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Stem Cell Therapy for Recalcitrant Diabetic Foot Ulcer: A Brief Report

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Abstract

Background: Diabetic foot ulcer (DFU) is one of the serious complications of diabetes mellitus, with high morbidity and mortality. A plethora of management types are available to treat, and quite often, these fail. We report here a chronic and recalcitrant DFU with autologous bone marrow-derived mesenchymal stem cells (ABMDMSC) with compelling results. **Case Presentation:** A 72-year-old female presented to the clinic with a 10-year history of Type 2 diabetes mellitus, with a partial amputated big toe 12 months ago, with an ulcer on the dorsum measuring 6.5 × 3.0 centimeters. She underwent various treatments in different hospitals and was advised to undergo a partial forefoot amputation. After counselling and informed consent, 2 injections of 10 million ABMDMSC were carried out on the edges of the ulcer, with complete recovery in 4 weeks. **Conclusion:** Our case report highlights that ABMDMSC can heal DFUs that cannot be treated by regular means. We believe that such a modality of treatment should be considered to avoid long-term hardships, ordeals, and morbidity.

Keywords

Diabetic Foot Ulcer, Non-Healing, Recalcitrant, Stem Cell Therapy

1. Introduction

DFU is one of the serious complications in Type 1 and Type 2 diabetes mellitus [1]. DFUs are a common, highly morbid consequence of long-standing and poorly managed diabetes. It is estimated that 537 million people worldwide have diabetes [2]. Morbidity following incident ulceration is high, with recurrence rates of 65% at 3 - 5 years, lifetime lower-extremity amputation incidence of 20%, and 5-year

mortality of 50% - 70% [3]. The underlying etiology of DFU is classified into three types: purely neuropathic (35%), purely ischemic (15%), and mixed neuro-ischemic (50%). The cost for the management of diabetic foot disease in the United States (US) ranges from US$9 to US$13 billion, in addition to the cost for the management of DM alone [4]. The standard of care (SOC) management of DFU includes surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment, and infection and glycemic control [5]. Many other techniques published were recommended, like hyperbaric oxygen therapy, the use of advanced wound care products, and negative-pressure wound therapy (NPWT). Growth factors like platelet-derived growth factor-beta (PDGF-beta), transforming growth factor-beta (TGF-β) were also used [6] [7]. Platelet-rich plasma (PRP) [8] [9], granulocyte colony-stimulating factor (G-CSF) [10], Epidermal growth factor acts on epithelial cells [11] [12]. Hyperbaric Oxygen (HO) has been in use for a long time in the healing of nondiabetic wounds and DFUs. The concept is that neutrophils can quickly neutralize bacteria effectively in an atmosphere of higher oxygen concentration. However, any chance of healing occurs in HO therapy, which involves 100% oxygen at a pressure greater than that at sea level and requires as many as 40 sessions to make a difference in the size of the ulcer [13] [14]. With all the available treatments, only 50% of foot ulcers heal, while 10% - 15% of them will remain active, and 5% - 24% of them will finally lead to limb amputation within a period of 6 - 18 months after the first evaluation [15]. We report a case of recalcitrant large DFU that did not heal with multiple modes of treatment and was advised to undergo amputation, but successfully healed under the influence of mesenchymal stem cells.

2. Case Details

A 72-year-old female patient with controlled type 2 diabetes presented to the clinic with a nonhealing ulcer on the dorsum of a partially amputated big toe for 12-month duration. She was diagnosed with type 2 diabetes and started using antidiabetic drugs: biguanide 500 mg twice a day, linagliptin 5 mg once a day, Insulin glargine 18 units at night, regular soluble insulin 12 units before breakfast, and 10 units at night. One year and 8 months ago, she injured her right big toe, which resulted in gangrene and led to the amputation of the proximal phalanx of the big toe (**Figure 1**). The wound did not heal and developed into an ulcer on the dorsum of the amputation. She underwent multiple procedures, including debridement with skin graft, negative-pressure wound therapy (NPWT), Platelet-rich plasma (PRP), and granulocyte colony-stimulating factor (G-CSF). It has been 12 months since the ulcer remained unhealed.

