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Granuloma Annulare: a Review of the Literature

Granuloma Anular: uma Revisão da Literatura

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Abstract

Granuloma annulare (GA) is a form of noninfectious skin granuloma, first described in 1895 as a rash in the form of a ring (annular), with regular, rounded edges. Around 50% of the cases are cured spontaneously within 2 years, however, a percentage of patients suffer from recurrent lesions or persistence for years. The pathogenesis of GA lesions is not well understood, with studies linking its expression to the presence of histocompatibility genes (HLA)-Bw35 or AH8.1 allele. These genes are related to the production of TNF-α (*Tumor Necrosis Factor*-α) by mononuclear cells. The pathogenesis includes the migration of macrophages to the dermis, the presence of cytokines, late hypersensitivity reaction, defects in regulating the neutrophil chemotaxis and degradation of the connective tissue. Its outbreak may be linked to predisposing factors, such as diabetes mellitus, thyroid changes and viral infectious diseases. The macrophages present in GA lesions may receive stimuli that result in its modulation to M1 or M2 activation patterns. The study of the M1 and M2 modulation mechanism in the lesion is important for an understanding of GA development.

Keywords: Granuloma Annulare. Macrophage. Immunology. Pathogenesis and Modulation.

Resumo

O Granuloma Anular (GA) é um tipo de granuloma cutâneo não infeccioso, que foi descrito em 1895, como uma exantema em formato de anel (anular), de bordas regulares e arredondadas. Cerca de 50% dos casos têm cura espontânea em 2 anos, mas parte dos pacientes apresentam recidivas das lesões ou persistência por anos. A patogênese das lesões do GA é pouco conhecida. Estudos relacionam sua expressão à presença de genes de histocompatibilidade (HLA)-Bw35 ou AH8.1, que são relacionados à produção de TNF-α (Tumor necrosis factor - α), pelas células mononucleares. A patogênese também inclui migração de macrófagos para derme, presença de citocinas, reação de hipersensibilidade tardia, defeito na quimiotaxia de neutrófilos e degradação do tecido conectivo. O surgimento das lesões pode estar associado a fatores predisponentes, como diabetes mellitus, alterações tireoidianas e doenças infecciosas virais. Os macrófagos presentes nas lesões de GA podem sofrer estímulos que acarretem sua modulação para os padrões de ativação M1 ou M2. O estudo de tais mecanismo de modulação é importante para a compreensão da instalação e desenvolvimento do GA nos pacientes afetados.

Palavras-chave: *Granuloma Anular. Macrófagos. Modulação. Imunologia e Patogênese.*

1 Introduction

Cutaneous granulomas, or cutaneous granulomatous reactions, comprise a group of skin diseases whose pathological mechanism is not well understood (BERETTA-PICCOLI *et al*., 2018; LO SCHIAVO *et al.,* 2014). Granulomatous reactions are caused by diverse stimuli: inflammatory, neoplastic, infectious or metabolic/chemical disorders. This variety might explain the cases' histological and clinical diversity (BERETTA-PICCOLI *et al.,* 2018; ASAI, 2017). These inflammatory lesions infiltrate the dermis and, on occasions, the hypodermis, and are characterized by the nodular, fence-shaped and/or interstitial arrangement (BERETTA-PICCOLI *et al.,* 2018; ASAI, 2017, MASSON, 2018).

This specific form of inflammation involves multiple cell types, primarily dendritic cells, auxiliary T lymphocytes and macrophages, which are the predominant cell type. The main functions of macrophages/histiocytes are phagocytosis and the elimination of microorganisms, as well as the presentation of antigens to other lymphocytes in the immune system, cytokine production, chemokines and production of arachidonic acid metabolites (BERETTA-PICCOLI *et al.,* 2018). Of the granulomatous lesions, granuloma annulare has a histological pattern that differs form the other lesions with the presence of macrophages and the destruction of collagen (BERETTA-PICCOLI *et al*., 2018; PICCOLI *et al.,* 2018; MUYLAERT; ALMADA; VASCONCELOS*,* 2017; GÜNES *et al.,* 2009; SANTAMARIA, 2018).

Our review intends to assemble the studies about this lesion, looking for associations with other comorbidities and evidence of macrophages patterns present in Granuloma annulare (GA) lesions.

2 Development

2.1 Methods

This article was based on a descriptive and qualitative

bibliographic review, which used as its sources of research a filtering of the following search engines: Scientific Electronic Library Online (SCIELO) and NCBI Pubmed. The following descriptors were employed to perform the search: granuloma annulare, M1 and M2 macrophages, hypothyroidism, diabetes, with the inclusion criteria being articles published between 2015 and 2018 and related to the keywords. Initially 63 articles were selected. As inclusion criteria, review articles were integrated, which relate granuloma annulare to other comorbidities. Exclusion was given to papers with a primary focus on diagnosis and treatment. At the end of the bibliographic compilation and applying inclusion and exclusion criteria, a total of 20 articles were used in the mentioned period.

