REVIEW

Necrobiosis lipoidica: a review of management and the role of compression

Daniel Zhang[1] and Gabrielle McMullin*[2]
[1]Sutherland Hospital, Caringbah, NSW 2229, Australia
[2]St George Hospital, Kogarah NSW 2217, Australia
*Corresponding author Email gmcmullin@ssvc.us

Abstract

Necrobiosis lipoidica (NL) is a rare skin disorder that causes significant distress due to its unsightly appearance and propensity to ulcerate. There is a poor understanding of the underlying pathophysiology which ranges from microvascular angiopathy to collagen disruption. Current treatment options, including corticosteroids, immunomodulators and phototherapy, have potentially serious side effects and limited effectiveness. Evidence is sparse and heavily varied, with no well-evidenced guidelines or management approaches that is agreed upon. Properly applied compression therapy has strong evidence in the management of lower limb wounds, and the same physiological effects may have a role in NL therapy. This review seeks to consolidate the current understanding of the underlying pathogenesis and explore current and potential treatment options, including compression therapy, with a focus on the proposed mechanisms of action of therapy for NL.

Keywords necrobiosis lipoidica, compression therapy, ulceration, skin disease

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Introduction

Necrobiosis lipoidica (NL) is a rare, non-infectious granulomatous skin disease of uncertain pathogenesis. Various epidemiological, pathological and therapeutic observations have been made, but with no absolute conclusions regarding precise pathogenesis pathways or correlation between process and presentation. This paper seeks to explore the current understanding and treatment options for NL while also exploring another treatment option, compression therapy. NL management remains a contentious topic, with anti-inflammatory pharmaceutical options generally regarded as the first-line, but with inconclusive evidence and variable effectiveness. Compression therapy has occasionally been used as an adjunct together with pharmaceutical options; however, it has not been used as the sole primary intervention. This review aims to expand the repertoire of treatment modalities with non-pharmacological management for which there are minimal side effects and is generally very well tolerated.

Clinical presentation

NL is characterised by well-demarcated plaques ranging from yellow to red or brown in colour with associated erythema (Figure 1) and a propensity to ulcerate (Figure 2), quoted in up to 30% of cases[1]. Its distribution is typically seen in the lower limbs bilaterally; however, there have been reports of histologically confirmed NL in other parts of the body including the abdomen, scalp, genitals, face and upper limbs. The lesions tend to begin spontaneously as small, asymptomatic red or violet papules that erode over the course of months to years and may eventually break down into the classical plaque appearance, with or without ulceration. It is predominantly an aesthetic issue but may be associated with pain and pruritus. Ulceration is not uncommon, particularly after a traumatic trigger, which increases the risk of developing an infection. There have also been links with NL and an increased risk of squamous cell carcinoma[2], although it is unclear if this is associated with the chronic inflammatory response or a sequelae of NL independently. These lesions persist for years if left untreated but typically remain confined to the region of onset and do not progressively spread.

Epidemiology

There is an historical association with diabetes mellitus (DM), but even that is disputed. Studies on patients with NL quote between a 11–62% association with a confirmed diagnosis of DM, and potentially even greater figures when

considering patients with impaired glucose tolerance[3,4]. Indeed, when first identified and named by Oppenheim and Urbach in 1929–1932, it was dubbed necrobiosis lipoidica diabeticorum[5]. However, epidemiological studies have since identified that there are cases of NL without any indication of DM or impaired glucose tolerance, and absolute figures of rates of NL in DM are low, from 0.3% to up to 2%[3,4]. It is noted that Type 1 DM has been associated with greater rates of NL; however, glucose control itself does not seem to correlate with disease progression[7].

Other epidemiological observations include higher prevalence in females compared to males, with up to a 5:1 distribution[7], although previous estimates demonstrate a 3:1 distribution[8]. The typical age of onset is between 30–40 years of age, but extreme variations such as presence at birth have also been reported. Other risk factor associations that have been identified include obesity, hypertension, dyslipidaemia and smoking[9,10].

Pathological processes

NL may resemble multiple other granulomatous skin diseases, including granuloma annulare, erythema nodosum or the even rarer necrobiotic xanthogranuloma[4,11]. While diagnosis can be made clinically, confirmed diagnosis requires histopathology, often, but not always, demonstrating features of blood vessel wall thickening, collagen and fibrin abnormalities and granulomatous inflammation with multinucleated giant cells.

