

**Granuloma annulare: review of cases in the Social  
Hygiene Service and a case-control study of its  
association with diabetes mellitus**

**Dissertation for exit assessment of higher physician training,  
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## Abbreviations used in text

CI	Confidence interval
CR	Complete remission
DM	Diabetes mellitus
FBS	Fasting blood sugar
HLA	Human leucocyte antigen
IFG	Impaired fasting glucose
IFN- $\gamma$	Interferon- $\gamma$
GA	Granuloma annulare
OGTT	Oral glucose tolerance test
PUVA	Psoralen plus ultraviolet A
SD	Standard deviation
TIMP	Tissue inhibitor of metalloproteinases



## Abstract

The study included thirty-one granuloma annulare (GA) cases. Male to female ratio was 1.82:1. Age of onset was distributed bimodally in both sexes, with a median age of onset of 45 in male and 61 in female. 38.7% had onset of disease in the first three decades. Localized, generalized, perforating and subcutaneous GA accounted for 67.8%, 25.8%, 3.2% and 3.2% of cases respectively. They were mostly found on distal extremities (excluding palms and soles). A predominantly annular morphology was the commonest (48.4%). In most cases, symptoms were absent (77.4%) and no precipitating factors could be identified (90.3%). Over 80% of GA cases were followed up for more than two years. Three localized GA resolved within one month after skin biopsy. Complete remission (CR) was achieved in 17 GA cases by either topical steroid alone (16 cases) or together with intralesional steroid (one case). Another generalized GA had CR after six months of oral isotretinoin. Dapsone was tried in one case but failed and CR was finally achieved after topical and intralesional steroid. Seven cases had persistent disease after topical steroid. The median time for first remission for localized and generalized GA were 39 months and 54 months respectively, but the difference was not statistically significant. Age, sex and DM status did not affect duration of disease. 33.3% of remitted cases had disease recurrence after a median time of 9.5 months.

Pre-existing diabetes mellitus (DM) was present in four cases before GA (median three years), DM occurred after GA in three cases (median five years) and impaired fasting glucose was detected 2.5 years after GA in one case. Twenty two GA cases, with enough age and sex matched controls in a 1 to 3 ratio, were used in a case-control study on the association of GA with DM and the result was not statistically significant.

*Keywords: granuloma annulare, diabetes mellitus, case-control study*

## **Chapter 1: Introduction**

Granuloma annulare (GA) is a degenerative disease of the skin, characterized by focal degeneration of collagen with surrounding areas of reactive inflammation and fibrosis.<sup>1</sup> The lesion of GA was first described by Colcott Fox in 1895 and was named by Radcliffe-Crocker in 1902.<sup>2</sup> There are several clinical manifestations, ranging from localized GA, which is the most common form, to less commonly seen variants, including generalized, subcutaneous and perforating GA.<sup>3,4,5</sup>

Etiology and pathogenesis of GA remains unknown and speculative. The relationship between GA and diabetes mellitus (DM) has been extensively studied. There is controversy over such an association, with some studies indicate a relationship<sup>6,7,8,9,10,11,12,13</sup> while others refute the linkage.<sup>14,15</sup> Some studies have shown relationship of DM with generalized GA,<sup>7,9</sup> whereas others have detected its association with localized GA<sup>10</sup> (Table 1). These studies, albeit with different conclusions, are not directly comparable to one another. Their differences can be broadly classified into the following categories:

- 1) Choice of GA cases: Different studies have variable proportions of GA subtypes. Moreover, not all GA cases are biopsy proven. Clear diagnostic criteria for GA have never been given.
- 2) Choice of controls: Controls are preferably matched in terms of age, sex and race, as these variables may affect the prevalence of DM. They should also be free of skin diseases that are related to DM.
- 3) Choice of measures for carbohydrate intolerance: The different methods include fasting blood sugar (FBS),<sup>7,9</sup> oral glucose tolerance test (OGTT),<sup>7,8,11</sup> haemoglobin A1c,<sup>14</sup> cortisone-glucose tolerance test,<sup>6,7,8,9</sup> insulin-glucose curve,<sup>8</sup> intravenous glucose tolerance test,<sup>7,9,11</sup> tolbutamide test<sup>9</sup> and postal questionnaire to attending general practitioner.<sup>10</sup> As different diagnostic criteria have been used, some authors prefer the term carbohydrate intolerance instead of DM.<sup>9</sup>

A retrospective study on GA has been carried out in the Social Hygiene Service of the Department of Health. The service comprises clinics covering the major territories of Hong Kong Special Administrative Region and is the major public centre receiving referrals for dermatological problems and sexually transmitted disease. The aims of the study are to review the clinical features of GA in our local population and to explore whether there is any association of GA with DM by a case-control study.

**Table 1. Summary of published articles on the relationship between GA and DM**

Source	Case	Control	Measures of diabetic state	Results
Rhodes EL, et al 1966 <sup>6</sup>	30 nondiabetic GA patients, not mentioned percentage of localized GA versus generalized GA, all were biopsy proven	15 hospital patients and staff of same age group, no family history of DM, recent infection, surgery or treatment with drugs that might alter carbohydrate metabolism	50 gm OGTT, prednisone glycosuria test	10 GA patients showed abnormal rise in glucose excretion in the prednisone glycosuria test, 2 of which also had abnormal glucose tolerance; whereas no abnormal values were obtained in controls of a similar age group
Haim S, et al 1970 <sup>7</sup>	8 generalized GA cases, all were skin biopsy proven	Nil	For nondiabetic cases, FBS was determined. For cases with normal FBS, oral or intravenous glucose tolerance tests were performed. If above tests all normal, prednisone glucose tolerance test was used	For the first patient, FBS was normal, but other tests were not carried out. 3 cases had DM before GA. For the remaining 4 cases, 2 had abnormal glucose tolerance test, another 2 had normal glucose tolerance test but pathological prednisone glucose tolerance test
Hammond R, et al 1972 <sup>8</sup>	10 nondiabetic adults with GA: 9 localized, 1 generalized; all were verified by skin biopsy; age 22 to 28	Normal adults, matching criteria and number of controls were not mentioned; age 20-62; all were subsequently normal on both OGTT and cortisone-glucose tolerance test	OGTT; cortisone-glucose tolerance test; Insulin to glucose ratio	OGTT: abnormal in 2 GA; Cortisone-glucose tolerance test: abnormal in another 3 GA, 1 GA borderline; Insulin to glucose ratio: lowered insulin response in remaining 4 GA; results suggested a decreased pancreatic beta cell sensitivity to glucose stimulation in GA
Haim S, et al 1973 <sup>9</sup>	52 GA cases: 39 localized, 13 generalized, all were proven by skin biopsy	2 control groups: 1) Same number of patients with other skin diseases unrelated to DM 2) 386 patients with conjunctival aneurysms in another medical centre	FBS for known DM; Prednisone-glucose tolerance test for non-diabetics; For borderline cases on prednisone- glucose tolerance test, intravenous glucose tolerance test and insulinogenic reserve by tolbutamide test were also determined	Carbohydrate intolerance in controls =23%, in conjunctival aneurysms controls= 11.67%, in generalized GA= 76.9%, in localized GA=23.1%. Incidence of carbohydrate intolerance was similar to controls in localized GA, but was higher than controls in generalized GA.
Muhlemann MF, et al 1984 <sup>10</sup>	557 GA cases: 511 localized, 38 generalized, 8 with insufficient information for classification; only 10% was skin biopsy proven	Age-matched population data on diabetic prevalence, one in Denmark, one in England	Questionnaire to patient's general practitioner on diabetic status	24 cases of DM were identified (18 type 1 DM, 6 type 2 DM); in all but one case DM was associated with localized GA; GA was associated with type 1 DM, no analysis was performed for type 2 DM

**Table 1 (continued). Summary of published articles on the relationship between GA and DM**

Source	Case	Control	Measures of diabetic state	Results
Kidd GS, et al 1985 <sup>11</sup>	21 GA cases, all biopsy confirmed, 3 disseminated, 1 perforating, 17 localized. Only 15 patients were included in formal study; 4 known DM patients and 2 obese patients were excluded	14 weight- and aged-matched controls, all were healthy and not on any medications	100 gm OGTT and 25 gm intravenous glucose tolerance test	OGTT: fasting plasma glucose, 2 hour glucose, 1 hour serum insulin, area glucose curve and area insulin curve were significantly higher in GA patients. Intravenous glucose tolerance test: fasting plasma glucose and area glucose curve were higher in GA patients. Results showed higher glucose value in association with higher insulin level, suggesting insulin resistance
Shimizu H, et al 1995 <sup>12</sup>	Literature review of 23 perforating GA cases; arbitrarily divided into 2 types: papular perforating type and ulcerative perforating type	Nil	Not stated in article, just mentioned whether DM was present or not	Overall 30% of reported perforating GA had DM. For those cases with DM, 86% had ulcerative lesions and 14% had papular perforating lesions. Authors concluded that DM played a role in the ulcerative perforating GA
Veraldi S, et al 1997 <sup>13</sup>	61 GA cases: 35 localized, 26 generalized, all were proven by skin biopsy	126 age- and sex-matched patients with different inflammatory skin diseases admitted to hospital	Plasma glucose, glucose tolerance test	Overall DM rate in all GA cases was not significantly different from controls. Subgroup analysis: type 1 DM was associated with GA, whereas type 2 DM was not associated with GA.
Gannon TF, et al 1994 <sup>14</sup>	23 GA cases: 13 localized, 10 generalized; all were proven by skin biopsy	No control was recruited because all GA cases had normal fasting plasma glucose and haemoglobin A1c	Fasting plasma glucose and haemoglobin A1c	Carbohydrate intolerance was absent in localized and generalized GA cases.
Nebesio CL, et al 2002 <sup>15</sup>	126 GA cases identified (only 18% biopsy proven), cases below 10 years old were excluded for lack of control, cases not seen by dermatologist were also excluded. 50 GA cases were finally recruited	50 psoriasis patients who were matched by age, sex and race	Blood glucose measurements, haemoglobin A1c, classification of DM as reported by care providers	No Type 1DM identified in GA cases. 22% of GA cases had type 2 DM, which was not significantly different from controls (20%).

## **Chapter 2: Methodology**

### **A) Identification and definition of GA cases**

The study was carried out in the Social Hygiene Service and was approved by the Ethics Committee of the Department of Health. The skin biopsy records of the following clinics were scrutinized manually from 1<sup>st</sup> January 1990 to 31<sup>st</sup> July 2002 and results with keywords 'granuloma annulare' were identified:

Chai Wan Social Hygiene Clinic  
Cheung Sha Wan Dermatological Clinic  
Lek Yuen Social Hygiene Clinic  
Sai Ying Pun Dermatological Clinic  
South Kwai Chung Social Hygiene Clinic  
Tuen Mun Social Hygiene Clinic  
Wan Chai Social Hygiene Clinic  
Yau Ma Tei Dermatological Clinic  
Yung Fung Shee Dermatological Clinic

The clinical records, pathology reports and clinical photographs were assessed to see whether cases met the diagnostic criteria of GA in this study (Table 2, p.5). The clinical study only included those cases meeting the diagnostic criteria of GA, had retrievable clinical record and were able to attend a personal interview or telephone interview with the author.

### **B) Interview with GA cases**

Details of GA and response to treatment were recorded in the patient data sheet during the interview (Appendix 1). Physical examination was performed for cases who were personally interviewed. For cases not having DM, FBS was arranged. A total of 83 cases of GA were identified. Only 31 cases were included in the present study (table 3).

**Table 3. Total number of GA cases identified and recruited into this study**

	<b>Number of cases</b>
GA identified by biopsy record	83
Record lost/ not retrievable	23
Histology suggestive of GA, but not confirmed clinically	2
Histology suggestive of GA, but rejected after subsequent biopsies	2
Case rejected after assessment with pathologist because histological criteria were not met	2
Failure to contact cases	18
Cases who refused to join the study	5
Cases personally interviewed	<b>29</b>
Cases interviewed over phone only	<b>2</b>

**Table 2. Diagnostic criteria of GA employed in the present study**

1. Clinically in typical GA, skin lesions are characterized by both:
  - a) skin-coloured, erythematous to violaceous dermal papules that may be solitary or arranged in an arciform and circular pattern. In circular form, the central surface may be slightly hyperpigmented;

**and**

  - b) lack of epidermal change

or in case of atypical forms of GA:

  - i) Subcutaneous GA- skin coloured subcutaneous nodule that may be solitary or multiple
  - ii) Perforating GA- skin-coloured to erythematous papules that may have central crust, umbilication, or pustular lesions that may exude creamy or clear discharge
2. Histologically, presence of **all** of the following features:
  - a) necrobiosis of collagen
  - b) a predominantly histiocytic infiltrate that can be arranged in a palisading, interstitial or sarcoidal pattern
  - c) mucin deposition which appears as basophilic stringy material between collagen bundles
  - d) lack of epidermal change except in perforating GA which may have minor epidermal thinning and parakeratosis as early features to complete perforation and extrusion of the necrobiotic material

Cases must fulfill the clinical criteria 1 (a) and (b), or in case of atypical GA, 1(i) or 1(ii) and all four histological criteria in order to be recruited into the study

### **C) Histopathology slide review**

The pathological features of skin biopsies of GA cases were reviewed with the generous help and supervision from four senior pathologists: Drs Lam Wing Yin (Tuen Mun Hospital), Lee Kam Cheong (Princess Margaret Hospital), Lee King Chung (Queen Elizabeth Hospital) and Yau Ko Chiu (Pathology Institute, Department of Health).

## **D) Recruitment of controls**

All GA cases and controls were Chinese. Controls were matched according to age (+/-3 years), sex and clinic. They were the first three age- and sex- matched dermatology patients in the individual clinic without the exclusion criteria listed in table 4 starting from 4<sup>th</sup> February 2003. These criteria were set to exclude dermatological diseases associated with DM.<sup>16</sup> If they refused to participate, family history of DM was noted. The matching would continue until a 3:1 control to case ratio was achieved. Data collected from controls included sex, year of birth, family history of DM and DM status (Appendix 2). If the control did not have DM, FBS was arranged.

