Generalized granuloma annulare: a report of 2 cases and literature review

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Granuloma annulare (GA) is an idiopathic benign skin disease, characterized by annular dermal plaques or papules. Much is still unknown concerning its aetiology, association, and pathogenesis. We report two patients with generalized GA (GGA), with different age of presentation, co-morbidities, and disease morphology.

Herein, we report two patients with GGA with different clinical features, disease morphologies, and histology patterns. We also illustrate the treatment used in our patients and the outcome.

GA is a self-limiting disease and can regress spontaneously. GGA tends to be more persistent and usually requires treatment for symptomatic or cosmetic reasons. Expert consensus on treatments recommends topical corticosteroid, psoralen and ultraviolet A (PUVA), and antimalarial drugs.

Keywords: generalized granuloma annulare, pallisade, interstitial, hydroxychloroquine, diabetes mellitus

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INTRODUCTION

Granuloma annulare (GA) is an idiopathic benign granulomatous skin disease, characterized by annular dermal plaques or papules with female predominance [1]. It can be divided into 4 main clinical forms, namely localized, generalized, subcutaneous, and perforating [2]. The histology shows that granulomatous lesion is composed of necrobiotic collagen mixed with mucin deposition in a palisading or interstitial pattern. Various pathomechanisms have been postulated, including delayed hypersensitivity response to an unidentified antigen [1,3].

Generalized granuloma annulare (GGA) is defined as multiple lesions over the trunk and limbs. Disseminated granuloma annulare is used when there exists more than 10 lesions [24]. GGA tends to affect middle-aged females, but is also a common pattern for children and adolescents. It is commonly associated with systemic diseases, such as diabetes mellitus, thyroid disorders, malignancies, lipid abnormalities, and infections [3]. However, its cause cannot be exactly elucidated.

Localized GA is usually benign and self-resolving. In the case where 50% of them are resolved within 2 years, 40% of the lesions tend to recur. GGA is usually asymptomatic, however, some may present with severe pruritus. Spontaneous clearing usually occurs at variable times, ranging from 4 months to more than 10 years [24]. They usually need treatment due to cosmetic nuisance and occasionally due to pruritus. However, there is no good evidence on the treatment of GGA, and the suggestions are based on case series and expert consensus. The treatment outcomes are also concerned with variables.

Herein, we report two patients with generalized GA (GGA), with different clinical features, disease morphologies, and histology patterns. We also illustrate the treatment used in our patients and the outcome.

CASE PRESENTATION

Our first case is a 26-year-old Malay gentleman with no known medical illness, presented with large, asymptomatic skin-coloured, annular plaques over the upper limbs, dorsal hands, upper back and trunk for 8 months (Figures 1A & 1B). He denied any constitutional symptoms. Our differential diagnoses included erythema annulare centrifugum, lepromatous leprosy, and cutaneous sarcoidosis. The histological examination (Figure 2A) showed predominantly perivascular and periadnexal lymphocytic infiltrate with the foci of epithelioid granulomas in an interstitial pattern. No necrobiosis or mucin deposition was seen. (Figure 2B). Negative Wade-Fite stain and slit skin smear examination excluded leprosy. His blood sugar, thyroid function test and fasting serum lipid were all within the normal range. On follow-up 2 months after the diagnosis, there was spontaneous partial resolution of skin lesions. He was lost to follow up subsequently.

Our second case was a 67-year-old Malay female with underlying diabetes mellitus (DM) presented with a two-month history of pruritic erythematous discrete papules over the extensor forearms, dorsal hands, upper back and lower limbs (Figures 3A and 3B). The histological examination (Figure 4A) showed an intradermal lesion composed of palisading granulomas with the central area of mucin deposition. The granuloma was composed of epithelioid cells mixed with occasional Langhans type multinucleated giant cells. Alcian-blue stain demonstrates mucin deposition mixed with dead collagen in the centre (Figure 4B). There was absence of fragmented elastic fibres trapped within the giant cells, excluding a variant form of GA called actinic granuloma. Her fasting serum lipid and thyroid function test were unremarkable. In view of extensive lesions and poor response to topical corticosteroids, hydroxychloroquine was commenced at a dose of 400mg/day (6mg/kg) adjunct to potent topical steroids, with which she responded only partially.