Vasculitic and inflammatory changes

Whilst there is no widely accepted pathogenesis pathway for NL, it is generally agreed that vascular changes and microangiopathy plays a part[4,12]. Features of vasculopathy such as inflammation and thickening of vessel walls, as well as immune complex deposition within vessels, have been identified on histological and immunofluorescence examination[12,13]. Common theories include glycoprotein deposition as seen in many complications associated with DM; indeed, it has been positively identified in patients with NL[9], yet this does not account for all cases. The rates of microvascular complications of diabetes such as diabetic nephropathy or retinopathy in patients with NL are not outside the expected range in the general diabetic population[7], suggesting that this follows a diabetic pathogenesis pathway. Other features such as immunoglobulins and complement factors in the vessel wall have also been identified, suggesting other aetiology paralleling autoimmune vasculitidies[9,13]. Indeed, vascular endothelial growth factor (VEGF) has been demonstrated to be involved in the pathogenesis of NL[14]. VEGF promotes proliferation of endothelial cells, which in excess is an observed phenomenon of microangiopathy[14]. Thus, while microangiopathy is clearly observed in cases of NL, the precise pathogenesis remains unclear and multiple postulations currently circulate in the literature.

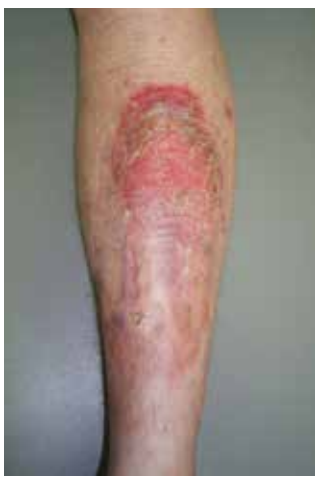

Figure 1. An example of NL's characteristic well-demarcated red or brown plaques

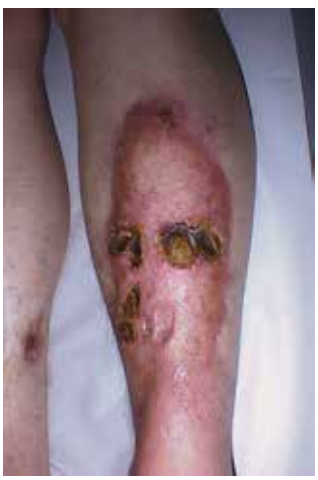

Figure 2. An example of NL's propensity to ulcerate

Interestingly, there are conflicting results regarding ischaemia as the primary aetiology, where Boateng et al.[15] observed decreased partial pressure of oxygen in the NL lesions, whilst Ngo et al.[16] identified increased cutaneous blood flow via laser Doppler flowmetry, suggesting a predominantly inflammatory process. Antibody-mediated vasculitis secondary to aforementioned immunoglobulin deposition may also play a role[4]. Inflammatory mediators such as tumour necrosis factor α (TNF-α) have been identified to be raised in NL patients compared to controls, suggesting an aetiological link with inflammation[14]. TNF-α is a potent stimulator of the cell cycle, inducing proliferation and apoptosis, and is an important regulatory factor in the pathogenesis of granulomas[4]. Nevertheless, there is no conclusive evidence that this is a primary aetiology for NL, although it is interesting to note that TNF-α as a therapeutic target has demonstrated promising results[4].

Collagen disruption

The other primary aetiological theory for NL stems from collagen abnormalities, in both its synthesis from fibroblasts and the ultrastructural layout within the dermis, subcutaneous tissue and basement membrane[4,11]. Light and electron microscopy of control-matched biopsies demonstrated collagen degeneration and necrosis surrounded by mononuclear cell infiltrates. Similarly, elastin was necrotic and the collagen-elastin bundles were disorientated or completed lost[17]; fibroblast function was also diminished[17]. NL lesions demonstrated disarrayed collagen fibrils and increased collagen cross-linking, likely secondary to elevated levels of lysyl oxidase[18]. Despite all these positive findings and potential aetiological links, the primary cause or trigger of NL is yet to be confirmed.

