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Sickle Cell Anemia and Comorbid Leg Ulcer Treated With Curative Peripheral Blood Stem Cell Transplantation

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Abstract

Allogeneic bone marrow transplantation or peripheral blood stem cell transplantation (PBSCT) are the only curative therapies for patients with sickle cell disease (SCD). Once the patients have successfully undergone transplantation and engrafted, the hallmark of hemolytic anemia resolves, and normal hemoglobin levels are achieved. Some transplant protocols exclude patients with open wounds, including leg ulcers, because of infection risks associated with transplantation and long-term immunosuppression required to prevent graft-versus-host disease. Recalcitrant and recurrent leg ulcers are a serious complication of SCD and a determinant of morbidity. Here, we report the case of a 37-year-old man with sickle cell anemia and a chronic leg ulcer, who underwent PBSCT, engrafted successfully, and then had complete healing of his ulcer 16 months posttransplant.

Keywords

sickle cell; leg ulcer; nonmyeloablative; stem cell transplant; immunosuppression; sirolimus

Sickle cell disease (SCD) is a hemoglobinopathy characterized by autosomal recessive inheritance of the sickle point mutation in the β -globin gene, leading to production of sickle hemoglobin (HbS). The HbS form long strands of polymers and result in abnormally shaped red cells. There are several forms of SCD, and sickle cell anemia (HbSS) is the most severe.¹

Leg ulcerations are a complication of SCD and cause significant morbidity.² These ulcers are difficult to treat because of their complex pathophysiology, including mechanical microvascular obstruction, hypercoagulability, venous insufficiency, hemolysis-vascular

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dysfunction, bacterial burden, and genetic predisposition.³ Environmental and socioeconomic factors are at play as well and affect the ability of the ulcers to heal.⁴

Patients with SCD are currently being cured with bone marrow or peripheral blood stem cell transplantation (PBSCT) from fully matched siblings, with success using either cell source.⁵ Patients with SCD leg ulcers have been unable to receive stem cell transplants because open wounds are perceived as a portal for infection and a risk for transplant-related complications. Furthermore, the wound-related outcomes of successful transplantation have not been previously described.

Case Description

A 37-year-old African-American man with HbSS was referred to our center to enroll in a nonmyeloablative PBSCT study (clinicaltrials.gov, NCT00061568).⁶ His indications for transplant included multiple vaso-occlusive crises, recurrent acute chest syndrome, proteinuria, and bilateral total hip replacements for avascular necrosis 15 years prior. Although not an indication for transplant, he had also had recurrent leg ulcers for the past 20 years.

At the first visit, a single left-lower-leg ulcer existed on the posterior aspect of the medial malleolus, measuring 3 cm long by 2.2 cm wide by 0.1 cm deep. Its surface area was 6.6 cm². No photo was obtained at that visit. Moderate serous, nonodorous drainage was present. Nearly 100% of the wound bed consisted of fibrinous slough, and the nonedematous periwound was hypopigmented with surrounding scar tissue from previously healed ulcers. Hemoglobin variant testing by high-performance liquid chromatography displayed 80.3% HbS and 15.1% fetal hemoglobin (HbF); complete blood counts showed a hemoglobin level of 9.1 g/dL.

Six months later, he returned to the National Institutes of Health for transplantation. The left-leg ulcer area had enlarged by 89% to 12.5 cm² (Figure 1A), and weekly wound care was initiated. A screening wound culture revealed colonization with *Streptococcus agalactiae* (Group B) and *Candida albicans*. Gram stain and fungal wet mount did not show neutrophils, bacteria, or fungi. No other clinical signs of infection were present. Magnetic resonance imaging of the ankles bilaterally confirmed skin ulcerations without osteomyelitis.

The patient had red cell exchange in preparation for transplant. His HbS had reduced to 35.4%, and HbF was 6.8%; hemoglobin remained at 9 g/dL. Hydroxyurea (HU) was discontinued on pretransplant day -8. Immunodepletion was composed of alemtuzumab on days -7 through -3, 300 rads of total body irradiation on day -2, and sirolimus loading on day -1.

On transplant day 0, he received unmanipulated granulocyte colony-stimulating factor mobilized peripheral blood stem cells from his fully human leukocyte antigen matched brother, who did not have sickle cell anemia or trait. Trough sirolimus levels were maintained near 10 ng/mL and then tapered to 5 to 10 ng/mL at 3 months posttransplant.

Per protocol, he received nystatin for 3 months and a 2-year course of prophylactic antibiotics with penicillin, acyclovir, and sulfamethoxazole/trimethoprim.

The leg ulcer area decreased by 1.4% to 12.32 cm² by posttransplant day 11. His neutrophil count was $<0.5 \times 10^9$ cells/L for 15 days and 0.24×10^9 cells/L at the lowest. His donor cells engrafted, and he was discharged on day 15. Two days later, the patient developed a nonneutropenic fever and was readmitted to the inpatient unit to start broad-spectrum intravenous antibiotics. A repeat wound culture showed the same microbial colonization as the pretransplant culture. The source of fever was thought to be a newly developed right oral ulcer and right otitis media. He was discharged 4 days later with a course of amoxicillin/clavulanic acid and subsequently transitioned to the aforementioned prophylactic antibiotic regimen. His clinical status improved, and he did not develop further infection. One month posttransplant, his hemoglobin was 10.1 g/dL, HbF 3.9%, and HbS 11.2%.

