AJH

How we treat sickle cell patients with leg ulcers

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Case 1. A 49 year old African American woman with sickle cell anemia, bilateral hip replacements for avascular necrosis of the femoral head, pulmonary arterial hypertension documented by pulmonary artery catheterization, and history of laser treatment and vitrectomy for proliferative retinopathy and vitreous hemorrhage, presented with a very painful ulcer at the right malleolus. She has had three previous ulcers, on both legs, the first at age 32 years, attributed to excessive standing at her job, no trauma, which had responded to topical care and healed within few months of presentation. At that time she was not taking hydroxyurea, but has been taking it now for longer than 10 years with good fetal hemoglobin response: 17%. This current ulcer developed while she was experiencing high personal stress but no physical trauma. She rarely experiences vaso-occlusive pain crisis and has very infrequent hospitalizations. She was referred to the wound care service and after 7 months of unfruitful therapies, including surgical debridement, MIST ultrasound therapy, antibiotics, and compressions, she was started on monthly transfusions and her ulcer healed 5 months later. She has had consistently elevated serum lactate dehydrogenase (LDH) (>600 IU/L), serum direct bilirubin 0.8–2.1 mg/dL and low hemoglobin, ~7 g/dL, despite adequate hydroxyurea therapy (25 mg/kg)and subcutaneous erythropoietin. Her tricuspid regurgitant velocity (TRV) is between 2.7 and 3.5 m/sec, her 6-minute walk distance has been declining from 445 to 387 meters. She has developed renal dysfunction, worsening pulmonary disease, and chronic thromboembolic disease, for which she has been prescribed warfarin. When she had the first ulcer, she suffered from clinical depression requiring counseling and antidepressant medications, but since her ulcer healed, about 4 years ago, she is off all antidepressants and now newly married. She remains on hydroxyurea and erythropoietin and her fetal hemoglobin is 15%. *Case 2*. 27 year old African male with sickle cell anemia, history of stroke at age 13 while in Ghana, with bilateral narrowing middle cerebral artery and moya-moya, with residual left distal arm and hand weakness with contractures, recurrent leg ulcers since age 18, systemic hypertension, and proteinuria. He was transfused at the time of the stroke, but not placed on chronic transfusions and when he reached the US he started hydroxyurea, 20-25 mg/kg daily at age 21 with initial good response (HbF 17%), now decreased to 4%, low Hb (6 g/dL), TRV between 2.7 and 2.5 m/sec. He reports infrequent pain crisis, and rarely takes medication for generalized pain. He reports frequent episodes of stuttering priapism. BMI is 18.4, last transfusion at age 14 while hospitalized in Africa with malaria and pneumonia. Initial ulcer sizes when 2006 were: 24 cm^2 and 15 cm^2. He complained of pain at ulcer site and periwound, had pitting edema to dorsal aspect of foot. He received coordinated care from the hematology, cardiology and nephrology team, as well as prompt wound care from the wound care nurses. Measures included starting hydroxyurea, treatment of hypertension, and proteinuria, and Unna boot and compression to facilitate wound healing and decrease edema in right lower leg. The ulcer closed within a year, only to reopen periodically, in the same or nearby location, but never becoming as large as the first time. The patient was instructed how to choose more adaptive foot wear, especially to avoid high top sneakers without socks and how to protect the area of the ankles. He is able to predict ulcer recurrence because of characteristic pain in the area one week earlier, and he arranges to see the wound care team promptly. Ulcers usually resolve in few weeks to months. He has a steady job and no depressive symptoms, and leads an active life. *Case 3*. A 40 year old African American woman with sickle cell anemia has been receiving wound care twice a week for many years for bilateral ulcers on her lower extremities. She has had chronic leg ulcers since age 14. She is thin and tall (BMI of 16.9), has very infrequent vaso-occlusive crisis, and no pain except for severe ulcer pain, which requires daily methadone and oxycodone. She has tried more than 10 conventional and unconventional therapies, which range from compression bandages to maggot therapy, acupuncture and nutritional

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supplements. She received wound debridement by medical maggot therapy twice, administered during hospitalization with patient controlled analgesia to treat the accompanying excruciating pain. She has chronic desaturation on pulse oximetry, but an extensive pulmonary evaluation is negative for asthma, pulmonary thromboembolism or pulmonary hypertension. She has refused red blood cell transfusions, despite very low steady state hemoglobin (5 gm/dL), very high serum LDH (between 616 and 1112 IU/L), high direct bilirubin (0.5–0.6 mg/dL), high uric acid (5–7.1 mg/dL), and declining renal function. She had an initial response to hydroxyurea, with increase in total Hb to the 7 g/dL range and fetal hemoglobin to 10–15%, but after a year, these effects did not persist, and hydroxyurea was stopped in the hope of facilitating wound healing, without the expected benefit. She had become unemployed because her wounds deteriorate every time she had to sit or stand for long periods of time or travel. She has avoided vacations and has not disclosed her condition to friends and family, in fear of stigma and shunning. Eventually her ulcers spread extensively across both lower extremities and on the digits, with significantly increase in pain, disability requiring a cane to walk, and suspected osteomyelitis. The patient was depressed and frustrated and requested bilateral amputation. After few meetings, reassurance, change in her social and physical environment, supplemental oxygen for nocturnal hypoxia, compression bandages, and improved diet, the ulcers healed and she was ulcer-free for more than one year. She was weaned off all opioids and went back at work. Unfortunately, she recently suffered from an episode of multi-organ failure, treated with prompt exchange transfusions, hemodialysis and ventilator support. Her serum creatinine has stabilized between 2 and 3 mg/dL one year later and the ulcers have recurred.
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Introduction

