Endocrinology, Diabetes & Metabolism CASE REPORTS

M J Verheyden and others

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A case series and literature review of necrobiosis lipoidica

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Summary

Necrobiosis lipoidica (NL) is a rare and chronic disease characterised by yellow-brown, atrophic, telangiectatic plaques usually located on the lower extremities, with pathological features of collagen necrobiosis and dermal inflammation. Most cases are seen in those with diabetes mellitus, particularly type 1 diabetes (T1DM), and many without diabetes have evidence of abnormal glucose tolerance or family history of autoimmune disease. In this study, we describe four patients with NL and T1DM. A common theme is late identification and delay in diagnosis. Hence, we discuss the clinical features, need for clinicopathological correlation, and the management and prognostic implications for this distinctive entity. While most remain relatively asymptomatic, others progress to debilitating disease with pruritus, dysesthesia, and pain. Pain is often intense in the presence of ulcerated plaques, a morbid complication of NL. Diagnosis requires the integration of both clinical and histopathological findings. NL has proven a challenging condition to treat, and despite the numerous therapeutic modalities available, there is no standard of care. Hence, in this study, we provide an overview of current management strategies available for NL.

Learning points:

- Necrobiosis lipoidica (NL) is classically seen in patients with type 1 diabetes.
- Koebner phenomenon, defined as the appearance of new skin lesions on previously unaffected skin secondary to trauma, is a well-recognised feature in NL.
- Background skin phototype contributes to variable yellow appearance of lesions in NL.
- Diagnosis of NL requires careful clinicopathological correlation.
- NL is a chronic disease often refractory to treatment leading to significant morbidity for the patient and a management conundrum for the multidisciplinary healthcare team.
- No standard therapeutic regimen has been established for the management of NL.

Background

Necrobiosis lipoidica (NL) is a rare condition, often associated with type 1 diabetes (T1DM). Endocrinologists have an integral role in early identification and referral to optimise outcomes for their patients. Diagnosis is challenging, requiring clinicopathological correlation in the setting of an extensive differential diagnosis. Although no standard of care for the management of NL has been established, a multidisciplinary approach to management is strongly advocated as it may reduce disease-related morbidity and psychological distress for patients with NL.

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Case presentation #1

A 24-year-old woman with T1DM recounted a 7-year history of erythematous plaques on the right anterior shin. A small patch arose that slowly enlarged in size, leading to presentation to primary care followed by referral to a dermatologist. T1DM was diagnosed at age 14 years. At diagnosis, HbA1c was 9.0% and serology was positive for glutamic acid decarboxylase (GAD). HbA1c ranged from 7.2 to 9.0%. She developed Hashimoto's thyroiditis, with elevated thyroid autoantibodies though normal thyroid-stimulating hormone (TSH). There was no personal history of other medical conditions. Family history was significant for relatives with Crohn's disease.

Investigation #1

A biopsy demonstrated extensive necrobiosis with palisading histiocytes extending into the subcutis; superficial and deep perivascular lymphocytic inflammation and scattered plasma cells; there were no organisms, tissue mucin, or evidence of dysplasia or malignancy. These findings were consistent with NL. At diagnosis, a thorough examination revealed a soft diffuse goitre.

Treatment #1

Six injections of intralesional steroid were administered over several months, followed by high-potency topical steroids under occlusion for 3–6 months. Nonetheless, the plaque continued to enlarge, albeit without ulceration. Given lack of response, and development of similar lesions on the other leg, a second dermatologist was consulted. Dermoscopy of the lesions was performed demonstrating arborising telangiectasia with a yellow to orange background (Fig. 1A and B). A second biopsy was not pursued given the prior biopsy was consistent with NL. Eight sessions of Q-switched Nd: YAG laser therapy were applied over 18–24 months, which was well tolerated. Pictures were taken at the start and end of the treatment course (Fig. 2A and B).

Outcome and follow-up #1

As there was minimal improvement after laser therapy, treatment was discontinued. Ongoing fluctuations in the appearance of the lesions persisted, particularly after vigorous exercise. No further treatment was sought and the NL is currently stable (Fig. 3). Diabetes remains well-controlled, with no evidence of macrovascular or microvascular disease. Dermatology Life Quality Index (DLQI) score is 10/30, indicating moderate effect on quality of life (QoL) mostly due to impact on self-esteem and self-image, influencing their activities and clothing choices.

