Rosacea
ROSACEA Despite universal recognition, rosacea remains a controversial topic in dermatology, largely because of its uncertain pathophysiology and clinical variation. Practitioners and the public can easily identify the prototypical red face of rosacea; however, confusion arises when photodamage, perioral dermatitis, post-adolescent acne, and topical steroid overuse present in a similar guise. Recent theory has shifted conceptually from staged progression of rosacea signs and symptoms to a new classification that defines four sub-types with variable severity and potential overlap.

Rosacea is characterized by erythema of the central face that has persisted for months or more. The convex areas of the nose, cheeks, chin, and forehead are the characteristic distribution. Primary features of rosacea, which may be observed but are not required for the diagnosis, include flushing, papules, pustules, and telangiectases. Secondary features include facial burning or stinging, edema, plaques, a dry appearance, phyma, peripheral flushing, and ocular manifestations. Erythema in peripheral locations (the scalp, ears, lateral face, neck, and chest) can be observed in rosacea but is also a common feature of physiologic flushing and chronic sun damage, and therefore must be interpreted carefully.

Sub-Type Classification

The sub-types of rosacea were defined provisionally by the National Rosacea Society (NRS) Expert Committee in 2002 and include erythematotelangiectatic, papulopustular, phymatous, and ocular sub-types. These represent the most common groupings of rosacea signs and symptoms. The sub-types coincide with the first rosacea “staging” classification devised by Plewig and Kligman. The erythematotelangiectatic sub-type is analogous to Plewig-Kligman stage I disease, the papulopustular sub-type to Plewig-Kligman stage II, and the phymatous sub-type to Plewig-Kligman stage III. In contrast, the NRS classification maintains that progression of rosacea in stages (from one sub-type to another) does not occur, but that sub-types may overlap in the same individual. A provisional grading system was also incorporated by the NRS Expert Committee to standardize the clinical assessment of rosacea. Rosacea severity assessments must additionally include consideration of the psychological, social, and occupational impacts of this disorder and individual responsiveness to treatment.
Epidemiology

Although the prevalence of rosacea is unknown, it is considered common in Caucasian populations. Although the vast majority of cases occur in fair-skinned individuals, persons of African and Asian descent may also develop rosacea. The NRS has estimated that rosacea affects 14 million Americans. Rosacea occurs in both men and women, and onset typically begins after age 30. However, children, adolescents, and young adults may develop rosacea.

Etiology and Pathogenesis

Because of prominent clinical variation among the rosacea sub-types, it has been hypothesized that etiologic and pathophysiologic differences may exist among them. Such differences may involve facial vascular reactivity, dermal connective tissue structure or composition, matrix composition, pilosebaceous structure, microbial colonization, or a combination of factors that alter the cutaneous response to rosacea trigger factors. Rosacea is unmasked or induced by chronic, repeated trigger exposure, in particular by triggers of flushing that may include hot or cold temperature, sunlight, wind, hot drinks, exercise, spicy food, alcohol, emotions, cosmetics, topical irritants, menopausal flushing, and medications that promote flushing. Both neural and humoral mechanisms produce flush reactions that are visibly limited to the face. Facial prominence occurs because baseline facial blood flow is increased compared with other body sites, and because the facial cutaneous vasculature is more superficial and comprised of larger and more numerous vessels when compared with other sites.

Dermal matrix degeneration and endothelial damage have been demonstrated histologically in rosacea specimens. Factors that contribute to matrix degeneration include inherent problems with vessel permeability and/or delayed clearance of inflammatory mediators and waste products. Alternatively, photodamaged connective tissue may alter vascular and lymphatic structure and support within the dermis. In either case, chronic and persistent dermal inflammation may occur and ultimately manifest as erythema of the facial convexities in predisposed individuals.

Sun damage is considered a contributing etiologic factor, but other factors must participate as well. Solar elastosis is a common background on which rosacea histologic features are superimposed. However, rosacea prevalence is not increased in outdoor workers, sun damage
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in non-facial locations does not progress to a rosacea phenotype, and photoprovocation studies in rosacea patients have not demonstrated increased cutaneous sensitivity to acute ultraviolet exposure.\(^9\) \(^{15,18,19}\)

It has long been debated whether oral and topical antimicrobial agents for rosacea exert their effects by anti-inflammatory or antimicrobial mechanisms. The concept of microbe-induced, follicle-based inflammation in rosacea is controversial. It is unclear whether commensal organisms such as Propionibacterium acnes and Demodex folliculorum, which reside in hair follicles and sebaceous glands, trigger folliculocentric inflammatory papules in rosacea patients.\(^9\)

