G ITAL DERMATOL VENEREOL 2009;144:663-71

The pathophysiology of rosacea

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Rosacea is thought to be a common skin disorder in the general population, presenting with many different clinical features and unknown causes. Theories of pathogenesis have been extrapolated from clinical observation of factors, leading to a definition of the etiology of rosacea which was very limited until recently. A recent upsurge in translational research in rosacea has significantly advanced the insight into this disease. In this review the authors discuss the pathogenesis of this disease, which could be determined by the following factors: 1) exposure to UV radiation; 2) reactive oxygen species (including superoxide and hydroxyl radicals, hydrogen peroxide and singlet oxygen); 3) vascular hyperreactivity; 4) neuropeptides; 5) exacerbation of innate immune response; 6) microbes, in particular H. pylori and environmental aggressors, such as Demodex mite. Even if the recent investigations have significantly improved the understanding of its pathogenesis, the authors conclude that the histopathology of rosacea remains to be clarified according to subtype and age of development of individual lesions.

KEY WORDS: Rosacea, etiology - Pathogenesis UV radiation - Innate immunity - Demodex.

Rosacea is a disease that in many ways is a conundrum. It is thought to be a common skin disorder in the general population, but how common is unclear. All clinicians are agreed that facial erythema is a primary feature of the disorder, but thereafter the clinical features are disputed. Some investigators include patients with transient facial erythema (due to frequent and profound flushing) in the clinical spectrum of rosacea and refer to these individuals as having a condition called "pre-rosacea". At the other end of the spectrum reports of patients (usually female) who have deep cystic lesions with a propensity to scarring, previously classified as having a variant of acne vulgaris, have been labelled as having "rosacea profunda". Between these polar extremes, many rosacea "experts" include those fair-skinned patients with a history of ultraviolet light exposure and who have fixed facial erythema and teliangiectasias in the category of erythematotelangiectatic rosacea (ETTR, also called subtype 1 rosacea), even though the clinical features are indistinguishable from heliodermatitis (the effects of sun exposure and "weathering" on sun sensitive individuals). Rhinophyma (enlargement of the nose due to sebaceous gland hyperplasia) is referred to as "subtype 3 rosacea" although such morphological nasal changes can be seen in some patients with longstanding acne vulgaris, following years of actinic damage to the nose in persons with skin type 3, or as a consequent of the development of telangiectatic vessels (neovascularisation) of the skin around the alae nasi and distal nose causing increased blood flow to the area. Another disorder that can result from acne vulgaris is "called solid facial oedema". Some patients with this type of facial swelling accompanied by erythema have been classified as having "edematous rosacea". Without the presence of preceding or concomitant inflammatory lesions (papules and pustules) the link between solid facial

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TABLE I.—*Clinical features of rosacea.*

Subtype	Features
1. Erythematotelangectatic rosacea	— Flushing, persistent central facial erythema, telangectatic vessels, easily irritated skin
2. Papulopustular rosacea	— Persistent facial erythema, erythematous papules surmounted by pustules, oedema.
3. Phymatous rosacea	— Distorted thickened skin with prominent pores, surface nodules
4. Ocular rosacea	— Itch, irritation, burning, stinging, watering, dryness, blurred vision; telangectasia and erythema of the lid margins, conjunctival injection, chalazion, hordeolum; interstitial keratitis, episcleritis, scleritis, iritis

