

## Subcutaneous Granuloma Annulare

Dear Editor,

Subcutaneous granuloma annulare (SGA) is considered a rare clinical variant of granuloma annulare, a common self-healing chronic inflammatory disorder that may appear in childhood as well as in adult age (1-3).

A 29-year-old female patient reported the onset of several small subcutaneous nodules on the dorsal aspect of the second interphalangeal joint of the left medius finger and the left elbow, accompanied by vague joint pain, had occurred 13 years ago. Specific markers for rheumatoid arthritis were negative, leading to a diagnosis of sero-negative rheumatoid arthritis, for which treatment with methotrexate was initiated. No clinical benefit was obtained and the treatment was abandoned. New nodules continued to appear on several distal joints of the fingers of both hands and, in the last 6 months, on the second right toe. The course of the disease included spontaneous remission of some of the nodules. Personal medical history was significant for a thyroid nodule, surgically removed at the age of 22.

A general physical exam did not reveal pathological changes. A clinical dermatological exam at the time of presentation revealed several round to oval,



**Figure 1.** Juxta-articular solitary and grouped nodules on the fingers of the right hand.

deep subcutaneous, indurated, asymptomatic, discreetly pigmented lesions with a diameter of 4-6 mm, located on the dorsal aspect of the interphalangeal joints of the fingers of both hands (Figure 1) and the second right toe.

Hematologic and biochemical tests were within normal limits, as well as the serological tests for rheumatoid factor, ANCA, ANA, and anti-CCP antibody. Hand radiographs did not show geodes, marginal erosions, or narrow joint spaces.

A pathological exam of a subcutaneous nodule showed focally altered collagen surrounded by fibroblasts, phagocytes, rare lymphocytes, and neutrophils, as well as small capillaries (Figures 2-5), compatible with the diagnosis of a pseudorheumatoid nodule or benign rheumatoid nodule in the clinical and paraclinical context.

SGA is considered a rare clinical and histological variant of granuloma annulare that predominantly affects children and occasionally young adults (1-6). In 1941, Ziegler first described a case of subcutaneous nodules that appeared concomitantly with classical cutaneous lesions of granuloma annulare, as well as the histological aspect of these nodules similar to that of rheumatoid nodules (RN) (7). Since then, several case reports in the literature refer to the subcutaneous lesions of GA as "pseudorheumatoid nodules", "deep granuloma annulare" or "palisading granuloma" (3,4,8). Most reported cases of SGA occur in the first three decades of life: 98% according to Muhlemann, 79% according to Andersen and Verdic, 62% according to Studer; most cases occur in children between 2 and 6 years of age (9). Lesions often regress spontaneously, but recurrences are common in 19%-75% of the patients, often on the same anatomical areas (9,10). Reported SGA cases in adult patients predominantly affected women, and typically involved multiple lesions located on the hands, feet, ankles, and inferior pretibial area (4-6).

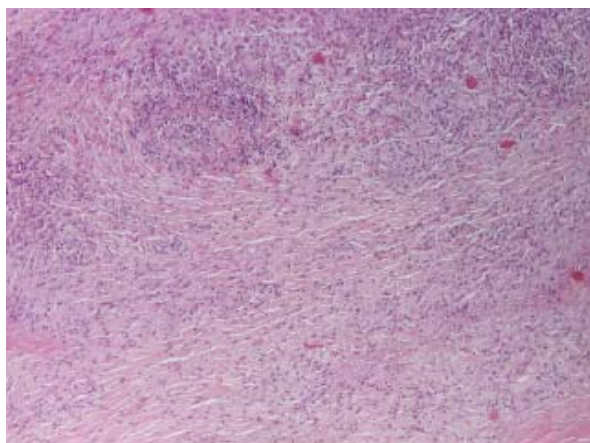
The etiology and pathogenesis of SGA are not completely understood. Precipitating factors such as insect bites, infections with *Borellia* spp., herpesic virus, EBV, *Streptococcus* spp., PUVA-therapy, several drugs, physical trauma, acute phlebitis, and post-surgery sepsis have been considered (8). There is evidence for the pathogenic involvement of an immunological mechanism, possibly a delayed type hypersensitivity reaction mediated by T-cells that triggers a panniculitis-type inflammatory response (8,10). Correlations between SGA and systemic diseases such as diabetes mellitus, sarcoidosis, HIV infection, or autoimmune diseases have not been found (8).

A positive diagnosis of pseudorheumatoid nodules relies on clinical and anamnestic data. Differential diagnosis includes rheumatoid nodules, benign rheumatoid nodules, foreign body reactions, hematomas, abscesses, and infectious granulomas (3,5).

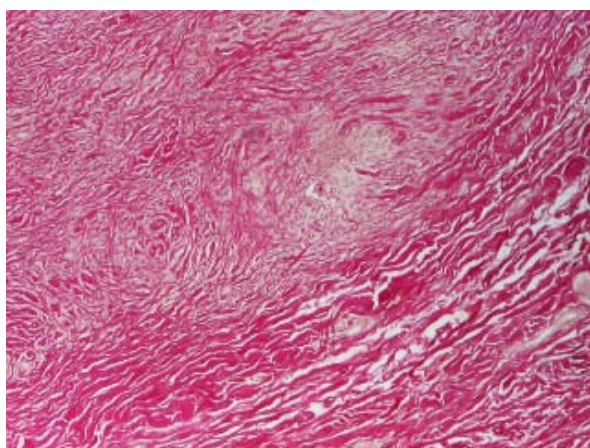
Pseudorheumatoid nodules and SGA have a low risk of progression to a systemic connective tissue disorder.

In the presence of subcutaneous nodular lesions with an uncertain clinical diagnosis, cutaneous biopsy, hematological and immunological tests, and imaging may be performed to establish a positive diagnosis.