**Table 4. Exclusion criteria for controls**

1) On systemic steroid in the recent one month	
<b>or</b>	
2) Having or being suspected to have the following skin diseases:	
a) Granuloma annulare	h) Acanthosis nigricans
b) Necrobiosis lipoidica diabetorum	i) Neuropathic/arterial ulcers
c) Diabetic dermopathy	j) Gangrene of extremities
d) Diabetic finger pebbles	k) Insulin induced lipoatrophy
e) Scleroedema of Busckhe	l) Insulin induced lipohypertrophy
f) Eruptive xanthoma	m) Drug eruptions secondary to hypoglycaemic agents
g) Reactive perforating collagenosis	

## **E) Choice of FBS as a measure for DM**

### **1) Reasons for using FBS**

The present study employed the diagnostic criteria proposed by the American Diabetes Association (1997).<sup>17</sup> It recommended that for epidemiological studies, estimation of DM prevalence should be based on FBS. This was made in the interest of standardization and also to facilitate fieldwork, particularly where OGTT was difficult to perform and cost and demands on subjects' time might be excessive. Besides its simplicity, FBS had less variability and was more reproducible than the 2-hour value of OGTT.<sup>17</sup> The World Health Organization also recommended that for epidemiological purposes, either FBS or 2-hour value after 75gm oral glucose might be used alone.<sup>18</sup> As a number of the GA cases were children and to facilitate the recruitment of controls, FBS was used alone. On the basis of FBS, patients were categorized into the following groups:

**Table 5. Values for diagnosis of DM and impaired fasting glucose<sup>17</sup>**

Category	Fasting plasma glucose (mmol/l)
Normal	<6.1
Impaired fasting glucose	≥ 6.1 and < 7.0
Diabetes mellitus	≥ 7.0

## 2) Limitations of using FBS alone

Despite its convenience, the use of FBS alone would lead to a slightly lower estimate of DM prevalence than the use of both FBS and 2-hour post value of 75gm OGTT. In a local population-based study involving 2900 Chinese aged 25 to 74 years using 75 gm OGTT,<sup>19</sup> the prevalence of DM was 6.2% and 9.8% based on the American Diabetes Association (1997) criteria<sup>17</sup> and World Health Organization (1998) criteria<sup>18</sup> respectively. The association of DM and GA was assessed by odds ratio. If we assumed a similar proportion of DM was missed in both case and control by using FBS alone, the final result, in terms of a fraction, would not be severely affected.

## 3) Problem of diagnostic bias

In order to reduce diagnostic bias, which meant more frequent testing of DM in GA cases would lead to more frequent detection of DM, the first FBS ever taken in our clinic was chosen for comparison with the controls. Moreover, age of control was matched with age of case when the first FBS was taken. If a case had pre-existing DM, the age of matching would be the time he had GA.

## 4) Reasons for not using other sensitive measures for carbohydrate intolerance

The diagnosis of DM by FBS or by 2-hour post value of 75 gm OGTT is not arbitrary. The prevalence of microvascular complications (retinopathy and nephropathy) and macrovascular complication (fatal coronary heart disease) increases dramatically at the chosen cutoff point for diagnosis of DM.<sup>17</sup> Although steroid glucose tolerance test, insulin secretion in response to glucose load and intravenous glucose tolerance test may have a greater sensitivity in detecting carbohydrate intolerance, the risk of subsequent development of DM is not known and population data are lacking in how these tests can predict future vascular complications. Hemoglobin A1c is not recommended for diagnosis of DM as there are different assays for glycosylated hemoglobin and further standardization is pending.<sup>17</sup>

Impaired fasting glucose (IFG) is a recently introduced entity. Data on cardiovascular risk of impaired glucose tolerance are mixed. Most people with impaired glucose tolerance do not progress to DM and many may revert to normal.<sup>20</sup> It is



suggested that when impaired glucose tolerance is combined with DM to produce a category of total glucose intolerance, an exaggerated prevalence will be obtained.<sup>20</sup> The same is probably true for IFG. Therefore the present study only compares prevalence of DM in the cases and controls, without inclusion of IFG.

All cases and controls with abnormal FBS were referred to the general outpatient clinic or specialist clinic for follow up.

### **E) Statistics**

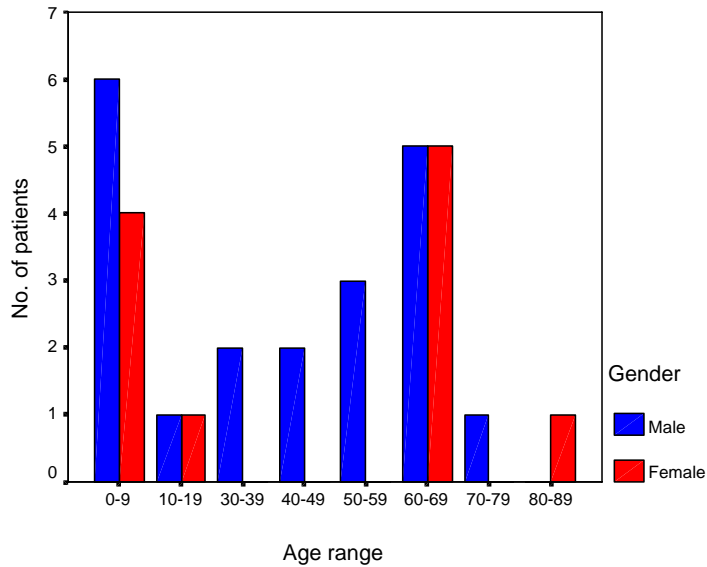
Mann-Whitney test was used for comparing continuous variables between groups. Chi-square test or Fisher's exact test was used for comparing proportions between groups. Binomial test was employed to test significance of sex ratio. Ages of cases and controls were compared by t-test. Mantel-Haenszel test was used for testing association of GA and DM across age-defined strata. Logistic regression was used to find predictors for DM. Remission data was documented by Kaplan-Meier survival curves with comparison between curves made by Breslow test. All calculations were made by using SPSS 10.0.

## **Chapter 3: Results**

## A) Demographic data

Average incidence of GA from 1990 to July 2002 was 0.81 per 10,000 new cases seen. Age of onset ranged from 2 to 81 with a median of 46 and an interquartile range of 60. As evident from figure 1, the age of onset in both male and female patients were distributed bimodally. 38.7% of cases had onset of GA in the first 3 decades.

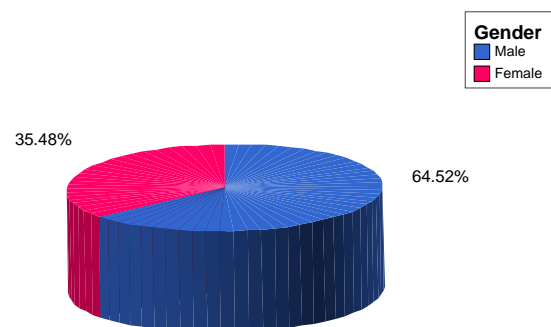
**Figure 1. Age of onset of GA in different sex**



**Table 6. Age of onset of GA in relationship with gender**

Sex	Age of onset		
	Median	Interquartile range	Mean
Male	45	55.8	37.0
Female	61	62.0	38.5
Both	46	60.0	37.5

**Figure 2. Sex distribution of GA cases**



Twenty males were affected as compared with eleven females, giving a male to female ratio of 1.82:1 (figure 2). Although there was a tendency of more male cases, the binomial test was not significant ( $p=0.15$ ). The median age of onset of GA was 45 in male and 61 in female (table 6), which were not significantly different (Mann-Whitney test,  $p=0.664$ ).

## **B) Clinical features**

The clinical features were documented during the interview for 16 cases (51.6%) with active disease. For the other 15 remitted cases (48.4%), morphology of lesions was obtained by history, clinical record and photo review. The latter group included two cases (patient no. 15 and 26) who were interviewed by phone.

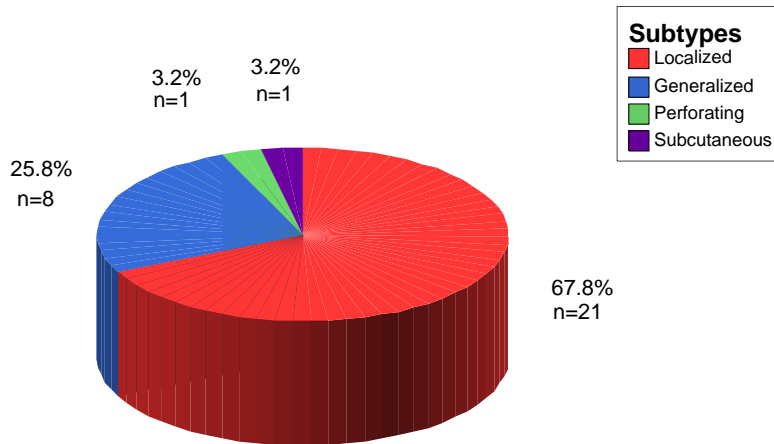
### **1) Classification of subtypes of GA**

Cases were classified according to table 7 and the percentages of various subtypes were shown in figure 3 (p.11). The commonest form was localized GA, accounting for 67.8%. 25.8% of cases had generalized GA. Perforating and subcutaneous subtypes each accounted for 3.2%.

**Table 7. Classification of subtypes of GA in this study**

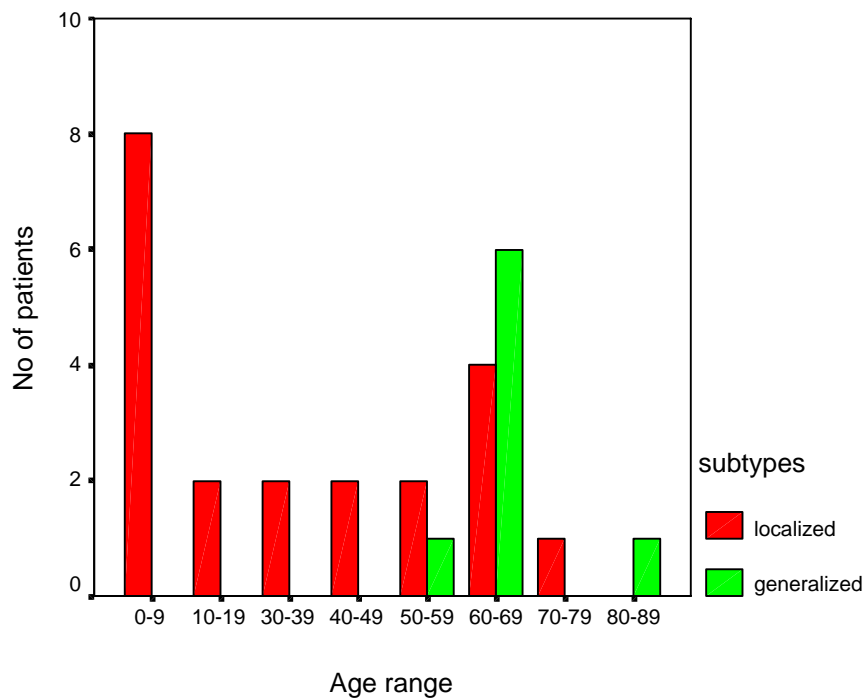
<p>1. Localized GA Cases of localized GA have single or multiple lesions that are confined to one or few anatomical areas. When more than one anatomical areas are affected, the trunk is spared.</p> <p>2. Generalized GA Generalized GA cases have extensive lesions affecting at least the trunk and either upper or lower or both extremities.</p> <p>3. Perforating GA Perforating GA is characterized clinically by umbilicated, crusted or pustular papules. Histological evidence of epithelial thinning, parakeratosis and/ or perforation with extrusion of necrobiotic material is present.</p> <p>4. Subcutaneous GA This variant is characterized clinically by subcutaneous nodule(s). Histologically, the necrobiotic granuloma involves the subcutaneous layer with/without extension to the adjacent dermis.</p>
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**Figure 3. Distribution of various GA subtypes**



The age of onset in localized GA was significantly lower than that in the generalized variant (figure 4, Mann-Whitney test,  $p=0.003$ ). However, there was no relationship between gender and subtypes of GA (Fisher's exact test,  $p=1.0$ ).

**Figure 4. Age of onset of GA in localized and generalized subtypes**



## 2) Distribution

**Table 8. Distribution of skin lesions in various subtypes of GA**

Region	Number of patients affected in various subtypes				Total
	Localized	Generalized	Perforating	Subcutaneous	
<b>Upper Limb</b>					
Arms	2	6	-	-	8
Elbows	8	4	-	1	13
Forearms	9	7	-	-	16
Wrists	4	4	-	-	8
Hand Dorsum	7	5	1	-	13
Palms	-	1	-	-	1
Fingers	2	-	-	-	2
Subtotal					61
<b>Lower Limb</b>					
Buttocks	2	2	-	-	4
Thighs	3	5	-	-	8
Knees	1	2	-	-	3
Calves/shins	4	3	-	1	8
Ankles	3	2	-	-	5
Foot Dorsum	4	2	-	1	7
Soles	-	-	-	-	0
Toes	-	-	-	-	0
Subtotal					35
<b>Trunk</b>					
Chest	-	4	-	-	4
Abdomen	-	6	-	-	6
Back	1	5	-	-	6
Genitalia	-	-	-	-	0
Subtotal					16
<b>Head and Neck</b>					
Face	-	1	-	-	1
Ear	-	-	-	-	0
Neck	1	4	1	-	6
Scalp	-	-	-	-	0
Subtotal					7

GA involved most often the upper limbs (51.3%), followed by lower limbs (29.4%), trunk (13.4%) and head and neck region (5.9%). In the upper limbs, GA commonly involved elbows and areas distal to them. Palms and fingers were rarely involved. In the lower limbs, a similar pattern was observed with most lesions located over knees and areas distal to them. Soles, toes, scalp, ears and genitalia were not affected in this series of patients. In generalized GA, lesions could be present on the chest wall, abdomen and back but the number of patients was too small for concluding the

preferential area of involvement. Only one patient had facial involvement and another one had palmar involvement (both cases had generalized GA).

### 3) Morphology of individual lesion (table 9)

Predominantly annular morphology was the most common (48.4%), followed by predominantly papular forms (22.6%) and mixed annular and papular forms (19.4%). Epidermal change was absent in all cases except for the only one perforating GA (patient no.9), in which the lesions occurred as tiny umbilicated papules over the hand dorsum and neck. Subcutaneous GA (patient no. 30) presented as deep nodules over left elbow, shin and foot dorsum. One patient described the lesions were in the form of plaque from coalescing papules without central clearing.

