Case Report

Management of Over-Granulation in a Diabetic Foot Ulcer: A Clinical Experience

Krishnaprasad I N[1], Soumya V[2], Abdulgafoor S[3]

Abstract

Over-granulation or exuberant granulation tissue is a common problem encountered in the care of chronic wounds, especially that of diabetic foot ulcers. There are several potential options for the treatment of this challenging problem. Some have an immediate short term effect but may have a longer term unfavourable effect, for example, silver nitrate application and surgical excision, which may delay wound healing by reverting the wound back to the inflammatory phase of healing. Other products, such as foams and silver dressings may offer some effect in short term, but their long term effects are questionable. The more recent research supports Haelan cream and tape as an efficacious and cost effective treatment for over-granulation in a variety of wound types. The future of treating over-granulation may lie with surgical lasers, since lasers can not only remove over-granulation tissue but will also cauterise small blood vessels and are very selective, leaving healing cells alone while removing excess and unhealthy tissue.

Recently Drs Lain and Carrington have demonstrated the utility of imiquimod, an immune-modulator with anti-angiogenic properties, in the treatment exuberant granulation tissue, in a patient with long standing diabetic foot ulcer, resistant to other forms of therapy. We adapted a modified version of their protocol in the management of a similar patient in our hospital and achieved a good result in lesser time than the former.

Keywords: ***Over-granulation, diabetic foot ulcer, imiquimod.***

Introduction[1-3]

Granulation tissue is composed largely of newly growing capillaries. If granulation is present in the wound, it is an indication that the wound is healing, and a dense network of capillaries, large number of fibroblasts, macrophages and new formed collagen fibres will be present. However, sometimes the granulation will 'over grow' beyond the surface of the wound and this is called 'hyper-granulation' or 'over-granulation'. Over-granulation is defined as granulation tissue which is in excess of required amount needed to replace the tissue deficit. It often results in a raised mass above the wound. It may be a difficult condition to manage as the presence of such tissue will prevent or slow epithelial migration across the wound, and thus delay wound healing.

Over-granulation usually presents in wounds healing by secondary intention. It is clinically recognised by its friable red, often shiny and soft appearance that is above the level of the surrounding skin and can be healthy or unhealthy. Healthy over-granulation tissue presents as moist, pinky-red tissue that may bleed easily. Unhealthy over-granulation tissue presents as either a dark red or a pale bluish purple uneven mass rising above the level of the surrounding skin which also bleeds very easily. However, whether healthy or unhealthy, the wound generally will not heal because, epithelial tissue will find it difficult to migrate across the surface and contraction will be halted at the edge of the swelling. The healthy granulation tissue has the potential to reduce naturally and to eventually heal without intervention although this may take longer than if it is treated.

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Particular care should be taken in differential diagnosis, as a fungating malignant ulcer can mimic a hypertrophic granulation tissue.

Case Report:

A 55 years old female patient, diabetic, on insulin therapy for the past few years, presented with a non-healing ulcer over the past 6 months, over the inferolateral aspect of left heel (Fig 1).

On examination the ulcer was about 5×5 cms, with slightly indurated and unhealthy margins. The ulcer floor had a dusky red fungating mass filling almost the entire floor, slightly indurated, fragile and adherent to the ulcer base. The mass was not tender but has occasional foul smelling discharge and caused difficulty in donning a foot wear. Also it bled whenever the patient walked barefooted for a few distances. She had symmetric sensory peripheral neuropathy of both lower extremities. Peripheral pulsations were all normal in the lower extremities. Because of the bleeding mass and ulcer, the patient was physically, socially and psychologically incapacitated. She had undergone multiple therapies, including indigenous treatment, but none has given her a permanent cure. She was advised surgical removal of the excess granulation tissue by her diabetologist, but she was not willing for surgery. Then she was referred to our department for any non-surgical options in her management.

