Granulomatous Rosacea and Periorificial Dermatitis

Controversies and Review of Management and Treatment

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KEYWORDS

• Granulomatous rosacea • Perioral dermatitis • Periorificial dermatitis

KEY POINTS

- Granulomatous rosacea (GR) is a rare inflammatory skin condition characterized by reddish brown papules favoring the face.
- GR is thought to arise from various antigenic triggers causing granuloma formation.
- Treatment of GR is difficult and often requires a trial of various topical and systemic therapies.
- Periorificial dermatitis (PD) is a self-limiting inflammatory skin condition characterized by erythema, papules, pustules, and a distinct sparing around the vermillion border.
- Management of PD should include ending use of any triggering topical medication, especially topical steroids.

INTRODUCTION

Granulomatous rosacea (GR) and periorificial dermatitis (PD) are inflammatory skin conditions characterized by erythematous papules most commonly affecting the face (**Figs. 1** and **2**). These entities have been the topic of controversy because they are similar in clinical presentation, yet have variable causes and prognoses. They are both benign and self-limiting but GR tends to have a chronic course compared with PD. Some clinicians consider PD and its clinical variants on the same spectrum as rosacea because these entities have the same clinical response to similar therapies. Although acknowledging this controversy, for the sake of clarity this article describes them separate clinical entities. This article attempts to explain the origin of each disease and the different perspectives in terms of nomenclature and causes, as well as summarize existing literature on each entity.

In 2002, rosacea was classified and standardized by the National Rosacea Society Expert Committee into 4 recognized subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.[1] Using this classification, epidemiologic studies show erythematotelangiectatic rosacea to be by far the most common type.[2] GR is not one of the subtypes of rosacea, but is thought to be a variant of rosacea based on unique clinical and histologic findings of granulomas.[1] At present, the Committee recognizes GR as a variant of

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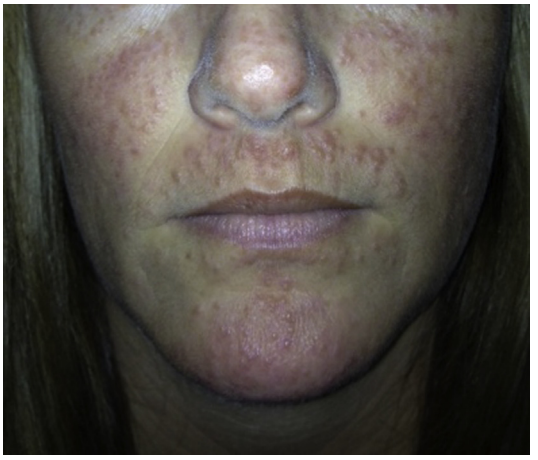

Fig. 1. GR. Firm papules involve the perioral, periocular, and perinasal regions.

rosacea and GR is diagnosed in the setting of histologically confirmed papular granulomas on the face after ruling out other entities, such as PD and sarcoidosis.

PD, which can involve the perinasal, perioral, and/or periorbital area, is an inflammatory skin eruption characterized by erythematous papules and pustules on the face. As such, PD has been erroneously referred to as perioral dermatitis even when lesions appear in locations other than the perioral area. In 1957, PD was first described by Frumess and Lewis[3] as a cyclic dermatitis called "light-sensitive seborrheid." In 1964 it became a distinct entity called "perioral dermatitis."[4] This condition is commonly found in young adult women between the ages of 16 and 45 years.[5] However, PD has also been reported in children between the ages of 6 months and 18 years.[6] Originally described in 1970by Gianotti and colleagues,[7] childhood granulomatous PD (CGPD) is a distinct subtype of PD typically seen in prepubertal children of darker skin color. Since then, several cases of children with a spectrum of skin colors with similar findings have been described.[8] In the literature, this entity has been given various names including childhood granulomatous perioral dermatitis, sarcoid-like granulomatous dermatitis, and facial Afro-Caribbean eruption (FACE). Currently, the most accepted term for this disease is CGPD, which the authors agree best describes the entity.[9] The granulomatous variant of PD can also be seen in adults and is clinically very similar to GR without the background erythema. The cause of this variant of PD is thought to be topical steroid use.[8]

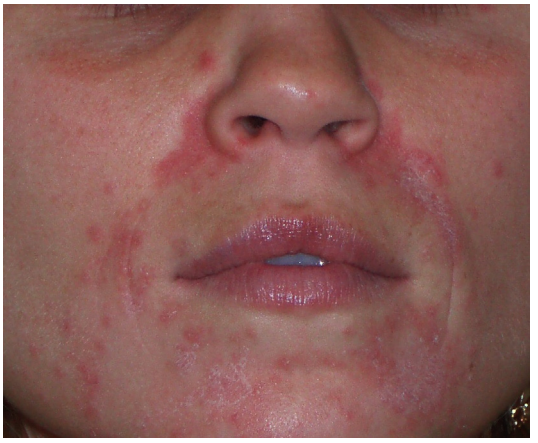

Fig. 2. PD from inhaled corticosteroids. The erythematous papules around the mouth spare the vermilion border of the lips.

