

Granuloma Annulare: A Review of 41 Cases at the National Skin Centre

H H Tan,**FAMS, MBBS, MRCP (UK)*, C L Goh,***FAMS, MD, FRCP (Edin)*

Abstract

Introduction: Granuloma annulare (GA) is a benign, inflammatory skin disorder that has no proven aetiology or widely accepted theory of pathogenesis. We present the results of a local study examining the characteristics of this disorder. **Materials and Methods:** This is a retrospective study of 41 patients with granuloma annulare seen at a tertiary dermatological skin hospital in Singapore. The disease was classified based on whether it was localised or generalised. Remission rates and associated diseases were documented. **Results:** The majority (93.9%) of lesions were localised. GA tends to occur within the first three decades of life, and 39.4% of patients were 10 years old and below. There was a slight female preponderance, and no predilection for any particular racial group. Remissions were seen in 67.6% of patients who were followed up for at least 12 months, and remissions only occurred with the localised form of GA. There were 4 cases of disseminated GA and 1 case of perforating GA. There were 6 patients with associated diabetes mellitus, 2 with pulmonary tuberculosis, and 4 patients each with hypercholesterolaemia and a history of atopy. **Conclusion:** The characteristics of GA in our local population do not differ significantly from that of overseas studies. While localised forms of GA have a high chance of resolving, the generalised forms of the disease are difficult to treat and do not tend to resolve totally.

Ann Acad Med Singapore 2000; 29:714-8

Key words: Disease association, Epidemiology, Histology, Inflammatory skin disorder

Introduction

Granuloma annulare (GA) is a benign, inflammatory disorder of the skin that has no proven aetiology or widely accepted theory of pathogenesis. There are several clinical manifestations, ranging from localised GA, which is the commonest form and is characterised by erythematous or flesh-coloured papules in an annular arrangement, to less commonly seen variants, including the generalised, subcutaneous and perforating types.

In this retrospective study, we have analysed the epidemiological data, associated disorders, treatment and outcome of patients with histologically proven GA in our local population.

Definition

GA is a benign, cutaneous, inflammatory disorder of unknown aetiology that is usually self-limited. The characteristic eruption often presents as annular, flesh-coloured grouped papules.

Localised GA: Cases of GA were classified as localised in our study, if by clinical description, the skin lesions were solitary or few and had a typical appearance of dermal papules in a ring-like arrangement.

Disseminated and generalised GA: These cases were

diagnosed based on the criteria used by Dabski and Winkelmann.¹ The condition is considered generalised when it affects at least the trunk and either the upper or lower extremities, or both. Extensive lesions confined to one anatomical site or the extremities only are considered disseminated GA, but not truly generalised.

Perforating GA: This is characterised by presence of multiple papules, mostly umbilicated and/or crusted, with histological evidence of superficial localisation of the necrobiotic granuloma and epidermal perforation.

Patients and Methods

This is a retrospective study conducted at the National Skin Centre, a tertiary dermatological referral centre in Singapore. From the indexing system of our medical records office, we have identified 53 patients who were diagnosed by skin biopsies to have GA over a 6-year period between January 1993 and December 1998. Case sheets were collated and analysed, and information studied included sex, age of onset, number and types of lesions, precipitating factors, sites involved, duration and recurrences of eruptions, associated medical conditions, treatments received and outcome of patients who had been followed up for a minimum period of 12 months. Any additional information that was required was obtained via

* Associate Consultant

** Senior Consultant and Medical Director
National Skin Centre

Address for Reprints: Dr Tan Hiok Hee, National Skin Centre, 1 Mandalay Road, Singapore 308205.

telephone interview. Out of the 53 cases identified, 41 patients (77%) were eventually included in our series. Death, change of address or telephone number and default of follow up visits after a period of review of less than 12 months were the reasons for excluding the other 12 patients. Statistical analysis was carried out using the chi-square, Student's *t*-test and Fisher's exact probability test.

Results

A total of 41 cases were included in our series.

Sex, Age and Racial Distribution

Figure 1 shows the distribution of cases according to age at onset.

There was a slight preponderance for females, with a female to male ratio of 1.56:1 (25 females, 16 males). There were 28 Chinese (68.2%), 4 Malays (9.8%), 5 Indians (12.2%) and 4 patients belonging to Other races (9.8%). Their ages ranged from 18 months to 80 years, with an average age of onset of 26.2 years. In the majority of cases (27 out of 41 or 65.9%), the onset of GA occurred in the first three decades of life.

Clinical Characteristics of GA

Table I summarises the clinical characteristics of patients with GA in our study.

There were 34 (82.9%) cases of localised GA, 2 (4.9%) cases of disseminated GA, 4 (9.8%) cases of generalised GA and 1 (2.4%) case of perforating GA.