Treatment options

There have been numerous treatment options, targeting the identified pathogenesis findings. Treatment rationale has been typically based off successful treatment results of similar pathologies such as granuloma annulare or skin granulomas secondary to sarcoidosis, with links to the

identified pathophysiological processes underlying NL. Topical and systemic corticosteroids have been the mainstay of treatment, with a view to reduce inflammation in the lesion[4]. Phototherapy has been studied, with very variable response rates. Other options included biologic agents such as infliximab, a TNF-α inhibitor, and immunomodulators or immunosuppressants such as methotrexate, tacrolimus and fumaric acid esters[4,19]. A questionnaire of German dermatology experts in 2012 rated topical corticosteroids first-line treatment, with compression, topical calcineurin inhibitors and phototherapy equal second line options[10,20]. There have been no reports on compression alone in the management of NL lesions.

Corticosteroids

Corticosteroids have been the first-line treatment for NL, with topical and intralesional applications preferred over systemic treatment due to reduced side effect profile. Nevertheless, despite the propensity for systemic steroids to cause hyperglycaemia and hypertension, particularly in the already diabetic population, a short-term course is not contraindicated and may lead to rapid cessation of progressive disease and potentially complete resolution[4]. These effects can largely be attributed to the up-regulation of anti-inflammatory proteins such as annexin-1 and mitogen-activated protein kinases from the activation of the glucocorticoid receptor[21]. There is good evidence for resolving active lesions with enlarging borders; however, lesions with features of atrophy or ulceration do not benefit from steroid therapy, in-fact it may worsen the disease[4,22]. Indeed, in many cases, NL is refractory to steroid treatment, prompting consideration of other options.

Phototherapy

Phototherapy has also been studied for treatment of NL, given its effectiveness in other inflammatory dermatological diseases. The mechanisms underlying the treatment are not well understood, with some demonstrated immunomodulatory effects on various cytokines including TNF-α, interleukins and granulocyte colony-stimulating factor[23]. Various methods have been examined, including photodynamic therapy (PDT) with methyl aminolevulinate and psoralen-UV-A (PUVA) therapies. Again, clinical effects see a reduction in active inflamed borders and may resolve superficial lesions; however, it does not have any effect on atrophied areas[4]. Response rates of PDT have been quoted to be around 40% with some improvement, but in 50% of patients there is no effect[19,23]. PUVA studies demonstrate up to two-thirds of patients have partial or complete resolution[19]. One of the main drawbacks to phototherapy is the associated pain with treatment[23].

Biological agents

With the identification the role of TNF-α in the pathogenesis of NL, drugs such as infliximab, a monoclonal antibody that binds directly to TNF-α to inhibit its action, have been used particularly in ulcerating NL, with promising results[4,19]. It has been shown to be particularly useful in ulcerative disease, where corticosteroids and phototherapy have proven ineffective, with complete resolution in 70% of cases after a course of infliximab[19]. Infliximab has been given intravenously and intralesionally and is generally well tolerated; however, there is an increased risk of serious infection, including reactivation of latent tuberculosis and infections by opportunistic pathogens[24]. Infliximab has also been used in non-ulcerated NL with complete resolution at 6 weeks and no significant adverse effects, thus may potentially be a viable first-line option[25].

Immunomodulators

Various immunomodulators, including cyclosporine and tacrolimus, as well as topical dermatological treatments such as fumaric acid esters have also been trialled in the management of NL lesions for their anti-inflammatory effects[4,10,19]. Through inhibiting calcineurin, cyclosporine and tacrolimus inhibit the production of inflammatory cytokines and thus have anti-inflammatory effects which has seen promising results when used both topically and systemically[4,19]. Various combination therapies of calcineurin inhibitors and other immunomodulatory drugs such as methotrexate have also been used successfully[26]. Fumaric acid esters have been extensively used in dermatology for inflammatory skin conditions such as psoriasis, with good outcomes due to their inhibition of inflammatory pathways including inhibition of T lymphocyte proliferation, TNF-induced tissue factor messenger ribonucleic acid and TNF-induced binding of inflammatory proteins[4,27]. It has seen good results in other granulomatous disorders such as granuloma annulare and cutaneous sarcoidosis, and similarly demonstrated promising outcomes in the treatment of NL with less than 10% of patients showing no improvement[19]. However, these immunomodulating agents are not without their drawbacks, with the calcineurin inhibitors associated with nephrotoxicity, especially relevant given the high incidence of diabetes and potential diabetic nephropathy[4]. Fumaric acid esters are associated with lymphocytopenia, reported to be as common as in 44% of the test population[27].

