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UNUSUAL CAUSES OF CUTANEOUS ULCERATION

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Synopsis

Skin ulceration is a major source of morbidity and is often difficult to manage. Ulcers due to an inflammatory etiology or microvascular occlusion are particularly challenging in terms of diagnosis and treatment. The management of such ulcers requires careful assessment of associated systemic conditions and a thorough analysis of the ulcer's clinical and histologic findings. In this report, we discuss several examples of inflammatory ulcers and the approach to their diagnosis and treatment.

Introduction

Skin ulceration represents a difficult clinical problem and a major source of morbidity for patients. The patient's quality of life is also significantly affected by pain, swelling, and management of wound drainage. Localized infection, wound colonization, and systemic symptoms add to the morbidity, and can lead to amputation and mortality. Wound care and therapy can be very challenging, and the use of wound dressings must rest on a rational basis and must not be too cumbersome or uncomfortable. Also, cutaneous ulcers take a considerable length of time to heal. The limitations to the patients' mobility, social interactions, and their ability to work result in feelings of helplessness and depression.¹ Most cutaneous ulcers of the lower extremity are caused by venous insufficiency, arterial insufficiency, or neuropathy (especially of diabetic etiology), and in general such ulcers are not difficult to diagnose. However, ulcers associated with or due to systemic inflammatory conditions are often a major diagnostic and therapeutic challenge. We generally call these chronic ulcerations "inflammatory ulcers" (i.e., pyoderma gangrenosum, vasculitic ulcers, cryoglobulinemic ulcers, etc.) because a major and primary component of their pathophysiology indeed rests on inflammation and immunologic phenomena. However, this group of ulcers also includes conditions due to microcirculatory occlusion; a primary localized inflammatory component is less obvious in these conditions. Therefore, for the purpose of our discussion in this report, we will use a broad definition of "inflammatory ulcers", which include these two aspects of chronic ulcers that are not due to classical

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vascular diseases or neuropathy. As with most complex conditions, inflammatory ulcers require a careful multidisciplinary consultation and treatment approach. The internist, dermatologist, surgeon, and rheumatologist are often called upon to contribute their expertise in order to establish the diagnosis and coordinate care.

Basic approach to patients with inflammatory ulcers

The diagnosis of inflammatory ulcers begins with a detailed history. Several important questions need to be asked (from the patient/records, or elicited by physical exam), and the following is a reasonable list. What was the primary lesion? How did the lesion progress? How fast was the progression to ulceration? Was the lesion painful? What management and treatment interventions took place and have they improved or worsened the condition? Has there been a similar problem in the past? Were any new medications started over the last couple of months? Was a surgical procedure performed in the last several months? Have there been any changes in the patient's general health? A thorough review of systems provides clues to diagnosis. A past medical history of connective tissue diseases, diabetes, heart disease, kidney disease, inflammatory bowel disease, hepatitis, hypertension, coagulopathies, prior pregnancy, and malignancies help support or suggest a particular etiology and diagnosis.

Physical examination needs to be comprehensive. Physical exam and attention to details must not be focused on the ulcer alone. Rather, careful observation of the surrounding skin and attention to other areas of the integument such as the oral mucosa and nails are essential. Cutaneous findings, such as livedo reticularis (a netlike violaceous discoloration surrounding a central paler area), palpable purpura, petechiae, nail splinter hemorrhages, and/or oral ulcers support an inflammatory cause of the ulceration. Lipodermatosclerosis, commonly presenting as redness, induration, and hyperpigmentation of the skin in the lower extremity, supports a diagnosis of venous insufficiency. Examination of the peripheral vascular system and testing for the presence of neuropathy are performed to exclude arterial insufficiency, venous disease, and/or neuropathy as causes of the ulceration. Examination of the ulcer involves recognizing features that are characteristic of certain types of ulcers and to identify problems that one can treat. For example, areas of necrosis and the presence of an eschar suggest a thrombotic disorder. Violaceous undermined borders are suggestive of pyoderma gangrenosum; A reddish yellow plaque surrounding the ulcer is characteristic of necrobiosis lipoidica diabetorum (NLD), which is typically associated with diabetes. Ulcers are often complicated by swelling, infection, irritant contact dermatitis from the wound drainage or dressings, or an allergic contact dermatitis from topical medications and dressings. An ulcer with foul odor and purulent drainage is most likely secondarily infected or heavily colonized and will benefit from systemic/topical antibiotics or topical antiseptic treatment. Areas with necrosis and eschar formation in a patient with good pulses would benefit from surgical debridement, most importantly in diabetic patients. Leg swelling should be addressed with compression, when this will not compromise blood supply. Use of a scoring system in addition to ulcer size may be a good objective way to track improvement (Figure 1). As always, the wound bed must be optimized according to the established principles of wound bed preparation (WBP) to promote healing and to make available treatments more effective.² Pain management is important to ensure compliance with treatment; referral to a pain management service may sometimes be necessary. Therefore, as just discussed, the workup and approach to inflammatory ulcers still requires careful attention to the principles of general wound care and management.

