

## Generalized perforating granuloma annulare<sup>\*</sup>

### Granuloma anular perforante generalizado

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**Abstract:** The authors present a clinicopathological case of Generalized Perforating Granuloma Annulare with extensive distribution of lesions, which are shown in various stages of development. Pustules, papular lesions in annular and arcuate distribution, erosions covered with hematic crusts, maculopapular atrophic areas and scars were the presentation forms of the disease. The histopathological aspects are discussed in detail within non-infectious granulomatous dermatitis. The text is based on the opinions of some authors in the literature. Furthermore, the therapeutic result obtained after three months of Dapsone at a dose of 100 mg per day was demonstrated by photographs.

**Keywords:** Granuloma; Granuloma annulare; Dapsone

**Resumo:** Os autores apresentam caso clínico-patológico de Granuloma Anular Perforante Generalizado, com extensa distribuição de lesões, as quais se mostram em diversas fases de evolução. Pústulas, lesões papulosas, em distribuição anular e arciforme, erosões recobertas por crostas hemáticas, áreas máculo-atróficas e cicatrizes foram as faces de apresentação da doença. Os aspectos histopatológicos são detalhadamente discutidos, dentro das dermatites granulomatosas não infecciosas. O texto baseia-se nas opiniões de alguns autores da literatura. Além disso, o resultado terapêutico obtido foi demonstrado por fotografias, resultado de 3 meses de Dapsona na dose de 100 mg por dia.

**Palavras-chave:** Granuloma; Granuloma anular; Dapsona

#### INTRODUCTION

Granuloma Annulare (GA) is a benign self-limited dermatosis of unknown cause, characterized by necrobiotic dermal papules that often assume an annular configuration. Clinically, GA can be divided into distinct types: localized, generalized, subcutaneous, perforating and macular.<sup>1,2</sup> Perforating granuloma annulare (GAP) is a rare subtype of GA, first reported by Owens and Freeman in 1971.<sup>3</sup> Itching may occur in about 25% of the cases, especially when there are lesions on palms. Painful symptom<sup>4</sup> has also been described.<sup>4</sup> The generalized form was described in 1973 by Duncan et al.<sup>5</sup>

Perforating granuloma annulare (PGA) has a chronic course and unknown etiology. It is characterized by papules of 1-5 mm; some are umbilicated, well

demarcated, with perforation in their central portion through which mucoid material is eliminated.<sup>5</sup> The lesions are preferably located on the extremities, but may also appear in other regions of the body.<sup>5</sup> The generalized form of perforating granuloma annulare is defined as affecting at least the trunk and upper and/or lower limbs.<sup>6</sup> Dabski and Winkelmann define another presentation, which is called disseminated form, as the form that shows extensive manifestation only on the extremities.<sup>3,6</sup> The variety, known as generalized PGA, constitutes only 5% of the cases of granuloma annulare.<sup>3,5,7</sup> The literature reports a sex ratio of female-male of 2.9:1 in the group of patients with annular lesions, and an average of 51.7 years of age, when evaluated at the initial period of the disease.<sup>6</sup>

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The cause of Generalized Perforating Granuloma Annulare (GPGA) is unknown, but some authors agree in asserting the existence of factors implicated in its pathogenesis, including insect bites, ultraviolet radiation, minor trauma, viral infection, thyroiditis and diabetes mellitus.<sup>8</sup>

In order for the process of perforation to start, direct contact between the epithelial structure (keratinocytes of the epidermis and of the pilosebaceous unit) and the granulomatous dermal component is possibly necessary. According to Bardach<sup>5</sup>, this close interrelationship would be the main factor causing the epithelial and follicular damage.<sup>5</sup> The presence of immunoglobulins IgM, complement (C<sub>3</sub>) and fibrinogen in the blood vessels, decreased in patients with PGA, suggests that a chronic immune vasculitis could be involved in its pathogenesis. Epithelial atrophy and, possibly, perforation could be explained by the expansive, multidirectional growth of the necrobiotic granuloma and by a possible deviation of blood supply to the epidermis.<sup>3</sup> Authors suggest that lymphokines and lysosomal enzymes released would lead to the destruction of collagen tissue.<sup>5</sup>

#### CASE REPORT

Forty-nine-year-old male patient reported appearance of asymptomatic pustules initially on the lower limbs 10 months before the medical appointment. There are no reports of previous recent infections or even family history of skin diseases or diabetes.

A physical examination showed erythematous papular lesions of annular or arciform aspect, some with central erosion and covered by sero-hematic crust, spread throughout the integument. Violaceous scars with up to 10 cm in diameter, mainly on the lower limbs, and lenticular hypochromic lesions could be seen on the trunk (Figure 1.2). There were scarce pustules on the legs (Figure 3).

