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Original Article

Granuloma annulare: review of 31 cases in Social Hygiene Service

環形肉芽腫：社會衛生科 31 例回顧

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A retrospective study on 31 cases of granuloma annulare (GA) had been carried out in the Social Hygiene Service. Male to female ratio was 1.82:1. Age of onset was distributed bimodally in both sexes, with median age of onset of 45 years in male and 61 years in female. 38.7% had onset of disease in the first three decades of life. Localised, generalised, perforating and subcutaneous GA accounted for 67.8%, 25.8%, 3.2% and 3.2% respectively. They were mostly found on distal extremities (excluding palms and soles). Symptoms were absent (77.4%) and no precipitating factors could be identified (90.3%) in most cases. Over 80% of GA cases were followed up for more than two years. Three cases of localised GA cleared without treatment within one month after skin biopsy. Topical steroid was the most common treatment employed in this study. Systemic isotretinoin cleared a generalised GA case but dapsone failed in another subcutaneous GA case. A total of 21 out of 31 GA cases (67.7%) achieved complete remission from one to 132 months. The present study demonstrates essentially similar clinical features of GA in the local population as compared with western literature. A tendency of less female cases in local Chinese remains to be proven by a larger series.

社會衛生科進行了 31 例環形肉芽腫的回顧性研究。男女比例為 1.82:1 。發病年齡於男女兩個組別均呈雙峰分佈。發病中位年齡於男性為 45 歲，女性為 61 歲。 30 歲前發病者佔 38.7%。局部性、廣泛性、穿透性、及皮下環形肉芽腫分別佔 67.8%， 25.8%， 3.2% 和 3.2%。好發部位為遠側肢體(掌蹠除外)。大部分患者無症狀(77.4%)及無誘因(90.3%)。隨訪兩年以上者佔 80% 以上。 3 例局部性環形肉芽腫於活檢後一個月內自行消退。最為常用的治療為局部皮質激素。口服異維甲酸於一例有效。氨苯碸於另一例無效。 31 例中的 21 例(67.7%)於 1 至 132 個月完全緩解。本研究發現本地環形肉芽腫病例的臨床表現與西方文獻所載基本相若。本地患者女性較少的現象須由規模更大的研究證實。

Keywords: Chinese, Granuloma annulare

關鍵詞：中國人， 環形肉芽腫

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Introduction

Granuloma annulare (GA) is a degenerative disease of the skin, characterised by focal degeneration of collagen with surrounding areas of reactive inflammation and fibrosis.[1] The lesion of GA was first described by Colcott Fox in 1895 and was named by Radcliffe-Crocker in 1902.[2]

There are several clinical manifestations, ranging from localised GA, which is the most common form, to less commonly seen variants, including generalised, subcutaneous and perforating GA.[3-5] Most case series in the literature describe Caucasian patients. Only one GA study in Singapore includes 68.2% of Chinese patients.[4] A retrospective study has been carried out in the Social Hygiene Service of the Hong Kong Special Administrative Region. The aim of the study is to review the clinical features of GA in our locality to see if there is any difference of the disease between Chinese and Caucasian.

Methods

The skin biopsy records of dermatology clinics in the Social Hygiene Service from 1st January 1990 to 31st July 2002 were scrutinised manually and results with keywords 'granuloma annulare' were identified. The clinical records, pathology reports and clinical photographs were assessed to see whether cases were compatible with the diagnosis of GA. All the cases had typical clinical morphology of GA, including its variants such as perforating and subcutaneous forms. In typical GA, skin lesions were composed of skin-coloured, erythematous to violaceous dermal papules that might be solitary or arranged in an arciform and circular pattern. Epidermal changes were absent. In subcutaneous GA, skin coloured subcutaneous nodule(s) was present. Perforating GA manifested clinically as skin-coloured to erythematous papules that might have central crust, umbilication, or pustules. In later stage of perforating GA, creamy or clear discharge might be present. The histopathology slides were reviewed together with senior pathologists. Histologically, all GA cases in this study showed necrobiosis of collagen, a predominantly histiocytic infiltrate that can be arranged in a palisading, interstitial or sarcoidal pattern and mucin deposition. Epidermal change was absent in typical GA except in the perforating variants which might have minor epidermal thinning and parakeratosis as early features and complete perforation and extrusion of the necrobiotic material as late features. This study only included those cases clinico-pathologically compatible with GA, had retrievable clinical records and were able to attend a personal or telephone interview with the author. Demographic data, clinical GA data including its age of onset, morphology, symptoms, sites of predilection, precipitating factors and response to treatment were recorded during the interview. Physical examination was performed for cases who were personally interviewed to detect remission status. Fasting blood sugar (FBS) was arranged for those GA cases that had no history of diabetes mellitus (DM) after obtaining informed verbal consent. The results of FBS were classified according to the criteria published by the American Diabetes Association (1997).[6] The data were analysed by using SPSS 10.0. 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.

