Simultaneous occurrence of ulcerated necrobiosis lipoidica and granuloma annulare in a patient - Case report *

Ocorrência simultânea de necrobiose lipoídica ulcerada e granuloma anular em um paciente - Relato de caso

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Abstract: Simultaneous occurrence of granuloma annulare and necrobiosis lipoidica is quite rare. There are seven reported cases in the literature, but only one presenting ulcerated necrobiosis lipoidica. We report a 39-year-old male with histopathologically confirmed granuloma annulare and ulcerated necrobiosis lipoidica, without diabetes mellitus.
Keywords: Diabetes mellitus; Granuloma annulare; Necrobiosis lipoidica; Skin ulcer

Resumo: Ocorrência simultânea de granuloma anular e necrobiose lipoídica é rara. Sete casos dessa associação foram encontrados na literatura, sendo somente um de necrobiose lipoídica ulcerada. Relata-se caso de concomitância de granuloma anular e necrobiose lipoídica ulcerada, não associada a diabetes *mellitus*, em paciente masculino de 39 anos, com confirmação histopatológica.
Palavras-chave: Diabetes *mellitus*; Granuloma anular; Necrobiose lipoídica; Úlcera cutânea

INTRODUCTION

Granuloma Annulare (GA) and Necrobiosis Lipoidica (NL) are pathological conditions of unclear etiology. They present similar histopathological findings and in some cases are clinically similar. NL has an association with *diabetes mellitus* (DM) and its ulcerated form may occur in up to 35% of patients. There are few cases in the literature with association of these two diseases, and it is even more rare to find GA and ulcerated NL concomitantly.[1-7] These concomitant diseases are reported without association with DM.

CASE REPORT

A 39-year old male reported the onset of asymptomatic cutaneous lesions on the abdomen and limbs, for 8 years. For the last 3 years, leg lesions appeared with overlapping painful ulcers that obliged the patient to walk with crutches and take tramadol daily. He denied having DM, was being treated for hypothyroidism with levothyroxine 100 mcg and used vitamin E 400mg/day. Upon examination, violaceous annular plaques were observed on upper limbs, thighs and abdomen, with infiltrated and defined borders (Figures 1 and 2). On the ankles there were brownish-yellow confluent plaques, with an atrophic centers, telangiectasia and overlapping ulcerations on the malleolar regions (Figures 3 and 4). The glycemic profile was normal and vascular echo Doppler of lower limbs did not show evidence of venous insufficiency. The patient had had a biopsy of upper limb lesion performed at another hospital that demonstrated palisade granuloma compatible with GA (Figure 5). He had also been prescribed systemic corticotherapy at another service, but he alleged that adverse effects led to suspension of this treatment. A biopsy of the ulcerated leg lesion was made and revealed ill-defined palisade granulomas in the deep dermis and subcuta-

Received on 08.03.2010.
Approved by the Advisory Board and accepted for publication on 28.08.2010.
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Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

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neous adipose tissue, with necrobiosis areas compatible with ulcerated NL (Figure 6). These clinical and histopathological findings make possible the diagnosis of GA concomitant with NL. The patient was treated with oral antibiotic therapy followed by oral pentoxiphiline 400mg 12/12 hours and topical gentamicin-betamethasone association, which resulted in partial resolution of ulcers.

DISCUSSION

Granuloma Annulare (GA) is a benign granulomatous disease of unknown etiology, characterized by groups of papules or annular plaques that appear predominantly on the back of hands and feet. It is more frequent in women, at a F:M rate of 2.3:1.[8] The association of GA and DM has been investigated many times, but it remains controversial, as well as its relationship with autoimmune thyroiditis. NL, in contrast, is considered a rare and degenerative disease of the connective tissue that presents with a palisade granulomatous cutaneous inflammation. It occurs mainly in young adults and is three times more frequent in women.[9] Sixty-five per cent of NL patients have DM, however, NL occurs in only 0.3% of the population with DM.[10,11]

