The Great Mimickers of Rosacea

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Practice Points
• Rosacea is characterized by frequent flushing; persistent erythema (ie, lasting for at least 3 months); telangiectasia; and interspersed episodes of inflammation with swelling, papules, and pustules.
• Rosacea is most commonly seen in adults older than 30 years and is considered to have a strong hereditary component, as it is more commonly seen in individuals of Celtic and Northern European descent as well as those with fair skin.

Although rosacea is one of the most common conditions treated by dermatologists, it also is one of the most misunderstood. It is a chronic disorder affecting the central parts of the face and is characterized by frequent flushing; persistent erythema (ie, lasting for at least 3 months); telangiectasia; and interspersed episodes of inflammation with swelling, papules, and pustules. Understanding the clinical variants and disease course of rosacea is important to differentiate this entity from other conditions that can mimic rosacea. Herein we present several mimickers of rosacea that physicians should consider when diagnosing this condition.

Rosacea Characteristics
Rosacea is a chronic disorder affecting the central parts of the face that is characterized by frequent flushing; persistent erythema (ie, lasting for at least 3 months); telangiectasia; and interspersed episodes of inflammation with swelling, papules, and pustules. It is most commonly seen in adults older than 30 years and is considered to have a strong hereditary component, as it is more commonly seen in individuals of Celtic and Northern European descent as well as those with fair skin. Furthermore, approximately 30% to 40% of patients report a family member with the condition.

Rosacea Subtypes—In a 2002 meeting held to standardize the diagnostic criteria for rosacea, the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea described 4 broad clinical subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular. More than 1 subtype may present in the same patient. A progression from one subtype to another can occur in cases of severe papulopustular or glandular rosacea that eventuate into the phymatous form. Moreover, not all of the disease features are present in every patient. Secondary features of rosacea include burning or stinging, edema, plaques, dry appearance of the skin, ocular manifestations, peripheral site involvement, and phymatous changes.

In erythematotelangiectatic rosacea, episodic flushing occurs, which can last longer than 10 minutes with the central face exhibiting the most intense color. The redness also may involve the peripheral portion of the face as well as extrafacial areas (eg, ears, scalp, neck, chest). Periocular skin is spared. The stimuli that may bring on flushing
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include short-term emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather, and hot water.1 Patients with papulopustular rosacea generally present with redness of the central portion of the face along with persistent or intermittent flares characterized by small papules and pinpoint pustules. There also is an almost universal sparing of the periocular skin, and a history of flushing often is present; however, flushing usually is milder than in the erythematotelangiectatic subtype. The constant inflammation may lead to chronic edema and phymatous changes, which occur more commonly in men than in women.3

Phymatous rosacea is characterized by marked skin thickening and irregular surface nodularities, most commonly involving the nose (rhinophyma), though the chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyelids (blepharophyma) also are occasionally affected. There are 4 variants of rhinophyma with distinct histopathologic features: glandular, fibrous, fibroangiomatous, and actinic.3 The glandular variant is most often seen in men who have thick sebaceous skin. Edematous papules and pustules often are large and may be accompanied by nodulocystic lesions. Frequently, affected patients will have a history of adolescent acne with scarring.

Ocular rosacea may precede cutaneous findings by many years; however, in most cases the ocular findings occur concurrently or develop later in the disease course. The most consistent findings in ocular rosacea are blepharitis and conjunctivitis. Symptoms of burning or stinging, itching, light sensitivity, and a foreign body sensation are common in these patients.3

Pathogenesis—Several investigators have proposed that Demodex folliculorum may play a pathogenic role in rosacea. Demodex is a common inhabitant of normal human skin, and its role in human disease is a matter of controversy.3 Demodex has a predilection for the regions of the skin that are most often affected by rosacea, such as the nose and cheeks. The clinical manifestations of rosacea tend to appear later in life, which parallels the increase in the density of Demodex mites that occurs with age.4 It has been hypothesized that beneficial effects of metronidazole in the treatment of rosacea may be related to an antiparasitic effect on Demodex; however, these mites can survive high concentrations of the drug.3 Moreover, modern techniques that employ cyanoacrylate surface biopsies, which are extremely sensitive, estimate that the prevalence of Demodex in healthy skin approaches 100%.4 Consequently, the simple identification of Demodex is by no means proof of pathogenesis. Whether Demodex is truly pathogenic or simply an inhabitant of follicles in rosacea-prone skin remains a subject for future investigation.