On physical examination of the foot, there was discoloration of the skin around the toes with minimal edema. Ankle-Brachial index was 0.79. There is a small amount of discharge with a foul smell. The ulcer measured 6.5 × 3.0 centimeters. The ulcer was labelled as Wagner grade 3. A culture swab was taken, and the ulcer

was cleaned with normal saline (Figure 1). An X-ray of the foot and blood investigations were requested (Figure 2). The results are enumerated in Table 1. After reviewing the results, the culture showed that the ulcer was infected with a heavy growth of Klebsiella pneumoniae sensitive only to colistin and Tigecycline. The patient and the family were counseled to have a course of antibiotic treatment to control the infection and then attempt to heal the ulcer with standard care. After the infection was controlled, standard care of the ulcer was carried out for 6 weeks and still the ulcer failed to heal. Since all the other available methods to treat this ulcer were exhausted, stem cell therapy was offered as an option. Approval of the treatment was obtained from the ethical committee of the StemCells Research and Regenerative Labs. After deliberations within the family, a decision was made to treat with stem cell therapy. The patient was started on tigecycline infusion of 100 mg as a loading dose and 50 mg every 12 hours for 10 days. A repeat culture after a week of discontinuation of the had no growth from the ulcer, and under local anesthesia and sedation, 40 ml of autologous bone marrow aspiration was done from the iliac crest. The samples were sent to StemCells Regenerative and Research Labs Inc., Hyderabad, for the isolation and in vitro expansion of Mesenchymal stem cells.

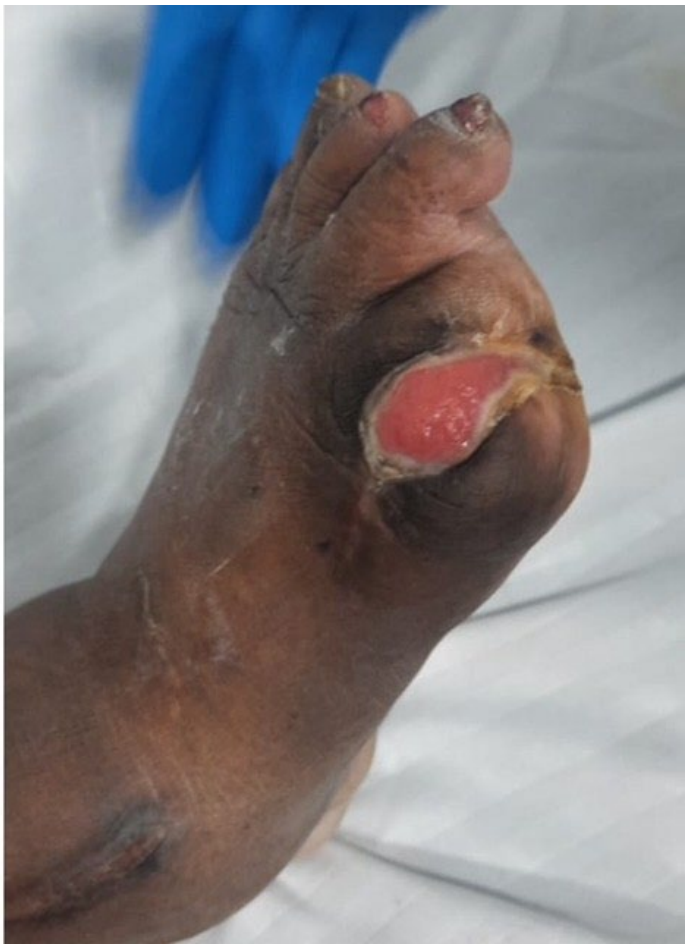

Figure 1. Clinical picture of the unhealed diabetic foot ulcer for 12 months.