GRANULOMATOUS ROSACEA

Etiopathogenesis

GR is a rare chronic inflammatory skin disease reported primarily in middle-aged women[10] that has been given various names in the literature. In 1896, Darier[11] first described the concept of tuberculids, which were defined as skin findings associated with a distant focus of active tuberculoid infection. In 1917, Lewandowsky[12] described a patient with a rosacea-like tuberculid granuloma that clinically mimicked the appearance of papular rosacea. Laymon[13] reported similar cases and called it "micropapular tuberculid." However, in 1949, Snapp[14] presented 20 patients with rosacea-like tuberculids; all except one displayed a low degree of tuberculin sensitivity. He concluded, therefore, that tuberculid rosacea does not exist and posited that it is a distinct form of rosacea.[14] Because the common features of rosacea (flushing, nontransient erythema, papules and pustules, and telangiectasia) are not necessary, or even typical, for the diagnosis of GR, it has been questioned whether the pathophysiology of GR is even related to that of rosacea.[15] For that reason, some investigators have even suggested the term granulomatous facial dermatitis for the condition.[15] Just as the nomenclature is controversial, the etiologic factors of both rosacea and GR are disputed. Several triggering and aggravating factors for rosacea have been described. These include systemic steroids, topical steroids, ultraviolet radiation (UVR), heat, spicy food, alcohol, and infectious organisms, including *Demodex* mites and GI bacteria.[16,17] Mullanax and Kierland[18] first reported cases of GR with the key pathologic finding of noncaseating epithelioid granulomas with a mixed inflammatory infiltrate. Because granulomas are thought to be a

response to persistent antigen presence, researchers subsequently looked for antigens as the triggering factors.[17] *Demodex folliculorum* has been at the center of this discussion ever since histologic examination of a facial papule from a patient with GR showed foreign body granulomas along with *D folliculorum* species within enlarged hair follicles. Most recently, in 2008, a study reviewed pathologic specimens from 24 subjects with GR and *D folliculorum* was identified in only 7 out of these 24 specimens.[19] However, in those that were positive for *D folliculorum*, the mites were found within the granuloma suggesting their role in the pathogenesis of at least some cases.[19] Other researchers suggest it may not simply be the presence of the *D folliculorum* mites but the combination of location of the mites, density of the organisms, and host susceptibility that may play a role in the pathogenesis of GR.[17,20,21] Another recent study suggests the role of UVR in causing both sun damage and increased matrix metalloproteinase (MMP)-2 and MMP-9, contributing to tissue remodeling and, thereby, recruiting inflammatory cells that contribute to the formation of granuloma in the dermis.[22] Also of note is the historical but unsupported association between gastrointestinal disturbances caused by *Helicobacter pylori* and GR. There is a study showing improvement of GR after eradicating *H pylori*; however, there are no large trials supporting this data.[23] Currently, the consensus is that GR is a histologic variant of rosacea, not a distinct clinical subtype, and may have multifactorial causes that are distinct from rosacea.

Clinical Presentation

The lesions of GR consist of monomorphic, firm, yellow, red, brown, or flesh-colored papules or nodules localized around eyes, nose, and mouth on relatively normal appearing skin.[24] Specifically, the characteristic papules are on the lateral side of the face and on the neck below the mandible.[17] Other signs of rosacea, such as flushing, erythema, or telangiectasia, may be seen but are not needed for diagnosis.[24] However, if patients have overlap of GR and rosacea, they can have symptoms of burning or stinging, pruritus, facial swelling, or irritation.[15] In a review study of 53 patients with GR, 15% had extrafacial lesions in the ears, neck, axilla, shoulder, groin, thigh, and knees.[17] GR tends to be a chronic condition that is difficult to treat and has unpredictable responses to standard rosacea treatments. Based on case reports in the literature, the clinical course ranges from 6 months to 4 years.[23]

