CASE REPORT

Ulcerated necrobiosis lipoidica to a teenager with diabetes mellitus and obesity

VIRGIL PĂTRAŞCU1), CLAUDIA GIURCĂ1), RALUCA NICULINA CIUREA2), CORNELIU CRISTIAN GEORGESCU3), MARIUS EUGEN CIUREA4)

1) Department of Dermatology, University of Medicine and Pharmacy of Craiova, Romania
2) Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania
3) Clinic of Anesthesia and Intensive Therapy, Emergency County Hospital Craiova, Romania
4) Department of Plastic Surgery, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Many skin lesions are associated with diabetes mellitus (DM) type 1 or 2, due to the use of antidiabetics or to metabolic and endocrine disorders caused by this disease. Necrobiosis lipoidica (NL) occurs more frequently in patients with DM. Painful ulcerations may occur on NL areas in about 20–25% of the cases and usually they are related to trauma. We present the case of a teenager, male, 17-year-old, having NL with multiple plaques, some of them spontaneously ulcerated after about 33 months of onset. He is known with type 1 DM from 2.5 years and the NL preceding the diagnosis of diabetes mellitus with about six months, presented erythematous-infiltrative skin plaques, some ulcerated for about three months, interesting both shins. Based on clinical, histopathological and paraclinical examinations, we established the following diagnoses: ulcerated NL, type 1 DM, moderate mixed dyslipidemia, class I obesity; commissural candidiasis, juvenile acne. Under treatment with Pentoxifyllinum, Sulodexidum, Ketotifenum and topical therapy with 0.2% Hyaluronic acid two months later, we have managed to heal two of the three ulcerated plaques and of the third has become superficial. We applied 0.5% Fluocortolonum on non-ulcerated plaques recording an improvement after two weeks of treatment. NL is a skin disease with a predilection for the shins, more frequent in patients with diabetes and is a part of palisading granulomatous dermatitis, which leads to skin atrophy. NL is found in the 0.3–1.2% of diabetic patients and is rare in children with diabetes (0.006%). It is more common in the patients with type 1 DM. The onset is in the third decade in diabetic patients and in the fourth decade in non-diabetics. There is no consensus concerning the treatment of NL, and the results are often modest. Antiplatelet agents, corticosteroids (local and general), immunomodulatory drugs, cyclins, wide synthetic antipaludics, heparin, Thalidomide are used. NL treatment is very difficult, especially in the ulcerated forms. Many of the drugs listed have proven efficacy only in isolated cases. Studies are necessary on large series of patients to determine the optimal therapy of NL.

Keywords: ulcerated necrobiosis lipoidica, diabetes mellitus, obesity, teenager.

Introduction

Many skin lesions are associated with type 1 or 2 diabetes mellitus (DM). They occur because of the use of antidiabetics or they are complications due to metabolic or endocrine disorders caused by this disease.

Necrobiosis lipoidica (NL) is a rare, idiopathic, chronic granulomatous inflammatory disorder being a part of palisading granulomatous dermatitis, involving a degeneration of collagen, which leads to skin atrophy. NL prevalence ranges from 0.3% to 1.2% among the patients with diabetes mellitus two-thirds of them with DM type 1. NL is characterized by a rash that appears on the lower legs and only rarely on the hands, fingers, face, and scalp [1]. NL is more common among women than in men and usually occurs in young or middle adulthood [2]; however, several cases were reported in childhood [3]. Lesions are frequently asymptomatic, except for the fact they are ulcerated [4].

Patient, Methods and Results

Patient, male, aged 17 years, known with type 1 diabetes mellitus (DM) from 2.5 years and the NL (Figure 1) preceding the diagnosis of diabetes mellitus with about six months, presented erythematous-infiltrative skin plaques, some of them ulcerated for about three months, interesting both shins.

Figure 1 – Necrobiosis lipoidica (NL), preceding the diagnosis of diabetes mellitus (DM).

From family history retain both parents and maternal grandmother with type 2 diabetes; the personal pathology was insignificant.

Clinical examination revealed good general status, a body mass index (BMI) 33.2 kg/m², blood pressure (BP) 130/80 mmHg, panicle of fat to the abdomen.