2.2 Granuloma annulare (GA) lesions definition

GA is a type of noninfectious, cutaneous granuloma, first identified on a girl's finger in 1895 by the physician Colcett Fox, as a ring-shaped eruption with regular, rounded edges. It usually occurs in adult women, though rarely in children (PICCOLI *et al.,* 2018; MUYLAERT; ALMADA; VASCONCELOS, 2017). Around 50% of cases are spontaneously cured within 2 years, but a proportion of patients present recurrent lesions, or persistence, for years, impacting the patients' quality of life (PICCOLI *et al.,* 2018).

GA is an inflammatory disorder of the skin; whose etiology is unknown and characterized by a varied number of non-pruritic papules that frequently coalesce into a ring- or arch-shaped format (arciform). The histological picture is characterized by the presence of complete or incomplete necrobiosis of the dermal collagen, linked to an inflammatory infiltrate of macrophages, which intersperses the areas of degraded collagen (BERETTA-PICCOLI *et al.,* 2018; PICCOLI *et al*., 2018; GÜNES *et al.,* 2009; SANTAMARIA, 2018). The histopathological, fence-shaped pattern denotes the arrangement of dermal histiocytes and lymphocytes, arranged in an interstitial pattern, the presence of giant cells, circumscribing the degenerated collagen, like the outline of a fence, and mild perivascular lymphocytic infiltrate (WANDERLEY SOUB; CARRIJO; CUZZI, 2013; GAVIOLI, 2017).

Clinically, the most common subtypes are localized GA, generalized GA, perforating GA and the maculopapular form of GA. of these, the most common is localized GA, representing up to 75% of cases of GA, common in children and young people, characterized by the presence of a single annular erythematous to violaceous lesion on the back of the hands and feet (WANG; KHACHEMOUNE, 2018; MASSUCATTI; VILLA; BEDIN, 2010).

Generalized GA is characterized by the presence of at least 10 lesions distributed over the body, including the trunk and limbs. The lesions of this subtype are erythematous papules with raised borders, central atrophy measuring approximately 4 cm and the presence of itching (MASSUCATTI; VILLA; BEDIN, 2010). Generalized GA may present lesions classified as deep or subcutaneous, characterized by lesions in granulomatous palisade, inflammation of the deep dermis and areas of necrobiosis (WANDERLEY SOUB; CARRIJO; CUZZI, 2013; MASSUCATTI; VILLA; BEDIN, 2010). In these lesions, it is also possible to observe nuclear remnants of neutrophils, as well as mucin deposits (WANDERLEY SOUB; CARRIJO; CUZZI, 2013; MASSUCATTI; VILLA; BEDIN, 2010).

The perforating GA has chronic evolution and unknown etiology, characterized by centrally umbilicated lesions with 1 to 5 mm. The differentiation of this subtype is by the presence of central perforation, with release of mucus secretion (DORNELLES, *et al*., 2011). Perforation occurs by contact of the epithelial structure with components of the dermal granuloma, causing follicular damage (DORNELLES *et al*., 2011). The perforating GA may also present itching and/or episodic pain (WANDERLEY SOUB; CARRIJO; CUZZI, 2013; DORNELLES, et al., 2011).

GA maculopapular plaques are characterized by erythematous-brownish lesions at the extremities of the body (WANDERLEY SOUB; CARRIJO; CUZZI, 2013). The differentiation between the subtypes of GA is due to the morphological characteristics of the lesions, body extension and the presence of symptoms, such as itching and/or pain (WANDERLEY SOUB; CARRIJO; CUZZI, 2013; DORNELLES, *et al*., 2011, MASSUCATTI; VILLA; BEDIN, 2010.

2.3 Pathogenesis of Granuloma Annulare

Little is known about the pathogenesis of GA lesions, but a number of studies have linked its expression to the presence of the histocompatibility genes (HLA)-Bw35 or AH8.1 allele (BERETTA-PICCOLI *et al.,* 2018; COHEN; CARLOS, 2015). These genes appear to be linked to an increase in TNF-α production by blood mononuclear cells from patients who are carriers (BERETTA-PICCOLI *et al.,* 2018; ERRICHETTI *et al.,* 2017; KEIMING, 2015).

