Sickle Cell-Associated Leg Ulcers: A Case Presentation and Discussion

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Abstract

This case describes a 46-year-old female with a history of sickle-cell disease and a non-healing ulcer on her lateral malleolus. Etiology, clinical presentation, and management of sickle-cell ulcers are discussed.

Introduction

Sickle-cell leg ulcers are a frequent complication of sickle-cell disease. While the pathogenesis of these ulcers is not completely understood, many factors are believed to contribute, including trauma, mechanical obstruction, venous incompetence, bacterial infections, abnormal autonomic control, thrombosis, anemia with decreased oxygen carrying capacity, and decreased nitric oxide bioavailability. Although management is often difficult, it should always include three key objectives: treatment of current ulcers, managing complications, and prevention of future lesions.

Case Report

A 46-year-old black female with a history of sickle-cell anemia treated with hydroxyurea presented to the dermatology clinic complaining of a non-healing wound on her right ankle for 10 to 12 weeks. She complained of a moderate, dull, constant pain and recalled wearing an ill-fitting shoe that had rubbed the area prior to the development of the wound. The patient had previously seen her internist, an infectious-disease physician, and a wound-care specialist for this condition. Previous treatments, including anti-gout medications, a six-day oral-prednisone taper, topical lidocaine and collagenase ointment, failed to improve symptoms. She was otherwise healthy and had no history of tobacco use or previous non-healing skin lesions.

On physical exam, there was a 4 cm x 3 cm ulcer overlying the right lateral malleolus with white-yellow adherent discharge centrally, undermined borders, and 1 cm of surrounding erythema (Figures 1, 2). The site was tender to palpation. No edema was present, and dorsalis pedis pulses were 2+ bilaterally. A biopsy was taken to rule out an underlying squamous-cell carcinoma and vasculitis.

The pathology revealed vaso-occlusion of superficial dermal blood vessels with overlying epidermal necrosis (Figures 3, 4). A bacterial culture taken after the biopsy demonstrated Pseudomonas aeruginosa, which was treated with ciprofloxacin. The patient was prescribed a trolamine emulsion for local wound care and zinc-sulfate supplementation, and her pain was adequately managed with a lidocaine patch and oral gabapentin. She was referred to vascular surgery for evaluation of possible venous insufficiency. Doppler ultrasound and MRI were negative for venous insufficiency and osteomyelitis, respectively.

Considering the patient's history and negative supplementary tests, the differential diagnosis included sickle-cell ulcer versus hydroxyurea-induced ulcer. Due to concern for potentially severe vaso-occlusive crisis, discontinuation of hydroxyurea was not recommended by hematology. She was referred to wound care, who reported positive improvement in size, depth and pain with a combination of weekly surgical debridement and alternating topical collagenase gel and a triple antibiotic gel containing amikacin, levofloxacin, and vancomycin.

Discussion

Sickle-cell disease (SCD) is an autosomal-recessive inherited blood disorder characterized by bone-marrow production of red blood cells with defective, sickled hemoglobin (hemoglobin S). This occurs due to a point mutation in the DNA of the α-globin subunit of adenine for thymine.[1] The resulting translated protein contains a substitution of the amino acid valine for glutamic acid in the beta-hemoglobin chain.[2] When the defective hemoglobin becomes deoxygenated, polymerization occurs, leading to misshapen, sickled, rigid red blood cells. Leg ulcers are the most common cutaneous manifestation of SCD and are a long-recognized complication of SCD, dating back to the first documentation of a sickle-cell patient by Herrick in 1910.[3,4] Reported prevalence is 2.5% in the United States, 1.5% to 13.5% in Africa, and >40% in Jamaica, with homozygous SS and SS α-thalassemia patients having the overall highest prevalence rate of all genotypes.[3,5,6] Sickle-cell-associated leg ulcers (SCU) are often painful and disabling, with slow healing times and frequent recurrence. Limiting mobility, they often become a hindrance to education and employment. For these reasons, they have a profound effect on patients' quality of life and can lead to mood disturbances.[7]

The pathogenesis of these ulcers is not completely understood, but it is generally believed to be a multifactorial process. Proposed potential contributing factors include mechanical obstruction by dense, sickled red cells, venous incompetence, bacterial infections, abnormal


