Is rosacea a systemic disease?

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Abstract Rosacea is a chronic inflammatory facial disease occurring world-wide. The incidence of rosacea is increasing with age, with the clinical course being characterized by relapses. The pathogenesis of rosacea is not completely understood, but neurovascular and immunologic mechanisms are involved. Rosacea has a number of known extrinsic triggers that should be avoided, such as sun exposure, heat and cold, alcoholic beverages, and spicy food. Of greater importance is the observation that rosacea may develop as a manifestation of systemic diseases with a significant morbidity and even mortality. Obesity, *Helicobacter pylori* infection, smoking, and inflammatory bowel disease bear a significant risk for the development of rosacea. Metabolic, psychiatric, and neurologic disorders and certain types of cancer show a significant association with rosacea. The possible link to cardiovascular events is debatable. There are extrafacial and extracutaneous manifestations of rosacea, such as the red scalp syndrome, ocular rosacea, and migraine. Rosacea should be considered a systemic disease.
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Rosacea is a chronic inflammatory facial disease with a global prevalence of 5.46%.[1] The prevalence is 12.3% in Germany and 5.0% in Russia.[2] Genetic factors may contribute to the prevalence of the disease, but extrinsic factors are also involved. There are a number of trigger factors, including sun exposure, heat and cold, hot drinks, like coffee and tea, and spicy food; however, such triggers may vary between individual patients. Both sexes are involved, and the incidence increases with age.[3]

Clinical features of rosacea

Clinically, rosacea may be categorized into the following diagnostic phenotypes: (1) fixed centrofacial erythema in a cloverleaf pattern, (2) papulopustular, (3) erythematotelangiectatic, (4) ocular, and (5) phymatous.

Rosacea may progress in severity and change in phenotype.[4] Occasionally, a patient may contract more than one subtype (Figure 1).[5] Rosacea is not restricted to any one race, sex, or location.[6]

Although rosacea is easily recognized, its pathogenesis is not. Aberrant innate immunity and a disturbed neurovascular regulation seem to be significant.[7,8] Rosacea is characterized by flushing and erythema. The basic abnormality in rosacea is disturbed microcirculation in facial angular veins. Flushing is prolonged in rosacea. Persistent centrofacial erythema is a key sign. Perioral and periocular area are spared. Whereas comedones are completely absent, granulomatous lesions may emerge in later stages. In papulopustular rosacea, inflammatory lesions are present, which may extend from the central portion of the face to the neck and scalp. Phymas can occur alone or in combination with other types of rosacea. The most common phymatous change is rhinophyma

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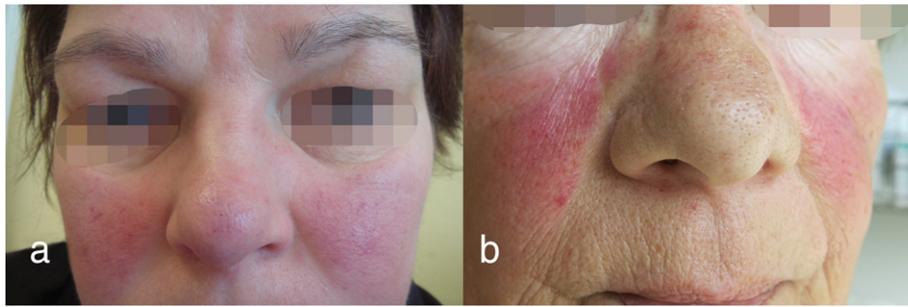*E-mail address:* Uwe.Wollina@klinikum-dresden.de.

Fig. 1 Erythematotelangiectatic rosacea with central facial erythema. A, Untreated. B, disappearance of erythema on the nose due to topical application of brimonidine tartrate gel.

with a predominance in men. Other phymas include gnatophyma (chin), metophyma (forehead), otophyma (ears), and blepharophyma (eyelids).[4,7,8]

The afflicted skin has a significantly lower heat pain threshold than healthy skin. Transient receptor potential ion channels of the vanilloid type 1 and ankyrin 1 function, as cellular sensors for cold and heat participate in the inflammatory process, possibly along with the neuropeptides, vasoactive intestinal peptides, and substance P.[8,9,10]