oedema and rosacea is tenuous to say the least. Morbihans disease is another term sometimes used to describe such patients with persistent non-pitting centrofacial oedema and erythema without preceding facial inflammatory lesions. A striking feature of the clinical presentation of rosacea is the frequent occurrence of mild ocular inflammation (such as dryness or conjunctivitis) in association with the skin changes in some patients. This association distinguishes rosacea from the many other facial dermatoses. However, such ocular changes, while characteristic of rosacea, are non-specific and can be seen in otherwise healthy individuals. This fact has not prevented publication of several series of patients with such ocular changes being labelled as having "ocular rosacea" even in the absence of preceding or accompanying cutaneous lesions. While it is generally agreed that rosacea is a disorder with peak onset in middle age (30 to 60 years), there are many reports of children with varying degrees of facial erythema and inflammatory lesions as having "childhood rosacea" and others with the non specific eye changes described above as having "ocular rosacea of childhood". A rare disorder which has been described under various titles such as Lupus miliaris disseminata faciei and Lewandowski's disorder is characterised clinically by firm, non-tender, persistent, erythematous facial papules and histologically by the presence of granulomatous inflammatory changes in the dermis has been classified by many investigators as "granulomatous rosacea". Other commentators have suggested that rosacea evolves in stages, beginning with transient facial erythema (as seen in patients who flush frequently) and terminating in the sebaceous hyperplasia of rhinophyma and edema, even though clinical experience does not support such an evolution in individual patients with disorders of flushing and many patients with inflammatory rosacea and rhinophyma deny a tendency to frequent flushing preceding the onset of their skin lesions. From the preceding discussion it is likely that several different disorders have been "lumped" together under the broad rubric of rosacea, having in common (in most instances) the presence of facial erythema but diverse other manifestations which are unlikely to constitute a single disease entity.

Because of the diverse clinical entities that have received the label of "rosacea" it is not surprising that there are confusing and often conflicting reports regarding its prevalence in the general population, the evolution of the clinical disorder, the typical histopathological changes that are found in lesional skin biopsies and the possible etiological factors at work in this disorder.

An attempt to give clarity to some of the issues was the publication of the expert group of the National Rosacea Society in 2002 which suggested dividing rosacea into four different independent subgroups without implying that one subgroup evolved into another in a progressive or staged manner.[1] This consensus document was intended to help clinicians and investigators to identify and classify the particular clinical features in the patients being treated or investigated in order to facilitate comparison of results of therapy or investigative studies across different groups (Table I). Using this classification it becomes clear that studies of patients in Subtype 1 (called ETTR) are likely to yield quite different results than investigative reports of patients in subgroup 3 (called phymatous rosacea). By comparing studies within fairly well-defined groups (or subtypes) of patients, the clinician/investigator is more likely to be comparing "like with like" rather than potentially different clinical entities being treated/investigated. In the classification of subtypes, subtype 2 (called papulopustular rosacea [PPR]) corresponds most closely to the original descriptions of this disorder (when it was referred to as "acne rosacea"). It is the opinion of these authors that the patients in this subgroup represent the "epicentre" of this condition, and it is likely that study of individuals afflicted with papulopustular rosacea will yield most information regarding the pathophysiology of this disorder.

Rosacea is estimated to affect over 14 million Americans.[2] Berg and Linden investigated 809 Swedish office employees and reported a prevalence of roscaea of 10%.[3] Their study predated the standard classification of rosacea. We investigated a random selection of 1 000 Irish individuals and, as defined by the standard classification,[1] demonstrated a prevalence of papulopustular rosacea of 2.7%.[4]

The cause of rosacea is unknown. Until recently theories of pathogenesis were extrapolated from clinical observation of factors that precipitated or exacerbated the condition and from treatments that improved the disease. Thus, our understanding of the etiology of this condition was limited. There has been a recent upsurge in translational research in rosacea that has significantly advanced our insight into this disease.