Dermatologic examination revealed to the right shank are observed four plaques infiltrated round, well defined, with dimensions of 10/3 cm one side and 10/4 cm on the other. The lesions have erythematous-violaceous borders and...
on the surface is observed three ulceration of 1.5–2 cm covered by necrotic deposit (Figure 2). At the same leg presents one plaque of 10/3 cm with erythematous border and yellow center with tendency to atrophy, covered with fine, adherent scales, located in external malleolar region. On the external front left shin, are present four plaques, with two ulcers on the surface, plus a plaque of 7/5 cm to the external malleolar region and a plaque of 3 cm on the external surface (Figure 3). Patient presented also on face papules and pustular rash and fissures to angle of lips.

Laboratory investigations results were: blood sugar levels between 159–280 mg%, erythrocytes 5 770 000/mm³, hemoglobin 17 g/dL, hematocrit 47%, mean erythrocyte volume 29, mean erythrocyte hemoglobin concentration 34, average volume of erythrocytes 81, thrombocytes 240 000/mm³, leukocytes 11 000/mm³, neutrophils 52%, lymphocytes 40%, monocytes 8%, erythrocyte sedimentation rate 20/38 mm, urea 32 mg/dL, cholesterol 24 mg%, triglycerides 176 mg/dL, total lipids 806 mg/dL, creatinine 0.7 mg/dL, GOT 27 U/L, GPT 48 U/L.

Urine examination: in sediment flat, rare epithelia, rare leukocytes, rarely calcium oxalate.

Histopathological examination showed granulomatous chronic inflammation consisting in epithelioid cells, Langhans cells and histiocytes (Figures 4 and 5) and a vasculitis process with a lymphocyte and plasma cell inflammatory infiltrate surrounding blood vessels, which have thickened, hypertrophied walls and a reduced lumen (Figures 6 and 7) with Hematoxylin–Eosin (Figure 8) and Van Gieson (Figures 9 and 10) staining showed alterations of collagen fibers.

Diabetes mellitus and metabolic disorders specialty consult diagnosed: type 1 diabetes mellitus, class I obesity, moderate mixed dyslipidemia.

We established the following diagnoses: ulcerated necrobiosis lipoidica, type 1 diabetes mellitus, moderate mixed dyslipidemia, class I obesity; commissural candidiasis, juvenile acne.
Ulcerated necrobiosis lipoidica to a teenager with diabetes mellitus and obesity

We have performed general treatment with Pentoxifyllinum two cp/day, Sulodexidum two cps/day, Ketotifenum one cp/day plus topical therapy with 0.2% Hyaluronic acid cream after disinfection with 3% Boric acid solution.

After discharge from the Dermatology Clinic, the patient followed the same medication, resulting epithelialisation in two months for two of the three ulcerated plaques of NL (Figure 11).

On non-ulcerated plaques, we applied 0.5% Fluocortolonum), recording an improvement by reducing inflammation after two weeks of treatment.

Figure 8 – Alterations of collagen fibers. HE staining, ×100.

Figure 9 – Alterations of collagen fibers. Van Gieson staining, ×40.

Figure 10 – Alterations of collagen fibers. Van Gieson staining, ×100.

Figure 11 – NL, aspect after treatment.

Discussion

NL was first called dermatitis atrophicans lipoidica diabeticata by Oppenheim, in 1929, in patients with DM. In 1932, Urbach named it necrobiosis lipoidica diabeticorum. The incidence is reduced, even in diabetics being encountered at 0.3% and 3% of patients [5]. NL is more common in women (75–80% of cases).

The disease onset is in the third decade in diabetic patients and in the fourth decade in non-diabetic ones. In 40% of cases occur in persons with normal serum glucose level, but then it precedes the discovery of the DM, sometimes several years, in more than one out of two cases [6]. Painful ulcers on plaques of NL may occur in approximately 20–25% of cases and usually are related to the trauma.

Despite the numerous studies, NL etiology remains unclear. Due to close relationship between the DM and NL, more researches focused on the diabetic microangiopathies as an etiopathogenic theory. Vascular alterations caused by DM in kidney and eyes are similar to the vascular changes observed in the NL. It is worth mentioning that patients with DM and NL have a higher risk of developing retinopathy or nephropathy [7]. High concentrations of serum proteins, especially alpha fractions encountered in diabetic patients appear to play a role in the development of microangiopathies. Deposits of α2-glycoproteins and hexose in blood vessel walls have been reported in patients with NL, but also elevated levels of ceruloplasmin. These abnormalities of plasma proteins affect directly blood viscosity and contribute to the development and maintenance of microangiopathies.

It is possible that vascular abnormalities present in the lesions of NL to be promoted or exacerbated by diabetic microangiopathy, together with other factors such as platelet aggregation disorders.