Case presentation #2

A 24-year-old woman was diagnosed with T1DM at age 10 years. Over months, skin-coloured papules developed on the distal aspect of the right shin, which gradually became erythematous. Lesions were painful and pruritic, but no ulceration developed. Dermatological opinion was sought, and a differential diagnosis of granuloma annulare or erythema nodosum was proposed. No treatment was instituted at that time; however, the rash progressed to involve the anterior shin on both legs (Figs 4A, B and 5) and the medial aspect of her left upper arm (Fig. 6). HbA1c at diagnosis was greater than 12.5%, with several presentations thereafter with diabetic ketoacidosis. Diabetes-related complication screening was regularly performed with recent recognition of microalbuminuria (urinary albumin–creatinine ratio: 3.7 mg/mmol, N < 2.5 mg/mmol). HbA1c ranged from 10 to 12.5%. Thyroid function tests were

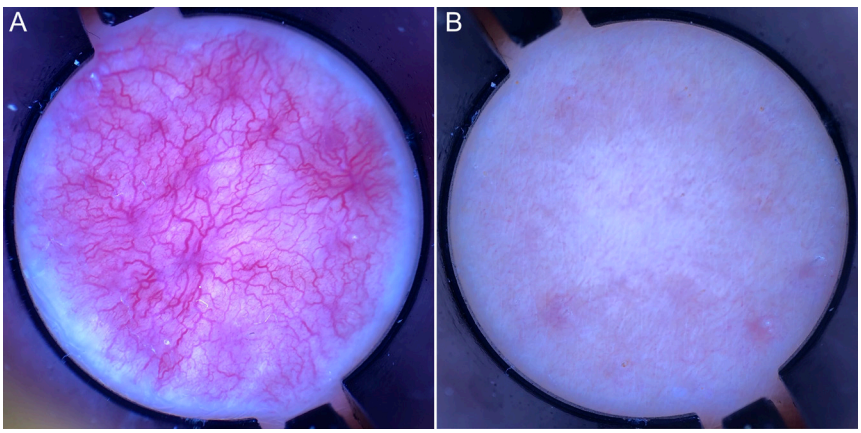

Figure 1
(A) Dermoscopy demonstrating arborising telangiectasia with yellow to orange background characteristic of necrobiosis lipoidica; (B) normal, unaffected skin on same individual as a comparator.

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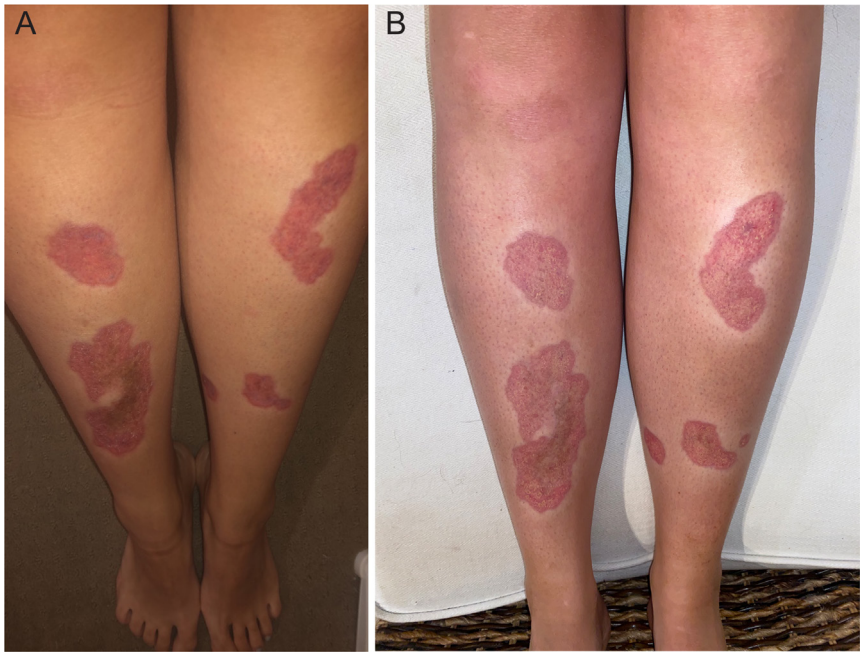

Figure 2
(A) Well-circumscribed erythematous, atrophic, telangiectatic plaques on the pretibial area immediately after receiving laser therapy; (B) end of laser treatment course demonstrating apparent progression manifested by enlargement of established plaques and emergent plaque on the left lower leg; circumferential hypopigmentation is appreciable surrounding each plaque.