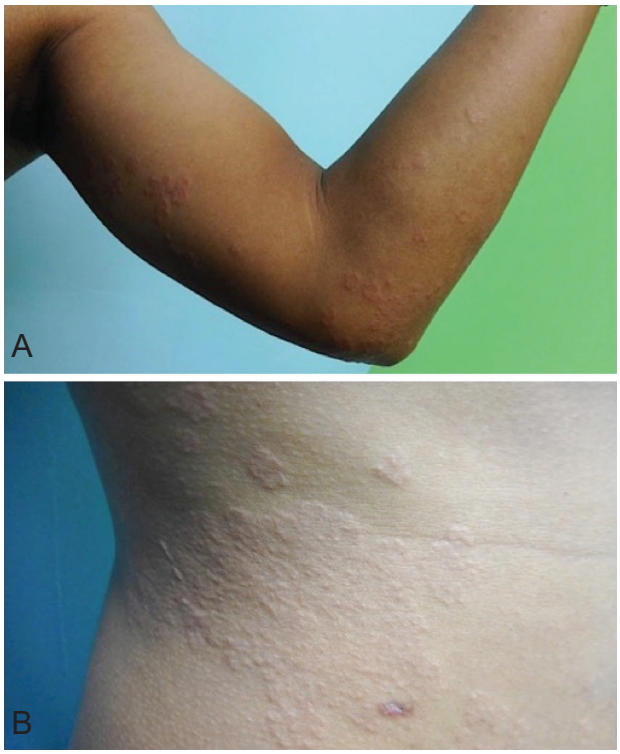

Figure 1. Large, asymptomatic skin-coloured, annular plaques over the upper limb (A) and trunk (B).

DISCUSSION

Granuloma annulare (GA) is an idiopathic benign granulomatous skin disease, characterized

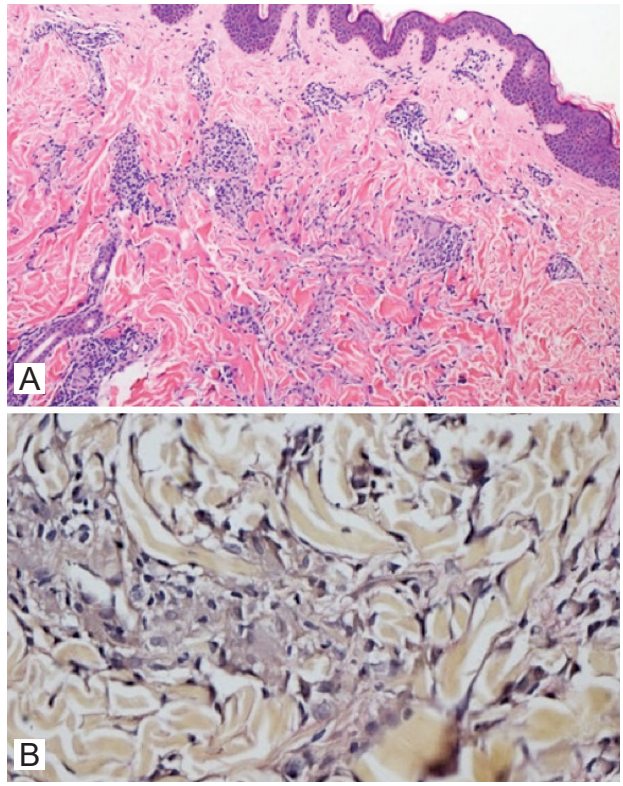

Figure 2. (A) Perivascular and periadnexal lymphocytic infiltrates with foci of epithelioid granulomas. No necrobiosis is seen. (Hematoxylin and eosin stain, original magnification × 100). (B) No mucin deposition is present. (Mucin stain, original magnification × 400).