Alternatively, a hypersensitivity reaction may be triggered by these microbes or by mite-associated bacteria such as Bacillus oleronius.\(^20\)

Compelling arguments in favor of a microbe-induced mechanism for papulopustular rosacea (PPR) include the observation that nonsteroidal anti-inflammatory drugs and corticosteroids do not clear rosacea papules and pustules as effectively as oral tetracyclines. Furthermore, benzoyl peroxide is quite effective for papules and pustules in rosacea patients who tolerate this drug. It remains unclear whether clinical improvement of PPR requires a quantitative reduction of P. acnes.

CLINICAL FEATURES

Erythematotelangiectatic rosacea (ETR) is characterized by persistent facial erythema and flushing along with telangiectases, central face edema, burning and stinging, roughness or scaling, or any combination of these signs and symptoms (Fig. 79-1). Mild, moderate, and severe sub-types are recognized. In contrast, PPR manifests as persistent, central-face erythema with papules and pustules that predominate in convex areas. Again, mild, moderate, and severe are distinguished. Burning and stinging of the facial skin may occur in PPR, but occurs less commonly compared with ETR. Flushing is often less severe in PPR compared with ETR. In both sub-types, erythema spares the periorbital areas. Edema can be mild or severe. Severe edema may take on the plaque morphology of solid facial edema.\(^1,21\) This occurs most often on the forehead and glabella, and it less commonly affects the eyelids and upper cheeks.

Phymatous rosacea is characterized by patulous follicular orifices, thickened skin, nodularities, and irregular surface contours in convex areas. Here also, mild, moderate, and severe sub-types are distinguished. Phyma most often occurs on the nose (rhinophyma), but may also develop on the
chin (gnathophyma), forehead (metophyma), eyelids (blepharophyma), and ears (otophyma). Women with rosacea do not develop phyma, perhaps for hormonal reasons, but they can manifest sebaceous or glandular features characterized by thickened skin and large follicular orifices.

Ocular rosacea may develop before cutaneous symptoms in up to 20 percent of affected individuals. In half of patients, ocular symptoms develop after skin symptoms. In a minority, skin and eye symptoms present simultaneously. Ophthalmic rosacea severity does not coincide with cutaneous rosacea severity. Ocular involvement may manifest as blepharitis, conjunctivitis, iritis, scleritis, hypopyon, and keratitis, and again mild, moderate, and severe sub-types are recognized. Blepharitis is the most common feature, characterized by eyelid margin erythema, scale, and crust, with the variable presence of chalazia and staphylococcal infections due to underlying meibomian gland dysfunction. Photophobia, pain, burning, itching, and foreign body sensation may be part of the ocular symptom complex. In severe cases, rosacea keratitis may lead to vision loss.

Granulomatous rosacea is considered the only true rosacea variant. Granuloma formation is a histologic feature of the condition; the clinical features of granulomatous rosacea include yellow-brown or red papules or nodules that are monomorphic and located on the cheeks and periorificial facial skin. Upon diascopy, these papules reveal apple-jelly-like change in color similar to sarcoidosis or lupus vulgaris. The background facial skin is otherwise normal. Other signs and symptoms of rosacea are not required to make a diagnosis of granulomatous rosacea.

Histopathology

Rosacea is a clinical diagnosis; histology may be helpful when the facial distribution is atypical or when granuloma formation
is suspected. In ETR, a sparse, perivascular lymphohistiocytic infiltrate is accompanied by dermal edema and ectatic venules and lymphatics.\textsuperscript{14} Severe elastosis may be present. Similar features are found in the papulopustular sub-type, but the inflammatory infiltrate also surrounds hair follicles and sebaceous glands. Phymatous rosacea is characterized by prominent elastosis, fibrosis, dermal inflammation, sebaceous hyperplasia, and hypertrophy of sebaceous follicles.\textsuperscript{14, 26} Epithelialized tunnels undermine the hyperplastic tissue and are filled with inflammatory debris. D. folliculorum mites may be found in all types of rosacea within the follicular infundibula and sebaceous ducts.

Differential Diagnosis

Systemic diseases that must be differentiated from rosacea include polycythemia vera, connective tissue disorders (lupus erythematosus, dermatomyositis), carcinoid syndrome, mastocytosis, and neurologic causes of flushing. Neurologic causes include brain tumors, spinal cord lesions, orthostatic hypotension, migraine headaches, and Parkinson disease.\textsuperscript{27} Unilateral auriculotemporal flushing may follow parotid gland injury or surgery.