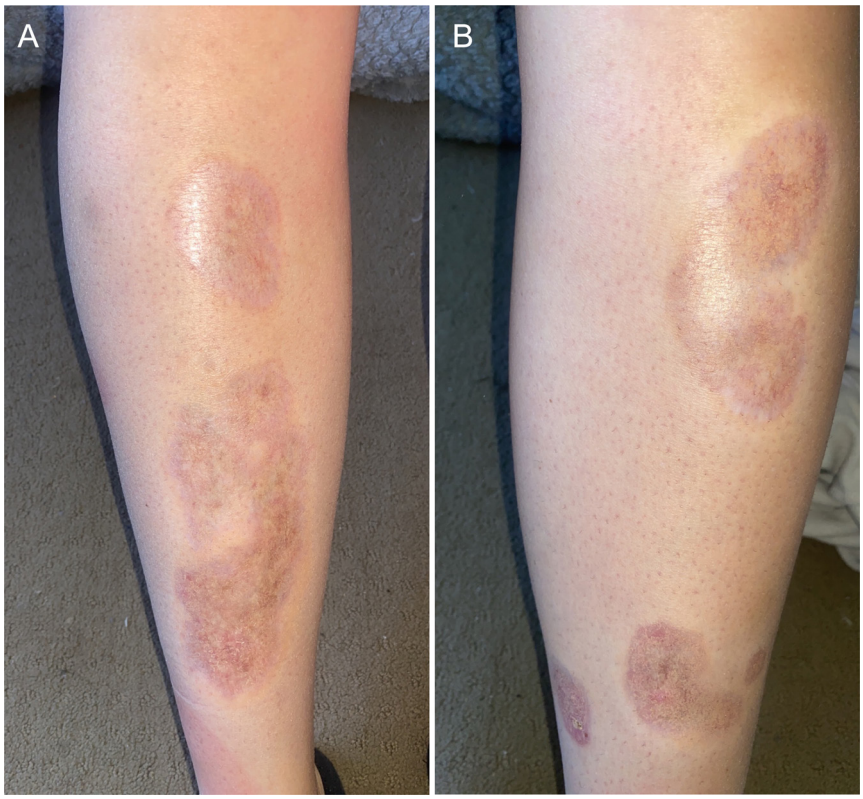

Figure 3
Well-circumscribed yellow-brown, atrophic, telangiectatic plaques on the pretibial area several years after completing laser therapy, remaining stable with low-level of disease activity.

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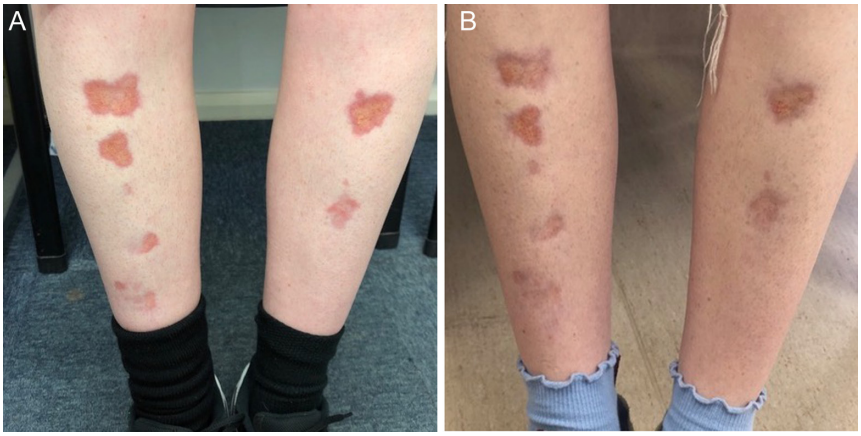

Figure 4
(A) Numerous well-circumscribed erythematous, atrophic, telangiectatic plaques on the pretibial area; (B) follow-up at 1-year demonstrating yellow-brown plaques with central atrophy.

normal and thyroid autoantibodies were undetectable. Coeliac serology was unremarkable.