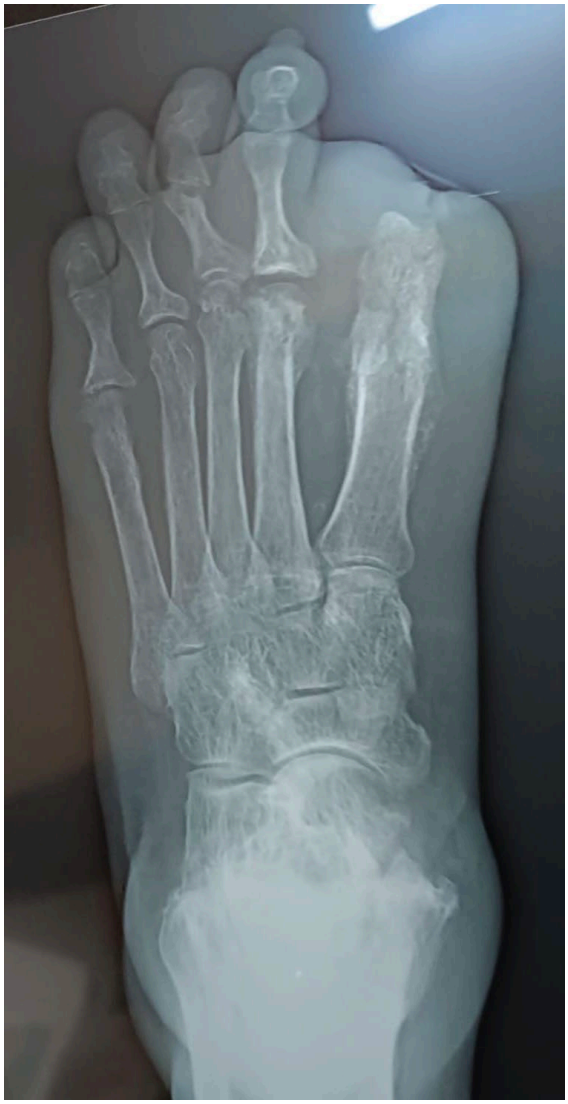

Figure 2. Radiograph of the foot amputated proximal Phalanx.

Table 1. Blood levels at the start of the therapy.

	Normal Lab Range	Patient
Haemoglobin (g/dL)	12.0 to 15.5	13.1
Total Leucocyte Count (ml)	5000 - 10,000	7600
Neutrophils (%)	50 - 70	62
Lymphocytes (%)	20 - 35	28
Monocytes (%)	3 - 10	7
Eosinophils (%)	2 - 7	3
Fasting Blood Sugar (mg/dl)	70 - 99	100
HA1C (%)	5.9	6.7
Erythrocyte Sedimentation Rate (mm/hour)	2 - 5	15
Serum C-Reactive Protein (mg/L)	<3	1.9

Protocol of MSC Isolation and Expansion: Bone marrow aspirate was collected in Hank's Solution (HSBB)-100%, supplemented with 5% antibiotic solution, viz., penicillin, streptomycin.

Ficoll-Paque Method: The aspirate was transferred into a 50 mL conical tube containing HBSS. Ficoll-Paque Plus solution with the help of syringe and transferred to a 50 mL conical tube and bone marrow aspirate was diluted with an equal volume of Ficoll-Paque Plus solution (Merck KGaA, Darmstadt, Germany) (1:1) ratio in the same 50 mL conical tube, and centrifuge at 6000 Revolutions Per Minute (RPM) for 45 minutes at RT. After centrifuging, the mononuclear cells (buffy coat) were carefully collected using a sterile pipette and seeded onto a T75 tissue culture flask (Greiner Bio-One GmbH, Frickenhausen, Germany) at the rate of 5000 cells/cm. Wash the cells twice with PBS, take 6 mL of PBS and centrifuge at 4000 g for 10 minutes. The sedimented cells were seeded on to 2 cell culture flask of T-25 and two cell culture flask of T-75 with prepared medium 20 mL of the MSC culture medium which consists of serum basal-Hi-media 500 mL, add MSC supplement −20.8 mL 10% Fetal bovine serum (Cell Technologies Inc, USA) and 5% penicillin/streptomycin (StemProTM MSC SFM, Thermo Fisher, Massachusetts, USA) was added, and the flask was incubated at 37˚C, with 5% CO_2 and 95% humidity in a incubator. Add 7 mL of media for T-25 and 12 mL for T-75. Adherent cells were cultured, and the process was continued with a change of the medium every second day till cells became confluent. The cells were tryptinized, harvested, and cryopreserved. On the day of injection, the cells were thawed at 37.5 degrees centigrade. The cryotube was centrifuged at 5000 RPM for 5 minutes. The media was siphoned without a pallet. One ml of normal saline was added to the cryotube and shaken well to dissolve the pellet, and was given for injection.

On the day of injection, the MSCs were injected using a U-100 1 mL/cc 31 G 5/16 (8 mm) inch syringe; MSCs were injected at the edges of the ulcer. The wound was covered with a dry dressing, which was changed every third day. On 15 the day (**Figure 3**), it showed that the size of the ulcer reduced to 50% of the original. On the same day, 10 million MSCs were injected again. The patient was examined after 2 weeks, and the ulcer had completely healed (**Figure 4**). Patient continues to be normal at 6 months follow-up (**Figure 5**).

3. Discussion

Our case report confirms that the use of autologous bone marrow-derived mesenchymal stem cells has the potential to heal DFU that fails to heal under the SOC modality of treatment. It was reported that about 30 % of DFUs recover within 5-6 months with standard treatment methods, 15, but this could improve with the interdisciplinary specializations getting involved in the management of DFUs that do not heal [16].