Until the 1960, sickle cell disease (SCD) was mainly a pediatric disease, with death at a median age of 10 years. In the 21st century the majority of patients reach adulthood [1–4] As patients become older, the challenge of end organ damage has risen and among those, chronic ulcers represent a particularly debilitating and poorly understood complication. Their incidence has remained steady despite successful preventative strategies against bacterial infection and stroke [5], and improved supportive care. Although the first patient with SCD described in the English medical literature more than 100 years ago suffered from leg ulceration [6], there continues today to be a frustrating lack of clearly effective treatment options. We summarize our approach to patients with SCD and ulcers, with recommendations based on our experience in the clinic as well as a critical review of the literature. Unfortunately, as a rare complication of a rare disease, there are few therapeutic trials of any kind and even fewer randomized controlled studies to provide clear evidence to guide practice in the clinic [7,8].

Epidemiology

The true incidence of leg ulcer in patients with SCD is unknown, as there is no registry specifically for this complication, and the only large prospective data set comes from the Cooperative Study of Sickle Cell Disease [9], now more than 20 years old. Moreover, interpretation of available studies is complicated by lack of clear separation between prior history of leg ulcers and active ulcer. A recent survey of North American hematologists specializing in SCD, estimated that 1% SCD patients have active ulcers [10], while in the Bethesda Cohort of more than 500 SCD patients, 22% of HbSS and 9% of HbSC patients reported "history of ulcer" [5]. Regardless, leg ulcers occur ten times more frequently in SCD than the general population and begin at a younger age [11]. There is a wide geographic variation, with an involvement of about 70% of patients with HBSS by the 30th year of life previously reported in Jamaica [12], and recent estimates decreased to a prevalence of 29.5%, and an incidence of 16.5% [13]. A report from Nigeria estimated a 27% prevalence [14], Brazil 43% [15], Sierra-Leone 13.2%, Ghana 10.6% [16], while in Saudi Arabia almost non-existent [17].

SCD patients are not the only patients with congenital hemolytic anemia to develop skin ulcerations, and they have been reported in thalassemia intermedia [18], hereditary spherocytosis [19], pyruvate kinase deficiency [20], and congenital dyserythropoietic anemia [21]. Ulcer prevalence in other types of congenital hemolytic anemias is not known, but their occurrence suggests that sickling is not a *conditio sine qua non* for ulcer formation, while chronic anemia and hemolysis appear to be common factors.

Sickle cell patients with leg ulcers constitute a relatively distinct sub-phenotype, characterized by less frequent hospitalizations for vaso-occlusive pain crisis [22,23], while they are prone to develop pulmonary hypertension [5,24–28], suggesting that the two complications share a common pathophysiology. In a cohort of 20 SCD patients with leg ulcer who underwent right hearth catheterization for suspected pulmonary hypertension, 15 had confirmation of PAH (personal data, this cohort has been described in Mehari et al. (2013) [24]. Both complications increase in prevalence with advancing age, and are associated with the most severe degree of hemolytic anemia among HbSS patients, characterized by the lowest hemoglobin levels and the highest serum levels of lactate dehydrogenase (LDH), a known biomarker of intravascular hemolysis, a process associated with impaired nitric oxide bioavailability [13,29–31].

Pathophysiology

The pathobiology of ulcer formation in SCD is not completely understood. It is most likely multifactorial and includes local factors as well as systemic dysfunction, such as vasculopathy and chronic inflammation. Skin ulcers in the general population rarely occur in individuals that are otherwise healthy, and it is plausible that SCD itself is strong risk factor for skin ulceration. As such, SCD ulcers may not be fundamentally different from other chronic ulcers, but a mix of venous and arterial ulceration components [11].