The expression of Langerhans cells in involved skin is lower in rosacea than in controls. Plasmacytoid dendritic cells have been found in skin samples of rosacea as isolated cells and small clusters. The expression of toll-like receptors-2, -4 and inducible oxide nitric synthase are higher in rosacea skin than in healthy controls. As a result, early- and late-stage components of innate immunity are altered in rosacea.[11]

Ocular rosacea is the most common extracutaneous manifestation of rosacea. The disease affects the Meibomian glands. The secreted meibum is changed in quantity and quality.[12] This leads to the dry eye syndrome with reduced tear production as measured by the Schirmer test. The mean fluorescein tear break-up time is approximately half the time of healthy controls, and mean tear osmolarity is higher in rosacea. Rosacea patients reach a higher mean score in the ocular surface disease index questionnaire. All of these clinical manifestations become evident before ocular clinical manifestations are reported by the patient.[13] Ocular rosacea patients will have meibomitis in 100% of cases, anterior blepharitis in 83%, punctate keratopathy in 67%, chalazion in 50%, corneal neovascularization in 50%, and subepithelial infiltrates in 16.6% (Figure 2).[14]

Rosacea fulminans is a rare, severe, acute subtype of rosacea. In a review published in 2018, only 135 cases have been identified with a clear predominance in women (91% of reported cases) and an average age of 31 years. The clinical picture characterized by papules, pustules, nodules, and draining sinuses of the center of the face (Figure 3). There is a risk of scarring and disfigurement.[15]

Morbihan syndrome is another rare entity most commonly seen in Caucasians (Figure 4). Recurrent flushing and telangiectasias are associated with a diffuse facial edema suggesting the involvement of lymphatic vessels.[16]

There are a number of possible triggers in rosacea. Factors promoting vasodilatation can aggravate the disease. Rosacea can be worsened by sun exposure and heat. The skin in rosacea becomes very sensitive to nonspecific factors pointing to a disturbed barrier function.[7,8] The role of alcoholic beverages and smoking is discussed in separate paragraphs. In the prospective Nurses' Health Study II, there was an inverse association with caffeine intake or caffeinated coffee consumption and rosacea, whereas decaffeinated coffee consumption had no preventive effect.[16] The most common medications that can induce or aggravate rosacea or rosacea-like dermatitis are corticosteroids and inhibitors of epidermal growth factor receptor.[17]

The role of spicy food in rosacea is questionable, because the disease is not more frequent in countries that are famous for their spicy food, such as India, Thailand, or Mexico.[6]
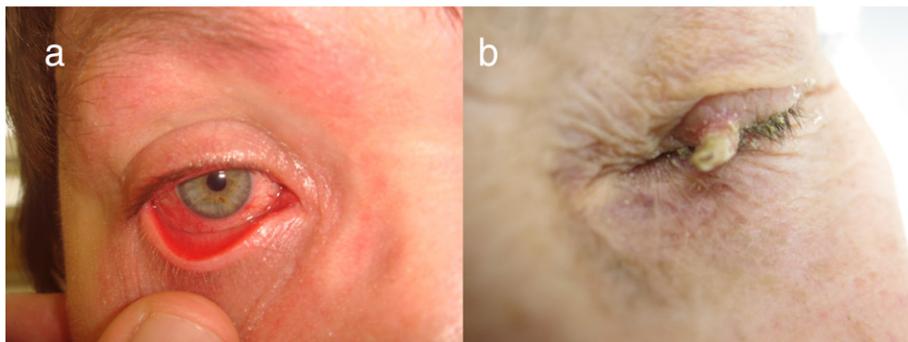

Fig. 2 Ocular rosacea. A, Blepharitis. B, Cornu cutaneous-like granulomatous rosacea of the upper eyelid.

Fig. 3 Rosacea fulminans.

History

Rosacea or "gutta rosacea" had been noticed in "Treatise of Diseases Incident to the Skin" (1718) by Daniel Turner (1667-1740) and was thought to be due to "hot but viscous and thick blood."[18] Rhinophyma had been described by Avicenna (980-1037) as "badschenan." The term rhinophyma, however, was not used until 1856, when Ferdinand von Hebra (1816-1880) in his *Atlas of Skin Diseases* from 1876 included a colored painting of hyperplastic rhinophyma by Carl Heitzmann (1836-1896).[19] Ocular rosacea was first described in 1865 by the Austrian ophthalmologist Carl Ferdinand Ritter von Arlt (1812-1887) who observed blepharitis, conjunctivitis, and corneal ulcers.[20]

