A LITERATURE REVIEW OF GRANULOMA ANNULARE

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ABSTRACT

Granuloma annulare (GA) is a benign, self-limiting granulomatous skin disorder of unknown origin, most commonly affecting young females. It presents as annular plaques or papules and may be associated with systemic conditions such as HIV and malignancies. Although its pathogenesis is unclear, immune-mediated mechanisms involving Th1 responses and matrix degradation are implicated. GA has several clinical variants-localized, disseminated, subcutaneous, patch-type, and perforating-with localized GA being the most common and often resolving spontaneously. Histopathology reveals collagen degeneration, mucin deposition, and distinct inflammatory patterns. Treatment is usually unnecessary, but persistent or disseminated cases may benefit from topical, systemic, or biologic therapies. Prognosis is favorable, though disseminated forms tend to be more resistant to treatment.

INTRODUCTION

Granuloma annulare (GA) is a granulomatous dermatologic condition of unknown etiology. It is the most common non-infectious granulomatous skin disease. GA is benign and typically self-limiting. Clinically, it presents as annular plaques or papules arranged in a ring-like configuration. Although benign, GA may be associated with systemic conditions such as HIV infection or malignancies. The estimated prevalence of GA ranges from 0.1% to 0.4%. Females are more frequently affected than males, and the condition spans all age groups. Over two-thirds of patients are aged 30 years or younger.

PATHOGENESIS

The precise cause and pathogenesis of GA remain largely unclear. However, associations have been noted with diabetes mellitus, thyroid disorders, trauma, hyperlipidemia, infections (including Epstein-Barr virus, HIV, varicella-zoster virus, and tuberculosis), vaccinations, malignancies, and certain medications (e.g., TNF-alpha inhibitors). Despite its association with diabetes, definitive evidence establishing a causal link is lacking. Malignancy screening is recommended in GA patients who are elderly, present with atypical or disseminated lesions, or have persistent disease. Studies indicate that HIV-positive individuals are more likely to develop disseminated GA. Additionally, highly atypical presentations of GA have been reported in HIV-infected patients. Newly diagnosed GA patients with risk factors for HIV should undergo HIV screening. Screening is also advised for patients with disseminated or perforating types of GA.

Several studies suggest that GA may result from a delayed-type hypersensitivity reaction, specifically a Th1-mediated response involving IFN-gamma stimulation of macrophages to release matrix metalloproteinases. This cascade ultimately leads to connective tissue degradation. Supporting evidence includes

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findings of differentiated macrophages in lesions expressing matrix metalloproteinases and TNF-alpha. Impaired neutrophil chemotaxis has been observed in GA patients. Researchers hypothesize that macrophages may compensate for neutrophil dysfunction, resulting in granulomatous inflammation rather than neutrophilic suppurative inflammation.

CLINICAL FEATURES

GA typically manifests on the dorsal aspects of the hands and feet in annular or circular patterns. Lesions are usually asymptomatic, with no associated pruritus. The localized form is the most common, accounting for approximately 75% of reported cases. Other clinical variants include disseminated, perforating, patch-type, and subcutaneous forms. Disseminated GA presents as multiple skin-colored annular papules on the trunk and extremities, often accompanied by pruritus-unlike the classic presentation. This variant comprises up to 15% of cases, rarely resolves spontaneously, and responds poorly to treatment. Subcutaneous GA appears as large nodules on the extremities, sometimes referred to as pseudo-rheumatoid nodules. It predominantly affects children aged 1 to 14 years. Patch-type GA presents as erythematous patches that may cover extensive skin areas. This form shares features with reactive granulomatous conditions, making differentiation challenging. The perforating type is characterized by annular plaques with central healing. Lesions may be confined to the extremities or involve both the trunk and limbs. Approximately half of patients with localized GA experience spontaneous resolution within two years. A single patient may exhibit multiple clinical variants.