The association of SCD leg ulcers with biomarkers of vascular dysfunction and pulmonary hypertension has been a recurrent theme [30,32,33]. Both conditions are associated with elevated plasma level of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide (NO) synthase [34,35]. Genomics analyses have shown an association in both conditions with genetic polymorphisms in the BMP6, TGFBR3 and Klotho genes, important in vascular biology, including regulation of NO production [29,36]. There has been evidence of severely impaired red cell deformability, increased density and altered rheology [22,33,37]. SCD leg ulcers have been linked to venous incompetence and vasomotor alterations [13,38,39]. Alpha thalassemia trait has been protective [9,29], although this is not always consistent [13,23,40]. Elevated levels of fetal hemoglobin are generally

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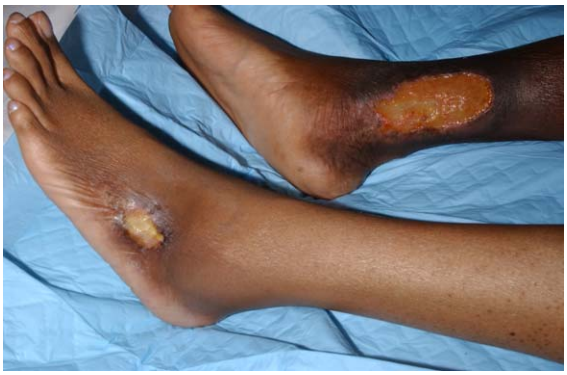

Figure 1. Example of bilateral, synchronous ulcers in a patient with SCD. Notice the thin extremities, the darkening of the skin around the ulcer, the lack of hair and the dryness of the skin. Ulcer's borders are raised and one of ulcers is on the foot instead of the ankle. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

protective [9,29,41], although this has not been true in all studies [33,42]. SCD ulcer patients have higher levels of soluble ICAM-1 and the key inflammatory cytokine IL-1beta [43]. We have found that the active ulcer and peri-ulcer area have higher blood flow than distant, non-ulcerated areas of the leg, are characterized histopathologically by venostasis, inflammation, and vasculopathy, with activated endothelium and evidence of thrombosis/recanalization (Figs. 3 and 4) [44]. Hypoxia is well known to induce angiogenesis, therefore it is conceivable that chronic hypoxia in ulcerated skin leads to increase in capillary proliferation and recruitment, with higher measured blood flow. Biopsies obtained in patients with SCD and leg ulcers demonstrated an increased number of capillaries (Fig. 3, panel C), but whether this leads to an effective increase in perfusion and oxygen delivery needs to be determined by further analysis. A possible role for *in situ* thrombosis is supported by plasma markers of thrombophilia [44–46] and 44% prevalence of venous thromboembolism in SCD ulcer patients [44], and by results of a pilot study of antithrombin use in treatment of SCD leg ulcer [47]. Oxidative stress plays an important pathogenic role in the development of SCD related complications, and patients with glutathione S-transferase polymorphism (GSTM1 and GSTT1 null phenotype) have recently been shown to have a high risk of developing ulcers [48]. These clues suggest that successful future therapeutic strategies might involve amelioration of vasculopathy, thrombophilia, and/or oxidative stress.

Pain at the wound site is one of the most striking differences between "other wounds" and SCD wounds, and neurogenic inflammation perpetuates tissue damage in animal models. Topical opioids have been suggested to not only relieve pain, but also facilitate wound healing [49], and most recently Gupta's group demonstrated in a sickle cell mouse model of wounds that peripheral nociceptor stimuli stimulate substance P secretion and increase inflammation and local fluid extravasation while topical morphine blunts this response, favoring angiogenesis and healing [50,51]. In individuals with ulcers without SCD, there is evidence that autonomic and sensorial dysfunction are involved in chronic ulceration [52,53]. Similarly, it is conceivable that peripheral neuropathy (probably itself secondary to vasculopathy) plays a role in the development of chronic ulcers in patients with SCD, as illustrated in Fig. 2.

We propose a stepwise, multifactorial model for SCD ulcer formation. Underlying vasculopathy, poor nutrition, thrombophilia, hyperinflammatory response, poor socioeconomic status, and other not yet defined risk factors damage blood vessels and impair perfusion in the distal lower extremities. Skin injury in this setting promotes an ulcer that heals slowly. This formulation is supported by data from our group and others concerning epidemiological association with low

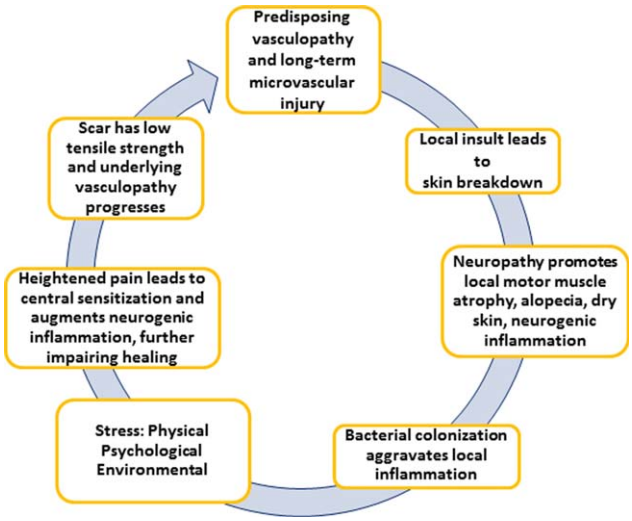

Figure 2. Proposed and simplified mechanism of ulcer formation in patients with SCD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

BMI, inflammation, thrombosis, hemolysis and vasculopathy [5,30,38,43,44,46,54,55]. Ensuing pain leads to central sensitization and neurogenic inflammation, with further impairment healing. Finally, the resulting scar has a low tensile strength with poor perfusion due to underlying cutaneous vasculopathy, and is prone to re-opening. Low subcutaneous tissue, local thrombosis, altered microcirculation and chronic inflammation favor the continuation of this cycle.

