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Successful Management of a Chronic Refractory Leg Ulcer in an Adolescent with Sickle Cell Anemia

Giovanni Paolino[1], Michelina Santopietro[2], Giovanna Palumbo[2], Maria Giuseppina Onesti[3], Alessandra Micozzi[2], Salvatore Venosi[4], Marica Laurino[2], Giancarlo Ferrazza[2], Pasquale Fino[3], Robin Foà[2], Fiorina Giona[2]

[1]Dermatologic Clinic, Sapienza University of Rome, Rome, Italy; [2]Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Rome, Italy; [3]Department of Plastic, Reconstructive and Aesthetic Surgery, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy; [4]Vascular Surgery, Department Paride Stefanini, Sapienza University of Rome, Rome, Italy

Corresponding author:
Giovanni Paolino, MD
Clinica Dermatologica
La Sapienza University of Rome
Viale del Policlinico 15
00186 Rome
Italy
gio8519@libero.it

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ABSTRACT Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by a wide range of clinical manifestations. Chronic leg ulcers are a disabling complication with repercussions on the quality of life. We report the case of a 14-year-old girl with a diagnosis of SCD who developed a chronic leg ulcer that was successfully treated with a multi-disciplinary approach, including local and systemic therapies. The role of different treatments, in particular low molecular weight heparin, in the refractory chronic leg ulcer healing process will be discussed.

KEY WORDS: sickle cell disease; chronic leg ulcer; hydroxyurea; NPWT therapy, low molecular weight heparin

INTRODUCTION

Sickle cell disease (SCD), an inherited hemoglobinopathy, is a multi-system disease characterized by a wide range of clinical manifestations that can result in pain, organ injury, and early mortality (1). Leg ulcers are a serious and disabling complication with a significant impact on the quality of life in patients with SCD, especially adolescents (1,2). Currently, most of the therapies offered to patients with SCD are supportive (e.g. antibiotics, routine immunizations, transfusions, hydration, and narcotic therapy to treat painful events) and do little to change the underlying pathophysiology of the disease (1). There are no definitive treatment guidelines available, and hydroxyurea (HU) is considered the only disease-modifying therapy for SCD. While such treatment may effectively control SCD, at the same time it can also induce side effects. It may be difficult for the clinician to distinguish if the cause is related to the disease itself or to the treatment with many related patient management problems, especially at the pediatric age (1). Hereby, we report a case of chronic leg ulcer that developed in a young girl with SCD during treatment with HU.

CASE REPORT

A 14-year-old girl from Ghana came to our Institute with a painful cutaneous ulcer in the medial lower third of her left leg (Figure 1, A). The patient denied possible traumatic origin of the leg ulcer; laboratory investigations showed a low hemoglobin value

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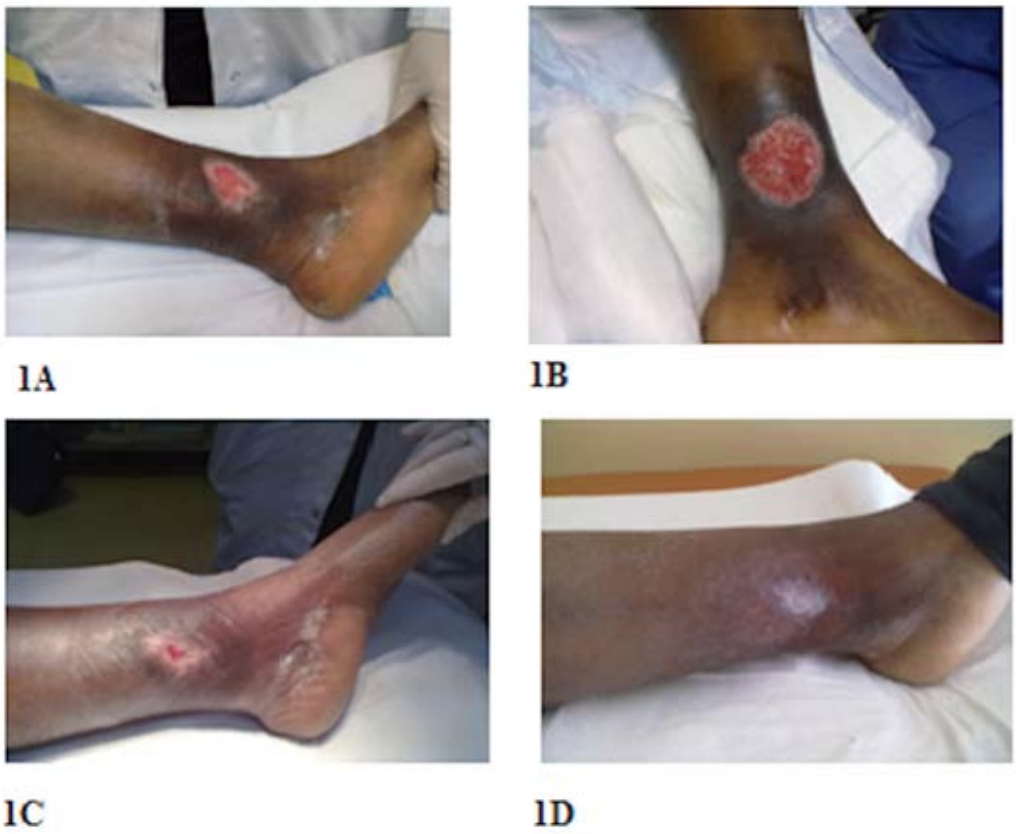