Some of the main causes of inflammatory ulcers may be classified into the following primary or associated categories: immunologic conditions (i.e., collagen vascular diseases and vasculitis); thrombotic or hypercoagulable states (i.e., cholesterol embolization and the

antiphospholipid syndrome); pyoderma gangrenosum and necrobiosis lipoidica (Figure 2A–I).

Specific Inflammatory Conditions

Pyoderma Gangrenosum

Pyoderma Gangrenosum (PG) was first described in patients with rapidly progressive, painful ulcers with violaceous undermined borders.³ It is a disorder characterized by pathergy and the development of a larger ulcer upon debridement or with trauma.⁴ When already present, it can also develop in other, distant, seemingly unrelated areas of the skin; hence autologous grafting is a relative contraindication in these patients. Several clinical variants of PG have been recognized. The classic variant starts as a pustule that develops into a rapidly enlarging ulcer with undermined borders, surrounding erythema, and a purulent base. Among other systemic conditions, PG is associated with rheumatoid arthritis, inflammatory bowel disease, Bechet's, a monoclonal gammopathy (typically IgA), myeloproliferative disease; many cases are idiopathic.⁵ The pustular variant of PG manifests as painful pustules with an inflamed border and may not necessarily progress to frank ulceration. Very importantly, the skin manifestations of PG often parallel the severity of the underlying systemic disease, and often resolve with control of their acute flare.⁶ The bullous variant of PG is characterized by painful bullae, which progress to superficial erosions and are associated with myeloproliferative disorders.⁷ The vegetative variant is a superficial painless ulcer with undermined edges. It slowly enlarges and may be exophytic with no clear pattern of specific associated disease.⁸ Parastomal PG presents as a non healing ulcer next to a colostomy site. It should be considered in all patients with inflammatory bowel disease and a peristomal ulceration; the ulcer is typically quite refractory to local wound care approaches.^{9–10} Extra-cutaneous involvement of PG has been reported as cavitary lung lesions, pulmonary infiltrates, episcleritis, development of a psoas muscle abscess, and splenic abscesses.^{11–14}

The onset of the systemic condition may precede, follow, or occur simultaneously with PG; they also may run an independent course. Asymmetric seronegative monoarticular inflammation involving large joints is also associated with PG. A monoclonal IgA gammopathy can be present in the setting of PG and is usually benign, although the development of multiple myeloma has been reported.⁵ Systemic malignancy has been estimated to occur in 7% of PG patients, with leukemia being the most common neoplasm.⁷ Certain drugs have also been implicated in the development of PG (GM-CSF, interferons, and antipsychotic drugs).^{15–18} The pathogenesis of PG is poorly understood. However, it is postulated to be the result of neutrophil dysfunction, which may either consist of a defect in chemotaxis or be due to neutrophil hyper-reactivity. Also, clonality of T- cells has been detected in patients with PG in the absence of myeloproliferative disease, possibly indicating an excessive response to antigenic stimuli.^{19–20}

Vascular and other types of ulcers may be misdiagnosed as PG. This can be a serious clinical problem because treatment of PG with immunosuppressants may ultimately worsen ulcers caused or complicated by infection or malignancy. For example, ulcers caused by atypical mycobacteria and deep fungal infections may be misdiagnosed as PG. Initial (and temporary) improvements in an ulcer upon immunosuppressive treatment do not prove that it represents PG, and should be analyzed with caution. Similarly, it is important to reevaluate the diagnosis of PG when the ulcers are recalcitrant to immunosuppressive therapy. Other inflammatory ulcers improve with immunosuppression, such as those associated with leukocytoclastic vasculitis, Wegener's granulomatosis, cutaneous polyarteritis nodosa, or the antiphospholipid antibody syndrome.⁴

PG is a diagnosis of exclusion, a fact that is not generally appreciated by many clinicians. Critical diagnostic procedures, including biopsy, and other laboratory work up are used to exclude other causes of the ulceration such as infections, malignancies, connective tissue diseases, or vaso-occlusive conditions. A skin biopsy is important to rule out other diagnoses more than to confirm a diagnosis of PG; the histology is never truly diagnostic and still requires exclusion of an infectious etiology. An adequate biopsy would be an excisional biopsy down to subcutaneous tissue, obtaining enough tissue for histology and culture for bacteria, fungi, and mycobacteria. Laboratory tests should include an analysis of and detection of abnormalities in CBC, ESR, c- and p-ANCA, basic metabolic panel, serum protein electrophoresis, coagulation panel, antiphospholipid antibody, cryoglobulins, cryofibrinogen, chest x-ray, colonoscopy, as well as venous and arterial studies.^{4, 21} A patient with inflammatory bowel disease may have minimal or no symptoms, but still have abnormalities upon colonoscopy.

