

Familial granuloma annulare: First report of occurrence in a father and daughter and updated review of the literature



Brian D. Rankin, PhD,^a and Richard M. Haber, MD, FRCPC^b
Calgary, Alberta, Canada

Key words: familial; granuloma annulare; granulomatous disease; hereditary.

INTRODUCTION

Granuloma annulare (GA) is a common, benign, often self-limiting granulomatous disease. The condition classically presents clinically with asymptomatic, flesh-colored to erythematous, nonscaling papules, often arranged in a ring or annular pattern. Histologically, GA is characterized by a perivascular lymphocytic infiltrate, the accumulation of macrophages in the dermis, and palisading of the macrophages around degenerated areas with altered collagen.

A delayed-type cell-mediated hypersensitivity reaction is the favored hypothesis; however, the etiology and pathogenesis of GA is not fully understood. It has been associated with various systemic diseases, including diabetes mellitus and dyslipidemia, and has also been reported to develop after exposure to assorted triggers, often cutaneous trauma.¹

Although uncommon, familial occurrences of GA have also been reported. Friedman and Winkelmann² last reviewed familial GA in 1987, describing 11 families and 21 cases of GA with at least 2 immediate family members affected. These authors also suggested that the incidence of specific human leukocyte antigens (HLAs) (eg, HLA-B35) within some of these family members might indicate that genetically predisposed individuals could develop a cell-mediated immune reaction in response to an unknown antigen.

In this report, we describe the cases of 2 patients, a father and his daughter, who presented with clinical and histologically confirmed GA. We also review all familial occurrences of GA since 1987.

Abbreviations used:

GA: granuloma annulare
 HLA: human leukocyte antigen
 TNF- α : tumor necrosis factor- α

CASE SERIES

Case 1

A 68-year-old man presented with asymptomatic annular lesions on his right forearm 9 years previously. These failed to respond to topical steroids and antifungal creams. He had 2 children; 1 daughter who also has GA (described below) and 1 unaffected son. He was on no oral medications and had no history of diabetes mellitus or hyperlipidemia. Physical examination revealed a 5-cm erythematous annular plaque on the dorsum of his left hand and 2 erythematous 4-cm plaques on his right forearm; 1 annular and 1 arcuate (Fig 1). A punch biopsy from the annular plaque on his right forearm was read by a dermatopathologist as GA. As his lesions were asymptomatic, he declined treatment. His HLA genotype study showed expression of HLA-B35.

Case 2

A 41-year-old woman and daughter of case 1, had a history of asymptomatic annular lesions that started on the right hand 4 years previously but then developed on her ankle, calf, and forearms. She was on no medications and had no history of diabetes mellitus or hyperlipidemia but did have a history of idiopathic uveitis. She has 2 children, both without similar skin lesions. Physical examination

From the Cumming School of Medicine^a and Division of Dermatology, Department of Medicine, University of Calgary.^b

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Richard M. Haber, MD, FRCPC, Division of Dermatology, Department of Medicine, University of Calgary, 1820 Richmond Road SW, Calgary, AB T2T 5C7, Canada. E-mail: Richard.haber@albertahealthservices.ca.

JAAD Case Reports 2021;17:61-4.

2352-5126

© 2021 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2021.09.023>



Fig 1. Granuloma annulare lesions on the right forearm of case 1 with localized granuloma annulare.

revealed multiple approximately 2-cm annular plaques on her right hand and forearm, a 4-cm erythematous annular plaque on her right wrist (Fig 2), and a 4-cm annular plaque on her right calf. A punch biopsy from the annular plaque on her right leg showed an interstitial histiocytic infiltrate that palisaded around zones of collagen necrobiosis. Colloidal iron showed focal staining within the necrobiotic zones and the features were consistent with GA. She wished to have treatment for the GA, and several of the plaques have been treated with intralesional triamcinolone acetonide over the years with a good result. HLA genotyping showed expression of HLA-B35 and B27.

DISCUSSION

Friedman and Winkelmann² provided the last detailed review of the literature on familial GA in 1987. The purpose of our report is to add, to our knowledge, the first cases of GA in a father and daughter, and update the literature of all reported cases of familial GA since 1987.

An additional 7 reports of GA involving at least 2 immediate family members have appeared in the literature since 1987 (Table 1).³⁻⁹ With these new additions, there are now 6 reports of GA occurring in successive generations, 12 reports of GA occurring in siblings, 5 reports of GA in monozygotic twins, and 1 report of GA in dizygotic twins in the literature. A variety of GA subtypes have been reported within this group, including localized, subcutaneous,



Fig 2. Granuloma annulare lesion on the right forearm of case 2 with generalized granuloma annulare.

generalized, and perforating. None of the newly reported patients were diabetic.

Distinct HLA associations have been reported in some patients with GA, especially an increased prevalence of HLA-B35 in patients with generalized GA but not in localized GA, and this association has been used to suggest a genetic predisposition to GA.^{2,10} HLA genotyping confirmed that both our patients also expressed HLA-B35 even though the father had localized GA and the daughter generalized GA. This is similar to Friedman and Winkelmann's² report on 2 sisters who both were determined to have HLA-B35 with the older sister having generalized GA and the younger sister, localized GA. The finding of HLA-B35 in both reports of familial GA cases adds further evidence to the association of HLA-B35 in patients with familial GA.