Presentation and Patterns

Medical history

We refer the reader to a comprehensive review on this topic by Graham Sergeant [12]. The first ulcer often occurs in the second decade of life. About 40–50% of patients recall prior trauma [44,56], often seemingly insignificant, and/or pruritus that provoke scratching and skin breakage. Half of patients will have two or more ulcers at the same time. Lesions are mostly localized in the peri-malleolar area, less frequently in the distal third of the lower extremity, and more rarely on the foot or the digits. Ulcers are often very painful, and patients frequently report a crescendo of localized pain just before new ulcers open. The size of the ulcer has no relationship to the intensity of the pain and very small ulcerations can be extremely painful. Most patients take chronic opioids for ulcer pain and often this is their only indication for opioids [44]. Exposure to air often intensifies the pain. Past medical history should include a careful documentation of previously attempted ulcer therapies, and special attention paid to complications that are reportedly more common in leg ulcer patients: pulmonary hypertension, stroke, priapism, acute chest syndrome [28,29], lower extremity venous thrombosis, and retinopathy (personal observation of a 22% incidence of retinopathy).

Physical examination should include careful assessment of wound size, with digital photography in addition to ruler measurement, which can overestimate wound sizes and is not suitable to irregularly shaped lesions [57]. Edema is often present in the affected extremity. Surrounding skin is often hypo- or hyper-pigmented from previous ulcers and blood extravasation, hair follicles are sparse and muscles atrophic (Fig. 1). Serous discharge and thickened fibrinous material is common, but periwound erythema, purulent discharge and increase in pain and size can indicate acute infection. Inguinal nodes are often enlarged, especially during ulcer exacerbations. Pulse oximetry often is low, as is systemic blood pressure [58].