Numerous theories were proposed for GA lesions pathogenesis. Vasculitis by immune complex deposition of immunoglobulin, complement and fibrinogen in blood vessels has been suggested. Lymphocyte-mediated hypersensitivity type IV causing degenerative alterations, monocyte lysosomal enzymes triggering necrobiotic degeneration, and a cell-mediated immune process were also proposed.[8] In addition, metabolic disorders and primary collagen and/or elastin lesions mediated by an immunologic mechanism have also been suggested. Some authors

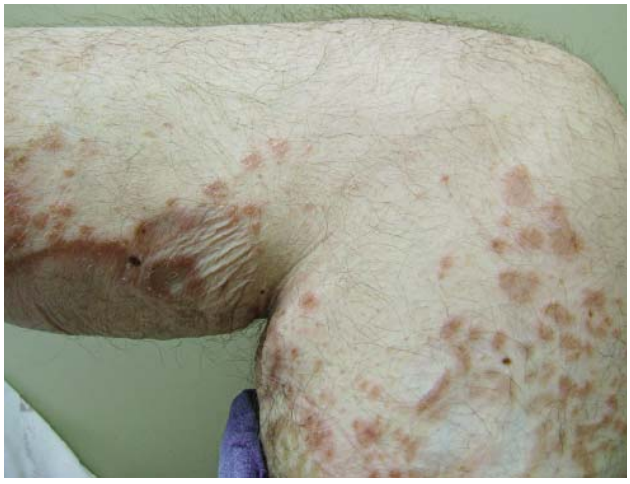

Figure 2: Disseminated granuloma annulare lesions

suggest that NL is vasculitis by immune complexes; other factors implicated in NL pathogenesis are abnormal collagen production, diabetic microangiopathy, or altered neutrophilic migration. Recent findings of Glut-1 (human erythrocyte glucose transporter) expression in areas of sclerotic collagen suggest that abnormalities in glucose transportation by fibroblasts may contribute to histopathological findings. [9]

The diagnosis of both diseases is based on clinical and histopathological data. GA lesions are usually asymptomatic, but there may be pruritus. Typical primary lesions present as erythematous papules, solitary or coalescent, frequently in annular configuration. Secondary lesions may become brownish and regress spontaneously, but 40% recur. There are different forms of GA: localized, generalized, perforating and subcutaneous. A macular form has been recently