**Table 9. Morphology of GA lesions**

Morphology	Distribution of GA		Total no.	%
	Localized	Generalized		
Predominantly annular	10	5	15	48.4
Predominantly papular	7	-	7	22.6
Mixed annular and papular	4	2	6	19.4
Perforating papules	1	-	1	3.2
Subcutaneous nodules	1	-	1	3.2
Plaque	-	1	1	3.2
Total	23	8	31	100

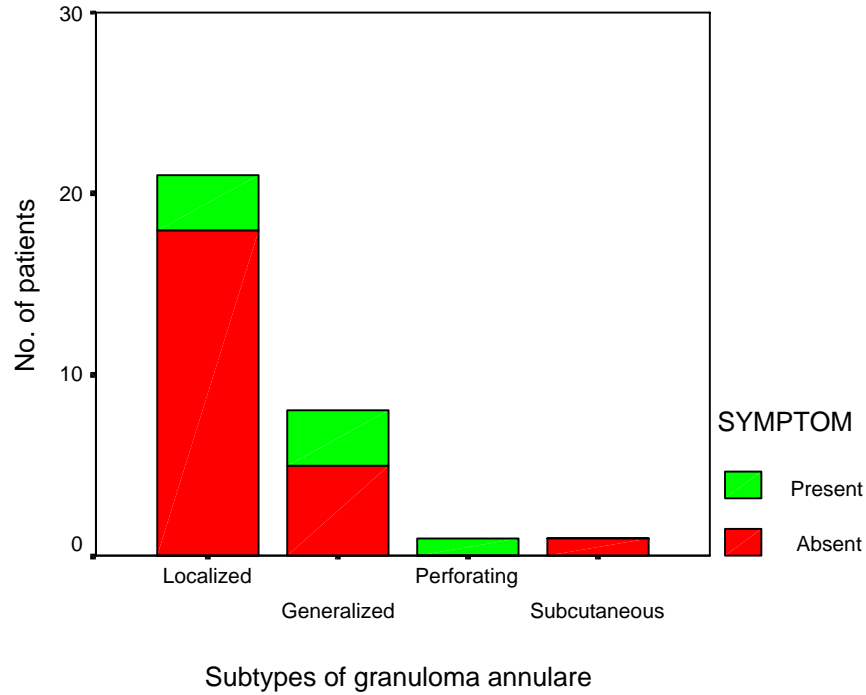
### 4) Number of skin lesions

Two localized GA cases had solitary lesion (6.5%). Fifteen cases (48.4%) had skin lesions number equal to or less than five, including one subcutaneous case. Eight patients had generalized GA with multiple lesions, but the exact number was difficult to ascertain. For the remaining six cases (five localized and one perforating), the total number of lesions could not be remembered exactly but each case had more than 10 lesions.

### 5) Symptoms

In 24 cases, GA lesions were asymptomatic (77.4%). Pruritus was present in six cases (19.4%), including three localized GA (one had underlying eczema), two generalized GA and one perforating GA. One generalized GA patient, with lesions on the first web space of hand, complained of pain on writing secondary to pressure effect. There was no significant relationship between presence of symptoms and the subtypes of GA (figure 5, Fisher's exact test,  $p=0.31$ ).

**Figure 5. Proportion of symptomatic skin lesions in various GA subtypes**



### 6) Precipitating factors (Table 10)

In 28 cases (90.3%), no precipitating factors could be identified. One patient with localized GA over her upper limbs (patient no.7) claimed that the lesions occurred after topical herbal application and that the severity of lesions increased in summer and sun exposure. Another patient (patient no.17) with generalized GA and facial involvement reported that the skin lesions increased with sun exposure. Patient no. 15 had GA over upper and lower limbs and reported an increase in the number of skin lesions after attacks of common cold and in summer.

**Table 10. Reported precipitating factors for GA**

Precipitating factors	No. of patients	%
Sunburn	2	6.5
Drug	1	3.2
Common cold	1	3.2
Trauma	0	0
Insect bite	0	0
Weather	2	6.5
Pregnancy	0	0
Stress	0	0

### **C) Pathological features**

A total of 32 skin biopsy specimens from 31 cases were assessed together with senior pathologists. Necrobiosis, a predominantly histiocytic infiltration and mucin deposition characterized the disorder and were present in all specimens. The main histology findings were summarized in table 11. The pathological process occurred in the dermis but the subcutaneous tissue was also involved in the only subcutaneous GA case. The epidermis was normal except in the only perforating cases (patient no.9) in which necrobiotic process occurred in the superficial dermis with extrusion of the degenerated material through the epidermis. Elastophagocytosis was occasionally present and in one case (patient no.6), there was extensive loss of elastic fibres on one side of skin biopsy compatible with annular elastolytic granuloma, a variant of GA.

**Table 11. Histology findings in GA**

<b>Pathology finding</b>	<b>%</b>
Necrobiosis	100
Mucin deposition	100
Predominantly histiocytic infiltrate	100
Palisading	58.1
Interstitial	25.8
Mixed Palisading & Interstitial	16.1
Sarcoidal	0
Nuclear dust in necrobiotic areas	25.8
Prominent perivascular mononuclear infiltrate	16
DM microangiopathy	0
Vasculitis	0

### **D) Concurrent diseases**

There were no co-existing diseases in nine cases (29.0%). The other 22 cases suffered from one or more medical illnesses (table 12). There was no malignancy reported. The only patient with dermatomyositis diagnosed 20 years ago (patient no.17) did not have internal malignancy. Human immunodeficiency virus infection, although not specifically tested in each subjects, had been checked by the medical unit for decreased white cell count in one patient (patient no. 29) and the result was negative.



**Table 12. Concurrent medical illnesses reported by GA cases**

Medical diseases	No.	Medical diseases	No.
<b><u>Skin</u></b>		<b><u>Cardiovascular</u></b>	
Eczema	3	Hypertension	9
Pityriasis alba	1	Ischaemic heart disease	1
Wart	2	Alcoholic cardiomyopathy	1
Tinea pedis	2	Varicose vein	1
Drug rash	1		
<b><u>Congenital</u></b>		<b><u>Gastrointestinal</u></b>	
Down's syndrome	1	Peptic ulcer	1
Thalassaemia trait	1	Intussusception	1
Congenital heart disease	1	Gallstone	2
		Hernia	1
<b><u>Metabolic/Endocrine</u></b>		<b><u>Infective</u></b>	
Gout	1	Pulmonary TB	2
Thyrotoxicosis	1		
Renal impairment	1	<b><u>Tumour</u></b>	
Hyperlipidaemia	4	Uterine fibroid	1
		Benign sweat gland tumour	1
<b><u>Respiratory</u></b>		<b><u>Others</u></b>	
Allergic rhinitis	1	Dermatomyositis	1
Asthma	1	Osteoarthritis	1
		Idiopathic leucopenia	1

### **E) Associated DM and previous DM screen in skin clinics**

Pre-existing type 2 DM was present in five patients at the time of study. Four had DM before onset of GA with a time interval ranging from 0.5 to 6 years (median 3 years). One patient had DM 5 years after onset of GA. DM was diagnosed by FBS in all except one case. The remaining one had an OGTT. No type 1 DM was identified in GA cases.

Apart from these known diabetic cases, previous screen for DM in our clinic was present in 15 cases (57.7%, table 13). Two cases were newly diagnosed GA and hence were not previously screened for DM. Three cases had multiple screening on follow up. Patient no. 7 had two urine sugar tests, patient no. 8 had one spot sugar, three urine sugar tests and patient no. 25 had two FBS. The remaining nine cases (34.6%) had never been screened for DM in our clinics.

**Table 13. Previous screen for DM and results**

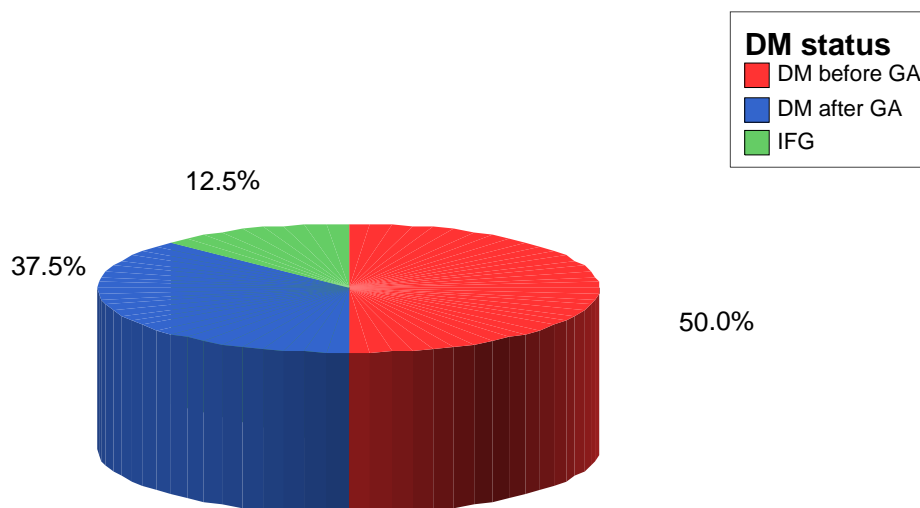
Methods	No.	Months after GA (mean)	Results
Urine sugar	8	35	All normal
FBS	7	14.4	Normal except 1 IFG
Spot sugar	5	43.8	All normal

FBS was checked in 22 cases after interviews with the author. The remaining nine cases consisted of five known DM cases, two cases that were interviewed by phone, one case that had FBS two months ago when her GA was newly diagnosed and one case that refused blood test at the time of interview but already had two FBS checked in our clinic and the results were normal. For the two cases that were interviewed by phone, one had normal spot sugar previously and one had never been screened for DM.

Of the 22 newly arranged FBS, one IFG and two DM cases were detected. All three patients were referred to the general outpatient clinic for follow up.

In summary, 7 out of 30 (23.3%) GA cases had DM (one case had never been screened for diabetes but refused to come back). Four cases developed DM before GA from 0.5 to 6 years (median 3 years) and three DM cases were detected after GA from 2 to 5.7 years (median 5 years). One case had IFG 2.5 years after GA (figure 6). DM was present in 15% and 50% of localized and generalized GA cases respectively. Although the percentage of DM was higher in generalized GA cases, they had a significantly higher age of GA onset as compared with localized GA cases. Both subcutaneous and perforating GA cases did not have DM. The time between onset of GA and the last FBS ranged from 1 to 206 months (mean 67.1 months).

**Figure 6. Type of glucose intolerance in GA cases**



## **F) Case-control study of association with DM**

The case-control study included only those cases with three matched controls found. Twenty-two cases were eligible, including thirteen localized, seven generalized, one perforating and one subcutaneous GA. The nine non-eligible cases consisted of two cases who were interviewed by phone and another seven cases without enough matched controls. The latter seven non-eligible cases did not have DM at first FBS screen. 9 out of 66 controls had family history of DM. This was not significantly different from the proportion of those who refused to participate, in which 5 out of 59 had family history of DM (chi-square test,  $p=0.36$ ).

Eight controls had pre-existing DM (all diagnosed by FBS except two by spot sugar and one by OGTT). Four new DM and two new IFG cases were found on screening. Both groups were referred for further management. The mean age of cases and controls were 52.2 (standard deviation (SD) 22.8) and 52.1 (SD 22.2) respectively, which were not significantly different (t test,  $p=0.99$ ).

The distribution of DM in cases and controls were shown in table 14. They were stratified into 3 age ranges. The ranges were chosen to reflect the prevalence of DM in a local population based survey,<sup>21</sup> which showed an age related increase in DM prevalence.

**Table 14. Distribution of DM in cases (at first FBS screen) and controls**

Age range	Group	DM		% DM	Total
		Absent	Present		
0-34	Case	5	0	0	5
	Control	17	0	0	17
35-54	Case	4	1	20	5
	Control	11	2	15.3	13
55-86	Case	7	5	41.7	12
	Control	26	10	27.8	36

Although the percentage of DM in cases seemed to be greater than that of controls, the difference was not statistically significant (Mantel-Haenszel test,  $p=0.56$ ). The Mantel-Haenszel odds ratio was 1.75 with a 95% confidence interval (CI) of 0.5 to 5.8. Logistic regression did not demonstrate presence of GA ( $p=0.36$ ) and family history of DM ( $p=0.23$ ) as significant factors in predicting DM. Subgroup comparison of localized and generalized GA with their respective controls did not reveal any significant association with DM (Mantel-Haenszel test,  $p=0.49$  for localized GA,  $p=0.83$  for generalized GA). There was no difference in family history of DM between cases and controls (Fisher's exact test,  $p=1.0$ ).

Two previous studies based on DM status (rather than sensitive tests for carbohydrate intolerance) gave a relative risk of 11.4 in one<sup>10</sup> and an odds ratio of 2.6 in another.<sup>13</sup> If we assumed a relative risk of 5, 18.2% DM prevalence in controls (12/66), case-control ratio of 1:3 and  $\alpha=0.05$ , the power of study was 88%.

### **G) Family history of GA and DM**

Family history of GA was absent in all cases. Three cases had positive family history of DM, in which two had DM themselves and one was free from DM at the time of the interview.

### **H) Duration of follow up**

The cases were followed up for a range of 14 to 206 months after the onset of GA with a mean and median of 67.5 and 68 months respectively. Over 80% of cases were followed up for more than 24 months.

### **I) Treatment (Tables 15, 16)**

**Topical steroid** (mostly of moderately potent or potent class according to the classification in Martindale<sup>22</sup>) was the most often employed treatment in this series (28 cases, 90.3%). In 16 cases, complete remission (CR) had been achieved with topical steroid alone. No treatment had been offered to three localized GA patients (patient no. 10, 21 and 24) as CR occurred within one month after skin biopsy. Six patients (patient no. 4, 9, 12, 16, 26, 27) had CR within two months after skin biopsy together with the use of topical steroids. Their GA lesions were disseminated, making it difficult to ascribe CR to biopsy alone. In patient no. 25, CR had been achieved by a combination of topical steroid and **intralesional steroid**.

Oral **dapsone** (50 mg/day) was used for five months in a paediatric patient (patient no. 30) with subcutaneous GA but no clinical response was noted. She was then treated with topical steroid and intralesional steroid for 5 courses and had first CR after 70 months. Patient no. 6 with generalized GA had persistent disease after five months of moderately potent topical steroid. Oral **isotretinoin** 0.5mg/kg/day was then given, resulting in CR after six months. Side effect of isotretinoin in this patient included mild cheilitis. The liver function and lipid profile remained normal during the treatment.