Rosacea and rhinophyma were noted by Geoffrey Chaucer (1346-1400), the famous Middle English chronicler, in *The Canterbury Tales*,[21] whereas Domenico Ghirlandaio (1449-1494), a renowned Florentine Renaissance painter, illustrated

Fig. 4 Morbihan syndrome with persistent edema of the forehead.

a hyperplastic rhinophyma in his painting *Portrait of an Old Man with his Grandson*.[22] In *The Life of King Henry the Fifth* by William Shakespeare (1564-1616), Fluellen described Bardolph – a companion of Fallstaff to the King:

> … if your majesty know the man: his face isall bubukles, and whelks, and knobs, and flames o'fire: and his lips blows at his nose, and it is likea coal of fire, sometimes plue and sometimes red;but his nose is executed and his fire's out.[23]

In modern times, some famous men were rosacea sufferers. Banker J. Piermont Morgan (1837-1913) and comedian W.C. Fields (1880-1946) were among them.[20] The icon of pop art Andy Warhol (1928-1987) underwent dermabrasion in 1957 to treat his rhinophyma.[24]

The term acne rosacea is a misnomer that occurs even in modern medical literature.[25,26] Rosacea—contrasted with acne—prefers the central area of the face. It is remarkable that all structures of the central part are of neuroectodermal origin, whereas the lateral parts are ectodermal. In rosacea, there is a complete absence of comedones. Rosacea becomes more frequent with increasing age in contrast to acne.[3]

Rosacea and cardiovascular diseases

In a trial from Brazil, rosacea patients had significantly higher epicardial fat thickness and carotid intima-media thickness volumes than controls. In the multivariate logistic regression analysis, epicardial fat thickness was independently related to the presence of rosacea ($P < .001$, odds ratio [OR] 13.31). In the multiple linear regression analysis, the epicardial fat thickness was independently associated with rosacea, carotid intima-media thickness, and systolic blood pressure.[27] Higher levels of neutrophils to lymphocytes ratio and insulin-resistance in rosacea support the concept of an increased level of cardiovascular risk factors in patients with rosacea.[28]

In a recent systematic review, cardiovascular disorders were significantly associated with rosacea. The authors argue that chronic inflammation in rosacea can be systemic. In analogy to psoriasis, systemic inflammation in rosacea can lead to vascular alterations, which increase the risk of cardiovascular events.[29]

The concept remains a matter of debate. Using a large commercial claims database of 21,801,147 lives in the Unites States with 2,105 rosacea patients, a propensity-matched logistic regression as performed to evaluate the association between rosacea and a 1-year risk of cardiovascular disease. The adjusted OR of cardiovascular disease was not higher in patients with rosacea (OR 0.894, $P = .2713$).[30]

In a nationwide study from Taiwan, 33,553 patients with rosacea and 67,106 age- and sex-matched control subjects were identified from the National Health Insurance Research Database. Dyslipidemia (OR 1.41, 95%CI [confidence

interval] 1.36-1.46), coronary artery disease (OR 1.35, 95% CI 1.29-1.41), and hypertension (OR 1.17, 95%CI 1.12-1.21) were significantly associated with rosacea. Men had a higher risk for comorbidities than women with rosacea.[31]

A Danish study investigated 4,948 patients with rosacea for cardiovascular disease. Adjusted incidence rate ratios (IRR) were 0.75 (95%CI 0.57-1.00) for myocardial infarction, 1.08 (95%CI 0.86-1.35) for ischemic stroke, 1.01 (95%CI 0.61-1.67) for hemorrhagic stroke, 0.99 (95%CI 0.80-1.24) for cardiovascular (CV) death, 0.99 (95%CI 0.86-1.15) for major adverse CV events, and 0.95 (95%CI 0.85-1.06) for all-cause mortality. The results argue against an association of rosacea with cardiovascular disease.[32] The ethnic background, nutritional status, and other factors may be of importance for the disparity of the results from various countries.

