

Use of Promogran on a necrobiosis lipoidica diabetorum lesion

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ARTICLE POINTS

1 Cases of necrobiosis ulceration are rare in most individual clinical caseloads making prospective study of treatments difficult.

2 A case study of the successful treatment of a lesion with Promogran is described.

3 A patient's account of living with a necrobiosis ulcer is given to illustrate the debilitating effect it can have on quality of life.

4 Discussion is provided to support the use of new therapies in previously untried or unreported situations.

5 A healing outcome was achieved but it is acknowledged that this may not necessarily be due to the therapy since the course of necrobiosis ulceration is unpredictable. However, the patient expressed improvement in symptoms during therapy providing a much needed psychological boost in a long running ulceration situation.

KEY WORDS

- Necrobiosis
- Promogran
- Quality of life
- Ulcer

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Introduction

Necrobiosis lipoidica is a rare ulcerative condition commonly associated with diabetes, though it can occur in its absence. Ulcers recur and their progress when active is unpredictable despite seemingly appropriate wound management. These chronic wounds can affect quality of life considerably. We present a case study about Promogran, a novel therapy for chronic wounds, which was used on a 3–4 year old ulcer until full epithelialisation occurred after 8.5 months of treatment. An account by the patient is detailed to illustrate the personal issues associated with the condition and the improvement to morale when the new treatment coincided with the relief of some of the symptoms.

When caring for patients who have had chronic lesions for many years, practitioners sometimes stumble across a good outcome using a novel approach. Such situations are then reviewed retrospectively, with the intention of describing the care in order to let others know what wound therapy directions might be worth considering in complex cases. Reporting such as this can be thought of as a quick postcard from the frontline rather than a considered letter from headquarters. It is a flawed method because it can neither produce cause and effect data nor potentially even allow any reasonable suggestion of a possible linkage between treatment and outcome since it may be nothing more than a chance produced outcome. However, intuition based on experience that there was something of value occurring makes a case study worth reporting because it signposts possible areas for future prospective study. The frequency of some diseases can mean that individual practitioners in non-specialist clinic situations may only see a single case.

It is worth acknowledging the primacy of evidenced based care in today's health service, but the use of new agents in complex wounds can lie outside these boundaries. Innovative care must rely on an understanding of both the wounding condition and the mode of action of the product, together with a clinical risk assessment suggesting at worst the product will be unlikely to cause harm and may be

likely to be beneficial. Taking these considerations into account and proceeding with the informed consent of the patient will reduce the potential problems of malpractice litigation associated with innovative care.

Utility of single case studies

A single case study was reported in a recent publication exploring management of necrobiosis lipoidica diabetorum (NLD; Onugha and Jones, 2003). Relative rarity makes conditions hard to study in an organised fashion. Longstanding complex and chronic wounds may be treated in many ways, often with the latest products in an attempt to get lucky on healing for the patient who may be low on hope of ever finding a resolution. This is not unreasonable providing the practitioner bases their decision to utilise a treatment on the most up-to-date knowledge of the wound's causative condition, wound healing physiology and the product's compatibility to the targets for wound care (Stotts and Wipke-Tevis, 1996; Schultz et al, 2003).

This is the basis of a considered and appropriate care plan which attempts to ensure that all measures are taken holistically to get the patient into the best health that is practically achievable to facilitate wound healing prior to initiating novel therapy. The application of new therapy must be in the context of good wound care, i.e. that which is required to reverse underlying aetiology if

LIVING WITH A NECROBIOSIS ULCER

Household/domestic routine

'Cleaning the bathroom is difficult as I find kneeling uncomfortable because of there being no give in the skin, and I am worried about knocking it. Bedmaking is also a worry for fear of knocking it on the bedframe as it is just at that height. Going up and downstairs is difficult and painful due to the lack of skin flexibility.'

Personal hygiene

'Showering is now easier because of using a Limbo waterproof protection system. Used to bathe but I only filled half a bath but it had a tendency to bleed and the horror of a bath full of blood.'