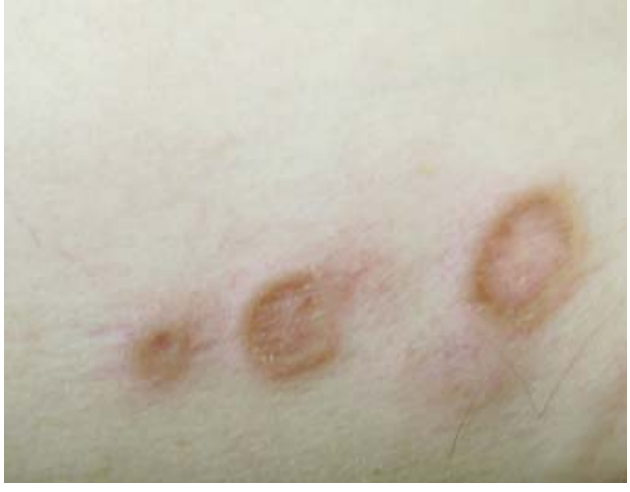

Figure 1: Granuloma annulare on limbs

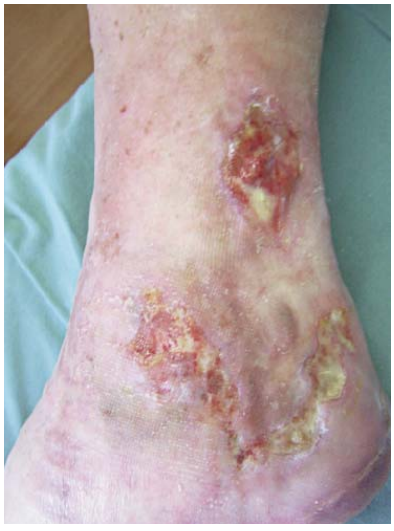

Figure 3: Ulcerated necrobiosis lipoidica lesions on ankle

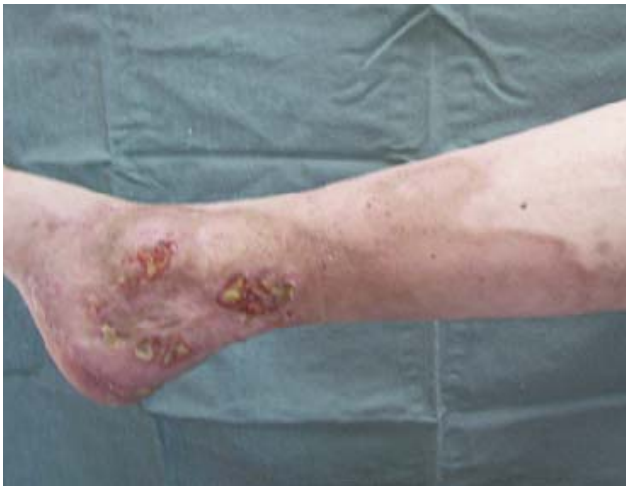

Figure 4: Necrobiosis lipoidica and granuloma annulare lesions

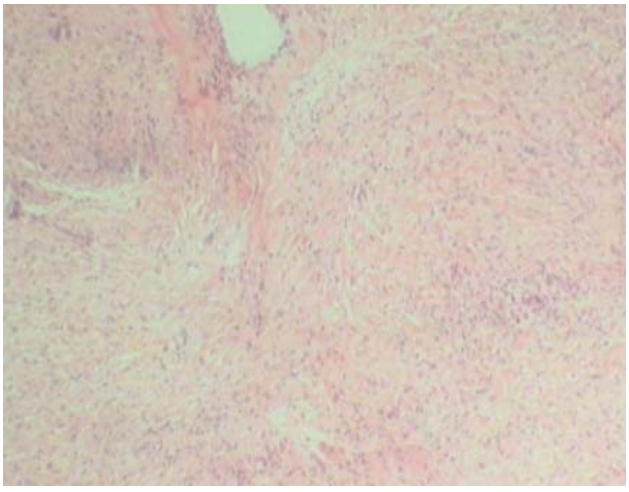

Figure 6: Ill-defined palisade granulomas in deep dermis and subcutaneous adipose tissue, with necrobiosis areas compatible with ulcerated necrobiosis lipoidica (HE, 40x)

reported. The prognosis for GA is similar in the generalized and localized forms, although its resolution is less probable in patients with the generalized form.[8] The NL lesions present as erythematous papules or plaques that grow centrifugally and become brownish-yellow, with atrophy and telangiectasia in the center and raised erythematous borders. They may be single or multiple and frequently coalesce. In most cases lesions are bilateral and occur on lower limbs. The pretibial area is the most affected, but lesions may appear on the scalp, face, trunk, penis or in diffuse form. The lesions tend to be chronic, of variable progression and may have long periods of quiescence or resolution. In 25-35% of the cases there is ulceration, and squamous-cell carcinoma has been reported for long-standing lesions.[9,10] NL should be differentiated from Necrobiotic Xanthogranuloma (NX), a rare and chronic disease, with lesions that are clinically and anatomopathologically similar to NL, frequently affecting periorbital and extracutaneous sites, besides showing strong association with lymphoproliferative diseases.[12]

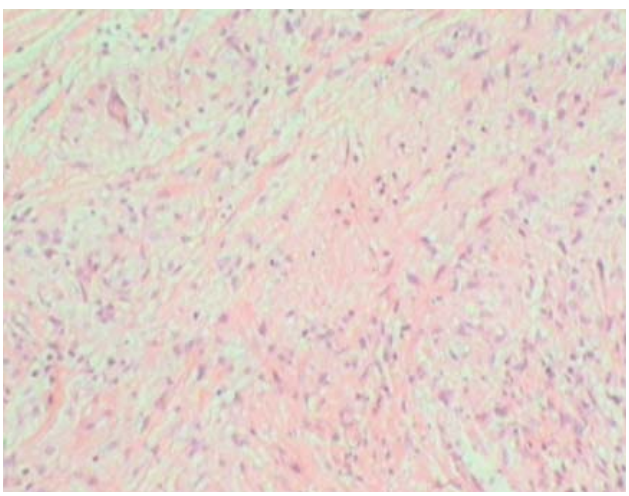

Figure 5: Palisade granuloma compatible with granuloma annulare (HE 100x)

