Necrobiosis lipoidica diabeticorum: A case-based review of literature

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ABSTRACT

Necrobiosis lipoidica diabeticorum (NLD) is a rare chronic and granulomatous skin disorder that affects 0.3% of diabetic patients. Although the etiology and pathogenesis of NLD is still controversial, it is thought that microangiopathy has an important role. The legs are the most common site for NLD, but involvement of other areas such as the abdomen, upper extremities and scalp has been reported. There is no rational therapy. However, benefit has been reported from different treatment regimens such as drugs acting on the hemostatic mechanisms, corticosteroid therapy (topical, intralesional and systemic), enhancers of wound healing, surgery and immunomodulating therapies (including photochemotherapy). We report a 59-year-old female, who was a diabetic patient with multiple, disseminated lesions on the legs, which tended to disappear as the glycemic control was achieved. Hereby, we also review the existing literature for the evolving aspects of etiopathogenesis and treatment.

Key words: Diabetes mellitus, necrobiosis lipoidica, necrobiosis lipoidica diabeticorum

Introduction

Necrobiosis lipoidica diabeticorum (NLD) refers to a skin rash that most commonly affects the shins and is seen more often in women. This is the most dramatic skin condition usually associated with diabetes. It is considered to be a rare complication with a reported frequency of 0.3% in diabetic patients.[1] More than 50% of these patients are insulin dependent.[1] We report a case of NLD which appeared on the legs of a poorly controlled diabetic lady, which tended to disappear as the glycemic control was achieved. Taking a cue from the current case report, hereby we have tried to sum up the literature pertinent to epidemiology, pathophysiology and various treatment modalities of necrobiosis lipoidica.

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Case Report

A 59-year-old lady presented to the outpatient department of endocrinology for routine follow-up after 6 months for diabetes mellitus. She was a diabetic for last 5 years, which was under control with oral antidiabetic agents. Her only concern was the red rash, not itching, on both her legs for last 10 days. Otherwise, she was asymptomatic without any significant past medical history. There was no history of past surgical procedures, undue medicine intake, allergy to drug or environmental agents.

On examination, her vital parameters were normal. Her weight was 70 kg and height was 160 cm, with a body mass index of 27.3 kg/m^2. General examination revealed acanthosis nigricans. Anterior aspect of both legs over shin of tibia had reddish brown papular rash with erythematous spreading borders. The rash was tender, non-blanching with reddish flakes over it [Figure 1]. There were no signs of atrophy or ulceration. Sensations over the lesions were preserved. Systemic examination was normal without any evidence of diabetic retinopathy or neuropathy. Vibration perception thresholds (VPT)

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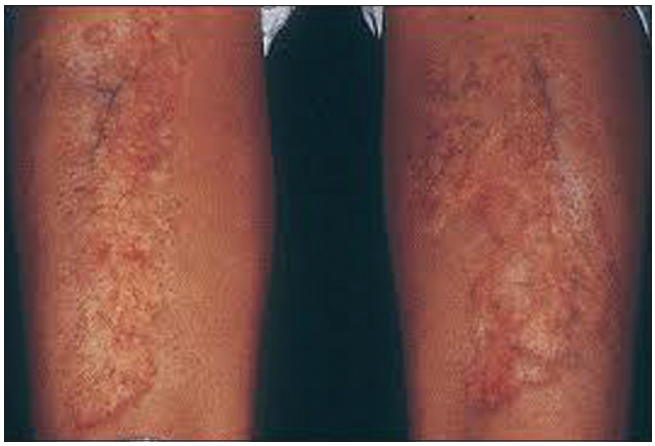

Figure 1: Erythematous, non-blanching rash with flakes on both the shins

over both feet were 9/15 and 10/18, revealing absence of any neuropathy. Her blood sugar levels were: fasting 250 mg/dl and postprandial 320 mg/dl with glycated hemoglobin (HbA1C) 9.8%. Blood picture, renal and hepatic parameters were within normal limits. Urine for microalbuminuria showed a value of 25 mg/dl. Biopsy of the lesions over leg revealed sandwich-like horizontal layers of necrobiotic collagen alternating with inflammatory cell infiltrate of lymphocytes, histiocytes, multinucleated giant cells and plasma cells. These changes involved the full thickness of the dermis sparing the subcutis [Figure 2]. It confirmed the diagnosis of NLD. The patient was prescribed subcutaneous premix insulin twice daily. The rash improved after glycemic control on follow-up after 2 weeks.