Shopping

'I avoid the sales as I worry about my leg being knocked in the large crowds. Shopping trolleys at the supermarket are a major hazard too. I tell people to go in front of me but they don't understand and sometimes insist I go first.'

Gardening

'Like with kneeling to do cleaning gardening is equally a problem because of the skin not stretching and it can cause a lot of pain. I also worry about getting it dirty.'

Leisure time

'Can't drive a manual car must have an automatic. We live near the beach and when we go there sand used to get into the wound and make it irritable so we tended not to go very often. Now that it has improved this summer I have been able to go to the beach with my grandson which has been great. I haven't been swimming for a long time and would love to go again if it ever heals up.'

Animals

'Dogs make a bee-line for me as they smell the wound and want to jump up at my leg making me embarrassed at the situation and worried about them making it worse. Last weekend though (20th Sept 2003) I had my first close encounter with a dog for ages and at no time did he go to smell it and I was thrilled.'

Personal relationships

'The condition can cause tension at times because my husband worries about me overdoing it standing and doing jobs in the house. It sometimes restricts what we do together as I like to avoid large crowds.'

'I have been paranoid about anyone including my husband seeing it. These feelings became steadily worse because of other people's cruelty. This turned me into a very insecure person which caused more personal problems.'

Other people's reactions

'Over the years I have had lots of comments, pity, sympathy and funny looks when people hear about it or see my leg bandaged up. I wear a lot of trousers these days to cover it up, but I do sometimes wear a dress as I don't worry so much as I did once about how it looks to other people. Everybody who knows me worries about my leg more than I do – "get Caz a chair 'cos of her leg" I hate it is just embarrassing, I really hate the fuss and it puts me off going to "do's."

Personal appearance

'I do like nice shoes but can't wear them because of the bandages. But this year I have worn some dresses because the dressings have not been so large since being on the Promogran.'

Figure 1. Living with a necrobiosis ulcer

this is possible, and remove any local wound factors that might delay healing, such as callus build up, hyperkeratosis at the wound edge, excess exudates and so on.

**Necrobiosis lipoidica
diabeticorum**

The following case study considers the application of Promogran (Johnson and Johnson Wound Management Worldwide), a protease modulation therapy, to the chronic lesion of a patient with NLD. The more common term for this condition is necrobiosis lipoidica which allows inclusion of

the significant minority of cases that occur in patients who do not have diabetes (Lowitt and Dover, 1991). This condition is associated with diabetes and usually affects women under 40 years with a female to male ratio of 3:1 (Lowitt and Dover, 1991). It is a rare complication that occurs in approximately 0.3% of all patients with diabetes. Lesions have been described as painless (Westerhof et al, 1993) though this is not consistent with the case described here when the lesions were open. However, in the case we describe the condition was complicated by an underlying ischaemia.

Lesions are usually located on the anterior surface of the leg although they can be elsewhere. They are atrophic in appearance, recessed below normal skin level and contain telangiectatic vessels (Westerhof et al, 1993). Ulcerations solely on the leg account for 85% of occurrences (Lowitt and Dover, 1991). These skin conditions are disfiguring and are likely to cause psychological discomfort especially when they appear on areas of commonly exposed skin.

Aetiology of NLD is unknown but microangiopathic and neuropathic processes have been suggested along with collagen abnormality, altered immune mechanisms and leucocyte functionality (Paquette and Golomb, 2001). Severe ulcerations often resist medical (corticosteroids, fibrinolytics, antiplatelet agents) and surgical treatment (deep excision and split thickness skin grafting, skin flap or allografted cultured keratinocytes) and have been known to develop into squamous cell carcinoma (Lowitt and Dover, 1991).

Case study

Caz is an optimistic outwardly fit 47-year-old married woman who takes pride in her appearance. She also undertakes a regular role in the daytime care of her grandson, a boisterous toddler of 2 years.