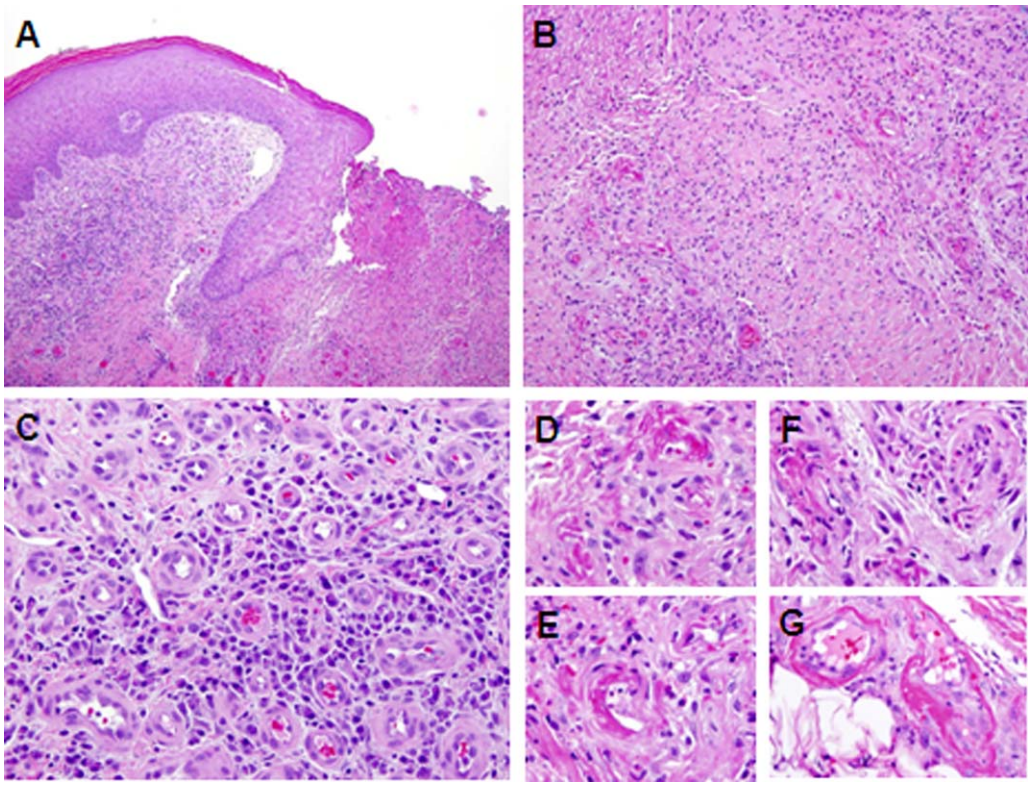

Figure 3. Microscopic analysis of skin biopsies. Evidence of increase in vascularity, chronic inflammation, vasculopathy with blood vessels occlusion, fibrin deposition in the intima, and microthrombi. (A) Scanning magnification view of the skin punch biopsy showing edge of an ulcer from the right ankle. The epidermal changes adjacent to the ulcer are characterized by acanthosis, hyperkeratosis, and attenuated rete ridges. There is increased vascularity and inflammation in the dermis (H&E, 100x original magnification). (B) The histological changes subjacent to the ulcer bed are characterized by chronically inflamed granulation tissue with vasculopathic changes involving some of the small blood vessels (H&E, 200× original magnification). (C) High magnification view of the superficial dermal vessels peripheral to the ulcer. Blue arrows show the proliferation of thick-walled capillaries and venules. There is a lymphoplasmacytic inflammatory infiltrate in the dermis (H&E, 400x original magnification). (D–G) Very high magnification view of involved vessels subjacent to the ulcer bed reveals eosinophilic fibrin deposits within the vessel wall and partial occlusion of the vascular lumen (H&E, 600x original magnification). (Reproduced from Ref. 44, with permission from John Wiley & Sons, Inc.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Laboratory testing and imaging

Because patients with leg ulcers tend to have few painful crises [22] they may not seek frequent medical attention and often have not received health maintenance screening tests. Occasionally this will be the first time a physician has evaluated them for end organ diseases. Complete blood count and chemistry panels will often reveal markers of particularly severe chronic hemolysis. Urinalysis often will show microalbuminuria. Serum C-reactive protein (CRP) and/or erythrocyte sedimentation rate are frequently elevated [44]. Patients with and without past history of venous thromboembolic disease may have low levels of antithrombin III, protein C or S, high level of factor VIII or positive lupus anticoagulant. Obtain echocardiography to evaluate TRV and 6MWT for exercise capacity. When interpreting 6MWT, be aware of shorter distances secondary to physical impairment and pain can be caused by the ulcer. Wound cultures usually reveal only superficial colonizing bacteria, and are rarely helpful. Imaging studies of bones commonly show demineralization, and bone infarcts. MRI should be obtained when osteomyelitis is suspected, but ultimate diagnosis will be made by bone biopsy. Osteomyelitis in the underlying bone is a rare occurrence, but, if not diagnosed and treated appropriately will prevent healing.

■ Presentations, Patterns, and Outcomes

The medical literature and personal experience lead us to formulate the following proposed patterns:

The "one time" ulcer

About half of the patients with SCD and leg ulcer will develop only one ulcer in their life time. The ulcer is usually experienced in the second decade of life that heals within several months with most types of wound care. About 20% of the 505 patients screened at NIH recalled having had an ulcer [5]. Occasionally these recur in periods of intense stress and heal promptly. These are representative of the majority of SCD ulcers, and physicians may not be aware that their patients have suffered from ulcers unless they ask directly or look carefully at their ankles. The patient described in the first case vignette has some of the features of the "one time ulcer," she also has the pulmonary and renal complications that typically occur in these patients, and the low frequency of pain crisis. These patients are often mistakenly considered as not having severe disease because the low frequency of pain crisis.

The stuttering ulcer

Approximately one-quarter of ulcer patients experience small, recurrent ulcers that recur every 6–12 months for many years. Early institution of local wound care measures may help to limit the size or duration of these ulcers. These individuals often live in constant fear of ulcer recurrence, but are not severely debilitated from them. The patient in the second case vignette exemplifies such a presentation.

The chronic, recurrent, disabling ulcer

Less than a quarter of SCD ulcer patients, or about 1% of US SCD patients develop an ulcer that persists for years or even decades, and/or ulcers that recur in the same or nearby sites. They account for about

