

Reactive granulomatous dermatitis: A useful and encompassing term



To the Editor: Cutaneous granulomatous eruptions occur in response to various stimuli such as medications, systemic and autoimmune diseases, and internal malignancies. Variable clinical patterns and histologic subtypes may occur with these cutaneous eruptions, including palisaded neutrophilic and granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), and interstitial granulomatous drug reactions.¹ An expanding number of reports detail overlapping clinical and histologic features and similar associated systemic diseases, often leading to ambiguity and confusion among clinicians. PNGD classically demonstrates symmetric, skin-colored or erythematous umbilicated or

crusted papules, often presenting on the elbows and extremities, with histopathologic findings of interstitial neutrophils and histiocytes, occasional leukocytoclastic vasculitis (30% of cases), and small granulomas; however, the spectrum of cutaneous morphologies and anatomic locations reported with histopathology consistent with PNGD has expanded.^{1,2} Similarly, the definition of IGD has evolved, with an initial description of an asymptomatic, firm, palpable, linear band on the upper portion of the trunk with histopathologic changes of variable interstitial histiocytes often surrounding areas of abnormal collagen producing the characteristic “clefing” and “floating sign” in patients with inflammatory arthritis.^{1,3} However, these classic subcutaneous cords may be present in

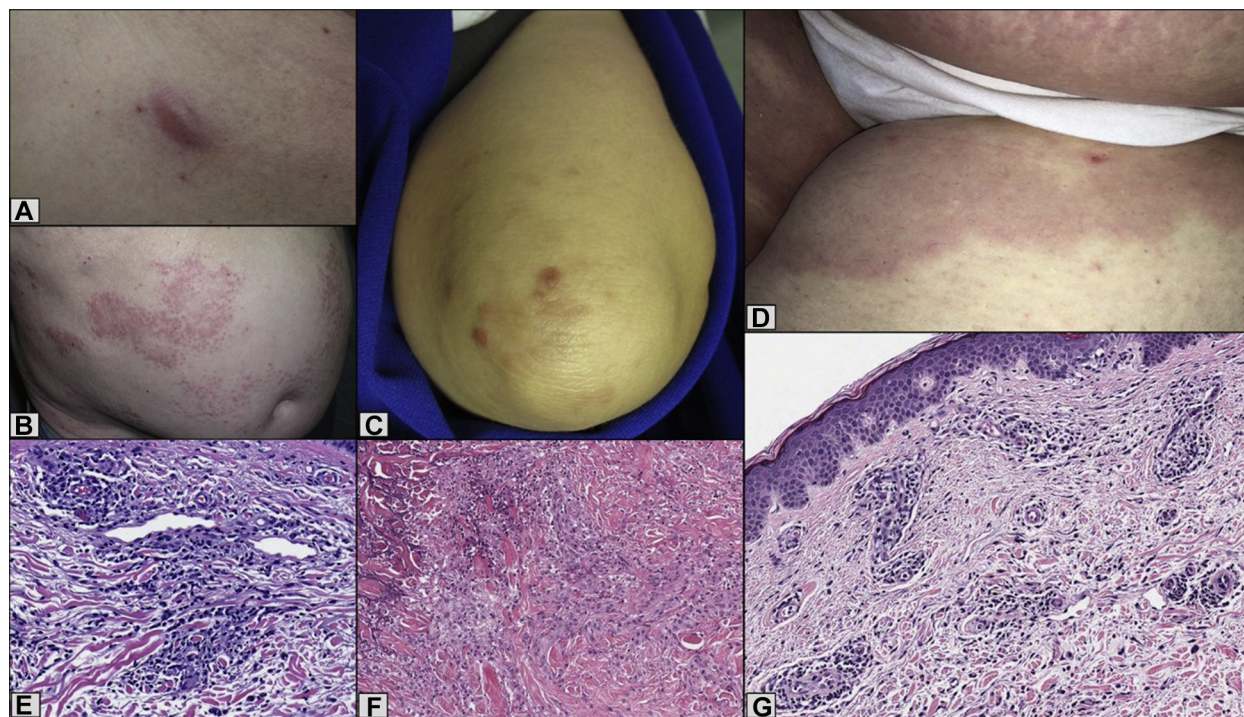


Fig 1. Clinical and histopathologic spectrum that can be seen in RGD. **A**, Thick erythematous plaque representing classic cord-like image seen in IGD. **B**, Polycyclic thin plaque representing polycyclic granuloma annulare–like IGD. **C**, Pink papules on the elbows described in PNGD. **D**, Pink thin plaques as described in IGDR. **E** to **G**, Histopathologic spectrum of RGD. IGD-like features demonstrating interstitial histiocytic inflammation with isolation of collagen bundles. Neutrophilic and histiocytic inflammation as observed in PNGD-like changes. Focal interface changes with papillary and mid dermis interstitial histiocytic inflammation with eosinophils described in IGDR. (**E** and **F**, Hematoxylin-eosin stain; original magnifications: **E**, $\times 10$; **F**, $\times 10$.) IGD, Interstitial granulomatous dermatitis; IGDR, interstitial granulomatous drug reaction; PNGD, palisaded neutrophilic and granulomatous dermatitis; RGD, reactive granulomatous dermatitis.

