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Rosacea and rhinophyma

Yalçın Tüzün, MD[a,*], Ronni Wolf, MD[b], Zekayi Kutlubay, MD[a], Özge Karakuş, MD[a], Burhan Engin, MD[a]

[a]*Cerrahpaşa Medical Faculty, Department of Dermatology, İstanbul University, İstanbul, Turkey*
[b]*The Dermatology Unit, Kaplan Medical Center, Rehovot, Israel. Affiliated with the School of Medicine, Hebrew University and Hadassah Medical Center, Jerusalem*

Abstract Rosacea is a common and chronic inflammatory cutaneous disease with unknown etiology. The pathophysiology of rosacea is still poorly understood. Epidemiological studies indicate a genetic component, but a rosacea gene has not been detected yet. Recent molecular studies propose that an altered innate immune response is involved in the pathogenesis of the rosacea disease. Signs of rosacea are indicated by the presence of characteristic facial or ocular inflammation involving both the vascular and tissue stroma. A wide range of drug options is available for the treatment of rosacea, including several topical ones (metronidazole, antibiotics, azelaic acid, benzoyl peroxide, sulfacetamide/sulfur, retinoids) and oral ones (mainly tetracyclines, metronidazole, macrolides, isotretinoin). This review highlights the recent clinical and pathophysiological developments concerning rosacea.

Introduction

Rosacea is a common inflammatory dermatosis characterized by facial erythema, telangiectasia, papules, pustules, and edema that is mostly seen on the central part of the face. Rosacea is a highly heterogenous entity with an unknown epidemiology and pathophysiology. Because there is no laboratory benchmark test, etiopathogenesis and physiology are not clearly understood. Many authorities believe that vascular changes, especially flushing, are the initial and constant feature, followed by progression to inflammatory changes such as papules and pustules, and that the development of chronic lymphedema, the thickening of the affected skin, and rhinophyma are later complications. *The National Rosacea Society's Expert Committee on the Classification and Staging of Rosacea* identified four subtypes of rosacea: (1) erythematotelengiectatic, (2) papulopustular, (3) phymatous, and (4) ocular. Although the diagnosis of rosacea is easily established, based on its characteristic clinical aspect, unusual manifestations of rosacea may be overlooked or misdiagnosed.[1-3]

Epidemiology

Rosacea is a common disease, frequently seen in people between 30 and 50 years of age. It is more common in certain ethnic groups, such as Caucasians. The prevalence statistics published in Europe and the United States are highly variable, ranging from less than 1% to more than 20% of the adult population; actually, the methods used and the populations studied vary greatly from one study to another; consequently, they cannot be compared. Rosacea prevalence has been reported to be 1-10%. Women are more commonly affected than men; however, men progress to the advanced stages of the disease more often than women. Eye involvement may be found in up to 58% of all cases. Rhinophyma is seen mostly in men over 40 years of age.[1,4]

* Corresponding author. Tel.: +90 212 414 3120.
E-mail address: yalcintuzun@gmail.com (Y. Tüzün).

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According to a study in the United Kingdom, 60,042 rosacea patients were identified, with a predominance of women (61.5 %). Rosacea was diagnosed in 80% of cases after the age of 30.[5] It is estimated that from 10 to 20 million Americans have the condition. In a Swedish survey of people between 20 and 60 years of age, approximately 10% were thought to have rosacea, with a female-to-male ratio of 3:1.[5] In Estonia, a study that investigated the prevalence of rosacea in a randomly selected working population, aged ≥30 years, using *National Rosacea Society's Expert Committee* (NRSEC) criteria, found a prevalence rate of 22%, which is significantly higher than that found in previous studies.[6]

Etiology and pathogenesis

The cause of rosacea is still unknown. Genetic and environmental factors are thought to have an influence in the etiology of rosacea. Family history is present in up to 30% of the cases. Exacerbating factors include drinking alcohol or hot beverages, eating chocolate, nuts, spicy foods, and cheese, taking some medications, sun exposure, hot and cold weather, wind, humidity, indoor heat, certain cleansers, moisturizers, cosmetics, and physical and emotional stress. Menstruation and pregnancy can also exacerbate rosacea. It is thought to be due to hormonal fluctuations that increase cutaneous vascularity.[2,3,7,8]