Results

Demographic data

This study identified 83 GA cases from the biopsy record of Social Hygiene Service from 1st January 1990 to 31st July 2002. But clinical records were not retrievable in 23 cases and another 18 patients could not be contacted because of either change in address or telephone number. Further analysis rejected six cases that did not have the typical clinico-pathological features of GA and five other cases refused to participate in the present study. A total of 31 GA cases had thus been finally recruited. The average incidence of GA from 1990 to July 2002 was 0.81 per 10,000 new cases seen. Age of GA onset ranged from 2 to 81 years with a median of 46 years and an interquartile range of 60 years. As evident from Figure 1, the age of onset in both male and female patients were

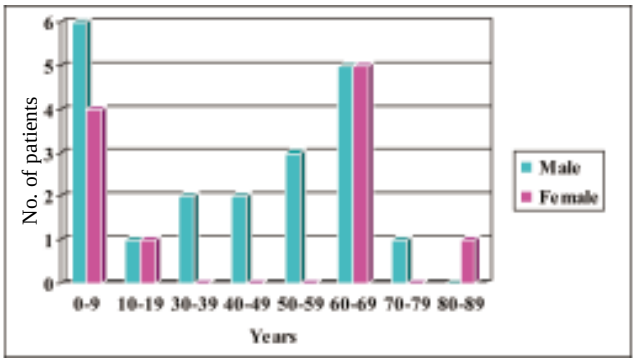

Figure 1. Age of onset of GA according to gender.

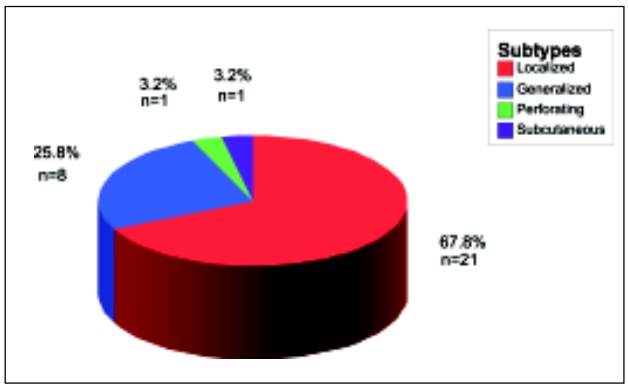

Figure 2. Distribution of various GA subtypes.

distributed bimodally. In 38.7% of cases, GA had its age of onset of in the first 3 decades. Twenty males were affected as compared with eleven females, giving a male to female ratio of 1.82:1. 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 years in male and 61 years in female, which were not significantly different (Mann-Whitney test, $p = 0.664$).

GA subtypes

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. Cases were classified into generalised, localised, perforating and subcutaneous GA. Localised GA had solitary or a limited number of skin lesions that might affect one or several anatomical areas and papules might be arranged in an annular or arciform pattern. Generalised GA, according to Dabski et al,[7] had widely distributed lesions of a large number affecting the trunk and at least one extremity. Perforating GA was characterised clinically by umbilicated, crusted or pustular papules.[8] Subcutaneous GA was characterised clinically by subcutaneous nodule(s). The commonest form was localised GA, accounting for 67.8%. This was followed by generalised GA, which represented 25.8% of cases. Perforating and subcutaneous subtypes each accounted for 3.2% (Figure 2). The median age of onset in localised GA was 34 years, which was significantly lower than the median age of onset of 64.5 years in the generalised variant (Mann-Whitney test, $p = 0.003$). However, there was no relationship between gender and subtypes of GA (Fisher's exact test, $p = 1.0$).

Site of involvement

GA involved most often 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 generalised 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 generalised GA).

Symptoms

In 24 cases, GA lesions were asymptomatic (77.4%). Pruritus was present in six cases (19.4%), including three localised GA (one had underlying eczema), two generalised GA and one perforating GA. One generalised GA patient, with lesions on the first web space of hand, complained of pain

on writing secondary to pressure effect. Symptoms were present in 37.5% and 14.3% of generalised and localised GA cases respectively, but the difference was not significant (Fisher's exact test, $p = 0.31$).

Precipitating factors

In 28 cases (90.3%), no precipitating factors could be identified. Reported precipitating factors in other cases included topical herbal application, sun exposure, attacks of common cold and summer season.

