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CASE REPORTS

Efficacy of Dapsone in Disseminated Granuloma Annulare: A Case Report and Review of the Literature

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Abstract. Granuloma annulare is a dermatosis of unknown cause that is generally self-limiting and has several clinical forms of presentation. It may be associated with pruritus or present asymptomatically. The disseminated variant of the disease accounts for 15% of all cases. Most authors consider that the duration of this form is longer and that treatment response is worse than for localized forms. A range of therapeutic options have been tried for this disease with a wide range of outcomes. We present a patient with disseminated granuloma annulare who started treatment with dapsone after several therapeutic failures. With dapsone therapy, her cutaneous symptoms showed a clear improvement without any relevant side effects. We then review reports in the literature of cases of disseminated granuloma annulare treated with dapsone.

Key words: disseminated granuloma annulare, dapsone, treatment.

EFICACIA DE LA DAPSONA EN EL GRANULOMA ANULAR DISEMINADO: PRESENTACIÓN DE UN CASO Y REVISIÓN DE LA LITERATURA

Resumen. El granuloma anular es una dermatosis de causa desconocida, habitualmente autorresolutiva, con varias formas clínicas de presentación. Puede asociar prurito o manifestarse de forma asintomática. La variante diseminada de la enfermedad supone el 15 % de los casos, y para la mayoría de los autores su duración es mayor y la respuesta al tratamiento peor que en las formas localizadas. Se han propuesto múltiples opciones terapéuticas para esta patología, con resultados muy variables. Presentamos el caso de una paciente con granuloma anular generalizado que tras varios fracasos terapéuticos inició tratamiento con dapsona, obteniéndose una clara mejoría de la clínica cutánea hasta su total resolución, sin efectos secundarios significativos. Aportamos una revisión de los casos de granuloma anular diseminado tratados con dapsona hallados en la literatura.

Palabras clave: granuloma anular diseminado, dapsona, tratamiento.

Introduction

Granuloma annulare (GA) is a benign dermatosis of unknown cause. It is characterized by granulomatous inflammation of the dermis and commonly manifests with papules in an annular distribution. The disseminated variant of the disease occurs in 15% of affected patients. Cases of localized GA tend to resolve spontaneously within months or a few years. The course of the generalized forms of the disease, however, is the subject of debate. Although most authors consider that these forms have a longer duration, poorer response to treatment, and higher recurrence than the localized forms, we were unable to find studies that support this opinion. Disseminated GA is more commonly associated with pruritus than the other clinical forms. The pruritus and the ungainly esthetic appearance caused by the disease have led to different treatments being tried with poor outcomes and, occasionally, important adverse effects.

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Case Description

We report the case of a 72-year-old woman who was receiving captopril for hypertension and who presented with pruritic lesions on the torso and limbs. The lesions

had appeared gradually over the previous 7 months. The patient presented no other symptoms.

Physical examination revealed erythematous plaques of several centimeters in diameter with irregular edges on the front of the torso, whereas the back of the torso and proximal third of the limbs presented a large number of nonscaly violaceous erythematous papules that were slightly infiltrated and confluent at some points (Figure 1).

Laboratory tests including basic biochemistry and complete blood count revealed no abnormal findings and fasting plasma glucose levels were normal.

A skin biopsy revealed necrobiotic collagen surrounded by palisading histiocytes forming the necrobiotic granulomas and a perivascular infiltrate composed of lymphocytes; all these findings were located in the mid-dermis. Colloidal iron staining for mucin was positive (Figure 2).

Clinical and histologic findings suggested a diagnosis of disseminated GA.

Because the patient complained of intense pruritus, a treatment regime was instated but proved to be ineffective. Treatment included topical corticosteroids for 8 weeks, oral corticosteroids (30 mg/d of prednisone) for 6 months, 3 weekly sessions of psoralen + UV-A treatment for 3.5 months, and oral potassium iodide for 2 months. Treatment with potassium iodide was suspended because the patient developed iatrogenic hypothyroidism. After 13 months of failed treatment attempts, treatment was instated with dapsone at a dose of 100 mg per day (after determining that levels of glucose-6-phosphate dehydrogenase were normal). The patient reported a clear improvement of the pruritus after 2 weeks and improvement of the skin was observed after 2 months. Clinical symptoms improved gradually and the only residual lesions remaining after 12 months of treatment with dapsone were macules and brown marks; no lesions remained after 15 months (Figure 3). Results of the periodic laboratory tests performed during treatment were normal and no adverse effects were observed.