The pathogenesis of GA, irrespective of its clinical form, includes the migration of macrophages to the dermis, the presence of cytokines, late hypersensitivity reaction, defects in the neutrophil chemiotaxis and degradation of the connective tissue (KEIMING, 2015; KNOELL, 2009; PIETTE; ROSEMBACH, 2016; MAGALHÃES; GUIMARÃES; PAULA, 2017). Degradation of the matrix occurs through the action of metalloproteinases released by the activated macrophages present in the dermis (MAGALHÃES; GUIMARÃES; PAULA, 2017).

With the GA lesion, the presence of T cells was identified, the population being predominantly auxiliary activated T cells of class TH1 (*T Helper-1*) (COHEN; CARLOS, 2015; PIETTE; ROSEMBACH, 2016). TH1 lymphocytes were

found inside the granulomas and surrounding the blood vessels (COHEN; CARLOS, 2015). As GA is a late hypersensitivity reaction with degradation of the extracellular matrix, the cytokine pattern involved appears to be fundamental to the lesion development.

Several studies have sought to evaluate the roles of IFN-γ (interferon-γ), matrix metalloproteinases and TNF-α in the pathogenesis of the lesion (COHEN; CARLOS, 2015; MEMPEL *et al*., 2002). Lymphocytes release IFN-γ, responsible for the activation of macrophages. This phagocyte acquires the ability to produce and release IL-12 (Interleukin-12), the main cytokine to modulate the differentiation of the TH0 lymphocyte (T Helper-0) in the TH1 phenotype. Immunohistochemistry revealed that macrophages also produce significant quantities of TNF-α and metalloproteinases 2 and 9. The outcome of this process is the characteristic degradation of the matrix of connective tissue present in the GA lesion (COHEN; CARLOS, 2015; MEMPEL *et al.,* 2002). Recent studies confirmed the presence of TH1 cells in granulomas and high levels of IL-12 (COHEN: CARLOS, 2015; PIETTE *et al.,* 2016). To summarize, we could suggest that the GA lesion is a cell response to an as-yet-unknown antigen (COHEN; CARLOS, 2015).

2.4 Predisposition to Granuloma Annulare

The manifestation of GA may be linked to predisposing factors, which include diseases such as diabetes mellitus and thyroid changes, infectious diseases like the human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and tuberculosis, minor skin traumas, such as bee stings, sunburn and tattoos (BONOMO; GHONUM; LEVITT, 2017; BUECHNER; WINKELMANN; BANKS*,* 1983). The patient's chronic clinical conditions reported also include fibromyalgia and psoriasis (MAGALHÃES; GUIMARÃES; PAULA, 2017). Psoriasis and GA are inflammatory processes characterized by an increase in the expression of TNF-α, extracellular matrix metalloproteinases and activated macrophages (MEMPEL *et al.,* 2002; FAYYAZI *et al.,* 2000). The studies that were conducted, to determine if the pathogenesis of psoriasis might be predisposing to cutaneous GA lesions, were inconclusive (COHEN; CARLOS, 2015; MAGALHÃES; GUIMARÃES; PAULA, 2017).

Diabetes mellitus is the most common metabolic disease in the world population, with a progressively increasing number of new diagnoses (VAZQUEZ-LOPEZ *et al.,* 2003). This disease is a global health problem with a great impact on health services (MEMPEL *et al.,* 2002; VAZQUEZ-LOPEZ *et al.,* 2003). Type 1 diabetes mellitus (DM 1) is characterized by the destruction of pancreatic β-cells that are responsible for insulin production (MEMPEL *et al.,* 2002; WILLEMSEN *et al.,* 1987). These patients possess autoantibodies against insulin, tyrosine phosphatases, islet cells antigens and glutamate decarboxylase that recognize the pancreatic β-cell producing inflammation and causing their destruction (WILLEMSEN *et al.,* 1987; FAYYAZI *et al.,* 2000). Patients with DM1 have a genetic predisposition, as 40% of patients have mutation in the locus of the human leukocyte antigen (HLA), in chromosome 6q21.3 (HITCHON *et al.,* 2002). Around 10 to 30% of patients with DM1 do not present a genetic association or autoimmune mechanism, with the idiopathic disease (WILLEMSEN *et al.,* 1987). Insulin replacement therapy is always needed with DM1. Type 2 diabetes (DM2) is the most common disease in which the patient develops insulin resistance. In these patients, we observe high levels of proinflammatory cytokines, oxygen reactive radicals, adipocytokines and free fatty acids, which have been linked to insulin resistance (MEMPEL *et al.,* 2002; LIMA *et al.,* 2017). Hyperglycemia acts on the keratinocytes and fibroblasts, leading to a change in protein synthesis, and cell proliferation and migration (JAACKS *et al.,* 2016).