Only 1 of the other 7 newly reviewed reports of familial GA provided HLA genotyping results.⁷ In that report of 2 monozygotic twin sisters, both had human ancestral haplotype 8.1, a genotype that has been associated with a tumor necrosis factor- α (TNF- α) polymorphism leading to production of TNF- α by peripheral blood mononuclear cells. As both sisters responded to a trial of adalimumab, it was speculated that patients with GA with TNF- α polymorphisms are more likely to respond to TNF- α blocking agents.

There are currently no standardized guidelines on the management of GA. Common treatments include dapsone, tetracyclines, fumaric acid esters, retinoids, antimalarials, cyclosporine, methotrexate, TNF- α inhibitors, phototherapy, lasers, and photodynamic therapy. In our cases, 1 patient declined treatment, whereas the other responded well to intralesional triamcinolone acetonide.

Table I. Reported familial occurrences of granuloma annulare since 1987

Source	Patients	Age at onset, y	Sex	Type of GA	Location of lesion(s)	Biopsy Confirmation	Duration	Treatment	Outcome
Abrusci et al ³	Brother	6	M	Generalized, perforating	Hands, elbows, knees, popliteal regions, ankles	Yes	5 y	Imidazole creams, trichloroacetic acid, topical corticosteroids	NR
	Sister	5	F	Generalized, perforating	Face, hands, elbows, chest, knees, popliteal regions, ankles	Yes	4 y	Imidazole creams, trichloroacetic acid, topical corticosteroids	NR
Suite and Jankey ⁴	Brother	10	M	Generalized, annular plaques	Arms, legs, lower portion of the buttocks	Yes	NR	No treatment but occurred after mosquito bites	NR
	Sister	5	F	Generalized, annular plaques	Arms, legs	Yes	NR	No treatment but occurred after mosquito bites	NR
Martinón-Torres et al ⁵	5 cases with 2 members in the family	NR	NR	NR	NR	NR	NR	NR	NR
Grant et al ⁶	Mother	37	F	Localized	Ring finger of the right hand	Yes	NR	NR	Spontaneously resolved after 10 mo; reoccurred 1 y later
Knoell ⁷	Daughter	5	F	Localized	Hand	No	NR	NR	NR
	Twins, monozygotic	67	F	Generalized, papules, macules, plaques	Arm, legs, torso	Yes	2 y	Adalimumab	Clear after 6 mo
Takcı and Simsek ⁸	Sisters	67	F	Generalized	NR	No	NR	Adalimumab	Clear after 6 mo
		8	F	Localized, annular plaque	Right leg	Yes	1 y	Topical corticosteroid and calcipotriol	NR
Mazzotta et al ⁹	Twins, monozygotic	3	F	Generalized, annular plaques	Leg, wrist, abdominal wall	Yes	5 mo	Topical corticosteroid and calcipotriol	NR
		8	F	Localized, nodular	Wrist, feet	No	d	NR	1 twin with regression of nodules after 20 d
Rankin and Haber (current cases)	Sister	8	F	Localized, nodular	Feet	No	d	NR	No change
	Sister	10	F	Localized, nodular	Feet	No	d	NR	No change
	Father	68	M	Localized, annular plaques	Forearm, hand	Yes	9 y	None	No change
	Daughter	41	F	Generalized, annular plaques	Hand, wrists, elbow, ankle, calf	Yes	4 y	Intralesional triamcinolone acetonide	Improved with intralesional triamcinolone acetonide

F, Female; M, male; NR, not reported.

Without a clear etiology and given the paucity of reported familial incidences of GA, there remains the possibility that the patients' clinical presentations and familial relationship are a chance observation. The only strong genetic predisposition appears to be an increased prevalence of HLA-B35 in patients with generalized GA although HLA-B35 has now been found in 2 families with both localized and generalized familial GA patients. We encourage further reports of familial GA to elucidate their incidence and more detailed genetic assessment in cases that do demonstrate a familial association.

Conflicts of interest

None disclosed.

REFERENCES

1. Piette EW, Rosenbach M. Granuloma annulare: pathogenesis, disease associations and triggers, and therapeutic options. *J Am Acad Dermatol*. 2016;75(3):467-479.
2. Friedman SJ, Winkelmann RK. Familial granuloma annulare. Report of two cases and review of the literature. *J Am Acad Dermatol*. 1987;16(3 Pt 1):600-605.
3. Abrusci V, Weiss E, Planas G. Familial generalized perforating granuloma annulare. *Int J Dermatol*. 1988;27(2):126-127.
4. Suite M, Jankey N. Familial granuloma annulare. *Int J Dermatol*. 1992;31(11):818.
5. Martínón-Torres F, Martínón-Sánchez JM, Martínón-Sánchez F. Localized granuloma annulare in children: a review of 42 cases. *Eur J Pediatr*. 1999;158(10):866.
6. Grant I, Mohammed P, Mahaffey PJ. Granuloma annulare in the hand. *J Hand Surg Br*. 2002;27(6):556-558.
7. Knoell KA. Efficacy of adalimumab in the treatment of generalized granuloma annulare in monozygotic twins carrying the 8.1 ancestral haplotype. *Arch Dermatol*. 2009;145(5):610-611.
8. Takci Z, Güler Simsek G. Familial granuloma annulare. Article in Turkish. *J Contemp Med*. 2015;5(1):189-191.
9. Mazzotta F, Troccoli T, Bonifazi E. Granuloma annulare and SARS-CoV-2 pandemic. *Eur J Pediatr Dermatol*. 2020;30(2):83-87.
10. Friedman-Birnbaum R, Gideon O, Bergman R, Pollack S. A study of HLA antigen association in localized and generalized granuloma annulare. *Br J Dermatol*. 1986;115(3):329-333.