Laboratory tests showed alterations in fasting glucose, with glucose of 138 mg / dl and 130 mg / dl, which confirmed diabetes mellitus. Blood count, erythrocyte sedimentation, liver and kidney function, cholesterol fractions and triglycerides, TSH (thyroid stimulating hormone) and anti-thyroid peroxidase antibodies were normal. The dosage of glucose-6-phosphate dehydrogenase did not show deficiency of the enzyme. Anti-nuclear factor, anti-HCV (anti-hepatitis C virus antibodies), HBsAg (surface antigen of hepatitis B virus), Anti-HBc IgG (antibodies of IgG fraction produced against antigens of the nucleocapsid of hepatitis B virus), anti-HIV I and II (antibodies against the human immunodeficiency virus type 1 and 2) were not reactive. An X-ray of the chest showed scars indicating tuberculosis in the upper half of both lungs and



FIGURE 1: Knee and leg in the diagnosis

pulmonary emphysema. He had no history of treatment of pulmonary tuberculosis.

A skin biopsy (March 6, 2008) showed ulcerated skin with hyperkeratosis, irregular acanthosis, dermal fibrosis and chronic inflammation with Langhans giant cells and foreign-body giant cells, with negative AFB. A new biopsy was performed on March 8, 2008, which showed histological results compatible with perforating granuloma annulare. (Figures 4,5,6)

This patient was referred for treatment of diabetes mellitus. The treatment began with 100mg/day of dapsone (diaminodiphenylsulfone), with therapy being partially successful in a course of 30 days, even before offsetting the glycemic condition.

#### DISCUSSION

In general, GA, in its localized form, is associat-



FIGURE 2: Lesion on the left flank in the diagnosis



FIGURE 3: Pustule as initial lesion

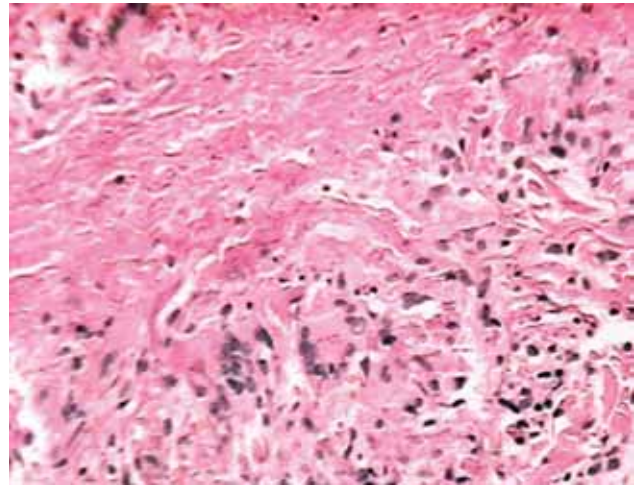


FIGURE 5: HE: 400X - giant cells and other palisading histiocytes with necrobiotic collagen in the center

ed with diabetes mellitus in a proportion of 16% of the cases; this association is 19% when it comes to the generalized form of GA and 17% in the perforating form.<sup>3</sup> The average age of onset is higher among diabetic patients, which is around 33 years for the generalized form.<sup>7</sup> The case that we described had a delayed onset.

Generalized PGA (GPGA) shows as important characteristics the following: pustular lesions and scarring located in the abdominal area, trunk, extremities, dorsal hands and palms, as we observed in the patient described.<sup>3,4</sup> Transepithelial elimination can be transepidermal and / or transfollicular<sup>9</sup>. In an article published by Pablo F. Peñas et al., it is observed that in the generalized form, pustuliform lesions and scarring appear in significantly higher percentages than in the localized and perforating variants.<sup>3</sup> In the case that we

reported, defined as a generalized and perforating form, the patient showed the initial characteristics of most lesions in the pustular lesion, a fact which reinforces the findings of the literature.<sup>3</sup>

Harsch Mohan et al. published a study with 586 cases of granulomatous dermatitis, of which 71 (12.11%) were classified as non-infectious granulomas by means of clinicopathologic analyses.<sup>10</sup> In this publication, the authors report how difficult it is to classify a granulomatous dermatitis, showing that it has been made based on physiopathological, etiological, immunological and morphological characteristics. They report that non-infectious granulomas have been categorized into four groups: epithelioid (sarcoid and tuberculoid), necrobiotic or palisading (granuloma annulare and others), and histiocytic or by foreign body.<sup>10</sup> In addition, the authors report two categories