**Table 15. Response to treatment in GA cases**

<b>Treatment modality</b>	<b>No. of cases</b>
CR by skin biopsy alone	3
CR by topical steroid alone	16
CR by topical and intralesional steroid	1
CR by isotretinoin	1
PD with dapsone, CR by topical and intralesional steroid	1
PD after topical steroid	7
Newly diagnosed, just started topical steroid	2
<b>Total</b>	<b>31</b>

Abbreviations: CR: complete remission; PD: persistent disease

**Table 16. Summary of treatment modalities used in GA cases**

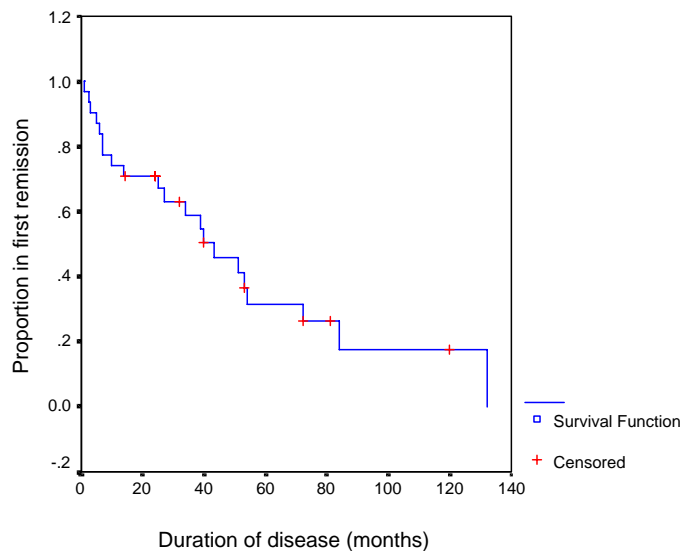
Patient no.	GA Subtype	Treatment	Duration of treatment (months)	Outcome	Recurrence
1	LGA	Potent TS	24	CR	Nil
2	LGA	Moderately potent TS	Just started	Newly diagnosed	Nil
3	LGA	Moderately potent TS	2	Defaulted, resolved after 24 months	Nil
4	LGA	Moderately potent TS	1	CR after 1 month	Nil
5	LGA	Potent TS	7	CR. Disease free for 10 months	Recurred for 10 months, put on potent TS again
7	LGA	Moderately potent TS Potent TS Potent TS	46 4 12	PD, defaulted FU 40 months PD, defaulted FU 11 months PD	Nil
8	LGA	Potent TS	20	CR	Nil
10	LGA	Nil		Subsided 1 month after biopsy	Nil
11	LGA	Potent TS	39	PD	Nil
15	LGA	Potent TS Mild TS	3 2	Defaulted FU, CR after 14 months	Nil
16	LGA	Potent TS	2	CR	Nil
18	LGA	Potent TS	Just started	Newly diagnosed	Nil
19	LGA	Potent TS	14	CR, disease free for 9 months	Recurred 1 month recently, just restarted potent TS
21	LGA	Nil		Subside 1 month after biopsy	Nil
23	LGA	Very potent TS Potent TS	6 20	CR after TS, disease free for 28 months	Recurred in recent 2 months, just restarted potent TS
24	LGA	Nil		CR 1 month after skin biopsy	Nil
26	LGA	Moderately potent TS	2	CR	Nil
27	LGA	Moderately potent TS Potent TS	1 1	CR after two months. Then had multiple recurrences and remission, patient could not remember the details. Now disease is still present	Yes, but defaulted FU, just started potent TS again
28	LGA	Potent TS	13	PD, defaulted FU. Disease is still present now	Nil
29	LGA	Potent TS	4	CR	Nil
31	LGA	Potent TS	4	Defaulted FU, PD	Nil
6	GGA	Moderately potent TS Oral isotretinoin (0.5 mg/kg/d)	5 6	PD with TS CR after 6 months of isotretinoin	Nil
12	GGA	Potent TS	2	CR	Nil
13	GGA	Moderately potent TS	5	Defaulted FU, PD all along, given TS on reassessment	Nil
14	GGA	Moderately potent TS	12	Default FU, CR after 43 months. In remission for 4 months	Recurred in recent 7 months, just started moderately potent TS
17	GGA	Potent TS	7	CR	Nil
20	GGA	Potent TS	4	PD, but defaulted FU, given TS again on reassessment	Nil
22	GGA	Potent TS	14	PD	Nil
25	GGA	Moderately potent and potent TS, intralesional steroid x 1	25	CR, disease free for 6 months	Recurred in recent 2 months, put on potent TS
9	PGA	Potent TS	2	CR	Nil
30	SCGA	Dapsone Moderately potent and potent TS, intralesional steroid x 5	5 70	No response to dapsone then CR after TS and intralesional steroid, disease free for 12 months	Yes, relapse treated with potent TS, intralesional steroid x 1. CR again 15 months later

Abbreviations: LGA, GGA, PGA, SCGA: localized, generalized, perforating and subcutaneous subtypes of GA respectively. TS: topical steroid; FU: follow up; CR: complete remission; PD: persistent disease

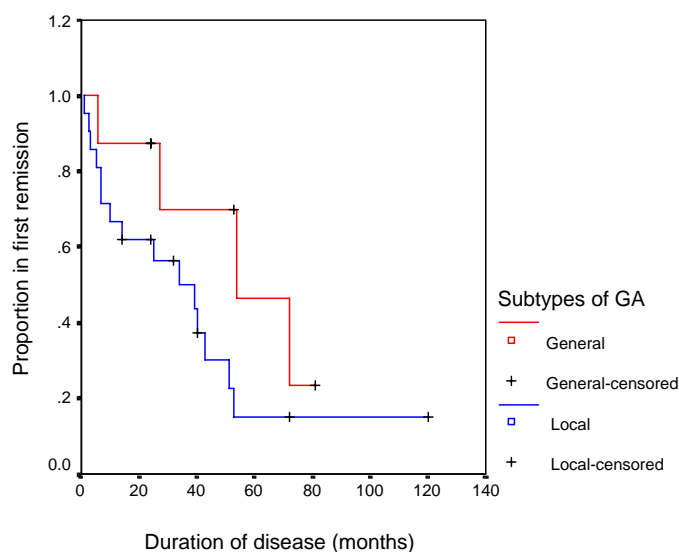
## **J) Prognosis**

CR had been achieved in 21 out of 31 (67.7%) GA cases. The median time for first CR was 43 months (CI 24.4-61.6 months) for all cases as a whole (figure 7). The median time for CR was 54 months (CI 11.3-96.7 months) for generalized GA and 39 months (CI 13.6-64.4 months) for localized GA, but the difference was not statistically significant (figure 8, Breslow test,  $p=0.13$ ). Likewise, despite cases with DM seemed to last longer than non-diabetic cases (figure 9), it was not significant (Breslow test  $p=0.37$ ). No significant difference was observed in chances of first CR between age of onset  $< 20$  and age of onset  $\geq 20$  groups (figure 10, Breslow test,  $p=0.73$ ) and between male and female (figure 11, Breslow test,  $p=0.89$ ).

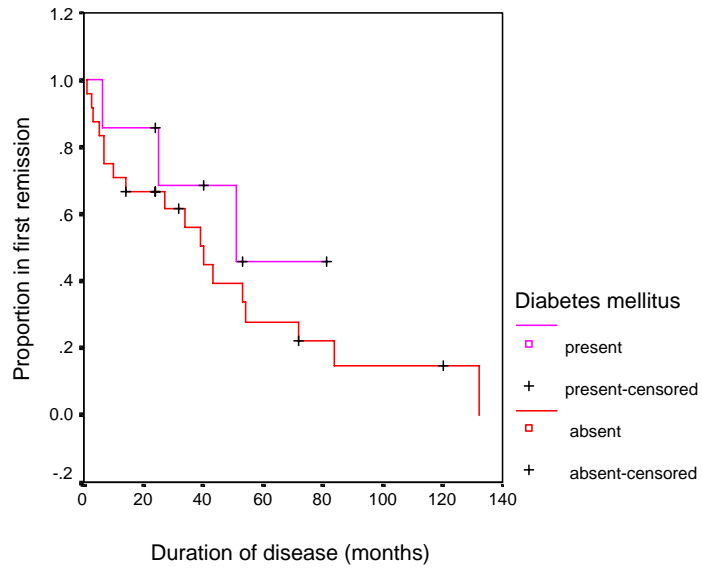
**Figure 7. Proportion of first CR of all GA cases with time**



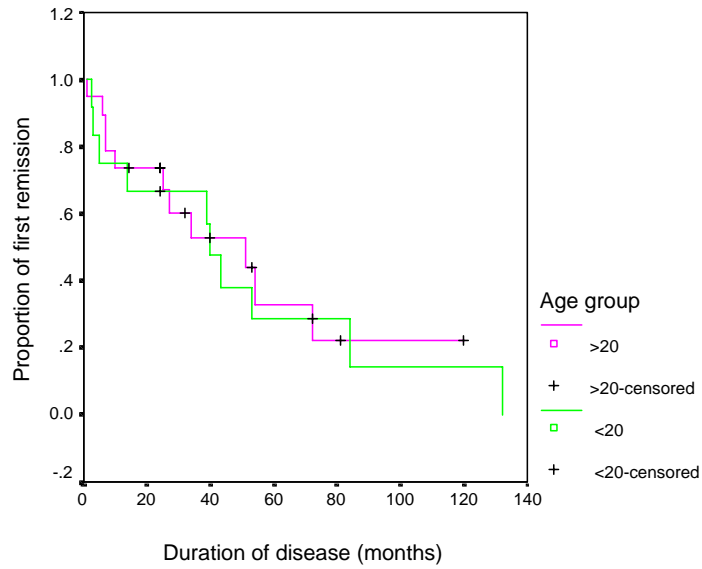
**Figure 8. Proportion of first CR in localized and generalized GA**



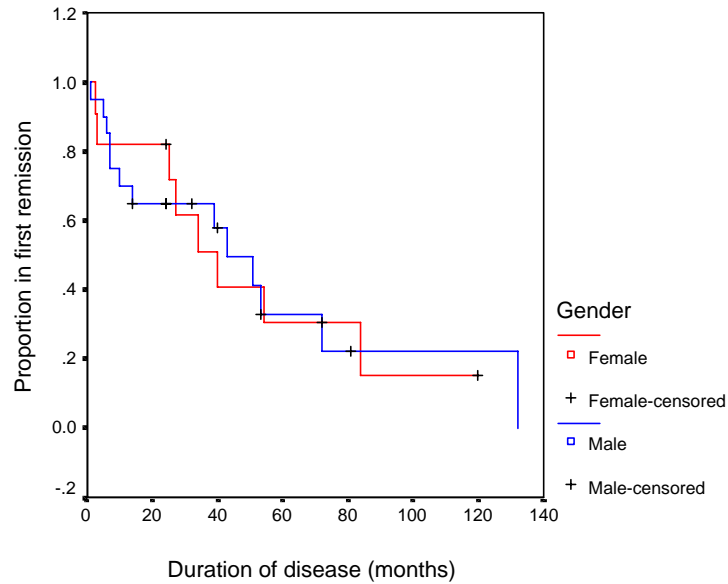
**Figure 9. Effect of diabetic status on first CR of GA**



**Figure 10. Effect of age of onset on first CR of GA cases**



**Figure 11. Effect of sex on first CR of GA cases**



7 cases out of the 21 cases (33.3%) recurred after the first CR. These comprised four localized, two generalized and one subcutaneous GA. The median time for relapse was 9.5 months. Only one patient in the relapsed group had DM. Patient no. 27 with localized GA had multiple recurrences but she forgot the exact details and duration. The range of follow up time after relapse was 1 to 15 months. Six relapsed cases had persistent disease at the time of interview. Only the subcutaneous case had second remission after treatment with topical and intralesional steroid.



## **Chapter 4: Discussion**

### **A) Epidemiology**

An incidence of 0.12% new patients was reported in one hospital<sup>23</sup> and an incidence of 0.1% to 0.4% new patients was reported in one review article.<sup>24</sup> An average incidence of 0.0081% new cases is calculated in the present study, which is an underestimation because not all clinical records are retrievable. In contrast with the literature (table 17), this study seems to have more male cases, but this is not statistically significant.

**Table 17. Age and sex distribution of GA in the literature.**

<b>Source</b>	<b>Localized GA (%)</b>	<b>Age of onset (% in first 3 decades)</b>	<b>Male to female</b>
Studer EM, et al <sup>3</sup>	75	62	1: 2.8
Tan HH, et al <sup>4</sup>	82.9	66	1: 1.56
Muhlemann MF, et al <sup>10</sup>	93	86	1: 1.25
Wells RS, et al <sup>23</sup>	95	71	1: 2.2
Dabski K, et al <sup>25</sup>	0	11	1: 2.2
This study	67.8	38.7	1.82:1

Onset of GA was mostly in the first three decades in the literature,<sup>3,4,10,23</sup> contrasting with only 38.7% of cases in this study. The difference can be attributed to the variation in proportion of GA subtypes. In a series of patients with generalized GA,<sup>25</sup> only 11% had their disease onset in the first three decades. In this study as well as in others,<sup>26</sup> the age of onset of GA is higher in the generalized than the localized variant. This study has 67.8% of localized GA, as compared with 75-95% in other series,<sup>3,4,10,23</sup> and this may be the cause of the later onset of disease in our series. A bimodal age of onset described for generalized GA<sup>24</sup> is not seen in the present study in which a single peak of onset in the sixth decades is present.

Subcutaneous GA occurs most often in children and young adults,<sup>2,24</sup> whereas in perforating GA, a later age of onset has been described.<sup>27</sup> In the present study, perforating and subcutaneous cases have age of onset at four year and three year respectively.

Familial GA has been reported in the literature,<sup>23,28</sup> but is absent in our series. Although there is no satisfactory explanation, a genetic component via human leucocyte antigen (HLA) association has been reported (see Etiology).

## **B) Clinical features**

### **1) Morphology of skin lesions**

Dabski K et al has divided the clinical appearance of generalized GA into two forms: the predominantly annular form (67%) and the predominantly nonannular form (33%).<sup>25</sup> In the present study, the predominantly annular form accounts for 48.4%, whereas the predominant papular form accounts for 22.6%. Some patients have a mixed papular and annular pattern and this accounts for another 21.2%. One patient has coalescing papules forming a plaque without central clearing. This has been classified as nonannular form in Dabski K et al series but the term “plaque form” may be more descriptive for the clinical appearance.

In perforating GA, umbilicated and crusted lesions are the commonest (> 70%), while pustular lesions occur in 26% of cases.<sup>27</sup> Lesions may heal with atrophic hyper- or hypopigmented scars. Clinically, perforating GA is a disseminated disease with multiple papules (only 9% has single lesion) and can be classified, according to their distribution, into localized and generalized variant. Only one case of perforating GA is present in this study, presenting with umbilicated papules over neck and hand dorsa.

Subcutaneous GA usually presents as painless skin- coloured deep dermal or subcutaneous nodules.<sup>2,24</sup> It is also called pseudorheumatoid nodule or benign rheumatoid nodule but no relationship with rheumatoid arthritis is observed. Superficial papular lesions are present in about one fourth of cases.<sup>24</sup> One subcutaneous GA is present in this study with painless skin –coloured papules distributed over the extremities.

### **2) Classification**

The definitions of various subtypes of GA are listed in table 7. Localized GA has solitary or a limited number of skin lesions that may affect one or several anatomical areas<sup>5</sup> and papules may be arranged in an annular or arciform pattern.<sup>29</sup> Generalized GA, according to Dabski K et al,<sup>25</sup> has widely distributed lesions of a large number affecting the trunk and at least one extremity. Tan HH et al has used the term disseminated GA to describe extensive lesions confined to one anatomical site or to the extremities only.<sup>4</sup> But this is the only case series, according to the author’s knowledge, classifying disseminated GA as distinct from localized and generalized type. The exact number of skin lesions that defined ‘extensive’ was not mentioned in their article and most other case series in the literature did not include a disseminated subtype.<sup>3,9,10</sup> Therefore this subtype is not employed in the present study. Subcutaneous<sup>2,24</sup> and perforating<sup>27</sup> subtypes differ from typical GA by the level of skin involvement: subcutaneous layer in the former and superficial dermis as well as epidermal involvement in the later. This pathological difference translates into difference in clinical characteristics of skin lesion as outlined above.