The differential diagnosis of GR includes PD, CGPD, lupus miliaris disseminatus faciei (LMDF), sarcoidosis, FACE, and cutaneous tuberculosis (**Table 1**). PD is a papulopustular facial dermatitis that typically spares the vermillion border. Clinically and histologically, PD can be similar to GR but typically has a less granulomatous histology, responds better to treatment, and has a shorter clinical course. CGPD is characterized by periorificial papules, pustules, and erythema and may be a subtype of GR. LMDF is a rare chronic skin condition characterized by papules distributed across the face symmetrically and can be differentiated by histologic findings of caseating granulomas.[26] LMDF tends to heal by leaving permanent scars.[26] Sarcoidosis can also cause granulomatous papules on the face but typically has other extracutaneous findings, such as granulomas, fatigue, fever, weight loss, pulmonary symptoms, and less mixed inflammation on histopathology.[27] FACE is similar to PD but is more commonly seen in children with dark skin. Some investigators think FACE is also a variant of GR.[5]

Systemic Associations

Involvement of other organ systems is not typically associated with GR. However, it is on the spectrum of rosacea. Ocular rosacea coexists in 50% of patients with cutaneous rosacea.[28] There is a case report of a patient with GR who developed lacrimal, parotid, and submandibular gland swelling after treatment with systemic steroids.[29] The scleritis, conjunctivitis, and parotiditis resolved after a month of minocycline therapy.[29] In fact, if patients have other systemic complaints, the clinician should seek out other possible diagnoses in the differential such as sarcoidosis.

Evaluation and Management

When approaching patients with facial papular dermatitis, differential diagnoses of GR, PD, CGPD, sarcoidosis, LMDF, FACE, and cutaneous tuberculosis should be considered. Diagnosis of these entities can be challenging and evaluation should include a thorough clinical history, physical examination, and skin biopsy. Depending on clinical suspicion of sarcoidosis or tuberculosis, evaluation can include routine complete blood cell count with differential, chemistry panel, purified protein-derived or QuantiFERON-TB Gold test (QTF-G, Cellestis Limited, Carnegie, Victoria, Australia), baseline pulmonary radiograph, and autoimmune panel.

Currently, there is no standard of treatment of GR and limited data on therapeutic effectiveness are reported in individual cases. With limited data

Table 1
Differential diagnosis of granulomatous papules on the face

	Patient Characteristics	Clinical Features	Histopathology
GR	Young adults, light skin	Periorificial, extrafacial papules	Noncaseating epithelioid cell granulomas with mixed infiltrate
PD	Children or young women	Periorificial erythema, papules and pustules	Perifollicular lymphocytic and perivascular infiltration
CGPD	Prepubertal	Periorificial, extrafacial papules	Perifollicular granulomatous infiltration on the upper half of body
LMDF	Adolescent or adult	Symmetric papules across central face	Perifollicular caseating granulomatous lymphohistiocytic infiltration with occasional neutrophils
Sarcoidosis	Any age	Noninflammatory facial papules and nodules May have systemic findings of fatigue, weight loss, joint pain, pulmonary symptoms	Naked, noncaseating granulomatous infiltration
FACE	Children, dark skin	Periorificial, favoring outer helix of the ear	Perifollicular granulomatous infiltration
Cutaneous tuberculosis	Any age	Systemic findings, weight loss, malaise, pulmonary symptoms	Caseating granuloma

Adapted from Refs.[5,18,25]

on treatment of GR, therapeutic efforts have been based on the use of medications that are effective for sarcoidosis and papulopustular rosacea, the 2 diseases with which it has the most in common. The tetracycline family of medications is the obvious first therapeutic choice. Use of tetracycline 250 mg daily to 500 mg 3 times a day, doxycycline 50 to 100 mg twice a day, or minocycline 50 to 100 mg twice a day has been reported in the literature.[10,18,30–32] Their mechanism of action against granuloma formation is thought to be due to inhibition of protein kinase C, a signaling enzyme in the inflammatory pathway.[33] Other therapeutic agents to consider include azelaic acid, benzoyl peroxide, topical metronidazole, topical corticosteroids, systemic corticosteroids, and oral erythromycin. There is a case report suggesting the role of *H pylori* in the pathogenesis of GR in which the patient's skin lesions resolved 2 months after taking clarithromycin 250 mg twice a day, oral metronidazole 500 mg twice a day, and pantoprazole 40 mg daily for 7 days.[23] There are 2 case reports of the use of pimecrolimus 1% cream applied to lesions twice a day with good efficacy.[34,35] One patient used pimecrolimus 1% topical cream combined with sun block twice a day resulting in complete resolution of lesions after 4 months of therapy.[35] The other patient responded well to pimecrolimus 1% cream after failing a 45-day course of topical metronidazole and oral doxycyline.[34] There was no evidence of relapse after stopping the medication.

