

Necrobiosis lipoidica

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Abstract

Necrobiosis lipoidica and granuloma annulare are granulomatous skin conditions that have been traditionally associated with diabetes mellitus, although recently the strength of association has been questioned. In the first section of this two-part article, we describe the suggested aetiology, clinical features, histology and treatment of necrobiosis lipoidica. It is found in 0.3% of patients with diabetes, but has also been reported with other systemic conditions. Clinically it appears as a waxy, atrophic, yellowish plaque with overlying telangiectasia and a brown border. Although usually asymptomatic, it may be extremely painful, especially if ulcerated. Squamous cell carcinoma has occasionally been reported with longstanding lesions. Treatment is often difficult: numerous topical and systemic agents have been employed, but evidence is limited to small case series and individual case reports.

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Introduction

Necrobiosis lipoidica (NL) and granuloma annulare (GA) are histologically similar granulomatous skin conditions.¹ Early reports suggested that NL may be a variant of GA, and it was not until the mid 20th century that recognition of subtle microscopic differences permitted classification as different conditions.² Historically, they have been considered to be closely associated with diabetes mellitus; more recently the strength of the association has been questioned.³⁻⁵

Aetiology

While the similar histological appearances of GA and NL could potentially suggest the same predisposing factors, their clinical appearance is usually quite different and there are only a small

number of case reports of the coexistence of the two conditions.^{1,2} Furthermore, Crosby *et al* argue that the subtle pathological, biochemical and immunological differences between the two conditions suggest different aetiologies.²

The aetiologies of NL and GA are unknown, although many theories have been proposed. The leading theory advocates that NL is a manifestation of microangiopathy resulting from glycoprotein deposition in blood vessel walls.^{6,7} Similar vascular changes involving glycoprotein deposition occur in diabetic microangiopathy of other organs, such as the eye and kidney, yet other microvascular complications of diabetes are relatively frequent and there is no evidence to suggest a shared aetiology with NL. Hypoxia has been suggested to play a role in the pathogenesis, however evidence for this is conflicting.⁷ Other possibilities include antibody-mediated vasculitis, collagen abnormalities, platelet aggregation, trauma, inflammatory and metabolic changes or a tumour necrosis factor mediated process.^{6,8} The finding of Glut 1 (human erythrocyte glucose transporter) expression in areas of sclerotic collagen suggest a possible role for abnormal glucose transport by fibroblasts.¹

Association with diabetes

NL is more common in females than males and onset is most frequently in young adulthood or middle age.^{3,9,10} The average age of onset is 30 years in people with diabetes and 41 years in non-diabetic individuals.¹⁰ The age of onset is earlier in type 1 than type 2 diabetes.¹¹ One early study found that up to 87% of patients with NL had diabetes at presentation.⁹ In the series reported by Muller and Winkelmann, 65% of patients with NL had diabetes at presentation with a positive family history of diabetes in 43% of diabetic and 26% of non-diabetic patients, respectively.¹⁰ However, Smith *et al* found that only 35% of patients with NL had diabetes.⁹ Dandona *et al* measured glycosylated haemoglobin in patients with GA and NL; although patients with known diabetes had elevated HbA1c, patients with GA and NL who did not have diabetes had similar levels to controls.¹² The authors concluded that in most cases the microangiopathic changes could not be due to hyperglycaemia or abnormal glucose tolerance and could not simply represent a reflection of hyperglycaemia. O'Toole *et al* found that only 11% of patients with NL were known to have diabetes at presentation, with a further 11% subsequently developing impaired glucose tolerance or diabetes.³ Two-thirds of patients with diabetes who develop NL have type 1 diabetes; however, only 0.3% of patients with diabetes develop NL.^{10,13} Large, recent series of patients attending diabetes clinics identified GA in 0–1.8% and NL in 0–1.4% of patients respectively.¹⁴⁻¹⁷

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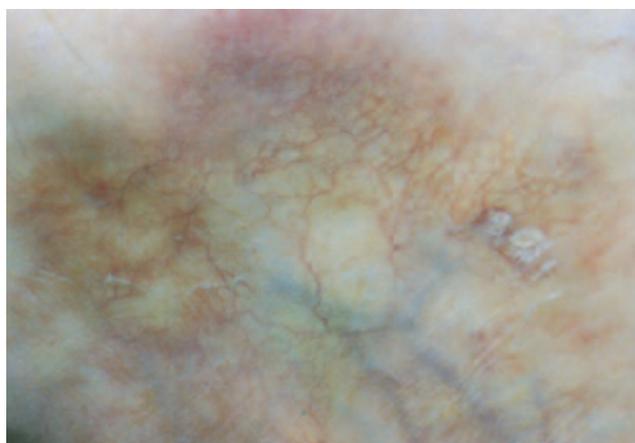
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Figure 1. Typical appearance of necrobiosis lipoidica: a well-demarcated, waxy, yellow atrophic plaque



Figure 2. Central part of lesion with prominent telangiectasia



Traditionally, it has been thought that glycaemic control has no effect on the course of NL, however Cohen *et al* challenged this view following reappraisal of the original data and argued that tighter glycaemic control may prevent or ameliorate the condition.¹⁸ Furthermore, they suggest the possibility that NL may be a separate condition in people with and without diabetes.