The percentages of each GA subtypes in this study and in various series are similar (table 18). Localized GA is the most frequent, followed by generalized subtype. Perforating and subcutaneous forms account for less than 10%. This study, as compared with other series, has a lower proportion of localized GA. Generalized GA accounts for 25.8%, which lies in the upper range of percentage as compared with the literature (5-25%, see table 18). Perforating and subcutaneous GA both occur in 3.2% in this study, which is comparable to 1.2% and 4.8% respectively reported by Studer EM et al.<sup>3</sup>

**Table 18. Subtypes of GA in various case series**

Source	Year	LGA %	GGA %	PGA %	SCGA %	DGA %
Studer EM, et al <sup>3</sup>	1996	75	19	1.2	4.8	-
Tan HH, et al <sup>4</sup>	2000	82.9	9.8	2.4	0	4.9
Haim S, et al <sup>9</sup>	1973	75	25	0	0	-
Muhlemann MF, et al <sup>10</sup>	1984	93	7	0	0	-
Wells RS, et al <sup>23</sup>	1963	95	5	0	0	-
Dabski K, et al <sup>25</sup>	1989	0	100	0	0	-
This study	2002	67.8	25.8	3.2	3.2	-

Abbreviations of GA subtypes: LGA: localized subtype; GGA: generalized subtype; PGA: perforating subtype; SCGA: subcutaneous subtype; DGA: only coined in one study, represent disseminated subtype

### 3) Other variants of GA reported in the literature

#### i) Papular umbilicated GA

It was described in four paediatric cases.<sup>30</sup> All occurred over dorsa of hands as firm umbilicated papules. Histologically, necrobiotic granulomas were present beneath areas of epidermal thinning and parakeratosis. There was no perforation. Similar epidermal changes were reported in early perforating GA.<sup>27</sup> The authors acknowledged that there was a disease spectrum from papular to perforating subtype and it appeared to be a variant of perforating GA.<sup>30</sup>

#### ii) Patch GA

It presented as asymptomatic erythematous to brown patches, without papules, scaling or induration.<sup>31</sup> Histologically, an interstitial histiocytic pattern was observed. 4 out of 6 patients in the original series were on long-term medications.<sup>31</sup> It was questioned as a genuine variant of GA, but rather represented an example of interstitial granulomatous form of drug reaction.<sup>29</sup>

#### iii) Follicular pustulous GA

It presented as recurrent eruptions of generalized pustules over trunk and palms.<sup>32</sup> Histologically, palisading necrobiotic granulomas occurred in a perifollicular distribution. Intense necrosis of follicular walls and neutrophilic infiltration of upper portions of

follicles were noted. Transepidermal perforation of the necrobiotic material was seen in palmar lesions. The adnexal affinity of the granulomatous process and superficial aggregation of neutrophils in follicular opening suggested a pattern different from ordinary GA. But in the presence of perforation, the authors could not exclude the possibility that it belonged to perforating GA.<sup>32</sup>

#### **iv) Linear GA**

It presented as a linear subcutaneous band over the lateral chest wall.<sup>33</sup> This entity is now regarded as a variant of interstitial granulomatous dermatitis with arthritis that can present as linear cords ('rope sign'), papules or plaques.<sup>29</sup> The disease is associated with rheumatoid arthritis. Histologically, as compared with GA, the histiocytes are usually scattered interstitially, especially marked in the lower dermis. Moreover, eosinophils and neutrophils are more noticeable and mucin deposition is less in this variant.<sup>29</sup> In some areas, a few degenerated collagen bundles are enveloped by neutrophils, eosinophils and histiocytes, forming Churg Strauss granuloma.

#### **v) Actinic granuloma**

In 1975, O'Brien described this entity, characterized clinically by annular plaque on sun-exposed areas; histologically by absence of elastic fibres in the post reactive central zone and granulomatous inflammation with giant cells at the edge of lesion.<sup>34</sup> The uniqueness of the condition and the concept of granulomatous response to solar elastosis were controversial. Ackerman AB considered it as a variant of GA that occurred on sun exposed skin.<sup>35</sup> Annular elastolytic giant cell granuloma was proposed by Hanke CW et al in 1979 to include the entity actinic granuloma.<sup>36</sup> They agreed that the mere occurrence of solar elastosis and adjacent granulomatous inflammation did not imply a cause-effect relationship. Further argument will be continued, unless the etiology of each condition is found.

### **4) Distribution of skin lesions**

The distribution of skin lesions is similar to that reported in the literature.<sup>3,4</sup> Distal extremities beyond the elbow or knee region are commonly affected. In perforating GA, the extremities especially the hands and arms are commonly involved.<sup>27</sup> Subcutaneous GA commonly involves not only distal extremities but also scalp and forehead.<sup>37</sup>

### **5) Symptoms (Table 19)**

Skin lesions of GA are basically asymptomatic. Pruritus and pain may be present in some cases. A study on generalized GA showed a higher proportion of symptomatic cases.<sup>25</sup> Our study also shows a similar trend. Symptoms are present in 37.5% and 14.3% of generalized and localized GA cases respectively, but the difference is not significant (Fisher's exact test,  $p=0.31$ ).

**Table 19. Proportion of symptomatic GA cases in the literature**

Source	GGA %	Asymptomatic%	Symptomatic%
Tan HH, et al <sup>4</sup>	9.8	85.4	14.6
Dabski K, et al <sup>25</sup>	100	66	34
This study	25.8	78.8	21.2

Abbreviation: GGA: generalized granuloma annulare

## 6) Precipitating factors

Most patients cannot identify any precipitating factors. Reported precipitating factors in the literature were sunburn, trauma, insect bite, drug, flu-like illness, reaction to intravenous contrast medium, phlebitis, sepsis after surgery and stress.<sup>3,4,25</sup> The present study also identifies some precipitating factors but cannot prove a cause-effect relationship or the mechanism involved in the exacerbation.

## C) Pathology

### 1) Necrobiosis and mucin deposition

GA is characterized by necrobiosis, granulomatous inflammation and mucin deposition. Necrobiosis refers to non-specific connective tissue alteration. It appears as blurring and loss of definition of collagen bundles, separation of fibres, a decrease in connective tissue nuclei and an alteration in staining by routine histological stains, often with increased basophilia or eosinophilia.<sup>29, 38</sup> Necrobiosis is usually minimal in interstitial GA and careful scrutiny is required. Mucin appears as bluish stringy and granular material on hematoxylin and eosin stain. It can be enhanced by alcian blue or colloidal iron stain.

### 2) Inflammatory cells

The inflammatory cellular component consists of predominantly histiocytes (some of which are epithelioid or multinucleated), lymphocytes (majority of which are T helper cells) and occasionally eosinophils.<sup>29,34</sup> Table 20 highlights the difference in histiocytic pattern between this study and the literature.

**Table 20. Pattern of histiocytic infiltration in GA**

Histiocytic infiltration	Umbert P et al <sup>38</sup>	This study
	%	%
Palisading	71	58.1
Interstitial	26	25.8
Mixed palisading & interstitial	-	16.1
Sarcoidal	3	-

Moreover, Dabski K et al found that generalized GA, in comparison with localized subtype, had less apparent collagen abnormality and fewer cases with palisading pattern.<sup>39</sup> Our study does not demonstrate such differences. The reason for difference of histology pattern between the present study and that of the literature may be related to the focal nature of the disease. Some skin biopsies show a mixture of histiocytic infiltration patterns and there are variable histology patterns depending on the sections.

### **3) Elastic fibre changes**

Elastic fibre reduction was present in 20-30% of GA cases in one series.<sup>39</sup> In our study, one case has almost complete loss of elastic fibres on one side of biopsy specimen compatible with annular elastolytic giant cell granuloma. Degenerated elastic fibres may initiate a granulomatous response or it may be lost secondary to the activity of elastase or phagocytosis of inflammatory cells. Clinically atrophic patches with histological features of mid-dermal elastolysis<sup>40</sup> or anetoderma<sup>41</sup> have been reported after resolution of GA.

### **4) Vascular changes**

A perivascular lymphohistiocytic infiltrate is frequently found<sup>24,35,38</sup> and in 16 % of cases in this study, this is especially prominent. Diabetic microangiopathy has been found in lesions of GA especially in the generalized subtype<sup>26</sup> but this feature is absent in our study even in cases with known DM. Vasculitic changes and positive immunofluorescence for C3 and IgM (in up to 50% of cases) had been reported and the author concluded vasculitis was possibly involved in the pathogenesis of GA.<sup>42</sup> However, the results were not reproducible, immunofluorescence for IgM and C3 was positive on blood vessels in only 9% of cases in another study.<sup>43</sup>

It has been suggested that the occurrence of nuclear dust in the necrobiotic area indicates vasculitis is an early event and may occur at the center of palisading granuloma, thus it may be missed by random section or biopsy done late in the disease course.<sup>35,44</sup> To test the hypothesis, skin biopsy with immunofluorescence study of early (< 1 week) localized GA and normal skin adjacent to spreading GA was performed.<sup>44</sup> The direct immunofluorescence was negative in all specimens and the result did not support the presence of vasculitis.

In the present study, nuclear dust is present in 25.8% of specimen and this may represent apoptotic histiocytes, fibroblasts or other cell types (personal communication with Dr. KC Lee, PMH). Vasculitic changes are absent in all specimens but direct immunofluorescence has not been carried out.

### **5) Subcutaneous and perforating GA**

Subcutaneous GA shows essentially the same histology located at subcutaneous tissue and deep dermis. Eosinophils are more commonly seen<sup>29</sup> and interstitial pattern is not observed in the septa.<sup>35</sup> Perforating GA has necrobiotic granuloma located at

superficial dermis.<sup>27</sup> Epidermal changes range from epithelial thinning, parakeratosis and perforation in the epidermis or follicular wall. There is controversy on whether the perforation is simply epidermal destruction by the inflammation process or the material is transepithelially eliminated.

## **D) Etiology**

### **1) Genetic Factors**

GA has been reported in families and twins.<sup>24</sup> Friedman –Birnbaum R et al reported increase HLA-A31 and B35 in Ashkenazi Jews of Eastern European origin in generalized but not in localized GA.<sup>45</sup> The authors have made comparison with other studies as well. HLA-A29 is increased in patients with localized GA from the Belfast area. Increase HLA- B8 is found in Danish patients with localized GA. Because HLA-B8 is associated with DM, this is the only study that points to a possible genetic association of DM with GA.

### **2) Physical Factors**

Trauma has been reported in 25% of children in subcutaneous GA.<sup>24</sup> The appearance of papular GA on exposed areas has prompted some authors to consider insect bite as a cause.<sup>24</sup> Sun exposure and photochemotherapy have been reported as provoking factors.<sup>1</sup>

### **3) Diseases associations**

The diseases reported in association with GA are summarized in table 21. These are mostly based on case report or small case series and there are neither direct evidence nor a proven mechanism of the diseases association. In the present study, apart from DM, only two cases have past history of pulmonary tuberculosis. The other diseases listed in table 21 are not present.

**Table 21. Reported diseases associated with GA**

<b>Factors</b>	<b>Article</b>	<b>Postulated mechanisms/ Remarks</b>
<b>Infections</b>	Varicella Zoster virus	Case report
	Epstein Barr Virus (EBV)	Case report <sup>48</sup>
	Hepatitis C virus (HCV)	Case report <sup>50</sup>
		Viral DNA detected by PCR in GA lesions, <sup>46</sup> but this was not reproducible by others <sup>47</sup>
		Original reported case was probably not GA. <sup>49</sup> Subsequent study using PCR and ISH failed to demonstrated EBV in GA <sup>49</sup>
		Liver epitheloid granulomas are present in 10% of HCV related cirrhosis, indicating the ability of virus in inducing granulomatous response

**Table 21 (continued). Reported diseases associated with GA**

<b>Factors</b>	<b>Article</b>	<b>Postulated mechanisms/ Remarks</b>	
Human Immunodeficiency virus (HIV)	Case series <sup>49,51</sup>	Characterized by a predominant CD8 positive lymphocytic infiltrate. Atypical presentations such as perforating GA, macular erythema may be present. One case series showed a higher generalized GA presentation (59%). <sup>49</sup> Skin biopsy is advisable in HIV positive cases to exclude other differential diagnosis.	
Mycobacteria	Case report <sup>52</sup>	Nil	
Borrelia burgdorferi	Case series <sup>53</sup>	Urine PCR for Borrelia positive in 60% of GA cases	
<b>Systemic diseases</b>	Autoimmune thyroiditis	Case control study <sup>54</sup>	Associated with localized GA in female, a common immunogenetic predisposition or immunopathogenetic mechanism proposed
	Sarcoidosis	Case series <sup>55</sup>	Both are characterized by granulomatous inflammation, delayed hypersensitivity to obscure antigens and macrophage migratory inhibitory factor is found in both. Presence of increased dermal mucin or eosinophils in GA may be helpful distinguishing features.
	DM		See table 1 and p.32
	Sweet's syndrome	Case report <sup>56</sup>	Generalized GA and Sweet's syndrome, both can be associated with malignancy, occur in a patient with breast carcinoma.
	Morphoea	Case report <sup>57</sup>	Autoimmune etiology is proposed; blood vessel damage and upregulation of collagen synthesis are present in both diseases.
	Temporal arteritis	Case report <sup>58</sup>	Both are characterized by granulomatous inflammation, giant cells and loss of elastic fibres and sunlight has been proposed as a causative factor in both.
	Malignancy	Case series <sup>59</sup>	Association with Hodgkin's disease, non-Hodgkin lymphoma, Sezary syndrome, Lennert's lymphoma, leukaemia, carcinoma of lung, cervix, colon, breast, prostate, stomach, thyroid and seminoma have been described. GA occurs 14 years before to 27 years after malignancy. No definite relationship is established. Occurrence of painful lesions or palmoplantar and facial lesions is said to be more frequent in this group.

Abbreviations: PCR: polymerase chain reaction; ISH: in-situ hybridization



#### **4) Association with DM**

Despite a substantial number of literatures linking GA with DM, the present study fails to detect such an association. Case-control studies like the present one only imply association with or without causation. In the absence of experimentation, several criteria have been advocated for assessing causality:<sup>60</sup>

**i) Temporal sequence**

A casual association requires causative factors precede results. In the present study, 3 patients had diabetes mellitus after GA, such occurrence has also been reported in other series.<sup>10</sup>

**ii) Consistency and strength of association**

Summary of some of the reported studies has been given in table 1. No consistent association has been demonstrated. Even in studies showing association, the strength of association is not consistently high (a relative risk of 11.4 in one<sup>10</sup> and an odds ratio of 2.6 in another<sup>13</sup>).

**iii) Dose-response relationship**

There has not been any study on the relationship between severity of GA and the degree of hyperglycaemia. Although reports on resolution of GA after chlorpropamide are present,<sup>7</sup> definite conclusions cannot be drawn as they are uncontrolled.

**iv) Biological plausibility**

The mechanism of DM causing GA is rarely studied. This may be due to the fact that the pathogenesis of GA itself is not known. The possible mechanisms are:

**a) Immunogenetic linkage**

HLA B8, B15, DR3 and DR4 are associated with DM, whereas HLA DR2 is 'protective' against development of DM. The only series showing possible association of GA and DM is increased frequency of HLA-B8 in Danish patients with localized GA, which is not reproducible in other populations.