Coexisting diabetes mellitus

There were five known DM cases. FBS was checked in another 22 cases that agreed for a blood test after interviews with the author. The remaining four cases who refused FBS at the time of interview consisted of 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.

Finally DM was found in 7 out of 30 (23.3%) GA cases (one case had never been screened for diabetes but he 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 impaired fasting glucose tests 2.5 years after GA.

Treatment and disease course

Topical steroid (mostly of moderately potent or potent class according to the classification in Martindale[9]) 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 localised GA patients as CR occurred within one month after skin biopsy. Six patients 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 another case, 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 with subcutaneous GA but no clinical response was noted. She was then treated with topical steroid and intralesional steroid for 5 courses and had CR after 70 months. Another patient with generalised GA had persistent disease after five months of moderately potent topical steroid. Oral isotretinoin 0.5 mg/kg/day was then given, resulting in CR after six months. In summary, GA cases were followed up for a range of 14 to 206 months after the onset of GA with a mean of 67.5 months. Over 80% of cases were followed up for more than 24 months. CR had been achieved in 21 out of 31 GA cases (67.7%) from one to 132 months. However, 7 out the 21 remitted cases (33.3%) recurred after the first CR. These comprised four localised, two generalised and one subcutaneous GA. The median time for relapse was 9.5 months. Six relapsed cases had persistent disease at the time of interview. Only one case had second remission after treatment with topical and intralesional steroid.

Discussion

An incidence of 0.12% new GA cases was reported in one hospital in England,[10] as compared with an average incidence of 0.0081% new cases in the present study. But our incidence figure is an underestimation because not all clinical records are retrievable and not all GA cases have skin biopsy. In contrast with the western literature (Table 1), this study seems to have more male cases, but this is not statistically significant.

Onset of GA was mostly in the first three decades in the literature,[3,4,10] contrasting with only 38.7%

Table 1. Age and sex distribution of GA in the literature

Source	Total number of patients	Localised GA (%)	Age of onset (% in first 3 decades)	Male to female
Studer, et al[3]	84	75	62	1: 2.8
Tan, et al[4]	41	82.9	66	1: 1.56
Wells, et al[10]	179	95	71	1: 2.2
Dabski, et al[7]	100	0	11	1: 2.2
This study	31	67.8	38.7	1.82:1

of cases in this study. The difference can be attributed to the variation in proportion of GA subtypes. In a series of patients with generalised GA, only 11% had their disease onset in the first three decades.[7] In this study as well as in the others, the age of onset of GA is higher in the generalised than the localised variant. This study has 67.8% of localised GA, as compared with 75-95% in other series, and this may be the cause of the later onset of disease in our series. A bimodal age of onset described for generalised GA in the literature[11] is not seen in the present study in which a single peak of onset in the sixth decades is present.

The percentage of each GA subtypes in this study and in various western series are similar (Table 2).[3,10,12] Localised GA is the most frequent, followed by generalised subtype. Perforating and subcutaneous forms account for less than 10%. This study, as compared with other series, has a lower proportion of localised GA. Generalised GA accounts for 25.8%, which lies in the upper range of percentage as compared with the literature (5-25%, see Table 2). 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 et al.[3] The distribution of skin lesions is similar to that reported in the literature.[3,4] Distal extremities beyond the elbow or knee region are commonly affected. In perforating GA, the extremities especially the hands and arms are commonly involved.[8] Subcutaneous GA commonly involves not only distal extremities but also scalp and forehead.[13]

Skin lesions of GA are basically asymptomatic. Pruritus and pain may be present in some cases. A study on generalised GA showed a higher proportion of symptomatic cases.[7] Our study also shows a similar trend. Symptoms are present in 37.5% and 14.3% of generalised and localised GA cases respectively, but the difference is not significant. Table 3 highlights the differences between localised and generalised GA.

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

Table 2. Subtypes of GA in various case series

Source	Year	LGA %	GGA %	PGA %	SCGA %
Studer, et al[3]	1996	75	19	1.2	4.8
Haim, et al[12]	1973	75	25	0	0
Wells, et al[10]	1963	95	5	0	0
This study	2002	67.8	25.8	3.2	3.2

Abbreviations of GA subtypes: LGA: localised subtype; GGA: generalised subtype; PGA: perforating subtype; SCGA: subcutaneous subtype

Table 3. Differences of localised GA and generalised GA identified in this study

	Localised GA	Generalised GA
Distribution	A limited number of skin lesions that may affect one or several anatomical areas	Widely distributed lesions of a large number affecting the trunk and at least one extremity
Median age of onset*	34	64.5
Symptomatic cases (%)**	14.3	37.5
DM prevalence (%)#	15	50

