A retrospective analysis of 44 patients with granuloma annulare during an 11-year period from a tertiary medical center in south Taiwan

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ABSTRACT

Background: Granuloma annulare (GA) is a benign, usually self-limited, inflammatory skin disease. Although there have been several studies that review pathoclinical features about GA, the relevant epidemiological study in Taiwan was lacking. The purpose of this study is to evaluate the pathoclinical features and treatment outcome of GA in Taiwan.

Methods: This study was performed by retrospective review of medical records and pathological slides of the patients diagnosed as GA in a tertiary referral medical center in Taiwan. Fisher exact test was performed to compare remission rate between adults and children, treatment and nontreatment groups.

Result: The study included 44 patients with GA: 23 male and 21 female. The incidence of GA showed a bimodal age distribution (peaks below 20 years and above 50 years). Localized type is most common, followed by generalized variant. Perforating GA is the rarest subtype and was exclusively found in children. The pathology of GA is characterized by necrobiosis (100%), palisading granuloma (81.8%), and mucin deposition (93.2%); 13.6% and 6.8% of GA patients had history of diabetes mellitus and dyslipidemia, respectively.

Conclusion: In contrast to the reported studies, the incidence of GA showed a bimodal age incidence with slight male preponderance. Our patients had higher prevalence of diabetes mellitus than the general Taiwanese population but had no increase in incidence of dyslipidemia. Whether patients received treatment or not does not affect the disease outcome. Overall, children have better prognosis than adults.

Introduction

Granuloma annulare (GA) is a benign, and usually self-limited, inflammatory skin disease. The disease incidence is estimated to be between 0.1% and 0.4%. The clinical manifestations vary, from localized, erythematous to flesh-colored papules with annular arrangement to the more generalized form. GA can develop in any skin areas, but it tends to occur on the lateral or dorsal surfaces of the hands and feet. GA is usually self-limited. The pathogenesis of GA remains unclear although abnormal repair in vascular injury or aberrant responses in delayed-type hypersensitivity may be involved. The diagnosis is made clinically or by skin biopsy with the typical histological findings of eosinophilic necrobiosis and pali-sading lymphohistiocytic infiltrates.

GA was reported to commonly affect children and young adults with a female preponderance based on hospital based studies performed in USA, Singapore, Switzerland, and UK. However, a recent study in Korea reported a bimodal distribution of onset age...
and a slight male predominance among patients with generalized GA. The mixed clinical and epidemiological pattern of GA might depend on the variations in clinical categorizations, races, and associated triggering factors. In Taiwan, several individual cases of GA have been reported; however, a comprehensive study to delineate the clinical categorizations, treatment outcome, associated disease, and histopathological features of GA is lacking. Therefore, we herein aimed to evaluate the clinical findings, histopathological features, associated diseases, and treatment outcomes in Taiwanese patients of GA.

Method

This study was performed by a retrospective review of medical records and pathological slides of the patients diagnosed as GA in Kaohsiung Chang Gung Memorial Hospital, a tertiary referral medical center from January 2002 to January 2013. In total, 44 patients were identified. Information including sex, age of onset, location, number and type of lesions, onset duration, clinical morphology, associated diseases, treatment and outcome were collected. Children were defined as those younger than 18 years. Skin specimens were fixed in formalin, later embedded in paraffin, and sectioned with 4-μm thickness. Sections were stained with hematoxylin and eosin and Alcian blue (pH = 2.5). Histopathological features including distribution patterns of inflammatory cells, mucin deposition, and infiltrative cell type were analyzed. The microscope slides were reviewed independently by one board-certified pathologist and one board-certified dermatologist. The diagnoses were made according to the constellation of clinical and pathological findings.

Based on clinical manifestations, the disease was classified into localized, generalized, subcutaneous, and perforating types. Solitary or a few lesions on a single anatomical site were defined as localized form. Generalized GA was defined as affecting at least the trunk and either upper, lower, or both limbs, based on the criteria initially stated by Dabski and Winkelmann. Subcutaneous GA was characterized by granuloma predominantly affecting subcutaneous tissue while perforating GA was featured by superficial umbilicated papules and transepidermal elimination of necrobiotic collagen. Representative clinical features for subtypes of GA are shown in Figure 1.

Treatment options with either systemic or topical medication were recorded. The treatment response was assessed by the dermatologist and by the patient. Follow-up was carried out by either medical charts or telephone interviews. Treatment response was classified as poor (no response), partial, or good (complete or nearly complete resolution).