**b) Diabetic microangiopathy**

Diabetic microangiopathy has been found in high frequency in generalized GA but not in localized type.<sup>26</sup> Palisading granulomas are suggested to be a consequence of tiny infarcts that cause collagen degeneration, to which histiocytes respond in a radial array. However in a large study on histology of GA<sup>38</sup> and in 100 patients with generalized GA,<sup>39</sup> diabetic microangiopathy is absent. There is no diabetic microangiopathy identified in the present study.

**c) Factor VIII related antigen**

High levels of factor VIII related antigen are linked with microvascular disease in DM. Factor VIII related antigen is raised in necrobiosis lipoidica and widespread GA, even in patients without DM, but not in localized GA.<sup>61</sup> Its enhancement of

platelet adhesiveness and aggregation may contribute to vascular injury. But evidence is lacking on whether the raised factor is the result of the disease process rather than the cause.<sup>61</sup>

In summary, there is no strong evidence of DM as a causative factor in GA.

## **5) Drugs**

Vaccinations including BCG, hepatitis B and antitetanus vaccines have been reported to induce GA. Vaccination may have initiated GA through traumatic or immunological mechanisms.<sup>62</sup>

Drug induced GA has been reported and drugs such as gold, allopurinol, calcitonin and diclofenac are incriminated.<sup>63</sup> An entity, interstitial granulomatous drug reaction, has been described in 1998.<sup>29</sup> The reported culprits included calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors, lipid-lowering drugs, antihistamines, anticonvulsants and antidepressants. Clinically, skin lesions are erythematous to violaceous plaques, often with annular configuration, affecting medial arms, thighs, intertriginous areas and trunk. The histology mimics interstitial GA. They are differentiated from GA by the absence of significant necrobiosis, predominance of lymphocytes over histiocytes, presence of eosinophils and interface changes with mildly atypical lymphocytes and focal epidermotropism.

## **E) Pathogenesis**

### **1) Cell mediated immunity**

Infiltrates of GA are characteristics of cell-mediated immunity, with histiocytes and variable lymphocytes (T helper > T-suppressor).<sup>64</sup> Serum macrophage inhibitor factor activity has been detected in patients with GA.<sup>65</sup> Its detection can be used as a correlate for cellular immunity status. Peripheral blood leukocyte function, including polymorphonuclear and monocyte chemotaxis, phagocytosis, oxidative burst and blastogenic response of lymphocytes have been found to be normal in one study in vitro.<sup>66</sup> But functional abnormality of leukocytes in vivo cannot be excluded.

The nature of the infiltrating T cells has been studied.<sup>67</sup> There is a selective infiltration of a limited number of skin-specific T cells clones together with a large number of non-specific T cells. This situation reflects a T cell infiltration model previously proposed for autoimmune diseases. A predominant interleukin-2 transcription is also found which may provide signal for ongoing inflammation and cellular recruitment.

Besides interleukin-2, interferon-gamma (IFN- $\gamma$ ) is expressed by a large number of lymphocytes, compatible with a Th1 cytokine pattern. Other cytokines involved are the tumour necrosis factor- alpha, interleukin-1 beta, interleukin-6 and matrix metalloproteinases. They all contributed to the inflammatory response in GA.<sup>68</sup>

It is proposed that sensitized lymphocytes in dermis release cytokines, resulting in accumulation and activation of macrophages and hence release of various enzymes that may contribute to connective tissue degeneration.<sup>64</sup> Potential antigens may include altered collagen, altered elastic fibres, bacterial/viral agents and antigens in saliva of arthropods.<sup>2</sup>

## **2) Immune complex vasculitis**

Detailed discussion has been given in pathology section. In general, this is not a favoured mechanism as subsequent studies failed to show the presence of vasculitis in as a high proportion as in the series of Dahl MV et al.<sup>42</sup> Furthermore, in inflammatory dermatosis, complement and immunoglobulin may sometimes be deposited in vessels without true vasculitis.<sup>24</sup>

## **3) Collagen abnormalities**

The synthesis of type I and III collagens are increased in GA and areas of collagen degeneration are surrounded by active collagen synthesizing fibroblasts. The number of pro $\alpha$ 1(I) collagen mRNA molecules is increased four to five fold as compared with nonlesional skin. This represents a reparative phenomenon in GA.<sup>69</sup>

The expression of various enzymes affecting collagen turnover in GA have been studied.<sup>70</sup> Interstitial collagenase is expressed in the peripheral rim of histiocytes in palisading granuloma of less than 1 year old. This spatial relationship suggests a centrifugal process whereby collagenolysis occurs, starting from the centre and expanding outward with active degeneration corresponding to the site of expression of interstitial collagenase, that is, rim of granuloma. This is not observed in interstitial granuloma annulare in which collagenase expression is consistently negative. Tissue inhibitor of metalloproteinases (TIMP)-1 regulates activity of collagenase. TIMP-1 is expressed in similar areas as interstitial collagenase and is present in young and old GA lesions. This inhibitor expression may be a homeostatic response to collagenase, to limit the damage and to allow for repair. 92-kDa gelatinase is expressed by eosinophils with no relationship to the granulomas, casting doubt on its role in elastolysis in the necrobiotic centre.

## **F) Differential diagnosis**

The differential diagnosis includes:

- Tinea corporis
- Subacute cutaneous lupus erythematosus
- Erythema marginatum
- Annular lichen planus
- Erythema multiforme
- Erythema annulare centrifugum
- Erythema migrans

- Leprosy
- Nodular tertiary syphilis
- Sarcoidosis
- In non-annular forms, cutaneous amyloidosis, scleromyxedema, papular mucinosis and erythema elevatum diutinum
- In subcutaneous form, rheumatoid nodules and other deep cutaneous tumours
- In perforating form, acquired reactive perforating dermatoses, perforating folliculitis, elastosis perforans serpiginosa, molluscum contagiosum and papulonecrotic tuberculid

## **G) Treatment**

GA is rare and there is no large-scale double blind randomized controlled trial on treatment. Together with the fact that spontaneous resolution may occur, it is difficult to interpret the reported efficacy of various treatments. Some authors stated that treatment of GA was generally unnecessary, owing to their spontaneous resolution.<sup>24</sup> But the persistence and disfigurement of generalized GA has prompted treatment in other cases.<sup>71</sup> The choice of therapy depends on GA subtypes, side effects and patient preference.

**Table 22. Therapeutics for GA (modified from reference<sup>72</sup>)**

<b>Localized GA</b>	<b>Generalized GA</b>
First line Cryotherapy Intralesional and topical steroid  Second line Intralesional interferon Surgery Topical imiquimod Cream PUVA	First line Photo(chemo) therapy Systemic isotretinoin Dapsone  Second line Cyclosporine Systemic steroid Chlorambucil Antimalarials Potassium iodide Pentoxifylline Niacinamide Vitamin E and 5-lipoxygenase inhibitor Fumaric acid esters

### **1) Resolution after skin biopsy**

Reports of resolution of GA after skin biopsy are present.<sup>31,73</sup> As they are uncontrolled, it is difficult to eliminate the element of natural regression. Three cases of localized GA in the present series resolved within one month after skin biopsy. The possible mechanism of biopsy-induced resolution is by initiating an orderly process of wound healing involving interactions of epidermal, inflammatory, fibroblastic and other cell types through cytokines.<sup>73</sup> However, it is not clear why only some GA cases resolve after biopsy.

## **2) Steroids**

91.2% and 5.9% of localized GA in one series (34 cases in total) were treated with topical and intralesional steroids respectively. 67.6% of patients had remission after one year of follow up.<sup>4</sup> In another study,<sup>74</sup> intralesional triamcinolone acetonide produced complete clearance in 68% (out of 25 cases) as compared with 44% (out of 27 cases) injected with normal saline after a mean treatment sessions of 2.4 at 6 to 8 weekly intervals. Lesions relapsed in about 42 to 47% in both groups. Transient atrophy at steroid injection sites was common.

The response to steroid therapy is consistent with the immune pathogenesis of GA. In the present study topical steroid is the most common treatment resulting in remission either alone (16 cases) or together with intralesional steroid (1 case). Seven cases have persistent disease with topical steroid.

## **3) Cryotherapy**

One freeze thaw cycle of 10-60s per session was used in 31 localized GA patients using either nitrous oxide or liquid nitrogen and treatment was repeated every 20 to 30 days.<sup>75</sup> 80.6% of patients had remission after a single treatment. Relapse occurred in 9% of patients who were followed up for more than two years. Atrophic scarring occurred in 21.1% of patients treated with liquid nitrogen but was absent in those treated by nitrous oxide.

## **4) Intralesional interferon**

Three localized GA patients were given intralesional recombinant human interferon gamma (IFN- $\gamma$ )  $2.5 \times 10^5$  IU/lesion on seven consecutive days and thereafter three times per week for two more weeks.<sup>76</sup> As a control, other lesions were treated with normal saline or steroid under occlusion. After three weeks, all IFN- $\gamma$  treated lesions improved but controls did not. Possible mechanism involves inhibition of delayed hypersensitivity reaction by IFN- $\gamma$ .

## **5) Surgery**

Scarification, using injection needle drawn across lesions to produce capillary bleeding, was used successfully in two cases.<sup>77</sup> In addition, razor blade subsection with healing by secondary intention was used in a patient with 'nodular' GA over fingers.<sup>78</sup>

## **6) Topical imiquimod**

Topical imiquimod nightly for six weeks resulted in resolution of GA in a case report.<sup>79</sup> Other lesions that were not treated remained the same.

## **7) Cream psoralen plus ultraviolet A (cream PUVA)**

Increased sensitivity to UVA was accomplished by topical psoralen cream (0.001% 8-methoxypsoralen). In this way, only selected body parts were included in the

therapy (with possible decrease in side effects).<sup>80</sup> Cream PUVA was used in five localized GA patients four times a week starting at 30% minimal phototoxic dose, with increments at 30% of last UVA dose and maximum increment at 0.5J/cm<sup>2</sup>. The treatment was continued up to two sessions after resolution. Four showed complete response while one showed significant improvement after a mean of 26 treatments (mean UVA dose 55.9J/cm<sup>2</sup>). No recurrence was noted after four months of follow up.

## **8) Photo(chemo)therapy**

Oral PUVA was used in five generalized GA cases, resulting in clearance of lesions in four cases within 3 to 4 months (21 to 35 treatments, cumulative exposure 100-237 J/cm<sup>2</sup>) and the remaining one with perforating lesions resolved after 95 treatments (total exposure 1859 J/cm<sup>2</sup>).<sup>81</sup> Recurrent lesions were present in four cases during maintenance or when PUVA was stopped. PUVA is useful to control GA; paradoxically it may trigger the disease. This is somewhat akin to diseases such as polymorphic light eruption which may both be induced and suppressed by PUVA.<sup>81</sup> Alternatively, bath PUVA can be used.<sup>82</sup> Both oral and bath PUVA have effect directly on inflammatory cells or indirectly through release of anti-inflammatory mediators from epidermal cells.<sup>80</sup>

High dose UVA-1 (daily 5 times per week for 3 weeks, starting at 60J/cm<sup>2</sup> on day 1, 90J/cm<sup>2</sup> on day 2 and thereafter at 130 J/cm<sup>2</sup>) was used in four generalized GA cases,<sup>83</sup> resulting in complete clearance in one case and partial improvement in the rest. As recurrence is possible, potential side effects of treatment should be considered, particularly in children and young adults. PUVA should be used when other approaches have failed and patient insists on treatment.<sup>84</sup>

## **9) Isotretinoin**

Isotretinoin has been used in resistant generalized GA.<sup>71,85,86</sup> One case was reported by Tang WYM et al (not included in the present study).<sup>86</sup> Initial isotretinoin dosage ranged from 40mg/day to 60 mg/day. A short course of treatment (3 to 4 months) was needed in most cases, with one case of 34-year duration requiring 1 year of treatment.<sup>85</sup> No patients experienced significant side effects requiring premature termination of treatment but tapering of doses was needed for deranged liver function and increased lipid.<sup>71,86</sup> Perforating GA also responded to isotretinoin.<sup>87</sup> The immunomodulatory action of isotretinoin might be important for its effect on GA.<sup>86</sup> Relapse in 3 out of 6 cases after several months was reported in one series,<sup>71</sup> although remission of up to one year was present in another.<sup>86</sup>

The present study has one case successfully managed with isotretinoin at 0.5 mg/kg/day for six months. Side effects included cheilitis that was managed with emollient.

## 10) Dapsone

The use of dapsone was evaluated in 16 patients with GA (six localized, ten generalized).<sup>88</sup> Complete remission, partial remission and no response were achieved in six, seven and one patient(s) respectively. Most response, if present, occurred within six weeks of treatment. Relapses within three months occurred in all but one responders. Because dapsone fails to clear the disease and carries risk of serious side effects, it should only be used in widespread disease with caution.

Dapsone has been used in one subcutaneous GA in the present study at 50 mg/day for six months. No clinical response is observed.

## 11) Other second line treatments for generalized GA

*Cyclosporine* was given at 4mg/kg/day for 1 month and then 2 mg/kg/day for 2 more months, which resulted in resolution of generalized GA in a case report.<sup>89</sup> Relapse occurred within one month after treatment was stopped. However, another generalized GA case failed to clear with cyclosporine at 5 mg/kg/day for 2 months in the same report.<sup>89</sup> Systemic *steroid* was reported to be useful in generalized GA.<sup>72</sup> Cyclosporin and systemic steroid probably act through their anti-inflammatory effects.

*Chlorambucil* inhibits T cells and in vitro inhibits lymphocyte blastogenesis induced by phytohemagglutinin.<sup>90</sup> It was used at 4mg/day, which resulted in complete healing in one within 12 weeks and partial improvement in another. Because of inherent risk of immunosuppression and carcinogenesis, for most patients, it should not be used. *Chloroquine*, 3mg/kg/day, and *hydroxychloroquine*, 6 mg/kg/day, were used in six children.<sup>91</sup> The doses were reduced to halved after three weeks and discontinued two weeks after complete remission. Remission was attained in all without relapse within a mean follow up of 2.5 years. Proposed mechanisms of antimalarials include anti-inflammatory effects through binding to nucleoproteins and interference with lysozyme function. Close monitoring is mandatory, especially on the ophthalmological side effects.

*Potassium iodide* was tested in a double blind, placebo-controlled, crossover study involving 10 patients.<sup>92</sup> The dosage was 3 drops increased to 10 drops three times daily in 2 weeks for 6 months. The effect of potassium iodide over placebo was not significant. Side effects include rhinorrhoea, metallic taste, transient acneiform eruption and iodide goitre with or without hypothyroidism when underlying thyroid disease is present.<sup>92,93</sup> Prior testing of thyroid functions is recommended before institution of treatment. It should not be given to pregnant women.

*Niacinamide*, 1500mg/day for 6 months, was useful for generalized GA in a case report.<sup>94</sup> This drug is a suppressor of antigen and mitogen induced lymphoblast transformation. Potential side effects include headache, gastrointestinal upset and hepatotoxicity. *Pentoxifylline* was used for GA in a case report.<sup>72</sup> Its effect on decreasing blood viscosity was proposed to explain the benefit, as vascular damage was one of the postulated mechanisms of disease.