Inflammatory characteristics found in patients with DM2 have been related to a greater predisposition to develop GA associated to the overall population (MASSUCATTI; VILLA; BEDIN, 2010). Studies that report an association between GA and diabetes have courted controversy (MEMPEL *et al.*, 2002; ATKINSON; EISENBARTH; MICHELS, 2014) and initial studies suggested a relationship between the two diseases (COHEN; CARLOS, 2015; EISENBARTH, 2017; HORENSTEIN; SHULDINER, 2004; BASTARD *et al.,* 2006). More recently, other researchers, retrospectively, found no statistically significant link between GA and DM disease (BLAKYTNY; JUDE, 2009; NEBESIO; LEWIS; CHUANG, 2002; MUHLEMANN; WILLIAMS 1984). In the same studies, in patients with DM and GA, GA lesions tended to demonstrate greater chronicity and recurrence of GA, when compared to non-diabetic patients (EISENBARTH, 2017; BASTARD *et al.,* 2006).

The literature presents clinical case reports in which was observe an association between GA and autoimmune diseases, of which thyroid diseases are the most prominent (HAIM; FRIEDMAN-BIRNBAUM; SHARFRIR, 1970; HAIM *et al.,* 1973). A study conducted by Vazquez-Lopez and colleagues (COHEN; CARLOS, 2015) sought to establish a prevalence of thyroid diseases in patients with GA. In the group of patients with localized GA, 12% presented autoimmune thyroiditis with hypothyroidism, while among the control groups, only 1% thyroid disease was observed. These results are significant, indicating a correlation between symptomatic autoimmune diseases of the thyroid and GA. Another study demonstrated that patients with GA associated with hypothyroidism presented a resolution of the lesions following treatment with synthetic thyroid hormone (COHEN; CARLOS, 2015).

GA is more likely to occur in patients with autoimmune diseases (HAIM; FRIEDMAN-BIRNBAUM; SHARFRIR, 1970; GROGG; NASCIMENTO, 2001; GANNON; LUNCH, 1994). Vázquez-López *et al.* (2003) suggested that localized GA belongs to the spectrum of autoimmune diseases, due

to the similarities in the pathogenesis between the lesions. In the autoimmune spectrum, patients tend to manifest other diseases, also of an autoimmune etiology, besides skin alterations, such as GA (ERRANTE *et al.*, 2016). The various autoimmune diseases may emerge from the loss of regulation of a common self-tolerance immune mechanism (KAPPELER; THOENDLE; MULLER, 2001).

2.5 Treatment of Granuloma Annulare

There are reports of the effectiveness of a variety of therapeutic approaches. The role of the cutaneous biopsy in the resolution of lesions continues to court controversy. Maschio *et al.,* (2013) reported a case of rapid resolution of biopsied lesions on two separate occasions with the same patient. Despite the fact that the mechanism involved is unclear, it is thought that the induction of wound healing changes the lesion pathogenesis, leading to substitution rather than the destruction of proteins in the extracellular matrix. Cryosurgery has also been reported in the treatment of GA lesions (VAL *et al.,* 2015). Other treatments with low doses of recombinant IFN-γ (MASCHIO *et al.,* 2013) and laser therapy (SUMIKAWA *et al.,* 2010) have also been effective in the resolution of lesions.

In the literature, the use of multiple medications can be found, such as allopurinol, diclofenac, quinidine, intranasal calcitonin, pentoxifylline dapsone and amlodipine, as well as corticosteroids (MAGALHÃES; GUIMARÃES; PAULA, 2017). Other studies have recommended the use of antibiotics from the tetracycline family and non-steroid anti-inflammatory drugs (VAZQUEZ-LOPEZ *et al.,* 2003).

As already demonstrated in this review, GA lesions are basically composed of macrophage cells, in a granulomatous organization. There is growing *in vivo* and *in vitro* evidence indicating that these cells, found in lesions, may present polarization in macrophages of the phenotype known as M1 (*Macrophage 1*) or M2 (*Macrophage 2*). This classification also may serve as a new strategy for diagnosis or treatment in multiple diseases (PIETTE; ROSEMBACH, 2016; BUECHNER; WINKELMANN; BANKS, 1983).