Histopathology of rosacea

Despite being a common condition, the histopathological changes have still to be clearly defined. The most comprehensive and frequently quoted study of the histopathology of rosacea was that of Marks and Harcourt-Webster in 1968.[5] They examined histological sections of skin biopsies taken from 108 patients with "rosacea". They defined "rosacea" as a "disease of the skin mostly affecting the cheeks and often the chin, nose, and forehead characterized by persistent erythema and often telangiectasias with acute episodes of edema, papules and pustules in some cases". They recorded that biopsies of papules or papulopustules were taken from 74 of the 108 patients. They observed acute folliculitis in 25% of specimens, an inflammatory reaction at the hair follicle in 19%, and in 7% of cases there was total destruction of the follicle with an intense granulomatous inflammatory reaction. They also recorded that in a further 37 specimens the inflammatory infiltrate was partially distributed at the hair follicle. However, in spite of these findings they concluded in their abstract that rosacea was not a condition related to the follicular apparatus, a conclusion that has been echoed since by may other authors. Basta-Juzbasic *et al.* found *Demodex folliculorum* in 43 of 50 biopsy specimens from rosacea patients, and recorded the presence of perifollicular abscesses and granulomas in some of these patients.[6] Roth took biopsies of eyelid skin from rosacea patients and showed perifolliculitis around 42% of follicles in which there were *Demodex* mites.[7] The histolopathology of rosacea has also been shown to vary with the stage of the condition biopsied [8] but more study is required to clarify this important aspect of the progress of the condition. Inflammatory changes are noted to be focused mainly around the follicle in papulopustular rosacea, although perivascular infiltrates are also prominent as are the histological changes of actinic damage in sun-sensitive middle aged individuals (solar elastosis with a varying degree of telangiectasias). In the early stages, the superficial perivascular lymphocytic infiltrate appears marked. In well established lesions a mixed lymphocyte/neutrophilic infiltrate is evident around the follicular infundibulum. Forton and Seys demonstrated a statistically significant relationship between *Demodex* infestation and this follicular orientated inflammation.[9] As the condition advances, neutrophils are found in the follicular walls as well as within the follicular canals with histiocytes, epitheliod cells and lymphocytes surrounding the follicle. As mentioned above, telangiectases and actinic elastosis are often very prominent histologically irrespective of the stage of the lesion studied.[8, 10] Granulomatous inflammation appears to be closely associated with follicular rupture suggesting a dermal foreign-body reaction to the discharged contents (keratin, sebum, mites, etc) of the disrupted follicular walls.[10]

Both a cell mediated and/or humoral immune responses are indicated in the inflammation reaction of rosacea. A study by Rufli and Buchner demonstrated that the perifollicular infiltrate in rosacea lesions consisted largely of T-helper lymphocytes.[11] More recent reports also confirm this finding. Georgala *et al.* indicated a delayed hypersensitivity reaction (type IV) in subjects with papulopustular rosacea, possibly triggered by antigens of follicular origin, most likely related to *Demodex folliculorum*.[12] They demonstrated that CD_4 helper T cells predominated in dermal infiltrates from inflamed *Demodex* infested follicles, with an increase in macrophages and Langerhans cells also being noted.[12] Grosshans *et al.* indicates a humoral response for the inflammatory reaction, showing that patients with rosacea have *Demodex*-specific antibodies to *D. caprae*, by assuming cross-antigenicity between *Demodex* species of man and animals.[13]

Ultraviolet light

Rosacea most commonly occurs in fair skinned, sun sensitive individuals and ultraviolet radiation (UVR) and sun exposure can exacerbate the symptoms of

rosacea.[14] Furthermore, solar elastosis is a frequent histological finding in the biopsies of facial skin of rosacea patients.[5] These observations suggested that UV radiation may be involved it in the pathogenesis of the disease. It had been postulated that UV radiation causes a loss of dermal connective tissue integrity resulting in inadequate dermal vascular support and subsequent telangectasias and erythema.[8] We studied 1 000 Irish individuals investigating the prevalence of papulopustular rosacea and its relationship to UV radiation exposure and cutaneous photodamage. No association between UV exposure and papulopustular rosacea was demonstrated.[4] The other subtypes of rosacea were also investigated in the course of the study. ETTR was significantly associated with UV exposure.[16] As previously discussed, the features of erythematotelangectatic rosacea and heliodermatitis are indistinguishable and this may have contributed to the significant association between UVR and ETTR observed in our study. These disparate findings in the two subtypes of rosacea (ETTR and PPR) also suggest that these are separate entities and that an evolution from erythematotelangiectatic to papulopustular rosacea does not occur.

