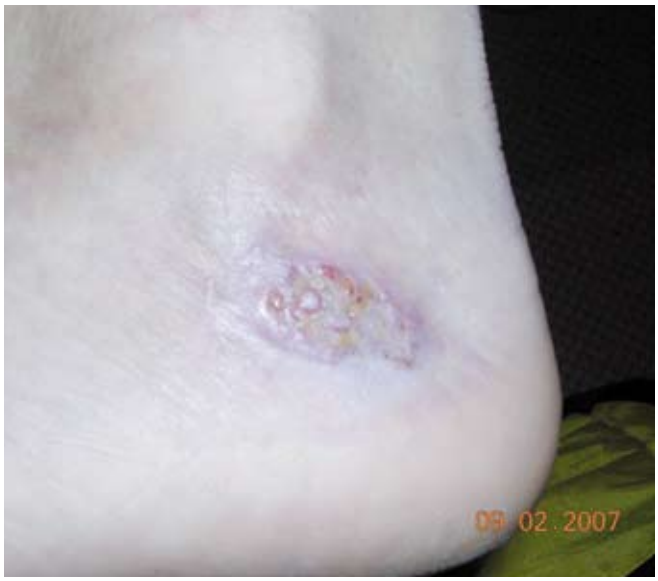

Figure 5. Leishmaniasis wound in a young man recently returned from India – has characteristic raised edge and develops a crusty cap.

Treatment depends on the species identified. Some lesions will heal spontaneously over quite a long period, 4-15 months. Standard treatment is antimony used parentally, intra lesionally or topically for recalcitrant lesions, although this has been replaced in more developed countries by Praziquantel (Biltricide) – one dose orally may be all that is required.

Dressings are best kept to basic and non-adherent as they will be changed daily after bathing and the lesions are not usually

painful. If not diagnosed early and treated with appropriate medication regimes, the resultant scar can be unsightly and scar management products may be required.

Melioidosis

Melioidosis is an infectious disease of animals and humans caused by a germ (bacteria) called *Burkholderia pseudomallei.* This bacterial infection is known to cause fatal pneumonia and septicaemia, with patients experiencing symptoms similar to tuberculosis – weakness, lethargy and extreme malaise in the acute phase. The single most important risk factor for developing melioidosis is diabetes mellitus. Other risk factors include thalassaemia, kidney disease, and some occupations (e.g. farmers). It can also be the cause of non-healing ulcers and skin abscesses in tropical areas; Queensland and the Northern Territory have reported several cases.

The treatment of melioidosis is divided into two stages – an intravenous high intensity stage and an oral maintenance stage to prevent recurrence. Intravenous meropenem is routinely used in Australia and results appear to be good, but meropenem has never been compared head-to-head with a much cheaper agent ceftazidime, regularly used in other countries. A randomised-controlled trial (called ATOM) to answer this question will start in Thailand in 2007, and is due to complete in 2009, with the results to be published in 2010 [12].

The preferred dressings for these lesions absorb exudate and are not occlusive. Simple dressings changed daily with good skin cleansing at each dressing change are generally enough. Pain is usually mild.

Mycobacterium ulcerans / Burulii ulcer
(also known as the Bairnsdale ulcer)

Mycobacterium ulcerans, which is in the same family as but not the organism that causes tuberculosis or leprosy [13], produces a polypeptide toxin called mycolactone. This toxin has been shown to cause cell rearrangement and subsequent destruction [14].

Most patients presenting with this ulcer are either resident in a known endemic area or have recently visited an endemic area. The ulcer is initially slow to progress from papule to necrosis. Theses ulcers are usually painless or minimally painful and generally the patient is well. Systemic symptoms are rare [13]. The mycolactone is a lipid toxin and so causes extensive undermining or tracking under the skin edge of the ulcer. Many of the cases also have extensive swelling (involving most of the limb affected). In patients with unresolved cellulitis or a suspected necrosing spider bite, it is suggested that *M. ulcerans* be considered [13].

Diagnosis is with acid fast bacilli swabs or biopsy specimens from ulcers. Polymeric chain reactions can be performed directly from ulcer swabs and this reportedly reaches 100% sensitivity and specificity. Johnson [13] has noted that in some cases a biopsy may exacerbate the ulcerative process and patients must be warned of this possibility.

Treatment in developed countries includes surgery, generally by a plastic surgeon, in conjunction with antibiotics. If these methods do not prove helpful, then hyperbaric oxygen therapy and heat therapy are other adjuvant therapies reported as useful in case reports [13].