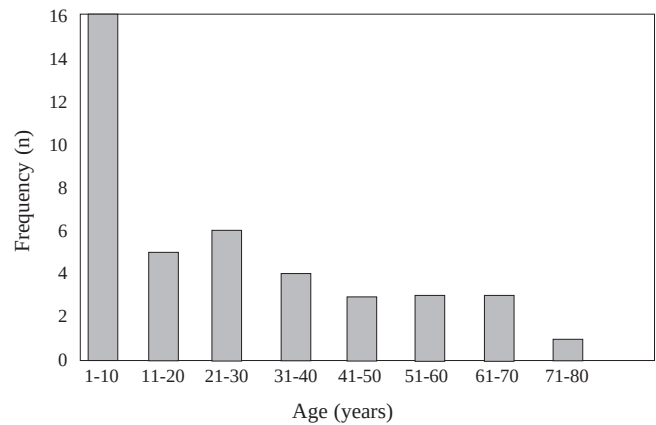


Fig. 1. Frequency of GA in various age groups.

There were no cases of subcutaneous GA in our series. There was no significant difference in age or sex between the patients with localised and generalised lesions ($P > 0.05$, using 2-tailed Fisher's exact probability test).

All areas of the body can be affected by GA, but hands, arms, feet, lower legs and the trunk were the most commonly affected sites. In localised GA, the arms and the hands were the 2 most commonly affected sites. The 2 cases of disseminated GA involved the limbs. All cases of generalised GA had involvement of the chest, abdomen and back. The patient with perforating GA had pigmented and ulcerated papules affecting the buttocks and thighs.

Most lesions were asymptomatic; the only common

TABLE I: CLINICAL CHARACTERISTICS OF GRANULOMA ANNULARE

Type of granuloma annulare	n	M:F	Mean age of onset (y)	Precipitating factors	Resolution after 12 months of follow up	Associated disease	Affected sites
Localised	34	11:23	23.5	Insect bites (4/34 cases)	23/34	Atopy-4 Diabetes mellitus-2 Hyperlipidaemia-2 Hypertension-2 Pulmonary tuberculosis-1	Ear-1 Arms-12 Hands-7 Chest-2 Abdomen-4 Back-2 Thighs-2 Calf-2 Foot-2
Disseminated	2	1:1	29.5	Nil	Nil	Diabetes mellitus-1	Arms-1 Thighs-1 Calf-1
Generalised	4	3:1	44.3	?Preceding kidney donation (¼)	Nil	Diabetes mellitus-2 Hyperlipidaemia-2 Hypertension-1	Arms-2 Chest-4 Abdomen-4 Back-4 Thighs-2 Calf-1
Perforating	1	1:0	39	Nil	Nil	Diabetes mellitus	Buttocks and thighs

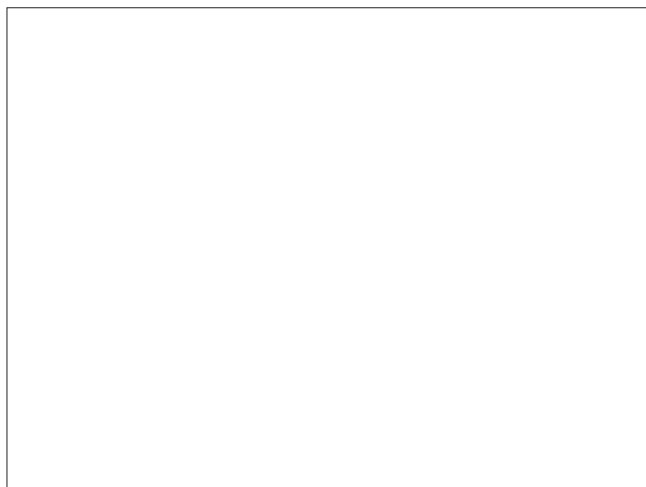


Fig. 2. Localised GA on the external ear showing papules in a ring-like fashion.



Fig. 4. Generalised GA presenting as confluent papules and plaques over the back.

symptom was itch, seen in 2 of the 4 patients with generalised GA and 3 patients with localised GA. The patient with perforating GA was the only one who complained of pain.

The majority of patients could not identify any precipitating factor. Four (11.8%) patients with localised GA gave a history of a preceding insect bite to the affected site. Three of the 4 patients with generalised GA could not identify any precipitating factors, but 1 patient developed generalised GA 4 months after he donated a kidney in a living-related renal transplant. No other factors such as drugs, other forms of physical trauma or preceding systemic illness were identified.



Fig. 3. Close-up of lesions of disseminated GA on the leg.



Fig. 5. Lesions of perforating GA on the buttocks and thighs.