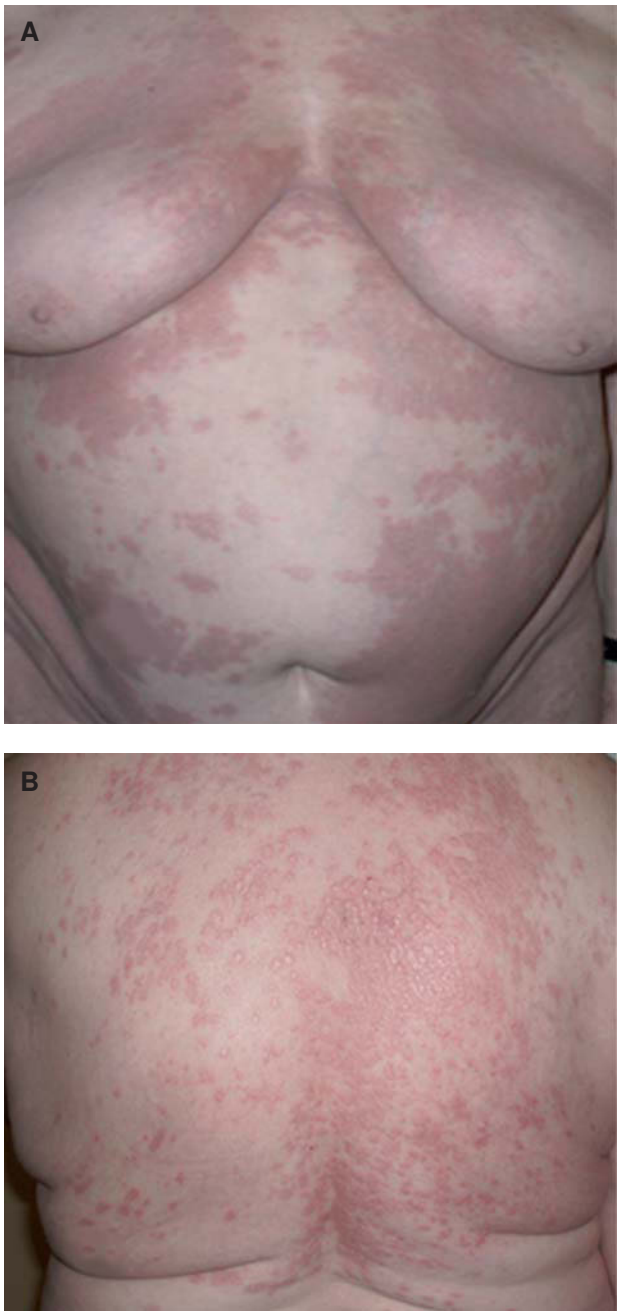

Figure 1. A. Erythematous plaques with clearly defined borders on the front of the torso. B. Large number of erythematous papules on the back.

Discussion

GA is a benign dermatosis that is generally self-limiting. Its cause has not yet been clearly determined, though most authors consider that it is an immune reaction with possible action on both cell immunity and immune complexes. The presence or absence of vasculitis is a matter of debate. Most cases of GA are considered to be idiopathic but appearance of the disease following insect bites, phototherapy, trauma, different infections, drug therapy, and other possible triggers has been reported. The association between GA and other diseases has been debated, including its relationship with diabetes mellitus—especially type-1.

