

# Granuloma annulare and mesenchymal cancer. Report of two cases

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## Abstract

Association between granuloma annulare and some neoplasms is controversial. However, there is an increasing number of case reports and correlation studies supporting the concept of granuloma annulare associated with certain types of hematologic neoplasms and solid tumors. Recently, it has been suggested that granuloma annulare should be included among paraneoplastic dermatoses.

We report two cases of granuloma annulare associated with mesenchymal cancer.

No similar association was found in the national and international literature. The relation between granuloma annulare and cancer is reviewed (Dermatol Argent 2008;14(2):113-117).

**Key words:** granuloma annulare, cancer, mesenchymal, neoplasms.

## Introduction

Granuloma annulare is an inflammatory dermatosis of unknown etiology. It has been related to different triggering factors, such as insect bites, sun exposure, trauma, PUVA, intestinal parasitosis, virus, emotional stress, and even genetic factors.<sup>1</sup>

As regards association with neoplasms, an increasing number of published cases and correlation studies exist, supporting the concept of association between granuloma annulare and certain types of hematologic neoplasms and solid tumors. Recently, it has been suggested considering granuloma annulare among paraneoplastic dermatoses.<sup>2</sup>

The first two cases of granuloma annulare associated with mesenchymal cancer are reported, and a review on the subject matter in the literature is carried out.

## Clinical cases

### Case 1. Gastrointestinal stromal malignant tumor and granuloma annulare

A 69-year-old male patient without pathological history. He appears at consultation for painful erythematous plaques located on palms and fingertips of both hands of one-month evolution (**Figure 1**).

*Skin biopsy:* epidermis without significant alterations; dermis with perivascular infiltrate, interstitial lymphocyte track and some histiocytes.

*Diagnosis:* granuloma annulare (**Figure 2**).

*Laboratory:* accelerated erythrocyte sedimentation rate of 19 mm/h. Rest without particulars.

The treatment was started with oral prednisone 20 mg/day, for a month, with slight alleviation of pain, but no lesion reduction.

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1. Dermatology Course and Division.

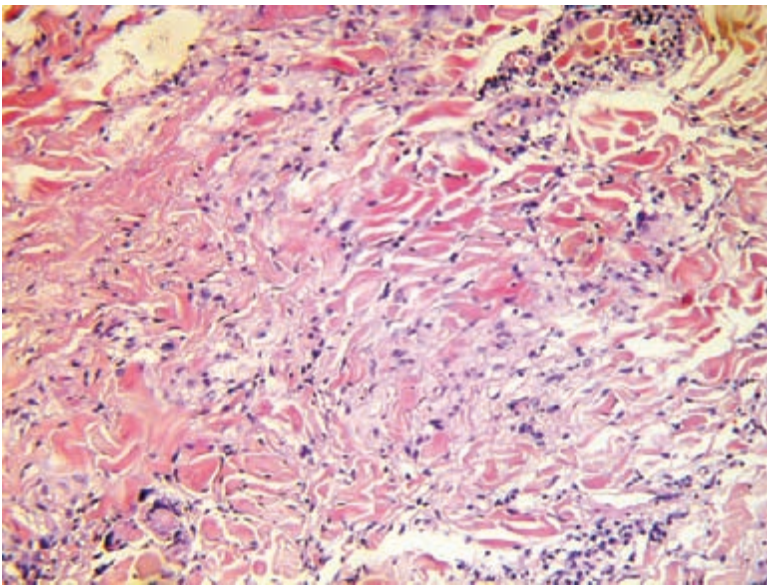
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**Figure 1.** Case 1: Painful acral granuloma annulare.



**Figure 2.** Case 1: Granuloma annulare. Perivascular lympho-histiocyte infiltrates and in interstitial track.



**Figure 3.** Case 2: Erythematous to violaceous plaques. Annular disposition.

Three months later, the patient was examined for abdominal pain. An abdominal ultrasonogram and a CAT were performed, with a 15 ' 11 ' 9.5 cm gastric tumor visualized and totally excised. Histopathological diagnosis was gastrointestinal stromal malignant tumor.