Histopathologically, GA shows focuses of chronic lymphohistiocytic inflammation, occasionally multinucleated cells, more commonly affecting the superficial and medium dermis, with interstitial arrangement or palisade granuloma formation, involving areas of collagen degeneration and with mucin deposition. NL lesions are, to some extent, similar to GA ones. The epidermis is normal, atrophic or absent, if there is ulceration. The granulomatous infiltration involves the entire dermis and often reaches the subcutaneous tissue, causing septal panniculitis. Palisade granulomas appear, with histiocytes surrounding areas of degenerated collagen within septa.[9,10] In these areas, lipids, cholesterol crystals and mucin may be found. Necrobiosis is more extensive and less defined in comparison with GA. The most marked characteristic for NL diagnosis as cause of the inflammatory process involving the subcutaneous is the coexistence of similar lesions in the dermis, with horizontal bands of inflammatory cells, intercalated with areas of degenerated collagen and fibrosis, affecting the entire thickness of the dermis. The presence of inflammatory infiltrate, predominantly composed of neutrophils in the septum, is a characteristic of early NL stages. Follicular lymphoid formation is observed in the thickened septum of old lesions. When the lesions become atrophic the inflammatory infiltrate decreases and small granulomas remain with giant multinucleated cells amidst fibrotic degenerated collagen.[9] NX should also be considered in differential diagnosis, as characteristic giant cells are found in this condition

with angulated forms, ample eosinophilic cytoplasm and grouped, hyperchromatic nuclei, as well as with more frequent presence of lymphoid nodules. NL, on the other hand, presents wider lipid deposition bands and cholesterol crystals more often.

The histopathological distinction between GA and NL may be difficult. GA is typically localized in superficial and medium dermis, while NL affects the entire dermis and subcutaneous tissue. The GA pattern is focal and palisaded, while NL is more diffuse, with horizontal bands of more pronounced collagen degeneration. In GA there is presence of mucin, while in NL there are deposits of extracellular lipids. [2] Due to the histological similarities between GA and NL, these conditions may represent two points of a continuous spectrum of the same process. [7]

Several modalities of treatment have been employed in the treatment of GA, including topical and intralesional corticosteroids; dapsone; gold and bismuth injections; antimalarial agents; isoniazid; colchicine; clofazimine; intramuscular testosterone; radiation treatment; fumaric acids; topical nitrogenated mustard; imiquimod; topical retinoids; ultraviolet light; pulsed dye laser and surgical treatments, including grafts, dermoabrasion, cryotherapy and electrodissection, among others, all achieving varied degrees of success.[8, 13]

Since NL lesions, besides being esthetically inconvenient, can be painful and become secondarily infected, they require treatment. Several therapeutic options have been described, all of them with limited success: corticosteroids - topical, intralesional and systemic; topical retinoids, topical tacrolimus, antiplatelet drugs such as aspirin or ticlopidine, agents that decrease blood viscosity, such as pentoxiphiline, mycophenolate mofetil, fumaric acid, cyclosporine, chloroquine, thalidomide, PUVA, photodynamic therapy and anti-TNF drugs. [9,10,11, 14,15]

Only 7 cases of concomitant GA and NL in the same patient have been reported, and only one case of ulcerated NL. [1-7] Despite being diseases with anatomopathological similarities, the biopsies made it possible to differentiate them in the case here described. Due to the rarity of the association, little is known about specific therapeutics. As the pathology with greater morbidity to the patient was NL, and considering the little adherence profile of the patient, the choice was oral pentoxiphiline and topical corticotherapy. These options required less monitoring, resulting in ulcer and pain reduction within a few months. The patient began to walk without crutches again and suspended the use of opiates, continuing to use simple analgesics. ❑

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Como citar este artigo/*How to cite this article*: Souza FHM, Ribeiro CF, Pereira MAC, Mesquita L, Fabrício L. Simultaneous occurrence of ulcerated necrobiosis lipoidica and granuloma annulare in a patient - Case report. An Bras Dermatol. 2011;86(5):1007-10.