Novel management of diabetic foot ulcers using AmnioFix®: two case studies



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The complications of chronic diabetic foot ulcers present a significant challenge, with infections more likely in chronic than acute ulcers. The presence of infection increases the risks of hospitalisation, lower-extremity amputation and 5-year mortality. The healthcare costs of a lower-extremity amputation and follow-up are considerable. As many amputations can be avoided, prompt, conservative treatment of diabetic foot ulcers is, therefore, essential. This article highlights two cases in which an innovative approach was taken to treat chronic diabetic foot ulcers refractory to conservative therapy. Patients were successfully treated in the outpatient setting utilising injectable micronised AmnioFix® (MiMedx, US), which is derived from dehydrated human amnion/chorion membrane.

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The healthcare crisis created by diabetes is of epidemic proportions. An estimated 422 million adults worldwide were living with the condition in 2014 and diabetes contributed to 1.5 million deaths in 2012 (World Health Organization, 2016). The annual incidence of foot ulcers in diabetes is reported to be 2% in most Western countries (Abbott et al, 2002); however, among Arab countries a recent systematic review revealed the prevalence to be much higher (Mairghani et al, 2017) *[Table 1]*. The lifetime incidence a diabetic foot ulcer (DFU) ranges from 19% to 34% (Armstrong et al, 2017).

The complications of chronic DFUs present a significant challenge for patients and for treating clinicians, from quality of life and economic perspectives. Individuals presenting with DFUs persisting for more than 30 days are 4.7 times more likely to develop a foot infection than individuals with an acute DFU (Lavery et al, 2016). Compared to individuals without a foot infection, the risk of hospitalisation is 55.7 times greater in patients with a foot infection and the risk of amputation is 154.5 times greater (Lavery et al, 2006). It has been estimated that worldwide a lower limb is lost every 30 seconds due to diabetes (Richard and Sculdiner, 2008). The impact and cost of a lower-extremity amputation are dramatic. The 5-year mortality rate for patients with diabetes following a single-leg amputation can be as high as 70% (Hambleton et al 2009). The total additional healthcare costs of a lower-extremity amputation, including 2-year follow-up, is estimated to be between USD40,000 and USD60,000 (Carls et al, 2011).

A foot ulcer precedes 85% of lower-limb amputations in patients with diabetes (Moxey et al, 2011). Having a solid understanding of peripheral vascular evaluation, nutritional requirements, infection diagnosis and management, wound-bed preparation and advanced closure techniques is therefore essential to positively impact the clinical and economic outcomes of DFU. It has been estimated that 49–85% of all amputations can be prevented (Driver and de Leon, 2008), so the

Table 1. Prevalence of diabetic foot ulcers in Arab countries (Mairghani et al, 2017).

Country	Prevalence (%)
Saudi Arabia	11.9
Egypt	4.0
Jordan	4.6
Bahrain	5.9
Iraq	2.7

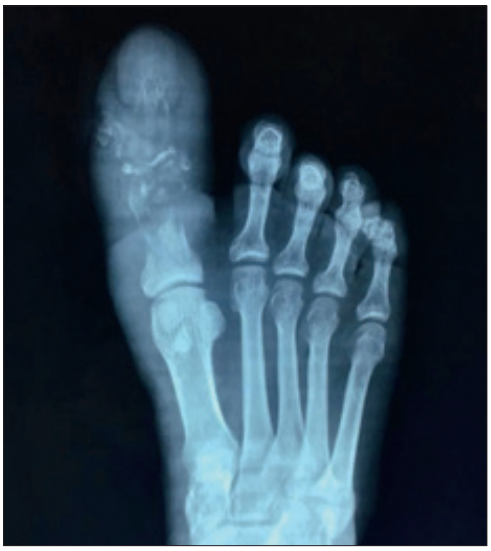

Figure 1. Osteomyelitis was present in the proximal, intermediate and distal phalanges on presentation.

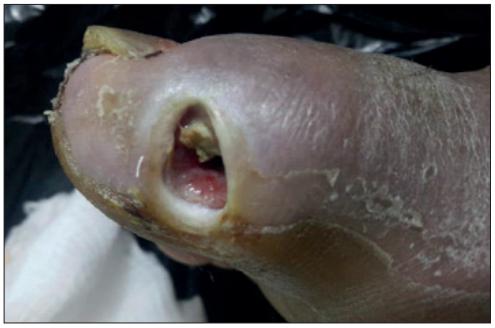

Figure 2. The ulcer before debridement (day 0).

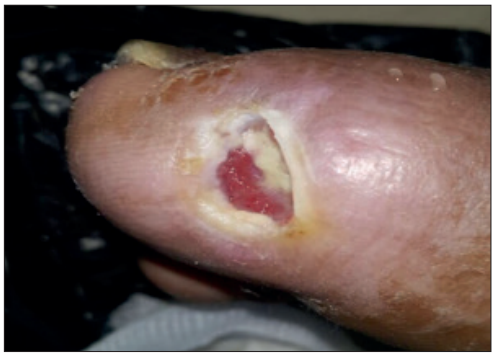

Figure 3. The foot ulcer 7 days after injection with AmnioFix (day 21).