GA has several clinical forms of presentation. The most common forms are localized, generalized, subcutaneous, and perforating GA. Varieties of GA considered as atypical include follicular, patch-type, linear, and fibroelastolytic giant cell GA. The latter has been linked to sunlight, though it has also been described in areas not exposed to sunlight.[1]

Disseminated GA accounts for 15% of all cases, except in patients infected with the human immunodeficiency

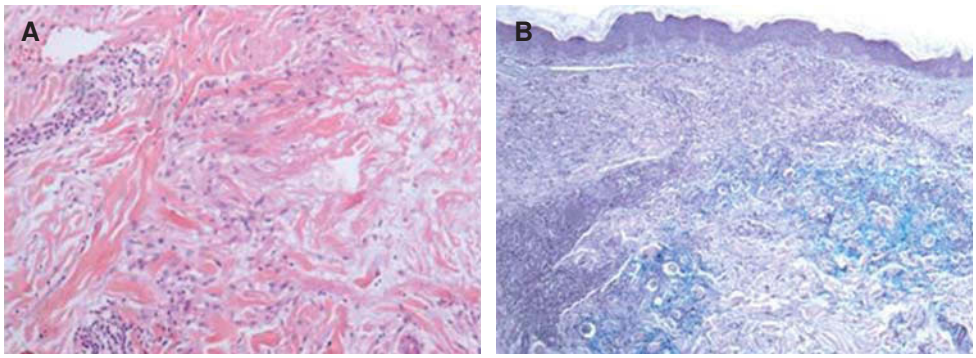

Figure 2. A. Necrobiotic collagen surrounded by palisading histiocytes. Perivascular lymphocytic infiltrate. Hematoxylin–eosin, ×100. B. Abundant mucin in the dermis. Colloidal iron, ×40.

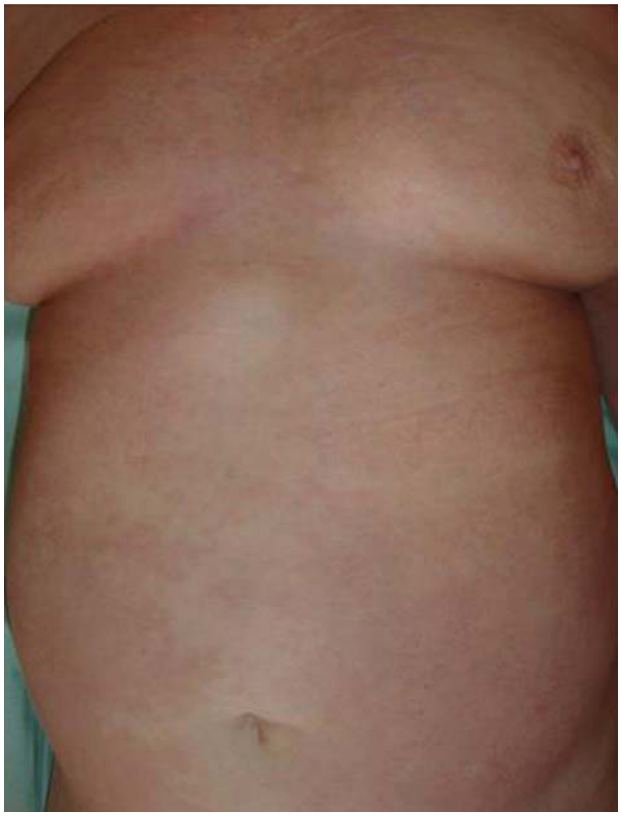

Figure 3. Residual macules and hyperpigmented marks following treatment with dapsone.

Table 1. Treatment Options for Disseminated Granuloma Annulare

Systemic corticosteroids	Fumaric acid esters
Chlorambucil	Nicotinamide
Potassium iodide	Niacinamide
Dapsone	Topical corticosteroids
Antimalarial drugs	Topical vitamin E
Cyclosporins	Pentoxifylline
Systemic retinoids	Thyroxin
Phototherapy inhibitors	Topical calcineurin
Dipyridamole	Biological therapies Infliximab Efalizumab Etanercept

virus[2]; disseminated GA is the most common variant in these patients. The mean age of onset is higher than for the localized variants; 70% of patients are over 40 years of age. A higher incidence has been reported of specific histocompatibility antigens in these patients than in the general population. These include human leukocyte antigen Bw35, suggesting a possible genetic predisposition to the disease.[3] Clinical manifestation includes 2 different patterns: annular plaques of several centimeters in diameter and a large number of skin-colored or violaceous erythematous papules. Suárez et al[4] reported a case of disseminated GA in areas exposed to sunlight.