Dressings for these ulcers need to be absorbent as the fat liquefies. A dressing which aids removal of any dead tissue (debriding agent) may also be useful. A superabsorber dressing such as Alione™ or Eclypse™ may be useful together with hydrofibres, hydrocolloid pastes or Cadexomer iodine products. Always listen to exactly what the patient finds the most distressing aspect of the wound and try to find a dressing that will suit them and ease their discomfort.

Haematological ulcers

Sickle cell anaemia, thalassaemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, thrombocythaemia, thrombotic thrombocytopenic purpura, polycythaemia and leukaemia have all been associated with ulceration of the lower leg. Clinicians should have a high level of suspicion of this type of ulcer in patients with known blood disorders and who have ulcers which are painful, indolent and occur over the lower leg and foot where there is less subcutaneous fat, thinner skin and decreased blood supply [15].

Diagnosis is assisted by a biopsy which may be non-specific but can show specific changes such as sickled red blood cells within the dermal blood vessels. Other blood tests may demonstrate exactly what type of haematological disorder the patient is suffering from.

Dressings for these wounds may need to be left in situ for several days as pain at dressing change is reported by some patients. The clinician needs to avoid shear and friction over the ulcer as this exacerbates the pain. One of the newer mesh dressings with absorbent secondary dressings would be considered e.g. Mepitel™, Mepilex™ or Exudry™.

Medication derived ulcers

Warfarin necrosis is rare but increasingly seen as warfarin is used more frequently. It is more commonly seen in middle-aged perimenopausal, obese women shortly after commencing warfarin. It can, however, have a late onset and be seen in people who have been taking warfarin for many years. Skin necrosis usually appears in areas where the blood supply is good, including muscle, breast and buttocks. The patient may initially complain of paresthesia, a sensation of pressure with erythema of the skin or a tight feeling. The lesions themselves rapidly develop and are well demarcated, looking like ruptured blood vessels (Figure 6) [16].

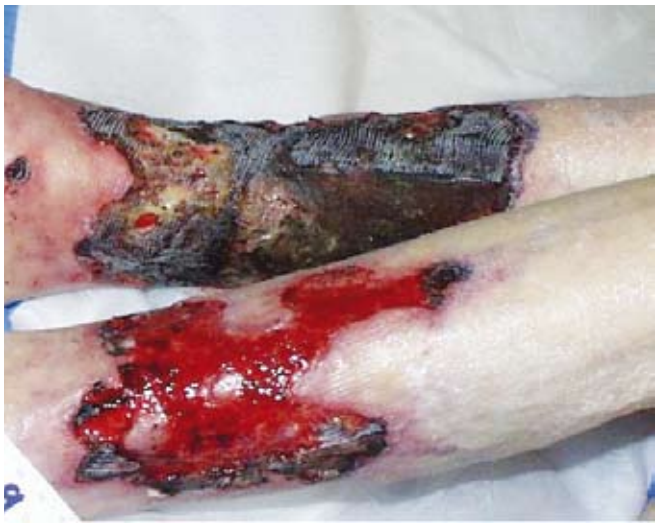

Figure 6. Warfarin necrosis – superficial necrosis – when therapy ceased. With careful management the necrotic area separates and healthy tissue is revealed.

Diagnosis is based on high level of suspicion in patients recently commenced on warfarin, or those who are on warfarin. Treatment is to cease the warfarin. If the areas remain dry they will separate themselves and then the area can be treated with a modern dressing such as Allevyn™, Biatain™ or Permafoam™. Some cases are so severe that surgical intervention is required with extensive skin grafting.

A medication often used in patients with myeloproliferative disorders, hydroxyurea, has also been linked with the development of very small, punctate, extremely painful ulcers An article by Hartmann [17] highlighted that while most people tolerate this medication well there had been reports of long standing leg ulceration, which was closely linked to the medication as the healing only occurred after cessation of the drug. The ulcers do not develop immediately, often appearing after many years on the medication [9]. These ulcers are extremely painful, relatively small and deep. They are usually located around the ankle/gaiter region and are very resistant to treatment. Often the only way to initiate healing again is to discontinue the medication [17].

Dressings do not alleviate the pain, and it is really trial by error until the clinician finds a dressing that eases the situation. Analgesia and counselling should be offered as some patients report horrific pain. Some patients may benefit from light supportive socks/hosiery.

Summary

This article has not covered all of the rarer causes of ulcers. A most important message is to observe the clinical features of the ulcer, compare these to what is known for most common causes of lower leg ulcers and, if in doubt, conduct a biopsy. Always first consider the most common causes before the rarer ones. If the patient has known diseases that may be associated with lower limb ulceration or slow to heal wounds, then make sure that this history is included in the pathology request that accompanies the biopsy.

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