One month after the oncology surgery, complete resolution of the granuloma annulare was observed. He remains free of lesions at seven months follow-up.

### **Case 2. Breast adenocarcinoma, post-radiotherapy breast angiosarcoma, and granuloma annulare.**

An 81-year-old female patient, with history of left breast adenocarcinoma treated with tumorectomy + lymphadenectomy, anterior radiotherapy and tamoxifen, in 1998. Seven years later, she develops post-radiotherapy angiosarcoma on the same location, which was not treated by patient's decision.

A year after the angiosarcoma diagnosis, she consults for multiple asymptomatic erythematous to violaceous plaques tending to an annular disposition in the anterior thoraco-abdominal area, bilateral submammary fold, and back (**Figure 3**).

*Histopathological study:* epidermis without alterations; dermis with degeneration foci of collagen bundles surrounded by histiocytes and lymphocyte inflammatory infiltrate with palisade pattern.

*Diagnosis:* granuloma annulare (**Figure 4**).

*Laboratory:* accelerated erythrocyte sedimentation rate, 40 mm/h; rest, without particulars.

*Treatment:* local, with clobetasol for two months, without significant results.

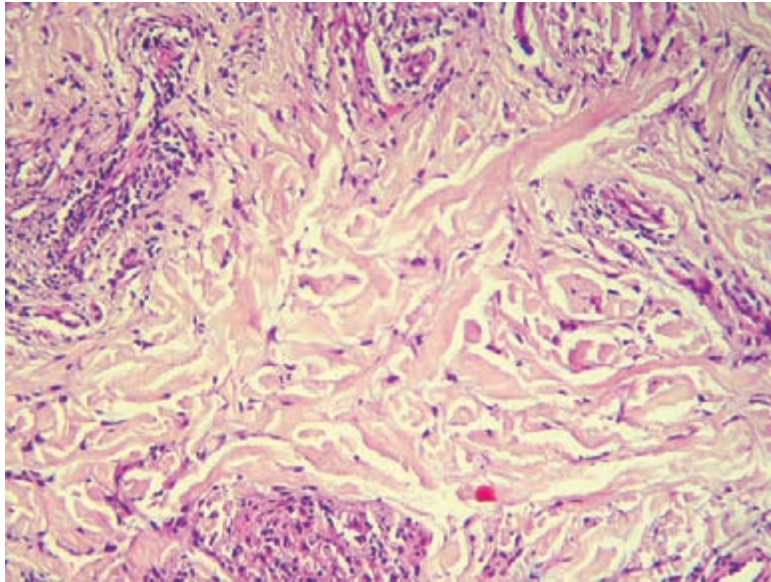
### **DISCUSSION**

Although it is a relatively unusual association, communications refer granuloma annulare with different types of neoplasms, since 1977.<sup>3</sup>

In a review from 1989, Dabski and Winkelman found a neoplasm incidence of 14 percent. The relation was suggested, although controversial, because of the variable period of time occurring between the two pathologies found in this series of cases.<sup>4</sup>

Barksdale et al.<sup>5</sup> noted in 13 patients with granuloma annulare and lymphoma the atypical clinical appearance of skin lesions, and granuloma annulare is construed as part of a generalized granulomatous reaction induced by the lymphoma.

In 2003, Ailing et al.<sup>6</sup> reviewed 16 cases of granuloma annulare related to neoplasms. They found some features of granuloma annulare, which



**Figure 4.** Case 2: Collagen bundles degeneration and histiocyte infiltrate surrounded by lymphocyte infiltrate in palisade.

