INTRODUCTION

Granuloma Annulare (GA) is a relatively common idiopathic disorder of the dermis and the subcutaneous tissue described by Colcott-Fox in 1905 for the first time, and then later by Radcliffe-Crocker in 1902. It occurs in all ages and all races, but it more frequently affects women (2:1). (1)

Clinically, it is characterized by papular-nodular skin lesions that have a polymorphic character due to the many variants of the disease (localized, generalized, subcutaneous and perforating). (2)

The histology is essential for the diagnosis of granuloma annulare and it is classically characterized by dermal palisading granulomas with central degeneration of collagen, the presence of mucin, and a lymphohistiocytic infiltrate. The presence of mucin is the histological key feature that distinguishes GA from other non-infectious granulomatous diseases. (2)

The localized type GA is the most common clinical form (75% of all cases). Lesions are represented by skin-coloured or red-purple papules and are disposed in groups, of annular or arched shape with a diameter ranging between 1-5 cm. Frequently, it is localized on the dorsal and lateral hand’s fingers, elbows, knees, ankles and the dorsal foot. This type occurs most commonly in patients under the age of 30 years. (2,3)

The generalized type occurs predominantly in adults and it is defined by the simultaneous presence of at least ten skin lesions, or by widespread annular plaques. It occurs in about 8-15% of patients with GA. (2) The torso is frequently affected by this type, in addition to the neck, extremities, face, scalp, palms and soles. Lesions are plaque-like with a coloration ranging from yellow to violaceous. (3)

The subcutaneous type, also known as pseudoeummatoid nodules, is more common in children and consists of firm subcutaneous nodules often localized on the lower legs. (4)

The perforating variation is clinically distinct from the other forms of GA because of a central umbilication of the lesions resulting from the elimination of collagen. (2)

Other rare subtypes of GA are macular or patch-type, palmar, photo-distributed, and pustular. (2)

In some 50% of cases, patients with the localized disease are healed within 2 years without the need for treatment. (5,6) However, patients are often interested in the treatment of localized GA when lesions are symptomatic or for cosmetic reasons. The remaining forms of granuloma annulare...
represent a real challenge in the literature, since there are a wide variety of treatments proposed. The choice of treatment must be individualized for the patient on the basis of comorbidities, baseline blood evaluation, drug interaction, compliance, adverse effect profiles, prior treatments, proximity to the clinic and reproductive status.(2)

Treatments used successfully are:
- Topical treatment with immunomodulator corticosteroids,
- Intralesional administration of corticosteroids,
- Systemic treatment with corticosteroids, antibiotics, sulfone, synthesis anti-paludic drugs, immunosuppressants, vasodilatatory, retinoids, biologic therapies,
- Cryotherapy, DTC
- Phototherapy, laser therapy(2)

CASE REPORT

A 14-year old patient from a rural environment suffering from a three-week left ear otitis externa and treated with antibiotics and AINS was hospitalized displaying for 1-week erythematosus nodules. Initially, the nodules were localized on the back side of the knees, and then extended to the shins and the posterior part of the legs. They appeared well defined, some presenting a discrete squamous collar at the periphery, with discrete pruritus (figures no. 1, 2, 3). Before the start of the eruption, the patient had been vaccinated for tetanus and diphtheria.

Lab test results were within the standard range, with the exception of ASLO (225,7 U/l), throat and nasal swabs (Staphylococcus aures with the following sensitivities in the diffusimetric antibiogram: Cefoxitin, Clindamycin, Erythromycin).

In order to exclude the possibility of a TBC infection, a pulmonary radiography (normal values) and an IDR at 2U PPD (negative) were conducted.

The histopathological exam from the dermis lesion has profoundly highlighted granulomas at the limit between the derma and the hypoderm, composed of histiocytes, fibrocytes, giant multinucleous Langerhans-type cells, lymphocytes and rare eosinophils (figures no. 4, 5). The semblance pointed to a granuloma annulare.

Based on the clinical exam, the histopathological findings and the epidemiological information, the patient was diagnosed with granuloma annulare - subcutaneous type.

A systemic treatment with Doxycyline (100mg/day), Ciprofloxacin (2x500 mg/day), Loratadine (2x10 mg/day) was prescribed, accompanied by local treatment with topical corticosteroids under which the clinical evolution has been slowly positive.