Demodicosis occurs mainly in immunosuppressed patients because immunosuppression influences the number of Demodex mites and the treatment response. Multiple patients with AIDS and/or those with a CD4 lymphocyte count below 200/mm³ have been reported to have demodicosis.5-11 In immunocompetent patients, pruritic papular, papulopustular, and nodular lesions occur on the face, but in immunocompromised patients, the eruption may be more diffuse, affecting the back, presternal area, and upper limbs.6 A correct diagnosis relies on suggestive clinical signs, the presence of numerous parasites on direct examination, and a good clinical response to acaricide treatment.

Helicobacter pylori seropositivity has been associated with various dermatologic disorders, including rosacea.12 However, robust support for a causal association between H pylori and rosacea does not exist. Several studies have demonstrated high prevalence rates of H pylori in rosacea patients, some even in comparison with age- and sex-matched controls.13,14 Moreover, treatments aimed at eradicating H pylori also beneficially influence the clinical outcome of rosacea; for instance, metronidazole, a common treatment of rosacea, is an effective agent against H pylori.

Understanding the clinical variants and disease course of rosacea is important to differentiate this entity from other conditions that can mimic rosacea. Laboratory studies and histopathologic examination via skin biopsy may be needed to differentiate between rosacea and rosacea-like conditions.

Common Rosacea-Like Conditions
Systemic Lupus Erythematosus—Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has protean clinical manifestations and follows a relapsing and remitting course. Characteristic malar erythema appears in approximately 50% of patients and may accompany or precede other symptoms of lupus. The affected skin generally feels warm and appears slightly edematous. The erythema may last for hours to days and often recurs, particularly with sun exposure. The malar erythema of SLE can be confused with the redness of erythematotelangiectatic rosacea. Nevertheless, the color of the skin in SLE has a violaceous quality and may show a more abrupt cutoff, especially at its most lateral margins. Marzano et al15 reported 4 cases in which lupus erythematosus was misdiagnosed as rosacea. All 4 patients presented with erythema that was localized to the central face along with a few raised, smooth, round, erythematous to violaceous papules.
over the malar areas and the forehead. This presentation evolved rapidly and was aggravated by sun exposure. The patients were all treated with medication for rosacea but showed no improvement. These patients originally presented with limited skin involvement in the absence of any systemic sign or symptoms of SLE.15

Dermatomyositis—Dermatomyositis (DM) is an inflammatory myopathy characterized by varying degrees of muscle weakness and distinctive skin erythema (Figure 1); however, some patients lack muscular involvement and initially present with skin manifestations only. Sontheimer16 described criteria for defining skin involvement in DM. Major criteria include the heliotrope rash, Gottron papules, and Gottron sign, while minor criteria include macular violaceous erythema (MVE), periungual telangiectasia of the nail fold, poikiloderma, mechanic’s hands, cutaneous calcinosis, cutaneous ulcers, and pruritus. With the exception of the heliotrope rash, facial erythema has drawn little attention in prior studies of DM-associated skin manifestations. Therefore, Okiyama et al17 performed a retrospective study on the skin manifestations of DM in 33 patients. The investigators observed that MVE in the seborrheic area of the face was most frequent.17 Therefore, it is critical to consider DM in the differential diagnosis of rosacea because the MVE seen in DM might be confused with the erythema seen in rosacea.

Polymorphous Light Eruption—Polymorphous light eruption (PMLE), the most common of the idiopathic photodermatoses, is characterized by erythematous papules, papulovesicles, and plaques on sun-exposed surfaces (Figure 2). The areas of the skin that are most commonly affected are the face, neck, outer aspects of the arms, and dorsal surfaces of the hands.18 Lesions may appear immediately but often develop several hours after sun exposure. Symptoms of itching and/or burning usually are mild and transient. The etiology of PMLE is unknown, though it is likely to be multifactorial. Similarities between PMLE and rosacea include exacerbation by sun exposure and a higher prevalence in fair-skinned individuals.19 Also, in both conditions erythematous papules appear on the face and may be pruritic and in some instances painful; however, unlike rosacea, which is chronic, PMLE tends to be intermittent and recurrent, typically occurring in the spring and early summer months. In contrast to rosacea, the onset of the erythema in PMLE is abrupt, appearing quickly after sun exposure and subsiding within 1 to 7 days. Furthermore, patients with PMLE may experience systemic flulike symptoms after sun exposure.19

