Approaches to Microthrombotic Wounds: A Review of Pathogenesis and Clinical Features

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GENERAL PURPOSE: To discuss the pathogenesis and clinical features of wounds caused by microthrombi formation under the following categories of systemic diseases: cold-related and immune-complex deposition diseases, coagulopathies, abnormalities in red blood cell structure, emboli, and vasospasm.

TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant should be better able to:

1. Recall the etiology, risk factors, and pathophysiology of the various types of microthrombotic wounds.
2. Describe the clinical manifestations and treatment of the various types of microthrombotic wounds.

ABSTRACT Typical wounds such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, and arterial ulcers are responsible for more than 70% of chronic wounds. Atypical wounds have broad differential diagnoses and can sometimes develop as a combination of different conditions. Regardless of the etiology, impaired blood circulation is characteristic of all chronic and acute wounds. Chronic wounds associated with microthrombi formation are an important group of atypical wounds commonly linked to an underlying systemic disease. In this perspective article, the pathogenesis and clinical features of wounds caused by microthrombi formation are discussed under the following categories of systemic diseases: cold-related and immune-complex deposition diseases, coagulopathies, abnormalities in red blood cell structure, emboli, and vasospasm.

KEYWORDS: antiphospholipid antibody, atrial myxoma, cholesterol emboli, cryoglobulinemia, cryofibrinogenemia, hydroxyurea-induced ulcer, livedoid vasculopathy, microthrombi, sickle cell anemia, skin necrosis, vasospasm, warfarin

INTRODUCTION

Effective treatment of leg ulcers relies on accurate diagnosis. More than 70% of wounds are classified as typical wounds, attributable to common etiologies such as arterial diabetic or venous ulcers.[1] However, wounds associated with microvascular occlusions often have atypical presentations and are therefore difficult to diagnose and manage. Because the majority of these wounds present with pain and inflammation as leading signs and symptoms, they can easily be confounded with pyoderma gangrenosum.

Atypical leg ulcers account for approximately 20% to 30% of cases of leg ulcers.[2] The wounds are considered atypical based on their morphologic features, incidence/prevalence, clinical presentations, unusual locations, and/or their inability to respond to conventional therapy. For example, it is uncommon for diabetic wounds to present on the thigh, and providers should therefore consider an atypical etiology.

One atypical etiology for chronic wounds is microthrombi formation. Although the pathogenesis of wounds attributable to microthrombi has not been completely elucidated, it is most likely linked to tissue hypoxia that leads to cutaneous ulcerations and necrosis. These lesions are extremely painful and commonly related to the occlusion of

small blood vessels from thrombi formation and not atherosclerosis. Diagnosis is often made based on a thorough clinical history, laboratory findings, and skin biopsy; however, these wounds may have features that can be mistaken for more common etiologies.

This review article focuses on the pathogenesis and clinical features of cutaneous ulcers caused by microthrombi formation, including cold-related and immune-complex deposition ulcers, ulcers associated with coagulopathies, emboli or microemboli, vasospasm, and blood cell-abnormal deformability. This review also discusses management plans for these ulcers and concludes with a brief discussion of the less common ulcers attributable to emboli.

BACKGROUND AND PATHOPHYSIOLOGY
Cold-Related Ulcers
The two most common cold-related ulcers are ulcers associated with cryoglobulinemia and cryofibrinogenemia. Cryoglobulinemia is a disorder characterized by the presence of serum cryoglobulin, which is an aggregate of immunoglobulins that precipitate in vitro at temperatures below 37° C and resolubilize upon rewarming.[3] According to the Brouet classification, type I cryoglobulinemia is characterized by monoclonal immunoglobulins (commonly either immunoglobulin M [IgM] or G [IgG]) often associated with immune system malignancies, including monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström macroglobulinemia, lymphoma, and chronic lymphocytic leukemia.[4] Types II and III cryoglobulinemia contain both IgG and IgM and are referred to as mixed cryoglobulinemia. Type II cryoglobulinemia has monoclonal IgM, polyclonal IgG, and rheumatoid factor, whereas type III cryoglobulinemia has polyclonal IgG and IgM with rheumatoid factor.[4] Both types II and III are strongly associated with the hepatitis C virus. Other cases can be idiopathic (essential cryoglobulinemia) or associated with other systemic diseases, such as Sjögren syndrome. Hepatitis C virus infection has been reported in 60% to 90% of patients with mixed cryoglobulinemia and is implicated in the disease process.[5,6]