Another etiopathogenic mechanism discussed is immunological vasculitis. Detection of IgM plus C3 fraction in blood vessel walls and also in dermo–epidermal junction suggested involvement of vasculitis by immune complex. This theory is criticized because it lacks other aspects of vasculitis such as the presence of neutrophils and nuclear dust. It remains to be clarified whether vasculitis is a primary pathological immunological phenomenon or is secondary to other vascular injuries. Magro et al. (1997) demonstrated histologically an active vasculopathy in most cases of NL associated systemic diseases. It is also known that microangiopathy observed in patients with diabetes could contribute to the degeneration of collagen and thereafter to dermal inflammation. Elevated plasma fibronectin (factor VIII...
related antigen) and α2-macroglobulines were detected in patients with NL, but the significance of these modifications has not yet been determined. Theories of abnormal growth of platelet adhesion with increased production of thromboxane A2 and increased blood viscosity in lesions of NL remain speculative [8].

The epidermis may be normal, atrophic or absent in the ulcerated injuries. In the initial lesion is observed interstitial inflammatory infiltrate with mixed cells. At the edge of NL, lesions are present histiocytes. In the superficial dermis side are deposits of extracellular lipids. Mucin may be present in the dermis, but not so prevalent as in granuloma annulare. Small superficial blood vessels are increased in number and are telangiectatic. Vessels in deep dermis have thin walls and proliferation of endothelial cells. Vessel walls are often infiltrated by PAS-positive material. Extracellular deposits of lipids and cholesterol were also noted in the superficial dermis. Anesthetic lesions appear to correlate with reduced local vasoconstriction [9].

NL starts as a red, small, firm, well defined, papule of 1–3 mm, covered by fine scales. By slow extension, it forms plaques, which are indurated, round/oval, with yellowish atrophic center, telangiectasia and brown-purple peripheral borders. The lesions may coalesce forming polycyclic placards. In our case, we observed a similar evolution.

The location elective is pretibial, bilaterally. In 15% of NL cases, the lesions may interests and other topographic areas: hands, forearms, face, scalp, and abdomen. Köbner phenomenon has been described for lesions of NL. Lesions are typically multiple and bilateral and are painless in 75% of cases. Our patient presented pain in the ulcerated lesions of NL. Regarding evolution, it is worth highlighting the risk of developing squamous cell carcinoma on chronic injuries.

Differential diagnosis of NL would be done with the lesions of granuloma annulare and sarcoidosis, necrobiosis xanthogranuloma, elastosis perforans serpiginosa, diabetic dermopathy and stasis dermatitis, erythema nodosum. The injection of substances such as paraffin, cottonseed oil, sesame oil or beeswax may cause plaque-like indurations with ulcerations mimicking NL, but the lesions are rarely located on the shins [7].

A study of Muller and Winkelmann, mentioned that, 111 patients of 171 patients with NL had DM and some of non-diabetic glucose tolerance tests were abnormal. In another study conducted in Ireland on 65 patients with NL, only seven patients were known with DM. NL is found in a proportion of 0.3% to 1.2% in diabetic patients and is rare in children with diabetes (0.006%) [8]. It is more common in patients with type 1 DM. The disease occurs in the third decade in diabetics and in the fourth decade in non-diabetic [10].

NL has been associated with other diseases: ulcerative colitis, Cohn’s disease, ataxia-telangiectasia disorder, but there are cases described after jejunal bypass surgery. Association with granuloma annulare and sarcoidosis has been also reported. Our patient investigation revealed mixed dyslipidemia whose pathogenic interference with NL and DN is observed in several studies.

In what concerns the treatment of patients with DM, control of serum glucose levels does not usually have a significant effect on the course of NL. Spontaneous remission after an average of 8 to 12 years was observed in only 17% of 171 patients with NL in one study.

References on antiplatelet drugs are present in the literature. A study on seven patients with ulcerated NL treated with 80 mg Acetylsalicylic acid and 75 mg Dipyridamol three times daily showed healing of all ulcers within 2–4 weeks while NL lesions remained unchanged [11]. Another studied inhibitor of platelet aggregation is Ticlopidinum that improves NL injuries. There are described some cases of ulcerated NL treated with Pentoxifyllinum, with rapid resolution of ulcers and lesions also in NL [12].

Pentoxifyllinum is a methylxanthine that inhibits platelet aggregation, decreases blood viscosity, probably by fibrinolysis and increases the deformability of red blood cells [13]. As for corticosteroids in the NL, it has been observed that rapid benefits by reducing local inflammation, but may increase serum glucose levels. Oral corticosteroids are reserved for severe ulcerated forms. Intraleosional Triamcinolone acetonide proved to be benefic, although there is a risk of ulceration and local atrophy.