Investigation #2

An initial biopsy was inconclusive and not repeated.

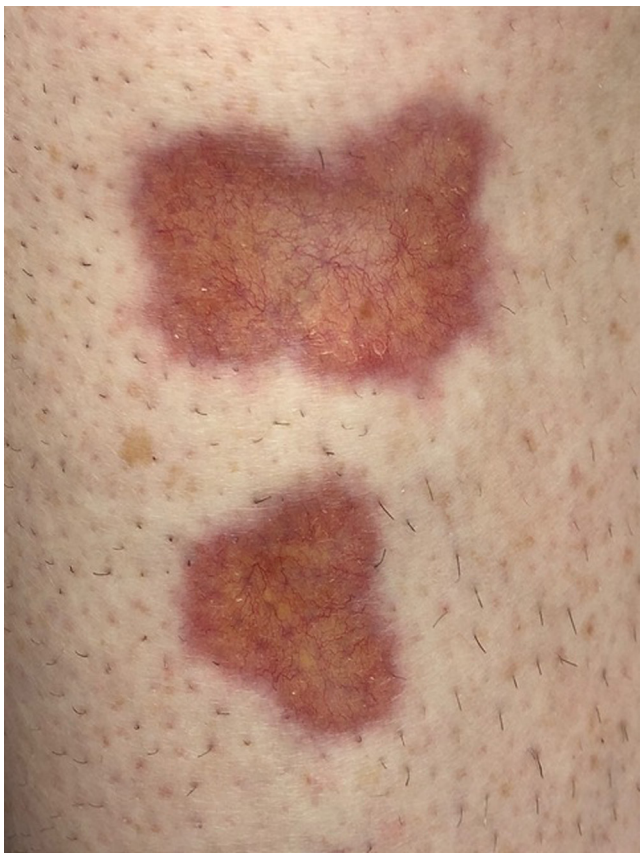

Figure 5
Irregularly shaped, well-circumscribed erythematous plaques with prominent telangiectasia on the proximal aspect of the right pretibial area.

Treatment #2

A clinical diagnosis of NL was established. Multiple modalities have been trialled, including high-potency topical steroids under occlusion, 3 monthly intralesional steroid injections and the combination of 0.1% tacrolimus ointment with hydroxychloroquine 200 mg twice daily for a period of 3–4 months. Given the poor response, cannabidiol oil, both topical and oral, was self-initiated, again with minimal efficacy. Recently, a regimen comprising doxycycline 50 mg twice daily, pentoxifylline 400 mg three times daily, and topical calcipotriol and betamethasone was trialled resulting in hyperglycaemia with minimal evidence of benefit over 3 months.

Outcome and follow-up #2

According to self-report, lesions have reduced in size, erythema, and discomfort. Regular exposure to sunlight

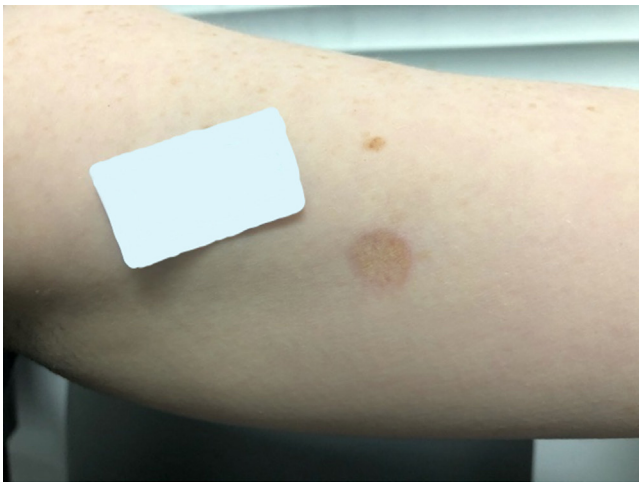

Figure 6
Circular, well-circumscribed, yellow-brown plaque with subtle overlying telangiectasia on the left upper arm.

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(containing UV light) has been encouraged and UV phototherapy or photodynamic therapy (PDT) has been considered. DLQI score is 10/30, indicating a moderate impact on QoL, mainly due to influences on self-esteem and self-image, alongside enduring fear regarding potential for ulceration.