Most authors consider that disseminated GA has a longer duration and worse response to treatment than the localized variant, though we have found no studies to support this opinion. The decision whether or not to treat each patient should be essentially based on the extension of the disease, the presence or absence of pruritus, and the psychological state of the patient. Several treatments for disseminated GA have been proposed, with highly variable outcomes (Table 1). These include systemic and topical corticosteroids, chlorambucil sulfone, antimalarial drugs, fumaric acid esters, phototherapy, systemic retinoids, potassium iodide, thyroxin, dipyridamole, pentoxifylline, defibrotide, niacinamide, nicotinamide, topical vitamin E, and, more recently, topical immunomodulators[5] and biological treatments.[6-8]

While most authors consider dapsone a possible treatment option for disseminated GA, few series have been reported. Of the published cases with a good response to the drug, most showed improvement after between 4 and 12 weeks

Table 2. Cases of Disseminated Granuloma Annulare That Responded to Dapsone[a]

Author	*Number of Patients*	*Duration*[b]	*Ineffective Previous Treatment*	*Time With Dapsone, mo*	*Time Without Recurrence, mo*	*Adverse Effects*
H López-Lucio[9]	1	2 y	Various authors	3	–	No
DB Czarnecki[10]	1	1 y	–	1	19	No
	2	1 mo	–	1	20	No
	3	1 mo	–	3	3	Fatigue
	4	5 mo	–	2	6	No
	5	7 years	–	2	4	No
	6	2 y	–	2	↓ dose	No
A Steiner[11]	1	6 y	–	1.5	–	No
	2	–	–	2	2	No
	3	8 y	Cryotherapy	3.5	–	Headache, fatigue
	4	1 y	–	0.5	–	Headache, fatigue
	5	8 y	Therapeutic PUVA	3	3	No
	6	1 y	–	3	–	Fatigue
	7	1 y	–	3	2	Headache
	8	3 y	–	4.5	–	No
	9	3 y	–	4	4	No
	10	3 y	Topical corticosteroids Retinoids	1	–	Headache, fatigue
N Saied[12]	1	2 mo	No	1.5	18	No
	2	1.5 mo	Topical corticosteroids	1 ↓ dose		

[a] – indicates no data provided; ↓, reducing.
[b] Duration of disseminated granuloma annulare before instatement of treatment with dapsone.

of treatment and a high percentage showed no recurrence months after suspension of dapsone (Table 2). The dosage recommended by almost all authors, and by us, is 100 mg per day.

We found few cases in the literature of disseminated GA that did not respond to dapsone and most of those cases also showed no response to other treatments.[13] We also found few cases of patients in whom dapsone had to be suspended due to adverse effects; these effects included headache and fatigue and other, more severe side effects such as agranulocytis[14] and aplastic anemia.[15]

Dapsone is a sulfone with many dermatologic indications. Its mechanism of action involves an anti-inflammatory effect although the pathways by which it acts are not yet understood. The main side effects of dapsone include hemolytic anemia and methemoglobinemia. Blood dyscrasias, heart, liver, and kidney abnormalities, pregnancy, and glucose-6-phosphate dehydrogenase or folic acid deficit should be ruled out with laboratory tests before beginning treatment.

During treatment, blood and urine tests should also be performed every week for the first month and every month thereafter.

In conclusion, we have presented the case of a patient with disseminated GA who, after several failed treatments, showed improvement and subsequent resolution of cutaneous symptoms following treatment with dapsone and who remained free of the condition for several months after treatment was suspended. While we cannot rule out the possibility that the disappearance of the lesions was due to the natural course of the disease, the clear clinical improvement of the skin and the pruritus immediately after instating treatment leads us to consider the drug as the cause of remission.

We have also reviewed the cases in the literature of disseminated GA treated with dapsone. These cases, though

few, and our own experience lead us to propose this treatment option as an effective alternative.

Conflicts of Interest
The authors declare no conflicts of interest.

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