The pathogenesis of tissue injury in cryoglobulinemia is complex. The mechanism by which cryoprecipitation occurs is thought to evolve from two primary factors working together simultaneously at different degrees.[3] Low temperatures also contribute to cryoprecipitation because of changes in antibody conformation.[7,8] Patients with type I disease have a lymphoproliferative disorder and thus produce high concentrations of the monoclonal components and have hyperviscosity syndrome. High levels of IgM and IgG precipitate within the blood vessels, leading to reduced blood perfusion to tissues, occlusion, and, eventually, tissue necrosis—particularly at cooler temperatures in the distal extremities. In types II and III, immune complex formation and complement fixation lead to vascular inflammation and vasculitis, often with microthrombi formation. In both cases, obstruction of blood vessels follows, causing ischemia, gangrene, and ulcer formation.[3]

Cryofibrinogenemia is a rare disease that occurs because of the precipitation of cryoprotein in plasma.[9] These cryoprecipitates, known as cryofibrinogen, are characteristically composed of fibrinogen, fibrin, fibronectin, and fibrin degradation products and may contain immunoglobulins. Patients with cryofibrinogenemia may be asymptomatic; therefore, the presence of nonhealing ulcers in otherwise healthy patients should raise suspicion of essential cryofibrinogenemia. In terms of etiology, cryofibrinogenemia can either be primary or secondary to infection, vasculitis, myeloproliferative disorders, solid malignancies, or diabetes mellitus.[10,11] Importantly, cryofibrinogen can be associated with the presence of a cryoglobulin.

Cryofibrinogen is an insoluble protein complex that is constituted from fibronectin, fibrin, fibrinogen, and, on occasion, small quantities of immunoglobulins in plasma (not serum) that reversibly precipitate at 4° C and resolve at 37° C.[12] It does not precipitate in serum because clotting factors, which are not found in serum, are substrates for cryofibrinogen. The exact mechanism of cryofibrinogenemia remains unknown. One theory is that elevated plasma α1 antitrypsin and α2 macroglobulin lead to a defect in the fibrinolysis pathway.[13] Both of these molecules are known to inhibit plasmin, which leads to impaired fibrinolysis at elevated levels. As cryofibrinogen levels increase in the plasma, clot formation occurs, and eventual blood vessel occlusion follows. The second leading theory proposes that a heightened thrombin-binding capacity may be the principal cause, as opposed to a deficiency in the fibrinolytic pathway.[9] In either case, there is obstruction of small and medium vessels, leading to hyperviscosity, vasospasm, ischemia, and vascular stasis.

Ulcers Commonly Associated with Coagulopathies
Examples of ulcers commonly associated with coagulopathies include those associated with antiphospholipid antibody syndrome (APLS), livedoid vasculopathy (LV), or the use of anticoagulants.

Antiphospholipid antibody syndrome is an autoimmune disease in which antibodies recognize cell membrane phospholipids, compromising vessel wall integrity.[14–16] Antiphospholipid antibodies (APLAs) are found in 10% to 20% of the population.[17] The syndrome can be an acquired primary condition occurring in isolation or (less commonly) secondary to an underlying disease such as systemic lupus erythematosus.[18] However, a distinction between primary or secondary APLS is difficult to make because of overlapping clinical similarities.