Case presentation #3

A primiparous 21-year-old woman presented for the management of T1DM in the context of early pregnancy, with bilateral plaques on the anterior shins consistent with known diagnosis of NL, which was established at age 14 years, 3 years after the diagnosis of T1DM. On the initial antenatal visit at 8 weeks' gestation, insulin pump therapy was utilised to manage diabetes and HbA1c was 7.2%. Medical history included generalised anxiety disorder treated with escitalopram and class II obesity. There were no diabetes-related complications. At diagnosis, HbA1c was 10.1% with serology positive for GAD. TSH was normal and thyroid and coeliac autoantibodies were negative. The erythematous plaques were detected first on the left anterior shin, then the right shin, and then slowly enlarged. These were not associated with pain, pruritus, or ulceration.

Investigation #3

A biopsy of the right-sided plaque demonstrated necrobiotic collagen bordered by irregular inflammatory infiltrate composed of histiocytes, lymphocytes, and occasional plasma cells (Fig. 7). These morphological features were quite typical for NL.

Treatment #3

When first diagnosed, a single intralesional steroid injection to each lesion was administered resulting in localised hyperpigmentation. Thereafter, no further treatment was pursued.

Outcome and follow-up #3

Disease activity was stable, with no substantial changes noted over several years or throughout pregnancy (Fig. 8). DLQI score of 1 suggested no significant impact on QoL, although the plaques are associated with self-consciousness.

Case presentation #4

A 22-year-old primiparous woman presented for the management of T1DM in the context of unplanned pregnancy. At the first appointment, she was at 7 weeks' gestation with blood glucose levels controlled with continuous s.c. insulin infusion. Her HbA1c was 8.0%. Antenatal blood tests were unremarkable. There was no personal or family history of thyroid disease. Examination was remarkable for bilateral erythematous plaques with prominent telangiectasia on the anterior shins. T1DM was diagnosed in the first year of life and led to frequent episodes of hypoglycaemia with rebound hyperglycaemia due to multiple factors. No information is available regarding autoantibody status in relation to known T1DM. TSH was normal and coeliac serology was unremarkable. At 13 years of age, erythematous plaques developed on the bilateral anterior shins. These plaques were not prioritised for investigation, but after persistent growth, referral to dermatology was arranged.

Investigation #4

A shave biopsy of the left-sided plaque demonstrated perivascular inflammation and altered collagen in the upper layers of the reticular dermis. Histopathological findings were consistent with NL.

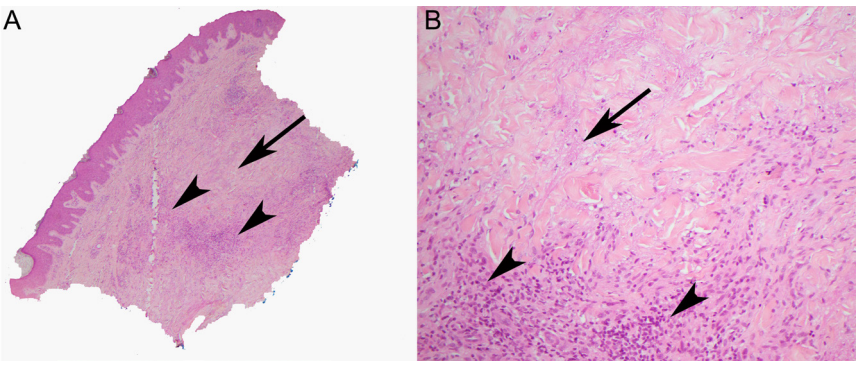

Figure 7
In the dermis, there is degenerate (so-called 'necrobiotic') collagen (arrows) bordered by an irregular inflammatory infiltrate (arrowheads) composed of histocytes, lymphocytes, and occasional plasma cells. Although this can be difficult to distinguish from other causes of so-called necrobiotic (collagenolytic) granulomas, such as granuloma annulare, the morphological features including the irregularity of the contours are quite typical for necrobiosis lipoidica (H&E original magnifications: A 40×, B 200×).

