Mixed Etiology Hydroxyurea-Related Lower Leg Ulcer that Masqueraded as Sequelae From Sickle Cell Disease and Venous Insufficiency

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Presentation
A 27 year-old African-American man with sickle cell disease (SCD) presented with a complaint of a “painful right leg ulcer” of 3.5 years duration. The wound was located 1 cm above the medial malleolus. The patient was followed by his physician on a regular basis for approximately 1 year using topical wound care modalities, however, his leg ulcer failed to improve. Due to the recalcitrant nature of this condition, the patient was advised to undergo a below-knee amputation in an attempt to prevent osteomyelitis and possible sepsis. Almost 16 months after initial evaluation, the patient consulted a wound care specialist for a second opinion in the hopes of saving his leg. History revealed longstanding SCD with no history of trauma, fever, or signs and symptoms of infection. The patient was taking hydroxyurea (HU) 1000 mg daily for 3 years, due to recurrent painful vaso-occlusive sickle cell crisis.

Physical Examination
Physical examination revealed an ulcer measuring 5.25 cm x 3 cm x 0.2 cm with irregular borders, located 1 cm above the medial malleolus of the right leg. The base of the ulcer showed 80% fibrosis and 20% granulation tissue. The lesion was surrounded by a hyper-pigmented area; however, there was no evidence of erythema, purulent discharge, or foul odor, and no bone was exposed (Figures 1 and 2). Increased temperature of the skin around the ulcer was noted with moderate pitting edema of the right leg. The skin was thin, shiny, atrophic, and eczematous. Varicosities, hemosiderosis, and lipodermatosclerosis were apparent. Vascular examination revealed bounding pedal pulses; capillary refill was within normal limits. Neurological examination uncovered normal deep tendon reflexes. Vibratory and sharp, dull sensations were intact. Orthopedic exam revealed normal range of motion at all major joints of the foot and leg. Muscle strength was adequate.

Diagnosis
A biopsy revealed evidence of chronic inflammatory cell infiltration without evidence of malignancy or vasculitis. Final diagnosis was HU-related right lower leg ulcer mitigated by sickle cell disease and venous insufficiency.
Treatment

Wound care included compression therapy, surgical and enzymatic debridement, as well as various antimicrobial agents as required based upon the clinical picture. A wound culture did not reveal growth of any organisms. The patient was medically managed with good hydration and control of anemia. Despite these efforts, however, the ulcer remained recalcitrant. The patient was regularly assessed to search for other etiologies that could cause delayed wound healing. Several months later, HU was discontinued by the patient’s medical doctor due to less-frequent attacks of vaso-occlusive crisis.

Serendipitously, 4 weeks after discontinuation of HU, the right lower leg ulcer dramatically improved with approximately 50% reepithelialization, (from 5.25 cm x 3 cm x 0.2 cm to 2.5 cm x 1.6 cm x 0.1 cm), with 80% granulation tissue, and 20% fibrotic tissue (Figures 3 and 4). The ulcer completely reepithelialized 7 weeks after discontinuation of HU (Figure 5).

Review of Literature

Sickle cell disease. SCD is a genetic hemolytic disorder. There is an autosomal dominant pattern caused by homozygous inheritance of a gene that leads to an
amino acid substitution in the hemoglobin (missense mutation in the \( \beta \)-globin gene). This malady is commonly observed in African, Mediterranean, and Hispanic populations.

According to the Center for Disease Control, the incidence of SCD is 1 out every 500 African-American births and 1 out of every 36,000 Hispanic-American births. Leg ulcerations are reported in 1.5% to 13.5% of these patients. SCD has been linked with several other pathological conditions that may exacerbate symptoms including acute stress, hypoxia, infection, and dehydration. Severe sickle cell crisis can lead to serious complications ranging from mild to severe disability to mortality. The resulting vascular damage of SCD has been implicated in the development of pulmonary hypertension, stroke, and leg ulceration.