Antiphospholipid antibody syndrome is defined as the presence of APLAs and a thrombotic event (vascular thrombosis or miscarriage).[14,19] In the presence of clinical manifestations suggestive of this condition, APLS must be detected twice at least 12 weeks apart to establish a diagnosis.[14] Skin manifestations are common but nonspecific.[20]

Skin ulcers associated with APLS are attributed to fibrin deposition in superficial dermal vessels.[21] Thrombosis is the main complication of APLS, occluding vessels of all sizes.[20] It is believed that the cardinal pathognomonic pathway for thrombosis is APLAs interacting with phospholipid-binding plasma proteins and interfering with the coagulation cascade leading to a procoagulant state. Other advanced mechanisms include inhibition of activating protein C and antithrombin III pathways, induction of tissue factors, and platelet activation.[14,22] This condition is associated with other autoimmune diseases, infection, malignancy, medications, heart vegetation, thrombocytopenia, nephropathy, ischemic attacks, and stroke.[14]

Livedoid vasculopathy is a chronic noninflammatory microthrombotic disorder involving the occlusion of small vessels that support the dermis.[14,23–25] It can result in painful, recurrent ulcerations that can be so incapacitating that they prevent engagement with normal activities of daily living.[26] The prevalence of LV in the US is 1 in every 100,000 persons annually.[25] The mean age of patients is 32 years, with a female-to-male ratio of 3:1.[24,25,27] Because of the rarity of LV, diagnosis can be lengthy and onerous, taking an average of 5 years.[23,25,28]

The main theorized genesis of LV is microthrombi in the superficial dermal vessels secondary to defective endothelial cell plasminogen activator, platelet dysfunction, and increased fibrin formation.[28] Livedoid vasculopathy is not a coagulopathy but has been reported in association with coagulopathy and underlying conditions in up to 50% of cases such as anticardiolipin antibody (most frequent), APLAs, protein C or S deficiency, factor V Leiden mutation, antithrombin III deficiency, hyperhomocysteinemia, prothrombin gene mutation, and decreased thrombomodulin expression on vessel endothelial cells.[14,24,27]

Warfarin-induced skin necrosis and heparin-induced ulcers are two examples of microthrombotic ulcers induced by coagulopathies,[29] affecting 0.01% to 0.1% of patients on warfarin therapy.[30] Typical patients with warfarin-induced skin necrosis are 50- to 60-year-old obese women on warfarin therapy for deep venous thrombosis or pulmonary embolism. Further, there have been reported cases of non-vitamin K antagonist oral anticoagulants such as dabigatran and rivaroxaban causing leukocytoclastic vasculitis.[31–33]

A reaction to warfarin will occur 3 to 5 days after initiating treatment. Warfarin will inhibit vitamin K-dependent factors II, VII, IX, and X. It will also inactivate vitamin K-dependent proteins C and S. Factors with shorter half-lives are depleted faster than those with longer half-lives. This imbalance leads to a transient hypercoagulable state when warfarin is started without prior heparin anticoagulation, raising the risk of venous thromboembolism and warfarin necrosis.[34] Warfarin-induced skin necrosis is more likely to occur in individuals with an innate, unknown deficiency in protein C, but it can also occur in individuals with other inherited coagulopathies such as factor V Leiden mutation, protein S deficiency, and antithrombin III deficiency.[35–37]

Ulcers Associated with Blood Cell Deformability
Examples of ulcers associated with blood cell deformability include those associated with sickle cell anemia or the use of hydroxyurea. Sickle cell disease (SCD) is an autosomal recessive condition causing irregular polymerization of hemoglobin, which results in rigidity of red blood cells and poor microvascular blood flow.[38,39] Poor blood flow can lead to tissue ischemia and infarction. The disease affects 300 million people worldwide, with the highest prevalence of individuals with SCD (approximately 30%–40% of all individuals with the diagnosis) in sub-Saharan Africa.[40] Sickle-shaped blood cells can cause acute deep tissue damage or skin complications (typically leg ulcers).[41] Leg ulcerations can be very disabling and are a risk factor for more severe forms of organ damage.[38,41] Chronic leg ulcers occur in 25% to 70% of adolescents and adults with SCD[39] and are most common in homozygous genotypes.[42] Leg ulcers are more commonly seen in males and patients with low hemoglobin levels, antithrombin III deficiency, certain human leukocyte antigens, and thrombocytosis.[38,43] In addition, SCD-associated leg ulcers are more common among certain populations; for example, they have been found in 75% of Jamaican patients who are homozygote for hemoglobin S.[38]

