NEWS, VIEWS, AND REVIEWS

Update on Granulomatous Dermatoses: Clinical Features and Therapeutic Advances

Nikkia Zarabian BS, Mina Farah BA, Dillon Nussbaum MD, Adam Friedman MD FAAD, Emily Nadelmann MD FAAD

Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

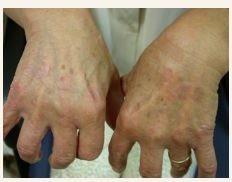
INTRODUCTION

Granulomatous dermatoses (GDs) are a group of diseases defined by organized granuloma formation within the dermis or hypodermis, often in response to infections, inflammation, neoplasia, or metabolic disorders.[1] Granulomas are thought to arise as a delayed hypersensitivity reaction to persistent antigens that cannot be eliminated by phagocytosis.[1] They consist of aggregates of activated macrophages that differentiate into epithelioid histiocytes, sometimes accompanied by multinucleated giant cells and dendritic cells, and a surrounding lymphocytic border.[1] Granulomatous inflammation is primarily driven by a T-helper (Th)1 response, via interferon (IFN)γ, tumor necrosis factor (TNF)-α, interleukin (IL)-2, and in some contexts, Th17 involvement.[1] While the immunologic basis of granuloma formation is shared across GDs, their clinical presentations, histopathologic nuances, and therapeutic responses differ. This review focuses on non-infectious GDs, including granuloma annulare (GA), sarcoidosis, and interstitial granulomatous dermatitis (IGD), highlighting their clinicopathologic overlap, distinguishing features, and management approaches.

Granuloma Annulare

GA is the most common non-infectious GD, with an estimated prevalence of 0.04% in the United States (U.S.).[2,3] Clinically, GA presents as asymptomatic, annular, erythematous papules or plaques, most commonly affecting the dorsal and lateral aspects of the hands and feet (Figure 1).[3] Most cases of GA are localized; however, other subtypes include generalized, perforating, patch, and subcutaneous forms.[3] The exact etiology of GA remains incompletely understood, but has classically been considered a Th1-mediated delayed-type hypersensitivity reaction, in which IFN-γ-activated macrophages release matrix metalloproteinases leading to collagen degradation.[3,4] More recent data also suggest potential Th2 involvement.[3,4] GA has been associated with diabetes mellitus, hyperlipidemia, autoimmune disease (rheumatoid arthritis and systemic lupus erythematosus (SLE)), thyroid disease, vaccinations, infections, and iatrogenic triggers.[3,4] Population-level data support baseline metabolic and thyroid screening, particularly in generalized or atypical presentations, while routine malignancy workup beyond age-appropriate guidelines is not indicated unless disease is recalcitrant or systemic.[2] Diagnosis is primarily clinical but may be confirmed histologically, with biopsy demonstrating focal collagen degeneration, mucin deposition, and an interstitial histiocytic infiltrate.[3]

Figure 1. Erythematous annular plaques on the bilateral dorsal hands, consistent with granuloma annulare.



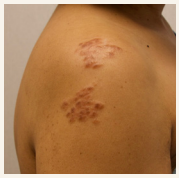
Although GA is benign and often self-limiting, recurrence is common and therapeutic response is often variable.[3] First-line management includes intralesional (IL) and topical corticosteroids (TCS).[2-4] Other common treatments include tetracyclines, hydroxychloroquine, and phototherapy.[2] Janus kinase (JAK) inhibitors have been reported as emerging therapies, with JAK1/3 inhibitor oral tofacitinib 5 mg twice daily demonstrating clinical and histologic remission in recalcitrant GA.[5] Delgocitinib 0.5% ointment, a pan-JAK inhibitor, has demonstrated preliminary efficacy after two months of twice-daily application, and ruxolitinib 1.5% cream, a selective JAK1/2 inhibitor, has been reported to achieve complete clearance of GA after three months of treatment.[6,7] Additionally, a 2026 retrospective cohort trial found that the Goeckerman protocol (coal tar, phototherapy, and TCS) significantly outperformed TCS (56.3%), combination TCS + phototherapy (69.6%), and phototherapy alone in treating GA (16.7%).[8] On multivariate analysis, the Goeckerman protocol was the strongest predictor of treatment response (Odds Ratio (OR) 32.52; $P<0.001$).[8] Other therapies, including apremilast, TNF-α inhibitors, methotrexate, isotretinoin, vitamin E, topical imiquimod, dapsone, and systemic retinoids, have been reported in small case series and case reports, but robust evidence supporting consistent efficacy remains limited.[3,4]