For recalcitrant GR, isotretinoin 0.7 mg/kg for 6 months as monotherapy showed some clinical resolution of disease without recurrence.[36] After failing systemic doxycycline, isotretinoin, and corticosteroid, 2 patients tried oral dapsone with clinical improvement.[37] Limited data on physical modalities as treatment options include laser and ablative laser therapy. One patient received 6 treatments at 2-week intervals of photodynamic therapy with aminolevulinic acid with improvement seen after the third treatment.[38] Another patient underwent 6 sessions of intense pulsed dye laser at 4-week interval with satisfactory improvement.[39]

Although unreported in the literature for specific use against GR, combination therapy with oral metronidazole and oral ivermectin has been shown to be the most effective regimen for

eradication of *D folliculorum*. Given the role this organism is suspected to play in GR, a trial of this regimen would be reasonable in a case that does not respond to therapy with oral tetracyclines. The studied regimen for *D folliculorum* is metronidazole 250 mg 3 times a day for 14 days along with ivermectin 0.2 mg/kg of body weight on days 1 and 7 of the metronidazole course.[40] For current available treatments for GR, see **Table 2**.

PERIORIFICIAL DERMATITIS

Etiopathogenesis

Currently, the causes of PD and its clinical variants, granulomatous form and CGPD, are unknown. The most common known triggering factor for PD is prior exposure to topical steroids of any potency for treatment of other facial dermatitides and cutaneous exposure to steroids via exhaled steroid in patients using corticosteroid inhalers or nasal sprays.[6,44] However, not all patients have this clinical history. Several case reports also consider various historical etiologic factors, such as topical medications, cosmetic products, physical factors, and microorganisms, among others.[45] (**Table 3**) Another study compared the skin of subjects with rosacea and PD and found an association between PD and atopic dermatitis, suggesting either impaired skin barrier or incidental transfer of topical steroid to the face as the underlying pathologic condition.[61] A commonality among most of these factors is their irritant nature to the skin and alteration of microflora in the pilosebaceous unit.[5] Based on the current available evidence, the authors think that PD is induced by exogenous factors, such as atopic dermatitis or hormonal disturbance, in a susceptible host.

Clinical Presentation

PD is an inflammatory disease limited to the face and characterized by erythema, papules, papulovesicles, papulopustules, and scaling with distinct sparing around the vermillion border. Most patients are women between ages of 20 and 45 years; however, PD can also affect children.[6,45] A variant of PD is CPGD, which occurs in prepubertal children typically presenting with monomorphic, yellow, reddish micronodular eruptions on the central face with predilection for the areas around the mouth, eyes, and nose.[62] Although rare, extrafacial involvement around the vaginal area has been described.[62] Adult patients commonly complain of an intense burning sensation accompanying skin erythema and scaling. Alternatively, a retrospective chart review from one institution of cases of children with PD showed 19% reporting pruritus with only 4% reporting burning.[6] The duration of disease ranged from 2 weeks to 4 years. Most of the cases resolved spontaneously with some patients reporting atrophic pinpoint scarring, likely from the inflammatory process.[9] The differential diagnoses for PD are similar to GR (see **Table 1**).

Systemic Associations

Both PD and CGPD are self-limiting conditions without associated systemic diseases.[62] However, some patients may develop emotional distress due to the disfiguring nature of the rash.[45] The lesions of PD may also run a chronic course and

Table 2
Therapeutic agents for granulomatous rosacea

Topical Agent	Level of Evidence[a]	Systemic Agent	Level of Evidence[a]
Azelaic acid	E	Clarithromycin, metronidazole, and pantoprazole combination[23]	D
Benzoyl peroxide	E	Dapsone[37]	D
Metronidazole[31,41]	D	Doxycycline[31]	D
Pimecrolimus[34,35]	D	Erythromycin[42]	D
Topical steroid	E	Isotretinoin[36,43]	D
—	—	Minocycline[10,32]	D
Other		Systemic steroid[43]	D
Intense pulsed dye laser[39]	D	Tetracycline[18,30]	D
Photodynamic therapy[38]	D	—	—

[a] D, case series or case reports; E, expert opinion.

Table 3
Causative factors of periorificial dermatitis

Medications	Topical steroids,[6] inhaled corticosteroids,[46,47] systemic corticosteroids[48]
Cosmetic products	Fluorinated toothpaste,[49] tartar control toothpaste,[50] moisturizers,[51] propolis,[52] sunscreens[53]
Physical factors	Ultraviolet light,[45] heat and cold[54]
Microorganisms	Fusobacteria,[55,56] *Candida* spp,[54] *Demodex folliculorum*[57]
Miscellaneous	Hormonal (oral contraceptives),[58] chewing gum,[59] amalgam dental filling[60]

evolve into lupoid form causing permanent scarring on the face.[44]

Evaluation and Management

Diagnosis of PD is made based on the typical clinical presentation and histologic examination is rarely necessary to exclude other diagnoses. Although the histology of CPGD is not diagnostic and can be very similar to GR, the age of the patient and the lack of pustules generally allow distinction.