Even with the SOC methods of management of DFUs, it is not free from complications, and sometimes more than one method has to be used in the attempt at healing. Negative Pressure Wound Therapy, Hyperbaric Oxygen Therapy, growth

factors therapy, PRP, and Maggot Debridement Therapy [17] [18]. Recently, low-intensity diagnostic ultrasound combined with microbubbles has shown promise in the healing of the DFUs, but it takes up to 150 days [19]. This sort of treatment is not readily available at smaller hospitals and centers. PRP, which is much advocated for use in DFUs, can cause serious side effects like infection at the injection site, pain, and bruising, with no or meagre effectiveness because of defective platelet function. On the other hand, HO therapy requires 40 sessions to make a difference in the magnitude of the ulcer [13] [14]. Moreover, the adverse effects of HO are serious, such as pneumothorax, changes in visual acuity, and seizures [20]. A recent guideline from Great Britain indicates that the routine use of HO therapy is not cost-effective [21].

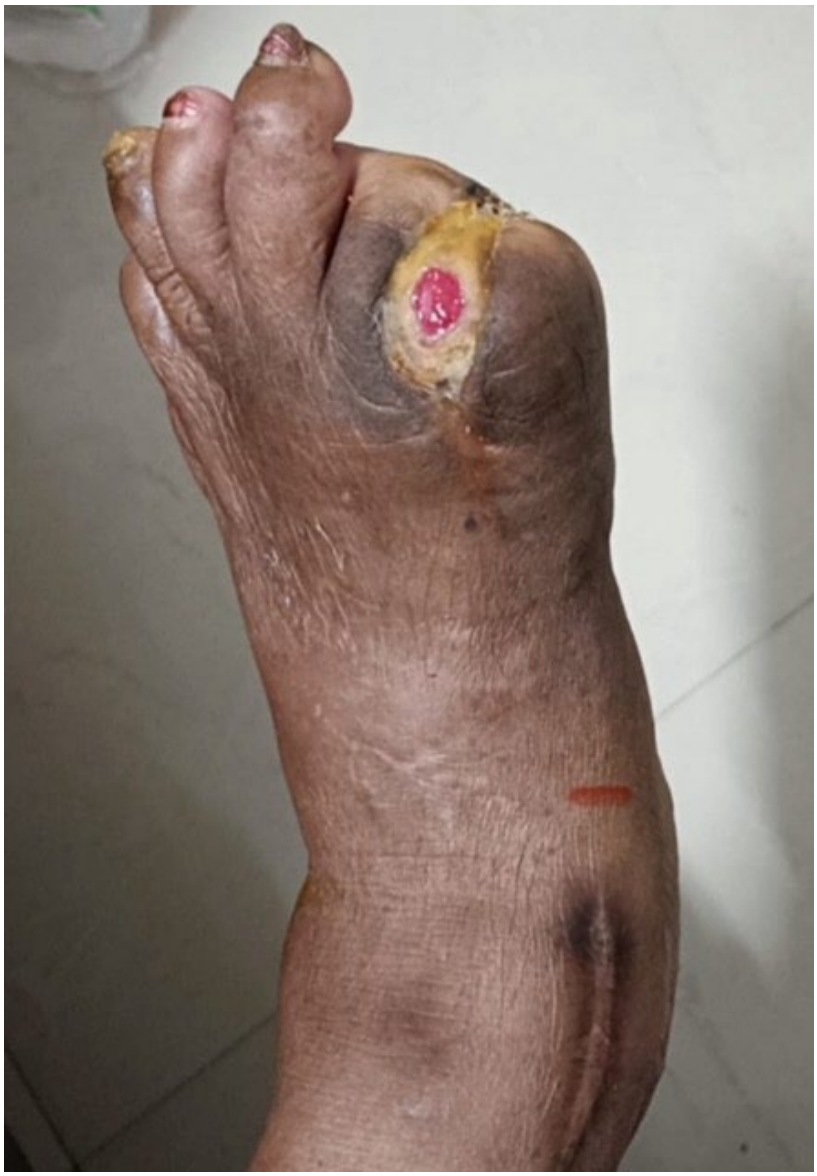

Figure 3. Clinical photograph of the diabetic foot ulcer after 2 weeks of stem cell injection with reduction of size of the ulcer.