Biopsy findings in PG are variable, depending on the area biopsied and stage of the ulcer. A biopsy taken from the erythematous zone peripheral to the ulcer might show thrombosis and a lymphocytic infiltrate which, when present around blood vessels, might qualify as a lymphocytic vasculitis; in general, the term lymphocytic vasculitis is somewhat controversial. The necrotic undermined border and the ulcer bed would typically show a dense mixed infiltrate and abscess formation. Concomitant leukocytoclastic vasculitis (with destruction of dermal blood vessel walls) is not uncommon but may be secondary to severe inflammation of the skin or even infection.²²

No prospective randomized trials have been performed to determine the optimal treatment of PG, and only a few studies with case numbers of more than 15 patients have been published. High oral doses of systemic corticosteroids (>60 mg/day) and cyclosporine are the best documented treatments and are often used as first line therapy. Both medications are useful for immediate control of the disease but are not suitable for long term use because of their side effects. It has been reported that methylprednisolone, 0.5 to 1.0 mg/kg/day, or cyclosporine at 5 mg/kg/day alone or in combination can be of benefit within 24 hours.^{23–27} Methylprednisolone might be preferable to prednisone, especially since the latter needs to be converted to the first in the liver for optimal effects. Patients with PG have to be on oral corticosteroids for at least several weeks, as short tapering courses of corticosteroids (over a week, for example, are ineffective.²⁴ Pulse therapy with intravenous (I.V.) corticosteroids can lead to rapid improvement (Figure 3A–D). Therapy with I.V. methylprednisolone (1g/day) for 3–5 days is the typical regimen. We prefer a duration of 5 days. In our opinion, methylprednisolone I.V. pulse therapy is most safely performed with the patient on telemetry, for unpredictable electrolyte imbalances may lead to fatal arrhythmias and even sudden death. Concomitant use of a diuretic is a relative contraindication to the use of pulse methylprednisolone therapy.^{25, 28–29}

Complications of therapy for PG need to be carefully considered. Patients on long term systemic corticosteroids are at a risk of developing adrenal suppression, osteoporosis, peptic ulcers, steroid psychosis, among other complications; avascular necrosis of the femoral head can occur very rapidly and at the onset of therapy. Nephrotoxicity, worsening of hypertension, congestive heart failure, increased risk of malignancy are associated with cyclosporine. We prefer not to use cyclosporine in patients with hypertension or evidence of coronary artery disease.

Tumor necrosis factor- α antibodies or inhibitors have been used for treatment of PG. The most studied anti-TNF- α drug for PG is infliximab. Infliximab is a humanized monoclonal antibody against TNF- α that prevents the activation of pro-inflammatory cytokines resulting from the recruitment of inflammatory cells to tissue sites.^{30,31} Generally, infliximab is

administered with an induction dosing regimen infused as 5 mg/kg at weeks 0, 2, and 6. The optimal dosing of infliximab for PG is not known. There is controversy about whether infliximab is effective in patients with PG but without underlying inflammatory bowel disease (IBD).^{32–36} Immune-related side effects to infliximab, such as fever, chills, pruritus, urticaria, low or high blood pressure, and dyspnea are most common reported. Infliximab therapy is associated with an increased risk of infections, including tuberculosis (TB). Reactivation of latent TB and hepatitis has been reported. It is not known whether infliximab increases the risk of solid tumors and malignancies; similar biologic drugs do increase the risk of lymphoma. Infliximab treatment may not be suitable for patients with congestive heart failure. Rare cases of neurologic side effects, such as optic neuritis, demyelinating disorders, and multiple sclerosis have been reported with infliximab. Furthermore, a lupus-like drug reaction has been associated with this biologic agent. Development of antibodies to infliximab increases the frequency of infusion reactions and shortens the duration of remission.³¹

Etanercept is a dimeric soluble form of the TNF- α receptor that prevents ligand binding to TNF receptors on the cell, thus rendering TNF α inactive. In several publications, etanercept has been reported to be beneficial in the treatment of PG, at dosages of 25 to 50 mg weekly.^{37–40} An advantage of using etanercept (over infliximab, for example) is that it can be self-administered subcutaneously by the patient. Side effects of etanercept are similar to those observed with infliximab. However, etanercept has been linked to the development of lymphomas in children treated with this drug before the age of 18.