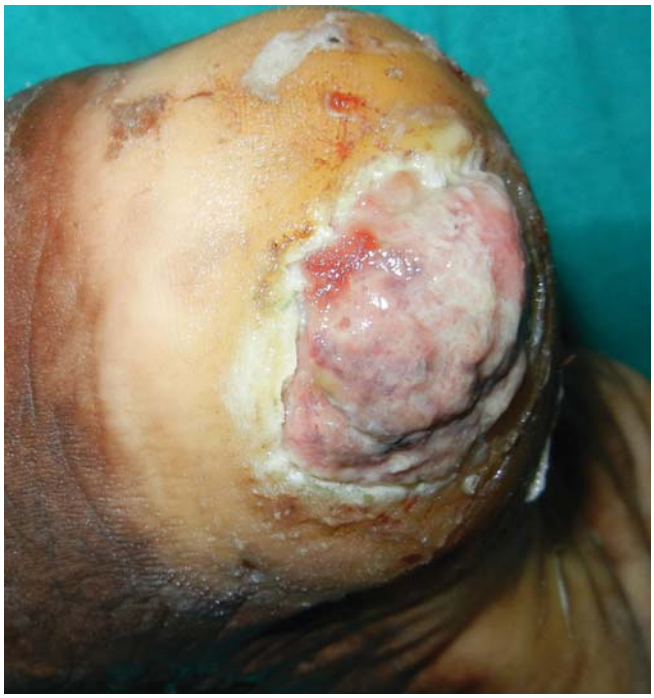

Fig 1- *Ulcer Pre treatment*

We did a thorough literature search for the possible management options and came across many different options, many of which she already had tried, and many which were not locally available. Among those methods, the utility of topical imiquimod, an immunomodulator with anti-angiogenic properties was demonstated by Lain and Carrington[4], in a patient with a diabetic foot ulcer with overgranulation. Their treatment protocol consisted of 4 days/week regimen of topical imiquimod at night, an enzymatic debriding agent for the remaining 3 days and morning application of mupirocin cream. They reported a good ulcer healing in 7 months time.

Imiquimod cream was locally available, since it is used by dermatologists in the management of perianal and genital warts, actinic keratosis, basal cell carcinoma, keloids etc. We discussed this treatment option with the patient and caregivers, with explanation of the benefits and possible side-effects and the need for a strict compliance to the regimen. We adopted a modified protocol since enzymatic debriding agents were not locally available. We used topical imiquimod 3 days per week and for the remaining 4 days, special moisture

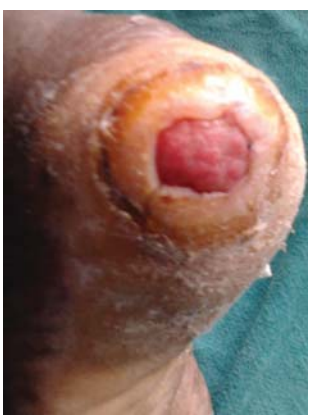

Fig 2- *6 Weeks Follow-up*

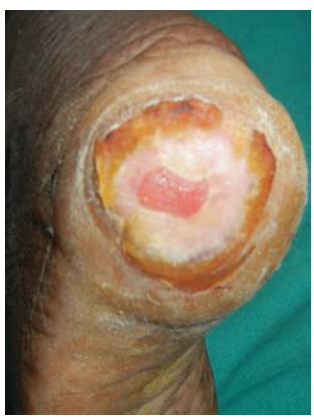

Fig 3- *12 Weeks Follow-up*

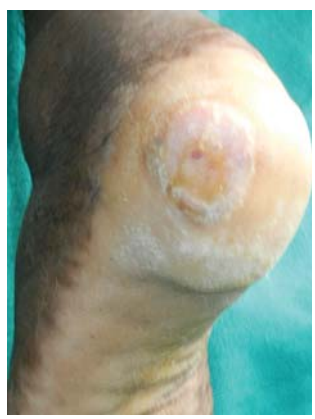

Fig 4- *18 Weeks Follow-up*

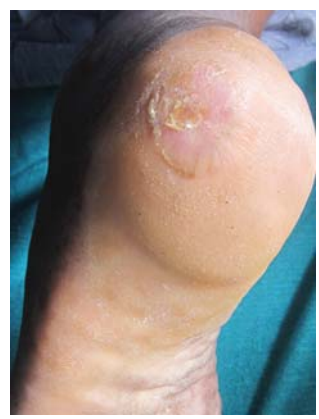

Fig 5- *24 Weeks Follow-up*

retaining dressings were given to promote autolytic debridement. Every morning a topical antiseptic preparation containing nano-crystalline silver was applied. Before starting treatment, malignancy and infection were ruled out by appropriate biopsy and culture methods. Correct application method was taught with special care to protect surrounding skin and the patient was asked to review every 6 weeks. We also emphasised the importance of proper foot care and diabetic control.