History

Caz has had NLD for over 26 years on the left anterior lower leg/foot and the current ulcer has been present for at least 4 years (see *Figure 1* for Caz's account of living with necrobiosis). Caz was diagnosed with diabetes in 1974 and took oral hypoglycaemics for 3 years. She started on insulin after a diabetes coma. Her most recent HbA_{1c} result from September 2003 was 10.5% (normal range given by local pathology laboratory 4.2–6.1%; DCCT target 7% or less (DCCT Research Group, 1993), indicating suboptimal control. Previous HbA_{1c} results from February 2002 and Oct 2000 were 9.3% and 8.2%, respectively, which demonstrates a long-term tendency to be above the desired range. Renal and liver function tests in February 2002 were normal but total cholesterol at 5.8 mmol/l was higher than the normal range (desired to be < 5.2 mmol/l). Cholesterol levels also remained

higher than desirable with values of 5.1 mmol/l during January 2001 and 5.4 mmol/l on August 2001. Caz is on a statin (simvastatin 40 mg) and her cholesterol level is now 4.8 mmol/l as at July 2003.

NLD lesion

In 1977 a tiny spot appeared on the top of Caz's left foot. Her GP, skin and diabetes specialists at that time were unable to provide any information on diagnosis or management. Diagnosis of necrobiosis lipoidica was made in 1978 by another diabetes physician, but no treatment was available. A biopsy was taken by a skin specialist in 1980. Subsequently care of the ulcer has been shared by her GP, diabetologist, surgeon and dermatologist, who have used various treatments, including eusol and paraffin, sticking plasters, steroid injections, steroid creams, Debrisan, curettage and nicotinic acid. According to Caz the latter treatment just turned her teeth black. The most valuable assistance came from a 1985 dermatologist referral to the Red Cross who instructed her on the use of make-up to conceal the lesion. However, Caz recalls that with this make-up in place there was 'no give in the skin causing more ulcers on foot and leg.' Further recollections demonstrated that the foot lesion had healed but the leg ulcer remained open constantly, at times bigger or smaller.

In June 2000, she was referred by the dermatologist to the podiatrist for care of a foot ulcer. At that time her leg lesion was under regular review by the dermatologist and locum surgeon, the latter of which requested daily salt baths and saw her fortnightly to scrub the ulcer bed, which Caz reported to be extremely painful. In November 2001, Caz was admitted to hospital by her GP with general unwellness and deteriorating ulcerations through which tendons were showing. It was during this time and thereafter that the podiatrist took over the regular aspects of care and review of both the leg and foot ulcers. In June 2000, Caz revealed symptoms of intermittent claudication necessitating referral to vascular surgery and ankle brachial pressure index (ABPI) testing. The result in the ulcerated leg was 0.33 and the result in the right leg was 0.46.

Angioplasty was performed in April 2001

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2 Caz has had various treatments, including eusol and paraffin, sticking plasters, steroid injections, steroid creams, Debrisan, curettage and nicotinic acid.

3 Caz was admitted to hospital by her GP with general unwellness and deteriorating ulcerations through which tendons were showing.

4 Angioplasty was done in 2001. Seven months later there was still significant peripheral vascular disease.

PAGE POINTS

1 Overall the condition restricts Caz's life in a number of ways. Firstly, the ulcer requires regular care by healthcare professionals; every 1–2 days by practice nurses and once a week by the podiatrist.

2 Secondly, her walking and exercise schedules are limited to reduce the risk of worsening the ulceration and she is advised to rest regularly with the legs elevated.

3 To some extent it could be said that the condition rules the patient. This is the case with many chronic wounds and becomes the way of life for the patient.