Compression therapy

Bandaging has been used to treat wounds for millennia, both to protect and to promote healing. There is strong evidence that compression bandaging is beneficial for wound healing, particularly with venous ulcers[28]. Well recognised clinical effects include reduction in oedema and improved venous and lymphatic outflow; however, less appreciated but just as significant effects include a reduction in inflammatory cytokines, increased local oxygen partial pressure, and reduced lymphocyte adhesion[28–30]. Local cytokines are reduced after 4 weeks of compression bandaging in lower limb ulcers, including TNF-α and various interleukins[29]. Furthermore, cutaneous microcirculation as measured by laser doppler fluxmetry somewhat counter-intuitively demonstrated improved flow in areas under and around where compression is applied, most pronounced

with pressures between 21–30mmHg but still improved with pressures 31–40mmHg[30]. It is hypothesised that there is an arteriolar vasodilatory response to compression, potentially induced via increased nitric oxide production, resulting in these findings[28,30]. Thus, there is physiological evidence that compression addresses many of the identified pathogenesis pathways of NL.

However, there is no clear literature on the use of compression in NL. While a survey of German dermatology experts demonstrated that 47% would recommend compression therapy, 13.3% of whom recommend it as first-line, it has not been examined independently[10]. Some case reports and case series document compression used concurrently with the aforementioned treatment options[1,10].

Compression bandaging is a relatively cost-effective treatment option with minimal side effects; indeed, it may improve cardiovascular function by improving venous return[30]. Unlike pharmacological treatments, however, there is an element of operator skill and requires trained staff to apply the compression bandaging for effective results[31]. Compression is graded based off interface pressure, with 'mild' compression below 20mmHg, 'medium' compression between 21–40mmHg and 'strong' compression from 41–60mmHg. Various elastic and inelastic bandages are used to apply and maintain this pressure, with the gold standard of triple-layer bandages to ensure static stiffness[28,31]. The optimal pressure range for clinical benefit and comfort lies between 35–45mmHg, where the benefits of significantly reduced oedema, reduced inflammatory cytokines and improved microcirculation have been observed, yet is not tight to the point of being uncomfortable[28–31]. However, there are contraindications for compression bandaging, especially at this pressure. Significant peripheral arterial disease with systolic pressures at the ankle less than 50mmHg and severe heart failure may lead to ischaemic limb or worsening heart failure respectively, and thus 'medium' to 'strong' compression is contraindicated[28]. There may be a role for a modified compression bandage with reduced pressures in these scenarios.

Conclusion

The pathophysiology of NL is still unclear. There have been pathological processes identified, and individual treatment options for particular pathways have demonstrated some degree of efficacy. The most common and recommended first-line option is corticosteroids; however, the evidence supporting its use is inconclusive, and it may in fact be detrimental for ulcerated disease. Newer treatment options such as tacrolimus have demonstrating positive results for all degrees of disease severity; however, these are associated with significant side effects such as severe immunocompromise. Furthermore, in the subset of patients with multiple other comorbidities, steroids and immunosuppressing agents may be ill-advised due these concerning adverse effects.

Given the strong evidence for compression bandaging in lower limb wounds, the recognised physiological benefits of compression, and the current understanding of some of NL's mechanisms, compression therapy can be considered for NL lesions. This is particularly relevant for ulcerated NL, where typical, least invasive options of topical steroids or phototherapy have proven ineffective or even detrimental. It has been used together with other treatments with variable results; however, this has not been documented independently. Nevertheless, compression bandaging remains a low-cost, non-invasive treatment option that has minimal side effects and may be considered in the growing arsenal for NL treatment.

Further research needs to be done to better delineate the underlying processes and hopefully identify a clear causative pathway which can then be addressed for direct management. Currently there is no gold-standard to management and treatment should be considered on an individual basis depending on the presenting lesion, the patient's priorities and the resources available.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

An ethics statement is not applicable.

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