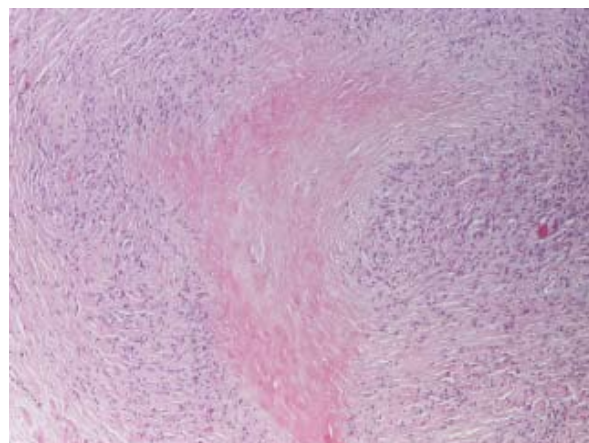
Skin biopsy is the most useful test for the diagnostic approach because, even though it is sometimes difficult to interpret, a pathological exam may offer important data to distinguish between rheumatoid and pseudorheumatoid nodules. Necrobiosis may be identified in the deep dermis and subcutaneous tissue, and rarely in the deep soft tissues. Necrobiosis is less important and less deep than in rheumatoid nodules, as well as less extensive and less diffuse than in lipoidic necrobiosis (6). Anomalies in the morphology of the deep cutaneous structures may coexist with typical changes in classical granuloma annulare. Immunohistochemical studies using specific histiocyte markers such as CD68/PGM1 proved to be occasionally useful in differentiating SGA from other granulomatous conditions (11).



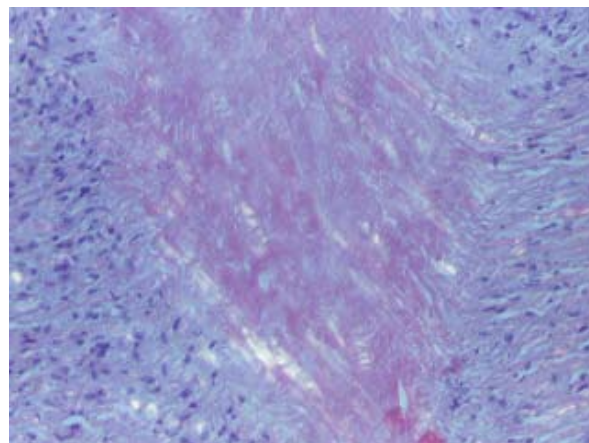
**Figure 2.** Subcutaneous nodule surrounded by chronic inflammatory infiltrate in the deep dermis (hematoxylin and eosin,  $\times 40$ ).



**Figure 3.** Altered and normal collagen bundles (VG  $\times 40$ ).



**Figure 4.** Fibrinoid necrosis (hematoxylin and eosin,  $\times 40$ ).



**Figure 5.** Fibrinoid necrosis (hematoxylin and eosin,  $\times 40$ , polarized).

Several tests are necessary to exclude an association with a systemic disease: hemoleucogram (absence of leucocytosis), ESR (normal values), acute phase reactants (negative fibrinogen, RCP), auto-antibodies (negative ANA), and rheumatoid factor (negative).

SGA is a benign disorder with esthetic implications and sometimes functional impairment. Surgical excision is only required for juxta-articular nodules causing functional impairment. Partial therapeutic benefit was reported after the administration of dapsone, clorambucil, isotretinoin, potassium iodide, or intralesional/topical steroids. Even though the risk of systemic involvement is low, periodical follow-up of these patients is required given the reported cases of associated systemic connective tissue disorders (8,12).

### References:

1. Argent JD, Fairhurst JJ, Clarke NM. Subcutaneous granuloma annulare: four cases and review of the literature. *Pediatr Radiol*. 1994;24: 527-9.
2. Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: a review of 47 cases. *Pediatrics*. 1997;100:965-7.
3. Requena L, Fernández-Figueras MT. Subcutaneous granuloma annulare. *Semin Cutan Med Surg*. 2007;26:96-9.
4. Mijlković J, Krajnc I. Subcutaneous granuloma annulare in an adult. *Wien Klin Wochenschr*. 2003;115:309-11.
5. Barzilai A, Huszar M, Shapiro D, Nass D, Trau H. Pseudorheumatoid nodules in adults: a juxta-articular form of nodular granuloma annular. *Am J Dermatopathol*. 2005;27:1-5.
6. Salomon RJ, Gardepe SF, Woodley DT. Deep granuloma annulare in adults. *Int J Dermatol*. 1986;25:109-12.
7. Ziegler E. Rheumatismus nodosus als einzige Manifestation der Rheumatischen Krankheit. *Arch. Kinderh*. 1941;1221-6.
8. Tse CT, Jong KK. Subcutaneous granuloma annulare presented as multiple nodules of the lower leg. *H K Dermatol Venereol Bull*. 2004;12:33-6.
9. Chung S, Frush DP, Prose NS, Shea CR, Laor T, Bisset GS. Subcutaneous granuloma annulare: Magnetic Resonance Imaging Features in six Children. *Radiology* 1999;210:845-9.
10. Grogg KL, Nascimento AG. Subcutaneous granuloma annulare in childhood: clinicopathologic features in 34 cases. *Pediatrics*. 2001;107:E42.
11. Pesce V, Notamicola A, Moretti B. Diagnostic dilemma of a subcutaneous nodule following a trauma in a child: immunohistochemical examination put the final diagnosis of deep granuloma annulare. *Musculoskeletal Surgery*. 2010;94:49-51.
12. Gale M, Gilbert E, Blumenthal D. Isolated rheumatoid nodules: a diagnostic dilemma. *Case Rep Med*. 2015;2015:352352.

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