**TABLE 1.** NEOPLASMS MOST FREQUENTLY ASSOCIATED WITH GRANULOMA ANNULARE.

<b>Hematológicas: 10</b>	
• Hodgkin's lymphoma	6/10
• Lennert's lymphoma	2/10
• Mycosis fungoides	1/10
• Follicular lymphoma	1/10
<b>Carcinomas: 6</b>	
• Uterine cervix Ca.	2/6
• Colon Ca.	1/6
• Breast Ca.	1/6
• Lung Ca.	1/6
• Seminoma	1/6

**TABLE 2.** PARANEOPlastic GRANULOMA ANNULARE. SUMMARY OF PUBLISHED CASES WHERE A PARANEOPlastic COURSE WAS SEEN.

Breast Ca.	(1989) <sup>11</sup>
Cervix Ca. (2)	(1992) <sup>13</sup>
AM Leukemia	(1993) <sup>14</sup>
Lung Ca.	(1995) <sup>15</sup>
NH Lymphoma	(1997) <sup>16</sup>
H Lymphoma	(1997) <sup>17</sup>
Ovary + stomach Ca.	(2006) <sup>18</sup>

**TABLE 3.** PARANEOPlastic GRANULOMA ANNULARE: DISTINCTIVE FEATURES.

• Atypical clinical presentation
• Elderly
• Pain
• Itching
• Unusual location

might be strongly associated with the presence of an underlying preceding or succeeding neoplasm.

Average age was 54 years, higher than the usual appearance age of granuloma annulare. Equal incidence was found for both genders, when usually female dominate.

Interval between diagnosis of dermatosis and neoplasm was variable: between 5 months before it to 3 years and a half after it.

Most frequently found were hematologic neoplasms (10 cases), and solid tumors in second place (Table 1).

Clinical manifestations included localized variant, generalized, subcutaneous, and perforating granuloma annulare. Three atypical manifestations must be pointed out: the presence of pain, itching, and unusual locations (palms, soles, and face).

Histopathology was typical of granuloma annulare in most cases, with usual histological patterns, without particular traits leading to a paraneoplastic origin. Hernández et al. reported a granuloma annulare case associated to esophagus neoplasm distinguished by having an atypical clinical appearance: single linear disposition plaque at neck level.<sup>7</sup>

Pathophysiologically, it is suggested that granuloma annulare is produced by a Th 1-type delayed hypersensitivity reaction.<sup>8,9</sup> Some authors suggest that neoplasms may be one of the triggering factor, through the expression of tumor antigens<sup>10</sup> and/or as a consequence of an aberrant cell-mediated immune response.<sup>11,12</sup>

In this review we found that in 8 patients, like in our first case, there was a synchronic course of both pathologies (Table 2). This strongly suggests the paraneoplastic feature of granuloma annulare.

In this sense, a recent article by Cohen suggests the inclusion of granuloma annulare among paraneoplastic dermatoses.<sup>2</sup>

Up to date, we have not found publications of granuloma annulare associated with mesenchymal cancer.

## Conclusion

So far, publications of granuloma annulare associated with neoplasms are scarce.

This association might not be a frequent occurrence, since if we include case reports and correlational studies, we only find a total amount of 38 cases. Only 8 of them describe a parallel clinical course between both pathologies, which proves a true paraneoplastic character.

After reviewing the literature, and in the light of the two reported cases, we may claim that there is a relation between granuloma annulare and neoplasms, and in some cases, a paraneoplastic behavior has been identified.

The temporal relation between the two pathologies is variable. Granuloma annulare may appear before or after the neoplasm diagnosis.

The dermatologist must be aware when facing a patient with an atypical presentation of granuloma annulare. The elements to be assessed in a possible association with neoplasms are elderly patients, with manifestations such as pain or itching, and unusual locations such as palms, soles, and face (**Table 3**).

According to the cases published so far, most frequently associated are hematologic neoplasms, and secondly solid organ tumors.

We report the first two cases related to mesenchymal neoplasms. The paraneoplastic course of granuloma annulare observed in the first patient must be noted.

We highlight that this is a rare pathology, not previously reported in the national literature.

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