Some laboratory studies suggest that UV radiation could induce erythema and telangectasias seen in rosacea by increasing angiogenic factors and degrading the extracellular matrix. Vascular endothelial growth factor (VEGF) and UVB are capable of stimulating endothelial proliferation. In the skin epidermal keratinoctyes are a major source of these angiogenic factors. UV-B radiation increases VEGF and Fibroblast Growth Factor 2 (FGF2) secretion from human keratinocytes in vitro and stimulates cutaneous angiogenesis leading to telangectasia and new blood vessels in mice.[16]

Fimmel *et al.* investigated the influence of UV irradiation on the synthesis of the angiogenic factor VEGF and corticotrophin releasing hormone (CRH) in human dermal micrvascular endothelial cells, keratinocytes, fibroblast and a sebaceous gland cell line SZ95. They reported that following exposure to a physiological dose of UVB radiation CRH synthesis significantly increased in keratinocytes, fibroblasts and moderately in the sebocytes while CRH levels decreased in the endothelial cells. They suggest that epithelial skin cells respond to environmental stress by increased CRH production and this has direct effects on vessel wall function and, hence, could be involved in rosacea pathogenesis.[17]

UV radiation also induces an increase in oxidative stress, excellerating vascular and dermal matrix damage, which will be further discussed below.[18]

UVR may play a role in the pathogenesis of the erythematotelangiectatic subtype of roscea. Alternatively UVR may be a coincidental factor in the sunsensitive rosacea population resulting in findings (erythema, telangectasias etc and histological evidence of solar elastosis in the dermis) that form a background of actinic damage on which the other clinical features evolve. Further studies investigating the role of UVR, using the defined criteria to strictly isolate the various rosacea subtypes, are required to dissect out its possible role in this disorder. In addition, consideration and research into the differences, if any, between erythematotelangectatic rosacea and actinic damage will aid to clarify aspects of this disease and its relationship to UVR.

Reactive oxygen species

Reactive oxygen species (ROS) may contribute to the pathophysiology of rosacea. ROS include superoxide and hydroxyl radicals and other inactivated forms of oxygen such as hydrogen peroxide and singlet oxygen. ROS are the key mediators of UV induced biological effects in the skin, and the skin is more susceptible than other tissues to damage caused by ROS.[19] ROS activates cellular signalling, mediates cytokine induction and chemokine production, stimulates fibroblasts and alters MMPs. Therefore, upregulated ROS activity in the skin could result in the inflammation, vascular changes, and collagen degeneration observed in rosacea.[20]

Öztas *et al.* found decreased activity of superoxide dismutase (oxygen radical quenching enzyme) and increased malondialdehyde levels (lipid peroxidation product as a result of free radical activity) in patients with severe rosacea compared with controls.[21] Another study investigated plasma ROS activity and the antioxidant status and their relationship with H pylori infection in 29 patients with rosacea. They found higher malondialdehyde levels and reduced antioxidant potential levels in rosacea patients compared with controls, but no correlation with H pylori seropositivity.[22] The role of ROS in rosacea aetiopathogenesis has been supported by the fact that effective treatments for rosacea inhibit ROS generation in neutrophils.[20] Furthermore, a decrease of ROS in rosacea skin was observed after azithromycin treatment.[23] These studies imply a antioxidant system dysfunction in rosacea,

however, whether this is a cause or as a result of inflammation requires more comprehensive investigation.