Fisher exact test was performed to compare remission rate between adults and children, with or without treatment.

Results

Demographic data and clinical features of GA

In this study, 44 patients with GA were identified, of whom 23 were male and 21 female. The age of onset widely distributed, ranging from 2 years to 75 years (average age = 36.55 ± 24.86 years, median age = 40 years). Sixteen patients were children (36.4%) and 28 were adults (63.6%). A bimodal age distribution (peaks below 20 years and above 50 years) was noted (Figure 2). Nearly half of the patients (43.2%) had the disease in their 5th decade. Among the four clinical variants, the localized type is the most common, followed by the generalized variant. Subcutaneous GA occurs most often in children and young adults. Perforating GA is the rarest subtype and exclusively occurred in children. The majority of the lesions exhibited the clinical pattern of annular arrangement and papular morphology (Table 1). The mean disease duration is 9.5 months.

Association of metabolic diseases and GA

Among the 28 adult GA patients, six had diabetes mellitus (DM; exclusively noninsulin dependent DM), four had hypertension, three had dyslipidemia (1 had hypertriglyceridemia and 2 had hypercholesterolemia), one had history of ischemic stroke, and one
had non-Hodgkin’s lymphoma. Two patients fulfilled the criteria of metabolic syndrome. DM was found in five of the 13 patients with generalized GA (38.5%) and in one of the 14 patients with localized GA (7.1%; Figure 3). It appears that patients with generalized GA are more likely to develop DM than those with localized disease, although the difference did not reach statistical significance (p = 0.0691). In contrast to adult patients, none of the pediatric patients had concurrent chronic disease.

**Histopathological findings**

In all cases, the pathological findings involved histiocytic infiltration with necrobiotic. The histiocytes were arranged with a palisading pattern in 28 patients (63.6%), with an interstitial distribution dissecting collagen bundles in eight patients (18.2%) and the other eight patients (18.2%) had mixed distribution pattern of palisading and interstitial infiltration. Of the 44 specimens, 41 stained positively for mucin (93.2%). The inflammatory infiltrates were predominantly lymphocytes in all cases although in eight patients concomitant eosinophil infiltrates were also present (18.2%). Multinucleated giant cells were observed in seven cases (15.9%).

**Treatment and recurrence rate**

We were able to follow up the treatment outcomes in 35 patients (79.5% follow-up rate) including 22 adults and 13 children. The average follow-up period was 66.9 months. Among the 17 adult GA patients with treatment, 12 received topical steroid or intralesional steroid, and three of them achieved complete remission. Overall remission rate (complete plus partial) in the treated group was 76.5% (13/17). Five adult patients received oral dapsone. Of those patients, two patients had partial response while three others reported good response. In adult patients without treatment (n = 5), four (80%) reported disease remission (good response).

In eight pediatric patients with treatment (n = 8), all showed good to partial response to treatments (100% remission rate; Table 2). Among five pediatric patients without treatment, only one showed no remission (80% remission rate). Pediatric patients have statistically higher percentage of remissions [complete remission rate 45.5% (10/22) vs 84.6% (11/13) in adult and pediatric patients, respectively; Table 3].

In terms of treatment choices in different GA subtypes among adult and pediatric patients, patients with generalized GA all received treatments (n = 13 and 3 in adult and pediatric patients, respectively). In subcutaneous variants, all patients did not receive any treatments (n = 1 and 3 in adult and pediatric patients, respectively). For the localized variants, around half of the adult and the children received treatments (4/8 and 3/5 in adult and pediatric patients respectively). Two pediatric patients with perforating GA received dapsone.

Recurrences, defined as new lesions attack after clinically complete clearance, were noted in three adult and two pediatric patients. The disease-free interval varied from 3 months to 10 years.

**Discussion**

GA is a chronic, benign inflammatory skin disease that usually presents as annular plaques located on the extremities of young people. Age onset of GA was reported mostly in the first 3 decades in the previous literature. Majority of previous studies demonstrate female preponderance. However, in our study, it has a bimodal age distribution (one peak below 20 years and the other above 50 years) with slight male preponderance (male: female = 1.09: 1). Most patients were older than 50 years. In this study, consistent with previous literature, localized GA is the most frequent clinical variant in either children or adults. However, in this study, the prevalence of generalized GA in our patients (36.4%) is higher than that reported in other previous studies (range, 5–25.8%). Dabski and Winkeiam divided the clinical appearance of generalized GA into two forms. In the present study, the predominantly annular form accounted for 45.5%, whereas the predominant papular form accounted for 38.6%. Subcutaneous GA occurs most often in children and young adults. Perforating GA was the rarest subtype and exclusively seen in children.

