DISSEMINATED GRANULOMA ANNULARE - STUDY ON 21 CASES

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Summary

Background: *Disseminated granuloma annulare is a rare clinical variant of granuloma annulare.inflammatory skin condition with unknown etiopathogenesis.*

Objective: *To study clinical aspects of granuloma annulare and its relationship with coexisting pathology and therapeutic options.*

Methods: *We performed a retrospective study in the Craiova Dermatology Clinic on cases of patients hospitalized with disseminated granuloma annulare during 2015-2023. A total of 21 patients were evaluated and monitored for a year after initial diagnosis.*

Results: *We found the following associated pathology: type 2 diabetes mellitus (12 cases), dyslipidaemia (11 cases), overweight and obese (10 cases), hypothyroidism (4 cases), rheumatoid arthritis (1 case) and neoplastic disease in 4 patients. Treatment was complex and effective.*

Conclusion: *Patients with disseminated granuloma annulare should be investigated for internal disease.*

Keywords: *disseminated granuloma annulare, comorbidities, diabetes mellitus, treatment.*

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Introduction

Granuloma annulare (GA) is a benign chronic inflammatory dermatosis of which clinical and histopathological appearance of palisading granuloma is suggestive of diagnosis. It was first described in 1895 by Thomas Colcott Fox, but the paternity of the name "granuloma annulare" belongs to Henry Radcliffe Crocker (1902). The etiopathogenesis of GA is still unknown, but associations with diabetes mellitus, disorders of lipid metabolism, malignancies, thyroid disorders, viral infections, certain medications, malignancies or minor injuries have been reported. It can occur in all age groups, with a lower frequency in childhood. GA takes several clinical forms: localised (75% of cases), generalised / disseminated (2.8-15% of cases), subcutaneous and perforating. GA disseminated form (GAD) affects women more frequently and is usually resistant to treatment. From a clinical point of view, in the disseminated form there are at least 10 lesions distributed in several topographic areas of the body. [1-3]

Patients and methods

The study was performed retrospectively, during 2015-2023 and monitored all patients with GAD hospitalised in the Dermatology Clinic of

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Craiova SCJUC. Demographic data, family medical history, personal pathologies and treatments administered were obtained from medical records. We have also written down the results of biological investigations and interdisciplinary consultations. Skin biopsy was taken from all patients and confirmed the diagnosis of GAD. Patients received topical and systemic treatment, and the therapeutic response was evaluated at one month, 3 months, 6 months, and 12 months respectively after the first hospitalisation. The agreement for the processing of personal and medical data was obtained from all patients.

Results

We identified 21 patients with GAD, 14 women (66.7%) and 7 men (33.3%) respectively, with a mean age of 57.71 years (39-75 years), with a history of the disease between 3 months and 15 years.

The clinical (Fig.1) appearance found in 19 cases was an eruption consisting of multiple asymptomatic, arciform or oval lesions, with a diameter between 1 and 5 cm. There were observed small united papules at the edge of the lesions, of firm consistency, having the colour of the skin or discreetly erythematous. The centre was slightly hyper or hypopigmented, without atrophy. The rash was spread at the extremities (upper limbs - 16 cases, lower limbs - 8 cases), in the cervical region (2 cases) and trunk (14 cases).

One patient shown a disseminated rash consisting of numerous micropapules (diameter ≤ 0.5 cm) discreetly erythematous. Another case had an eruption consisting of disseminated annular plaques and firm, well-defined, mobile, asymptomatic subcutaneous nodules, clinically specific lesions of *GAD and subcutaneous granuloma*.

A 75-year-old patient presented multiple lesions with an arciform contour, measuring between 0.3–5 cm, discreetly embossed edges, erythematous and pale centre, disseminated at the level of the upper limbs. At the level of the calves and the dorsal face of the legs, there were plaques and placards with a polycyclic contour, hyperpigmented, with a slightly atrophic centre, yellowish and fine scales on the surface, symmetrically arranged (Fig. 2). These lesions began simultaneously in the upper and lower limbs a year before hospitalization, and over time have increased in number and size. Biopsy revealed *GAD* (upper limbs) and *lipoid necrobiosis* (lower limbs), diseases that simultaneously started 1 year ago. The patient was found in our Clinic with type 2 diabetes and thrombocytopenia.

Patients had the following **associated pathology**: type 2 diabetes mellitus (12 cases), dyslipidaemia (11 cases), overweight and obese (10 cases), hypothyroidism (4 cases), rheumatoid arthritis (1 case), neoplastic disease in 4 patients (carcinoma basal cell carcinoma - 2 cases; breast carcinoma -1 case; thyroid papillary carcinoma - 1

Figure 1. Disseminated annular granuloma clinical aspect.

