NECROBIOSIS LIPOIDICA

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Abstract

Necrobiosis lipoidica is a rare inflammatory disorder, which was mainly observed on diabetic patients. The skin lesions classically described in necrobiosis lipoidica initially appear as nodules or papules well circumscribed that expand later on, becoming plaques with central atrophy. Even though many theories have been suggested regarding the etiopathogeny of this disorder, the real cause of cutaneous colagen deterioration remains unknown. The lack of understanding of the etiology makes difficult to establish an optimal manner of therapy, even thought numerous treatments have been tried.

KEY WORDS: necrobiosis lipoidica, Oppenheim-Urbach disease, dermatitis atrophicans lipoidica, diabetic microangiopathy.

Introduction

The necrobiosis lipoidica (NL) is an inflammatory disease of unknown etiology which determinates the destruction of the collagen fibers and the granulomas production and the apparition of some characteristic cutaneous lesions, placed especially on the front side of the shanks. LN was particularly described on diabetical patients. That is why the main incriminated pathogenic mechanism was the diabetic microangiopathy.

NL was described for the first time in 1929 by Moriz Oppenheim[(1)], being called "dermatitis atrophicans lipoidica diabetica".[(2)] Eric Urbach renamed it in 1932 as "necrobiosis lipoidica diabeticorum".[(3)] That is why NL is also known as the " Oppenheim-Urbach disease".

The first case of NL at a nondiabetic patient is described by Goldsmith in 1935, some other cases of NL at nondiabetic patients are described by Meischer and Leder in 1948, and than by Rollins and Winkelmann in 1960, taking into consideration the elimination of the "diabetic" word from its name.[(4)] The term of "necrobiosis lipoidica" is now used for naming the characteristic cutaneous affection suffered by the diabetic patients as well as the nondiabetic ones.

Epidemiology

NL is a rare cutaneous affection which affects about 0.3% of the diabetic patients. It is more frequently found on the insuline-necessitant diabetes mellitus patients.[(5,6)] The cutaneous lesions can precede the onset of the diabetes mellitus(15%), being simultaneously diagnosed with this one (25%) or, more frequently, can appear at a patient with diabetes mellitus diagnostic already settled (60%).[(7)]

The progression rate of the disease can't be influenced by the diabetes control, but the smoking diabetic patients are more frequently affected by the NL comparatively with the non-smoking ones.[(8)]

The NL was described at the nondiabetic patients, these representing about 1/3 of the cases.[9] At the nondiabetic patients with NL a more frequent association was observed with the inflammatory bowel disease, sarcoidosis or granuloma annulare.[10]

There have been described some NL cases of all ages[11]; the NL onset of the medium age at the nondiabetic patients is of 40 years old, being with a decade more advanced compared to the diabetic ones.[12]

Women are more frequent affected by NL, the report between women and men being 3:1.[5] At the NL nondiabetic patients some familial cases have been noticed.[13,14]

Physical

The NL lesions appear like papulas or nodules of small dimensions (1-3mm), usually placed on the anterior side of one or both shanks. In 15% of cases some lesions appear also in some topographic regions (hands, head, face), but these are usually associated with the pretibial lesions.[15,16]

These small, red-brownish, skinny, oval papulas grow slowly in dimensions, in months and years and can gather forming big parts, of irregular plate . The plates are well-delimited, they have an easy proeminent brownish-violet outlying, the center is atrophic, a yellowish one, with telangiectatic vessels and sometimes with some ulcerations on the surface. By conflation, they can form polycyclical placard. After some traumatisms, they can develop in these areas cutaneous ulcers, their cure being difficult.

There have been described some NL perforating cases, when the elimination of the necrotic material is transfoliculary and transepidermically made. This form of NL is always associated with diabetes mellitus (about 1/3 of NL can ulcerate).[17] It isn't known why the suprainfection of the ulcers in the NL case is rare.

Very rare, it has been noticed, in the case of the prolonged evolution, the appearance of squamous cell carcinomas at the level of NL lesions(some cases reported in the literature).[18,19,20]

The symptomatology is absent in most of the NL cases due to the peripheral neuropathy associated, the esthetical aspect of the cutaneous lesions being generally the main accuse. The teguments of the affected regions become friable, are hardly cured so that any traumatism, even minor, can determinate a new lesion or a painful ulcer.