Remissions and Recurrences

All patients had a minimum follow-up period of at least 12 months. The duration of disease before consulting a doctor ranged from 2 weeks to 1 year, with patients having the lesions of GA for an average of 3 months before

consulting a physician. Twenty-three (67.6%) patients with localised GA were documented to have remission after 1 year of follow-up; the average duration of disease was 10 months. Of these 23 patients, 3 subsequently had a recurrence of GA lesions after remission of previous disease (relapse rate of 13%). Of these 3 cases, 2 patients experienced a relapse over the same anatomical site (hands) whilst 1 patient who had localised GA over the foot subsequently developed a new lesion over the forearm. These relapses took an average of 7 months to occur. All remissions occurred only in the localised forms of GA. At the time of this report, 10 patients (29.4%) were still having active disease, while the rest had defaulted follow-up. None of the 4 patients with generalised GA has had a complete remission after a follow-up period ranging from 12 months to 48 months and remain on follow-up. The patient with perforating GA was followed up for 14 months and was still having clinically active lesions when he defaulted follow-up.

Associated Conditions

Among the 34 patients with localised GA, there were 2 patients (5.9%) with diabetes mellitus, 2 (5.9%) with hypertension, 1 (2.9%) with pulmonary tuberculosis, 4 (11.8%) with a history of atopy and 2 (5.9%) with hypercholesterolaemia. Of the 4 patients with generalised GA, there were 2 (50%) patients with diabetes mellitus, 2 (50%) patients with hyperlipidaemia and 1 (25%) patient with hypertension. There were no other associated diseases noted. There was 1 patient with diabetes mellitus among the 2 patients with disseminated GA. The sole patient with perforating GA also had diabetes mellitus. Diabetes mellitus was thus the commonest associated medical condition seen among the patients with GA (6 out of 41 cases or 14.6%).

Treatment of GA

Of the 34 patients with localised GA, 31 (91.2%) received treatment with topical steroids. This was the most commonly used treatment modality. Two (5.9%) patients received treatment with intralesional corticosteroid injections.

All 6 patients with disseminated and generalised GA received treatment with topical steroids. Three of the 4 patients with generalised GA were given a trial of pentoxifylline ranging from 1 month to 6 months. One patient reported a significant reduction, but not clearance, of the extent of involvement, while the other 2 patients reported no significant improvement. One patient with generalised GA was given a course of photochemotherapy with PUVA but requested to stop the treatment after 15 sessions, as he did not improve. Two patients were given short courses of prednisolone. The patient with perforating GA was treated with courses of systemic and topical

antibiotics as well as topical corticosteroids and analgesics and antihistamines for symptomatic relief.

Discussion

Based on the histologic evidence of lymphocytic involvement and the presence of various cytokines and cellular products in lesions of GA, there have been several hypotheses as to its pathogenesis. Degenerative foci in GA lesions usually demonstrate incomplete collagen degeneration surrounded by palisading inflammatory cells. Affected areas demonstrate granulomatous inflammation and collagen alterations in the dermis of the affected site. The collagen appears both degenerated and fibrotic and is termed necrobiotic.

The various postulated mechanisms include:

- i) primary necrobiosis, induced by trauma—there have been reports implicating insect bites,² post-tuberculin skin tests³ and physical trauma;⁴
- ii) the release of lysosomal enzymes such as nonspecific esterase, acid phosphatase and lysozyme from tissue histiocytes;⁵
- iii) a vasculitis affecting dermal vessels, leading to necrotising changes;⁶ and
- iv) a type IV lymphocyte mediated delayed hypersensitivity reaction causing degenerative changes.⁷

A complex interaction of hypersensitivity mechanisms together may play the central role in the pathologic changes of GA, rather than any one single process;⁸ there have also been association with lymphoproliferative diseases.^{9,10} However, much is still unknown with regards to the initiating antigenic stimulus or stimuli.

The findings of our local study broadly agree with several overseas studies regarding the higher incidence in females and the distribution of the lesions, as well as the propensity for the majority of lesions (65.1%) to occur in the first three decades of life, in particular the paediatric age group.^{2,5,11} The majority of GA lesions are localised, and remission is seen in two-thirds of the cases followed up, with an average duration of disease of 10 months. The question of whether an association between GA and other internal diseases has been a matter of debate for many years. Diabetes mellitus is the most frequently reported disease association, but this linkage remains controversial. Some investigators suggest a relationship of generalised GA to a latent or clinically manifest GA,^{1,3,4} while others provide no evidence of such an association.^{12,13} There were 6 patients with diabetes mellitus in our series; the association was higher in patients with generalised and disseminated GA. However, as this was a retrospective study, not all patients were tested for diabetes mellitus and the question of whether some cases of latent diabetes were missed and whether the disease might manifest itself later on remains

unanswered. It would be a reasonable approach to screen for diabetes in patients with generalised GA. The causes for GA remain unclear. It is evident that localised GA has a different prognosis from the generalised form. A large number of treatment options for management of GA are available; these include the use of steroids (intralesional triamcinolone, topical and oral steroids), destructive methods such as cryotherapy, laser and surgical excision, and systemic drugs.