Seborrheic Dermatitis—Seborrheic dermatitis is a chronic relapsing papulosquamous skin disease most commonly involving sebum-rich areas such as the scalp and face. The prevalence of seborrheic dermatitis is higher in human immunodeficiency virus–positive individuals and in patients with neurologic conditions such as Parkinson disease. The pathogenesis of seborrheic dermatitis has been linked to the yeast of Malassezia species, immunologic abnormalities, and activation of complements. A clinical diagnosis usually is made based on a history of waxing and waning in severity and by the sites of involvement.20

Similar to rosacea, seborrheic dermatitis is a chronic and relapsing erythematous rash with well-demarcated erythematous patches, papules, or plaques; however, unlike rosacea, the distribution...
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varies from minimal asymptomatic scaliness of the scalp to more widespread involvement (eg, scalp, ears, upper aspect of the trunk, intertriginous areas). Also, although macular erythema and scaling involving the perinasal area (Figure 3) may be seen in either rosacea or seborrheic dermatitis, a greasy quality to the scales and involvement of other sites such as the scalp, retroauricular skin, and eyebrows suggest a diagnosis of seborrheic dermatitis.

Acne Vulgaris—Acne vulgaris is the most common skin disease in the United States. It is characterized by noninflammatory; open or closed comedones; and inflammatory papules, pustules, and nodules. Acne vulgaris typically affects the areas of skin with the highest density of sebaceous follicles including the face, upper aspect of the chest, and back. It is the most common skin disease in the differential diagnosis of the papulopustular form of rosacea. Inflammatory lesions in both acne vulgaris and rosacea may be clinically identical; however, unlike acne vulgaris, rosacea is characterized by a complete absence of comedones. A prominent centrofacial distribution also favors rosacea. As a general rule, acne peaks in adolescence, years before papulopustular rosacea usually becomes prominent. However, some acne patients who are prone to flushing and blushing may develop rosacea later in life.

Topical Steroid–Induced Acne—Chronic use of topical corticosteroids on the face for several months can result in the appearance of monomorphic inflammatory papules (Figure 4). Corticosteroids can cause a dry scaly eruption with scattered follicular pustules around the mouth (perioral dermatitis). This acneform eruption is indistinguishable from rosacea. However, the monomorphic inflammatory papules generally resolve within 1 to 2 months following discontinuation of the corticosteroid therapy.

Multiple pathways have been proposed as the mechanism for such reactions, including rebound vasodilation and proinflammatory cytokine release by chronic intermittent steroid exposure. At first, the vasoconstrictive and anti-inflammatory effects of the steroids result in what seems to be clearance of the primary dermatitis for which the steroids were being used. Unfortunately, persistent use of steroids, particularly high-potency products, leads to epidermal atrophy, degeneration of dermal structures, and destruction of collagen, rendering the skin vulnerable to bacterial, viral, and fungal infections. In the end, the skin has the appearance of bright red rosacea with red scaly papules.

Rare Rosacealike Conditions

Carcinoid Syndrome—Carcinoid syndrome typically develops after hepatic metastasis from a carcinoid tumor when the circulating neuroendocrine mediators produced by the tumor can no longer be adequately cleared. Flushing is characteristic of carcinoid syndrome and usually presents on the face, neck, and upper trunk. Although rare, other types of cutaneous involvement also have been reported. Bell et al concluded that skin involvement is not uncommon in carcinoid syndrome, as all 25 patients with carcinoid syndrome showed cutaneous involvement in their case series. The investigators observed that chronic flushing eventually may become permanent and evolve into a rosacealike picture.

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Cases of carcinoid syndrome that were misdiagnosed as rosacea have been reported in the literature. Creamer et al reported a case of a 67-year-old woman who initially was diagnosed with rosacea; it took 1 year to finally arrive at the correct diagnosis of multiple endocrine neoplasia type 1 after developing a malignant carcinoid tumor and a parathyroid tumor.

