DISSEMINATED GRANULOMA ANNULARE: 3 CLINICAL CASES

GRANULOM INELAR DISEMINAT: 3 CAZURI CLINICE

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Abstract

Introduction: Granuloma annulare (GA) is a chronic, benign inflammatory dermatosis that appears in all group ages, but it is less frequent in childhood and prevails in women. The condition is clinically characterized by multiple annular or aciform plaques, with coalescence of small, firm, skin-colored or erythematous papules on the edges. We present 3 patients with disseminated granuloma annulare (DGA), with emphasis on the clinical aspects, the comorbidities associated with the disease and the therapeutic response.

Patients and Methods: We present 3 cases diagnosed with DGA both clinically and histologically. In two of the cases the treatment was Ofloxacin (400 mg/day), Doxycycline (100 mg/day) and Rifampicin (600 mg/day) 3 consecutive days per month for 4 months and topically with Tacrolimus 0.1%, one application daily, in the evening. The third patient received Pentoxiphylinum 1200 mg/day, Hydroxychloroquine 400 mg/day and corticosteroid class III topically. We evaluated our patients 2 months and 4 months after initiating the treatment.

Results: The following comorbidities were present: dyslipidemia (2 cases), diabetes (1 case), high blood pressure (2 cases), overweight (1 case), obesity (1 case). Histopathological exam established: lesions located in the middle and superficial dermis, characterized by the presence of granulomas with sparsely arranged histiocytes, surrounding necrobiotic collagen, with rare multinucleated cells and a perivascular lymphocytic infiltrate. The treatment of the 3 patients led to improvement of clinical appearance without significant differences between the two treatment schemes.

Conclusions: Further research is needed to establish the optimal therapy for the patients with DAG.
Introduction

Granuloma annulare (GA) is a benign chronic inflammatory dermatosis, with characteristic clinical and histological aspects (palisading granuloma). It was first described in 1895 by Thomas Colcott Fox, but the paternity of its name “granuloma annulare” belongs to Henry Radcliffe Crocker (1902).

GA may occur in all age groups with a lower frequency in childhood.

Generalized/disseminated GA represents between 2.8% and 15% of all cases with higher prevalence in women vs. men (sex/ratio 6/1).

It is clinically characterized by multiple annular or aciform plaques, with coalescence of small, firm, skin-colored or erythematosus papules on the borders.

There is no consensus for the therapy for disseminated GA (DGA), affection is usually treatment resistant. The lesions may improve in winter and worsen in summer.

The exact cause of DGA is unknown, but in 60-75% of the cases it is associated with metabolic disorders.\(^{(1,2)}\)

We present 3 cases of DGA, with emphasis on the clinical aspects, the comorbidities associated with the disease and the therapeutic response.

Patients and Methods

We performed a retrospective study in our clinic, between 2013 and 2014, regarding disseminated/generalized GA, aiming to highlight the epidemiology, clinical evolution (before and after therapy), and the connection to comorbidities of the patients.

3 cases with GAD were clinically and histologically diagnosed. The patients were investigated (biologically and interdisciplinary) for the diagnosis of the associated comorbidities. We initiated general therapy (for 3 days consecutively per month, for 4 months) with: Ofloxacin (400 mg/day), Doxycycline (100 mg/day) and Rifampicin (600 mg/day), 3 zile consecutiv pe lună timp de 4 luni, iar local Tacrolimus 0.1%, o aplicație pe zi seara. Cel de-al treilea bolnav a primit pe cale generală pentoxiphylinum 1.200 mg/zi, Hydroxychloroquine 400 mg/zi şi local dermatocorticoizi clasa a III-a. Am evaluat cazurile la 2 şi la 4 luni după iniţierea tratamentului.

We present 3 cases of DGA, with emphasis on the clinical aspects, the comorbidities associated with the disease and the therapeutic response.
We present 3 cases with the following characteristics:

Case I. A 65 year old male, overweight (BMI = 27), who lives in an urban environment is hospitalized for 17 annular lesions, formed by coalescence of small firm papules with erythematous borders, without atrophy, ranging in size between 1-7 cm, localised on the upper limbs and on the trunk. (Figures 1, 2)

The disease had a history of 15 years, with the onset on the dorsal side of the right hand. The disease had a chronic evolution, with little improvement in cold seasons and with the appearance of new lesions in time, most of them the past 2 years, without any treatment. The patient was hypertensive for 3 years, he received no therapy during this period. Simultaneously we have diagnosed the patient with type II diabetes mellitus.