* Difference is statistically significant; ** Difference is not statistically significant; # Direct comparison was not made as an important confounding factor, age, is different between the two subgroups

medium, phlebitis, sepsis after surgery and stress.[3,4,7] The present study also identifies some precipitating factors but cannot prove a cause-effect relationship or the mechanism involved in the exacerbation. The relationship between GA and DM is controversial.[1] In the present study, DM is present in 23.3% of GA cases. A case-control study carried out in Hong Kong showed that the prevalence of DM in GA was not differed from age and sex matched controls.[14]

GA is rare and there is no large-scale double blind randomised 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.[11] But the persistence and disfigurement of generalised GA has prompted treatment in other cases.[15] The choice of therapy depends on GA subtypes, side effects and patient preference (Table 4).[16] In the present series, topical steroid mostly of moderately potent or potent class is the most often employed treatment, probably reflecting the familiarity of use by physicians and its lack of serious side effect. Dapsone has been tried in one case but it fails to clear the skin lesions. Systemic isotretinoin has been successful in clearing the skin lesions of a generalised GA case. An interesting phenomenon observed in this study and in the literature is resolution of GA after skin biopsy.[17] As they are

Table 4. Therapeutics for GA[16]

Localised GA	Generalised GA
First line	First line
Cryotherapy	Photo (chemo) therapy
Intralesional and topical steroid	Systemic isotretinoin
	Dapsone
Second line	Second line
Intralesional interferon	Cyclosporine
Surgery	Systemic steroid
	Chlorambucil
	Antimalarials
	Potassium iodide
	Pentoxifylline
	Niacinamide
	Topical vitamin E

uncontrolled case series, it is difficult to eliminate the element of natural regression. Three cases of localised 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.[17] However, it is not clear why only some GA cases resolve after biopsy.

Conclusion

In conclusion, 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 generalised GA is significantly higher than that of localised GA. And this may account for the later age of onset of GA in this study, as compared with the western literature. A tendency of less female cases in local Chinese remains to be proven by a larger series.

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References

1. Cunliffe WJ. Necrobiotic disorders. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors. Textbook of Dermatology. 6th ed. Oxford: Blackwell Science, 1998:2297-309.
2. Dahl MV. Granuloma annulare. In: Freedberg IM, Eisen AZ, Wolff K, et al, editors. Dermatology in General Medicine. 5th ed. New York: McGraw-Hill, 1999:1152-7.
3. Studer EM, Calza AM, Saurat JH. Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. Dermatology 1996;193: 364-8.
4. Tan HH, Goh CL. Granuloma annulare: a review of 41 cases at the national skin center. Ann Acad Med Singapore 2000;29:714-8.
5. Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. Int J Dermatol 1997;36:326-33.
6. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26 Suppl 1:S5-20.
7. Dabski K, Winkelmann RK. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. J Am Acad Dermatol 1989;20:39-47.
8. Penas PF, Jones-Caballero M, Fraga J, Sanchez-Perez J, Garcia-Diez A. Perforating granuloma annulare. Int J Dermatol 1997;36:340-8.
9. Sweetman SS. Corticosteroids. In: Martindale: the complete drug reference. 33rd ed. London: Pharmaceutical Press, 2002:1039-81.
10. Wells RS, Smith MA. The natural history of granuloma annulare. Br J Dermatol 1963;75:199-205.
11. Muhlbauer JE. Granuloma annulare. J Am Acad Dermatol 1980;3:217-30.
12. Haim S, Friedman-Birnbaum R, Haim N, Shafrir A, Ravina A. Carbohydrate tolerance in patients with granuloma annulare. Study of fifty-two cases. Br J Dermatol 1973;88:447-51.
13. Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: a review of 47 cases. Pediatrics 1997;100:965-7.
14. Chan PT. Granuloma annulare: review of cases in the Social Hygiene Service and a case-control study of its association with diabetes mellitus. Dissertation for exit examination of Hong Kong College of Physicians, 2003.
15. Schleicher SM, Milstein HJ, Lim SJ, Stanton CD. Resolution of disseminated granuloma annulare with isotretinoin. Int J Dermatol 1992;31:371-2.
16. Ilchyshyn A. Granuloma annulare. In: Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I, editors. Treatment of skin disease comprehensive therapeutic strategies. London: Mosby, 2002:247-50.
17. Levin NA, Patterson JW, Yao LL, Wilson BB. Resolution of patch-type granuloma annulare lesions after biopsy. J Am Acad Dermatol 2002;46:426-9.