Other therapies for PG, such as mycophenolate mofetil, dapsone, thalidomide, and I.V. immunoglobulins have been used alone or in combination with systemic corticosteroids.^{41–45} For patients with limited and superficial PG, topical or intralesional corticosteroids and topical tacrolimus have been reported to be effective.^{46–47} Goals of local wound care are relief of pain, prevention of colonization/infection, and to support rapid reepithelialization. Bioengineered skin has been successfully used to stimulate reepithelialization and reduce pain, while circumventing the problem of pathergy associated with the use of autologous grafts.⁴⁸

Vasculitis

Inflammatory processes involving blood vessels can lead to skin ulceration. Vasculitis results from inflammation of the blood vessel wall leading to hemorrhage, ischemia, and infarction. This sequence of events may be associated with connective tissue diseases (collagen vascular diseases), malignancy, or a drug reaction. Systemic symptoms of fevers, malaise, and joint pains necessitate further workup for a connective tissue disease.^{49–50} Differently sized blood vessels may be affected. Vasculitis of the small dermal vessels manifests as palpable purpura, vesicobullous lesions, and superficial ulcers with regular borders. Vasculitis of the muscular arteries presents as painful red nodules, punched-out irregularly shaped ulcers, or gangrene⁵¹ (Figure 4). Often, patients with vasculitis will have systemic symptoms. The lower extremities are most commonly affected; involvement of the upper extremity, trunk and head is an indication of more severe systemic disease.⁵²

The key steps in the diagnosis of vasculitis are to determine blood vessel damage and the vessel size involved. The histologic pattern, supported by immunofluorescence findings, ANCA status, and workup for systemic disease, are the essential elements for diagnosis and for appropriate treatment. Skin biopsies for routine studies as well as immunofluorescence should be performed on the most recent lesions, preferably those present for <48 hours. Since many ulcers due to vasculitis involve the medium sized vessels, a skin biopsy extending to the subcutaneous fat is necessary. In skin lesions presenting with a livedoid pattern, the skin biopsy must be taken from the paler center. Non-ulcerated areas are

preferred for biopsy. However, when biopsies are taken from the ulcer bed, it is important to include the ulcer's edge^{49, 53–54} (Figure 5). In addition to the biopsy, a complete blood count (CBC) with differential, renal and liver function tests, urinalysis, fecal occult blood testing, hepatitis B and C serologies, antiphospholipid antibody testing, immunoglobulin levels, complement levels, ANA, RF and p- and c-ANCA testing are recommended. Blood cultures and echocardiography may be considered in patients with a history of intravenous drug use or a high fever and a heart murmur.⁵¹ Vasculitis may present as a single episode 7–10 days after exposure to a systemic drug or from infection; the vasculitis may resolve in 1–3 months, but an intermittent and relapsing course with ulceration is seen in connective tissue disease (CTD) associated vasculitis, cryoglobulinemia, and malignancy.⁴⁹

Microvascular occlusive processes due to cryofibrinogenemia, the antiphospholipid antibody syndrome, hypercoagulable states from protein C and S deficiency, or caused by medication (such as warfarin) are important differential diagnoses to consider when livedoid skin lesions are observed. In many cases, the red or hyperpigmented cutaneous streaks are subtle (microlivedo), and certainly don't resemble the full-blown net-like hyperpigmentation one sees in livedo reticularis.

Leukocytoclastic vasculitis may present as superficial ulcerations and with hemorrhagic bullae on the lower portion of the leg and often without extra cutaneous involvement. However, constitutional symptoms may be present. A minority of patients may have renal or gastrointestinal involvement. Skin biopsy will show a small vessel vasculitis, while immunofluorescence may reveal complement and immunoglobulin deposition on vessel walls. Trigger factors for vasculitis are drugs, infection, and, rarely, an underlying connective tissue disease. Septic vasculitis is generally a small vessel vasculitis, as in leukocytoclastic vasculitis, that is immune complex negative and is often caused by endocarditis and septicemia from a variety of microorganisms. Typical skin findings are purpura, pustules, hemorrhagic bullae and ulcers. Blood cultures and echocardiography are essential for diagnosis.⁵⁵ Cutaneous small vessel vasculitis occurs frequently in SLE, RA, and Sjogren's. In general, there is multi-organ involvement. The vasculitis may also affect larger blood vessels, as shown by the histology. Physical findings vary from palpable purpura, to ulcers, to digital gangrene indicating significant arterial involvement.⁵¹

However, certain conditions affect larger blood vessels more commonly. Wegener's granulomatosis is a disease that presents with lung, kidney and skin involvement. It is associated with a destructive upper respiratory tract disease, saddle-nose deformities, erosive sinusitis, and subglottic stenosis. Patients will often have multiple lung nodules, infiltrates or alveolar hemorrhage, and segmental necrotizing glomerulonephritis. Skin findings may be palpable purpura, subcutaneous nodules, ulcers and digital infarcts, vesicobullous lesions, and gingival hyperplasia. Vasculitis in this systemic condition affects small to medium sized vessels. Biopsies from the upper respiratory tract may be diagnostic. A pattern of positive c-ANCA and PR-3- ANCA is strongly associated with WG. When untreated, the condition may approach a mortality of 80%.⁵¹ Cutaneous polyarteritis nodosa (PAN) manifests as painful nodules progressing to ulceration with neuropathy. The clinical manifestations of PAN represent a spectrum, varying from nodules, livedo reticularis, and polyneuropathy, to severe disease with cutaneous ulcers, pain, sensory neuropathy, fever, malaise and arthralgia and progressive systemic disease; acral gangrene, foot drop, mononeuropathy multiplex, and musculoskeletal involvement can occur.⁵⁶ When the medium-sized blood vessel involvement of PAN is strongly suspected, multiple deep punch or incisional biopsies down to the fascia may be required to diagnose this disorder. Moreover, serial sections through the specimen are frequently necessary, because the vasculitis is focal and segmental.⁵⁷ (Figure 6A)