We have diagnosed DGA during hospitalization, based on clinical and histopathological exams.

Histopathological exam showed: lesions localized in the middle and superficial dermis, characterized by the presence of granulomas with sparsely arranged histiocytes, surrounding necrobiotic collagen, rare multinucleated cells in the infiltrate, nearby degenerated collagen and a perivascular lymphocytic infiltrate (Figures 3, 4).

Case II. A 64 year old female, who lives in an urban environment, known with: grade II obesity (BMI = 36), high blood pressure for 7 years (under therapy with Candesartan cilexetil, Indapamide, Lercanidipine, Bisoprolol) and dyslipidemia for 6 years (under therapy with Simvastatin), requires dermatologic consult for 12 annular plaques, 6-8 cm in diameter with micropapular edges and erythematous center, localized on the upper limbs (Figures 5, 6) and trunk (Figure 7).

The disease has a history of 5-6 years, with chronic evolution and exacerbation in the warm seasons despite topical repeated treatments with corticosteroid class III.
Histopathological exam certifies the diagnosis of DGA.

Case III. A 52 year old female, from rural environment, requires dermatologic consult for 11 ovalar and aciform plaques 4-9 cm in diameter, with coalescent small, firm erythematous papules on edges, with a slightly hypopigmented center, without atrophy of the plaques, localized on the hands (Figure 8), forearms (Figure 9) and legs. The condition had a history of 18 months.

The patient’s history showed a right suborbital basal cell carcinoma, surgically excised 8 years ago, dyslipidemia, and the histopathological exam confirmed the diagnosis of DGA.

The treatment of the 3 patients has led to improved clinical appearance without significant differences between the two treatment schemes.

Discussions

Many clinical types of granuloma annulare (GA) have been described in the literature:

- localized GA: is the most common form (75% of cases) and occurs with predilection on the back side of the hands, elbows, knees, ankles and on the back side of the legs. Lesions are represented by skin-coloured or flesh-coloured papules. They are common in patients under 30 years-old.

- disseminated/ generalized GA (2.8 to 15%): predominates in adults and is characterized by the occurrence of at least 10 skin lesions or generalized annular plaques. The trunk is frequently involved but also the neck, extremities, face, scalp, palms and soles. (3,4)

In our patients, DGA lesions were localized in the upper limbs (3 cases), trunk (2 case), and legs (1 case).

- subcutaneous GA: occurs predominantly in children. It is characterized by asymptomatic, firm pink or erythematous nodules, located in the deep dermis or subcutaneous tissues, frequently as individual lesions of 5 mm - 4 cm in diameter. It appears predominantly on the front side of the legs,
ankles, cheeks, the back side of the hands and scalp. Imagistic exams are not generally necessary in diagnosing GA. However, radiography, CT scan and IRM may be helpful in evaluating atypical subcutaneous lesions. (5, 6, 7)

- perforating GA: is a rare condition (5%) and it is usually located on the hands and the fingers or it can be generalized on the trunk and extremities. Superficial umbilicated papules appear, healing with scars. Subcutaneous and perforating GA occurs especially in children. (1)

Other rare subtypes of annular granuloma are: macular or in plaque (9), palmar (9,10) and pustular (11,12) subtype.

Some authors consider actinic granuloma as a peculiar subtype of GA, while others consider it a different category. 

**Etiopathogenesis** of GA is still unclear.

More pathogenic hypotheses have been issued: microangiopathy, immunological vasculitis, delayed hypersensitivity reaction, neutrophil migration flaw with abnormal neutrophil accumulation, β-glucuronidase high serum titer, involved in degradation of mucopolysaccharides. (2)

GA is most commonly associated with diabetes mellitus (13), but it may be associated with dyslipidemia (14), thyroid disorders (autoimmune thyroiditis) (15), malignancies (Hodgkin’s disease, lung adenocarcinoma, breast carcinoma, ovarian cancer) (14), insect bites, trauma, sun exposure (17) and tuberculosis (18,19).

Comorbidities found in our patients were: dyslipidemia (2 cases), diabetes mellitus (1 case), high blood pressure (2 cases), overweight (1 case), obesity (1 case). A female patient had basal cell carcinoma, but the large interval of time between the surgical excision of the tumour and the onset of DGA makes us not take into consideration the potential interference between the two diseases.

