The role of anti-tumour necrosis factor in wound healing: A case report of refractory ulcerated necrobiosis lipoidica treated with adalimumab and review of the literature

Vijay Kumari Sandhu1 and Afsaneh Alavi2,3

Abstract
Necrobiosis lipoidica is a chronic granulomatous disease historically associated with diabetes. Necrobiosis lipoidica commonly presents with erythematous papules or plaques on the anterior lower extremities, which can be ulcerated in up to 30% of patients. The pathophysiology of necrobiosis lipoidica is unknown but proposed to be predominantly linked to microangiopathy. No treatment option for necrobiosis lipoidica has shown consistent efficacy. Previous case reports have shown immune-modulating agents to be reasonable treatment options for ulcerative necrobiosis lipoidica. However, evidence for the tumour necrosis factor-alpha inhibitor, adalimumab, is limited and contradictory. We report a case of a 74-year-old type 2 diabetic female with a 2-year history of multiple ulcerated necrobiosis lipoidica plaques resistant to topical and systemic therapy. Treatment with adalimumab showed complete re-epithelization of all ulcers by week 28. Adalimumab may be an effective treatment option for ulcerated necrobiosis lipoidica that has failed traditional therapies. Further reports of adalimumab treatment of necrobiosis lipoidica and other chronic inflammatory wounds are needed.

Keywords
Necrobiosis lipoidica, biologic agents, adalimumab, tumour necrosis factor-alpha, wound healing

Introduction
Necrobiosis lipoidica (NL) is a chronic granulomatous disease characterized by collagen degeneration within the dermis. It presents with well-circumscribed yellow-brown plaques commonly involving the lower extremities.1 In approximately 30% of the cases, there is concomitant ulceration and subsequent treatment challenges.2,3 Multiple treatments have been used in the management of NL; however, the management of chronic, ulcerated lesions remains a challenge. Tumour necrosis factor-alpha (TNF-α) inhibitors have shown some promise in treating ulcerative NL in previous case reports; however, the literature in this area remains limited. Adalimumab is an anti-TNF monoclonal antibody approved for management of several cutaneous and systemic autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, plaque psoriasis and, more recently, hidradenitis suppurativa. Herein, we present a case of a woman with ulcerated NL refractory to topical and systemic treatments successfully treated with adalimumab. We also review the literature on anti-TNF therapy for NL and comment on the role of TNF in chronic inflammatory wounds.

Case
A 74-year-old Caucasian female presented with a 2-year history of multiple non-healing ulcerated plaques on her right pretibial area (Figure 1). The patient reported that these erythematous plaques on her lower extremities had started approximately 20 years ago as small scattered red papules...
which had enlarged over the years and subsequently ulcerated 2 years ago. Her medical history included an 8-year duration of poorly controlled type 2 diabetes, psoriasis of the scalp and ears, and remote hysterectomy for endometriosis. Her regular medications were metformin, rosvuavastatin and enalapril. Her HbA1c was 10.1%, with rest of her blood work being unremarkable. She had previously been treated with topical and intraleisional corticosteroids and multiple courses of oral antibiotics for superimposed infection.

On physical examination, she had seven ulcerated plaques of varying size on her right anterior and lateral lower leg, with the largest measuring 8.9 × 7.0 cm (Figure 1). There was associated serosanguineous drainage. Biopsy of the plaques showed histological changes consistent with NL, specifically necrobiosis of collagen throughout the superficial and deep dermis with surrounding palisaded histiocytes and multinucleated giant cells.

Initial management involved treatment with pentoxifylline 400 mg three times a day and hydroxychloroquine 200 mg twice a day with no response in 3 months; she eventually was unable to tolerate these oral medications, leading to discontinuation. She was also treated with a course of doxycycline with minimal effect. In addition, she received proper wound care and compression therapy for 2 years. Given the extensive burden of disease and the failure of all treatment options thus far, the patient was consented for adalimumab treatment. She was started on adalimumab with an initial dose of 80 mg subcutaneously, followed by 40 mg weekly thereafter. At week 4, her wounds were much improved, with no drainage and reduced pain. By week 11, only two open wounds remained. By week 28, she had complete re-epithelization of all wounds, with only atrophic scars remaining (Figure 2). She tolerated adalimumab well, with no adverse effects. Adalimumab was discontinued given the complete resolution of her chronic ulcers, and she remained healed over the last year and up to the publication of this report.

Discussion

Ulcerative NL is notoriously challenging to treat, and response to current treatments is inconsistent. Traditional treatments for NL include topical and intraleisional steroids, topical calcineurin inhibitors, anti-platelet drugs, immunosuppressants, phototherapy and hyperbaric oxygen therapy. However, none of these therapies have shown consistent and effective results in the treatment of NL.