Figure 1


Figure 2

Figure 3

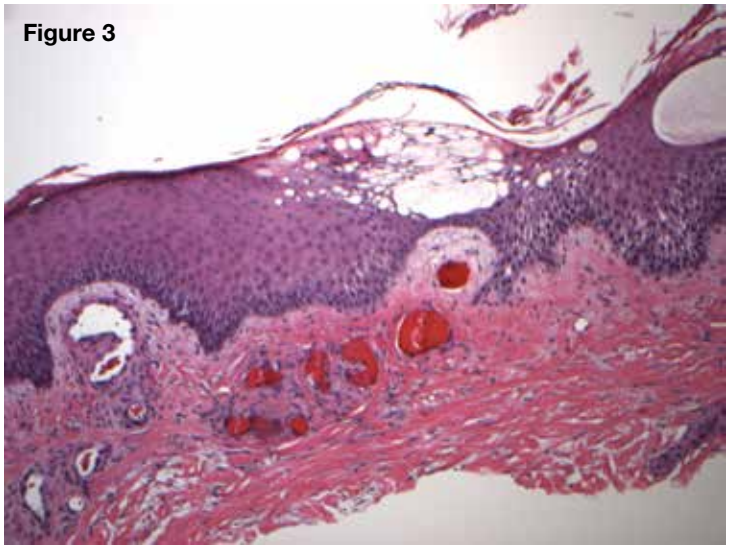
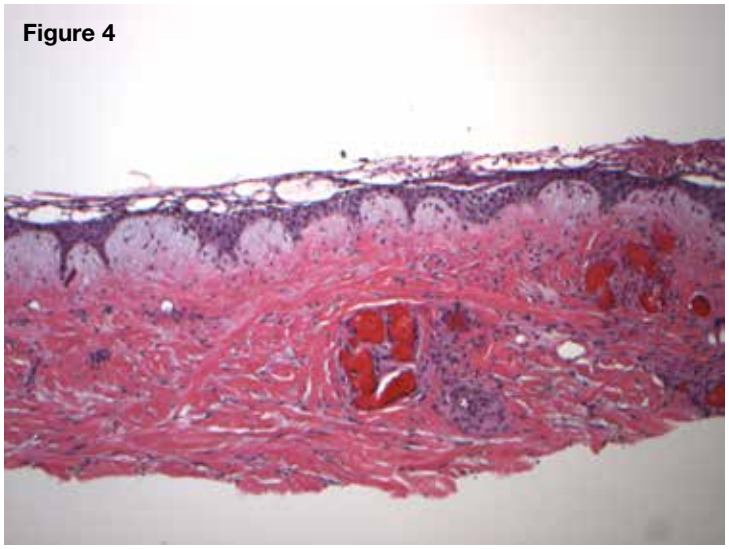


Figure 4



autonomic control with excessive vasoconstriction when in the dependent position, in situ thrombosis, anemia with decrease in oxygen carrying capacity, and decreased nitric oxide bioavailability leading to impaired endothelial function.[8] Trauma is also believed to contribute to the development of these ulcers by triggering sickling of the red blood cells.[9] Areas with less subcutaneous fat, thin skin, and decreased blood flow (such as the malleoli, anterior tibia, dorsal foot, and Achilles tendon) are frequently involved, with the medial malleolus being the most common location for sickle-cell ulcers.[8] Other risk factors include age greater than 20 years old, male gender, hemoglobin less than 6 g/dL, lower fetal hemoglobin, antithrombin III deficiency, and HLA types B35 or Cw4.[9]

Clinically, SCU appear as round, punched-out ulcers with raised borders, deep bases, necrotic slough, and at times surrounding hyperpigmentation and scaling. These surrounding changes are also frequently seen with venous ulcers. Having an active ulcer carries a 146-fold increased risk of developing further ulcers, so nearby additional ulcers or scarring from previous ulcers may be observed.[3] Biopsies are often nonspecific; however, vascular obstruction of superficial dermal blood vessels by the rigid, inflexible, sickled red blood cells with overlying tissue necrosis may be seen. Additional work-up of a patient with suspected SCU includes venous and arterial studies to assess underlying peripheral vascular status, peripheral blood smear, complete blood count, folate, iron, vitamin $B_{12,}$ homocysteine, liver enzymes, renal function, urinalysis, D-dimer, and hemoglobin electrophoresis to measure the levels of hemoglobins A, S, and F.[9]

Management of SCU includes three key points: treatment of current ulcers, managing complications, and prevention of future lesions. Preventative measures include maintaining the skin barrier function with liberal use of emollients, evading trauma by wearing properly fitting shoes and using insect repellent, and promoting good venous drainage and minimizing stasis through compression stockings, leg elevation, and salt restriction. Patients should be educated regarding these preventive measures as well as on how to recognize early signs of skin injury. Treatment of existing ulcers can be challenging, and thus far there is no general consensus as to the gold standard of therapy. Treatment options include local wound care, surgical interventions, and systemic medications.[9] Topical therapies for local wound care include triple antibiotic ointment, arginine-glycine-aspartic tripeptide bound to hyaluronate, and topical oxygen with a tent.[3] In addition, various wound-care dressings have been used, such as wet-to-dry dressings, Unna boots, hydrocolloid dressings, collagen matrix dressings, hemodialysate, and hydrophilic polyurethane film.[3,5,10-12] Compression and activity restriction can be critical to healing. Surgical interventions include debridement to remove non-viable tissue as well as myocutaneous flaps and split-thickness skin grafts for extensive or recalcitrant ulcers.[9] Unfortunately, most allografts fail due to the preexisting circulatory problems. A bilayered skin-equivalent graft manufactured from neonatal foreskin was reported to cause rapid healing without recurrence.[13]