We reviewed the patient every 6 weeks (Figs 2-5) and the progress was assessed. The unhealthy edge of the ulcer was curetted at each visit to improve the chance of re-epithelisation. Blood sugar level was optimised and nutritional anaemia was corrected. There was a dramatic reduction in the size of hypertrophied granulation tissue over a period of 12 weeks, and by 18 weeks the epithelisation was almost complete covering the entire ulcer area.

The patient was extremely happy with the result and had very good functional improvement. She did not complain of any local or systemic adverse reaction during the therapy. She was given a proper foot wear and instructed a proper foot care plan.

Discussion:

There are many treatment options for over-granulation with limited research to support their use or to clearly suggest which is the most effective.

A "wait and see" approach was suggested by Dunford[3] but the last decade has seen some significant developments in this area of tissue viability and a more pro-active approach should be taken.

Inflammatory response may be related to infection and the use of an antibacterial dressing such as sliver, cadexomer iodine, honey, PHMB (polyhexamethylene biguanide) can assist with managing local colonisation and reduce the potential and also reduce the over-granulated tissue[5].

The earliest recommendation for treating over-granulation was foam. Harris and Rolstad[6] reported the findings of a prospective non-controlled correlation study with 10 patients and 12 wounds using a polyurethane foam dressing to reduce over-granulation tissue. The results demonstrated a reduction in granulation tissue. It was concluded that the pressure of the foam on the granulation tissue reduced the oedema and flattened the over-granulation tissue. Pressure from foam was then replaced by the suggestion of double application of hydrocolloid. Controversially an occlusive dressing is thought to be a possible cause of over-granulation but potentially the pressure of the double application may reduce the excess tissue.

Morison *et al*[7] noted that silver nitrate reduced fibroblast production. However, the use of silver nitrate directly reduces fibroblast proliferation and is therefore, not recommended for prolonged or excessive use[8] and should never be considered first-line therapy and should only ever be used with great care for the more stubborn area of granulation. This is particularly important as chemical burns have been reported and more likely to occur with longer application times. When it is necessary, a topical barrier preparation such as petroleum jelly or white soft paraffin should be applied to protect the normal skin surrounding the area of over-granulation[9].

Another highly successful method of treatment would be a short course of a topical steroid to suppress the inflammatory process[10,11] and tri-adcortyl was often the chosen steroid to be used in this case. However, it is no longer recommended for this purpose as it contains auromycin, an antibiotic, and it is indiscriminate use of such antibiotic therapy that may have initiated MRSA. Reducing the bacterial burden with auromycin may be one of the possible reasons for the success of tri-adcortyl in reducing over-granulation as reducing the bacteria load would remove the infection that stimulated the tissue to overgrow while the steroid reduces the inflammation that also stimulates overgrowth.

Lloyd-Jones[12] reported resolution of over-granulation tissue using a silver hydrofibre dressing, but this took some weeks to resolve which is much longer than other treatments.

Haelan tape[13] is a transparent, plastic surgical tape, impregnated with 4 mg/cm^2 fludroxycortide, which allows steady distribution of the steroid to the affected site. Fludroxycortide is a fluorinated, synthetic, moderately potent corticosteroid. As with other topical steroids, the therapeutic effect is primarily the result of its anti-inflammatory, antimitotic and antisynthetic activities.

Because granulation tissue is very delicate, it can sometimes be removed by wiping with a cotton swab. However, this should only be undertaken by an experienced person, as the wound could be traumatised

and healing could be further delayed. Surgical debridement is also an option, but should only be undertaken by an experienced surgeon.

Imiquimod, first approved by the Food and Drug Administration in 1997 for the treatment of external genital and perianal warts, has since been approved for treatment of actinic keratoses and has shown activity against basal cell and squamous cell cancers, melanoma, other verrucae, keloids, cutaneous T-cell lymphoma, morphea, and other viral infections[14,15]. As a synthetic ligand for toll-like receptor 7 at therapeutic doses, imiquimod stimulate immature, plasmacytoid dendritic cells, which secrete very large amounts of interferon. Interferon has numerous clinical effects including anti-proliferative, immunomodulatory, and anti-angiogenic effects[16,17]. Angiogenesis, whether in tumours or as part of wound healing, requires the correct cytokine milieu, including VEGF, MMP 9, bFGF, and TIMP1. Interferon achieves its anti-angiogenic effects by tilting the balance of cytokines to decrease those cytokines that favour angiogenesis, such as VEGF and MMP 9, and promote those that cause vessel involution, such as TIMP 1.

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