The pathogenesis for sickle cell ulcers is unclear but is likely multifactorial, implicating mechanical obstruction by red blood cells, venous incompetency, and thrombosis.[38,43–45] Pathologically, intravascular fibrin and microthrombi deposition in and around ulcers is present.[44] A large variation of organ complications is associated with SCD leg ulceration including priapism, pulmonary hypertension, stroke, acute chest syndrome, retinopathy, and osteonecrosis.[41]

Hydroxyurea is used to treat different hematologic disorders and SCD.[46,47] Leg ulceration is a rare complication, found in patients receiving high-dose, long-term hydroxyurea therapy.[47] Approximately 9% of patients on hydroxyurea therapy develop skin ulcers.[48] The hydroxyurea-associated ulcers are commonly seen in older adults, patients on long-term treatment, and patients

with myelodysplastic disorders.[46,47] The presence of hydroxyurea-associated ulcers in patients with sickle cell ulcers is uncommon.[46,47]

The pathogenesis of ulceration remains unclear and could be multifactorial.[46,48] In myeloproliferative disorders, an increase in platelets can lead to local inflammation by producing platelet-derived inflammatory mediators and activating interleukins 1 and 8 and granulocyte macrophage colony-stimulating factor, causing tissue damage.[47,49] Hydroxyurea acts by inhibiting DNA synthesis and promoting cell death via inhibition of ribonucleotide reductase.[50] Therefore, hydroxyurea itself can cause ulceration as it targets cell death in basal keratinocytes and inhibits collagen synthesis.[47] Inhibition of DNA synthesis can cause a buildup of toxicity in the basal layer of the epidermis,[46] causing slow keratinocyte turnover, thinning of the epidermis, and basal layer damage.[49,51]

CLINICAL FEATURES

The Table lists the main clinical features associated with atypical wounds. The similar clinical picture of ulcers from microthrombi makes the etiologic diagnosis very challenging.

LESS COMMON ULCERS ATTRIBUTABLE TO VASCULAR OCCLUSION
Cholesterol Emboli

Cholesterol embolism occurs when cholesterol is released from atherosclerotic plaques in large blood vessels, commonly from dislodgement with cardiac interventions. The embolus can then lead to occlusion of medium and small vessels, resulting in extracutaneous and cutaneous manifestations.[57] Endovascular surgical procedures and anticoagulant therapy have also been reported as triggers for cholesterol embolism.[57] This diagnosis is often missed; providers should consider it when a patient presents with limb pain, livedo reticularis, and palpable peripheral pulses.[57] Risk factors for cholesterol emboli include hypertension, age older than 60 years, diabetes, cerebrovascular disease, smoking, obesity, and lack of physical activity.[57]

The pathogenesis of leg ulceration after cholesterol emboli involves plaque rupture and thrombus formation.[58] This rupture leads to the release of cholesterol crystals, which occlude smaller arterioles downstream.[57] An acute inflammatory response ensues, followed by microvascular ischemia and eventual gangrene.

Cutaneous changes are typically seen first in cholesterol embolism. Livedo reticularis is the most common skin finding, but gangrene, nodules, ulceration, blue toe syndrome, purpura, and petechiae are also common.[59] Ulceration occurs in 17% to 39% of patients.[60] These ulcers are classically located on the feet and are unilateral. In some cases, they may present atypically; that is, refractory to treatment and recurrent.

Providers should biopsy the skin of patients suspected of having cholesterol emboli. Tender nodules or areas of livedo reticularis are ideal sites and typically show biconvex needlelike cleft in blood vessels.[61] Laboratory findings are nonspecific. Eosinophilia, eosinophiluria, leukocytosis, and elevated blood-urea-nitrogen/erythrocyte sedimentation rate are often observed.