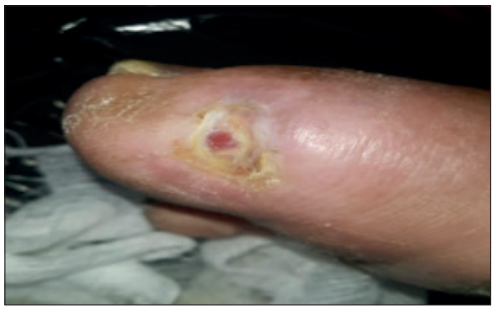

Figure 4. The foot ulcer a week after the second injection of AmnioFix (day 28).

reasonable use of regenerative therapies should be considered when ulcers do not respond sufficiently to appropriate standard care, in order to stimulate delayed wound healing. This report highlights a two case studies in which an innovative approach was taken to the management of chronic DFUs refractory to conservative therapy.

AmnioFix

Amniotic membrane-derived products are a relatively new technology that has shown promise in ophthalmology, plastic surgery and wound care (Kotoin et al, 2015; Illic et al, 2016; Haugh et al, 2017). AmnioFix® (MiMedx, US) is a placental tissue allograft composed of the amnion and chorion layers of the amniotic sac, and is delivered as an injection. AmnioFix contains 285 regulatory proteins, growth factors, specialised cytokines, and enzyme inhibitors known to help enhance healing (Koob et al, 2014; Lei et al, 2017):

- Extracellular matrix proteins, such as collagens and proteoglycans
- Growth factors, such as transforming growth factor beta, fibroblast growth factor and platelet-derived growth factors
- Cytokines
- Other proteins that aid healing.

It is intended for use to reduce scar tissue formation, modulate inflammation, enhance surgical wound healing and act as a barrier membrane. AmnioFix is delivered as an injection and can cause some localised soreness and discomfort, which typically subsides within 2–3 days.

Case studies

Case 1

A 45-year-old male diagnosed with diabetes mellitus over 14 years ago presented to an outpatient wound care clinic with a non-healing DFU that had persisted for 3 weeks. The ulcer was located on the right great toe. The patient's diabetes had been poorly controlled in the past.

Initial outpatient work-up included a bone culture, radiologic imaging, calculation of ankle-brachial index and a monofilament/tuning fork test. Results indicated that the patient had peripheral neuropathy, an ankle-brachial index of 0.9 and underlying osteomyelitis confirmed by X-ray *[Figure 1]*. On presentation, the DFU measured 3cm × 2cm and was 2.5cm deep *[Figure 2]*.

The patient was immediately started on empiric intravenous meropenem and a swab sent for culture. Once the culture results confirmed

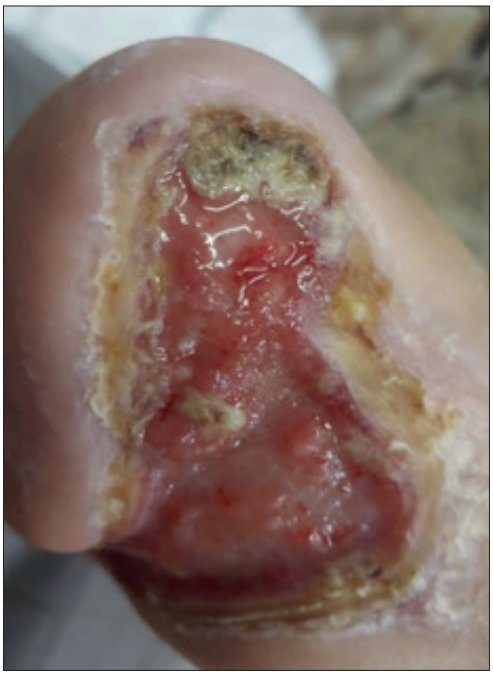

Figure 5. Right transmetatarsal ulcer on day 0.

the presence of *Escherichia coli*, the antibiotic regimen was switched to oral levofloxacin. The patient received a total of 6-weeks of systemic antimicrobial therapy.

On day 0 and day 7, the right toe ulcer underwent sharp excisional debridement in the outpatient setting with removal of necrotic tissue and infected bone. In addition to debridement, the ulcer was managed with silver alginate dressings, which were changed daily, pressure was offloaded via a toe splint.

After 2 weeks of standard topical management and systemic antibiotics, the DFU had not demonstrated any significant signs of healing and was at risk of amputation. On day 14, the physician injected 40 mg of AmnioFix around the perimeter of the ulcer and into the underlying wound bed. A week after later, the depth of the ulcer had decreased from 2.5cm to less than 0.3cm *[Figure 3]*.

A second injection of AmnioFix was given on day 21. One week later the ulcer was essentially healed *[Figure 4]*. Total time to healing from the day of presentation to closure was less than 30 days.

Case 2

A 65-year-old female with diabetes that had been poorly controlled for 22 years and past right transmetatarsal amputation. She developed to a non-healing DFU that had persisted for 3 weeks prior to presentation to an outpatient wound clinic. The ulcer was located on the right distal transmetatarsal site.