In PAN, treatment of the underlying disease often leads to resolution of the vasculitis. Mild disease may be treated with dapsone or colchicine. More severe or unresponsive PAN is managed with prednisone and/or with a corticosteroid sparing agent. Systemic vasculitis with internal organ involvement may require the use of prednisone and cyclophosphamide, frequently in combination. Once remission has been achieved, maintenance with methotrexate or azathioprine alone is recommended.^{58–59}

Cholesterol embolism (CE) (Figure 6B_[E1])

Patients present with varied skin manifestations such as livedo reticularis, purpura, cyanosis, blue toes, digital gangrene, painful subcutaneous nodules, renal failure; interestingly, arterial hypertension is very uncommon. Patients may also have fever, weight loss, myalgia, and anemia. Large vessels may be the source of the embolus, from which fragments separate and occlude the microcirculation. Several organ systems may be affected, with azotemia, abdominal pain from mucosal ulceration, gastrointestinal involvement from bleeding, ischemia, infarction, and perforation. Myocardial infarction, stroke, and transient ischemic attacks are not uncommon.^{60–64} Cholesterol embolism (CE) occurs spontaneously or may be iatrogenic. Pathophysiologically, CE is the result of shearing forces causing atherosclerotic plaque rupture. Iatrogenic CE is caused by an endovascular surgical procedure or the initiation of anticoagulant therapy (warfarin, heparin). However, in some cases CE can develop weeks to months from the time of surgery/endovascular procedures or initiation of anticoagulation.^{61, 65}

Patients at high risk for CE are those with severe atherosclerotic disease. The formation of a fibrofatty plaque within the vessel wall, composed of a necrotic core of cell debris, foam cells, lipid and cholesterol crystals and an overlying fibrous cap, is the central pathologic entity in atherosclerosis. When a plaque ruptures, a thrombus forms and breaks up, leading to <100 μ cholesterol fragments that embolize and occlude vessels in distant sites and affect different organ systems, including the skin. After the cholesterol crystals occlude the microcirculation, inflammation ensues, followed by a foreign body reaction with thrombus formation and eventual fibrosis. This sequence of events results in ischemia and infarction.⁶⁶ The presence of skin findings, such as livedo reticularis, microlivido, or the blue toe syndrome, in addition to progressive renal failure, is highly suggestive of cholesterol crystal embolization.⁶⁵ However, a skin biopsy showing characteristic biconvex needle like cleft in vessels on histology is detected in up to 92% of patients and is specific for CE⁶¹(Figure 6C). An optimal biopsy site is a tender nodule. However, the livido area also has a high yield. CE has a high mortality rate; in one review of 221 patients mortality was 81%.⁶²

There is no established treatment for CE. When possible, anticoagulants should be withdrawn and further vascular procedures should be avoided after a diagnosis is established.^{67–68} Aggressive supportive treatment has been reported to improve one year survival rates.⁶⁵ In that report, this approach included maintaining the patient's nutritional status, treating or preventing cardiac failure, and using hemodialysis. Systemic corticosteroids were started with evidence of recurrent CE or inflammation. However, the use of systemic corticosteroids is not consistently successful. Care must be exercised when patients are treated with corticosteroids, as fluid retention and alterations in electrolyte imbalance will further complicate the patient's cardiac status.⁶⁹ Statins, which can stabilize plaques, have been shown to decrease the risk of progression to end stage renal disease and have improved the one year cumulative survival.⁷⁰ Surgical intervention (i.e., removing the thrombus) in CE patients is associated with significant morbidity, and its use is reserved for cases where immediate survival is at stake.⁶⁵