*Vitamin E*, 400 IU daily, and the *5-lipoxygenase inhibitor*, zileuton 600mg four times daily, were reported to be useful in a series of three cases.<sup>68</sup> Remission occurred within 3 to 4 months. Vitamin E decreases interleukin-1 beta and interleukin-18 (interleukin-18 stimulates Th1 response through induction of IFN- $\gamma$ ). Whereas, 5-lipoxygenase inhibitor decreases production of leukotrienes which are important inflammatory mediators. *Fumaric acid esters* were successful in one generalized GA lasting 25 years.<sup>95</sup> The exact mechanism is not known but in psoriasis, fumaric acid esters reduce proinflammatory cytokines production and antigen presenting capacity of monocytes as well as immunomodulate towards a Th2 response. Possible side effects include flushing, gastrointestinal symptoms and lymphopenia.

## **H) Prognosis**

The comparison of prognosis across various studies is difficult, as they have been reported in a different way. In the series by Wells RS et al,<sup>23</sup> of those who had remitted, 73% did so within 2 years and 41% of them relapsed in 1 to 8 years. In our series, of those who have remitted, 42.9% do so within 2 years and 33.3% of them relapse in a median of 9 months. In the series by Tan HH et al,<sup>4</sup> 67.6% of localized GA remitted after 1 year, but relapsed in 13% while their generalized GA cases did not remit after 1 to 4 years. In our series, 33% of localized GA have remission within 1 year, relapse in 19% while 50% of generalized GA remit after a follow up of 6 to 81 months.

Besides the differences in presentation of prognosis, studies are different in terms of follow up time and proportion of various GA subtypes and this may explain the variation in prognosis, if any, across studies.

The present study conforms to previous series in that age and sex do not affect the total duration of disease.<sup>3,23</sup> Generalized GA were said to have a more protracted clinical course than the localized subtype.<sup>25</sup> Although a similar trend is observed in the present study, it does not reach statistical significance.

## **D) Limitations of the present study**

Being a case-control study, potential bias is present in the following areas:

### **1. Diagnostic bias**

More frequent blood sugar monitoring in the case group may lead to higher probability of DM detection in the cases as compared with controls. The present study uses the first FBS ever checked in our clinic for comparison. However, this does not completely solve the problem as urine sugar and spot sugar tests have been done before in 9 cases.

### **2. Nonresponder**

Cases still having the diseases may be more likely to attend the interview with the author. On the other hand, subjects with a positive family history of DM may be more likely to participate in the control group for blood sugar test.



### **3. Confounding factors for DM**

While efforts have been made to minimize confounding factors in the present study (age, sex, race-matched and skin diseases with higher DM prevalence are excluded), the list is not exhaustive. Reported risk factors for DM are obesity, physical inactivity, high fat diet, low birth weight and maternal gestational DM.<sup>96</sup> It is desirable that controls have the same profile in all these confounding factors as cases, but too much matching will result in difficulty in recruitment of enough controls.

### **4. Recall bias**

Some patients have defaulted follow up and their previous remissions or exacerbations are documented by history alone that may be subjected to bias.

## **J) Conclusions and suggested further study**

This study shows that the clinical picture and distribution of various subtypes of GA in the local population are similar to the western literature. Age of onset of localized GA is significantly lower than that of generalized GA. A tendency of less female cases in local Chinese remains to be proven by a larger series. The prognosis of GA in our population is defined, which is helpful in patient counseling and management.

Although in the present study, DM seems to be more prevalent in cases than controls, the difference is not statistically significant. Literature review does not reveal strong evidence in favour of DM as a causative factor for GA. But it does not exclude the possibility of their association in other populations (where Type 1 DM is more common) through a common autoimmune mechanism (like the association of pernicious anemia with type 1 DM). The present study is a cross-sectional one on the prevalence of DM in order to reduce the diagnostic bias. As a circumstantial evidence of an association through an autoimmune mechanism, prospective follow up of GA cases and controls with a similar schedule of DM detection will be helpful in detecting rate of DM development over time.

OGTT is a more sensitive test than FBS alone in DM detection but it requires more time and an additional venepuncture. As a result, recruitment of control may be more difficult. It will be interesting to find out if there is any difference in results using OGTT as a diabetic measure.

The way in which resolution of GA is reported in various series is different. Point estimate of remission rate at various times is most often employed. Kaplan- Meier estimate is theoretically better as it includes the survival experience of censored data (data from non-remitted and defaulted cases). Standardization on reporting is suggested to allow direct comparison of data from different studies.

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# Appendix 1

## Granuloma annulare case data

### Demographic data:

Clinic: \_\_\_\_\_ Patient no.: \_\_\_\_\_  
 Name: \_\_\_\_\_ Sex: M/F Age: \_\_\_\_\_  
 Clinic no: \_\_\_\_\_ Ethnic group: \_\_\_\_\_

### Clinical Data:

**Onset of lesion** Age: \_\_\_\_\_ Date: \_\_\_\_\_

**Morphology of lesion:** Annular/ papular/ perforating/ Others/ Mixed:  
 subcutaneous

**Distribution:** Arm:\_\_\_ Elbow:\_\_\_ Forearm:\_\_\_ Wrist:\_\_\_ Hands(D/P):\_\_\_  
 Thigh:\_\_\_ Knee:\_\_\_ Calf/Shin:\_\_\_ Ankle:\_\_\_ Feet(D/S):\_\_\_  
 Chest:\_\_\_ Abdomen:\_\_\_ Back:\_\_\_  
 Face:\_\_\_ Scalp:\_\_\_ Ears:\_\_\_  
 Genitalia:\_\_\_ Others:

Total no. of lesions: \_\_\_\_\_ Generalized or Localized

**Symptoms:** pruritic/ pain/others:

? in remission now Y/N If yes, duration of disease: \_\_\_\_\_

? Ever remitted Y/N

### **Recurrence:**

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**Precipitating Factors** Sunburn Drug URTI Trauma  
 Insect bite Weather Pregnancy  
 Stress Others

**Past Health:** DM: Y/N for \_\_\_\_\_ yrs If DM+ve on insulin Y/N

DM diagnosed by FBS/spot sugar/OGTT

Others: 1. \_\_\_\_\_ 2. \_\_\_\_\_  
 3. \_\_\_\_\_ 4. \_\_\_\_\_  
 5. \_\_\_\_\_ 6. \_\_\_\_\_

**Family History:** 1. GA Y/N 2. DM Y/N

**Agree for blood test** Y/N FBS: \_\_\_\_\_ ( / / )

**Previous DM screen** Y/N Method: urine sugar/FBS/spot sugar/OGTT

### **Treatment:**

Type	Duration	Response
1.		
2.		
3.		

## Appendix 1

## Appendix 2

Clinic:

Date: \_\_\_\_\_

### Data for Granuloma annulare control cases

1. Year of birth \_\_\_\_\_

2. Sex     M / F    

3. Family history of DM     Y / N    

4. Agree for study (0=disagree, 1=agree) \_\_\_\_\_

If agree for study, proceed to the following sessions:

5. Personal history of DM

a) ? DM (0= -ve, 1= +ve) \_\_\_\_\_

b) Method used if (a) is +ve (0=urine sugar, 1= spot sugar, 2= FBS, 3= OGTT) \_\_\_\_\_

c) If DM +ve, on oral drugs or insulin? (0= OHA, 1=insulin) \_\_\_\_\_

6. Dermatology diagnosis \_\_\_\_\_

7. Clinic no.: \_\_\_\_\_

8. FBS: \_\_\_\_\_

## Appendix 3

### Memo to Granuloma Annulare Clients

#### **Granuloma annulare: review of cases in the Social Hygiene Service and a case-control study of its association with diabetes mellitus**

We are conducting a study of granuloma annulare. The aetiology of the disease is still not known and its relationship with diabetes mellitus is inconclusive. Some studies showed a relationship of the disease with diabetes mellitus while others did not. Most of the studies were carried out in the Western population. We are collecting information from clients with granuloma annulare in the Social Hygiene Service. The required data include age of onset, sex, region of involvement, response to therapy, recurrence history and past medical illness of the clients especially the diabetic status, etc. If you are not known to have diabetes mellitus in the past, we would like to invite you to have a fasting blood sugar test. All information collected is confidential. If there is any abnormality detected in the fasting blood sugar, we shall refer you to the government general outpatient clinic or the specialist clinic for follow up.

You are reminded that participation in the study is entirely voluntary. There will be no difference in the quality of care you will receive in this clinic whether you agree to participate in the study or not.

Social Hygiene Service, Department of Health

#### **環狀肉芽腫病人備忘**

##### **環狀肉芽腫：病歷回顧及與糖尿病關連之對照研究**

我們正從事皮膚病環狀肉芽腫的研究。這種皮膚病的成因仍然不明。有部份的研究顯示此病與糖尿病有關連，但亦有研究否定這一點，現在還沒有結論，而且大部份的研究是在外國進行。我們希望集合在香港社會衛生科內證實患有這種皮膚病患者進行研究；範圍包括發病年齡、性別、發病範圍、對治療之反應、有否復發等及與其他病患尤其是與糖尿病之關係。若果你沒有糖尿病，我們會邀請閣下空腹檢驗血糖。所有個人資料，絕對保密。若血糖出現不正常的情況，我們會轉介你往其他政府或專科門診進行跟進。

你是否參加這項研究，純屬自願，你不會因為拒絕參加而受到次等待遇。

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## Appendix 4

### Memo to control clients

#### **Granuloma annulare: review of cases in the Social Hygiene Service and a case-control study of its association with diabetes mellitus**

We are now conducting a study to assess the relationship between granuloma annulare (a skin disease) and diabetes mellitus. You have been chosen as a subject in the control group. We would like to collect data on the diagnosis of your skin problem, and personal and family history of diabetes mellitus for analysis. If you are not known to have diabetes mellitus, we would like to invite you to have a fasting blood sugar test. All information collected is confidential. If there is any abnormality detected in the fasting blood sugar, we shall refer you to the government general outpatient clinic or the specialist clinic for follow up.

You are reminded that participation in the study is entirely voluntary. There will be no difference in the quality of care you will receive in this clinic whether you agree to participate in the study or not.

Social Hygiene Service, Department of Health

### **對照病人備忘**

#### **環狀肉芽腫：病歷回顧及與糖尿病關係之對照研究**

我們正在進行關於環狀肉芽腫（一種皮膚病）與糖尿病關係之研究。閣下已被抽選為對照之組別以作比較。所需要的資料包括閣下之皮膚病診斷，本人及家族糖尿病的病史。若果閣下沒有糖尿病，我們將誠邀閣下空肚抽驗血糖。所有個人資料，絕對保密。如發現血糖有不正常的情况，我們將轉介閣下往政府門診或專科進行跟進。

你是否參加這項研究，純屬自願，你不會因為拒絕參加而受到次等待遇。

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## Appendix 5

### Definitions of terms

Age of onset	Age when skin lesions were first noticed
Family history of DM	Family history of DM in first degree relative
Granuloma	An accumulation of histiocytes
Palisading granuloma	Histiocytic infiltration surrounding altered collagen, with the long axis of cells perpendicular to the necrobiotic areas
Interstitial granuloma	histiocytes infiltrating between and about the collagen fibres
Sarcoidal granuloma	Aggregations of epithelioid histiocytes, occasional giant cells and a rim of lymphocytes that resemble sarcoidosis
Granuloma annulare	A degenerative disease of the skin, characterized by focal degeneration of collagen with surrounding areas of reactive inflammation and fibrosis
Mucin	Appears as faint blue material with a stringy and granular appearance on routine hematoxylin and eosin stain, can be highlighted by alcian blue stain or colloidal iron stain
Necrobiosis	Refers to non-specific connective tissue alteration, usually associated with various granulomatous inflammation of skin
Time for complete remission	Interval from onset of disease to complete remission
Time for relapse	Interval from complete remission to recurrence of disease



## Appendix 5

Treatment response	Owing to the retrospective nature of study, partial remission is difficult to assess and response is divided into persistent disease and complete remission
Complete remission	Disappearance of all skin lesions, sometimes with residual hyperpigmentation or scarring
Persistent disease	Evidence of active skin disease of various severity
Relapse	Recurrence of skin lesions after complete remission

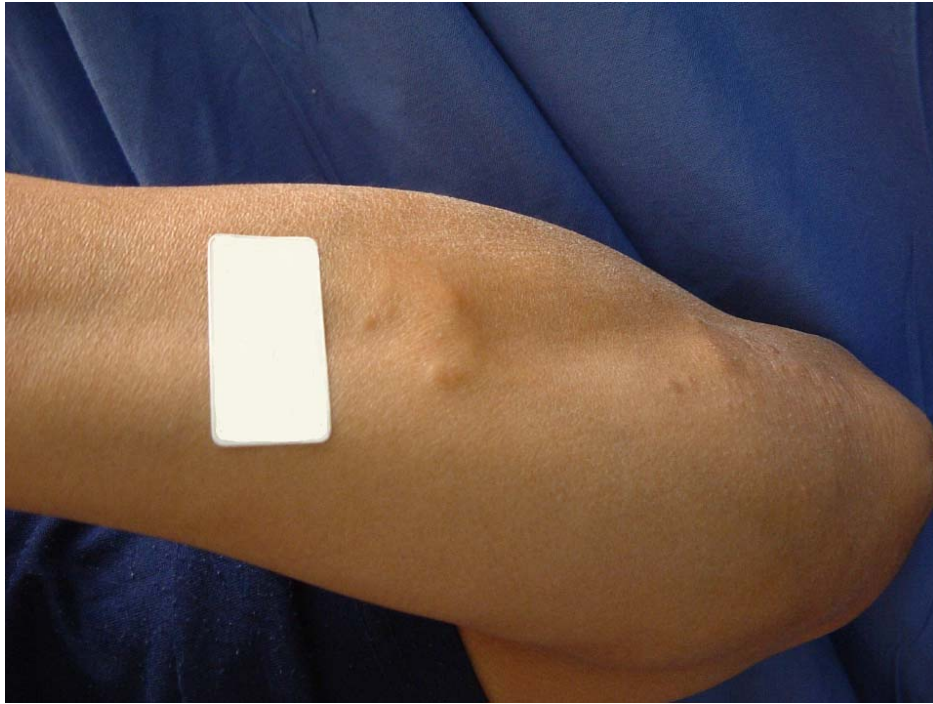


Plate 1. Localized GA with skin coloured papules over the left elbow. A vague arciform pattern is noted in the centre. There is no epidermal change.



Plate 2. Typical GA with erythematous nonscaly arciform lesions over the left elbow.



Plate 3. GA with annular lesions over both hand dorsa and papular lesions over the distal forearms. Edge of skin lesions is raised.



Plate 4. GA: predominant papular form with slightly erythematous papules over the distal forearms.



