Resolution of refractory generalized granuloma annulare after treatment with alitretinoin

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Key words: alitretinoin; generalized granuloma annulare; refractory.

INTRODUCTION

Granuloma annulare (GA) is an inflammatory skin disease that can be divided into localized, generalized, subcutaneous, perforating, and patch subtypes. Generalized granuloma annulare (GGA) is defined as GA that affects at least the trunk and the upper and/or lower extremities.[1] Multifactorial causes, including infection, sun exposure, drugs, and trauma, seem to contribute to the disease development. A histopathologic examination may reveal changes in mainly the papillary and mid dermis with lymphohistiocytic granuloma. Inflammatory infiltrates may show palisaded or interstitial patterns or a mixture of both. Herein, we report a case of GGA that was refractory to multiple drugs but successfully treated with alitretinoin.

Abbreviations used:

GA: granuloma annulare
GGA: generalized granuloma annulare

CASE REPORT

A 72-year-old man with an 8-year history of widespread, asymptomatic, erythematous papules and plaques on the arms, legs, and trunk visited the clinic. The lesions were discrete, pinpoint-to-pinhead–sized, and confluent (Fig 1, *A*). He had been prescribed medicine for 4 years at a local clinic without improvement. His past medical history included acute myeloid leukemia that had been in complete remission for 19 years, anti–hepatitis C virus antibody positivity, and cerebral stroke. He was taking levetiracetam for epilepsy and antihypertensive drugs. Laboratory findings, including antinuclear antibodies and rheumatic factor, showed no abnormalities. A punch biopsy was done, and the histopathology showed chronic granulomatous inflammation in the papillary dermis with mostly perivascular lymphohistiocytic and neutrophilic infiltration (Fig 2). He was diagnosed with GGA; 30 mg of oral alitretinoin daily, antihistamines, and topical tacrolimus ointment were started. After 7 months of treatment, partial remission was achieved, but several new lesions appeared on his extremities. The alitretinoin was discontinued, and 200 mg of hydroxychloroquine twice daily was started. Two months later, he returned with the exacerbation of skin lesions (Fig 1, *B, C*), with lesions extending to his neck and the greater part of his trunk. The hydroxychloroquine was switched back to alitretinoin with no washout period. Within 8 months, all lesions flattened, some with post-inflammatory hyperpigmentation, and no new lesions were seen (Fig 1, *D-F*). Topical tacrolimus was continued throughout the whole period. Alitretinoin was administered for a total of 15 months to achieve remission, and the aggravation of GGA was present only in the first break in medication. The posttreatment laboratory results showed no abnormalities, and there were no adverse events.

DISCUSSION

The pathogenesis of GA is not well understood. Many case reports have described relationships