The pathogenesis of GA has not been fully elucidated. Most patients cannot identify any precipitating factors. Reported precipitating factors in the literature were trauma, sunburn, insect bite, Bacillus Calmette–Guérin vaccination, drugs, upper respiratory infection, reaction to intravenous contrast medium, phlebitis, sepsis after surgery, and stress.
Many investigators have attempted to demonstrate a relationship between GA and other systemic diseases, with DM most noteworthy. The association of GA with DM remains controversial. Studer et al\(^1\) noted that 10 of 84 adult patients (12%) with GA (localized or generalized) had DM, as opposed to the 5% prevalence of DM among the regional population. However, other studies\(^13,14\) that looked for carbohydrate intolerance by performing glucose tolerance testing or assessing the hemoglobin A1c values failed to find an increased prevalence of altered carbohydrate metabolism in the patients with GA. Our study showed that the prevalence of DM in GA patient is 13.6% (5 generalized GA and 1 localized GA), which is higher than general adult population in Taiwan (6.38%).\(^15\) In our study, patients with generalized GA were more likely to develop DM than those with localized disease, although the difference was not statistically significance (\(p = 0.0691\)). Although the association between GA and DM is not settled, we recommended DM workup for the GA patients, especially for those who presented generalized type GA and age over 50 years.

Recently, several authors suggest a possible relationship between GA and dyslipidemia. In the study by Wu et al,\(^16\) dyslipidemia was more common in generalized than localized disease, and the annular lesion morphology was associated with hypercholesterolemia. Their cases with hyperlipidemia improved in their GA after effective lipid-lowering treatment. However, the prevalence of dyslipidemia in our patients was 6.8%, which seems not significantly higher than general population in Taiwan (11.2%).\(^17\) Dyslipidemia work up may be recommended in generalized GA, but further study for association between GA and dyslipidemia is needed.

GA is characterized by necrobiosis, granulomatous inflammation and mucin deposition. Necrobiosis was the most common pathological presentation in our study (100% in all biopsy specimens). Mucin was noted in 93.2% of all biopsy specimens. The presence of mucin helps differentiate GA from other dermatoses with palisading granuloma. The inflammatory cellular component consists of predominantly histiocytes (some of which are epitheloid or multinucleated), lymphocytes (the majority of which are T helper cells) and occasionally eosinophils. All patient with subcutaneous GA (n = 4) in our study had eosinophils infiltration and this is compatible with previous observation\(^1\) in which eosinophils are more commonly seen in subcutaneous GA.

Because localized GA is self-limited and asymptomatic, treatment usually is not necessary. Systemic therapy may be required for disseminated GA, and many different treatments have been proposed. Dapsone,\(^18\) isoretinoin,\(^20,22\) antimarial agents,\(^23\) cyclosporine,\(^24\) psoralen combined with ultraviolet A,\(^25,26\) topical imiquimol,\(^27\) or potassium iodide\(^28\) have shown positive outcome for generalized GA treatment. 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. According to our study, there are differential responses to treatment between adults and children. Adult patients without treatment had better disease outcome (good response rate) than those with treatment (good response rate, treatment: no treatment, 35%; 80%). The possible reason for this is that the patients receiving treatment clinically had more extensive disease and longer disease duration, which may imply that it is refractory to treatment. By contrast, 87.5% of children patients can achieve complete remission after treatment. In addition, 80% of pediatric patients without treatment also reported complete remission. Overall children have better prognosis than adults, especially in localized type GA (Table 3). Watchful waiting or symptomatic treatment may be sufficient for children.

It was not possible to determine the remission period due to recall error. Therefore, whether the treatment hastens the disease remission or not cannot be evaluated. Future study may be needed to record the period from the onset of the disease to complete remission. Detailed records may help in reaching better cost-effectiveness and decision-making in treating GA.

### Conclusions

GA is a benign, usually self-limited, inflammatory skin disease. In contrast to reported studies, the age distribution of GA in Taiwan showed a bimodal-age incidence with slightly male preponderance. Patients with GA, with the generalized form in particular, are more likely to develop DM. Whether patients received treatment or not does not significantly affect the disease outcome. Overall, the children had better prognosis than adults in our study.

### References