A large armamentarium of treatment options is available based on the etiologic factors for PD. The first question the clinician should ask is whether the perioral skin has been exposed to steroids. If the patient cannot recall, the clinician should still maintain a high index of suspicion for exposure via any route, including topical application, inhaled steroids, or even "connubial" exposure from kissing another individual who uses topical steroids, and question the patient accordingly. If steroid use is ascertained, a frank discussion with the patient should ensue; there will be a direct correlation between reduction in steroid exposure and severity. In the authors' experience, a cold-turkey approach, with abrupt discontinuation of the steroid, leads to the worst flare but the most rapid resolution (1–3 months). When using this approach, we give the patient a class 1 topical steroid to use for 1 to 2 days up to twice a month for important social or work events. An alternative approach is to wean the patient off steroids, either by decreasing the potency, the frequency of application, or both. This approach generally leads to a significantly less severe flare but a much slower resolution (often greater than a year). The severity of the flare is directly proportional to how quickly the steroid is weaned, whereas the speed of resolution is inversely proportional.

All patients should be treated with topical and/or oral medications whether or not a steroid has been discontinued. Oral tetracycline is proven to be an effective agent for PD as seen in a randomized, multicenter clinical trial comparing it with topical metronidazole.[63] The recommended dosage varies from 250 mg 2 to 4 times a day to, in severe cases, up to 500 mg twice a day with treatment

Table 4
Therapeutic agents for periorificial dermatitis

Topical Agents	Level of Evidence[a]	Systemic Agents	Level of Evidence[a]
Metronidazole[63,70]	A	Tetracycline[63,71]	A
Erythromycin[71]	A	Erythromycin[62,68,69]	D
Pimecrolimus[72,73]	A	Doxycycline[66,74]	D
Sulfacetamide or sulfur[75]	B	Minocycline[67]	D
Azelaic acid[76,77]	B	Cefcapene pivoxil hydrochloride hydrate[55]	D
Clindamycin[66,78,79]	C	Isotretinoin[80]	D
Tacrolimus[67,81]	D	Other	—
Adapalene[82]	D	Zero therapy[71–73]	A
—	—	PDL[78]	C

[a] A, high-quality randomized controlled trial (RCT) or prospective study; B, lesser quality RCT or prospective study; C, case-control study or retrospective study; D, case series or case reports.

duration between 4 to 8 weeks.[5,64,65] Tetracycline also has been reported to help with CGPD, and can be considered in children older than age 9.[62] Doxycycline and minocycline, second-generation tetracyclines, in combination with other topical agents have also been used in CGPD with reasonable efficacy.[66,67] As a second-line agent especially for patients with contraindication to tetracycline, such as pregnant women or children younger than age 8, oral erythromycin can be considered; several reports show its efficacy for both PD and CGPD.[68] Dosages for oral erythromycin are generally in the range of 250 mg to 500 mg a day.[68,69] For patients who do not respond to conventional therapies as described above, the clinician can consider low-dose oral isotretinoin, initially 0.2 mg/kg/d, then lowering the dose to 0.1 mg/kg/d or to 0.05 mg/kg/d.[45] For PD in children, an effective treatment was reported with oral or topical metronidazole either alone, or in combination with erythromycin, that resulted in resolution of the primary and secondary lesions within 7 weeks.[6] Other topical agents that have shown effectiveness in case studies and series include pimecrolimus, tacrolimus, azelaic acid, sulfacetamide, topical adapalene, metronidazole, erythromycin, and clindamycin (**Table 4**).

SUMMARY

GR is a variant of rosacea that can occur with or without typical subtypes of rosacea. The cause of this entity is unknown but there are several reported antigenic factors triggering the granuloma formation. Clinically, the monomorphic papules favor periorificial areas on the face but can rarely occur in the extrafacial region. Treatment of this condition is difficult and the disease tends to be chronic but several modalities, including topical agents, oral antibiotics, oral retinoids, and laser, can be considered. PD shares similar clinical features with GR but is a common self-limiting inflammatory condition affecting young women. There are several triggering factors that may aggravate this condition. Management approach should include discontinuing any triggering factors, especially topical steroids. For children younger than 8 years of age, the first line agents to consider are topical metronidazole, erythromycin, and pimecrolimus. For patients older than 8 years of age, oral tetracycline is the first-line treatment.

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