Medication-induced flushing has been associated with all vasodilators, calcium channel blockers, nicotinic acid (niacin), morphine, amyl and butyl nitrite, cholinergic drugs, bromocriptine, thyroid releasing hormone, tamoxifen, cyproterone acetate, systemic steroids, and cyclosporine.\textsuperscript{27, 29} The flush associated with nicotinic acid may be blocked with aspirin or indomethacin.\textsuperscript{30} Disulfiram, chlorpropamide, metronidazole, phen tolamine, and cephalosporins induce flushing when they are combined with alcohol.\textsuperscript{27}

Amiodarone has induced rosacea and multiple chalazia.\textsuperscript{31} Food additives, including sulphites, sodium nitrite, nitrates, and monosodium glutamate, may also cause flushing.\textsuperscript{27}

Dumping syndrome following gastric surgery is characterized by flushing, sweats, tachycardia, and abdominal pain.

Cutaneous conditions that may mimic rosacea include topical steroid-induced acneiform eruption (formerly steroid-induced rosacea), acne vulgaris, perioral dermatitis, inflammatory keratosis pilaris, and chronic photodamage. In particular, acne vulgaris and rosacea may co-exist, although rosacea most often begins and reaches its peak incidence in the decades after acne declines. The primary differentiating feature between acne vulgaris and rosacea is the presence of open and closed comedones in acne alone.
Rosacea fulminans, also known as pyoderma faciale and rosacea conglobata, occurs mainly in women in their 20s.\textsuperscript{2,32,33} It is characterized by the sudden onset of confluent papules, pustules, nodules, and draining sinuses on the chin, cheeks, and forehead within a background of diffuse facial erythema. Rosacea fulminans has proved controversial in its classification and was not included as a rosacea sub-type or variant by the NRS Expert Committee.

Perioral dermatitis (see Chap. 80) differs from rosacea in its facial distribution, signs, symptoms, and patient demographic. It is characterized by perioral, and sometimes periornital, microvesicles, micropustules, scaling, and peeling. It affects younger women and also occurs in children. Central face erythema and inflammatory papules are not features of perioral dermatitis. Therapy includes topical and oral antimicrobials. Perioral dermatitis is exacerbated by topical steroid use.

Steroid-induced acneiform eruption can mimic PPR. With prolonged use of topical steroids on the face, monomorphic inflammatory papules may develop. The treatment is discontinuation of the topical corticosteroid and initiation of an oral tetracycline, a topical antimicrobial, a topical calcineurin inhibitor, or a combination of these agents. This regimen is generally continued for 1 to 3 months, and relapse does not tend to occur as long as topical steroids are not reintroduced.

In chronic photodamage, telangiectases and erythema are prominent features. However, unlike rosacea, actinic damage affects the periphery of the face and neck, the upper chest, and the posterior auricular skin. Hyperpigmentation and hypopigmentation are additional feature of sun damage not observed in rosacea. Chin involvement is both mental and submental in rosacea, while in chronic photodamage there is submental sparing.

THERAPY

Before implementing therapy, rosacea trigger factors specific to each individual must be identified. Patient education should stress trigger avoidance. Other key aspects of prevention
include the daily application of gentle, broad spectrum ultraviolet A and ultraviolet B sunscreen, hat use, avoidance of midday sun, and seeking shade. Physical sunscreens (zinc or titanium-based) are best tolerated. Chemical sunscreens are better tolerated when barrier protective silicones (dimethicone, cyclomethicone) are included.

Cosmetic intolerance and facial skin sensitivity are common features of the erythematotelangiectatic and papulopustular sub-types, perhaps due to inherent barrier dysfunction or facial vascular hyperreactivity. As many as 75 percent of these individuals may experience burning, stinging, pruritus, or dryness and scaling in affected areas. Avoidance of harsh products and ingredients, including astringents, toners, menthol, camphor, and sodium lauryl sulfate, is important when sensitivity is present. A soap-free cleanser applied with the fingers is best tolerated. A protective, gentle emollient should be applied once or twice daily before application of other products. Light liquid foundation makeups are the best choice for patients with sensitivity. Greentinted makeup can be applied before foundation to further mask red areas.