Sarcoidosis

Sarcoidosis is a multisystem inflammatory GD characterized by the formation of non-caseating granulomas that can involve nearly every organ system, most commonly the lungs and skin.[9,10] In the U.S., sarcoidosis disproportionately affects Black individuals, with a consistent female predominance across populations.[9] Although the pathogenesis of sarcoidosis is not fully understood, it is believed to arise from a combination of genetic susceptibility, immune dysregulation, and environmental exposure.[9]

Cutaneous involvement occurs in approximately 20% to 30% of patients and may represent the initial manifestation of systemic disease.[9,10] Specific cutaneous lesions are a result of granulomatous inflammation and often present as papules, plaques, lupus pernio, subcutaneous nodules, or scar sarcoidosis (Figure 2).[9,10] Given its

Figure 2. Cutaneous sarcoidosis characterized by grouped violaceous papules and plaques.



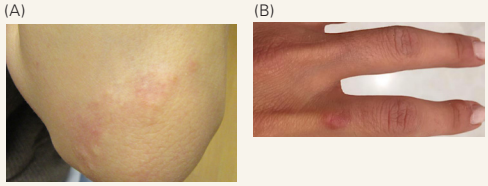
broad clinical spectrum, diagnosis of cutaneous sarcoidosis (CS) often requires histopathologic confirmation via biopsy demonstrating non-caseating granulomas composed of tightly aggregated epithelioid histiocytes.[9,10] As cutaneous disease may precede or accompany systemic involvement, baseline screening including chest radiography, laboratory evaluation, and ophthalmologic examination should be considered.[9]

First line treatment for mild and localized CS includes IL or TCS.[10] More extensive or recalcitrant disease may warrant systemic therapy, including oral corticosteroids, methotrexate, tetracyclines, hydroxychloroquine, TNF-α inhibitors, thalidomide, JAK inhibitors, and selective tyrosine kinase (TYK)2 inhibitors.[9-11] Multiple case reports, case series, and an open-label clinical study have described the use of off-label oral and topical JAK inhibitors in the treatment of recalcitrant CS.[9,12] A 65 year-old woman with extensive CS was treated with oral tofacitinib 5 mg twice daily, and experienced complete clearance of lesions within 6 months.[12] Another female patient with sarcoidosis and polycythemia vera was treated with ruxolitinib 5 mg twice daily, and experienced complete clearance of CS within 3 months.[13] Topical JAK inhibitors have also been implicated in the treatment of CS; a 50 year-old female with recalcitrant CS on the face and arms was treated with topical tofacitinib 2% ointment twice daily for 10 weeks, with significant improvement in erythema and induration, but required 3 treatments of pulsed dye laser therapy for improvement of telangiectasias.[14] The JAK-signal transducer and activator of transcription (STAT) pathway plays an important role in mediating cytokines involved in granuloma formation, providing a promising strategy for refractory cases.[15] TYK2 inhibitors have also been implicated in the treatment of CS, evident in a case report of a 46 year old female with recalcitrant sarcoidosis who experienced near-total improvement within a few months of deucravacitinib 6 mg daily treatment.[11] Although preliminary results for JAK and TYK2 inhibitor therapy appear promising, further evaluation in larger randomized controlled trials are needed to establish long-term efficacy, optimal dosing, and safety.[9,11-14]

Interstitial Granulomatous Dermatitis

IGD is an uncommon GD characterized by symmetric erythematous to violaceous patches, papules, or plaques, most commonly involving the extremities and upper trunk (Figure 3A and 3B).[16] A classic but uncommon presentation is the "rope sign," which refers to linear, erythematous or skin-colored subcutaneous cords or bands, often along the proximal trunk.[16] IGD is thought to represent a non-specific cutaneous manifestation of underlying immune dysregulation.[16] Many cases occur in association with underlying inflammatory or autoimmune disorders, including inflammatory arthritides (rheumatoid arthritis, seronegative