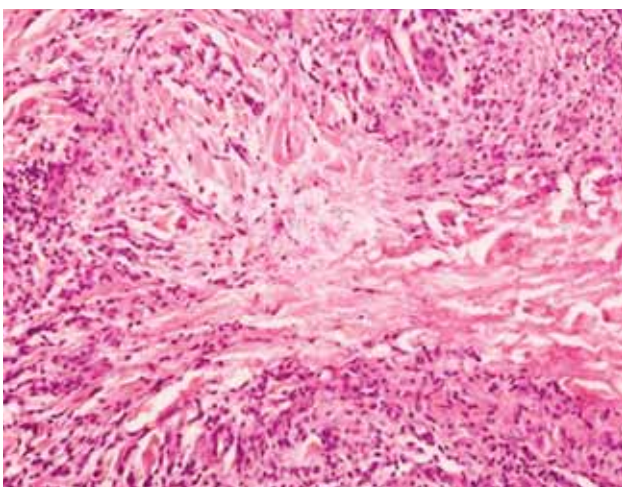


FIGURE 4: HE: 200X - palisading granuloma surrounding necrobiotic collagen

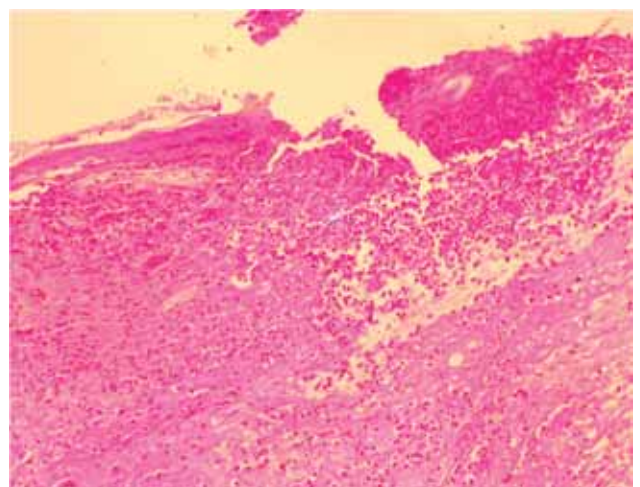


FIGURE 6: HE: 200X - neutrophils, degenerated collagen and fibrinoid in area of perforation



of necrobiotic granulomas: the “blue collagenolytic granuloma”, whose central area is basophilic, either by deposition of mucin or nuclear dust (it includes granuloma annulare, Wegener’s granulomatosis and others) and “red collagenolytic granuloma”, whose central area is eosinophilic due to hyalinization of collagen, fibrin or degranulation of eosinophils (it includes necrobiosis lipoidica, necrobiotic xanthogranuloma, rheumatoid nodules and others).<sup>10</sup>

In accordance with what the literature has shown, cases like the one presented here are characterized by the presence of granulomas with histiocytes sparsely arranged or arranged in a palisading pattern, surrounding necrobiotic collagen, which is typically represented by deposition of mucin, and rarely fibrin. Often, the histiocytes may become epithelioid and multinucleate and be found phagocytizing elastic fibers. The lesion is often present in the superficial and deep reticular dermis and may also involve the subcutaneous tissue. In the perforating granuloma annulare variant, the process is preferentially located in the superficial reticular dermis, causing perforation of the epidermis which is acanthotic and forming a channel for extrusion of degenerated collagen.<sup>11,12</sup> The extruded material is seen in preparations of hematoxylin and eosin, but special stains such as alcian blue and colloidal iron can be made to highlight mucin.

As in most cases, GA presents with histiocytes arranged diffusely between the collagen, with little mucinous degeneration. In these cases, the main differential diagnosis involves necrobiosis lipoidica, which is also characterized by a diffuse aspect of the histiocytes; however, the latter tends to affect the entire dermis in the biopsy sample, that is, the adjacent dermis and deep dermis. As for the differential diagnosis of PGA, it is made between PGA and perforating dermatoses.<sup>11,12</sup>

The anatomopathological differential diagnosis of GPGA also includes sarcoidosis, tuberculids, drug-induced eruptions, mycosis fungoides, mycobacteriosis, epithelioid sarcoma, rheumatoid nodule, perforating osteoma, calcinosis cutis, perforating folliculitis and reactive perforating collagenosis.<sup>11,12</sup>

Systemic therapy is necessary for the treatment of disseminated granuloma annulare; however, several treatments have been proposed. Topical therapy includes corticosteroids, tacrolimus, pimecrolimus

and vitamin E. Systemic therapy includes dapsone, retinoids, antimalarials, pentoxifylline, nicotinamide, dipyridamole and Infliximab. Phototherapy is also included in this therapeutic arsenal. The possible benefits of treatment, which is uncertain due to lack of clinical trials, must be balanced against the risk of toxicity presented by most of these treatments.<sup>13</sup>

Considering the therapeutic difficulty of these cases, our patient showed surprising regression of lesions after 30 days of treatment with dapsone 100 mg / day, and after 3 months of treatment, almost all lesions were virtually inactivated (Figures 7.8). □



FIGURE 7: Knee and leg 3 months after treatment



FIGURE 8: Lesion on the left flank after 3 months of treatment

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