Figure 2. Patient with disseminated granuloma annulare and lipoid necrobiosis.

case;). Another 66-year-old patient, a new case of GAD, had grade III hypertension, grade I obesity, type II diabetes mellitus and severe psoriasis vulgaris under treatment with adalimumab for 4 years.

Histopathological examination (Fig. 3, 4), performed in hematoxylin-eosin staining, revealed the presence of granuloma with diffuse histiocytes, surrounding necrobiotic collagen, located in the middle and superficial dermis, inflammatory infiltrate with multinucleate cells in the vicinity of degenerate collagen, periphytic fibrosis infiltrate, lymphocytic infiltrates vascular with occlusion of the vascular lumen.

The treatment initiated in the Clinic consisted of topics with class III corticosteroids (18 cases), the combination of calcipotriol / betamethasone dipropionate (3 cases), calcineurin inhibitors (tacrolimus 6 cases, pimecrolimus 4 cases), and in general pentoxifylline (21 cases), antihistamines (21 cases), hydroxychloroquine 400 mg / day (9 cases), systemic corticosteroid therapy (5 cases), sulodexidum (4 cases). In 6 patients, along with topical treatment (dermatocorticoids and calcineurin inhibitors), we administered the combination of doxycycline (100 mg / day), ofloxacin (400 mg / day) and rifampicin (600 mg / day), 3 consecutive days per month, for 4 months.

The evolution after treatment, at the end of the study, was favourable, with the improvement of the lesions in 15 patients (71, 42%) and the complete remission of the lesions in 6 patients (28.57%). We observed more obvious improvements in the cases that received dermatocorticoids, pentoxifylline, hydroxychloroquine and in the cases in which we administered the combination with the 3 antibiotics.

Discussions

GA is a rare chronic inflammatory dermatosis, with an estimated prevalence of 0.1-0.4% of the general population. GAD predominantly affects adults over the age of 40, especially women. HLA-A29 and HLA-BW35 phenotypes have been reported to be more common in these patients.

GA is classified as a non-infectious granulomatous skin disease, along with sarcoidosis, lipoid necrobiosis, and interstitial granulomatous dermatitis. The etiopathogenesis of GA is not

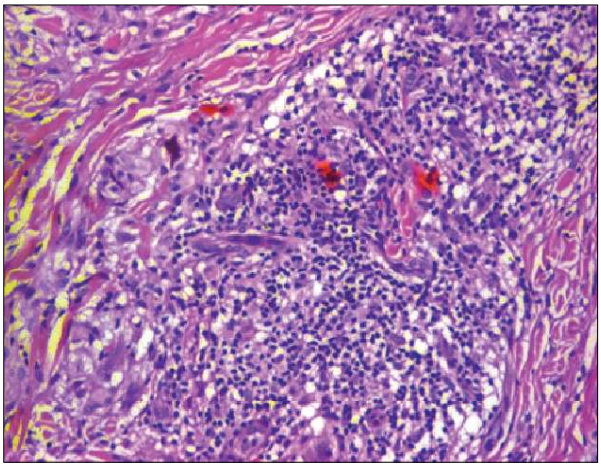

Figure 3. Disseminated annular granuloma – histopathological (multinucleated cells in the inflammatory infiltrate, in the vicinity of the degenerated collagen), appearance, hematoxylin-eosin staining 100x.

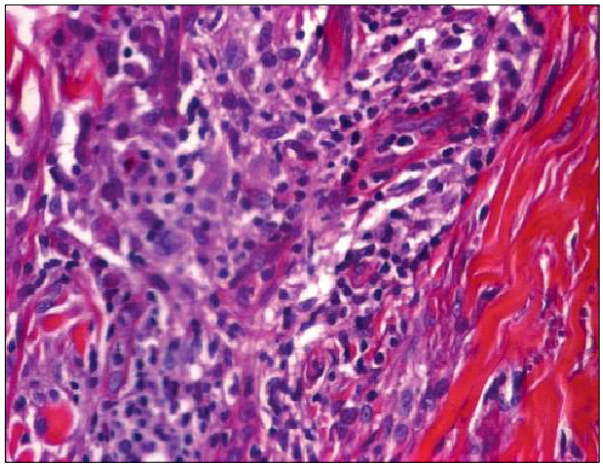

Figure 4. Perivascular lymphocytic infiltrate and fibrinoid deposits in the vascular wall with occlusion of the vascular lumen, hematoxylin-eosin staining, 200x.