There are no established guidelines for cholesterol embolism management. One published case states that the use of anticoagulant therapy appeared to be safe and feasible in a patient with cholesterol embolism and a coexisting indication for anticoagulation.[62] Treatment should be supportive.[63]

Drug-Induced Vasculitis

The mechanism by which drug-induced vasculitis occurs with cocaine and methamphetamines includes vasospasm, vascular inflammation, and vascular injury. Cocaine commonly is tainted with levamisole (a bulking agent), which can cause lesions on the extremities, ears, and face. Levamisole causes either leukocytoclastic or thrombotic pseudovasculitis.[64,65] It occurs more often in females and presents with a reticular pattern with or without necrosis.[64–69] The discontinuation of cocaine resolves symptoms, although steroids have shown variable response. Steroids, however, increase the risk of infection and should be reserved for severe cases.[65]

Methamphetamine-induced vasculitis management includes withdrawal of the drug, as well as immune suppression with high-dose glucocorticoids followed by steroid-sparing agents (cyclophosphamide, azathioprine, or methotrexate).[69,70] Further, severe arteritis has been seen in cases of long-standing cannabis consumption, with claudication, acral pain, Raynaud syndrome, distal necrosis, and venous thrombosis.[71]

Calciphylaxis

Calciphylaxis, also known as calcific uremic arteriolopathy, and Martorell hypertensive ischemic leg ulcer (HYTILU) are two other important differential diagnoses for microthrombotic ulcers. Both ulcers are attributable to blood vessel wall calcification.

Calciphylaxis is an extremely rare but detrimental systemic disease that commonly occurs in the later stages of chronic kidney disease and in patients on dialysis.[72] Clinically, this disease can manifest early on as livedo reticularis.[73] Later in the disease course, it is most commonly characterized by violaceous, painful, plaque-like subcutaneous nodules or lesions. If these nodules are untreated, and if vascular thrombosis is advanced, then they typically progress to a necrotic ulcer with thick eschar surrounded by indurated, tender, retiform plaques.[74] These ulcers are commonly distributed onto areas of increased adiposity.

Table. CLINICAL FEATURES OF COMMON ATYPICAL WOUNDS

Atypical Wound	Location	Clinical Features	Diagnostic Factors
Cryglobulinemic ulcer	Lower extremities, typically above the malleoli	Livedo reticularis, livedo racemosa, palpable purpura, ischemic necrosis, and vasculitic lesions[8,52] Well demarcated, painful, bilateral, numerous, and surrounded by purpura[52] Abdominal pain, hepatomegaly, glomerulonephritis, nephropathy, arthralgia, myalgia, peripheral neuropathy, and/or neurological symptoms	Skin biopsy Laboratory interpretation that detects serum cryoglobulin often needs to be repeated A positive rheumatoid factor (but negative anticyclic citrullinated peptide) and a low complement C4 fraction (but normal or slightly low C3) are suggestive of cryoglobulins Serum protein electrophoresis, antinuclear antibody, extractible nuclear antigen, and hepatitis C virus serology must be done systematically
Cryofibrinogenemia ulcers	Lower extremities, typically above the malleoli. They can occur anywhere, particularly in areas with cooler temperature such as acral skin and ears	Cutaneous ulcers similar to cryoglobulinemia Cold intolerance Myriad skin symptoms including purpura, acral ulceration, gangrene, and systemic findings	Skin biopsy Elevated circulating cryofibrinogen in the plasma The presence of vasculitis in histology should raise suspicion of an associated cryoglobulinemia
Antiphospholipid antibody syndrome (APLS)	Above the malleoli; presentation on the arms, flanks, and breasts has been reported[15,53]	The most common presentation is with livedo racemosa/livedo reticularis Ischemic leg ulceration and necrosis can also occur[53] Other cutaneous findings include purpura, ecchymosis, subcutaneous nodules, splinter hemorrhages, fixed digital cyanosis, Raynaud syndrome, acrocyanosis, superficial thrombophlebitis, digital gangrene lesions, Degos disease, anetoderma, superficial skin bullae, and polychondritis[14,53]	Vascular thrombosis[53] and pregnancy morbidity Laboratory criteria include immunoglobulin G (IgG) or IgM anticardiolipin antibodies, lupus anticoagulant, prolonged phospholipid-dependent coagulation, failure to correct prolonged coagulation time, shortening or correction of prolonged coagulation time through the addition of excess phospholipid, and/or IgG/IgM anti-β2 glycoprotein I[53] Testing should be repeated after at least 12 wk to confirm
Livedoid vasculopathy	Often occurs bilaterally on the lower extremities	Ulcers vary from a small point (4–6 mm) to larger, irregularly shaped ulcers[26,27] Characterized by livedo reticularis, small painful ulcers, and atrophie blanche[24,27] Initially presents with papules, purpura, or petechiae with surrounding telangiectasia; over time, superficial painful ulcers These ulcers usually heal with atrophie blanche on the ankles and dorsal foot[25,54] Commonly smaller than the ulcers caused by APLS or warfarin-induced skin necrosis	Clinical diagnosis Punch biopsy or fusiform incisional biopsies that includes subcutaneous fat should be performed Histologic findings: intraluminal thrombosis, endothelial proliferation, and subintimal hyaline degeneration[55]
Warfarin-induced skin necrosis and heparin-induced ulcers	Over subcutaneous adipose tissue including the thighs, abdomen, buttocks, legs, and breast tissue	Manifests clinically with paresthesia and edema, followed by petechiae and erythematous ecchymosis, and a progression to well-demarcated hemorrhagic bullae	Histopathologic findings are nonspecific Patients who have recently used warfarin Look for low proteins C and S levels
Sickle cell ulcers	The lateral and medial malleoli and over Achilles tendon	Appear round and punched-out, with raised margins and occasional surrounding brown hyperpigmentation and scaling[43,56] Cutaneous hemosiderosis, dermatosclerosis, and visual presence of superficial veins[44]	Peripheral blood smear to visualize sickled red blood cells Complete blood count to identify anemia and white blood cell levels Liver and renal function blood tests Hemoglobin electrophoresis[43]