NL has also been reported in association with sarcoidosis, inflammatory bowel disease, autoimmune thyroiditis, monoclonal gammopathy and in healthy individuals.⁷

Figure 3. Early lesions of necrobiosis lipoidica on lower legs (reproduced with permission of Dr Niels Veien, Dander)



Clinical features

Early lesions of NL present as well circumscribed erythematous papules or nodules that coalesce into plaques with a waxy, atrophic central area, with telangiectasia and an active red-brown border (Figures 1–3).^{6,7} They are usually painless, but may be exquisitely painful, especially if ulcerated (Figure 4). Lesions are most frequently located bilaterally on the lower extremities, but may occasionally occur at other sites (Figure 5).^{6,7} NL may Koebnerise, although this has rarely been reported.¹⁹ Ulceration may arise due to trauma and occurs in up to 35% of cases.¹⁰ Ulcerated lesions may be more common in patients with diabetes, than those without.⁹ Squamous cell carcinomas have occasionally been reported to complicate long-standing lesions.^{7,10,20,21,22}

Diagnosis

The diagnosis of NL may be clinically obvious, although sometimes a skin biopsy is performed to confirm the diagnosis. Diagnosis of NL should prompt investigations for diabetes.

Histopathology

Histological examination of NL biopsy specimens reveals degeneration of collagen and interstitial and palisaded granulomas in the mid dermis consisting of multinucleated histiocytes, lymphocytes, plasma cells and eosinophils. Other features include extracellular lipid deposits, depletion of intradermal nerves and, in the mid to deep dermis, thickening of blood vessel walls and endothelial cell swelling.^{4,6,13} The central yellow area is likely to be subcutaneous fat necrosis made visible by the thin dermis.⁴

Figure 4. Large lesion with central ulceration

Treatment

Treatment of NL, and ulcerated lesions in particular, is often difficult.²³ Suspicion of early NL warrants referral to a dermatologist for diagnostic confirmation. Reid *et al* summarised the evidence for the various therapeutic approaches in a recent review.⁷ Optimising glycaemic control does not alter progression of the lesions. Therapeutic strategies involve avoiding trauma to minimise the risk of ulceration and treating infections with antiseptics or antibiotics. Many treatments have been described, with variable success, although evidence is limited to small trials and individual case reports. Topical or intralesional steroids can be applied to the active edge, with avoidance of the central atrophic area, which may be worsened by steroid use. Topical steroids and topical tretinoin have also been used in combination.²⁴ Oral steroids²⁵ and intravenous methylprednisolone²⁶ have also been found to be effective. Improvement has been reported with topical calcineurin inhibitors,²⁷ bovine collagen and intra-lesional infliximab. Systemic infliximab²⁸ and other anti-TNF agents, etanercept,²³ thalidomide and pioglitazone²⁹ have been found to be helpful in individual cases. Suarez-Amor *et al* reviewed the literature on the use of biologics for NL, with success reported with infliximab, subcutaneous and intralesional etanercept in seven cases, six of which were ulcerated.²³ Some improvement has been documented with anti-platelet agents (aspirin, dipyridamole and pentoxifylline). Other treatments described include nicotinic acid, ciclosporin, antimalarials, colchicine,³⁰ clofazimine, mycophenolate mofetil, fumaric acid esters³¹ and intravenous immunoglobulin.²⁶ Improvement has been

Figure 5. Lesions are frequently found on the lower leg and may be bilateral

Key messages

- Necrobiosis lipoidica manifests as a waxy, yellow, atrophic plaque most frequently on the lower legs
- It is reported to occur in 0.3% of patients with diabetes
- Although usually asymptomatic, ulcerated lesions may be extremely painful and development of squamous cell carcinoma is a rare, but serious complication
- The condition is difficult to treat and although various therapeutic options have been described, evidence is limited to case reports or small case series

reported following physical treatments, including psoralen combined with ultraviolet A,¹⁹ photodynamic therapy³² and CO₂ laser. Berking *et al* reported complete response in 1/18 patients treated with photodynamic therapy with partial response in 6/18 and no response in the other 11.³² Surgical excision is not recommended for NL. The skin on the lower legs heals slowly and surgical treatment for any reason at this site may result in ulceration.

Ultimately NL remains a challenging condition to manage effectively and with no robust evidence base or guidelines to direct therapy, treatment choice will be influenced by clinical experience and patient comorbidities.

Conflict of interest None

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