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Case Report

Macrophage-Regulating Drug Treatment Promotes Tissue Proliferation in a Diabetic Foot Ulcer Patient with Exposed Anterior Tibialis Tendon - A Case Report

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Abstract

A 53-year-old woman with type 2 diabetes mellitus (DM), peripheral arterial disease (PAD), hypertension, and hyperlipidemia was sent to the emergency department with exposed tendon and soft tissue necrosis from a diabetic foot ulcer (DFU). After 10 days of treatment with broad-spectrum antibiotics and angioplasty, tissue proliferation was still halted by persistent inflammation. Despite multiple interventions, the wound did not heal. Therefore, the topical macrophage-modulating drug, ON101, was used twice daily. The ulcer area then completely closed after 16 weeks. In our study, macrophage modulation can be a new approach to promote tissue repair and rescue difficult wounds.

Keywords: Diabetic foot ulcer; Inflammation; Macrophage-regulating drug; Tissue proliferation; Wound healing

Introduction

According to the International Diabetes Federation (IDF), the prevalence of diabetes in adults worldwide is expected to increase from 536.6 million people in 2021 to 783.2 million people in 2045. [1] People with diabetes (type 1 or 2) may have a lifetime risk of developing foot ulcers as high as 34%. Diabetic foot ulcers are the leading cause of morbidity, accounting for at least two-thirds of all nontraumatic amputations in the United States.

Standard principles for the management of diabetic foot ulcers (DFU), including debridement, infection control, pressure offloading, and revascularization. [2] However, inflammation often prevents the final step of complete healing after multiple interventions and is one of the mechanisms by which DFUs delay healing. [3] Dysregulated M1/M2-type macrophages could prolong inflammation reaction. To restore the balance between these macrophage types is deemed as a new strategy in wound healing. [4] Here, we reported a case of an adult Asian woman with type 2 diabetes who presented with a chronic right dorsal foot ulcer with exposed anterior tibial tendon, was successfully treated with macrophage modulating drugs.

Case Report

A 53-year-old woman with type 2 DM (HbA_{1c} 11.7%), PAD, hypertension and hyperlipidemia was sent to the emergency department of Kaohsiung Medical University Hospital due to the presence of an infected chronic ulcer with exposed anterior tibialis tendon and extensive ischemic necrosis at the edge of her right ankle wound. The ankle-brachial index of her right leg was 0.8, so a cardiac consultation was arranged for further examination. Angiography showed 100% occlusion of anterior tibial artery, 80~90% stenosis of tibioperoneal trunk and 80% stenosis of posterior tibial artery. Angioplasty was successfully completed after discussing with her family. However, 10 days after successful angioplasty, tissue proliferation was stopped by persistent inflammation and ischemia (Figure 1). After receiving angioplasty for three months and regularly following up in our plastic surgery outpatient department, there had been little improvement in the wound. To break the vicious cycle of inflammation and stimulate tissue proliferation, fat grafting was performed. We found Pseudomonas aeruginosa contamination in subsequent wound cultures due to prolonged wound care.

We applied artificial dermis for the ulcer defect after further debridement and intravenous antibiotics. However, the graft remained poorly taking. Stalled wound healing process was noted as the ulcer area measured by imitoMeasure (imito AG, Zurich, Switzerland) was 7.59 cm^2, which decreased to 7.23 cm^2 two weeks after surgery (Figure 2). The patient refused further surgical reconstruction, so a new macrophage modulating drug, ON101 (Oneness Biotech Co, Ltd, Taiwan), was instead applied topically with gauze twice daily and the wound healed completely after 16 weeks (Figure 3). According to our observation, no obvious adverse or unanticipated events were noted. At 13-month follow-up, her range for right ankle joint dorsiflexion was 11 degrees. Now she can walk without crutches or walking equipment and she is satisfied with her normal gait.

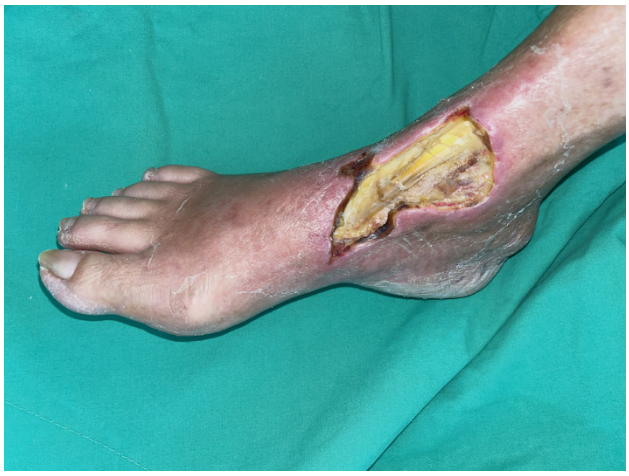

Figure 1: Although downgraded to Wagner grade II after treatment, the ulcer remained in a state of persistent inflammation and ischemia.