Calciophylaxis

Calciophylaxis has been classically described as the sudden development of tender, violaceous, and reticulate lesions that progress to necrotic ulcerations of the lower extremities in patients with renal failure on chronic hemodialysis. These ulcers heal poorly and are very painful. Areas commonly affected are those with thick adipose tissue, such as the abdomen, breasts, and buttocks. There is often an elevated parathyroid (PTH) level (secondary to renal failure), with abnormal calcium and phosphate metabolism.⁷¹ Some authors suggest that proximal ulcerations involving the abdomen and buttocks have a worse prognosis.⁷² Recently, this classical concept and clinical context of calciophylaxis have been changing, as shown by several published case reports indicating a similar clinical course in the absence of renal failure, no obvious dysregulation of calcium and phosphate metabolism, and with normal PTH levels. However, a consistent histologic finding is calcification of the vessel walls, eventually leading to thrombosis and infarction of the skin. Other risk factors associated with the development of calciophylaxis include the following: obesity, liver disease, systemic corticosteroid use, and an elevated calcium phosphorus product.⁷³ In addition, contributing factors are diabetes mellitus, warfarin use, decreased functional protein C and S activity, vitamin D supplementation, and low albumin levels. Thus, in the proper clinical context from physical examination and histologic findings, calciophylaxis should be considered even in the absence of kidney disease.⁷⁴ Peripheral pulses are preserved, since only the smaller vessels are affected by calciophylaxis. Histology of the cutaneous lesions shows calcium deposits within the blood vessel walls, mainly in the media and intima of small arterioles and venules, frequently with a concentric, circumferential, and ring like pattern (Figure 6D). These findings are seen in the dermis and the subcutaneous fat. Septal and lobular fat necrosis and epidermal ulceration with dermal necrosis are also identified.⁷⁵

Treatment of calciophylaxis is mainly supportive. The goals of local wound care are to manage drainage with wound dressings, improve pain, treat infection, and stimulate healing (Figure 7A–D). If altered calcium metabolism and hyperparathyroidism are identified, treatment is directed to normalize these abnormalities. Several therapeutic measures have been tried, and with varied success. Simple approaches, such as establishing a diet with low phosphate intake and initiating oral phosphate binders, can be started. Bisphosphonates have been used because of their inhibitory effect on macrophages and pro-inflammatory cytokines to prevent further calcification. For example, pamidronate and etidronate have been used with some success.^{76–78} Cinacalcet is a new calcimimetic agent that works by increasing the sensitivity of the calcium sensing receptor on the parathyroid gland, thereby decreasing PTH levels and normalizing calcium levels.⁷⁹ This drug has been useful in patients with secondary hyperparathyroidism.^{80–81} Sodium thiosulfate is thought to dissolve calcium deposits in tissues by forming soluble calcium thiosulfate complexes. It is given I.V. and has been reported to improve pain and wound healing.^{82–84} Parathyroidectomy in patients with calciophylaxis and elevated PTH benefits wound healing and improves short term mortality; the long term benefits of this approach are unknown.^{85–87}

The prognosis of calciophylaxis is generally poor, and the condition is associated with a mortality as high as 60–80%.⁷³ Sepsis occurs commonly, with the ulceration as the probable portal of entry for infection.

Cryofibrinogenemia and Cryoglobulinemia

Signs and symptoms of cryofibrinogenemia are due to cutaneous ischemia. Patients present with livedo reticularis or subtle areas of microlivedo, purpura, ecchymoses, and painful ulcerations that, strangely, are not commonly precipitated by cold ambient temperatures. Systemic symptoms of malaise and fever are common. Often, there is an underlying

inflammatory disease such as malignancy, diabetes mellitus, collagen vascular disease, or an infection. Essential cryofibrinogenemia occurs without a secondary cause and should be considered in healthy patients presenting with unexplained areas of cutaneous ischemia.⁸⁸ Rarely, other thrombotic events such as myocardial infarction, thrombophlebitis, and cerebral infarction are seen. Paradoxical spontaneous bleeding due to consumption of clotting factors may occur.⁸⁸

One needs to contrast cryofibrinogenemic versus cryoglobulinemic ulcers. The diagnosis of cryofibrinogenemic ulcers is made in a clinical setting of sudden onset of skin changes and ulcerations in the presence of elevated plasma cryofibrinogen and without serum cryoglobulins and evidence of other inflammatory causes of micro-occlusive diseases; the relationship of onset of pain, discomfort, and ulceration to cold exposure is uncommon. In contrast, cryoglobulinemic ulcers are definitely accompanied by purpura triggered by cold exposure or prolonged standing plus arthralgia and weakness; cryoglobulins are detected in serum. Cryoglobulins are associated with connective tissue diseases, hematologic malignancies, and hepatitis. Cryofibrinogenemia is commonly idiopathic, but can be associated with myeloproliferative disorders and connective tissue diseases. Treatment of the underlying disease causing these cryoproteinemias leads to improvement of symptoms and physical findings.

On skin biopsy of ulcers due to cryoproteinemias, one sees small and medium sized vessel vasculitis. In terms of distinction, cryofibrinogens are a cold, insoluble complex of fibrin, fibrinogen and fibrin split products with albumin, plasma proteins and immunoglobulins. Cryofibrinogen forms a clot with thrombin and reversibly precipitates in plasma at 4° celsius⁸⁹, whereas cryoglobulins are cold precipitating immunoglobulins in serum and dissolve when warmed. A skin biopsy showing fibrin occluding the dermal blood vessels, angiogram with abrupt occlusion of small to medium sized arteries, and elevation of serum levels of α -1 antitrypsin and α -2macroglobulin support a diagnosis of cryofibrinogenemia. High levels of α -1 antitrypsin and α -2- macroglobulin inhibit plasmin and fibrinolysis, which leads to the thrombotic occlusion of small to medium arteries by the cryofibrinogens.⁹⁰⁻⁹¹ The detection of cryofibrinogens in plasma requires special handling and attention. Blood must be collected in tubes containing oxalate, citrate, or ethylenediaminetetraacetic acid as the anticoagulant. After collection, the blood must be quickly centrifuged at 37° C. Blood should also be collected in a plain glass tube, allowed to clot, and then processed in a similar fashion in order to detect the presence of cryoglobulins.