Table I. Reactive granulomatous dermatitis (palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, and interstitial granulomatous drug reaction)

Dermatitis	Clinical features	Histopathology	Associations	Workup
PNGD	Symmetric, smooth, umbilicated, or crusted, skin-colored to erythematous papules found primarily on the elbows and extremities*	Early: neutrophil predominant inflammation, karyorrhectic debris, leukocytoclastic vasculitis, minimal mucin Late: piecemeal collagen degeneration, small granulomas, histiocytic palisades	Systemic disease (SLE, inflammatory arthritis, ANCA associated vasculitis, limited systemic sclerosis, Sjögren syndrome, inflammatory arthritis) Hematologic disorders (acute myelogenous leukemia, multiple myeloma, lymphoma, IgA gammopathy, anemia, thrombocytopenia, leukemia, lymphoma, and myelodysplastic disorders) Solid organ malignancies: breast, endometrial, lung, esophageal Infections: cellulitis, hepatitis, streptococcal infection, AIDS Medications: in particular, biologics, antihypertensives, and antiseizures; however, many case reports exist for a range of medications ³	ANA, ANCA, double stranded DNA, anti-La(SS-B) and anti-Ro(SS-A) antibodies, anti-Scl70, anticentromere, RF, antiCCP [†] Age-appropriate cancer screenings CBC with differential serum protein electrophoresis/immunofixation electrophoresis and serum free light chains, chest radiography Review supplements, diet, medications, including less frequently associated medications
IGD	Firm, asymptomatic, linear truncal bands in patients with inflammatory arthritis*	Interstitial inflammation characterized by histiocytes frequently surrounding the foci of abnormal collagen and “clefing away”; absence of vasculitis and mucin		
IGDR	Erythematous-to-violaceous, often annular, plaques on the inner portion of the arms, proximal medial aspect of the thighs, trunk, and intertriginous locations in the setting of medications	Diffuse interstitial histiocytes with granulomas surrounding degenerating collagen, scant mucin with absent vasculitis, interface dermatitis with basal vacuolar degeneration along with areas of dyskeratotic keratinocytes and prominent eosinophilia	Medications: antihypertensives (in particular, calcium channel blockers, β blockers, ACE inhibitors) and lipid-lowering drugs; however, many case reports exist for a range of medications ³	

Adapted from Rosenbach and English,¹ *Dermatol Clin* (2015).

ACE, Angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood cell count; CCP, cyclic citrullinated peptide; IGD, interstitial granulomatous dermatitis; IGDR, interstitial granulomatous drug reaction; PNGD, palisaded neutrophilic and granulomatous dermatitis; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

*Denotes original descriptions. Evolving definitions and descriptions include many overlapping clinical morphologies between PNGD and IGD.

[†]Evaluation based on patients’ signs and symptoms can be expanded to less frequently associated systemic diseases, including mixed cryoglobulinemia, undifferentiated connective tissue disease, erythema elevatum diutinum, ankylosing spondylitis, Takayasu arteritis, type 1 diabetes mellitus, sarcoidosis, ulcerative colitis, celiac disease, pernicious anemia, primary biliary cirrhosis, antiphospholipid antibody syndrome, polymyositis, uveitis, vitiligo, chronic inflammatory demyelinating polyneuropathy, Behçet disease, and multiple sclerosis.³

<10% of cases.^{1,3,4} Other presentations include symmetric erythematous/violaceous patches or plaques on the proximal aspects of the trunk and limbs,

skin-colored papules, annular plaques, subcutaneous nodules, and papules on the elbow (classically, a sign of PNGD).^{1,3}

Importantly, the underlying associations in PNGD and IGD are similar. PNGD is reported most often in the setting of lupus and connective tissue diseases but may occur in inflammatory arthritis, lymphoproliferative disease, and other inflammatory settings.^{1,3} IGD now includes associations with connective tissue diseases, including lupus, lymphoproliferative diseases, and other inflammatory disease states.^{1,3}

Interstitial granulomatous drug reaction (referred to separately as a distinct entity from “drug-induced forms of IGD”) was initially described as annular erythematous or violaceous plaques located on the inner portion of the arms, proximal aspect of the inner portion of the thighs, proximal aspect of the trunk, and intertriginous areas and associated with the medication use.⁵ The main histologic findings include diffuse interstitial histiocytes with granulomas surrounding piecemeal fragmentation of collagen, scant mucin without vasculitis, and interface dermatitis with vacuolar degeneration and areas of dyskeratotic keratinocytes with prominent tissue eosinophilia.⁵ However, PNGD and IGD may also be seen with similar medications without the histologic changes described in interstitial granulomatous drug reactions.¹

We encourage using “reactive granulomatous dermatitis” (RGD) as a unifying term to describe these overlapping entities, simplify the nomenclature, and provide a framework for dermatologists to use when evaluating these patients (Fig 1). This terminology has already been used in various circumstances by dermatologists and dermatopathologists.^{1,3,4} Although RGD may represent a spectrum, with patients with PNGD-like RGD, IGD-like RGD, or even polycyclic or granuloma annulare-like RGD (RGD differing from classic granuloma annulare by histology, specifically the lack of increased mucin levels),³ the overarching term is a helpful concept for clinicians and pathologists to guide appropriate evaluation for systemic disease and search for potential triggers. Patients presenting with any of these 3 entities require similar systemic evaluation, medical history review, probing regarding medications, and evaluation for potential triggers (Table D). Using the umbrella terminology “RGD” allows for a more efficient systematic workup and treatment initiation for patients with granulomatous inflammation.

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Conflicts of interest

None disclosed.

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