Rosacea 2000

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Rosacea is not a new disease. First described more than 200 years ago,[1] neither its pathogenesis nor its etiology is entirely understood. It is defined as a chronic inflammatory cutaneous disorder that manifests as erythematous papules on the cheeks, forehead, and chin of affected persons (Figures 1 and 2). Although the elementary lesions of the disease are initially less prominent, intermittent episodes become more permanent and the lesions more prominent over time. It occurs more commonly in female patients, but affected males tend to have more severe disease.[2] More advanced cases can lead to the development of rhinophyma (fibrous swelling of the nose). Important variants include ocular rosacea (Figure 3), which involves ocular erythema and telangiectasia; meibomian gland dysfunction; and rosacea fulminans comprised of severe erythema, large coalescing nodules, and draining sinuses on most of the face.[3]

History

The first known medical description of rosacea was by Dr. Guy de Chauliac in the 14th century. He described "red lesions in the face, particularly on the nose and cheeks" and termed it *goutterose* (French for "pink droplet") or *couperose*, which is now a common French term for rosacea.[4]

Early literature also mentions rosacea with descriptions of men with red faces and enlarged noses (eg, Chaucer's *Canterbury Tales* and Shakespeare's *Henry V)*. Painters also have depicted rosacea in their art. A well-known example is Ghirlandaio's *The Old Man and His Grandson*, a 15th century painting that now hangs in the Louvre.[5]

Early treatments for rosacea included blood-letting from veins in the arm, forehead, and nose and applying leeches on affected areas of the face. The use of topical treatments in the form of salves was first referred to in the 16th century.[5]

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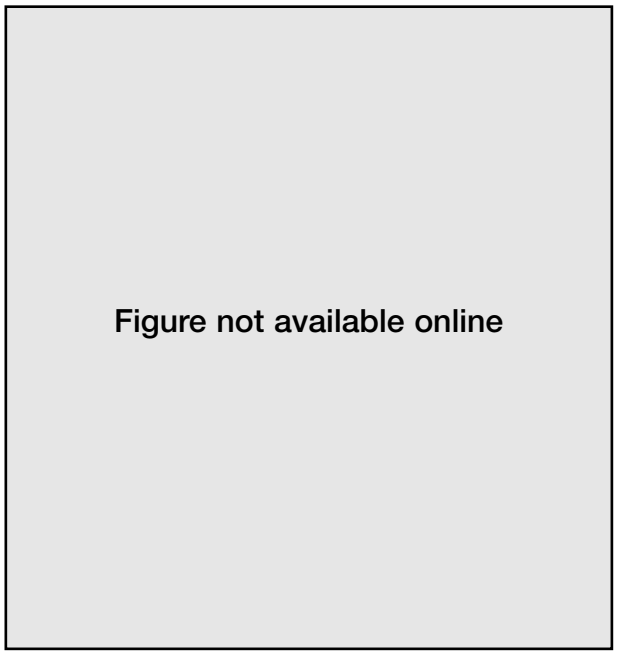

FIGURE 1. Erythematous papules on the cheeks, forehead, and chin that are consistent with rosacea.

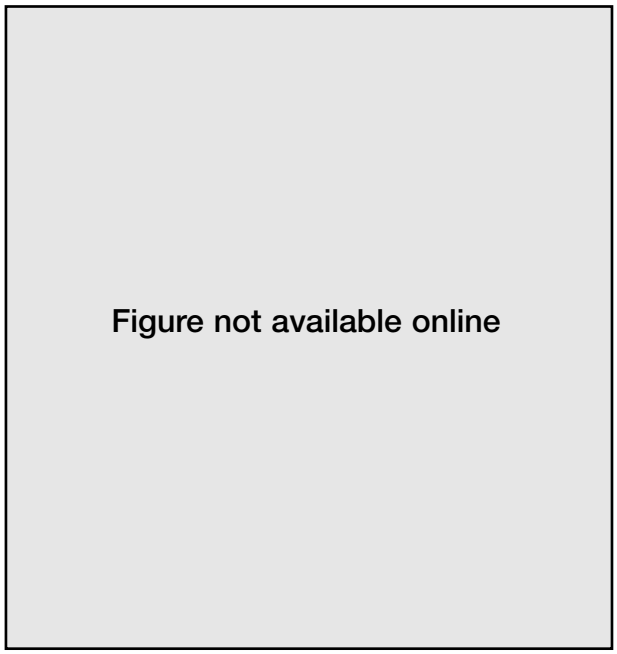

FIGURE 2. Papular lesions of rosacea.