**Cutaneous Lymphoma**—B-cell neoplasms with skin involvement can present as primary cutaneous lymphomas or as secondary processes, including specific infiltrates of nodal or extranodal lymphoma or leukemia. B-cell lymphomas involving the skin have a distinct clinical appearance, presenting as isolated, grouped, or multiple erythematous to violaceous papules, plaques, or nodules, usually in an asymmetric distribution (Figure 5). B-cell lymphoproliferative diseases simulating rosacea are extremely rare. Nevertheless, B-cell lymphomas mimicking rhinophyma has been documented in the literature. Barzilai et al described 12 patients with B-cell lymphoproliferative neoplasms presenting with facial eruptions that clinically mimicked rosacea or rhinophyma. The clinical presentation included small papules on the nose, cheeks, and around the eyes mimicking granulomatous rosacea, and/or nodules on the nose, cheeks, chin, or forehead simulating phymatous rosacea. Three patients had preexisting erythematotelangiectatic rosacea and 1 had rhinophyma.

**Lupus Miliaris Disseminatus Faciei**—Lupus miliaris disseminatus faciei (LMDF) is an uncommon chronic inflammatory skin disorder characterized by the appearance of asymptomatic small, red to yellowish brown papules on the face. This rare dermatologic disease usually is self-limited with spontaneous resolution of the lesions occurring within months or years; however, residual disfiguring scars may persist and usually are characteristic of LMDF. The pathogenesis of LMDF is unclear, and controversy remains as to whether it is a distinct cutaneous entity or a variant of granulomatous rosacea. It usually develops slowly as small, dome-shaped, red to yellowish brown papules in adults, most commonly appearing in men. Lupus miliaris disseminatus faciei shares several common features with both acne vulgaris and rosacea. For example, the inflammatory lesions of LMDF are located on the central face and usually respond to treatments that typically are used to treat acne vulgaris and rosacea. However, LMDF can be distinguished histologically by more intense granulomatous inflammation and central caseation, occurring in the absence of an apparent infectious origin.

**Tyrosinase Kinase Inhibitor Drug Eruptions**—Sorafenib and sunitinib malate are multitargeted kinase inhibitors approved for the treatment of cancers such as renal cell carcinoma. A study by Lee et al reported that approximately 75% of patients treated with either sorafenib (n=109) or sunitinib (n=119) went on to develop at least one cutaneous reaction. Although hand-foot skin reaction was the most common and serious cutaneous side effect, other dermatologic manifestations, including alopecia, stomatitis, discoloration (hair or face), subungual splinter hemorrhages, facial swelling, facial erythema, and xerosis, were described. Facial changes such as swelling, yellowish discoloration, erythema, and acneform eruptions were described more frequently in patients treated with sunitinib than in those treated with sorafenib.

Other reports have described facial erythematous papules with sorafenib. In these patients, facial erythema usually occurs within 1 to 2 weeks after initiation of treatment, unlike hand-foot skin reaction, which usually develops later.

**Epidermal Growth Factor Receptor Inhibitor Drug Eruptions**—Monoclonal antibodies against the epidermal growth factor receptor (EGFR) (eg, cetuximab, panitumumab) and EGFR tyrosine kinase inhibitors (eg, gefitinib, erlotinib) are used in the treatment of several cancers. Use of these drugs has been associated with various dermatologic side effects, including rashes, paronychia and fissuring of the nail bed, hair changes, dry skin, hypersensitivity reactions, and mucositis. The most frequent dermatologic side effect is a sterile follicular and pustular rash, often affecting the face, that is seen in more than half of the patients treated with these drugs.
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rosacealike facial lesions are accompanied by diffuse erythema and telangiectasia. In some cases, the pustules leave areas of erythema covered with greasy scaling, thus resembling seborrheic dermatitis.\textsuperscript{43} In general, the pustular rash manifests within 1 to 3 weeks after the onset of treatment with EGFR inhibitors. The reaction typically resolves within 4 weeks of stopping treatment.\textsuperscript{44} The etiology of the rash is unknown, but inhibition of EGFR may result in occlusion of hair follicles and their associated sebaceous glands, producing a rosacealike appearance.\textsuperscript{45}

Conclusion
Since its first medical description, rosacea has undergone extensive study regarding its pathogenesis and management. The most current investigations indicate microorganisms such as \textit{D folliculorum} and \textit{H pylori} as etiologic factors, though several other possibilities (eg, vascular abnormalities) have been suggested. Understanding the clinical variants and disease course of rosacea is important in differentiating this entity from other conditions that can mimic rosacea.

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