Figure 3. Interstitial granulomatous dermatitis characterized by subcutaneous, skin-colored papules on the left elbow (A) and an erythematous plaque on the left dorsal index finger (B).



arthritis), connective tissue diseases (CTD) (SLE, undifferentiated CTD), and hematologic abnormalities and malignancies (monoclonal gammopathies, cytopenias, lymphoma, solid organ malignancies).[16] Medication-induced cases have also been reported, particularly with TNF-inhibitors, angiotensin converting enzyme inhibitors, and furosemide.[16] Proposed mechanisms include immune complex deposition and vascular injury within the dermis, leading to collagen degradation, chronic inflammation, and subsequent granulomatous infiltration.[16] Histopathologically, IGD is characterized by an interstitial histiocytic infiltrate distributed throughout the dermis.[16] Neutrophils and eosinophils may be present, while mucin deposition is typically minimal or absent.[16] Histiocytes may align around altered collagen, producing areas of clefting referred to as the "floating sign," though not a universal diagnostic feature.[16]

Given the frequent association with systemic disease, evaluation for underlying pathology is recommended.[16] Management is largely guided by treatment of the underlying condition, which may lead to resolution of cutaneous findings, with systemic and TCS also commonly used for therapeutic relief.[16,17] Additional reported treatments include hydroxychloroquine, dapsone, nonsteroidal anti-inflammatory drugs, cyclosporine, ustekinumab, tocilizumab, and narrow-band ultraviolet B phototherapy.[16,17] However, the evidence remains limited to case reports and small case series.[16,17]

Distinguishing Features

Several overlapping features between sarcoidosis, GA, and IGD can challenge clinical distinction. However, GDs can be differentiated by anatomic distribution, morphology, systemic involvement, and key histopathologic features (Table 1). Sarcoidosis is more commonly multisystem, especially with pulmonary involvement,

Table 1. Distinguishing Characteristics of Granuloma Annulare, Sarcoidosis, and Interstitial Granulomatous Dermatitis

Feature	Granuloma Annulare[3]	Sarcoidosis[9]	Interstitial Granulomatous Dermatitis[16]
Classic Morphology	Annular, erythematous papules or plaques	Papules, plaques, lupus pernio, scar infiltration	Symmetric patches, papules, plaques; "rope sign"
Typical Distribution	Dorsal hands and feet	Face, nasolabial folds, nose	Proximal trunk, extremities
Key Histopathology	Mucin deposition, collagen degeneration, interstitial histiocytes	Non-caseating "naked" granulomas, tightly aggregated epithelioid histiocytes	Interstitial histiocytes around degenerated collagen, "floating sign"
Systemic Associations	Diabetes mellitus, hyperlipidemia, thyroid and autoimmune disease	Systemic sarcoidosis (pulmonary, ocular, hepatic, cardiac)	Rheumatoid arthritis, systemic lupus erythematosus, malignancy, drug-induced

whereas GA is more often limited to the skin with minimal systemic implications.[3,9,10] Thus, pulmonary symptoms or other organ involvement with cutaneous findings should favor sarcoidosis. A history of autoimmune disease or medication exposure in a patient with symmetric cutaneous eruption should raise concern for IGD, and localized cutaneous annular papules and plaques point toward GA.[9,10,16] Given the potential for clinical overlap, diagnosis often depends on histopathologic findings. However, it is important to note that interstitial-type GA may still be indistinguishable from IGD.[16] Several groups have proposed that these entities exist on a reactive GD spectrum rather than as discrete diagnoses, a conceptual framework that may account for the frequent clinicopathologic overlap.[16]

CONCLUSION

GDs represent a heterogeneous group of inflammatory skin disorders unified by a shared histopathologic pattern but differ in systemic involvement, morphology, and pathophysiology. Careful integration of these features is essential to accurately diagnose and guide evaluation for associated systemic disease. Recent advancements in targeted therapies for GDs, particularly JAK and TYK2 inhibitors, demonstrate promising efficacy in refractory disease however further evaluation in larger randomized controlled trials are needed to establish long-term efficacy.

DISCLOSURES

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AUTHOR CORRESPONDENCE

Emily Nadelmann MD FAAD

E-mail:..... enadelmann@mfa.gwu.edu