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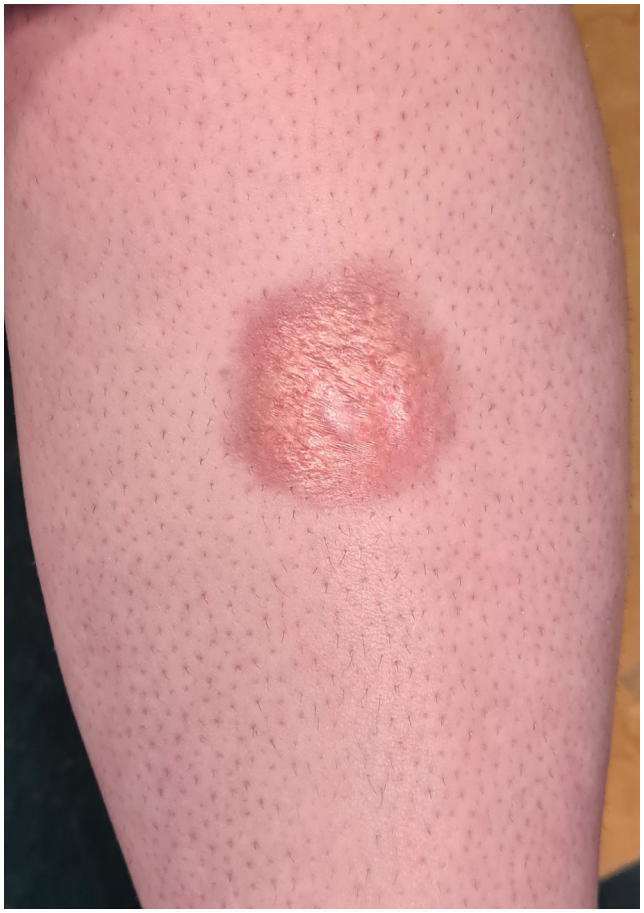

Figure 8
Well-circumscribed erythematous, telangiectatic plaque on the pretibial area.

Treatment #4

After referral to dermatology, a shared decision-making approach was used to discuss the risks, benefits, and alternatives to treatment. Treatment has not been sought for this condition.

Outcome and follow-up #4

The disease is stable, with no substantial changes noted over several years (Fig. 9A and B). The plaques are pruritic and have led the patient to feel self-conscious at times but have no significant impact on QoL, as evidenced by DLQI of 2. During the last 3 months of pregnancy, small papules arose on abdominal striae and breasts that were pruritic. These findings were consistent with polymorphic eruption of pregnancy (PEP). Pregnancy had no impact on disease activity of NL. A healthy child was born with prompt resolution of PEP. No evidence of microvascular or macrovascular complications of T1DM was identified on screening.

Discussion

NL is characterised by yellow-brown, atrophic, telangiectatic plaques most often identified on the pretibial area of the lower limb. These plaques are well-circumscribed with erythematous, violaceous elevated rims. Initially, small red-brown papules and plaques emerge that enlarge slowly with concomitant development of central epidermal atrophy and prominent arborising telangiectasia. Erosions and ulceration are common, often following minor trauma to the affected area (1, 2, 3). Trauma may induce the development of additional lesions on previously unaffected skin through the Koebner phenomenon (4). While most remains relatively asymptomatic, pruritus, dysesthesia, and pain can occur. Pain is often intense in the presence of ulcerated plaques. Other locations are less commonly affected including the scalp, face, trunk, and upper extremities, although these are largely seen along with lesions on the lower extremities (2), which is a phenomenon seen in one of our patients.

NL is a rare disorder that predominantly affects young to middle-aged adults, with a 3–5:1 female preponderance and no racial predisposition (1, 2, 5, 6). NL is more common in those with T1DM. The prevalence of diabetes at the time of diagnosis ranges from 11 to 65% (1, 2, 3). Nevertheless, the overall incidence of NL in those with diabetes remains low, affecting between 0.3 and 1.2% (1, 4). NL is also associated with autoimmune thyroiditis, coeliac disease and metabolic syndrome including obesity, hypertension, and dyslipidaemia (6, 7). Age at diagnosis is younger in patients with diabetes compared to those without diabetes, with a mean age of 25 vs 46 years, respectively (1). Glycaemic control (e.g. HbA1c) is not associated with NL, although diabetes-related microvascular complications do demonstrate association (8).

Patients without a known diagnosis of diabetes should have screening with a fasting blood glucose concentration or HbA1c level at NL presentation given the well-established association with diabetes. Regular annual screening should be performed in people with prediabetes and has been suggested even in patients with normal fasting glucose (1, 9). Given the association with thyroid disease, clinicians should undertake a targeted history and physical examination for signs and symptoms of thyroid dysfunction and if evident, pursue additional testing with TSH levels (3).