The Koebner phenomenon, witch is typically associated with the psoriasis and the plane lichen, was described also in the NL case (it was observed that the NL lesions appear preferentially in the areas which suffer various traumatisms). [21]

Pathogenesis

Although there have been some attempts of evading some mechanisms of the pathogenic process, this still remains unknown. The result of the study haven't brought any proof regarding the role of the glicemic control of the diabetic patients in report with NL evolution[22] or regarding the involvement of the genetical factors in the NL etiopathogeny.[23]

Due to the strong association between the NL and the diabetes mellitus (65% of the NL patients have diabetes mellitus and 40 % of the rest present an impaired glucose tolerance

[7]); a hypothesis has been emitted that the diabetic microangiopathy is involved in the NL pathogeny. The glycoprotein warehouses noticed at the level of the blood vessel walls involved in the NL case are similar to the ones noticed in the diabetes at the ocular and renal level, observation which back-ups this theory. But not all the biopsies of the NL patients showed changes at the vascular level and then when there is a vascular affection, for many times the caliber of the involved arteries is bigger than in the case of the affection from the diabetic microagiopathy.[24]

The observation of the collagen deterioration from the NL level of the lesions leaded to the hypothesis that its direct affection could be the main pathogenic way. The excessive hydratation of the collagen fibers is produced as a result of the osmotic effect of final products belonging to the poliol way. The rising of the lizine-oxidasis level has been noticed at some diabetic patients, being responsible with the crossed connection of the collagen molecules and thus explaining the base membrane.[25] In the diabetes mellitus there have also been described the accelerated aging phenomena of the collagen fibers, along with the alteration of the normal function of these.[26]

Another theory is that of the presence of an autoimmune vasculitis as a substratum of the vascular alteration and then of the necrobiosis. The presence at the level of the vascular wall of the immunoglobules warehouses, components of the complement (C3) and the fibrinogen sustained this theory. [27]

Also, it was incriminated as factor in the etiological process a migration defect of the neutrofilas which could produce the rising of the local macrophage number, thus explaining the granuloma formation at the level of the NL lesions.[28] Another possible pathogen mechanism is a defect at the glucoses transporter level from the erythrocytes level.[29]

Histopatology

The histopathological exam shows two types of reactions which are present at the level of the NL lesions, the necrotic and granulomatose reaction.

At the start of the affection, the lesion hardly has a characteristic aspect, this being as an unspecifical inflammatory process. At a vascular level, the early changes are those of vasculite of the small arteries, which progress to the vasculite of larger arteries and the collagen degeneration with the derme involvement and of the thick subcutaneous tissue (with pattern of septal paniculite).

The microscopic exam using a direct immunofluorescence emphasized the presence of the immunoglobulin A and M warehouses, complement C3 and fibrinogen in the sanguine arteries walls establishing the thickening of their walls. [27]

Modifications, including the thickness of the vascular walls and also an increasing volume of the endothelium cells from the medium and deep derma are elements which also appear in the diabetic microangiopathy. As a comparison, the vascular modifications from NL noticed in nondiabetic patients are less conspicuous.

Moreover than the vascular changes, NL is a palisade granular dermatosis (the palisadic granuloma being an inflammatory reaction histiocitary essentially, organized in a

palisade). The NL granulomas are sometimes formed, beside the histiocite cells, also of multinuclear lymphocytes, plasmocytes and eosinophiles. The limphocitary component of the dermic infiltrate is most of all formed of T lymphocytes, predominantly LT helper.[30] The NL granulomatous reaction is accompanied by a necrothic reaction, the granulomas are noticed around the areas of degenerated collagen.[31]

Diagnosis

The NL diagnosis is generally clinical, the aspect of the cutaneous lesions being typical. The certainty diagnosis is put by cutaneous biopsy under local anesthesia and anathomo-pathologic examination.

The differential diagnosis is with: granuloma annulare (especially at the beginning for superficial lesions), xanthoma (because of the yellow color and the greasy aspect of the lesion), sarcoidosis (histologicaly both of them having granulomatous reaction), rheumatoid nodules (mostly in case of their ulceration), stasis dermatitis (complicated with variceal ulcer), nodos erithema (when, at the beginning, the lesions are nodular).

Fig. 1a,b – Patient with Necrobiosis lipoidica

Treatment

Though numerous therapeutic categories have been tried it hasn't been proved the certain efficiency of any treatment, the failure being caused also by the fact that the NL etiopathogeny remains unknown.