4 There have been a number of approaches to wound care in the past 3 years, some producing only transient success.



Figure 2. Leg ulcer approximately 7 months after angioplasty (22/11/01)



Figure 3. Granulation and epithelialisation but a new lesion appearing 1.5 cm distal to it (3/1/02)



Figure 4. Closure continuing on leg and foot but lesion distal to leg ulcer remains (17/1/02)



Figure 5. Ulcers back at Nov 2001 position – dark area distal point in leg ulcer shows head of track (6/12/02)



Figure 6. Improved colour of wound bases and track head in leg ulcer resolving (12/12/02)

but Caz has so far declined to pursue vascular grafting. Figure 2 shows the leg approximately 7 months post-angioplasty. Inflammation distal to the foot ulcer indicated an active inflammatory process although there were no obvious signs of infection. A black spot on the lateral edge of the leg ulcer is a sign of infection particularly if its appearance is sudden and in the presence of good care. In May 2002, the ABPI in the leg affected by necrobiosis ulceration was 0.46 and there was an ABPI of 0.6 in the other leg, despite the continuing peripheral vascular disease. Caz remains an occasional smoker. Figures 3–6 show the improving and deteriorating nature of NLD prior to application of Promogran.

Lifestyle factors

Overall the condition restricts Caz's life in a number of ways. Firstly, the ulcer requires regular care by healthcare professionals; every 1–2 days from practice nurses and once a week from the podiatrist. Caz also has to undertake part of the maintenance care

herself. The professional care requires her to attend her GP surgery in her home village for nurse wound care and she makes regular visits to the chiropody clinic in the nearest market town 10 miles from home. This wound care schedule restricts her potential employment opportunities and disrupts her social schedule. Secondly, her walking and exercise schedules are limited to reduce the risk of worsening the ulceration and she is advised to rest regularly with the legs elevated. Thirdly, her style of clothing is restricted up to a point because clothing must provide some protection against minor trauma from everyday knocks, such as jeans rather than skirts. Her ability to play with her grandson is also limited in order to prevent unnecessary trauma to the ulcerated area. During the diathesis of the ulcerations, there are times when they deteriorate from the disease process or from infection causing pain and anxiety. To some extent it could be said that the condition rules the patient. This is the case with many chronic wounds and becomes the way of life for the patient.

Wound care approaches

There have been a number of approaches to wound care in the past 3 years, some producing only transient success. These have included alginates (Sorbsan) and hydrogels (Granugel), the latter sometimes in combination with silicone net (Mepitel). Since

her hospitalisation in November 2001, Caz has also been taking antibiotics constantly starting with flucloxacillin and metronidazole, then 500 mg flucloxacillin four times daily. This was then reduced to 250 mg four times daily as a maintenance dose elevating at times to 500 mg when wound conditions deteriorated.

The standard care provided by the chiropody service since June 2000 has ensured close observation, regular debridement of callus and fibrin deposits that might hinder epithelialisation, provision of wound dressings consistent with moist wound healing, aspects of wound bed preparation, monitoring for early signs of infection and adjustment of antibiotics and also the coordination of care/interventions from other specialists, such as the diabetologist, diabetes nurses, vascular surgeon and tissue viability nurse.

During a joint consultation with a podiatrist and tissue viability nurse specialist in April 2003 it was discussed and agreed with Caz to try Promogran. This is a protease modulating therapy that binds excess matrix metalloproteases, known to be present in chronic wound fluid, and prevents them from deconstructing extracellular matrix in the granulation tissue at the wound base. It also protects growth factors allowing them to contribute to production of granulation tissue (Moore, 2003).

Promogran is suited to application on indolent wounds free of necrotic tissue and excessive slough. It is applied as the primary contact layer and is commonly backed with an antimicrobial dressing such as Actisorb Silver 220, Inadine or Acticoat since clinical experience with the product shared nationally shows that critical colonisations with *Pseudomonas aeruginosa* and local infections with other pathogens can sometimes occur after start of therapy (Johnson and Johnson Wound Management Promogran Symposia 2003, UK). To date there are no data to suggest this apparent phenomenon has anything to do with the use of Promogran and it may just be chance outcomes in the chronic wound target group that will all no doubt be either colonised or critically colonised with bacteria (Kingsley, 2001). However, given

AFTER THE INTRODUCTION OF PROMOGRAN

'The reduction in pain has been huge, from the very first time Promogran was used. There was no leakage from the first dressing, which makes a difference to the comfort. When the first dressing was removed I was completely amazed as the open area was significantly smaller.'