Figure 1. (A) Wound with partial thickness skin loss, presenting an abrasion and a shallow crater; (B) after about 10 months the ulcer extended, with full thickness skin loss, involving damage to the subcutaneous tissue; (C) at 23 months, the wound showed an initial reduction ≥20-30%; (D) after 39 months the ulcer completely closed and the painful symptoms completely disappeared.

of 7.6 g/dL with a reticulocyte count of 417 000 and a hematocrit of 22.8%, high white blood cell counts (13.54 $\times 10^9$/L; with 51% neutrophils and 36% lymphocytes), a normal platelet count (286 $\times 10^9$/L), and high levels of bilirubin (2.12 mg/dL, direct 0.4 mg/dL), lactate dehydrogenase (318 U/L, with a normal upper range of 190 U/L), and ferritin (1 890 ng/mL). Other biochemical parameters, including those that could influence clotting, were within the normal ranges. Chest radiography was normal, as well as eco-color Doppler of the lower limbs.

She was first diagnosed with homozygous SCD (quantitative analysis of 56.5% of hemoglobin S (HbS)) at the age of 2 years. The girl did not need red blood cell (RBC) transfusions until the age of 10, when she presented with pains in the legs and arms combined with severe anemia (5.6 g/dL) and required RBC transfusion. In the subsequent years, she experienced several vaso-occlusive episodes with limb pains, osteonecrosis of the femoral head, interstitial pneumonia, and osteomyelitis of the 4th dorsal vertebra. Additionally, she required a RBC transfusion regimen consisting of one transfusion every 3 weeks. At the age of 11, it was decided to start therapy with HU and folic acid in order to reduce transfusion requirements and the clinical manifestations. Progressive improvement of the painful symptoms was noted starting from the first month of treatment with HU. Furthermore, a decrease in RBC transfusion requirements to one transfusion every 2 months was observed.

Ten months before the appearance of the leg ulcer, the patient suffered from interstitial pneumonia and synovitis with blood cultures positive for coagulase-negative staphylococci, successfully treated with levofloxacin and piperacillin-tazobactam. An 8 by 4.5 cm wound appeared above the left medial malleolus 9 months after recovery from pneumonia, with no traumatic event to cause it. At the beginning the wound showed partial thickness skin loss, abrasion, and a shallow crater (stage II) (Figure 1, A). A multidisciplinary approach was used to manage this complication. The bacterial culture was positive for both Gram+ and Gram– agents and, accordingly, a long-term treatment with specific antibacterial agents was administered. Several surgical curettages were performed on an inpatient basis. Meanwhile, iron che-