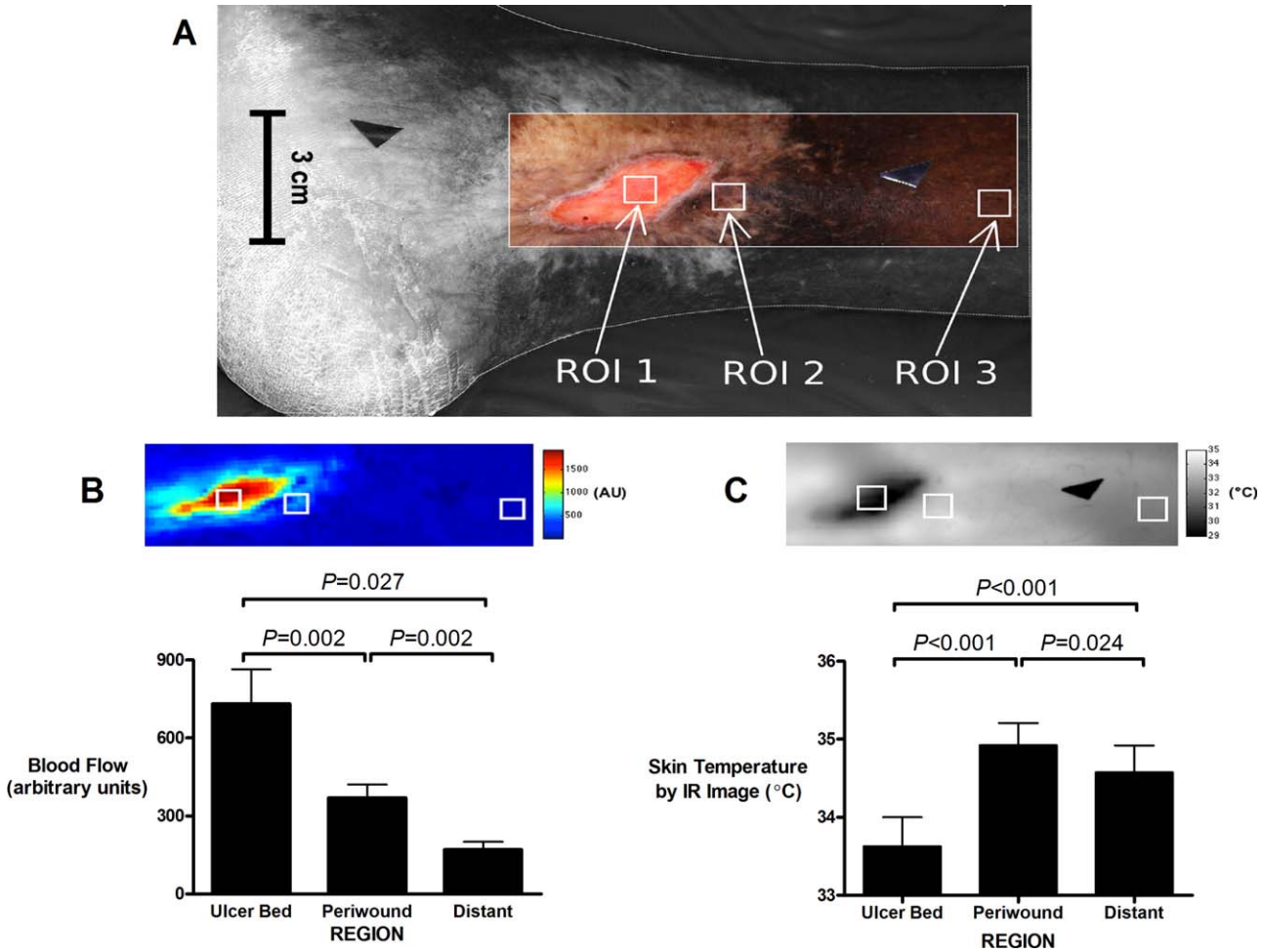

Figure 4. Microvasculature analysis of ulcer area and surrounding tissue compared to a distant, unaffected skin area. (A) Visible light photograph of the imaged ulcer area for a representative subject. Selected regions of interest are indicated with white squares. Region of interest (ROI) 1 is the ulcer center, ROI 2 is the periwound area, directly adjacent to the ulcer, and ROI 3 is an area >5 cm from ulcer. (B) Laser speckle contrast image of a representative patient and a graph that represents the average regional blood flows among 11 subjects. There is significantly different blood flow among the three regions of interest, with the highest mean blood flow in the ulcer center (ROI 1) and lowest distant from the ulcer (ROI 3) ($n = 18$, $P < 0.01$; paired Wilcoxon test; $P < 0.01$. (C) Infrared image of the same representative patient. Temperatures as measured by infrared thermography in the ulcer bed (ROI 1), the periwound area (ROI 2) and a distant skin region (ROI 3). Temperature is highest in the periwound area compared to the ulcer bed due to evaporative cooling ($P < 0.01$) and when compared to a distant area ($P = 0.01$). Bar graph indicates mean values, and error bars indicate standard error of the mean, paired Wilcoxon tests. (Reproduced from Ref. 44, with permission from John Wiley & Sons, Inc.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

0.5–1% of all SCD patients and are the patients that suffer the most devastating disabilities, chronic pain, unemployment and depression. Rare patients with the most severe and persistent cases may be considered for amputation which may result in improvement in quality of life [59]. Better risk predictors are needed to assist in this difficult recommendation. Although 75–80% of patients will achieve healing, in some patients, ulcers persist for over 20 years and may never heal. The patient described in the third case vignette exemplifies this pattern. These patients are often tall but asthenic, have poor appetite, are very anemic with evidence of high hemolytic rate, have nephropathy, are rarely hospitalized for vaso-occlusive crisis, have trouble with employment, have limited social interaction, are depressed; eventually they and their caregivers may feel that an amputation is better than "living with the current reminder" of their illness. As in our patient, a recent survey of practitioners in the US confirmed that none of them had recommended amputation to their patients [10].

Systemic and Local Therapies

In our experience, a multipronged approach of systemic and local therapy is usually necessary to achieve wound healing.