From the diverse findings, the pathology of rosacea was thought to be unknown and was suspected to be from multiple factors. The multiple factors that lead to a trigger of the innate immune system seem to explain the diverse findings in rosacea etiology and why the current therapies are effective. Pathological mechanisms of rosacea are due to innate immunity, vascular changes, reactive oxygen species released by neutrophiles, ultraviolet radiation, and microbes.[1,2,9]

Abnormal vascular reactivity has been argued to play the central role in pathogenesis. Most patients develop erythema and telangiectasia in the same flushing areas. Expansion of dermal microvascularization with grossly dilated, irregular vascular channels can be seen in the lesional skin. Vascular endothelial growth factor (VEGF), VEGF receptors, CD 31, and lymphatic endothelium maker D2-40 expressions appear to be increased in the vascular endothelium of the affected skin. Elevated expression of VEGF, CD 31, and D2-40 in rosacea suggests that the affected skin has more stimulants for vascular and lymphatic endothelial cells and increases the amount of endothelial cells. Also, mast cell numbers were found to be significantly greater in lesional skin compared to nonlesional skin.[10-13]

Rosacea is associated with an exacerbated response by the innate immune system. In innate immunity, the pattern recognition system, which includes the TLR (toll-like receptor) and NLR (nucleotide-binding domain and leucine-rich repeat-containing) families, responds to environmental stimuli such as UV, microorganisms, and physical and chemical trauma. Triggering the innate immune system normally leads to a controlled increase in cytokines and antimicrobial molecules in the skin. One of the most important peptides is cathelicidin. Rosacea patients express abnormally high levels of cathelicidin. Cathelicidin peptides are effector molecules that modify local inflammatory response, exert angiogenic activity, promote and regulate leukocyte chemotaxis, and increase vascular permeability. The presence of vasoactive and inflammatory cathelicidin peptides in rosacea leads to the production of tryptic enzymes (kallikrein-5) in the stratum corneum that activates cathelicidin in the epidermis.[9,10,14,15]

Sun damage and sun exposure are considered to be contributing etiological factor. It is well known that facial erythema and flushing may be precipitated by sun exposure. The presence of solar elastosis also suggests that UV light plays a role in rosacea. Chronic actinic damage leads to solar elastosis, which brings on inadequate support to small vessels, leading to the persistent erythema and telangiectasia. Also in mice, UVB induces cutaneous angiogenesis that is histologically similar to the telangiectasia seen in rosacea. UVB increases VEGF and fibroblast growth factor 2 (FGF2) expression in the keratinocytes and epidermis of mice.

Recent evidence suggests that inflammation is associated with reactive oxygen species (ROS) produced by neutrophiles in rosacea. Changes in redox status with reduced levels of superoxide dismutase have been observed in the skin in cases of inflammatory rosacea, but it is not exactly known whether these are the causes or the effects of the inflammation. In one study, serum peroxide levels were found to be significantly higher and serum total antioxidative potential levels were found to be lower in patients with rosacea than in healthy groups. In support of the importance of oxidative pathways in rosacea, the antioxidant metronidazole, tetracyclines, and azithromycin have been shown to be clinically effective in treating rosacea symptoms by decreasing neutrophile-generated ROS at the sites of inflammation.[1,10,16,17]

Demodex mites are found in very large numbers in the general population; with recent sensitive techniques, the prevalence approaches almost 100% among rosacea patients. Many studies have shown that an increased number of mites (density 5 mites per follicle) may play a role in the pathogenesis of rosacea by triggering inflammatory or specific immune system response, mechanically blocking the follicles, or acting as a vector for bacteria. It may also trigger a delayed hypersensitivity reaction that may contribute to the formation of papules and pustules. *Demodex* mites, especially *Demodex folliculorum,* cause a rosacea-like eruption called rosacea-like demodicidosis. One bacterium found in association with *Demodex* is *Bacillus oleronius;* proteins from this organism have the potential to induce an immune response in patients with rosacea.[18-20]