(continues)

Table. CLINICAL FEATURES OF COMMON ATYPICAL WOUNDS, Continued

Atypical Wound	Location	Clinical Features	Diagnostic Factors
Hydroxyurea-associated ulcers	Lateral malleoli or circumferential ulcers[46] Lower leg, over Achilles, dorsal foot, toes, forearms, hands, and face[46,47,51]	Commonly multiple, shallow, and bilateral[51] Erythematous, shallow ulcers with yellowish necrotic base surrounded by atrophie blanche[50]	History of drug use Histopathologic findings will display no specific changes

Martorell HYTILU is also characterized by localized subcutaneous arteriolosclerosis that leads to rapidly progressive and extremely painful necrosis. Patients with HYTILU characteristically have hypertension; half also have diabetes mellitus. It is one of the most painful ulcers of lower extremities and is classically located at the posterior lateral aspect of the lower leg and the Achilles tendon region. The clinical presentation and history are highly characteristic, with a bilateral distribution and often unpredictable recurrences and evolution. Livedo reticularis, pigmentation, and "shin spots" often precede the ulceration.

TREATMENT

To ensure adequate wound healing, providers must ensure the basic principles of wound management are performed. The principles of local wound care are applied to all ulcers associated with microthrombi, including devitalized tissue debridement, infection and inflammation control, and proper dressings for moisture balance.

Further, there are many modifiable risk factors associated with impaired wound healing. Smoking tobacco and the use sympathomimetic drugs are detrimental to proper wound healing. Patients should discontinue the use of these substances to promote adequate blood perfusion to the wound site.

Cryoglobulinemia

Treatment options should be assigned according to the underlying cause of the ulcers. The treatment of hepatitis C virus-associated cryoglobulinemic vasculitis mainly relies on direct antiviral agents, such as sofosbuvir, ledipasvir, and/or daclatasvir, which are very effective (but expensive). The initial addition of glucocorticoids is often needed to rapidly improve some manifestations, but should be time-limited. Many treatment options exist for patients with essential cryoglobulinemia, including immunosuppressive medications such as high-dose glucocorticoids and cyclophosphamide or rituximab. Targeted biologic therapies, such as rituximab, have shown long-term efficacy for mixed cryoglobulinemia. In some cases of hepatitis C virus-associated cryoglobulinemic vasculitis,[75–77] symptomatic hyperviscosity or life-threatening disease can be treated with plasma exchange. Finally, education on cold exposure and foot care is important.