Treatment of cryofibrinogenemic ulcers includes avoidance of cold exposure and local wound care. The anabolic steroid stanozolol has an established fibrinolytic effect and has been used with considerable success in the past.⁹²⁻⁹³ However, this drug has now been withdrawn from the market and is no longer easily available as a reliable preparation. However, we have now used danazol with success (V. Falanga, unpublished). Systemic corticosteroids alone do not appear to be an effective therapy. Treatment of the underlying condition may lead to improvement. Plasmapheresis has been effective in a few reports.⁹³⁻⁹⁷ We have had success with the use of combined pentoxifylline and colchicine in one patient with cryofibrinogenemic ulcers.⁹⁸ (Figure 8A,B)

Necrobiosis Lipoidica Diabeticorum

Necrobiosis lipoidica diabeticorum (NLD) is characterized by single or multiple asymptomatic red to yellow shiny plaques that gradually enlarge and within which, due to atrophy, dermal blood vessels are readily apparent. Ulceration is a complication of NLD, and commonly develops after trauma to the lesions. Almost all patients with NLD have diabetes mellitus, or will develop it, or have a strong family history of it. However, less than 1% of diabetic patients have NLD.⁹⁹⁻¹⁰⁰ The pathogenic steps leading to NLD are

unknown. Skin biopsy of the lesions shows an atrophic epidermis and dermal areas of necrobiotic collagen surrounded by palisading histiocytes and extending to the subcutaneous fat. Spontaneous resolution of NLD has been reported to occur in about 20% of cases. A variety of treatments have been used for treatment of NLD, including topical and intralesional corticosteroids, topical tacrolimus, psoralens plus UVA (PUVA), and antimalarials. In patients with severe ulcerations within NLD, infliximab, etanercept, pentoxifylline, cyclosporine and thalidomide have been used. Interestingly, tight control of the patient's diabetes does not improve NL.^{101–108}

Warfarin Induced Skin Necrosis

Sudden development of paresthesia, edema, petechiae, and ecchymoses progressing to full-thickness necrosis and deep ulcers within 3–10 days after the initiation of warfarin therapy should alert the clinician to the possibility of warfarin-induced skin necrosis (WISN).^{109–111} WISN has been described in patients on anticoagulation, typically several days after therapy is stopped or on re-treatment.^{111–113} WISN is thought to be the result of a paradoxical hypercoagulable state, possibly due to inhibition of vitamin K dependent coagulation factors relative to other factors, thus producing a transient imbalance that predisposes to clotting. Protein C deficiency, protein S deficiency, and anti-thrombin III deficiency are considered a risk factor in the development of WISN. However, not all patients with protein C, S and anti-thrombin III deficiencies will develop WISN.^{111, 114–116}

The diagnosis of WISN is made by history and/or with a skin biopsy showing histologic findings of microthrombi and thrombi within the blood vessels of the dermis and subcutaneous tissue, including capillaries and venules; typically, there is no vasculitis. WISN needs to be differentiated from heparin-induced necrosis associated with heparin-induced thrombocytopenia and thrombosis (HITT), since both warfarin and heparin are frequently used concurrently. Both conditions present with skin necrosis. HITT is associated with a 50% reduction in platelet levels from baseline or a platelet count less than 150. However, platelet counts are frequently normal in HITT with skin ulceration. Symptoms begin at 4–12 days after starting heparin. The heparin PF-4 antibody is frequently present.^{109, 117} In contrast to WISN, the thrombus in HITT is mostly composed of platelets; true arterial thrombosis is common.¹¹⁸

Early diagnosis and immediate withdrawal of warfarin improves the prognosis of WISN. Replacement of clotting factors with fresh frozen plasma and the use of an alternate anticoagulant such as heparin may be required. Thus, it is important to distinguish between WISN and HITT, because the mainstay of treatment of HITT is discontinuation of heparin and switching to a different anticoagulant such as argatroban; warfarin use alone is contraindicated in HITT.¹¹⁹ Aggressive wound care and surgical intervention to remove devitalized tissue are needed in many patients. Antibiotics are also frequently used but given with caution, since antibiotics may alter or decrease the vitamin K-producing flora in the gut. Treatment with systemic corticosteroids or vasodilators has not improved WISN.^{109, 115} Useful measures to prevent warfarin necrosis are to avoid initial loading with warfarin and starting anticoagulation first with unfractionated heparin and overlapping with warfarin for about five days.^{114–115}