The difficulty in treating NL may stem from our limited understanding of the pathogenesis of the disease. Previous theories about the pathogenesis of NL had favoured microangiopathy, given the increased prevalence of the disease in insulin-dependent diabetes. In a recent retrospective study of 236 American patients with NL, 58.5% had diabetes, with patients with diabetes developing NL earlier in life. Despite this association, gaining control of blood sugars has not been consistently shown to effectively treat NL. Doppler studies have also refuted the role of microvascular ischaemia in NL. Other theories to explain the pathogenesis of NL include abnormal glucose transport by fibroblasts and antibody-mediated vasculitis, with direct immunofluorescence microscopy demonstrating deposition of IgM, IgA, C3 and fibrinogen in blood vessels.

Histologically, NL is noted to have interstitial and palisaded granulomas within the subcutaneous and dermis tissues. TNF-α is a pro-inflammatory cytokine believed to have an important role in granulomatous inflammatory diseases. TNF recruits inflammatory cells, such as macrophages and T cells, to the site of infection and also promotes increased macrophage phagocytic activity. Once the granuloma is formed, TNF acts as a survival factor promoting macrophage viability and thus maintenance of the granuloma.

In keeping with this, anti-TNF therapies are known to cause granuloma breakdown in infectious granulomatous disorder and subsequent dissemination of mycobacterium infections. Using the anti-granuloma effect, anti-TNF has been used to successfully treat several cases of cutaneous granulomatous diseases, such as sarcoidosis and granuloma annulare. We searched MEDLINE and Embase databases and identified several case reports supporting the use of TNF-α inhibitors for NL (Table 1). However, the majority of these reports use etanercept or
Table 1. Summary of cases of tumour necrosis factor-alpha (TNF-α) inhibitor therapy for necrobiosis lipoidica (NL).

| Author (year) | Age, sex | Diabetes (yes or no) | Ulceration (yes or no) | Disease duration | Previous treatment | Biologic, dose, duration | Clinical outcome | Adverse events |
|---------------|----------|----------------------|------------------------|------------------|--------------------|------------------------|------------------|---------------|
| Kolde et al. (2003) | 33, M | Yes (type 1) | Yes | Not reported | Topical corticosteroids, photochemotherapy, excision and grafting, and cyclosporine | Infliximab (5 mg/kg/month) for 2 months | Healing of all ulcers. Sustained after treatment cessation | Miliary TB reactivation |
| Drosou et al. (2003) | 32, F | Not reported | Yes | Not reported | Corticosteroids and clofazimine | Infliximab (5 mg/kg/month) for 2 months | Complete healing of lesions after second infusion | None |
| Cummins et al. (2004) | 14, M | No | Yes | 13 years | Topical corticosteroids, prednisone, dapsone, debridement and grafting | Etanercept (2.5 mg twice weekly) for 16 months | Healthy granulation tissue and epithelialization with no loss of autograft. No recurrence 2 years after the last surgical procedure without immunomodulatory medication | None |
| Zeichner et al. (2006) | 35, F | Yes (type 1) | No | Several years | Topical corticosteroids and pulse dye laser | Etanercept (25 mg/week) for 8 months | Improvement after first injection, with complete resolution after 8 months | None |
| Hu et al. (2009) | 84, F | Yes (type 1) | Yes | 3 years | Intralerial corticosteroids and local wound management | Infliximab (5 mg/kg) for 12 weeks | Complete wound healing at week 6. No recurrence at 9 months | None |
| Zhang et al. (2009) | 29, F | Yes (type 2) | Yes | 9 years | Topical and intralerial corticosteroids, pentoxifylline and cyclosporine | Etanercept (50 mg twice weekly) for 3 months, followed by adalimumab (40 mg biweekly) for 3 months | Initial improvement by 2 months with etanercept. No improvement when switched to adalimumab. Improvement with etanercept when re-initiated over a 6-month period | Tiredness after treatment |
| Suarez-Amor et al. (2010) | 50, M | Yes (type 1) | Yes | 7 years | Topical and intralerial corticosteroids, pentoxifylline and cyclosporine | Etanercept (25 mg twice weekly) for 5 months | Almost complete healing of ulceration by 3 months with no ulceration after 9 months | None |
| Conte et al. (2011) | 27, F | Yes (type 1) | No | 3 years | Topical tacrolimus, intralerial triamcinolone acetonide | Infliximab (5 mg/kg) for 12 weeks | Complete wound healing at week 6. No recurrence at 9 months | None |
| Barde et al. (2011) | 34, F | Yes (type 1) | No | 6 years | Topical and intralerial steroids, calcineurin inhibitors, retinoids, balneo-PUVA therapy, hydroxychloroquine | Intralerial infliximab for 3 weeks | Improvement after first injection with substantial improvement after second injection. Relapse of erythema after 1 month of treatment interruption with new plaque development | Pain during injection |
| | 65, M | No | Yes | 4 years | Topical tacrolimus, topical steroids, PUVA therapy, lymphatic drainage and elastic contention | Sodium hyaluronate dressing | Improvement after first injection with maintenance of result for 1.5 years after treatment cessation | Pain during injection |
| | 24, F | Yes (type 1) | Yes | 11 years | Sodium hyaluronate dressing | Sodium hyaluronate dressing | Decreased depth of ulcer after first injection | Recurrent streptococcal pharyngitis |
| Guedes et al. (2012) | 65, F | Yes (type 2) | Yes | 6 years | Topical corticosteroids, tacrolimus and cyclosporine | Etanercept (50 mg/week) for 6 months | Complete healing of all ulcerative lesions by week 8. No recurrence at 6 months | None |
| Leister et al. (2013) | 71, F | No | Yes | NR | Corticosteroids, clofazimine, retinoids, fumaric acid esters, cyclosporine and tacrolimus | Adalimumab (40 mg biweekly) for 10 months, then 40 mg/month for 5 months | Complete resolution of lesions. No recurrence 5 months after treatment cessation | None |
| Basoullis et al. (2016) | 19, F | Yes (type 1) | Yes | 2 years | Topical corticosteroids and hyperbaric oxygen | Infliximab (5 mg/kg/week) for 4 months | Healing of ulcers with marked overall improvement | None |
| Present case | 74, F | Yes (type 2) | Yes | Over 20 years, with ulceration for 2 years | Pentoxifylline, hydroxychloroquine, doxycycline, local wound care | Adalimumab (40 mg/week) for 28 weeks | Complete re-epithelialization of all plaques by week 28 | None |

