

SUBCUTANEOUS GRANULOMA ANNULARE IN CHILDREN AND DIPHTHERIA - TETANUS VACCINATION

MARIA ROTARU¹, FLORINA LIGIA POPA²

^{1,2}“Lucian Blaga” University of Sibiu

Keywords:

subcutaneous
Granuloma Annulare,
tetanus and diphtheria
vaccine, children

Abstract: *Introduction: Granuloma Annulare (GA) is a relatively common idiopathic granulomatous disorder of the dermis and subcutaneous tissue, clinically characterized by papular-nodular skin lesions with polymorphic character. Clinical case: We are presenting the case of a 14-year old female patient with a relatively recent onset of well-defined erythematous nodules on the back side of the knees, which then extended to the shins and legs, presenting a discreet squamous collar at the periphery with discreet pruritus. Before the start of the eruption, the patient had been vaccinated against tetanus and diphtheria. From a clinical point of view, the lesions posed some problems with differential diagnosis of other diseases such as: erythema elevatum et diutinum, verrucous lichen, erythema nodosum, panniculitis, sarcoidosis etc. The histopathological exam confirmed the diagnosis of granuloma annulare of the subcutaneous type. Conclusion: Subcutaneous granuloma annulare represents a rare clinicopathological form of granuloma annulare; the change of the immune status post vaccination could be a trigger for the onset of the disease, characterized by the occurrence of lesions.*

Cuvinte cheie:
granulom inelar
subcutanat, vaccin
diftero-tetanic, copii

Rezumat: *Introducere: Granulomul inelar (GI) reprezintă o afecțiune idiopatică granulomatoasă relativ frecventă a dermului și a țesutului subcutanat ce clinic se caracterizează prin leziuni cutanate papulo-nodulare cu caracter polimorf. Caz clinic: Prezentăm cazul unei paciente de 14 ani, ce se prezintă pentru apariția relativ recentă, inițial la nivelul feței anterioare a genunchilor, ulterior cu extindere la nivelul gambelor, fața anterioară a picioarelor de noduli eritematoși, bine delimitați, unii dintre ei cu discret guleras scuamos în periferie și prurit discret. Anterior debutului erupției pacienta a efectuat vaccinare antitetanică și antidifterică. Clinic leziunile au pus probleme de diagnostic diferențial cu alte afecțiuni cum sunt: erythema elevatum et diutinum, lichenul verucos, eritemul nodos, paniculita, sarcoidoza, etc. Examenul histopatologic a confirmat diagnosticul clinic de granulom inelar forma subcutanată. Concluzie: Granulomul inelar subcutanat reprezintă o variantă clinicopatologică rară a granulomului inelar; modificarea statusului imun post vaccinare fiind un trigger pentru declanșarea afecțiunii cu apariția leziunilor.*

INTRODUCTION

Granuloma Annulare (GA) is a relatively common idiopathic disorder of the dermis and the subcutaneous tissue described by Colcott-Fox in 1895 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 pseudoreumatoid 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

¹Corresponding author: Maria Rotaru, B-dul Mihai Viteazul, Nr. 25, Sibiu, România, E-mail: mrotaru07@gmail.com, Tel:+40269 235541
Article received on 31.03.2014 and accepted for publication on 12.05.2014
ACTA MEDICA TRANSILVANICA June 2014;2(2):205-208

CLINICAL ASPECTS

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 imunomodulator corticosteroids,
- Intralesional administration of corticosteroids,
- Systemic treatment with corticosteroids, antibiotics, sulfone, synthesis anti-paludic drugs, immunosuppressants, vasodilatory, 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 erythematous nodules. Initially, the nodules were localised 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.

Figure no. 1. Multiple lesions of subcutaneous granuloma annulare



Figure no. 2. Multiple lesions of subcutaneous granuloma annulare



Figure no. 3. Multiple lesions of subcutaneous granuloma annulare



Lab test results were within the standard range, with the exception of ASLO (225,7 U/1), throat and nasal swabs (Staphylococcus aureus 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 Doxycycline (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.

Figure no. 4. Histopathological appearance of granuloma annulare

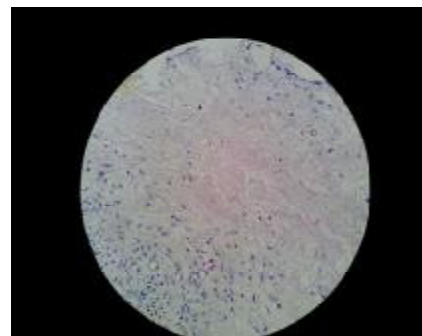
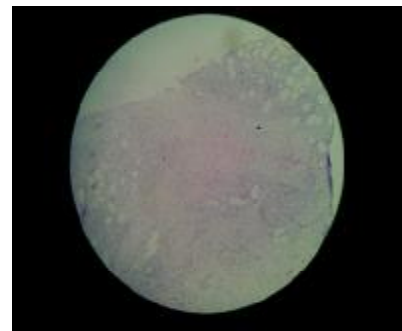


Figure no. 5. Histopathological appearance of granuloma annulare



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.