Conclusion

The sudden development of painful ulcerations with systemic symptoms in the context of an underlying disease, change in medications, and/or recent surgical intervention points to an inflammatory cause of the ulceration. A broad differential diagnosis exists for these ulcers. History, physical examination, and laboratory workup should be done, with careful consideration of an autoimmune, infectious, and/or occlusive process as the cause of

ulceration. Providing wound care with the goals of optimizing wound healing by decreasing swelling, controlling the bacterial burden, and avoiding an irritant or allergic contact dermatitis are equally important. Treatment of the underlying illness will often improve the ulceration as well. Since these diseases are not so common, no specific guidelines have been developed. Treatment should be carefully chosen, with emphasis on minimizing possible complications with its use. A multi-disciplinary approach is necessary to manage these patients, and consultations with different specialties should be the rule. Re-evaluation of the diagnosis and management are advised if the ulcers fail to respond to treatment.

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Wound Bed Score			
	Scores of 0	Scores of 1	Scores of 2
Black Eschar	0	1	2
Eczema/Dermatitis	0	1	2
Depth	0	1	2
Scarring (fibrosis/callus)	0	1	2
Color of wound bed	0	1	2
Oedema/Swelling	0	1	2
Resurfacing epithelium	0	1	2
Exudate Amount	0	1	2
Add scores for each column →			
TOTAL SCORE			

Figure 1. Wound Bed score (WBS) and its individual features

The total WBS adds each individual score for each characteristic to give a total score. ● Percent of eschar present (>25, 1–25%, none); Severity of peri-ulcer dermatitis (severe, moderate, none or mild); Depth of the wound (severely depressed or raised compared to peri-wound skin); Severity of callus/fibrosis (severe, moderate, none or minimal); Percent of pink granulation tissue present (<50%, 50–75%, >75%); Severity of edema (severe, moderate, none/mild); Percent of healing edges (<25%, 25–75%, >75%); Frequency of dressing changes (severe, moderate, none/mild)

Figure 2. Examples of some inflammatory ulcers

(A) Pyoderma gangrenosum in a patient with rheumatoid arthritis. (B) The more 'granulomatous' appearance of Pyoderma gangrenosum. (C) Typical Pyoderma gangrenosum with purple edges. (D) Undermined ulcer of Pyoderma gangrenosum. (E) The undulating borders of a rheumatoid ulcer. (F) Eschar in an ulcer due to polyarteritis nodosa. (G) Same patient shown in (F), after successful use of immunosuppressants. (H) The 'angular' ulcers seen in patients with collagen vascular diseases, often mimicking factitial ulcers. (I) Livedo reticularis and small ulcers in a patient with cholesterol embolization.

Figure 3. Patient with pyoderma gangrenosum treated with pulse steroids overlapped with mycophenolate mofetil as corticosteroid sparing agent
(A) The appearance of a PG ulcer prior to treatment. (B) Dramatic improvement after second day of pulse methylprednisolone. (C) Six days after pulse steroids the ulcers decreased markedly in size. (D) Healed ulcer 3 weeks after treatment.

Figure 4. Diagrammatic representation of the difference in small versus medium-sized (deeper) vessel vasculitis and the impact on skin findings

A superficial vasculitis (left side of diagram) leads to a wedge-shaped area of necrosis and, thus, a well defined and regular skin purpura or necrosis. Conversely, occlusion of a deep vessel (right side of diagram) leaves open the chance for anastomosing vessels to alter the effect at the skin.

Figure 5. Example of a biopsy for an inflammatory ulcer
Excisional biopsy marked on edge of ulcer including surrounding erythema.

*Please see attached pdf for re-letter of figure 6.

Figure 6. Histologic findings in different inflammatory ulcers

(A) Dense inflammation around a medium sized artery seen in polyarteritis nodosa. (B) Cleft like spaces inside a vessel seen in cholesterol emboli. (C) Fibrin thrombi inside a vessel seen in cryofibrinogenemia. (D) Calcification of medial layer of a blood vessel seen in calciphylaxis.

Figure 7. Patient with calciphylaxis without renal failure, normal parathyroid levels, normal calcium and phosphate product

(A) Painful ulcer with background livedo reticularis. (B) Worsening ulcer not responsive to pulse steroids, azathioprine, pentoxifylline, antibiotics and debridement. Skin biopsy showed calciphylaxis. (C) Repeat debridement, IV antibiotics, bioengineered skin applied to ulcer with good response; Azathioprine discontinued after one month, compression therapy, pain management, antiseptic dressings were used. (D) Ulcer healed after 3 months.

Figure 8. Patient with cryofibrinogenemia
(A) Typical presentation of livedo reticularis. (B) Ulcers healed with compression pentoxifylline and colchicine.