Granuloma Annulare

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Abstract: Granuloma annulare is a benign, usually self-limited granulomatous disease of the dermis and subcutaneous tissue. Several distinct subtypes have been recognized, namely localized granuloma annulare, generalized or disseminated granuloma annulare, subcutaneous granuloma annulare, papular granuloma annulare, interstitial or patch granuloma annulare, and perforating granuloma annulare. Localized granuloma annulare is the most common form in children and comprises 75% of cases. Clinically, the condition is characterized by asymptomatic, flesh-colored or erythematous-brown papules, frequently arranged in a ring or annular pattern on the distal extremities. It is estimated that 0.1 to 0.4% of new patients attending dermatologic clinics have granuloma annulare. Most cases of granuloma annulare occur before the age of 30 years. A delayed hypersensitivity and cell-mediated immune response to an antigen contributes to the pathogenesis. Histologic examination of the lesion shows central collagen degeneration and mucin deposition surrounded peripherally by palisading histiocytes and inflammatory cells. Most cases of granuloma annulare are asymptomatic and self-limited; and reassurance is often sufficient. Treatment is mainly for cosmetic purposes and various modalities of treatment options are discussed.

Keywords: Granuloma annulare, ring/annular pattern, collagen degeneration, mucin, palisading histiocytes, benign.

INTRODUCTION

Granuloma annulare is a benign, usually self-limited granulomatous disease of the dermis and subcutaneous tissue [1]. The condition was first described in 1895 by Colcott-Fox who reported an 11-year-old girl with a “ring eruption of the fingers” [2]. The term “granuloma annulare” was coined by Radcliff-Crocker in 1902 [3]. Clinically, the condition is characterized by asymptomatic, flesh-colored or erythematous-brown papules, frequently arranged in a ring or annular pattern on the distal extremities [4]. Several distinct subtypes have been recognized, namely localized granuloma annulare, generalized or disseminated granuloma annulare, subcutaneous granuloma annulare, papular granuloma annulare, interstitial or patch granuloma annulare, and perforating granuloma annulare [1, 5].

PREVALENCE

Although the point prevalence of granuloma annulare in the community is not known, it is estimated that 0.1 to 0.4% of new patients attending dermatologic clinics have granuloma annulare [6]. Most cases of granuloma annulare occur before the age of 30 years [7]. The female to male ratio is approximately 2:1 [7].

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ETIOLOGY

In the majority of cases, the etiology is not known. Occasionally, granuloma annulare has been reported to follow trauma, insect bites, tuberculin skin tests, immunizations (e.g., hepatitis B, diphtheria-tetanus, bacillus Calmette-Guérin), viral infections (e.g., herpes zoster, Epstein Barr virus, hepatitis B, hepatitis C, human immunodeficiency virus), medications (e.g., amlodipine, allopurinol, diclofenac), diabetes mellitus, autoimmune thyroiditis, rheumatoid arthritis, and malignancy [6-13]. These associations have been reported mainly in adult populations [6]. Familial cases of granuloma annulare have also been reported [8, 14]. Certain human leukocyte antigen phenotypes (e.g., HLA-A29, HLA-A31, HLA-B8, HLA-B14, HLA-B15, HLA-B35) occur with increasing frequency in patients with granuloma annulare [8].

PATHOGENESIS

The presence of T-helper cells with histiocytes in the inflammatory infiltrate in granuloma annulare suggests that a delayed hypersensitivity and cell-mediated immune response to an antigen contribute to the pathogenesis [7, 8].

HISTOPATHOLOGY

Histologic examination of a classic lesion shows central collagen degeneration and mucin deposition surrounded peripherally by palisading histiocytes and inflammatory cells [1, 8, 15]. The presence of mucin is

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a key histological feature that helps to distinguish granuloma annulare from other non-infectious granulomatous diseases [13]. In the interstitial variant, the dermis contains a focal interstitial infiltrate of histiocytes and giant cells [16].

CLINICAL MANIFESTATIONS

Localized granuloma annulare is the most common form in children and comprises 75% of cases [6, 7, 17]. The lesion starts as a ring of small, smooth, firm, asymptomatic, erythematous, violaceous, brown or skin-colored papules [7, 8]. As the condition progresses, there is some central involution [7]. The ring of papules often becomes coalescent to form an annular plaque. The lesion gradually enlarges to usually less than 5 cm in diameter. Typically, lesions are solitary or few in number [15]. Sites of predilection include the lateral or dorsal surfaces of the hands and feet (Figure **1**) [7]. Involvement of the palms is rare, but has been reported [18]. In most patients, the condition is often asymptomatic [19] Rarely, it can be mildly pruritic [7].

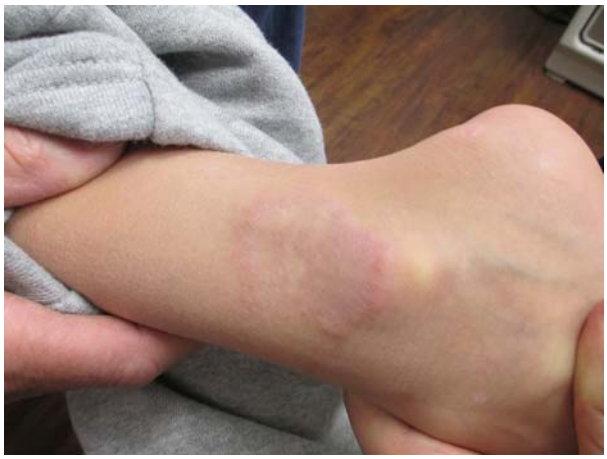

Figure 1: Classic violaceous lesion of granuloma annulare on the lateral aspect of the left ankle.