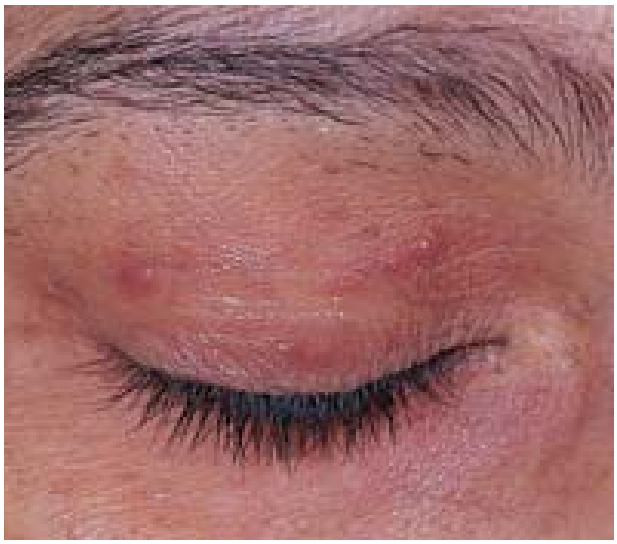

FIGURE 3. Blepharitis in a patient with rosacea.

Clinical Classification

Clinically, rosacea can be classified into prerosacea and several subsequent stages. Prerosacea is characterized by a tendency towards episodic facial flushing and irritation by cosmetics and cleansers often in the setting of a positive family history of the disorder. The first stage is the vascular one, characterized by prolonged erythema that can last for hours or days; very sensitive skin; and the development of telangiectasia on the nose, nasolabial folds, cheeks, and glabella. The second or acneiform stage is highlighted by the development of facial acneiform papules and pustules. The third stage involves large inflammatory nodules, furuncles, and tissue hyperplasia, as is the case with rhinophyma.[6]

As part of its symptom complex, the facial edema, papules, and pustules can clinically resemble acne. However, the pathogenesis of rosacea does not involve the overproduction of sebum, abnormal follicular keratinization, or the presence of follicular bacteria.[7] A major predisposing factor in the development of rosacea is the tendency towards vascular overreactivity in certain patients who are fair-skinned and flush easily. In certain countries, such as Sweden, prevalence is estimated at 10% of the adult population.[8]

Etiology

The etiology of rosacea remains elusive. Many elements have been investigated as pathophysiologic sources of the disease, but none has been deemed the actual cause. Categorically, they include endocrine, psychologic, pharmacologic, immunologic, infectious, thermal, and alimentary. Rosacea can be viewed as a vascular disorder of the skin with flushing as the first clinical event.[6]

Helicobacter pylori is a spiral-shaped gram-negative rod implicated in the etiology of gastritis as well as gastric and duodenal ulcers. Over the past decade, a growing body of worldwide reports has accumulated, suggesting that there might also be an etiologic role for *H. pylori* in rosacea. In Italy, Rebora *et al*[9] suggested a causative association between rosacea and *H. pylori*, noting gastroscopic presence of the bacteria in 90% of rosacea patients as compared to 50% prevalence in the general Italian population. In the Ukraine, Abrahamovych[10] reported 155 of 158 (98%) patients to have gastroscopic evidence of *H. pylori*. In Russia, Kolibasova *et al*[11] reported one patient whose rosacea cleared only after *H. pylori* eradication. As recently as 1999, Utas *et al*[12] concluded that *H. pylori* may be involved in rosacea and that eradication treatment may be helpful.

This relationship was further supported by the response of rosacea patients to metronidazole, a drug that had been used for treatment of the gastric disease for many years. Additionally, it has been noted that peptic ulcer disease and rosacea share their seasonal behavior.[12] However, recent reviews have cast doubt on the validity of this association.[13] In a randomized, double-blind, placebo-controlled clinical trial reported by Bamford *et al*,[14] rosacea abated in most study participants, whether they were in the treatment or the control cohort. There was no statistical difference when the results of active treatment were compared with those of placebo. Treating *H. pylori* infection had no short-term beneficial effect on the symptoms of rosacea to support the suggested causal association between *H. pylori* infection and rosacea.[14]

Treatment

Rosacea is often difficult to treat. Because a cure is not yet attainable, the goal of treatment is control. Current management emphasizes the use of topical antibiotics, including erythromycin and clindamycin.[15] The use of long-term oral antibiotic therapy is poorly tolerated because of side effects, including gastrointestinal upset and candidal vaginitis associated with tetracycline.

Early rosacea, limited to vasodilatation, is very difficult to treat. Though tempting, the use of topical steroids should be avoided during this time because it predisposes the patient to the development of atrophy. This episodic erythema is best managed by the identification and careful avoidance of triggers. In severe cases, the vasoconstrictor clonidine,[16] the beta-blocker nadolol,[17] and the antihistamine cyproheptadine[18] have been used with variable success. However, all of these medications have signifcant side effects and are therefore best reserved solely for intractable cases.

Persistent erythema characteristic of the later stages of rosacea, generally but not always, responds to systemic antibiotics such as tetracycline, doxycycline (Monodox®), and minocycline. Topical therapy with clindamycin,[19] sulfacetamide,[20] erythromycin,[21] and metronidazole all have been reported to improve facial redness. Topical treatments may have a particular role in the treatment of patients who cannot tolerate oral antibiotics.