DISCUSSIONS

The subcutaneous form of granuloma annulare occurs predominantly in children, but it has also been described in adult patients.(3)

It is characterized by firm to hard, usually asymptomatic nodules located in the deep dermis and subcutaneous tissues, without presenting inflammatory signs on the skin surface. They may extend to the underlying muscle; the nodules on the scalp and orbit are adherent to the underlying periosteum.(3)

Individual lesions measure from 6 mm to 3,5 cm in diameter and are distributed most often pretibially. Other sites of predilection are: the ankles, dorsal feet, buttocks and hands.
Nodules on the scalp, eyelids and orbital rim may present an diagnostic challenge.(3)

The precise etiology of the disease is unknown but several systemic associations with granuloma annulare have been reported, including DM, thyroid disease, lipid abnormalities, malignancy (lung adenocarcinoma, cervical cancer, prostate cancer, breast cancer, mycosis fungoides, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic myelomonocytic leukemia), HIV, hepatitis B, hepatitis C, rheumatoid arthritis.(2,7,8,9) Other trigger factors include insect bites or other traumas, herpes zoster (2) as well as the diphtheria and tetanus vaccination – this latter factor being observed in our case but also in other clinical cases mentioned in the literature.(10,11)

The differential diagnosis of skin lesions is made with:

- Other clinical forms of granuloma annulare:
  - Granuloma annulare localized type: the lesions are represented by skin coloured or erythematous-violaceous papules, clustered, with an annular or arched shape and a diameter ranging between 1 and 5 cm. The annular margin is firm to palpation and may be continuous or consist of discrete or coalescent papules in a partial or complete circle. The dorsal hands and feet, ankles, lower limbs and wrists are the sites of predilection.(3) Histopathologically, collagen necrosis is usually more prominent than in the generalized type.(2)
  - Granuloma annulare generalized type: widespread papules, some of them tend to confluence in small annular plaques or patches with a raised and arched margin. Lesions may be skin-coloured, pink, violaceous or yellow.(3)
  - Granuloma annulare perforating type: superficial small papules that develop central ombilication or crusting; there may be a discharge of a creamy fluid (collagen). Lesions heal with atrophic or hyper pigmented scars. It is often localized on the dorsal hands and fingers or generalized over the torso and extremities.
  - Other skin disorders:
    - Erythema elevatum diutinum: papules, plaques and nodules symmetrically distributed on extension areas, predominantly on the limbs (hands, elbows, knees, ankles), with a red-purple or yellow aspect that spreads across the torso, growing slowly over the course of months or years, and which may resolve spontaneously.(12,13)
    - Verrucous lichen: papulovesicular skin lesions that confluence in red-purple colour plaques and patches, hyperkeratotic, sometimes with a superficial fine scaly network, localized on the shins and interphalangeal joints, intensely pruritic.(14)
    - Erythema nodosum: erythematous nodules, warm, painful, round-ovalar, slightly elevated from the surrounding tissue with a diameter ranging between 4-5 cm, localized on the pretibial knees and ankles.(15)
    - Panniculitis: single or multiples nodules pink or yellow with sizes between 0.5 and 10 cm, firm or fluctuant consistency, painful, located in the adipose tissue, often on the lower limbs.(16)
    - Sarcoïdosis: painful, erythematous, imprecise delimited nodules, located on the front of the leg, accompanied by pain and swelling of the surrounding joint. Histopathologically, sarcoïdosis presents non-caseous granulomas, an minimal inflammatory infiltrate and an absence of mucin.(17)
    - Necrobiosis lipoidica: extending papules and nodules that result in circular plaques and present central atrophy. Frequently it occurs prethibially.(18) Histopathologically, the dermis displays diffuse granulomas, which are organized in horizontal layers and degenerated collagen; plasma cells are present; mucin is absent.(2)
    - Pool granuloma: single or multiple skin lesions as nodules or papules located on the fingers, hands, elbows, knees and feet.(19)
    - Rheumatoid nodules: firm, well defined, sometimes adherent to the periostum, tendon or tendon sheaths; they develop insidiously, persisting for a long time and are located on extension or pressure surfaces.(20)
    - Sporotrichosis in incipient phase: subcutaneous or systemic mycosis, caused by Sporothrix Schenckii; an ulcerating node appears at the inoculation place, along with lymphatics other nodular formations.(21)

CONCLUSIONS

Subcutaneous granuloma annulare represents a clinicopathological rare form of granuloma annulare.

The diagnosis of the subcutaneous granuloma annulare is based upon the clinicopathological correlation (the cutaneous biopsy confirms the histopathological findings that characterise the disease).

The etiology remains uncertain: in the scientific literature, only few cases in which the trigger was represented by the tetanus and diphtheria vaccination, as in our case, were published so far.

The change of the post-vaccination immune status could be a trigger for the start of the disease, marking the appearance of lesions.

Treatment is frequently not necessary in many granuloma annulare cases since the lesions regress spontaneously; the real challenge is posed by identifying the particular clinical forms of granuloma annulare.

REFERENCES