Discussion

In 1929, Oppenheim first described NLD and called it dermatitis atrophicans lipoidica diabetic,[2] but it was later renamed NLD by Urbach in 1932.[3] In 1935, Goldsmith reported the first case in a nondiabetic patient. This was followed by description of NLD in nondiabetic patients by Meischer and Leder in 1948. Rollins and Winkelmann in 1960 again described this condition in nondiabetic patient, leading to a suggestion that diabetes be excluded from the term.[4] The term necrobiosis lipoidica (NL) encompasses the same clinical lesions regardless of the association with diabetes. The average age of onset is 30 years, with females being affected more commonly. There are reports of its occurrence in children also.[5] Its incidence is 0.3% in diabetic patients.[1] In one study, NLD preceded the onset of diabetes in 15% patients, with 60% patients having diabetes prior to the onset of NLD, while 25% had NLD simultaneously appearing with the onset of diabetes.[6] Sixty-five percent of subjects of NLD have diabetes mellitus and the rest have abnormal glucose tolerance test.[6]

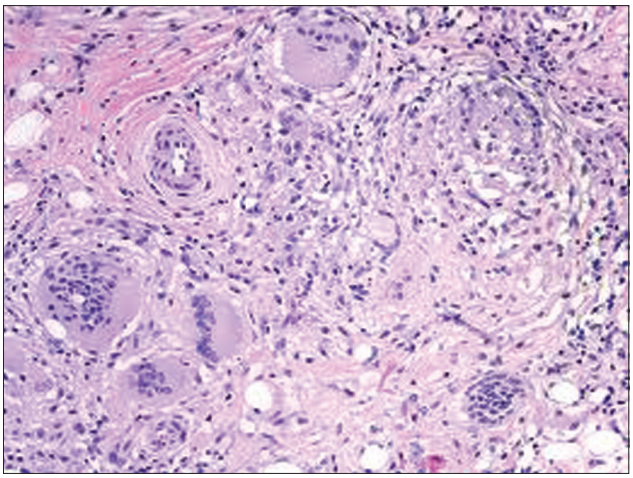

Figure 2: Biopsy of the skin showing necrobiotic collagen alternating with inflammatory cell infiltrate of lymphocytes, histiocytes, multinucleated giant cells and plasma cells in the dermis (H and E, ×200)

Etiopathogenesis

Its etiology still is elusive, with none of the genetic factors implicated in pathogenesis.

There are certain possible theories for etiopathogenesis, which are given below.[7]

- Because of the strong relationship diabetes and NLD, many studies have focused on diabetic microangiopathy as the leading etiologic theory. Diabetic alterations of the kidney and eye vasculature are similar to the vascular changes seen in NLD. A deposition of glycoprotein in blood vessel walls may be the cause of diabetic microangiopathy. A similar glycoprotein deposition is seen in NLD. Doppler flow study showed lowered O_2 tensions within the lesions.[8]
- Another theory is based on the deposition of immunoglobulins, the third component of complement and fibrinogen in the blood vessel walls of patients with NLD. Some believe an antibody-mediated vasculitis may initiate the blood vessel changes and subsequent necrobiosis in NLD. The immune complex deposition along with enhanced platelet aggregation and coagulation plays a role.[9]
- An additional etiologic theory focuses on the abnormal collagen in NLD. Defective and abnormal collagen fibrils are established cause of diabetic end-organ damage and accelerated aging. Higher lysyl oxidase levels in diabetic persons are responsible for increased collagen crosslinking. Increased collagen crosslinking could explain the basement membrane thickening in NLD.[10]
- Other theories link trauma, inflammatory and metabolic changes as a possible etiology. There may be impaired neutrophil migration leading to an increased number of macrophages, possibly explaining the granuloma formation in NLD.