TOPICAL THERAPY

The topical agents approved by the U.S. Food and Drug Administration for rosacea include 15 percent azelaic acid gel, 0.75 percent and 1 percent metronidazole (available in cream, gel, and lotion vehicles), and 10 percent sodium sulfacetamide with 5 percent sulfur (available in cleanser, cream, suspension, and lotion vehicles). Each has proved effective for clearance of inflammatory papules and pustules and for erythema reduction when applied once daily. Twice-daily application or combinations of these agents may be necessary when topical monotherapy is inadequate. Metronidazole and azelaic acid are pregnancy category B, whereas sodium sulfacetamide and sulfur is category C. Azelaic acid may be associated with initial tingling or burning that can disappear with continued use. Sodium sulfacetamide/sulfur medicated cleansers are better tolerated in sensitive patients compared with “leave-on” topical formulations that may increase burning and stinging. Daily use of a barrier repair emollient is important in these patients.

Off-label topical formulations used for rosacea include benzoyl peroxide, clindamycin, erythromycin, calcineurin inhibitors, and topical retinoids. Benzoyl peroxide is effective for clearance of papules and pustules but should be avoided in sensitive patients. Twice-daily
topical clindamycin was more effective than oral tetracycline for the eradication of pustules in one series. Tacrolimus ointment and pimecrolimus cream are most beneficial for topical, steroid-induced acneiform eruptions, but they may offer a useful therapeutic alternative in some patients with rosacea.

“Manual” therapy should also be considered adjunctively in rosacea patients. Facial massage is performed in the direction of the lymphatic flow, according to Soybe's technique, beginning at a central location on the face (the glabella and nose) and pressing the fingers in a sweeping motion toward the inferolateral face (the mandibles and lateral neck). This can help to mobilize edema and speeds clearance of dermal inflammation.

Tretinoin cream promotes connective tissue remodeling and minimizes dermal inflammation with long-term use. Topical retinoids have demonstrated benefit for rosacea in small clinical series. The clinical response to retinoids is delayed in the rosacea setting; generally 4 to 6 months of use is required to see significant effects. Because of their potential for irritation and concerns regarding promotion of angiogenesis, retinoids are often avoided for rosacea. However, their long-term use does not appear to promote the development of telangiectasia. Retinoids inhibit vascular endothelial growth factor production by cultured human skin keratinocytes via their anti-AP1 transcription factor activity.

The use of barrier emollients in conjunction with gradual introduction of topical retinoids allows them to be tolerated early on in treatment when retinoid dermatitis is a problem. Topical retinoids are especially useful for long-term maintenance in rosacea.

ORAL THERAPY

Topical management of rosacea is possible and generally preferable, especially when considering issues of antimicrobial resistance and the risks associated with long-term use of oral antibiotics. Furthermore, because rosacea is photoaggravated in many affected individuals, photosensitizing oral agents must be used with caution in this population. Oral antimicrobials in particular are useful short-term tools that can achieve rapid control of symptoms, but long-term topical maintenance should be the eventual therapeutic goal. All of the oral therapies herein discussed are used off-label for rosacea.

For moderate to severe flushing or erythema, short-term oral therapy (2 to 4 months) with a tetracycline or isotretinoin may be useful for initial control. Tetracyclines achieve faster reduction
of papules, pustules, and erythema when compared with isotretinoin, and since the 1950s, rosacea has been treated and maintained with both antimicrobial and sub-antimicrobial dosages of the tetracyclines. Relapses occur in approximately one-fourth of patients after 1 month off tetracycline, and in over one-half of patients at 6 months off therapy. Topical maintenance therapy is therefore advised. Oral tetracyclines should be avoided in pregnant women and in those contemplating pregnancy.

In one small series, a significant reduction of facial cutaneous blood flow, measured by laser-Doppler, was achieved in isotretinoin-treated patients (30 mg daily for 10 weeks), whereas no significant change in facial blood flow was observed in those treated with 250 mg of tetracycline twice daily for 10 weeks. Low-dose isotretinoin (10 to 40 mg daily or less than 0.5 mg/kg/day) can be effective and is better tolerated in rosacea patients. Isotretinoin is teratogenic, and its use is strictly monitored in women of child-bearing potential.

Other oral agents used for rosacea include macrolides, metronidazole, anti-androgenic agents (oral contraceptives, spironolactone, and cyproterone acetate), β blockers, clonidine, naloxone, and selective serotonin reuptake inhibitors. In patients with a history of acne vulgaris or overlap of acne vulgaris with rosacea, spironolactone in low doses (25 to 50 mg daily) and/or oral contraceptive pills may prove helpful.