Reported systemic treatments for SCU include zinc sulfate, pentoxifylline, antithrombin III, L-carnitine, arginine butyrate, hydroxyurea, erythropoietin, and transfusions. Oral zinc sulfate improves the anemia of SCD and is also a key element in wound healing.[14] Pentoxifylline, an effective medication for decreasing vaso-occlusive crises in SCD, was reported successful in one case of SCU.[15] It is thought to work by decreasing sickling of red blood cells, increasing erythrocyte deformability, increasing leukocyte flexibility, inhibiting platelet aggregation, reducing blood viscosity, and decreasing plasma fibrinogen levels.[9] In a case of concomitant antithrombin III deficiency, heparin and antithrombin III concentrate successfully treated a patient's ulcer.[16] L-carnitine, an efficacious treatment for ischemic heart disease, peripheral arterial disease, and vasculopathic leg ulcers, has been demonstrated to aid in healing of SCU in case reports.[17] Arginine butyrate, which increases fetal hemoglobin synthesis, rapidly healed one patient's ulcer.[18]

Hydroxyurea (HU) is an antimetabolite that inhibits ribonucleotide reductase, thereby inhibiting DNA synthesis. It increases fetal hemoglobin levels and red-blood-cell water content while decreasing deformability and adhesion to vascular endothelium. Its efficacy in treating SCD was first demonstrated in 1990 and has decreased the number of vaso-occlusive crises in severe cases.[19,20] It is currently the only FDA-approved drug for SCD. While some authors report improvement of leg ulcers with hydroxyurea, others state development or worsening of leg ulcers with this drug.[3,13,21-23] Theoretically, the increase in fetal hemoglobin should be beneficial, as populations of sickle-cell patients with high spontaneous rates of hemoglobin F (such as in Saudi Arabia) have a low incidence of leg ulcers.[21] However, it has been hypothesized that the reduced susceptibility of erythrocytes to deformation caused by HU may impair blood flow in the microcirculation, leading to anoxia and consequent cutaneous ulceration after a minor trauma.[24] Average healing time for a hydroxyurea ulcer after discontinuing the drug is four months, which coincides with the known 120-day survival of the circulating red blood cells.[22] While definitive, randomized controls are still needed to further elucidate the relationship between this drug and SCU, careful attention should be given to skin changes during HU treatment in patients with SCD.[21] Adding recombinant human erythropoietin aided in ulcer healing in one case study and may be an option for patients who are unable to discontinue HU.[25]

Transfusions of packed red blood cells are commonly used to prevent and treat many complications of SCD, including anemia, acute chest syndrome, and pulmonary hypertension.[26] Despite a lack of controlled trials, they have also been utilized as a mode of therapy for recalcitrant SCU. However, the procedure has several risks including iron overload and alloimmunization.[27]

Other recent, developing advances in therapy include topical granulocyte-macrophage colony-stimulating factor, negative-pressure therapy, low-level laser therapy, oral bosentan, and heparin sulfate.[28-32] Additional randomized, controlled

trials are required to better assess their use in a more widespread population.

Infections are a common complication of sickle-cell ulcers. The most common organisms are Staphylococcus aureus and Pseudomonas aeruginosa.[27] As bacteria may impair would healing, the use of appropriate antimicrobials is an important component of treatment. Additionally, if underlying osteomyelitis is suspected, MRI, bone scan or bone biopsy may be required to rule out this severe complication.

Pain management is another integral part of SCD therapy. Commonly used oral pain medications include acetaminophen, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, opioids, antihistamines, antidepressants, and anticonvulsants.[9] However, there are anecdotal reports of topical opioids offering total pain relief for SCUs. Ballas described two patients, one treated with one tablet of oxycodone dissolved in 1 mL to 2 mL of water mixed with debridement ointment, the other with one 100 mg tablet of meperidine dissolved in water and applied with xylocaine ointment. Both patients reported almost immediate pain relief and an ability to significantly reduce their consumption of oral opioids.[33]

Conclusion

Sickle-cell ulcers are a common and difficult complication of sickle-cell disease. They present as round, punched-out ulcers on areas with thin skin and decreased blood flow, most commonly the medial malleolus. Their pathogenesis is not yet fully elucidated but seems to be multifactorial. Management consists of prevention, controlling complications, and treating existing wounds. Treatment of the ulcers is difficult and often requires a combination of topical medications, dressings, compression, debridement and even systemic therapies. The role of hydroxyurea is not yet fully determined; it could possibly help, worsen, or have no effect on patients' ulcers. The risk-to-benefit ratio must be considered when initiating or discontinuing this medication in a patient with sickle-cell disease.

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