'Obviously the best thing has been the huge reduction in the size of the ulcer, but all of this has been added to by the secondary improvements such as less pain and leakage. When the dressing is changed it hasn't got the "horror" factor and it doesn't stick or pull. The shape of my leg is better too, I have an ankle again, and people have remarked on how much better I am walking which is a boost to morale.'

'No dressing has ever been as good as Promogran as it has made my life so much better because there is almost no leakage, something which used to happen a lot and I always had to take spare dressings with me everywhere.'

'Hot weather has always caused swelling but since Promogran there has been no swelling even on very hot days.'

Figure 7. Caz's life after the introduction of Promogran

experience and the unlikelihood of harm when using a slow release/safe antiseptic wound formulation of silver or iodine in a chronic inflammatory wound it is not an unreasonable standard application combination.

Promogran was initiated on April 23 2003 and applied in two gently normal saline moistened layers to the open base of the ulcer. The moistening of the Promogran is valuable in activating the dressing when the wound is in a drier phase. This was covered by Inadine to provide an antimicrobial backdrop, absorbent pad and secured using a retention bandage. The care plan was for the practice nurse to change the therapy and retention dressings

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Figure 8. Ulcer after Promogran for 1 week (2/5/03)



Figure 9. Ulcer after Promogran for 7 weeks (11/6/03)



Figure 10. Ulcer after Promogran for 13 weeks (24/7/03)



Figure 11. Ulcer after Promogran for 26 weeks (24/9/03)

inflammation surrounding the wound was visible to the podiatrist (Figure 8).

Conclusion

At 19 weeks after initiation of therapy the wound had reduced in size by approximately 75–90% and was well on the road to healing (Figures 9–11). Caz noticed that there was much less local redness and that the shape of her ankle had changed, which suggests a reduction of inflammation. Whether this will lead to a stronger scar that remains closed for longer between ulcerations remains to be seen. Promogran was continued until full epithelialisation which occurred in early January 2004, following an 8.5 month course of therapy. Whilst this is the desired outcome it has to be acknowledged that the natural history of this ulcerative condition is one of unpredictable change and the outcome may only be coincidental to the use of Promogran, especially considering the duration of therapy. If the necrobiosis causes a further lesion or the scarred area is disrupted by trauma it will be part of the care plan to start Promogran as soon as possible and appropriate (i.e. when the wound is free of necrotic burden and excess slough) rather than wait until chronicity is confirmed by healing delay.

One of the challenges for use of protease modulation therapy, as unit cost is a little more expensive than standard moist wound healing products, is when should it be started. The authors suggest that if despite appropriate wound care there is no progression towards healing at 4–6 weeks, treatment should start at this point. In patients with risk factors for chronicity (such as diabetes, rheumatoid arthritis, ischaemic lesions) treatment should be as early as possible and appropriate. In those with a history of delayed wound healing treatment should start as early as possible and appropriate.

What is clear from discussions with Caz is that she had an improved quality of life during the treatment period with Promogran and she is delighted that healing was achieved, giving her hope for effective treatment for future ulcerations from her NLD. ■

Acknowledgement to 'Caz' for her consent to use her experience for this case study and provide her personal account.

every 2–3 days and for the podiatrist change it once weekly to enable regular review of progress. On the basis of data on the effectiveness of Promogran (Wound Care Device Expert Meeting, 2001) it was decided to continue treatment for 6 weeks, stopping at this point or earlier if infection or other obvious deterioration occurred or if no improvement was visible or experienced by Caz in terms of pain control, for example. At 6 weeks if improvement was visible the protocol would be continued for a further period of 6 weeks and reviewed again. In this case, it was felt that the therapy could be continued until epithelialisation was completed as the underlying chronicity factors of the disease process would still be present and could cause an immediate cessation of healing if therapy was discontinued before epithelialisation.

After the first application Caz noticed a number of interesting features in terms of symptom control (Figure 7). After 7 days there were signs of improvement, and a notable amount of granulation and less

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