Generalized granuloma annulare occurs in approximately 15% of patients with granuloma annulare [20]. The condition manifests as numerous (at least 10, often hundreds to thousands) small, asymptomatic, erythematous, violaceous, brown or skin-colored papules [21]. Lesions are symmetrically distributed on the trunk, extremities, and neck [21]. Generalized granuloma annulare has a bimodal peak age of presentation, in the first decade of life and between the fourth and sixth decades of life [17]. It has been associated with diabetes mellitus [22].

Subcutaneous granuloma annulare is diagnosed primarily in children and young adults [23]. The lesion usually presents as a painless flesh-colored subcutaneous nodule with no inflammatory appearance at the skin surface [1, 23]. Sites of predilection include the pretibial areas, feet, forearms, hands, fingers, scalp, and forehead [5, 6, 23]. It rarely occurs in the periocular area. When it does occur, the annular pattern is often absent [24].

Papular granuloma annulare presents as asymptomatic, skin-colored or hypopigmented papules [25]. The papules usually measure 1 to 3 mm in diameter and the consistency is firm. Papular granuloma annulare most commonly affect children, predominately on the dorsal surface of the hands [25].

Interstitial granuloma annulare manifests as asymptomatic erythematous or light brown patches without scales or papules that may or may not have an annular configuration [21]. Sites of predilection include the trunk and extremities [21].

Perforating granuloma annulare is rare. It presents with papules that are 1 to 5 mm in diameter and occur more often on the dorsal aspects of the hands and feet [21, 22]. Characteristically, these papules have central umbilication or crusts and are well demarcated [21]. Perforation occurs in the central portion of the lesion through which mucoid material consisting of degenerated collagen is eliminated [13, 22]. Itching occurs in up to 25% of cases, especially when there are lesions on palms [22].

LABORATORY INVESTIGATIONS

Children with granuloma annulare are generally healthy and no laboratory investigations are usually necessary [1]. Nevertheless, a recent case-control study shows that adult patients with granuloma annulare are more likely to develop dyslipidemia (odds ratio: 4.04; 95% confidence interval: 2.53-6.46) [26]. It has been suggested that it is reasonable to test for fasting serum lipid levels in adult patients with granuloma annulare, especially if there are other risk factors for dyslipidemia [13, 27]. Patients with generalized granuloma annulare should be checked for the presence of diabetes mellitus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is mainly clinical. The differential diagnosis of localized granuloma annulare includes tinea corporis, pityriasis rosea, pityriasis rotunda, erythema annulare centrifugum, nummular eczema, discoid lupus erythematosus, psoriasis, sarcoidosis,

mycosis fungoides (plaque stage), mastocytoma, dermatofibroma, necrobiosis lipoidica, morphea, hypertrophic lichen planus, or erythema chronicum migrans [7, 8, 28]. Subcutaneous granuloma annulare has to be differentiated from sarcoidosis, rheumatoid nodule, and panniculitis [13]. The differential diagnosis of generalized granuloma annulare includes eruptive xanthoma, lichen nitidus, lichen scrofulosorum, sarcoidosis, interstitial granulomatous dermatitis, non-X histiocytosis, and papular xanthoma [9, 29, 30]. On the other hand, perforating granuloma annulare may mimic elastosis perforans serpiginosa, perforating collagenosis, perforating folliculitis, and perforating sarcoidosis [31]. The clinical features of granuloma annulare are so distinct that usually there is little difficulty in diagnosis for an experienced physician. In particular, lack of symptoms, scaling or associated vesicles helps to differentiate granuloma annulare from most other skin conditions. If the diagnosis is in doubt, a biopsy should be considered.

COMPLICATIONS

In the adult population, granuloma annulare is associated with diabetes mellitus in 16-19% of cases [22]. Dyslipidemia is more common in patients with granuloma annulare [26]. Rarely, granuloma annulare may be complicated by nerve involvement as a result of granulomatous inflammation surrounding cutaneous nerves and perineural infiltrates of histiocytes in the dermis [16].

PROGNOSIS

Localized granuloma annulare usually resolves without scarring within one to two years [15, 32]. Other forms may persist for a few years or longer [7]. Shorter duration is associated with younger age and recent onset [23]. The recurrence rate is approximately 40% [15].

MANAGEMENT

Most cases of granuloma annulare are asymptomatic and self-limited, treatment is usually not required other than reassurance [6, 15]. For patients who insist on treatment for cosmetic reasons, options include topical or intralesional corticosteroids, imiquimod cream, topical calcineurin inhibitors (tacrolimus, pimecrolimus), cryotherapy, and pulsed dye laser [7, 15, 34-36]. Surgical removal is an option for the nodular lesion seen in subcutaneous granuloma annulare [32]. Systemic therapy may be required for generalized granuloma annulare which is often resistant to treatment [15]. Interventions that have been used with varying degrees of success include oral corticosteroids, fumaric acid esters, dapsone, isotretinoin, hydroxychloroquine, methotrexate, cyclosporine, niacinamide, calcitriol, vitamin E, tumor necrosis factor (TNF)-α inhibitors (adalimumab and infliximab), and several variants of phototherapy [7, 13, 19, 20, 37-41].

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