His medical course over the next 2 months included recurrent waxing and waning patterns of pain at the leg ulcer that required intermittent doses of IV hydromorphone for dressing changes. He also developed leg pain and edema, which were reminiscent of an impending ulcer, in his nonulcerated right leg. Venous Doppler studies performed on both legs were negative for thrombosis. His right leg pain was controlled with changes to his opioid regimen and a short course of topical nitroglycerin on the right popliteal fossa. He continued to receive wound care once to twice per week. He also received two 10-day courses of minocycline when he reported left inguinal lymphadenopathy, to treat inflammation associated with left ankle ulcers. No ulcer developed in the right leg.

At 3 months posttransplant, the left leg ulcer area improved by 23.2% to 9.6 cm² (Figure 1B). Hemoglobin was 10.8 g/dL, HbF 1.1%, and HbS 0%. The patient then returned to his out-of-state home, where he continued to receive outpatient wound care.

His hemoglobin level remained >12 g/dL with no detectable HbS from 6 months posttransplant. At 6 and 12 months posttransplant, the ulcer area improved by 73.1% and 86.8%, respectively (Figures 1C and 1D). At 12 months posttransplant, the leg ulcer healed in a transverse bridging pattern that resulted in 2 smaller ulcers with a summated area of 1.65 cm². Sirolimus was further reduced at that time and discontinued 15 months posttransplant. The left leg ulcer healed completely 1 month later.

Other SCD-related complications improved over the posttransplant course as well. Prior to transplant, he experienced an average of 1 hospital admission and 2 emergency department visits per year for vaso-occlusive pain crises. Both reduced to none posttransplant. His elevated markers of hemolysis, including lactate dehydrogenase and bilirubin, resolved. Additionally, his opioid use decreased from daily hydromorphone use for chronic ulcer pain and mild pain crises to days with wound dressing changes only. Opioid use subsequently ceased once the ulcer healed.

Discussion

We describe the first reported case of a successful curative stem cell transplant for SCD in the presence of an open leg ulcer. The wound was not a source of infection during

transplantation and did not lead to any transplant-related complications. There was no posttransplant enlargement of the wound, including in the first 2 weeks when he was neutropenic. This raises the possibility that patients with sickle-related leg ulcers could safely undergo allogeneic stem cell transplantation when a short duration of neutropenia is expected or nonmyeloablative conditioning is used. The use of prophylactic antibiotics was protocol driven and was not to treat wound colonization or active wound infection. It is possible that prophylactic antibiotic and minocycline use promoted a clean wound environment.

Ultimately, the leg ulcer healed after treating the underlying SCD. Higher hemoglobin levels were observed 2 months posttransplant without pathological HbS. The patient experienced complete healing of his leg ulcer 16 months after PBSCT (Figure 2). This is likely an improvement over his previous chronic nonhealing state, considering the patient's 2-decade history of refractory leg ulcers.

His previous ulcer treatments consisted of numerous topical compounds, including collagenase, antibacterial ointments, silver sulfadiazine, IODOSORB gel, and MEDIHONEY. These were in addition to compression socks or wraps, bedside sharp debridements, surgical debridements, various synthetic grafts, skin split-thickness autografts from his thighs, and hyperbaric oxygen therapy. None of these resulted in closure of his left medial malleolar full-thickness leg ulcer.

Our patient had his first ulcer develop 8 years prior to taking HU. He then took HU for the next 12 years with repeated cycles of ulcer healing and recurrence. Retrospective studies have shown an association between HU and leg ulcers.⁷⁻⁹ Our literature search revealed a systematic review of randomized controlled trials and publications linking HU to the development of cutaneous ulcers in myeloproliferative conditions but not in SCD.^{10,11} At our tertiary institution, no difference in incidence of SCD leg ulcers was observed between those taking HU and those who did not.¹² Because this patient had leg ulcers prior to starting HU, the role of HU discontinuation in promoting posttransplant healing is not clear. Further studies are necessary to define the correlation between HU-induced ulcers and SCD.

Sirolimus administration has been reported to delay healing after surgical procedures and increase wound complications after kidney or liver transplants.¹³⁻¹⁵ It is tempting to link this ulcer's healing with the discontinuation of sirolimus. However, the ulcer was nearly 87% healed 4 months prior to sirolimus discontinuation. Future trials studying the effects of sirolimus on wound healing would be needed for clarification.

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Figure 1.

Photographs of the left-medial malleolus leg ulcer were taken serially. The left sides of photos are proximal, and right sides distal. A. One week prior to transplant: wound bed approximately 85% fibrinous slough and 15% pink granulation tissue, minimal serous drainage, periwound maceration inferior to wound border. B. Three months posttransplant: wound bed nearly 95% fibrinous slough and 5% pink granulation tissue, minimal serous drainage, periwound hypopigmented with mild hyperkeratinization on the inferior border of the wound, epithelium present in the superior aspects of the wound bed. C. Left leg ulcer 6 months posttransplant: wound bed approximately 70% slough and 30% pink granulation tissue, minimal serous drainage, periwound macerated on lateral borders, epithelium present at superior aspect of wound. D. One year posttransplant: note that the ulcer has healed in a pattern resulting in 2 smaller ulcers. Wound bed nearly 99% pink granulation without drainage, periwound macerated, epithelium bridged cephalad-caudal across wound center.

Figure 2.

Pretransplant wound extension and posttransplant wound healing are represented here by leg ulcer area over the transplant timeline. The arrow is placed at the time of transplant (month 0). The respective hemoglobin levels are provided next to each data point on the line. Note the decrease in leg ulcer area correlates with the increase in Hb level as the patient produced nonsickling hemoglobin over time.