The trauma, since it can be the yield point for new lesions or can favor ulcers developing at the already formed lesion level, must be avoided.[21]

As smoking being a negative prognosis factor for NL, it is necessary to insure patient counseling regarding smoking.[8]

Although the role of controlling diabetus mellitus for the favorable NL evolution hasn't been proved, the diabetic patients are recommended a good glicemic control. Using oral anti-diabetics such as glitazone class has proven benefic for the NL lesions.[32]

Topic corticosteriode treatment can reduce local inflammation and favorize healing; this fact was proved by studies using topic

administration of Triamcinolon and Clobetasole propionate. [32,34,35] Because it increases the risk of cutaneous atrophy, those are applied only inside the lesion.

The systemic administration of corticosteriodes in short term cures can rapidly reduce the inflammatory process from NL.[36,37,38] For all this, the systemic corticosteroid administration remains controversial, regarding the corticosteroid influence on glicemic control.

To favorize healing of the NL lesions, it was attempted the treatment with drugs that increase peripheral blood flow. For this purpose there had been used platelet aggregation and vasodilatators.

If primarily the aspirin treatment in low doses seemed efficient, noticing a cutaneous lesion improvement at the patients using the treatment[39], the further studies haven't confirmed the benefit.[40,41] The aspirin and dipyridamole association in order to obtain a faster healing wasn't efficient for the aspect of NL lesions,[42] but it seems to favorize the healing of associated ulcers.[43] The results of the studies using another inhibitor of platelet aggregation, Ticlopidine, were favorable, showing an improvement of the NL plaque aspect with this particular treatment.[44,45]

The utilization of vasodilatator treatment with Pentoxifylline, which lowers the blood density, increases fibrinolisis and the deformability of eritocyte membrane, was proven efficient.[46,47,48]

Also, for the improvement of peripheral circulation were attempted treatments with Prostaglandin E1 [49,50] or stanazolol and inositol nicotinate [51], but with uncertain results.

The surgical treatment, with deeper excision of the affected tissue and region reconstruction with cutaneous graft, was used with some benefits.[52,53] Many times the negative result regarding the esthetics, as well as the lesion tendency to recidivate at the postoperative scar level do not grant an efficient response.[54,55] The laser surgery was used for esthetic purpose but data concerning this trend are still insufficient.[56,57]

For local treatment of the ulcerate lesions there have been successfully used products that promote healing. Therefore, the recombined human granulocyte-macrophage colony stimulating factor was used for topic treatment of the young diabetic patients with ulcerate lesions.[58,59] Other used products: matrix metaloproteases inactivatores[60], tissue-engineered human dermis, formed of human fibroblast-cells placed on a polymeric base, this product being the source for growing factors and matrix proteins [61,62], bovine collagen gel containing mostly type I collagen.[63]

The introduction in practice of the immunomodulatory therapy has opened new therapeutical options.

Many studies using Cyclosporin, the interleukin production inhibitor by the T helper lymphocytes, showed pleasing results, mostly for ulcerate lesions.[64,65,66]

The Mycophenolate mofetil which has important citostatic effects on the lymphocytes, used on a patient with bad evolving cutaneous ulcers for 18 months, has cured them in 4 weeks. [67]

The usage of Infliximab, a monoclonal antibody to TNF-alpha, has proven promising in many inflammatory dermatosis. [68,69] It was successfully used in ulcerate lesion cases and

will remain the backup treatment for multiple therapeutic lines resistant ulcers.[70]

Tacrolimus, in topical application, was efficient in the nonulcered lesions treatment from the beginning of the disease.[71,72] Also with imunomodulatory role, the fumaric acid esters were successfully used in multiple resistant ulcers.[73]

Many studies have analyzed the phototherapy and PUVA treatment efficiency, systemic or local, considering their anti-inflammatory role. Results have showed an improvement of the NL lesions in case of associated treatment.[7] One of the concerns regarding the usage of phototherapy is an increasing risk of developing squamos cell carcinoma at the lesion place.

Conclusions

Although many researches concerned NL, the pathogenic mechanism remains unknown, probably multifactorial, with certain features for the diabetic patient. The unknown etiopathogeny makes it very difficult to establish the optimal therapeutic conduct. Therefore it must insure proper attention to an efficient therapeutic strategy adapted for each case in particular. The treatment must be initiated in the first stages when is probably more efficient.

NL, a rare inflammatory disorder strongly attached to diabetes mellitus, remains a theme of interest for further investigations.

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