2.6 Macrophage Polarization

The macrophages in different lesions may suffer stimuli that result in their modulation to M1 or M2 activation patterns (MARTINEZ; HELMING; GORDON, 2009; BARBOSA, 2015). Classic activation of macrophages leads to a cell with a high capacity for antigen presentation, producer of IL-12 and IL-23, and to the production of high rates of reactive kinds of oxygen and nitric oxide. This macrophage is classified as an M1 cell (RAJARAM *et al.,* 2010; GORDON; MARTINEZ; HELMING; GORDON, 2009). This cell is a powerful eliminator of tumor cell and microorganisms, as well as being a producer of inflammatory cytokines. The stimulation of M1 macrophages is obtained through the action of IFN-γ, TNF-α and lipopolysaccharides (LPS) (RAJARAM *et al.,* 2010).

An alternative route for the stimulation of macrophage cells is obtained through the action of IL-4 and IL-13 (PESCE *et al.,* 2009). This a phenotype of M2 modulation leads to a cell with a pattern of inhibition of inflammation, elimination of detritus, stimulation of angiogenesis, tissue remodeling and repair (PESCE *et al.,* 2009; ZHU *et al.,* 2014). M2 macrophages are present in the processes of tissue remodeling, parasite resistance, regulation of the immune response and tumor promotion (PESCE *et al.,* 2009).

In response to stimuli derived from pathogenic environments, macrophages are induced to the polarization of phenotype, classically M1 induced by Toll-like receptors (TLR) and IFNγ receptors, and alternatively, M2 induced by IL4 / IL13 (M2a), immune complexes (M2b) and anti-inflammatory cytokines IL-10 or transforming growth factor-β (TGF-β) (M2c), which mirrors TH1/TH2 polarization, which modulates the immune response (PESCE *et al.,* 2009; ZHU *et al.,* 2014). The lesion microenvironment determines the properties of the macrophages and the state of activation (PORQUERAY *et al.,* 2005). M1 and M2 patterns may be induced and quickly inverted, through interacting, complex endogenic cell signaling and their modulators. Collectively, the plasticity of macrophage polarization has implications for treatment. The macrophages in the GA are extremely positive for CD68, totaling practically 100% of the cells present in the lesion, and this marker may be used as an indicator of a lesion presenting a granulomatous outline (GROISMAN *et al.,* 2002).

A study conducted by Töröcsik *et al.* (2014) examines the presence of the protein Factor XIII subunit A (FXIII-A) in the cytoplasm of the cells in GA lesions and necrobiosis lipoidica (NL). Although FXIII-A is an important molecule in the blood coagulation process, myeloid cells produce it but do not release it, maintaining a cytoplasmic concentration. Macrophages and dendritic cells in dermatological lesions, such as granuloma, sarcoidosis and tumors, show a high level of positivity for FXIII-A. In these lesions, we also see high levels of IL-4 and IL-13, which modulate the macrophages to an alternative activation pattern for tissue remodeling.

Töröcsik *et al.* (2014) results demonstrate that both GA and NL show FXIII-A positivity in macrophages and myeloid dendritic cells. This positivity is consistent with a similar positivity for CD68, and the lesions also present IL-4 and IL-13, indicating the modulation of macrophages to an alternative activation of M2 tissue remodeling (TÖRÖCSIK *et al.,* 2014). These results contradict other authors who demonstrated the TH1 activation in the GA with the presence of IFNγ and TNFα. With this profile, we would expect to find M1 modulation, classical activation for the elimination of the pathogen (COHEN; CARLOS, 2015; PIETTE; ROSEMBACH, 2016; MEMPEL *et al.,* 2002).

Within the context of GA, this polarization would likely give rise to macrophage cells, initially with an M1 pattern, which should promote resolution of the lesion with

phagocytosis to subsequently modulate tissue response, to an M2 phenotype and stimulate tissue repair. What was found, however, is a granulomatous lesion that is difficult to resolve, and that one of the more effective treatments is to perform a biopsy (MASCHIO *et al.,* 2013).

With the removal of a fragment of the lesion, a local inflammatory process is created that appears to change the lesion, in a state of rest in the macrophage polarization, reactivating the inflammatory cells and resolving the lesion (MASCHIO *et al.,* 2013). One of the known factors is that any lesion leads to cell dead and the releasing of cell debris indicators known as DAMPs (Damage Associated Molecular Patterns) (VÉNÉREAU; CERIOTTI; BIANCHI, 2015). These cytoplasmic molecules, when released, signal the occurrence of a cell lesion to the inflammatory cells (VÉNÉREAU; CERIOTTI; BIANCHI, 2015).

3 Conclusion

This review demonstrates that Granuloma Annulare (GA) lesion develops through the action of inflammatory macrophages and local cytokine production. Due to these characteristics, it is necessary to study the pattern of macrophages present in GA lesions, evaluating which modulation of these cells lead to the formation of lesions. This study brings a better understanding of the macrophage action within the GA lesion, elucidating its pathophysiology and contributing to more effective therapeutic approaches.

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