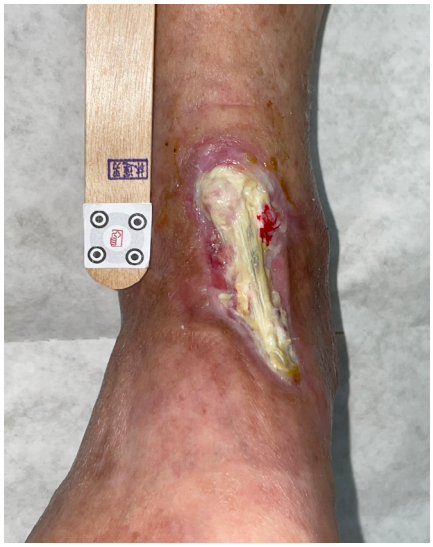

Figure 2: The wound picture before ON101 topical application. Note the exposure of the anterior tibial tendon.

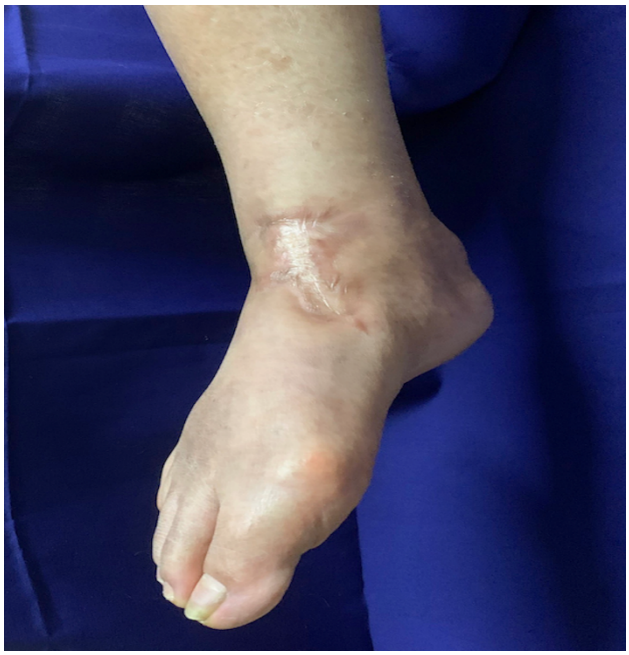

Figure 3: After 16 weeks, the ulcer had healed well.

Discussion

DFU is one of the most debilitating complications of diabetes. [5] Despite with hypoglycemic therapy, clinical trials have shown that the risk of DFU still persists. [6, 7] This suggests that the unmet need for DFU drugs is urgent. Surgical reconstruction using various flaps has been reported. However, these are complex procedures and may be associated with surgical complications. Some researchers have proposed that impaired wound healing in DFU is due to excess pro-inflammatory cytokines [8].

Macrophages are essential in tissue repair. Macrophages are heterogeneous and differentiate into a plethora of subtypes depending on the local tissue environment. Accumulating scientific evidence suggests that targeting the macrophage phenotype may be a potentially effective therapy for the treatment of DFU, as hyperglycemia increases the ratio of pro-inflammatory M1 to pro-regenerative M2 macrophages. [9] In a multicenter randomized clinical trial, ON101 (Oneness Biotech Co, Ltd, Taiwan) exhibited better healing efficacy than hydrofiber dressings alone in the treatment of DFUs. [4] ON101, consisting of the active pharmaceutical ingredients PA-F4 and S1, has been reported to inhibit NLRP3 inflammasome signaling and modulate macrophages. [4] ON101 reduces chronic inflammation by directly inhibiting M1 macrophage polarization and activity, thereby accelerating diabetic wound healing. ON101 also facilitates the enrichment of pro-healing M2a and pro-remodeling M2c macrophages by stimulating adipocyte progenitor cells (ADPCs) to secrete CXCL3 and GCSF, creating an environment conducive to promoting skin regeneration and diabetic wound repair [10].

This study had some limitations. Firstly, this study combined series of treatments, such as debridement, angioplasty, fat grafting, artificial dermis, and the macrophage-regulating drug. We follow protocols to treat DFUs, but it is up to the surgeon what type of reconstructive surgery is planned and when. Secondly, our study did not show to what extent ON101 altered the balance between patients' M1 and M2 macrophages, although it theoretically did.

Conclusion

Chronic inflammation hinders wound healing despite the application of multiple interventions. We propose a new strategy to add novel drug, which regulates the ratio of pro-inflammatory M1 and pro-regenerative M2 macrophages to promote tissue repair in diabetic foot ulcer patients.

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Disclosures

Conflict of interest: JCC and SGC are employers in Oneness Biotech Co., Ltd. YNL, KIL and YRK: None. This case was presented as a poster in the American Diabetes Association's 82nd Scientific Sessions.

Approval of the research protocol by an institutional reviewer board: KMUHIRB-E (I)-20210136.

Informed consent: Yes.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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