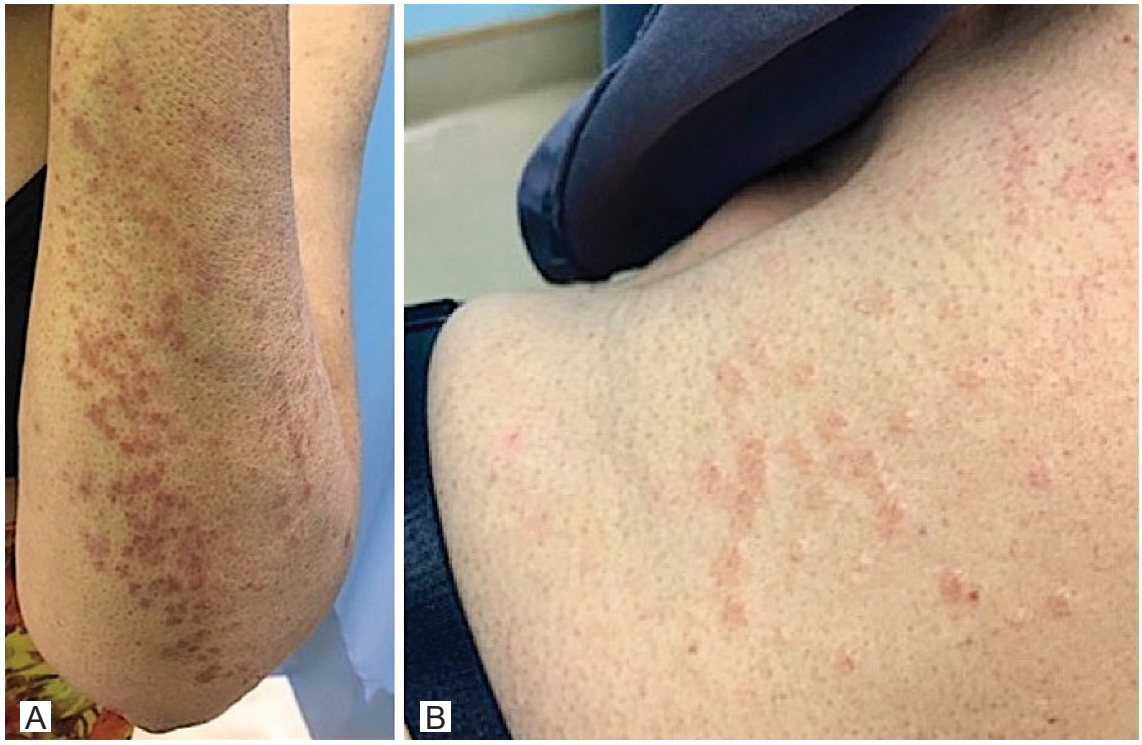

Figure 3. Erythematous discrete papules over the extensor forearms (A) and upper back (B).

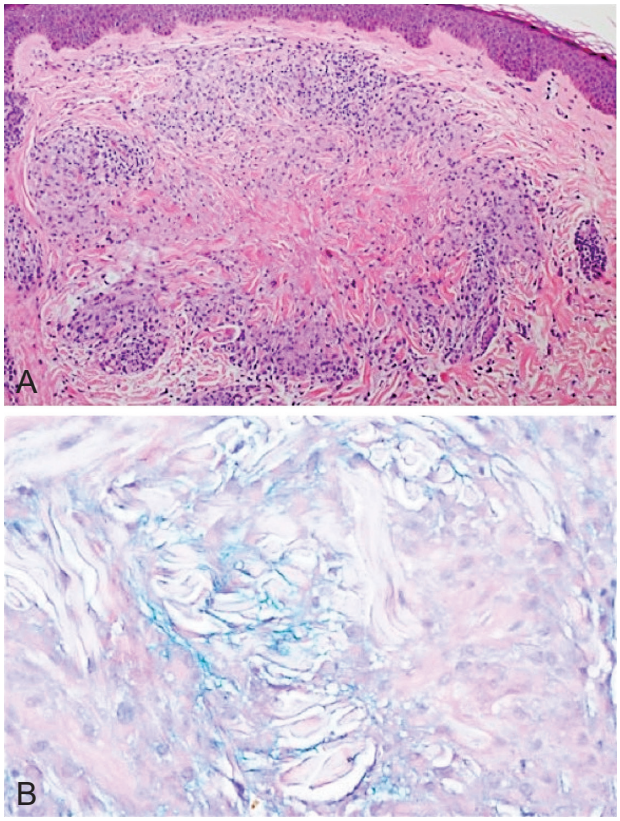

Figure 4. (A) Palisading granulomas with the central area of necrobiosis. (Hematoxylin and eosin stain, original magnification × 100). (B) Mucin deposition with dead collagen. (Alcian-Blue (AB) stain, original magnification × 400).

by annular dermal plaques or papules. GA is the most common type of palisading granulomas, others are necrobiosis lipoidica, rheumatoid nodule, and necrobiotic xanthogranuloma. The prevalence of GA is unknown [4]. It is estimated that approximately 0.1-0.4% of new patients referring to dermatologist were diagnosed as GA [5]. Localized GA has single or multiple lesions confined to one or few anatomical areas. When more than one anatomical areas are affected, the trunk is often spared. In generalized GA, the lesions are extensive affecting at least the trunk and either upper or lower or both extremities. Annular lesion is the most common morphology seen, followed by papular or mixed annular-papular lesion [6]. Our first case presented with classical annular lesions, whereas the second case had papular lesions only. Localized GA is more common and only approximately 15% of GAs have generalized lesions [7]. It can occur in all age groups with the most common age of onset in the third [8] and fifth decades with slight female predominance (1.2:1) [4].

The exact pathomechanism is unknown [3]. Multiple different hypotheses are made based on relatively limited evidence. It has been postulated that it may be a delayed type hypersensitivity response to an unidentified antigen. Excessive

production of TNF- has been associated with GA in myelodysplastic syndrome [22]. Given the multitude reported of associations and triggers, there is no "single" cause of GA but multiple different causes that might contribute to the disease [1,3].