Vascular changes

Many patients with rosacea complain of frequent and more persistent flushing. Laser-Doppler flowometry demonstrated that lesional blood flow in patients with rosacea was 3-4 times that of control subjects.[24] Guzman-Sanchez *et al.* investigated 16 individuals with rosacea (8 ETTR, 8 PPR) and 8 controls to assess burning perception, heat pain threshold, skin blood flow, and skin temperature. Quantative thermal sensor testing and laser doppler imaging were used. They demonstrated that individuals with rosacea had increased sensitivity to noxious heat stimuli and that PPR affected skin had increased blood flow compared with unaffected skin. There was no significant increased blood flow in ETT lesional skin compared with unaffected skin.[25] Further supporting the role of vascular hyperreactivity in rosacea, application of a topical alpha-adrenergic receptor agonist resulted in resolution of erythema and flushing in individuals with rosacea.[26] The skin of rosacea patients has been shown to have increased expression of vascular endothelial growth factor (VEGF), that causes proliferation of vascular endothelial cells and increases permeability of vessels, as well as the lymphatic endothelium marker D2-40.[27] These findings suggest that rosacea skins have stimulants for vascular and lymphatic endothelial cells. As previously discussed, UVR induces VEGF in keratinocytes and may explain the photodistribution and reported photoaggrevation of rosacea. Yamanaski *et al.* postulate that the antimicrobial peptide cathelicidin could be a trigger for the observed increased vascularity in rosacea, and unifies the innate immune system dysregulation (discussed later) and increased vascularity in roscaea. Cathelicidin induces endothelial cell changes through various pathways, including angiogenesis via formyl peptide receptor like 1(FPRL1) and transactivation of epidermal growth factor receptor (EGRF) that induces VEGF in keratinocytes.[20]

Neuropeptides

The rapid responses of flushing, stinging and itch experienced by many rosacea patients have suggested to some investigators that the cutaneous neurovascular system plays a role in the condition.[28, 29] The temporal relationship between the onset and exacerbation of inflammatory skin conditions and psychological stress also has provided support for a connection between the central nervous system and the peripheral cutaneous neuroimmune systems. It has been reported 60-91% of individuals with rosacea associated the onset or flares of their condition with emotional stress [30, 31] and hypnosis of patients was found to be helpful for the treatment of established rosacea [32] providing circumstantial evidence of a link between the psyche and cutaneous inflammatory changes.

Individuals with rosacea have been shown to have increased serum substance P (SP) compared with a control group. When the SP level was measured in 23 rosacea patients, 9 had elevated levels, compared with none of the control group.[33] In another study, SP immunoreactive neurons were increased around the blood vessels of lesional skin in 9 rosacea patients, compared with non-lesional skin in the same individuals.[34] Lonne-Rahm *et al.* investigated the effects of pulsed dye laser treatment on 31 patients with erythematotelangectatic rosacea with regards to skin sensitivity, nerve density, contacts between nerves and vessels, and the expression of the neuropeptides SP, Calcitonin-Gene related peptide (CGRP), and Vasoactive Intestinal Peptide (VIP).[28] Three months after pulsed dye laser treatment was completed, a significant number of patients had decreased facial skin sensitivity and a significant reduction in superficial nerve fibre density with a reduced number of neurons immunoreactive to SP.

Vasoactive intestinal peptide (VIP) has also been shown to be increased in the skin of some patients with rosacea. Five patients with rhinophyma were shown to have a more dense distribution of VIP receptor (VIP-R) positive cells within the endothelium and perivascular large cells compared with the control group.[35]

Calcitonin gene related peptide (CGRP) is one of the most prominent neuropeptides in the skin.[36] Lonne-Rahn *et al.* found vascular related CGRP positive fibres in the dermis of rosacea patients. Following the pulsed dye laser treatment there was a no significant decrease in the numbers of CGRP positive fibres compared with before treatment.[28]

Somatostatin (SST) activity has been demonstrated in Merkel cells associated with sweat glands, in keratinocytes, Langerhan cells, suprabasal cells of the epidermis and in dendritic cells and neurons.[37] Four

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