fully elucidated and is most likely multifactorial. Several pathogenic hypotheses have been issued: microangiopathy or immunological vasculitis; delayed lymphocyte-mediated hypersensitivity reaction; primary connective tissue degradation; neutrophil migration defect with accumulation of abnormal neutrophils. It is thought that an unknown antigen (bacterial lipopolysaccharides, DNA, tumor cells, apoptotic cells, intracellular proteins or extracellular matrix fragments resulting from tissue injury) is initially recognized by fixing specialized Toll-like and NOD-like receptors, then release of proinflammatory cytokines TNF α, interferon γ, interleukins 1, 6 and chemokines. Macrophages, lymphocytes and dendritic cells are recruited at the site of inflammation. Macrophages are the main cells that form the granulomatous infiltrate, turning into epithelioid histiocytes. Depending on the specific stimulation, macrophages express 2 main phenotypes, M1 and M2, both forms involved in GI pathogenesis. M1 phenotype produces IL-1, IL-6, TNFα, oxygen free radicals, activates Th 1 and 17 helper T lymphocytes. The M2 phenotype releases anti-inflammatory cytokines, activates Th2 lymphocytes, promotes tissue remodeling and cell proliferation through the synthesis of matrix metalloproteinases and growth factors. [4,5]

The histological appearance is that of a palisading granuloma or interstitial pattern in the dermis or hypodermis, consisting of a central area of degeneration and / or necrobiosis of collagen, surrounded by an infiltrate consisting of epithelioid histiocytes and giant cells. At the perivascular level there is present an inflammatory infiltrate consisting of T lymphocytes and macrophages. The presence of mucin deposits differentiates GA from lipoid necrobiosis and sarcoidosis. Eosinophil or plasma cells are inconstantly observed in infiltrates and vasculitis of small vessels. [6]

Unlike GA localised form, often spontaneously resolving, GAD has a long clinical evolution, being usually resistant to regular treatments. In our study, 5 patients had an evolution of the disease between 5 and 15 years.

Although there are controversies regarding the relationship of GAD with associated diseases, it is accepted that GAD and perforating GA are significantly associated with diabetes mellitus (60-75% of cases), found by us in 12 of the 21 cases (57,14 %). Other common associations are dyslipidaemia (present in 52.38% of our cases), thyroid disease (19% of our patients) or malignancies (lung adenocarcinoma, breast cancer, ovarian neoplasm, fungal mycosis, Hodgkin's lymphoma, chronic lymphocytic leukaemia). Cases of GAD after vaccination

against hepatitis B, tuberculosis or tetanus have been reported in the literature. Also, in some cases, the triggers were viral infections (HIV, Epstein-Barr, hepatitis B and C viruses, varicella-zoster virus), insect bites, tattoos, trauma or sun exposure. Drug-induced cases have also been reported, such as: allopurinol, diclofenac, quinidine, calcitonin, angiotensin converting enzyme inhibitors, calcium channel blockers (amlodipine), anti TNF-α, topiramate, tofacitinib, secukinumab. The interval of occurrence of the annular granuloma after the administration of the incriminated drugs is between five days and nine years. [7-9]

The concomitant association of GA with necrobiosis lipoidica (NL) is rare and may suggest a common pathogenic mechanism. Were described 12 such cases in the literature (10F, 2 M, 4 cases being pediatric). Of these, 8 patients (66%) were pre-diabetic or had diabetes, as in our case. [10] Clinically, NL is manifested by oval plates or yellowish polycyclic plaques, telangiectatic, with atrophic centre and embossed periphery. The location of choice is pretibial, usually bilateral, less often are affected hands, forearms, face and scalp. Histopathologically, the appearance of NL is of palisading granuloma like GA, inflammatory infiltrate consisting of Th lymphocytes, histiocytes, plasma cells and eosinophils. Additionally, there is atrophy of the epidermis, granulomatous vasculitis, extracellular lipid deposits and reduction of the number of intradermal nerves, distinctive elements compared to a GI. NL lesions can heal spontaneously or have a chronic, persistent evolution, with the appearance of painful ulcers in 1/3 of cases.

Various GAD treatments are described in the specialised literature, based on isolated cases, small clinical or retrospective studies, with variable results. Topically there are administered dermatocorticoids with high potency and superpotent, calcipotriol, tacrolimus or pimecrolimus. Local therapy is usually ineffective and requires systemic association.