Approximately 15-30% of subjects with granuloma annulare were associated with systemic diseases, such as HIV, malignancies (i.e. breast, cervical cancer and myelodysplastic syndrome), thyroid disease, systemic infections, and atopy [8,9,22]. The most common reported associations are diabetes mellitus and dyslipidemia. Winkelmann et al. reported that 20% of patients with GGA were diagnosed with diabetes mellitus. However, this association is rejected by several other studies [6,10-12]. Retrospective study conducted in Korea reported that 4 out of 52 patients (7.2%) with GA had diabetes mellitus [9], while another similar study in Singapore reported that 6 out of 41 patients (14.6%) had diabetes mellitus [8]. Despite all these studies published on GA and DM, there is no definitive evidence for its association.

The pathology of localized or generalized GA is similar. Histologically, mucin deposition coupled with a palisading or interstitial pattern of granulomatous inflammation represents the principal finding in all subtypes of GA, and other patterns may be rarely seen. Winkelmann revealed that palisading pattern was only found in approximately 25% of cases [13,14]. However, more recent retrospective studies have indicated a higher incidence of a palisading pattern [6,9]. GA is a disease characterized by necrobiosis and mucin deposition. However, not all histologic samples demonstrate positive mucin stains [9,14]. The hematoxylin-eosin stain section may be at a distance from the section taken for mucin stain, and thus does not represent the same cutting plane. Fixation and processing may have affected the tissue reactivity to mucin stain. Utilization of at least two different mucin stains could improve the sensitivity of mucin detection in GA [14]. This explains why the mucin stain is negative in our first case.

The spontaneous resolution of GA occurs within 2 years in 50% of patients, but there is a 40% recurrence rate. The recurrent lesions tend to occur at the original sites, but clear more rapidly (80% within 2 years). The duration of untreated lesions has been reported to range from few weeks to several decades [15]. GGA tends to be persistent, and poorly responds to treatment [6,8,9,16,17]. Our first case demonstrated a partial resolution of GGA after the skin biopsy to confirm its diagnosis without any treatment.

Treatment is desired in view of its appearance, tendency to recur and occasional widespread distribution [3]. Treatment of GGA is limited to individual case reports and small series of patients treated without a control group [1]. Treatment can be divided into topical (corticosteroid, calcineurin inhibitor), systemic (antimalarial, dapsone, antibiotics, retinoids, or TNF- anatgonists) or physical therapy (PUVA, UVA1 and excimer laser) [3]. In patients with localized disease requiring treatment, topical or intralesional corticosteroid is the preferred approach. Psoralen plus ultraviolet A (PUVA) light phototherapy has demonstrated good response in patients with GGA [3]. Cunningham et al. conducted a review on 20 of their patients who had undergone 15 sessions of PUVA and 12 courses of NBUVB. Remission was for six months and extended to one year or more in 5 patients. The study demonstrated at least 50% of improvement, however, patients' satisfaction was lower than that was measured by the dermatologist's assessment [25].

The effectiveness of hydroxychloroquine (HCQ) in the treatment of GA was demonstrated in 1987 [3]. It is recommended as the first line treatment in view of its good clinical response [3]. The action mechanism of HCQ in the treatment of GGA involves immunosuppressive and anti-inflammatory functions. It stabilizes the lysosomal membranes, and inhibits prostaglandin synthesis and possibly other enzyme systems, contributing to its anti-inflammatory properties. It also inhibits DNA replication and transcription, thus decreasing protein synthesis [18]. Based on the previous reported data, Cannistraci et al, successfully demonstrated its effectiveness in 9 patients with GGA independently of the age of onset, by introducing HCQ at a dosage of 9mg/kg/day for the first two months, 6mg/kg/day for the third month and 2mg/kg/day for the fourth month. No side effects were reported in the study [20]. Our patient failed to demonstrate a good response probably due to the relatively lower dose that had been commenced. However, the dosage used by Cannistraci et al, is markedly higher than the recommended dose of 5mg/kg of actual body weight and 6.5mg/kg of ideal body weight in obese patient, and with a maximum of 400mg/

day [21]. In the availability of whole blood HCQ (WB-HCQ), it will be beneficial to be considered before considering treatment failure for HCQ [21]. An adjustment of the HCQ doses according to the WB-HCQ level, might demonstrate effectiveness.

CONCLUSION

GA is not uncommon, yet under research. Further studies are necessary to better elucidate the cause, triggers, associations, and treatment of this condition.

Conflict of Interest: None declared.

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