Wound culture was negative for bacterial growth and there was no evidence of osteomyelitis on X-ray. Her ankle-brachial index of 0.6. No monofilament/tuning fork test was performed. The DFU measured 15cm x 10cm and was 0.5cm deep *[Figure 5]*.

After 8 days of conservative topical therapy consisting of silver alginate dressings changed daily and offloading with a wheelchair, the DFU did not show any significant signs of closure. At this point, the treating physician decided to

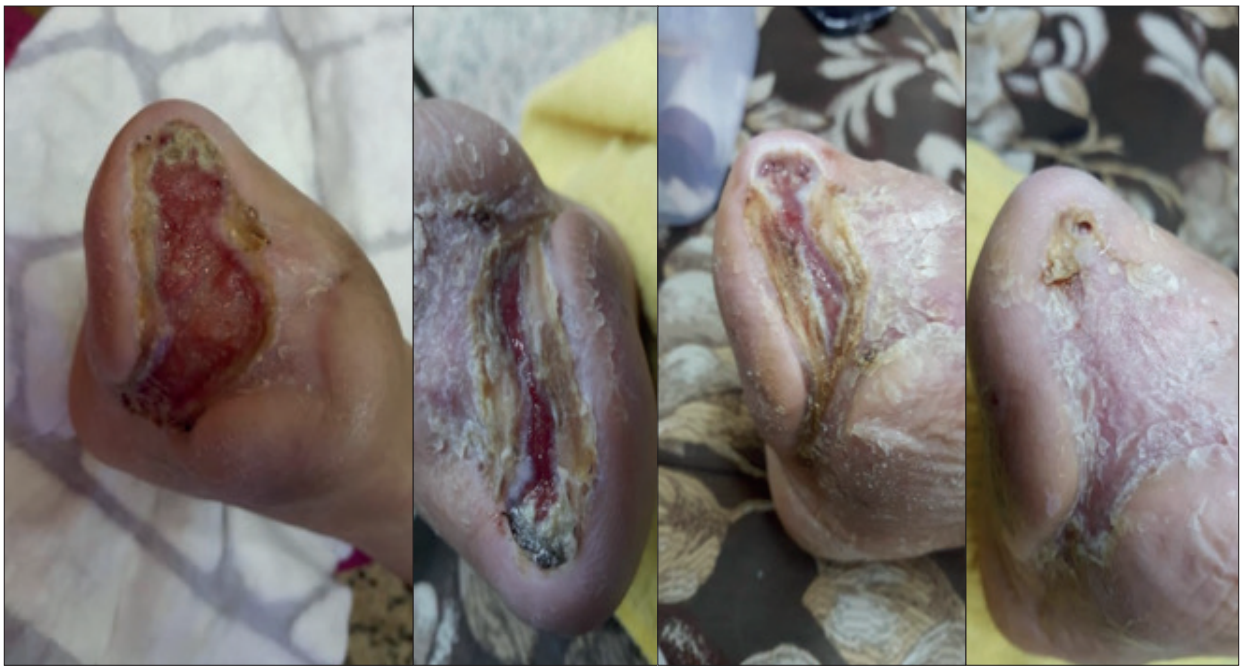

Figure 5. Trajectory to closure of the stalled right transmetatarsal ulcer after a single course of injection of 40mg AmnioFix over a course of 50 days.

inject 40 mg of AmnioFix into the surrounding wound bed and beneath the ulcer itself. Silver alginate dressings continued to be used to dress the wound.

Following the injection with AmnioFix, the speed of the ulcer's trajectory toward healing increased *[Figure 7]*. The ulcer had closed 60 days after the patient initially presented at the wound care clinic.

Discussion

All wound care providers are faced at some point by a problematic wound or difficult social situation where the placement of a biologically active amniotic tissue may be the next best logical step in the treatment pathway. The effectiveness of biologically-active amniotic tissue could be nullified by poor drainage control or a patient's inability to change a dressing regularly without disruption of the underlying amniotic-derived tissue that has been applied directly to the wound bed. This is where an innovative approach, such as injecting micronised dHCAM around the periphery of and beneath the open ulcer, affords a new option utilising the stimulatory properties of amniotic-derived tissues, like AmnioFix, in scenarios where a topical application may be rendered ineffective. In the two cases presented here, despite the presence of exposed bone in case 1 and evidence suggesting insufficient circulation in case 2, the hard-to-heal DFUs that had not responded to standard therapy completely resolved after being injected with AmnioFix.

There has recently been a paradigm shift in how we view DFUs that have healed. In the not-too-distant past, wound care providers have considered them as being definitively closed cases. However, as wound care providers we should be thinking of our healed patients as being in remission, as up to 40% of healed DFUs recur within the first year after closure (Armstrong et al, 2017). Educating patients with diabetes on foot care, aiding them to obtain appropriate protective footwear and understanding the patient's social situation can have a positive impact on long-term outcomes related to DFUs.

Conclusion

Over time, the costliest wound care-related expenses are associated with treatments that do not work, be they products or processes. Injectable AmnioFix has the potential to help patients afflicted with hard-to-heal DFUs and further studies on the use of this innovative approach in these types of wounds is warranted. DFJME

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