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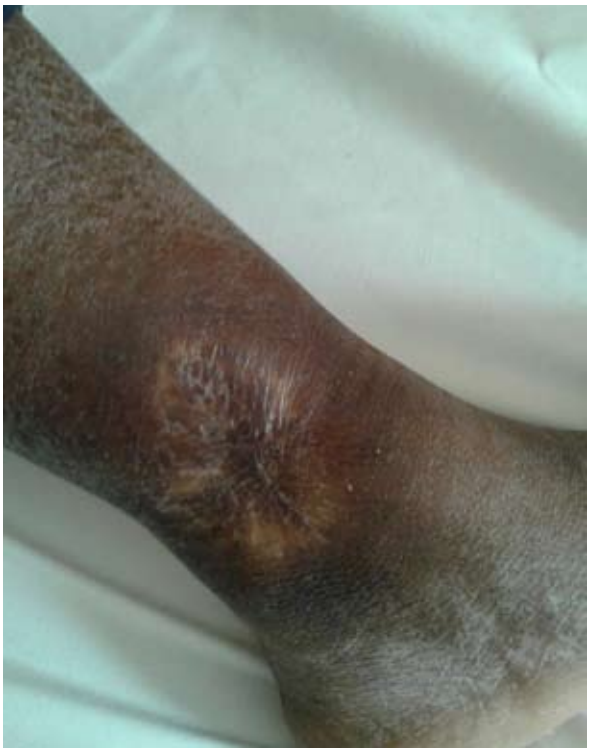

Figure 2. After 24 months since the ulcer healed, the skin surface is completely devoid of alterations.

lation therapy with deferasirox was started because of the increased plasma ferritin values. However, the ulcer extended with full thickness skin loss, involving damage to the subcutaneous tissue; it presented as a deep crater with undermining of the adjacent tissue (stage III) (Figure 1, B). It is important to note that the patient was poorly compliant to both treatment and medical controls, probably due to youth age and socio-economic status. Accordingly, we decided to treat her as an inpatient with Negative Pressure Wound Therapy (NPWT) for 10 days, which resulted in minimal improvement of the lesion (3). We also performed daily medication of ulcerative lesions, disinfecting them with sodium hypochlorite 0.05% cutaneous solution, a cutaneous solution based on 10% povidone iodine, and applying a film of about 2 mL of Bionect Start® (a topical cream containing hyaluronate acid, bacterial fermented sodium hyalunorate salt, and bacterial collagenase obtained from nonpathogenic Vibrio alginolyticus) ointment on the lesions and zinc oxide paste onto the surrounding skin. At the same time, two skin grafts were also performed, without engraftment. The patient presented with progressive anemia (hemoglobin 5.7%), with significant increase in transfusion requirements (1 RBC transfusion every twenty days, then weekly).

One year later, despite adequate care, an increase of the ulcer was noticed combined with an underlying osteomyelitis. Accordingly, a different therapeutic approach was planned: surgical curettages, an erythrocytes-apheresis procedure, and intravenous broad-spectrum antibiotic therapy were combined with applications of a platelet gel (PLT-gel) counterpart (4). The platelet-rich plasma was obtained by centrifuging the blood so that the components were separated by density gradient. The final product was a gel rich in growth factors that act in tissue repair by activating fibroblasts and inducing extracellular matrix remodeling. HU was discontinued at this time, 23 months after the onset of the leg wound. No improvement of the leg ulcer after 2 months of this treatment was observed.

Consequently, we decided to change the treatment strategy. Local therapy with weekly elastic bandage compression type Peha-Haft-knee, irrigation with saline solution (0.9% NaCl) every 2 hours and boric acid 3% once a day, combined with systemic treatment with enoxaparin, a low molecular weight heparin (LMWH), at 4.000 IU daily given subcutaneously, and intra-venous antibiotic therapy were started. The wound decreased by 20-30% over 1 month (Figure 1, C) and the fast healing process allowed us to replace the elastic bandage compression with a knee-high elastic stocking type. A topical cream with Vitamin E was also employed to ease tissue repair. After one week, the leg ulcer was found to be colonized by Extended-spectrum beta-lactamases postitive *Escherichia coli* (E. Coli ESBL+), for which a targeted antibiotic treatment intravenously for 3 weeks was installed.

LMWH was continued for a total of 3 months. Meanwhile, the ulcer continued to shrink in size, the pain decreased, and healing was achieved after 9 months from the start of the last treatment. The patient continued to apply the topical cream with Vitamin E locally (Figure 1, D); 24 months after the ulcer healing, the skin surface is completely devoid of alterations (Figure 2).