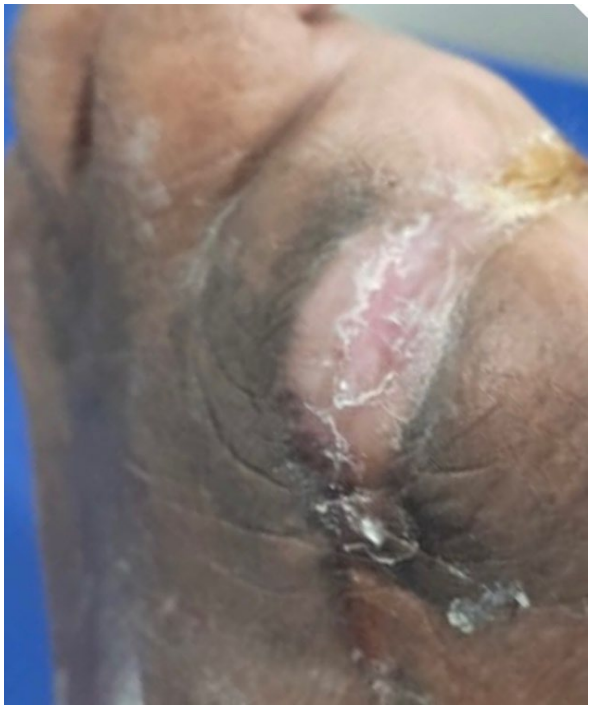

Figure 4. Clinical Picture of the foot with total healing of the ulcer.

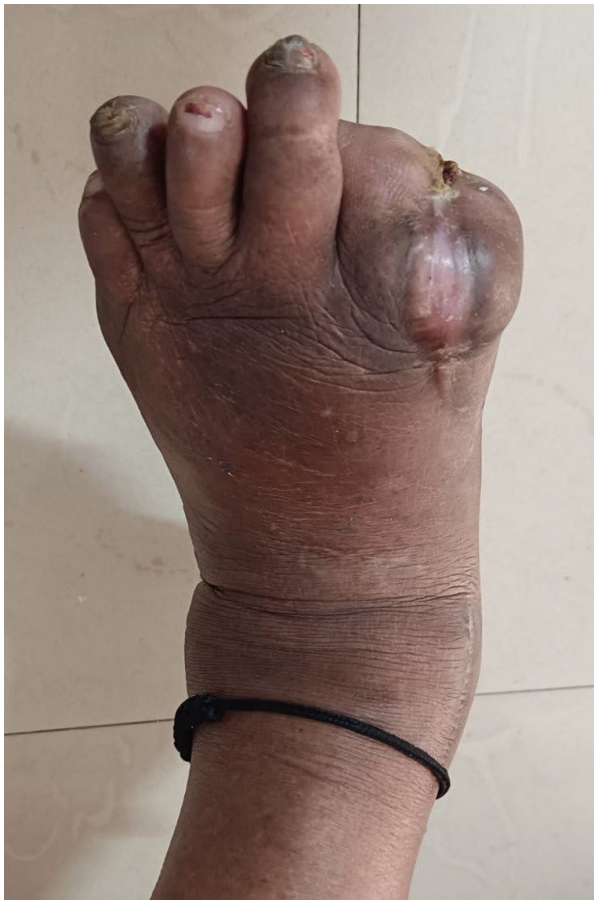

Figure 5. Clinical Picture of the foot after 6 months of follow up.

Mesenchymal stem cells can differentiate into various cell types within the mesoderm, including bone, fat, cartilage, muscle, and skin. They are known to act by using their cytoplasmic bodies like VEGF, FGF-2, PGF, TGF-β, PDGF, ANG1, MCP-1 (Pro-Angiogenesis factors), anti-microbial activity using TLR3, IDO, TGF-β IL1-β, IL-6, IL10, Anti-inflammatory M2 proliferation, and a decrease in cytotoxic activity proliferation. In patients with DFU, which function of MSCs plays in healing of the ulcers are not known and the scope of this report does not entail us to do that. The end product of using stem cells induces new blood vessels, clears the infection, and ultimately heals the refractory ulcer. Our case study shows one such example where a recalcitrant non-healing DFU was treated successfully with stem cell therapy. However, similar treatment can be employed in a large sample size to conclusively demonstrate the effectiveness of stem cell therapy in the healing of DFU.

In conclusion, the successful healing of the ulcer under the influence of MSCs provides valuable insights and in-depth understanding that MSCs are a potential modality to treat recalcitrant DFUs. It is to be understood that a generalizable conclusion should not be drawn from our case report. Stem cell-based interventions to promote health are expanding rapidly and assessing the preliminary efficacy of these interventions can be achieved by employing single-case experiments referred to as n-of-1 studies.

There should be adequate glycemic control and the ulcer free of infection. We need more structured clinical trials to put MSCs under the umbrella of SOC for DFUs. This will not only save many patients from amputations, but also improve the quality of life, and have a tremendous impact on overall savings in health care costs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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