CLINICAL ASPECTS

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 umbilication 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: papulous 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)

Sarcoidosis: painful, erythematous, imprecise delimited nodules, located on the front of the leg, accompanied by pain and swelling of the surrounding joint. Histopathologically, sarcoidosis presents non-caseous granulomas, a 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 pretibially.(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

1. James WD, Berger TG, Elston DM. *Andrews Diseases of the Skin Clinical Dermatology*, Tenth Edition 2006;31:703-705.
2. Thornsberry LA, English JC. *Etiology, Diagnosis, and Therapeutic Management of Granuloma Annulare*. *Am J Clin Dermatol* 2013;14(4):279-290.
3. Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Wolff W. *Fitzpatrick's Dermatology in General Medicine*, Eighth Edition 2012;1(44):467-472.
4. Requena L, Fernandez-Figueras MT. Subcutaneous granuloma annulare. *Semin Cutan Med Surg* 2007;26(2):96-9.
5. Hawryluk E, Izukson L, English J. Non-Infectious granulomatous diseases of the skin and their associated systemic diseases. *Am J Clin Dermatol* 2010;11(3):171-81.
6. Bronfenbrener R, Ragi J, Milgraum S. Granuloma annulare treated with excimer laser. *J Clin Aesthet Dermatol* 2012;5(11):43-5.
7. Andreu-Barasoain M, Gomez de la Fuente E, Pinedo F et al. Long lasting interstitial generalized granuloma annulare on sun-exposed areas. *Photodermatol Photoimmunol Photomed* 2012;28(4):216-8.
8. Toro JR, Chu P, Yen TS. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999;135(11):1341-6.
9. Maschio M, Marigliano M, Sabbion A et al. A rare case of granuloma annulare in a 5-year-old child with type 1 diabetes and autoimmune thyroiditis. *Am J Dermatopathol* 2013;35(3):385-7.

10. Baykal C et al. Granuloma annulare possibly triggered by antitetanus vaccination. *J Eur Acad Dermatol Venereol* 2002;16:516.
11. Baskan EB et al. A case of granuloma annulare in a child following tetanus and diphtheria toxoid vaccination. *J Eur Acad Dermatol Venereol* 2005;19:639.
12. Muhlenstadt E, Mokosch A, Homey B, Reifemberger J. Erythema elevatum et diutinum. *Hautarzt* 2011;Apr;62(4):252-5.
13. Rotaru M, Stanciu M, Popa FL. Eritema elevatum et diutinum și rolul factorilor triggeri în patogeneza afecțiunii – exemplificare clinică, *Acta Medica Transilvanica* 2013;2(4):107-110.
14. Nedelcu L, Grigoriu A, Pîrvu A, Badea R, Andrei R, Stăniceanu F, Staicu M, Salavastru C, Tiplica G-S. Lichen Plan Hipertrofic – prezentare de caz. *Dermatovenerologie Revista SRD* 2010;2:55:133-139.
15. Requena L and Requena C. Erythema Nodosum. *Dermatology Online Journal* 8(1):4.
16. Abbas O, Salman S, Kibbi AG, Chedraoui A, Ghosn S. Localized involutinal lipoatrophy with epidermal and dermal changes. *J Am Acad Dermatol Mar* 2008;58(3):490-3.
17. Tong C, Zhang X, Dong J, He Y. Comparison of cutaneous sarcoidosis with systemic sarcoidosis: a retrospective analysis. *Int J Clin Exp Pathol* 2013 Dec 15;7(1):372-7.
18. Georgescu I, Cristovici FI, Georgescu AC, Parga G. Necrobioza lipoidică. *DermatoVenerol (Buc)* 2007;52:39-48.
19. Slany M, Jezek P, Fiserova V, Bodnarova M, Stork J, Havelkova M et al. Mycobacterium marinum infections in humans and tracing of its possible environmental sources. *Can J Microbiol* Dec 19 2011.
20. Sayah A. *Journal of the American Academy of Dermatology*. 2005;53:191.
21. Greenfield RA et al. Sporotrichosis, Medscape, accessed in 10.03.2014 from <http://emedicine.medscape.com/article/228723-overview>.