Systemic interventions are indicated for management of concurrent SCD complications (Table I), including vasodilators and diuretics for systemic hypertension, hydroxyurea for recurrent pain, ACE inhibitor or ARB for proteinuria or microalbuminuria, chelation therapy for iron overload, correction of vitamin D or zinc deficiency, nutritional management for underweight status, management of pulmonary hypertension, psychological support for stress and depression. One interesting case report noted leg ulcer healing during treatment of pulmonary arterial hypertension with an endothelin receptor antagonist [60], while others reported healing with erythropoietin use [61], or blood transfusions [62]. Systemic antibiotics need to be used only sparingly, as most wounds are colonized by skin flora, and may have a thick biofilm, which does not respond to systemic therapy. While hypothetically the local wound area is ischemic and anecdotally some kind of oxygen delivery to the wound has been attempted [63], we and others have seen no sustained benefit from hyperbaric chamber treatment [64], which is cumbersome, and potentially risky in SCD as there have been anecdotal reports of adverse events caused by this treatment modality [65].

Local measures involve conventional wound care and interventions. Lower extremity edema interferes with healing, and its presence

TABLE I. Wound Care Principles in Patients With Sickle Cell Disease and Ulcers

Systemic treatment	Local wound care
Vasodilators for systemic hypertension	Debridement
ACEI/ARB for proteinuria/microalbuminuria	Identify and treat infection
Hydroxyurea for recurrent pain, ACS, severe anemia	Absorb excess exudate
Chelation for iron overload	Maintain moist wound surface
Pulmonary vasodilator and/or diuretics for pulmonary hypertension	Open or excise closed wound edges
Correction of vitamin D or zinc deficiency	Protect healing wound from infection or trauma
Supplements for protein-calorie malnutrition	Relieve periwound edema by compression
Anticoagulation for newly diagnosed DVT	Comfortable footwear
Psychological support	
Pain control	

should prompt investigation for its etiology and correct management. Doppler ultrasonography should be performed, with appropriate anticoagulation if a new deep vein thrombosis is suspected. Approaches that diminish swelling include lower extremity elevation, avoidance of long periods of standing and compression bandages. Unna boots have fallen out of favor, and are often replaced by Coban compression. Comfortable footwear and range of motion exercises should be encouraged, because leg ulcer pain may be exacerbated by some forms of footwear, and may promote maladaptive gait and loss of joint mobility.

Hydroxyurea has been suspected to promote ulceration in patients with SCD [66–68] and other hematological disorders [69–71]. A recent study of 3,411 patients with Philadelphia chromosome negative myeloproliferative neoplasms treated with hydroxyurea reported 5% incidence of mucocutaneous complications, 80% of which were leg ulcers [72]. Many patients had other predisposing factors. Much anecdotal and some long-term experience in SCD patients raises skepticism of association of hydroxyurea with ulceration. Half of the subjects with SCD and leg ulcers enrolled in our phase 1 study were taking hydroxyurea, and there was no apparent difference in duration of ulcer, or response to treatment between them [44]. Moreover, there was no difference in ulcer prevalence (40%) between SCD patients that were taking or not taking hydroxyurea in a study of 505 patients at the NIH [5]. Several other authors are skeptical of a link between hydroxyurea and ulcers in SCD patients based on their own data [73–75], and many practical considerations preclude the randomized prospective trials needed for definitive evidence regarding this issue. There are many potential benefits of hydroxyurea use in SCD patients with ulcers: decrease in leukocyte count, decrease in inflammatory cytokines [76,77], increase in hemoglobin, increase in HbF, decrease in hemolysis, increase in oxygen carrying capacity, improved RBC rheology [78], and NO donor properties [79,80]. Our approach to the use of hydroxyurea in SCD is to aim for maximal fetal hemoglobin response, continue therapy unless there strong suspicion that hydroxyurea contributed to ulcer formation, and then consider switching to chronic transfusion therapy. We will measure the wound carefully before stopping hydroxyurea and if there is not at least 50% reduction in ulcer size within 6 months, we strongly consider resumption of hydroxyurea.

Transfusions. While there have been anecdotal reports of transfusions effectiveness in stimulating ulcer healing [62,81], no prospective data is available to support this recommendation, and ulcers are not an generally approved indication for chronic transfusions. We routinely use this modality, but consider it as an option on a case by case basis, as indicated in vignette 2. When we make a decision to institute chronic transfusion is made, we re-evaluate the situation after 6 months and consider whether continuation is warranted. We usually offer transfusional support for patients undergoing surgical interventions to attempt to promote ulcer healing, such as surgical debridement, skin grafts, or muscle flaps with a goal of attaining a hemoglobin level of 10 g/dL.

Nitric oxide (NO) based therapies

In the past two decades, NO has emerged as a critical molecule in the wound healing process. Nitric oxide is beneficial in the early and late phases of wound healing, as it increases extracellular matrix production, modulates immunologic response to wounding, stimulates keratinocyte's proliferation, angiogenesis, and has antiplatelet activity and bactericidal properties. NO regulates vascular homoeostasis, including vasodilation, and affects growth factors involved in endothelial homoeostasis [82,83].