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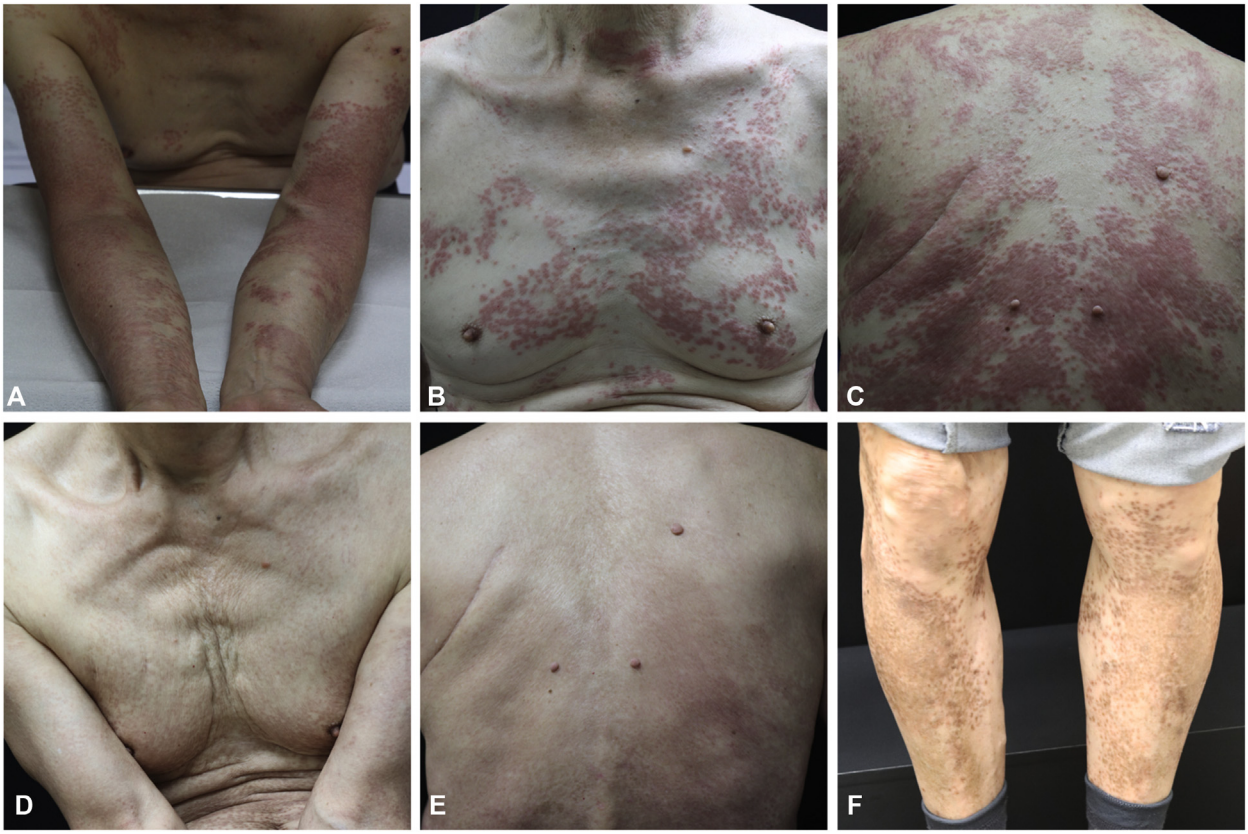

Fig 1. A, Multiple erythematous papules and plaques were seen on the arms and trunk of the patient at the first visit. **B, C,** After switching to hydroxychloroquine, the patient visited the clinic with the exacerbation of skin lesions. **D-F,** Photographs after successful treatment with alitretinoin, with fading and flattening and of all lesions.

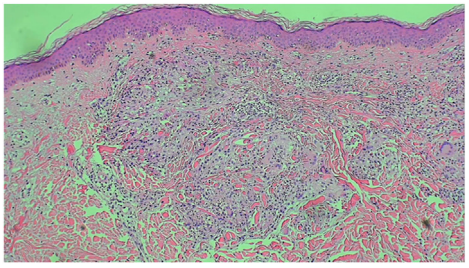

Fig 2. Punch biopsy from the upper portion of the arm revealing chronic granulomatous inflammation in the papillary dermis without necrosis, perivascular lymphohistiocytic infiltration, and a few polymorphonuclear leukocyte infiltrates. Multinucleated giant cells are also present. (Hematoxylin-eosin stain; original magnification: ×100.)

between GGA and systemic diseases; few large series have been published, and these associations have been debated.[2] Multifactorial causes, including infection, sun exposure, drugs, and trauma, seem to contribute to the disease development. Activation of T cell–mediated immune response is thought to be the pathologic mechanism of GGA.[3] In this case of GGA, there was no definite cause of the disease. The history of malignancy may have had an impact, but it is known that myeloid leukemias are less commonly associated with GGA compared to other lymphomas.[4] Moreover, the fact that the leukemia had been in complete remission for 19 years before the occurrence of GGA makes the association of the 2 conditions highly unlikely.

While localized GA often resolves spontaneously or responds to topical glucocorticoids, GGA may last for years. Various treatments, such as topical or systemic steroids, antimalarial drugs, immunosuppressants, isotretinoin, photodynamic or psoralen plus UV-A therapy, and adalimumab, have been reported to successfully treat GGA (Table I), but most of these reports were case reports or small case series, with an absence of randomized controlled trials.[5] Most of these treatment options' mechanisms of action are not well known, but T cell inhibition, immune modulation, and anti-inflammation are regarded as key factors. Among retinoids, etretinate, and isotretinoin have been used to treat GGA, as they

Table I. Practicable treatments for GGA and their regimens and levels of evidence