The localization of lesions on sun exposed areas cannot exclude the aetiologic role of actinic damage in the pathogenesis of DGA.

Literature reported similar cases occurring after vaccination (hepatitis B vaccine), or after infection (HIV (20), Epstein-Barr virus, B or C hepatitis viruses, Varicella-Zoster virus (23)).

There have also been reported cases induced by drugs, such as: allopurinol, diclofenac, quinidine, calcitonin, inhibitors of angiotensin converting enzyme and calcium channel blockers. (1,2)

In the second case, the role of Lercanidipine therapy was suspected; hypothesis also issued by other authors who reported the involvement of calcium channel blockers in the aetiology of this disease.

Cases of familial GA have been observed in twins and siblings throughout several generations and the association with HLA phenotype suggests the possible contribution of a hereditary component. The frequency of HLA-B8 has been increased in some cases of localized GA, while HLA-A29 and HLA-BW35 were reported to be more common in patients with generalized/disseminated GA.

There are not enough arguments in order to establish a causal relationship between these factors and granuloma annulare.

Some authors associate chronic stress as being the trigger of the disease. (1)

**Differential diagnosis** of DGA must be done firstly with the other types of GA and, depending on the clinical aspects, with: sarcoidosis, necrobiosis lipoidica, tinea corporis, interstitial granulomatous dermatitis, nummular eczema, cutaneous lupus erythematous, hansen disease, eruptive xanthomas, annular lichen planus, erythema nodosum, insect bites, psoriasis and granulomatous mycosis fungoides.

Subcutaneous lesions must be differentiated from rheumatoid nodules, sarcoidosis, panniculitis and certain infections in the appropriate clinical context.

DGA has a chronic evolution, with poor response to treatment and frequent relapses. (1)

**Treatment**

There are no data to support a certain optimal therapy on DGA.

Marcus et al. have studied 6 patients with generalized GA resistant to treatment. The patients were treated with the combination of Rifampicin 600 mg, Ofloxacin 400 mg and Minocycline hydrochloride 100 mg one day a month, for 3 months. Three to five months after the initiation of treatment, the plates have completely disappeared. Some patients have reported post-lesional hyperpigmentation. Although the treatment was successful, the authors have suggested that further studies are needed to confirm this combined therapy as a successful option for GA. (24)

The reason for using this combined therapy in
treating DGA is based on histopathological similarities between DGA and leprosy. The granulomatus appearance in the histopathological exam and the annular clinical appearance are common to both DGA and Hansen disease. Based on several studies, the infections may represent etiologic factors of GA. Shelley reported the successful resolution of some cases of DGA by treating the underlying infection with antibiotics such as cefaxor, cefixime, penicillin, amoxicillin, ciprofloxacin, erythromycin, clarithromycin and trimethoprim-sulfamethoxazole. (25,26,27)

In a recent paper, the authors report two cases of generalized GA effectively treated with triple therapy (Rifampicin 600 mg/day, Ofloxacin 400 mg/day and Doxycycline 100 mg/day), scheme that we applied in two of the three cases studied. (28)

The mechanism of cyclins in GA remains uncertain. The conjugated anti-inflammatory, immunomodulatory and antiinflammatory properties of these molecules are probably part of their effectiveness. In vitro there has been proved the immunomodulatory action of cyclins on lymphocyte T proliferation and the formation of granulomas. Also other mechanisms such as metalloproteinase and phospholipase A2 inhibition and synthesis of various proinflammatory cytokines lead to reduced inflammatory phenomena. (29) Treatments that can be used in the DGA are:

- dermocorticoids,
- calcineurin inhibitors (tacrolimus, pimecrolimus) (30)
- antimalarial synthesis and general corticotherapy
- retinoids, cyclosporine, dapsone, doxycycline, infliximab
- phototherapy (PUVA, UVB) (31)
- photodynamic therapy (with methyl aminolevulinate) (31)

The evaluation of our cases after 2 months and 4 months of initiating treatment has shown us clinical improvement, but without significant differences of therapeutic response in relation to the two schemes applied.

Conclusions

DGA is more common in women and in people over 50 years old. Extensive investigations are necessary in order to diagnose associated diseases. Further researches are needed to establish optimal therapy of patients with generalized/ disseminated granuloma annulare.

Bibliography

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