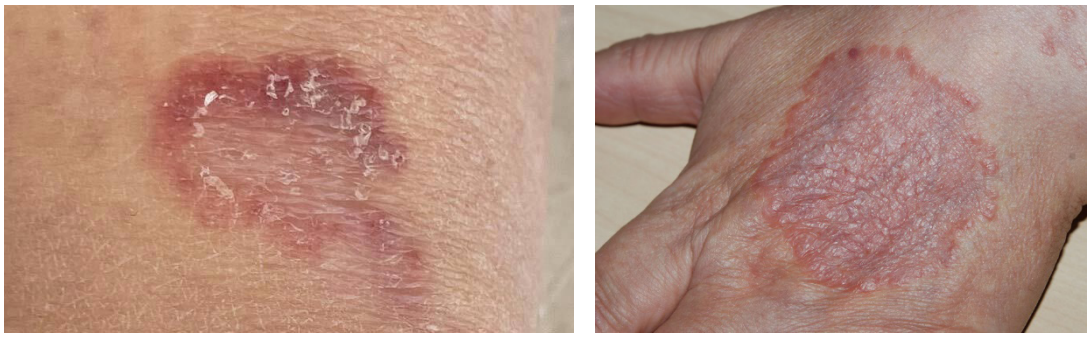

Figure 1. Clinical presentation of granuloma annulare

HISTOPATHOLOGY

Histologically, GA is characterized by focal collagen degeneration, interstitial inflammation with histiocytes, and mucin deposition. Four histopathologic patterns have been identified: interstitial (57.9%), palisading granuloma (26.3%), sarcoidal granuloma, and mixed types. The palisading pattern features histiocytes and lymphocytes encircling necrotic collagen. The interstitial pattern consists of histiocytes dispersed among collagen bundles and dermal vasculature. A patient may exhibit more than one histologic pattern.

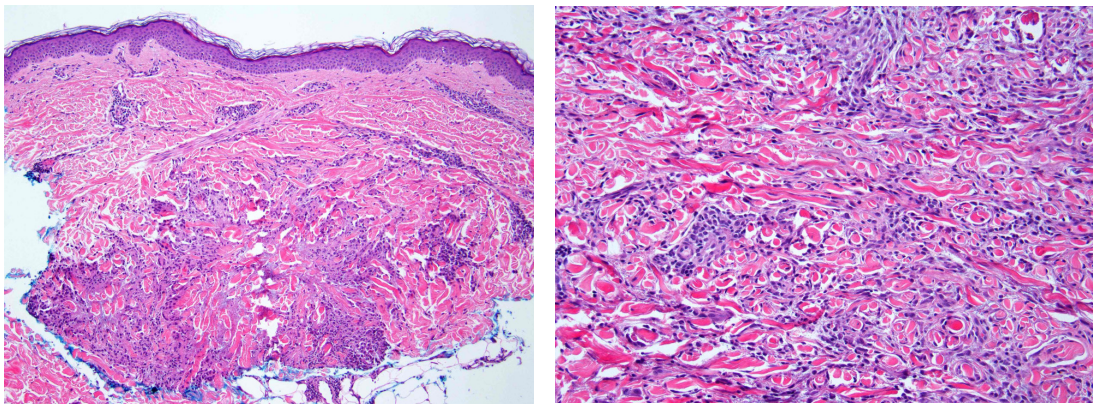

Figure 2. Histopathology of granuloma annulare

Differential diagnosis

- Actinic granuloma.
- Dermoid cyst.
- Erythema nodosum.
- Erythema annulare centrifugum.
- Foreign body granuloma.
- Insect bites.
- Lichen planus.
- Sarcoidosis.

TREATMENT

In most cases, GA does not require treatment, as lesions typically resolve within several months without residual scarring. However, some cases may persist for years.

Topical therapy

Consider the following options:

- Topical corticosteroids.
- Intralesional corticosteroid injections.
- Cryotherapy or laser ablation.
- Imiquimod cream.
- Topical calcineurin inhibitors (tacrolimus and pimecrolimus).

Systemic therapy

Systemic treatment may be considered for disseminated GA. The following therapies have shown efficacy in certain cases:

- Systemic corticosteroids.
- Oral agents: Isotretinoin, methotrexate, potassium iodide, dapsone, hydroxychloroquine, pentoxifylline, allopurinol (note: Allopurinol has also been implicated as a potential cause of disseminated GA), ciclosporin.
- Psoralen plus ultraviolet A (PUVA) photochemotherapy.
- Photodynamic therapy.
- Biologic agents, particularly TNF-alpha inhibitors such as adalimumab and infliximab.
- Oral and topical Janus kinase (JAK) inhibitors, including tofacitinib.

PROGNOSIS

GA is a benign, self-limiting condition. Lesions typically resolve spontaneously within months to years without sequelae. No single treatment modality is universally effective. For most patients, the disease resolves within a few years.

Disseminated forms tend to be more persistent than localized variants.

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