- Abnormality of glucose transport by fibroblast in individuals with NLD is noted.[11]

It is a chronic disfiguring condition. Most rashes are located on the legs, especially above the tibiae, but may also occur on the face, scalp, forearm and trunk. Lesions may be single, but multiple lesions are also common. NLD may present as red papules which may enlarge to form patches or plaques with an atrophic yellowish brown and slightly depressed center. It may start as small red spots or raised areas, which develop a shiny, porcelain-like appearance. The lesions may resolve spontaneously or become persistent chronic lesions which may ulcerate. Painful ulceration occurs in approximately 15% of cases, and in rare instances, can be aggressive.[12] Squamous cell carcinoma has been reported as a rare complication.[13]

Histology

In a fully developed case, the characteristic features are present at the edge of the lesion. Histopathologically, NLD presents with interstitial and palisaded granulomas that involve the subcutaneous tissue and dermis.[14] The earliest change is noticed in the form of small vessel vasculitis, progressing to large-vessel granulomatous vasculitis and collagen degeneration involving the dermis and subcutaneous fat (with the pattern of a septal panniculitis). The lymphocytic component of the dermal infiltrate is composed predominantly of T-cells, principally T-helper cells.[15] The granulomas are arranged in a tier-like (layered) fashion and are admixed with areas of collagen degeneration.[14] The granulomas are composed of histiocytes, and some of them are multinucleated lymphocytes, occasional plasma cells and eosinophils. Reduction in the number of intradermal nerve is an additional feature of NLD. The main findings on histopathology are thickening of the blood vessel walls and endothelial cell swelling found in the middle to deep dermis, the characteristics shared with diabetic microangiopathy. Biopsy in our patient revealed sandwich-like horizontal layers of necrobiotic collagen alternating with inflammatory cell infiltrate of lymphocytes, histiocytes, multinucleated giant cells and plasma cells. These changes involved the full thickness of the dermis sparing the subcutis.

Direct immunofluorescence microscopy of NLD has demonstrated IgM, IgA, C_3 and fibrinogen in the blood vessels, which cause the vascular thickening.[16] In nondiabetic subjects, the vascular changes are not that prominent.[17] The rash of reddened, raised patches occurs as a result of a degenerative condition affecting the infrastructure of the underlying skin. Small blood vessels develop on the surface, and the areas may become extremely painful following trauma, ulceration and scarring, which has occasionally been associated with development of skin cancer over long periods of time.[18]

Differential diagnosis

The differential diagnoses for this dermatological condition is

- Granuloma annulare (Binkley's spots): They are found most commonly in children and in adult females <30 years. They usually manifest as groups of 1- to 2-mm papules that range in color from skin colored to violaceous, often in an annular arrangement over distal extremities. Grouped lesions may expand into annular plaques or nodules measuring 1–5 cm in diameter. Histologically, there are not as much of plasma cells and necrobiosis found as that in NLD. Mucin stains such as colloidal iron and alcian blue may be used to highlight the increased connective tissue mucins in granuloma annulare, which is negative in NLD (lacks mucin).
- Sarcoidosis: It manifests as maculopapular eruptions, with erythema nodosum being the most common lesion. It is usually associated with involvement of other systems like eye, lungs, musculoskeletal systems, lymph nodes, etc.
- Necrobiotic xanthogranuloma: It can manifest as eruptive, tuberous, tendinous xanthoma. Histologically, cholesterol clefts are found in the lesion.

Treatment

NLD is not related to any other complications of diabetes. In particular, NLD does not presage eye, kidney or vascular problems. The presence or progression of NLD does not correlate with glycemic control. The danger is that of secondary infection, which is aggravated by lack of good surface circulation. Trauma should be avoided by protection of legs with elastic supporting stocking.[2] In our case, we did not institute any specific treatment. Achievement of euglycemia only could lead to reversal of the lesion.

Possible explanations for healing of lesions after achievement of euglycemia include the following:

a. Reversal of hyperglycemia-induced microangiopathy and collagen crosslinking
b. Decreased inflammation with reduced number of macrophages
c. Normalization of abnormal glucose transport by fibroblasts

Treatment options

1. **Cutaneous blood flow enhancers:** Inhibition of platelet aggregation with a combination of aspirin and dipyridamole was proposed as a treatment for NLD, but one of the controlled trials suggested that a combination of 300 mg of aspirin and 75 mg of dipyridamole thrice daily for 8 weeks did not confer any benefit.[19] This was

quickly challenged by an uncontrolled trial of aspirin given in much lower doses, in which six out of seven patients showed an improvement,[20] although a further randomized, placebo-controlled trial subsequently demonstrated no benefit from low-dose aspirin.[21] However, an uncontrolled trial of seven patients with ulcerated NLD then reported that 80 mg of aspirin and 75 mg of dipyridamole given thrice daily resulted in healing of all ulcers within 2–4 weeks, although the lesions of NLD were otherwise unchanged.[22] There are reports of ticlopidine, also an inhibitor of platelet aggregation, clearing or improving plaques of NLD.[23] An early report suggested stanozolol, an anabolic steroid with fibrinolytic activity, and inositol nicotinate, a vasodilator, to be beneficial for NLD, albeit with slow improvement.[24]