TB: tuberculosis; PUVA: psoralen and ultraviolet A.
infliximab,14,15,18,21,22,25 with the literature on use of adalimumab in NL being limited. We identified only two published case reports of adalimumab use in NL with contradictory findings. In Zhang et al.,19 a 29-year-old type 2 diabetic female with ulcerated NL of the lower extremities and trunk showed improvement with etanercept over a 2-month treatment period, but no improvement with adalimumab. In Leister et al.,24 a 71-year-old non-diabetic female with ulcerated NL of the lower extremity exhibited complete resolution of her NL with adalimumab, with no recurrence 5 months after completing the treatment. Evidently, in contrast to the many case reports that exist supporting the efficacy of infliximab and etanercept for NL, the literature on adalimumab is limited.

Wound healing is a complex process that progresses through four stages: haemostasis, inflammation, proliferation and remodelling. As reviewed in Winston and Kirsner,26 a prolonged inflammatory phase involving TNF-α has been implicated in chronic wound development. Chronic wounds have higher systemic and local levels of TNF-α.27 As wound healing progresses, levels of TNF-α decline.28 Blockade of TNF-α has been noted to promote collagen deposition,27 and case series have shown improved healing of chronic wounds with topical application of the anti-TNF agent, infliximab.29 The success of TNF-α inhibitors in treating chronic ulcers has also been seen in other inflammatory ulcerative conditions such as pyoderma gangrenosum.30 Traditionally, biologic agents were held before surgery due to a potential impact on wound healing or wound infection. However, recent data support that the risk of infection is not higher in patients going to surgery while they are on biologics, including anti-TNF agents.31 Therefore, the role of TNF inhibitors in preventing and treating chronic wounds should be further explored. This study supports the role of anti-TNF in wound healing, particularly in inflammatory wounds.

In conclusion, NL is a chronic granulomatous disease of unknown aetiology, commonly seen in diabetic patients. Ulcerated NL is particularly challenging to treat and contributes greatly to the burden of disease. This case report demonstrates successful treatment of ulcerative NL with adalimumab. However, further reports of adalimumab use in NL with a larger sample size are needed. The response to TNF-α inhibitors in diabetic and non-diabetic patients should also be explored, given the possibility of different underlying disease processes in these two different patient populations. Finally, further research into the role of anti-TNF therapies in chronic wound healing is also needed.

Declaring of conflicting interests
Dr Alavi has consulted for AbbVie, Janssen, LEO, Galderma, Novartis and Valeant, and is also an investigator for AbbVie, Novartis, Regeneron, Pfizer, Boehringer-Ingelheim, Glenmark, Merck Serono, Roche, Xoma and Xenon. She received an unrestricted educational grant from AbbVie. Ms Sandhu has no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Informed consent
Informed consent was obtained from the patient for the publication of this case report and the images contained within this report.

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