The pathogenesis remains uncertain in NL. Given the association with diabetes, it has been theorised that microangiopathy resulting from glycoprotein deposition in the vessel wall contributes to the pathogenesis through

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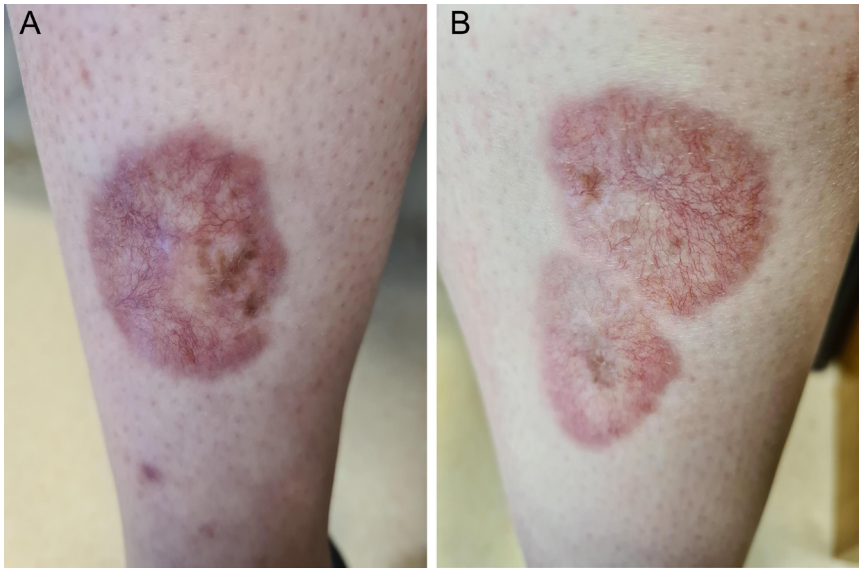

Figure 9
Well-circumscribed erythematous, atrophic, telangiectatic plaques on the pretibial area of the (A) left and (B) right leg. Yellow-brown pigmentation is seen in discrete areas of the plaque. An active erythematous border is evident on both legs.

degenerating collagen and ensuing dermal inflammation (4). In addition, immunoglobulin deposition in the vessel wall has been demonstrated in affected and unaffected skin in those with NL, which is further reinforced by immunofluorescence studies demonstrating immune-mediated vasculitis in NL. These immune-mediated processes are believed to contribute to the alteration of collagen seen in NL. Other proposed theories include tissue damage secondary to hyperlipidaemia, or venous reflux; abnormalities of collagen; and impairment of neutrophil migration (4). Ongoing investigation is needed to further elucidate this.

NL often requires a clinicopathological diagnosis, an approach that integrates both the clinical and histopathological findings (4). The differential diagnosis includes granuloma annulare (GA), necrobiotic xanthogranuloma (NXG), cutaneous sarcoidosis, and diabetic dermopathy. Depending on the clinical circumstance, an extended differential may encompass panniculitis, granulomatous infections, morphea, lichen sclerosis, and sclerosing lipogranuloma. Clinical features alone may be suggestive of the condition, though a skin biopsy should be considered to confirm the diagnosis and to exclude similar appearing conditions (4). Expert recommendations for biopsy are inconsistent, with a recent study showing that only half of the practitioners recommend biopsy in any case, with the remainder recommending biopsy only when clinical findings are unclear (3). To perform the biopsy, an appropriate site on the leading edge of the lesion is selected and then by using a 3–5 mm punch, a cylindrical core of tissue extending into the s.c. fat was collected (10). Histologic features comprise diffuse palisading and interstitial granulomatous dermatitis with epithelioid histiocytes and degenerated collagen that appears as 'layered' tiers (9). These changes are accompanied by a superficial and deep perivascular lymphocytic infiltrate, with plasma cells in the deep dermis. The epidermis may appear normal or atrophic. When compared with GA, there is a relative absence of mucin in the centre of the palisading granuloma (9). Cholesterol clefts are an infrequent finding and should prompt consideration of NXG. Dermoscopy is a non-invasive technique used in the examination of skin lesions with reports supporting an adjunctive role in the diagnosis of NL (11). Dermoscopic features include arborising telangiectasia with yellow to orange background, which corresponds with the vascular plexus overlying granulomatous inflammation (12). At present, diagnostic value of dermoscopy remains uncertain.