There are several individual case reports of pentoxifylline therapy rapidly resulting in both the healing of ulcerated NLD and the fading of plaques.[25] Pentoxifylline is a methyl xanthine derivative that inhibits platelet aggregation and decreases blood viscosity, probably by increasing fibrinolysis and red blood cell deformability. A recent single-case report attests to the efficacy of pentoxifylline for NLD when used in a dose of 400 mg thrice daily for at least 6 months.[26] Prostaglandin E1 used as treatment for vascular occlusion in a young nondiabetic woman also improved the appearance of her NLD.[27] An indirect reference to the Russian literature suggests that perilesional heparin may be effective.[28]

2. **Corticosteroid therapy:** Topical and intralesional steroids can lessen the inflammation of early active lesions and the active borders of enlarging lesions, but these have little beneficial effect on atrophic lesions that are burned out. In fact, with atrophic lesions, steroid use may cause further atrophy. Intralesional triamcinolone has been reported as effective,[29] and the natural concern regarding the risk of inducing further atrophic change or ulceration may not be warranted according to this study. Two case studies attest to the potential for the topical application of clobetasol propionate under polythene occlusion to effect improvement,[30] and two more reports suggest that a short course of systemic corticosteroid may rapidly resolve the inflammatory element of NLD,[31] although the issue of glycemic control with prednisolone in diabetes would require consideration.
3. **Wound healing enhancers:** There have been several recent reports of the successful use in ulcerated NLD of a variety of topical preparations that are thought to act by promoting wound healing. A case report has described the efficacy of topical recombinant human granulocyte–macrophage colony stimulating factor, a hematoopoietic growth factor, in ulcerating NL in young people with diabetes.[32] However, becaplermin gel, a hematopoietic human platelet-derived growth factor which promotes chemotaxis and proliferation of cells involved in wound repair, when applied to NLD in five diabetic subjects was found to confer no significant improvement.[33]

Physical modification of the wound microenvironment may also be beneficial in promoting wound repair. Promogran™, a novel protease-modulating matrix consisting of collagen and oxidized regenerated cellulose, has been reported as effective in ulcerated NLD.[34] This preparation appears to inactivate matrix metalloproteases and other enzymes which, when present in excessive quantities, may have a detrimental effect on wound healing by degrading naturally occurring growth factors. Tissue-engineered human dermis, consisting of human fibroblasts cultured on a polymer scaffold and thought to provide growth factors and matrix proteins, resulted in the healing of ulcerated NLD in two diabetic women.[35] Bovine collagen gel, consisting mainly of type I collagen, applied under occlusion for 6 weeks to ulcerating NLD in a nondiabetic man resulted in healing at 24 weeks with no recurrence after a further 5 months.[36] Collagen probably promotes wound healing by facilitating hemostasis, enhancing debridement and encouraging angiogenesis and re-epithelialization. Collagen is also believed to improve granulation tissue by supporting fibroblast activity and promoting wound debridement by increasing the number of macrophages and neutrophils at the wound site. The inhalation of hyperbaric oxygen in two diabetic women with ulcerated NLD resulted in healing after 98 and 113 sessions, and it is tempting to speculate that this improvement was the result of the correction of tissue hypoxia.[37]

4. **Immunomodulation:** Recently, immunomodulatory drugs have shown promising results in ulcerating NLD. Case studies of cyclosporin used for ulcerating NLD reported healing of the ulcers, usually without immediate relapse,[38] although with questionable benefit to the remainder of the lesions. Cyclosporin inhibits interleukin 2 production by T-helper cells, preventing clonal T-cell proliferation and thereby possibly suppressing the immune response in NLD.

Mycophenolate mofetil, which has a potent cytostatic effect on lymphocytes, has also been reported to accelerate the healing of ulcerated NLD in a nondiabetic patient[39] whose ulceration of 18 months duration healed within 4 weeks of commencing treatment, only to recur on stopping it.