Chronic venous insufficiency. Chronic venous insufficiency (CVI) includes a group of venous disorders characterized by retrograde flow of blood in the lower limb. Chronic venous insufficiency associated with varicose veins and venous hypertension is one of the most common disorders that affect the human condition. The etiology is multifactorial, but valvular incompetence appears to be the most common pathway. If the structural integrity of veins is poor with absence of inciting events, such as deep vein thrombosis, this is termed primary valvular incompetency. The function of the valves may also be impaired by venous outflow obstruction, such as deep vein thrombosis, pregnancy, or compression of left iliac vein by left iliac artery (May-Thurner syndrome). Similar symptoms may be seen in individuals exhibiting ankle equinus and subsequent calf muscle pump dysfunction. Signs of CVI include varicose vein, edema in the distal calf and foot, hyperpigmentation of perimalleolar area due to hemosiderin deposition, scaling skin of the calf and foot, and in some, venous ulcers near malleoli. Diagnosis of CVI is established by history, physical examination, and a confirmatory test such as venous duplex imaging.

Hydroxyurea and leg ulcers. Hydroxyurea is an effective treatment for many conditions including SCD, chronic myeloproliferative disorders, and acute myelogenous leukemia. It is typically well-tolerated with a low toxicity profile. In SCD, HU increases levels of fetal he-

Acquired conditions include pregnancy, oral contraceptives, hormone replacement therapy, antiphospholipid syndrome, and myeloproliferative disorders. Vasculopathy is characterized by purpuric macules or papules located on the legs, but especially on the ankle and foot, producing painful ulcerations. These lesions heal slowly, leaving small white scars called atrophie blanche.

In SCD, vasculopathy is described by hemoglobin polymerization and red blood cell morphological changes to sickle shape that cause poor micro vascular blood flow with subsequent ischemia and infarction. However, leg ulceration pathogenesis is usually multifactorial and includes mechanical obstruction, venous insufficiency, bacterial infection, as well as thrombosis. It was recently discovered that diminished levels of nitric oxide bioavailability could lead to abnormal endothelial function, thus potentially contributing to ulcer formation. It is hypothesized that a combination of the aforementioned factors, along with the mechanical vaso-occlusion due to decreased levels of nitric oxide could contribute to the pathophysiology of lower extremity ulceration in patients with sickle cell disease.
moglobin, thus helping to reduce episodes of sickle-cell crisis, and could decrease the number of hospitalizations and blood transfusions. However, chronic usage of HU (ie, 7 + years) could induce cutaneous leg ulcers mainly in the lateral malleoli where there is an absence or paucity of subcutaneous fat. These ulcers are usually painful and resistant to almost all traditional wound care treatments other than cessation of the drug. The ulcer may also be associated with brown discoloration of nails and diffuse hyperpigmentation. These features may help to distinguish this ulcer from other etiologies.

Discussion

This case represents a classic presentation of recalcitrant sickle cell leg ulcer; however, the proximate cause was ultimately discovered to be HU-related and further complicated by SCD and venous insufficiency.

Initially the lesion was treated as a sickle cell ulcer by the standard wound care methods. Secondary causes that could impair wound healing were not initially considered due to strong clinical findings and a frank association of SCD and leg ulceration; sickle cell ulcer management is often challenging; therefore, it was not unusual to have ulcerations of long-standing durations.

Hydroxyurea has been recognized to cause poor wound healing. This drug inhibits DNA synthesis, which leads to megaloblastic erythrocytes that are susceptible to destruction by microvasculature structures that eventually lead to cutaneous anoxia. This mechanism is important when considering treating for sickle cell patients with HU. It is also well known that lower leg ulcerations can occur with chronic use of HU; however, these sequelae are usually not seen until patients are on the drug for 6-7 years; this patient was taking the medication for 3 years, thus making this ulcer etiology less likely.

Based on a review of the literature, the following can be supported regarding this case study:

- Treatment of ulcerative conditions, such as those observed in this patient, should address all underlying etiologies; in this case cessation of HU, local wound care, and compression were essential.
- Physicians who prescribe HU for SCD must determine if advantages outweigh the disadvantages of this therapy because the drug may cause lower leg ulcers. Additionally, patients who already have sickle cell-related leg ulcers may experience delayed healing.
- Lower leg ulcerations that fail to respond to diagnosis-driven treatment protocols should be reassessed for other possible etiologies.

- Careful review of current active medications remains essential.
- Not all ulcerations present as “textbook” cases; keep an open mind.

Treatment of recalcitrant ulcerations, such as those in patients with SCD or those induced by medications, requires a multidisciplinary approach. In this case close follow-up with the patient’s hematologist was imperative to ensure appropriate management of potential sickle cell crisis.

Reference