We have recently conducted a phase I study in patients with sickle cell and chronic leg ulcers of topically applied sodium nitrite, a known NO donor [84] which showed promising preliminary efficacy data. Others have used NO nanoparticles platforms successfully in animal models [85].

If these early data are confirmed in larger randomized human trials, NO-based therapies could revolutionize ulcer therapy in these subjects.

■ Principles of Wound Healing and Wound Care for the Practicing Hematologist

Wound healing is a complex, dynamic process that can be simplified in three phases:

1. *Inflammatory phase*, which lasts normally 3–5 days, when tissue injury causes blood extravasation and the resulting clot provides extracellular matrix to facilitate cell migration, platelets secrete mediators of wound healing, such as platelet-derived growth factor, that attract and activate macrophages and fibroblasts. Inflammatory leukocytes are recruited [86]. During this phase, therapeutic focus is on debridement and infection control. Most chronic wounds, including SCD ulcers, are stuck in this phase. The longer the inflammatory phase goes on, the less collagen deposition there is and less tensile strength of the new skin [87].
2. *Proliferative phase*, where epithelialization is initiated, granulation tissue forms and contraction occur. This phase starts as early as the second day after injury and lasts 10–12 days. During this phase there is neovascularization and stroma formation.
3. *Maturation and remodeling phase* lasting up to 30 days, during which collagen degradation is controlled by proteolytic enzymes termed matrix metalloproteinases, secreted by macrophages, epidermal cells, and endothelial cells, as well as fibroblasts.

There are a few treatment principles that guide chronic wound therapy by the practicing sickle cell clinician (Table I): (1) Debride to remove dead tissue and biofilm; (2) open or excise closed wound edges to stimulate proliferation; (3) identify and treat infections; (4) absorb excess exudate to avoid maceration; (5) maintain moist wound

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surface ("a dry cell is a dead cell"); (6) protect healing wound from infection/trauma; and, most importantly, (7) use some type of compression to avoid venostasis.

Role of Consultants

In the care of SCD patient with ulcers, several different consultants can be helpful. The first is a referral to a wound care center that has expertise and experience in general with patients with chronic skin ulcers, better if they have expertise with sickle cell patients. They will teach the patient the basics of wound care. Patients will most likely experience work or school absences, and emotionally and socially stressful symptoms, and may benefit from therapeutic counseling and other social work assistance. Nutrition is an important and often forgotten aspect of the care of the patients with ulcers. Often these patients report low appetite, possibly because of the chronic inflammatory state and inadequate education concerning nutritional requirements; many patients have several nutritional deficiencies and low BMI. Their diet need to be carefully prescribed by experienced nutritionist, as studies outside of SCD have supported the importance of a positive nitrogen balance as essential to proper collagen formation and improved healing [52].

In the case of large, slowly healing wounds, a general surgeon or a plastic surgeon experienced in chronic wounds may offer surgical debridement removing chronic, fibrotic edges with low mitotic activity to stimulate healing. In our experience, skin biopsies and surgical interventions heal well and are not contraindicated. Surgeons may offer placement of skin grafts, either partial or full thickness, or even vascular pedicle skin grafts [88–90]. Grafts have a high rate of failure, and we consider preoperative and postoperative red cell transfusion in an attempt to facilitate engraftment, although this is of uncertain benefit. Even with the involvement of consultants, it is important for the primary hematologist to coordinate care, as appropriate and attentive general SCD management is of paramount importance. For most patients, the development of an ulcer is a watershed event, representing a biographical disruption with associated stigma, loss of control of the body, changes in pain pattern: now intense and daily [91,92].

Durability of Response and Prevention

Responders should be followed for recurrences, and all precautions should be used to protect the affected area, as the new skin has less tensile strength than the original skin and it is prone to re-opening. Stressful situations, increase in lower leg edema, local trauma, and other not yet known events, can cause a recrudescence of the ulcer. In an informal follow-up of 44 patients with chronic leg ulcers seen at NIH over the past two years, two patients have died of complications of SCD (one had healed), 24 had healed completely (54%), nine are lost to follow-up and nine still have active ulcers (20%)(Unpublished data, C. Minniti).

Conclusions

At this time, the approach to the patient with sickle cell, or other hematologic disorder, and leg ulcer is fragmented and inadequate, involves specialized wound care specialists only in about half of the cases in North America [10], often working in isolation from the primary care team and the hematologist. Access to care and quality of care varies widely within the US and abroad. Ulcer healing is most successful with a combination of systemic control of SCD and intensive local therapy with attention to psychosocial issues. The predictive value of a skin ulcer in a young patient with sickle cell has not fully been appreciated. These patients deserve careful long-term follow-up, as they are prone to developing other, life threatening vasculopathic complications, such pulmonary hypertension, renal and ocular disease. More clinical trials and longitudinal trials are needed to develop better therapeutic approaches.

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