Once inflammatory lesions have developed, metronidazole is the mainstay of therapy. Multiple studies done with metronidazole, a broad-spectrum antibiotic, have shown that both the oral and topical (0.75% cream) formulations are effective for the treatment of the erythema, pustules, and papules characteristic of rosacea.[22] A recent study suggests that topical metronidazole 0.75% gel maintains the remission of moderate to severe rosacea, induced by treatment with oral tetracycline and topical metronidazole gel. In this study, 113 patients with moderate rosacea were treated with oral tetracycline at a dosage of 250 mg four times daily and topical metronidazole 0.75% gel twice daily for 12 weeks or clearance of lesions, whichever came first. The doses of tetracycline were then tapered over 4 weeks. Those patients with a minimum of 70% improvement were then randomly assigned to a second arm of the study consisting of twice-daily application of metronidazole 0.75% gel or its vehicle. This went on for 6 months with monthly evaluations. Relapse occurred in 42% of patients assigned to apply the vehicle, compared with 23% of those randomly assigned to receive metronidazole ge1.[23]

In recent years, a 1% cream formulation of metronidazole (Noritate™) has entered the dermatologist's rosacea armamentarium. A double-blind, 10-week vehicle-controlled trial was performed comparing the efficacy of once- or twice-daily application of 1% metronidazole cream with its vehicle applied twice daily. No significant difference in efficacy parameters between the once-daily and twice-daily application of the 1% metronidazole cream was identified.[24]

A randomized, double-blinded, clinical trial has been reported within the last year in which the authors found that azelaic acid 20% cream was an effective alternative to metronidazole 0.75% cream.[25] Azelaic acid is a naturally occurring dicarboxylic acid with antibacterial, comedolytic, and anti-inflammatory properties. It has known efficacy in therapy for acne vulgaris, as well as several disorders of cutaneous hyperpigmentation. This is presumed secondary to azelaic acid's inhibition of the production of reactive proinflammatory oxygen species from neutrophils.[26]

Papules or nodules are characteristic of the second acneiform stage of rosacea. While often resistant to topical metroniadazole, they are usually responsive to oral tetracycline. The dose of the oral antibiotic is first reduced when papules and pustules improve (approximately 3 weeks) and then continued at 250 to 500 mg/day for a treatment duration of 2 months. Oral antibiotics are reintroduced when the patient flares.

Severely inflamed rosacea patients or those with a marked nodulocystic component can also be treated with isotretinoin at 0.5 to 1.0 mg/kg/day for 6 to 8 months.[27] In a recent study, 22 patients with mild to moderate rosacea were treated for 16 weeks with 10 mg of isotretinoin daily. Significant reductions in erythema, papules, and telangiectasia were noted after 9 weeks of treatment through 16 weeks. No further follow-up data were available.[28]

Rosacea fulminans, previously termed pyoderma faciale, is the only indication for use of glucocorticosteroids in the management of rosacea. We generally start with a short course of oral prednisone to decrease inflammation and then introduce low-dose isotretinoin as the steroid is tapered.

Laser

Recent developments in vascular lasers allow for rapid and effective treatment of telangiectasias and can also ameliorate the erythema of rosacea. High-energy carbon dioxide lasers used for a variety of resurfacing procedures offer a new therapy for rhinophyma.[29] These lasers work by employing wavelengths preferentially absorbed by hemoglobin. This hemoglobin is located in the tiny superficial blood vessels located just below the skin's surface; it is when these vessels burst that patients develop the appearance of purpura and telangiectasia.

Tiny red telangiectasis on the face are preferentially treated with a 585-nm pulsed dye laser. For moderately affected rosacea patients, good success has been achieved with the 532-nm Nd:YAG laser (VersaPulse®; Coherent). This is presumed because its lower wavelength heats the treated vessels more slowly and, therefore, creates less purpura with therapy.[30] The main adverse outcome of treatment with the pulsed-dye laser seen in approximately 5% to 20% of those treated is temporary hyperpigmentation. It is usually responsive to treatment with hydroquinone, glycolic acid, and retinoic acid, singly or in combination.[31]

Most patients (75%) with mild to moderate rosacea achieve satisfactory fading and clearing after one treatment.[29] Occasionally, patients may require a minor second treatment to even out a cobweb pattern of remaining vessels or to blend treatment edges into natural shadows or normal skin tones. Patients with involvement of large caliber vessels or severe disease also may require additional rounds of treatment.

For the treatment of mild soft-tissue hypertrophy, pulsed-dye laser can be very effective. For severe bul-

bous rhinophyma, carbon dioxide resurfacing tools such as the SilkTouch (Sharplan) may be needed in cutting mode to debulk the hypertrophic tissue. Sculpturing and contouring are then completed with the laser in vaporization mode. The fluence and number of passes are determined on a case-by-case basis.[32]

Laser treatment of rosacea can reasonably provide a more optimistic outlook for the rosacea patient and is an area of continuing and active research by dermatologic surgeons.

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