LASER AND LIGHT THERAPY

Vascular lasers and intense pulsed light (IPL) therapy are useful alternatives to oral rosacea therapies; they may be used adjunctively with topical and oral rosacea regimens for faster and more complete symptom resolution. These non-ablative modalities can eliminate telangiectasia, reduce or eliminate erythema, reduce papule and pustule counts, and they appear to extend the duration of remission. Their drawbacks are cost and side effects, which may include transient erythema, edema, purpura, blistering, dyschromia, burns, and, rarely, scarring.

Vascular lasers include short and long wavelength devices with a variety of pulse durations. Short wavelength lasers emit light that is selectively absorbed by oxyhemoglobin absorption peaks that occur at 541 nm and 577 nm. This allows for superficial vessel destruction without collateral tissue damage. Short wavelength lasers include the pulsed dye laser (585 nm or 595 nm), long pulsed dye laser (595 nm), the potassium-titanyl-phosphate laser (532 nm), and the diode-pumped frequencydoubled laser (532 nm). Long wavelength vascular lasers can eradicate deeper and larger vessels by targeting the oxyhemoglobin spectral peaks at 800 nm.
and above 1000 nm. These lasers include the long pulsed Alexandrite (755 nm), the diode laser (810 nm), and

the neodymium:yttrium-aluminum-garnet laser (1064 nm).

The success and tolerability of laser therapy for rosacea have been improved by modified pulse duration parameters and by advances in epidermal cooling mechanisms. Longer pulse durations can deliver equivalent energy at a slower rate to heat vessels uniformly and gently, minimizing tissue trauma and purpura. Epidermal cooling gels and sprays prevent epidermal damage and can help to minimize pain, erythema, and edema and help to ensure safe delivery of laser energy. Generally, two to four laser treatments are required to achieve best outcomes for rosacea; purpuric treatment settings may eradicate telangiectasia more quickly. Multiple laser passes and pulse-stacking on larger vessels may improve treatment outcomes when subpurpuric settings are utilized.

Unlike laser devices that emit a single wavelength, IPL (broadband light) emits a broad wavelength spectrum, ranging from approximately 550-nm visible light to 1200-nm infrared light. Filters are used to establish the short end of the spectrum, which varies depending on the device. Fluence and pulse width also vary with the system used. IPL may cause transient erythema, transient hyperpigmentation, or hypopigmentation, and, rarely, purpura, burns, and scarring. Epidermal cooling mechanisms are necessary to protect the epidermis. IPL effectively reduces facial erythema and telangiectases and is generally well tolerated. Vascular lasers and IPL may also impact rosacea by inducing fibroblasts to increase dermal collagen production, perhaps achieving some degree of dermal remodeling and rejuvenation.

TREATMENT OF PHYMA

Oral isotretinoin monotherapy is beneficial for early to moderate phymatous change. Advanced phyma is treated with surgical therapy or the combination of surgery followed by isotretinoin therapy. Surgical approaches to the reshaping of rhinophyma have included cold scalpel tangential excision, heated scalpel excision, electrocautery, dermabrasion, laser ablation, tangential excision combined with scissor sculpturing, radio-frequency electrosurgery, or a combination of these approaches. Techniques that use partial thickness tangential excision and contouring with preservation of the underlying sebaceous glands allow spontaneous re-epithelialization within 2 to 3 weeks, result in minimal scarring, and give an excellent
aesthetic result with a low risk of recurrence.

TREATMENT OF OCULAR ROSACEA

Ophthalmologic referral should be made for patients with ocular symptoms. For mild blepharitis, careful use of a gentle nonmedicated or sodium sulfacetamide/sulfur cleanser may be used once to twice daily as initial therapy. Sodium sulfacetamide 10 percent ophthalmic ointment is also effective for control of blepharitis. When topical management is inadequate, oral tetracyclines are generally effective.

Summary

To effectively treat rosacea, practitioners must recognize the clinical spectrum of rosacea phenotypes and what lies outside that spectrum. Sub-typing of rosacea is a useful guide to establish a multimodality approach to therapy. Therapeutic success is achieved by inducing remission of signs and symptoms, and by minimizing and controlling relapses. Ultimately, early recognition of this disorder, some key behavioral modifications, and the combination of sunscreen and topical agents can achieve safe, effective, and long-term control of rosacea, while avoiding the risks of oral pharmaceuticals and the financial strain of laser and light therapies.