Immunomodulatory medication is another class of drugs taken into account for NL therapy. Experience is limited, being used in isolated cases of ulcerated forms.
Motivation of Cyclosporin administration is that this molecule inhibits the production of IL2 by T-helper lymphocytes, preventing T-cell proliferation, which can decrease the immune response of NL. Mycophenolate mofetil, by its cytostatic effect on lymphocytes was observed to accelerate healing of ulcerated NL in non-diabetic patients whose ulcers were present for 18 months long. Healing with this medication has been obtained in four weeks from the start of therapy [15].

Promising results were obtained with Infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α). It was presented a case of ulcerated NL and insulin-dependent DM, successfully treated with Infliximab, but the patient developed miliary tuberculosis during treatment [14].

In 2005, Clayton and Harrison reported a case of ulcerated NL successfully treated with 0.1% Tacrolimus in two applications per day, for one month [16]. In one case of ulcerated NL, healing was achieved after three months of topical treatment with 0.1% Tacrolimus (two applications/day) and systemic with Hydroxychloroquine (400 mg/day) [17].

In some studies, local or systemic phototherapy (or PUVA) [18] proved beneficial, probably by immunomodulatory effect, while in others have not seen spectacular improvements. It was presented a case of ulcerated NL treated with PUVA therapy, in which it included retinoids, heparin, Thalidomide, Doxycyclinum, Sulodexidum, Ketotifenum, and 0.2% Hyaluronic acid cream. Wound healing enhancers agents inactivate matrix metalloproteinases and other enzymes, which, if they are present in excessive quantities, can have a negative effect on wound healing, by degradation of local growth factors. An NL ulcer healing was achieved in two patients presenting diabetes, using cultures of human fibroblasts on the polymer, to provide growth factors and matrix proteins. A preparation with human granulocyte-macrophage colony stimulating factor and hematopoietic growth factor it was successfully used in two cases of ulcerated NL in young diabetics [21].

Spenceri and Nahass (1997) [22] presented a case successfully treated with bovine collagen gel, which contained mainly collagen type 1. This was applied in occlusion for six weeks on ulcers of NL to a non-diabetic male. Healing was achieved after 24 weeks and there were no recurrences in the next five months. Collagen promotes ulcer healing probably by facilitating hemostasis, consolidation and stimulating debridement, angiogenesis and epithelialisation.

We used as treatment 0.2% Hyaluronic acid cream, which together with systemic medication (Pentoxifyllinum, Sulodexidum, Ketotifenum) allowed us healing of two ulcers and reduction of another one in two months.

Another treatment mentioned in the medical literature is oxygen therapy. Thus, the inhalation of hyperbaric oxygen in two diabetic women with ulcerated NL 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 [23, 24].

The wide range of therapeutic means used in NL also includes retinoids, heparin, Thalidomide, Doxycyclinum (2×100 mg/day for one month, and then 100 mg/day for three months, with good effect in ulcerated NL). Several observations have shown efficacy of cyclins in other skin granulomatosis, palisading or not, sarcoidosis, silicotic granuloma, granulomatous cheilitis, annular granuloma. Cyclins’ mechanism of action in these diseases remains unclear. Probably it is conjugated anti-infective, immunomodulatory and anti-inflammatory effects. In vitro studies show cyclins immunomodulator action on T-lymphocyte proliferation but also in the formation of granuloma. Also, through different mechanisms (inhibition of metalloproteinases, phospholipase A2 and synthesis of various proinflammatory cytokines) cyclins can reduce inflammatory phenomenon [25].

**Conclusions**

Finally, we can say that the NL treatment is very difficult, especially in ulcerated forms. Many of the listed drugs have proved effective only in isolated cases. Studies are needed on large series of patients to determine optimal therapy of NL. We have found interesting this case by the presence of ulcerated NL to an adolescent diabetes and mixed dyslipidemia, which evolved favorably, with ulcer healing after treatment with Pentoxifyllinum, Sulodexidum, Ketotifenum and 0.2% Hyaluronic acid cream.

**Contribution Note**
The authors contributed equally to this paper.

**References**


**Corresponding author**

Virgil Pătrașcu, Associate Professor, MD, PhD, Department of Dermatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Romania; Phone +40724–273 676, e-mail: vm.patraescu@gmail.com

Received: October 7, 2013

Accepted: February 6, 2014