Infliximab, a monoclonal antibody to tumor necrosis factor (TNF)-α, has proved to be a promising

therapeutic agent for a variety of inflammatory dermatoses. There is a single-case report of its successful use in recalcitrant ulcerated NLD in a patient with insulin-dependent diabetes, although the recipient developed miliary tuberculosis during treatment.[40] Nonetheless, TNF-α antagonists may prove helpful in NLD unresponsive to other treatment modalities.[41] Fumaric acid esters, which have well-defined immunomodulatory effects, resulted in the virtual clearance of a case of recalcitrant non-ulcerating NLD.[42] Thalidomide has anti-TNF effects and has also been reported as a successful therapy.[43] Etanercept too has been used successfully.[44] Topical tacrolimus (0.1%) ointment has been successfully employed in the treatment of early non-ulcerated NLD.[45]

Several uncontrolled studies published over the last 3 years have suggested that topical or systemic photochemotherapy may be beneficial to inflammatory plaques of NLD, perhaps via an immunomodulatory effect. In two of these studies, all patients improved,[46] but results of another study were not quite as impressive, with only 2 of 10 patients clearing completely and 4 improving substantially, once the cosmetic effect of tanning had been taken into account; the remaining 4 did not benefit.[47] Similar results were obtained in a multicenter prospective study of topical Psoralen UltraViolet A(PUVA).[48] A case study of ulcerating NLD in a diabetic patient treated with topical PUVA reported a reduction in pain after only three treatments and subsequent complete healing of ulceration.[49] These results from PUVA therapy warrant further controlled trials to assess its efficacy as a systemic or topical treatment. One concern with phototherapy is whether this modality of treatment may increase the risk of squamous cell carcinoma in NLD, although measures to settle the inflammatory element of NLD, and thereby presumably minimize subsequent scarring and atrophy, may actually reduce the, albeit low, risk of malignant change.

5. **Surgery:** The surgical management of NLD has proponents,[50] although its rationale is still not clear. It has been recommended that excision down to deep fascia or periosteum is undertaken, followed by split skin grafts to cover the defect.[50] However, the tendency of NLD to koebnerize on surgical scars[51] means that curative surgery cannot be guaranteed. Moreover, the inevitable resulting disfigurement in a cosmetically sensitive site such as the shins of young women is a major disadvantage.

   Two single-case studies of the use of the pulsed dye laser to treat the prominent vascular component of NLD have been published: one demonstrated a cosmetic improvement in erythema and telangiectasia[52] and the other reported skin breakdown with higher fluences, with the authors advising caution with respect to laser surgery.[53]
6. **Miscellaneous:** The final miscellaneous group of therapies includes nicotinamide, clofazimine, chloroquine and topical tretinoin. A single study of nicotinamide reported improvement in NLD in 8 of 15 patients, although none cleared; healing occurred in 3 of 4 patients with ulcers.[54] Clofazimine, which has both anti-microbial and anti-inflammatory properties, has been documented as improving NLD in 60% of cases.[55] Topical tretinoin in two single-case reports resulted in a significant reduction in the atrophic element of NLD:[56] the retinoids are thought to promote wound healing by influencing angiogenesis and collagen formation. The application of benzoyl peroxide to ulcerating NLD has also been reported to be beneficial.[57] Oral chloroquine, which has immunosuppressive and anti-inflammatory properties, improved the inflammatory element of a plaque of NLD on the shin of a non-diabetic woman, possibly via inhibition of macrophage migration, inhibition of prostaglandin synthesis or inhibition of platelet aggregation.[58] Durupt *et al*. reported successful treatment of NLD with chloroquine and hydroxychloroquine. Improvement was seen within 3–6 months of treatment.[59]

Boyd reported that the thiazolidinedione drug class has been used with some success in NLD. These drugs function as potent agonists for peroxisome proliferator-activated receptor-gamma (PPAR gamma). These receptors have been found in adipose tissue and function as important mediators in lipid storage and adipocyte differentiation.[60] PPAR gamma activation diminishes TNF-α production and inhibits the action of proinflammatory cytokines, which may help healing in NLD.[60]

Conclusion

Although details of NLD remain still elusive, significant insights have been made into its pathophysiology and treatment. We are spoilt for choice of treatment options that are there in our pharmacological armory to fight with this benign devil which accompanies diabetes.

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