DISCUSSION

The pathogenesis of leg ulcers in SCD includes different factors, such as vessel obstructions by dense sickled cells, trauma, insect bites, lactic acid dehydrogenase (LDH) values, in situ thrombosis, anemia, low socio-economic status, and abnormal autonomic control with excessive vasoconstriction; in addition, warm and humid climates also play a pivotal role (1,2,5). Increased nitric oxide (NO) catabolism and reduced NO production due to arginine deficiency lead to vasoconstriction, thereby reducing blood flow and exacerbating local ischemia (5).

Acta Dermatovenerol Croat
2015;23(3):213-217

HU, a cytostatic agent, has demonstrated efficacy in improving health outcomes for children with SCD who have medical complications (6-8). However, this drug is known to produce several adverse cutaneous side effects, including leg ulceration. The leg ulcer that occurred in our young patient with SCD seemed to be worsened by the use of HU.

Since the crucial point is to prevent the onset of a leg ulcer through hygiene, reducing venous stasis, and avoiding traumas, the standard treatment of this complication includes wound care with wet to dry dressings leading to healing in a few weeks (2). In persistent ulcers, other therapeutic strategies are required: blood transfusion, skin grafting, Unna boots, zinc sulphate, hyperbaric oxygen, arginine butyrate, and topical herbal applications (2). NPWT is a treatment usually employed for infected ulcers, especially with involvement of the bone tissue (3,9). It is a new method utilized in wound care which speeds wound healing by creating a vacuum, improving tissue perfusion, and suctioning the exudates (3). The use of collagenase is normally based on performing lysis of fibrin and necrotic tissue, allowing the regeneration of a new extracellular matrix and favoring the migration of fibroblasts and keratinocytes.

There is also some evidence for the efficacy of PLT-gel in treating resistant chronic ulcers. PLT-gel releases growth factors and cytokines able to stimulate the proliferation, migration, and differentiation of fibroblasts and endothelial cells (4,9,10). It also forms a biological scaffold that helps and guides the migration of the mesenchymal cells, derived from populations of resident stem cells or circulating precursors, from the base and the margins of the wound (10-12). Unfortunately, all the above-mentioned strategies were unsuccessful in our patient.

HU discontinuation, antibiotic therapy, and several transfusions showed to be effective when combined with enoxaparin, a LMWH, resulting in improvement in the leg ulcer. According to the literature, the use of LMWH appears to be associated with rapid and effective endothelial cell repair and enhanced angiogenesis as well as neo-vascularization (13-14). LMWH exerts its major anticoagulant effect by binding to antithrombin via a pentasaccharide, consequently inactivating factor Xa and factor IIa. Furthermore, LMWH has anti-inflammatory properties in addition to its anticoagulant properties, in part induced by suppression of tumor necrosis factor alpha, which is released during blood clotting, and in part because of binding to P-selectin to inhibit leukocyte migration. Vaso-occlusion also leads to an altered NO (vasodilator) metabolism and contributes to vascular dysfunction, whereas LMWH increases NO production and enhances vasodilation effects (15-19. Heparin, with its antithrombotic and anticoagulant effects, may then interrupt the natural disease progression of an ulcer, increasing its chances of recovery. We did not observe any side effects due to LMWH (such as bleeding) and, even if the transfusion requirements remained unchanged before and after the introduction of LMWH, there was a marked improvement in the ulcer. This supports the role of LMWH as a possible and useful treatment in ulcers that occur in patients with SCD.

Finally, a good response was observed with the use of Vitamin E as co-adjuvant in the treatment of the leg ulcer. Vitamin E induces vasodilatation, reduces the ischemic damage, and induces re-epithelization by increasing the expression of cytosolic phospholipase A2 and cyclooxygenase (20).

CONCLUSION

LMWH should be used to facilitate the healing of chronic leg ulcers in patients with SCD. A systemic, supportive treatment that includes an adequate blood transfusion regimen, broad spectrum antibiotics, and local therapy with Vitamin E, could contribute reducing healing time and pain (20).

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