Cryofibrinogenemia

In these ulcers, inaugural treatment limits cold exposure and maintains an environmental temperature of at least 37° C. The anabolic steroids stanozolol and danazol are safe and efficacious.[78,79] Fibrinolytic medication (streptokinase and plasminogen activator inhibitor 1) is an effective and safe treatment protocol. Glucocorticoids in conjunction with low-dose acetylsalicylic acid, aggressive immunosuppressive treatment, plasmapheresis, and fibrinolysis should be used for more severe variants.[80]

Antiphospholipid Antibody Syndrome

Experiencing one thrombotic event is an indication for lifelong anticoagulation therapy.[18] Other treatment choices include glucocorticoids, plasmapheresis, IV immunoglobulin, and cyclophosphamide. More novel therapies for APLS include rituximab, which may be helpful in the treatment of skin ulcers.[81]

Livedoid Vasculopathy

Typically, anticoagulants and fibrinolytic agents are first-line therapies[82] Rivaroxaban, a direct factor Xa inhibitor, can prevent thrombus formation and reduce pain.[83] Immunosuppressive agents, IV immunoglobulin, low-dose danazol,[79] and hyperbaric oxygen therapy[84] have been used in pilot studies.[23,27]

Warfarin-Induced Skin Necrosis

Typical management includes discontinuation of warfarin treatment. If anticoagulation is necessary, IV heparin or an alternative should be administered, followed by low-molecular-weight heparin until the necrosis shows signs of improvement. Further, vitamin K, protein C concentrate, and/or fresh frozen plasma should be administered to facilitate healing. New treatments discussed in case reports include novel oral anticoagulants such as dabigatran.[85,86] Negative-pressure wound therapy can promote wound healing and closure when used as an adjuvant therapy.[87]

Sickle Cell Ulcers

These ulcers are difficult; they recur and are slow to heal, sometimes taking months to years.[38,43,41] Management includes blood transfusion, exsanguino-transfusions,

oxygenotherapy, arginine butyrate, and hydroxyurea. A recent study by Meneses et al[88] demonstrated stem cell therapy with bone marrow mononuclear cells as a safe and efficacious therapeutic option in healing sickle cell ulcers.[88]

Hydroxyurea-Induced Ulcers

These ulcers often do not respond to typical local and systemic therapies. Instead, they resolve with withdrawal of hydroxyurea treatment,[47] although complications can also occur years after withdrawal.[48] Management includes stopping the drug, decreasing the dose, or prescribing alternatives such as ruxolitinib.[89]

CONCLUSIONS

Microthrombotic disorders are rare but debilitating disorders presenting with cutaneous ulceration. These atypical ulcers commonly present as painful and inflammatory skin wounds linked to underlying disease. Patient history, concomitant diagnosis, wound characteristics, and histology and laboratory findings can help with diagnosis.

Dermatology providers should be reluctant to prematurely label every painful and inflammatory ulcer. Many patients are misdiagnosed and may be exposed to unnecessary high-dose immunosuppression. This review highlights the features of atypical wounds to facilitate diagnosis and management.

PRACTICE PEARLS

• Typical wounds such as diabetic foot ulcers, venous ulcers, pressure ulcers, and arterial leg ulcers comprise more than 70% of chronic wounds.
• Chronic wounds associated with microthrombi formation are a salient group of atypical wounds that are associated with a common underlying systemic disease.
• These rare cutaneous ulcers are typically very painful, and misdiagnosis may expose patients to unnecessary high-dose immunosuppressive agents.
• Diagnosis of these atypical wounds can be facilitated by a thorough patient history, concomitant diagnosis, histology, wound characteristics, and laboratory findings. ●

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