Treatment	Regimen	Level of evidence
Antimicrobials		
Amoxicillin/clavulanic acid	Amoxicillin/clavulanic acid 875/125 mg twice daily	D
Dapsone	25-200 mg (mean 100 mg) daily	C
Doxycycline	100 mg twice daily	D
Minocycline + ofloxacin + rifampin	Once monthly single dose of 600 mg rifampicin, 400 mg ofloxacin, and 100 mg minocycline hydrochloride	D
Apremilast	Initial dose of 10 mg, increasing by an increment of 10 mg daily until maintenance dosage of 30 mg twice daily	D
Biologic agents		
Adalimumab	80 mg subcutaneously, followed by 40 mg every other week, 1 week after initiation	D
Infliximab	5 mg/kg at weeks 0, 2, 6, 14, and 24	D
Dupilumab	Loading dose of 600 mg subcutaneously at week 0 and then decreased to 300 mg every 2 weeks	D
Corticosteroids		
Intralesional corticosteroids		C
Topical corticosteroids		C
Hydroxychloroquine	200 mg twice daily	C
Methotrexate	12.5-15 mg weekly	
Oral isotretinoin	0.5 mg to 1 mg/kg daily or 40-80 mg daily	D
Pentoxifylline	400 mg 3 times daily	C
Phototherapy		
Narrowband-UVB		C
psoralen plus UV-A		C
UV-A1		C
Potassium iodide	150-450 mg daily, gradually increased to 900-1500 mg daily	D
Radial Pulse therapy		D
Sulfasalazine	500 mg daily to 1.5 g twice daily depending on tolerance and efficacy	C
Tacrolimus ointment		D
Tofacitinib	Oral: 5 mg twice daily Topical: 2% ointment twice daily	D

GGA, Generalized granuloma annulare.

inhibit delayed hypersensitivity responses, cellular immunity, and the proliferation of fibroblasts.[5] Etretinate (0.8 mg/kg/day) was given for 7 months to achieve resolution, although the patients suffered from hair loss.[6] Patients with GGA treated with isotretinoin were between 0.5 to 1 mg/kg/day and 40 to 80 mg/day for a treatment duration of 2 to 14 months. Two of the 7 patients showed relapses of GGA after the discontinuation of the drug. Adverse effects, such as cheilitis, dryness of mucosae, and moderate increases in cholesterol and triglyceride serum levels or abnormal liver function tests were reported.[7] Alitretinoin, a 9-cis-retinoic acid, is a pan-retinoid receptor agonist that has been approved for chronic hand eczema because of its immunomodulatory and anti-inflammatory effects; it halts chemokine-induced leukocyte recruitment and inhibits dendritic cell—mediated T cell activation. The action mechanism of alitretinoin is believed to involve the regulation of the expression of genes that control cellular differentiation and proliferation.[8] The shortest half-life among the retinoids and the nonaccumulating nature of metabolites make alitretinoin a safer alternative than isotretinoin or acitretin.[9] Compared to isotretinoin and acitretin, alitretinoin exerts stronger anti-inflammatory and immune-modulatory effects without suppressing the activity of the sebaceous glands, leading to fewer side effects (eg, xerosis or mucosal dryness).[10] In this case of GGA, we started alitretinoin at 30 mg/day, which is a common dosage for hand eczema. Before alitretinoin treatment, a lipid panel test, complete blood cell count, and liver function test—and, in women, pregnancy testing—are necessary. A follow-up liver function test and complete blood cell count were done after 1 year of alitretinoin administration. If abnormal laboratory results are anticipated, follow-up tests might be needed. In this case, despite

the strong anti-inflammatory properties of alitretinoin, the slow therapeutic response may have been due to advanced age, a long disease duration, and extensive disease activity. Since alitretinoin acts as an anti-inflammatory agent, the treatment response may be monitored by the fading and flattening of erythematous lesions. When alitretinoin was discontinued and the patient was switched to hydroxychloroquine, he suffered from GGA aggravation. This could be supporting evidence that the improvement of the disease was not a part of its natural course. Although alitretinoin shares common molecular structures with other retinoids, there have been no reports of GGA successfully treated with alitretinoin to our knowledge.

Herein, we report a case of GGA that was refractory to multiple drugs but successfully treated with alitretinoin, and we suggest that alitretinoin can be a treatment option for this frustrating condition since it exerts anti-inflammatory effects without immunosuppression. Compared to other retinoids, alitretinoin is better suited for elderly patients because it is less drying and less desquamative.

Conflicts of interest

None disclosed.

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