Rosacea and the metabolic syndrome

Clinical manifestations of the metabolic syndrome, such as insulin resistance, may be present in patients with rosacea. Screening for the metabolic syndrome in rosacea patients could lead to early detection of the metabolic syndrome, and vice versa, and can also diminish the severity of rosacea.[33] Diabetes mellitus and dyslipidemia are comorbidities of rosacea.[29,34]

The risk for rosacea is elevated in patients with increased body mass index. Compared with a body mass index of 21.0 to 22.9 kg/m^2, the hazard ratio (HR) of rosacea was 1.48 (95% CI 1.33-1.64) for body mass index ≥35.0 kg/m^2. There is a significantly increased risk for rosacea with higher waist circumference and hip circumference independent of body mass index.[35]

Rosacea and *Helicobacter pylori* infection

The role of *Helicobacter pylori* in rosacea pathogenesis is controversial. *H. pylori* is a gram-negative bacterium involved in chronic gastritis, gastric ulcers, and even gastric cancer.

In a meta-analysis, 27 studies have been reevaluated. Epidemiologic investigations and experiments have confirmed that *H. pylori* infection is associated with the development of rosacea. In *H. pylori*–positive rosacea patients, anti–*H. pylori* therapy is more effective than the routine treatment. *H. pylori* can stimulate the immune system to produce a large number of inflammatory mediators, leading to the occurrence and aggravation of rosacea inflammation.[29]

Rosacea and chronic inflammatory bowels diseases

In a meta-analysis of 5,051,356 patients the relative risk of rosacea in overall inflammatory bowels diseases, ulcerative colitis, and Crohn's disease were 1.66 (1.50-1.84), 1.69 (1.48-1.93), and 2.08 (1.26-3.46), respectively.[36]

Celiac disease is an immune-mediated, gluten-induced enteropathy that affects predisposed individuals of all ages. In a nation-wide study from Denmark, adjusted HR revealed a significant association between rosacea and celiac disease (HR 1.46, 1.11-1.93).[37]

Rosacea and musculature

The relative muscle mass has a beneficial role in prevention of the metabolic syndrome. Relative muscle mass is negatively associated with an increased risk of more severe rosacea, suggesting that skeletal muscle can have a protective effect on rosacea exacerbation.[38]

Rosacea and kidney disease

A study from Taiwan identified 277 patients with rosacea in the Taiwan National Health Insurance Research Database during 2001-2005. These patients were matched for age, sex, and comorbidities with 2,216 patients without rosacea. All subjects were individually followed up for 8 to 12 years to identify those who subsequently developed chronic kidney disease. Patients with rosacea had an increased risk of chronic kidney disease (adjusted subdistribution HR 2.00, 95%CI 1.05-3.82). The hazard rates were higher for moderate-to-severe rosacea compared with mild disease.[39]

Rosacea and autoimmune disorders

In a population-based, case-control study from Demark, patients with rosacea had significantly increased ORs for diabetes mellitus Type 1 (OR 2.59, 95%CI 1.41-4.73), celiac disease (OR 2.03, 95%CI 1.35-3.07), multiple sclerosis (OR 1.65, 95%CI 1.20-2.28), and rheumatoid arthritis (OR 2.14, 95%CI 1.82-2.52) with a predominance in women[40] Another systematic analysis found that rosacea is associated with rheumatoid arthritis.[29]

Rosacea and hair disorders

Frontal fibrosing alopecia is a chronic cicatrical alopecia of unknown cause. For women, there is a statistical association between alopecia and presence of rosacea (OR = 1.91, 95%CI 1.07-3.39).[41]

The red scalp syndrome is defined as an erythematous scalp disorder resistant to treatment with potent topical steroids or antiseborrhoeic therapy. Clinical manifestations are itching stinging, or burning sensations, papules, pustules, and telangiectasias with or without androgenetic alopecia.

Fig. 5 Red scalp syndrome with pustules and redness of the scalp.

The red scalp syndrome is a possible extrafacial manifestation of rosacea (Figure 5).[42]

Rosacea, stigmatization, anxiety, and depression

Rosacea patients often are burdened with embarrassment, social anxiety, and psychiatric comorbidities. In an online survey of a representative sample of the adult population in the United Kingdom, France, Germany, and the United States, one-third of rosacea patients reported feelings of stigmatization with a predominance of men. Feelings of stigmatization were associated with avoidance of social situations and depression.[43] Recurrent flushing is important for the development of anxiety in rosacea patients.[44]

The Patient Health Questionnaire-9—a validated and reliable self-administered tool for diagnosis of depression and calculation of depression severity—has been used among rosacea patients. The authors came to the conclusion that there is a direct relationship between rosacea severity, as shown by the Patient Health Questionnaire-9 and the level of depression.[45] Men are more affected by anxiety and depression than women.[44]

A Chinese study investigated the quality of life by the Dermatology Life Quality Index and the psychologic situation with the Hospital Anxiety and Depression Scale in 201 rosacea patients and 196 healthy controls. The investigators reported significantly higher Dermatology Life Quality Index, anxiety, and depression scores in the rosacea group.