Generalised GA is a chronic granulomatous skin disease for which no good treatment exists, although there have been reports on success with agents such as systemic corticosteroids,¹⁴ chloroquine,¹⁵ potassium iodide,¹⁶ niacinamide,¹⁷ and chlorpropamide.⁴ Patients with generalised GA in our series have not experienced remission (longest follow-up period, 5 years) of disease despite systemic therapy including pentoxifylline, photochemotherapy and topical corticosteroids. Data from a large series of patients with generalised GA by Dabski and Winkelmann¹ showed that at least 25% of the patients in their series had disease that lasted 5 or more years. As long as the cause for this clinical entity remains elusive, the search for an effective means of treating it is likely to be difficult. There was a single case of perforating GA in our series. Perforating GA may resemble other conditions such as perforating folliculitis, annular lichen planus or rheumatoid nodules. They can present with pustular-like lesions as well as papular, umbilicated, and crusted lesions. It is a very rare disease, and mechanisms leading to perforation are unknown.¹⁸

In summary, GA is a disease that can present in several forms, on any part of the body. The different clinical manifestations have characteristics particular to each. There remains no confirmed aetiology or disease association.

REFERENCES

1. Dabski K, Winkelmann R K. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. *J Am Acad Dermatol* 1989; 20:39-47.
2. Andersen B L, Verdich J. Granuloma annulare and diabetes mellitus. *Clin Exp Dermatol* 1979; 4:31-7.
3. Binazzi M, Simonetti V. Granuloma annulare, necrobiosis lipoidica and diabetic disease. *Int J Dermatol* 1988; 27:576-9.
4. Haim S, Friedman-Birnbaum R, Shafrir A. Generalized granuloma annulare: relationship to diabetes mellitus as revealed in 8 cases. *Br J Dermatol* 1970; 83:302-5.
5. Muhlemann M F, Williams D R R. Localized granuloma annulare is associated with insulin-dependent diabetes mellitus. *Br J Dermatol* 1984; 111:325-9.
6. Huerter C J, Bass J, Bergfeld W F, Tubbs R R. Perforating granuloma annulare in a patient with acquired immunodeficiency syndrome. *Arch Dermatol* 1987; 123:1217-20.
7. McGregor J M, McGibbon D H. Disseminated granuloma annulare as a presentation of acquired immunodeficiency syndrome. *Clin Exp Dermatol* 1992; 17:60-2.
8. Nevo S, Drakos P, Goldenhersh M A, Zlotogorski A, Or R, Naparstek E, et al. Generalized granuloma annulare post autologous bone marrow transplantation in a Hodgkin's disease patient. *Bone Marrow Transplant* 1994; 14:631-3.
9. Barksdale S K, Perniciaro C, Halling K C, Strickler J G. Granuloma annulare in patients with malignant lymphoma: clinicopathologic study of thirteen new cases. *J Am Acad Dermatol* 1994; 31:42-8.
10. Schwartz R A, Ronald M P H, Lynch P J. Hodgkin's disease and granuloma annulare. *Arch Dermatol* 1981; 117:185-6.
11. Atuder E M, Calza A M, Saurat J H. Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. *Dermatology* 1996; 193:364-8.
12. Dicken C H, Carrington S G, Winkelmann R K. Generalized granuloma annulare. *Arch Dermatol* 1969; 99:556-63.
13. Cannon T F, Lynch P J. Absence of carbohydrate intolerance in granuloma annulare. *J Am Acad Dermatol* 1994; 30:662-3.
14. Takigawa M, Aoshima T. Generalized granuloma annulare in a 15-month-old infant. *Dermatologica* 1976; 153:202-6.
15. Mandel E H. Disseminated granuloma annulare: report of a case treated with chloroquine phosphate (Aralen). *Arch Dermatol* 1959; 79:352-3.
16. Giessel M, Graves K, Kalivas J. Treatment of disseminated granuloma annulare with potassium iodide [letter]. *Arch Dermatol* 1979; 115: 639-40.
17. Ma A, Medenica M. Response of generalized granuloma annulare to high-dose niacinamide. *Arch Dermatol* 1983; 119:836-9.
18. Penas P F, Jones-Caballero M, Fraga J, Sanchez-Perez J, Garcia-Diez A. Perforating granuloma annulare. *Int J Dermatol* 1997; 36:340-8.