NL is a challenging condition to treat, with multiple therapeutic modalities to consider as exemplified by those in this case series. There remains no established standard of care (13). Evidence relies primarily on case reports, case series, and other uncontrolled studies (3). In up to 20% of cases, NL may undergo spontaneous remission, although residual cutaneous atrophy, scarring, or pigmentary changes are observed, particularly in ulcerated lesions (1). Treatment goals are centred on addressing signs and symptoms through mitigating the underlying inflammatory processes and reducing the risk of ulceration. This is often pursued using high-potency topical corticosteroids applied under occlusion for early lesions, which may be further supplemented with intralesional corticosteroid injected at the active border of

more established lesions (4). An approach used in cases 1–3. Topical corticosteroids should be limited to a maximum of 2 consecutive weeks per month to limit adverse effects, in particular further atrophy (4). Systemic corticosteroids are effective in rapidly progressive lesions, though are associated with hyperglycaemia and hypertension, particularly problematic in those with diabetes (4).

In those who were unable to achieve an adequate response, the decision to pursue further therapy should be made in consultation with the patient. Options include immunomodulators, UV light therapy, biologics, a range of systemic anti-inflammatory agents (4). A multicentre, retrospective study provided expert recommendations for topical and systemic treatment favouring glucocorticoids, compression therapy, calcineurin inhibitors, and phototherapy as effective topical options and glucocorticoids and fumaric acid esters as systemic therapy (3). A prospective, uncontrolled study evaluated fumaric acid esters in 18 patients over 6 months with substantial clinical improvement, though moderate side effects including gastrointestinal upset and flushing occurred (14). In another uncontrolled case series, topical tacrolimus 0.1% ointment applied once or twice daily for 8 weeks was beneficial (4). Psoralen plus UV A (PUVA) applied twice weekly with a cumulative dose of 200 J/cm^2 was effective in managing active lesions, though areas of prior atrophy were unreceptive (4). Variable responses are seen with PDT in both non-ulcerated and ulcerated NL (4). In a recent review, laser and light therapy was evaluated, revealing inconsistent efficacy and side effect profiles for all modalities other than pulsed dye laser, which consistently showed successful outcomes (15). TNF-alpha inhibitors, including etanercept and infliximab, have been used successfully as monotherapy in lesions with ulcerations (4).

Several case reports suggest the efficacy of antimalarials, pentoxifylline, when used as adjunctive therapy, topical tretinoin, and hyperbaric oxygen (4). In those with severe, refractory ulceration, excision to the deep fascia or periosteum followed by split-thickness skin grafting has even been successfully performed (4). Platelet-rich plasma has also shown efficacy in a small study aimed at overcoming NL-associated recalcitrant wounds (16).

Our case series highlights that NL is an important dermatological condition that can occur in those with autoimmune conditions, particularly T1DM, that requires awareness from healthcare professionals managing those with diabetes. Dermatologists also need to be aware of the association of NL with diabetes, so that screening for diabetes is pursued. A common theme highlighted by this case series is the late identification and delay in diagnosis, which can have profound implications on the patient experience including the development of more extensive disease. NL has considerable implications on patients' QoL, particularly when ulceration arises. As exemplified in this case series, NL is notoriously refractory to treatment with no established standard of care. Future research is required to guide evidence-based management of NL.

Patient's perspective

QoL is frequently impacted in affected individuals due to the symptoms and the recalcitrant nature of the condition. Patient-reported outcome questionnaires, including the DLQI, are useful to assess health-related QoL in dermatological disease. The four patients in this case series had varied DLQI scores, with the two patients with more extensive disease experiencing moderate impact on QoL, due to the physical appearance of NL impacting self-esteem and body image. Clinicians managing patients with NL should be aware of the psychosocial implications.

Declaration of interest

The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of their clinical details and images was obtained from each of the patients included in this case series.

Author contribution statement

M V: data collection, intellectual input, manuscript drafting, and finalising. N R: data collection, intellectual input, manuscript editing, and review. A G: data collection, intellectual input, manuscript editing, and finalising. S G: intellectual input, manuscript editing, and review.

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