The Dermatology Life Quality Index was associated with anxiety and depression.[46]

A Danish study confirmed the association of rosacea with anxiety and depression. Mild and moderate-to-severe rosacea increased the adjusted IRR of both depression (IRR 1.89 [95%CI 1.82-1.96] and IRR 2.04 [95%CI 1.96-2.12]) and anxiety disorders (IRR 1.80 [95%CI 1.75-1.86] and IRR 1.98 [95%CI 1.91-2.05]).[47]

Rosacea, dementia, and Parkinson's disease

In a nation-wide Danish study of adults, 82,439 patients with rosacea could be identified. The adjusted HRs of dementia and Alzheimer's disease in rosacea patients were 1.07 (95%CI 1.01-1.14) and 1.25 (95%CI 1.14-1.37).[48]

The Northwestern Medicine Enterprise Data Warehouse electronic medical records data repository (>5 million patients) of 15 years was searched for adult patients and clinic encounter followup ≥5 years for a possible relationship of rosacea with Parkinson's disease. A significant association between rosacea and Parkinson's disease was determined after adjusting for age, sex, race, and Charlson comorbidities index (OR 1.39, 95%CI 1.04-1.85).[49] Flushing and rosacea have been observed in 31.9% and 18.8% of patients with Parkinson's disease.[50]

A systematic review[29] reported dementia, Parkinson's disease, facial dystonia, and multiple sclerosis to be associated with rosacea.

Rosacea and migraine

Migraine is a complex disorder with episodes of headache, nausea, photophobia, and phonophobia. There is an association between rosacea and migraine.[29] In a meta-analysis, a pooled OR of 1.96 (95%CI 1.41-2.72) was found for migraine in rosacea patients.[51]

Rosacea, alcohol consumption, and smoking

The strong association of alcohol consumption and rosacea in nonmedicals is one reason for stigmatization of rosacea patients. But is there enough scientific evidence? In an analysis of 4,945 women with rosacea, an increased alcohol intake was associated with a significantly increased risk of rosacea. The multivariate-adjusted HR for alcohol intake of ≥30.0 g/d was 1.53 (1.26-1.84). White wine and liquor were significantly associated with a higher risk of rosacea.[52]

A nation-wide analysis of mortality in rosacea patients in Denmark reported an increased risk of death due to hepatic disorders. This could also be a link to increased alcohol consumption among patients with rosacea.[53]

Smoking is a risk factor for rosacea. In multivariate analysis, the prevalence of smoking was significantly higher (66%) among rosacea patients compared with controls. The erythemato-telangiectatic rosacea subtype was found to be significantly higher among active smokers.[54]

Rosacea and cancer

In a nationwide cohort study of the adult Danish population 49,475 patients with rosacea and 4,312,213 subjects from the general population were analyzed for cancer comorbidity. In rosacea patients, there was an increased risk of hepatic cancer (HR 1.42, 95%CI 1.06-1.90), nonmelanoma skin cancer (HR 1.36, 95%CI 1.26-1.47), and breast cancer (HR 1.25, 95%CI 1.15-1.36), whereas the risk of lung cancer was significantly decreased (HR 0.78, 95%CI 0.69-0.89).[55]

In the Nurses' Health Study II from the United States, rosacea was associated with an increased risk of thyroid cancer and basal cell carcinoma in women.[56]

Rosacea patients have an increased risk for glioma. Patients with a primary diagnosis of rosacea by a hospital dermatologist had an adjusted IRR of 1.82 (95%CI 1.16-2.86).[57]

Conclusions

Rosacea is a chronic inflammatory disorder having a strong association with internal diseases, such as gastric diseases, inflammatory bowels diseases, and the metabolic syndrome. The possible association with cardiovascular disease is still a matter of controversy. Depression, anxiety, and degenerative neural disorders have been detected in a significant percentage of rosacea patients. Rosacea may be considered as a manifestation of several conditions with significant morbidity; therefore, rosacea can be considered a systemic disease.

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