Plate 5. Generalized GA: coalescing papules without central clearing, forming plaques over both elbows.



Plate 6. Generalized GA with well defined erythematous plaques over the abdominal wall. Surface changes are absent (same patient as Plate 5).





Plate 7 a and b. Generalized GA with extensive coalescing papules over the chest, abdomen, back and arms.



Plate 8. Generalized GA with annular lesions over the abdominal wall.



Plate 9. Generalized GA with multiple lesions over the right elbow. Some of the lesions have fused to give a serpiginous outline (same patient as Plate 8).



Plate 10. Generalized GA, same patient as Plate 8. Central clearing is less evident in the right shin and foot dorsum giving a plaque appearance.



Plate 11. Generalized GA with annular and serpiginous lesion over the right abdominal wall and right hip. Postinflammatory pigmentation over the centre of lesions can sometimes occur.





Plate 12. Perforating GA with skin colour papules over the hand dorsum. Umbilication is present in papules over dorsum of the third metacarpophalangeal joint.

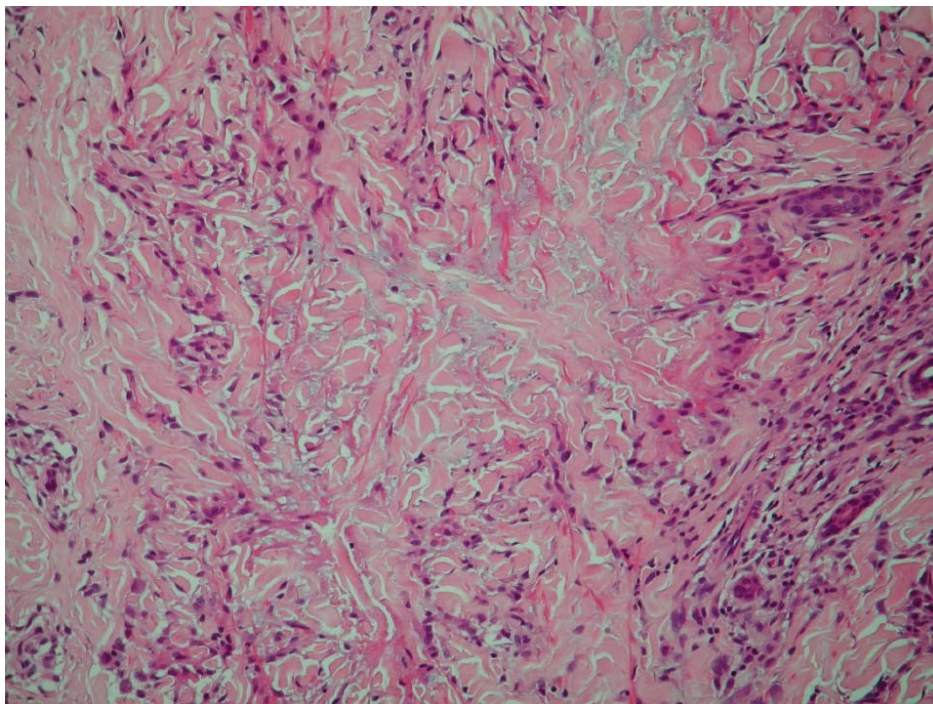


Plate 13. Histology: typical palisading granuloma with central necrobiosis. The collagen fibres are more fragmented and separated from each other. Mucin, which appears as bluish stringy and granular material between collagen fibres, can sometimes be noted on hematoxylin and eosin stain.



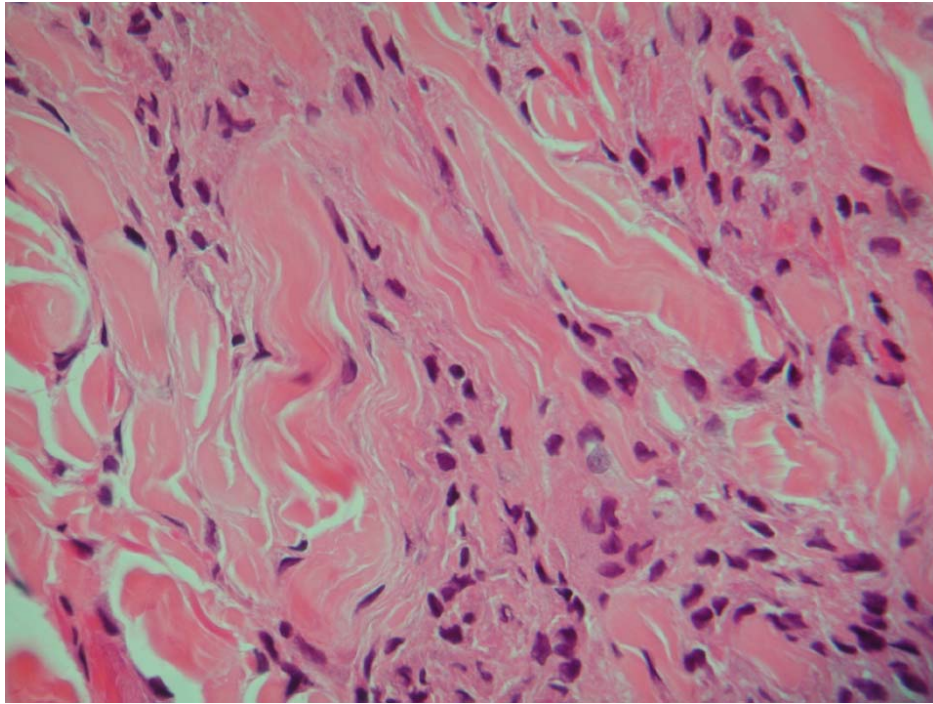


Plate 14. Histology: interstitial pattern showing histiocytes, with large and occasional reniform nuclei and prominent cytoplasm, infiltrate between collagen fibres. Necrobiosis is less prominent in this form of GA.

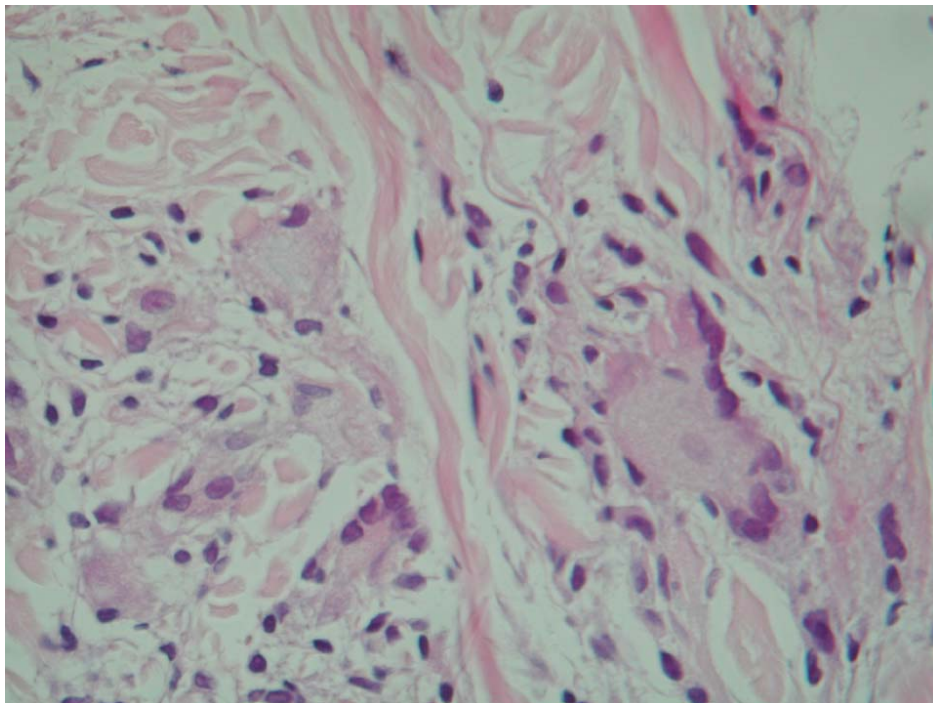


Plate 15. Histology: histiocytes and occasional giant cells are the main inflammatory cells in GA.

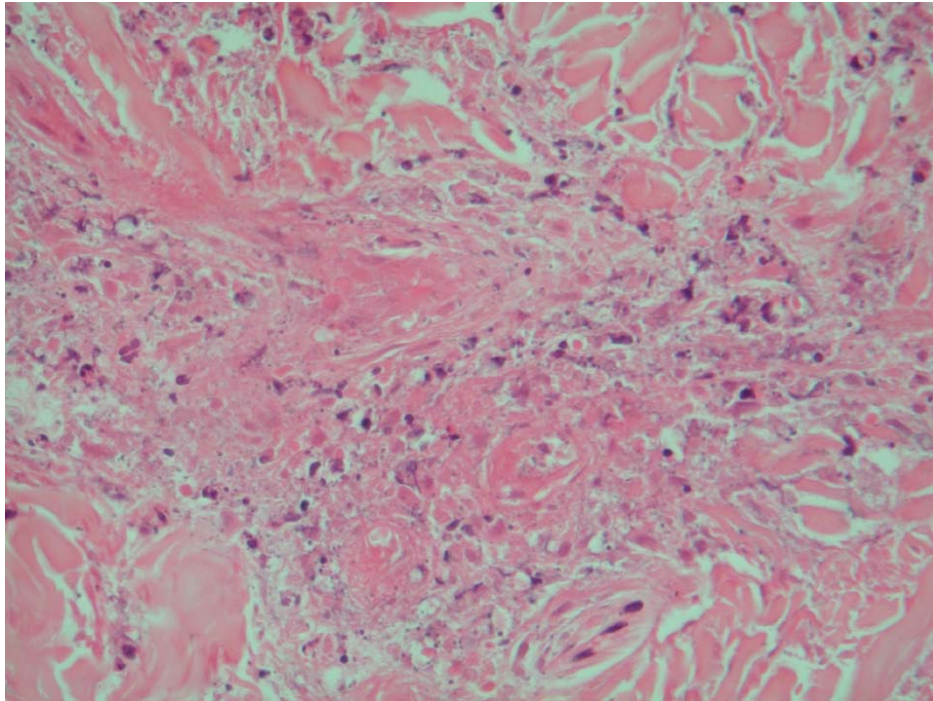


Plate 16. Histology: nuclear dust can sometimes be identified in GA lesions. They may represent apoptotic inflammatory cells or other cell types.

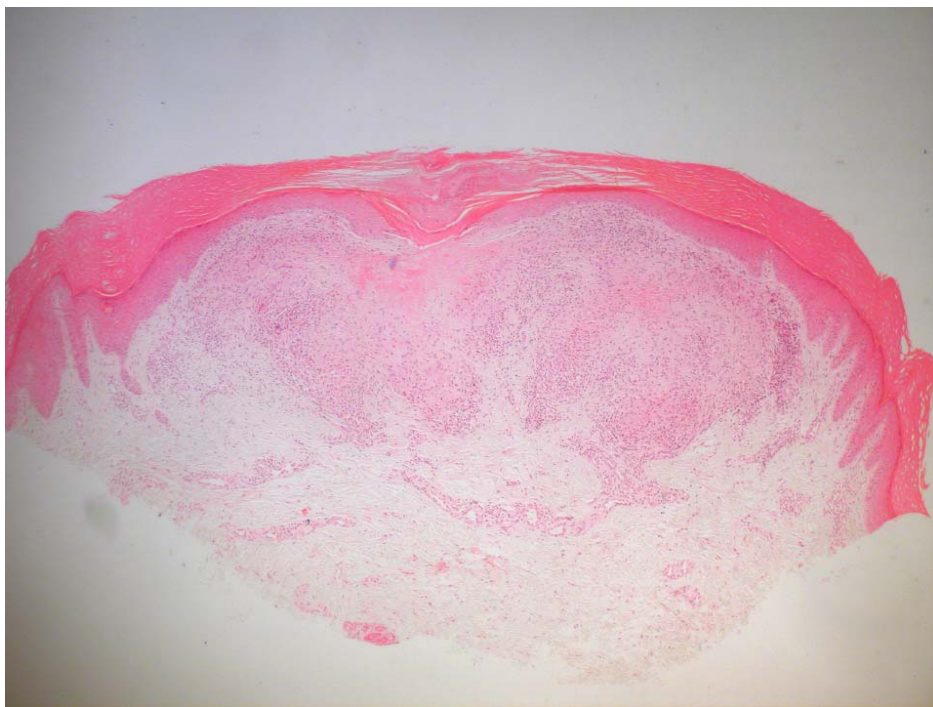


Plate 17. Histology: perforating GA with a 'busy looking' superficial dermis. Necrobiosis, which appears as pinkish material, is already evident in this scanning view. A central 'dip' is also present, which corresponds clinically to the umbilicated papule.



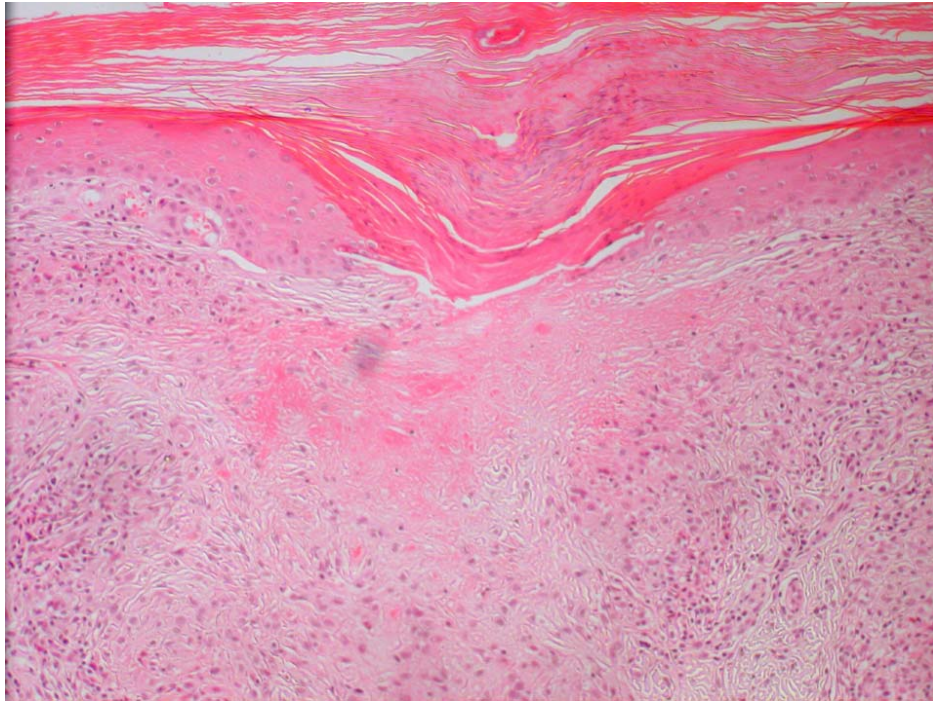


Plate 18. Histology: perforating GA (higher power of Plate 17). Note the palisading granuloma, epidermal destruction and impending rupture of epidermis.