PUVA-therapy and photodynamic therapy are frequently used in the treatment of GAD. Narrowband ultraviolet (NB-UVB) therapy has been used by Muylaert *et al.* to treat a patient with sugar diabetes, hypothyroidism, dyslipidaemia, and GAD resistant to topical and systemic treatments. After 48 sessions and a cumulative dose of 13.440J / cm^2, total remission of lesions was observed. Pavlovsky *et al.* administered NB-UVB to 13 patients with GAD. Treatment was well tolerated and 54% of patients had total or partial resolution of lesions. Occasional good results were after cryotherapy, electrocautery puncture of the edges of the lesions or laser therapy. [11,12]

Prednisone, synthetic antimalarials (hydroxychloroquine, chloroquine), fumaric acid esters, dapsone, niacinamide, cyclosporine, methotrexate, pentoxifylline, chlorambucil, retinoids, antibiotics, biological therapy, etc. can be used systemically. Prednisone in short cures provides good results, but recurrences are common at discontinuation, and the risk of corticosteroid dependence and contraindications limits its use. Synthetic antimalarials have an anti-inflammatory effect through a complex mechanism of inhibition of intercellular signalling via Toll-like receptors. It is inhibited the production of interleukins IL-1, IL-2, Il-6, IL-17, IL-22, interferon α and γ, TNF-α, also decreases the recruitment and proliferation of CD4 + Th1 lymphocytes and macrophages. The therapeutic effect is obvious after 4-6 weeks and is maximum at 3-6 months, with a dose of 200-400 mg daily for hydroxychloroquine or 250 mg /day 3-5 days / week for chloroquine. In addition, they lower blood sugar and glycated haemoglobin in diabetic patients, correct dyslipidaemia, have antithrombotic and anti-infective effect. [13,14]

Anti-TNF alpha agents were used *off the label* in the case of recalcitrant GAD. *Chen et al.* counted 16 cases treated with adalimumab, the success rate being 87.5% and 3 cases treated with infliximab, the remission being 100%. Adalimumab and infliximab are recombinant IgG1 monoclonal antibodies that inactivate both soluble and transmembrane alpha TNF forms. These results indicate an important role of alpha TNF in the pathogenesis of GAD. Paradoxically, GAD started in patients with rheumatoid arthritis or severe vulgaris psoriasis in treatment with anti-TNF alpha medication. Voulgari *et al.* reported 9 cases of GAD in a group of 199 patients with rheumatoid arthritis, and Clark *et al.* and Bonomo *et al.* each reported a case of GID associated with secukinumab therapy. [15-18] A

possible mechanism for this reaction would be by inducing autoantigens, inhibiting regulatory T lymphocytes, and activating helper T lymphocytes. The paradoxical reaction to adalimumab is likely in our patient, given that diabetes mellitus is therapeutically controlled. I administered tacrolimus 0.1% topically, and systemically the combination with the three antibiotics. Although adalimumab treatment for psoriasis was continued, the evolution of GAD was favourable.

Based on certain studies, which state that infections may be etiological factors for granuloma annulare, antibiotics have been used to treat cases of refractory GAD. Dapsone and doxycycline were used alone, with favourable results in some cases. Marcus et al. used, in a group of 6 patients, the combination of rifampicin 600 mg, ofloxacin 400 mg and minocycline hydrochloride 100 mg once a month for 3 months. At 3-5 months after starting treatment, the plaques disappeared completely. The same treatment regimen was effective in other clinical trials. We administered to 6 patients Rifampicin 600 mg / daily, Ofloxacin 400 mg / daily and Doxycycline 100 mg / daily 3 days a month, for 4 months. The treatment was well tolerated and the skin lesions recovered completely. In addition to the antibacterial effect, these molecules have immunomodulatory and anti-inflammatory properties. Rifampicin influences the secretion of proinflammatory cytokines by monocytes. In vitro, the inhibitory action of cyclin on the proliferation of T lymphocytes, the formation of granuloma, the release of matrix metalloproteinases and on the activation of macrophages has been shown. [19-21]

Conclusions

It is confirmed that GAD predominates in women and people over 40 years, the rash being distributed mainly on the upper limbs and trunk. GAD is frequently associated with diabetes mellitus and dyslipidaemia, which encourages the investigation of patients in this direction. Therapeutic management of GAD is difficult. The associated pathology and the extent of the lesions may limit certain therapeutic options. There is also no established therapeutic guide and criteria for choosing the optimal treatment. Triple antibiotic therapy is an effective, affordable and well-tolerated method by patients. New research is needed to establish therapeutic protocol in patients with GAD.

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Conflict of interest
NONE DECLARED

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