Ocular rosacea: Common and commonly missed

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Rosacea is a prevalent disorder that may be disfiguring and cause significant ocular morbidity, if not diagnosed and managed appropriately. Ocular rosacea, in particular, is often left undiagnosed as no specific test is available to confirm the diagnosis. Accurate diagnosis is further complicated because symptoms of ocular rosacea are not always specific to the disorder alone. Other ophthalmic disorders may present with similar findings. Further challenges exist because the severity of ocular symptoms is often not related to the severity of cutaneous findings in rosacea. Isolating a disease marker may facilitate earlier diagnosis and treatment, and could also contribute to better understanding of disease pathogenesis. The glycomics of tear fluid and saliva in patients with rosacea shows promise as an initial step in the search for a biomarker specific to the disease. We have previously found potentially important disease biomarkers in roseatic tear and saliva samples. Further investigation should prove important in the early stages of developing a set of markers for accurate disease identification. (J Am Acad Dermatol 2013;69:S36-41.)

Key words: biomarker; conjunctivitis; disease triggers; ocular rosacea; rosacea; saliva; tear break-up time; tear fluid.

Rosacea is a chronic condition that affects the axial facial skin, more specifically, cheeks, chin, nose, and central forehead. The manifestations include transient or persistent erythema, telangiectasias, papules, pustules, and phymatous changes.[1] Symptoms may show periods of exacerbation and remission, but the disease usually progresses over time. Certain trigger factors are known to worsen the symptoms of rosacea, including sun exposure, spicy foods, alcohol consumption, extreme temperatures, physical exercise, emotional distress, and menopause, among others.

In 2002, the American National Rosacea Society published a standard classification system for rosacea and divided the disease into 4 clinical subtypes, according to the patterns of signs and symptoms: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. A variant form of the disease (granulomatous rosacea) was also described.[2]

Ocular rosacea may result in varying degrees of eyelid and ocular surface inflammation.[1,3] Up to 58% to 72% of patients with rosacea present with ocular involvement. In addition, about one third of these patients may develop potentially sight-threatening corneal findings.[3] Starr and Macdonald[1] found corneal involvement in 33% of the patients with cutaneous rosacea. Quarterman et al[4] observed punctate epithelial keratitis in 39% of the patients.

To date, there is no diagnostic test for either cutaneous or ocular rosacea.[5,6] The diagnosis of associated eye disease is, therefore, clinical and relies on observation and the correct interpretation of both ocular surface and accompanying skin manifestations. This, however, may be challenging, because the severity of ocular symptoms is often not related to the severity of cutaneous findings.[4,5,7,8] In fact, in 20% of patients, ocular findings may precede characteristic skin involvement, and in up to 90% of cases of ocular rosacea, the skin findings may be very subtle, and the disease may remain undiagnosed.[3] In addition, the manifestations of ocular rosacea are not always specific to the disorder alone. Other ophthalmic disorders of the ocular surface may present with similar findings, making the diagnosis even more difficult.

As a result of the foregoing, ocular rosacea is often underdiagnosed. Patients with mild rosacea may not seek medical treatment, and those who do seek professional help may not mention their ocular

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symptoms in dermatology clinic, unless directly asked about them. Similarly, ophthalmologists frequently overlook dermatologic signs, leaving many cases undetected.

Chronic, untreated rosacea may cause potentially sight-threatening ocular disease, along with facial disfigurement, emotional distress, and social impairment. The need for early diagnosis and appropriate treatment cannot be overemphasized.

This review article blends expertise of ophthalmology and dermatology in the hope of providing a new perspective on ocular rosacea to the dermatology readership.

CAPSULE SUMMARY

- Ocular rosacea, in particular, is often undiagnosed or underdiagnosed.
- Tear fluid and saliva glycomics in patients with rosacea present potentially important disease biomarkers.
- Finding positive disease biomarkers may not only facilitate accuracy of diagnosis but early and appropriate disease management.

EPIDEMIOLOGY

Rosacea affects over 16 million Americans, and a survey found prevalence as high as 10% in Sweden.[9,10] A recent large observational study on the epidemiology of rosacea in the United Kingdom revealed an incidence rate of 1.65/1.000 person-years as diagnosed by general practitioners.[11]

Rosacea is most frequently observed in fair-skinned patients of European descent. However, other ethnicities such as Asians and Africans may also be given the diagnosis of this disorder.[12-14] It typically affects middle-aged adults over 30 years of age with a peak in incidence rate between the ages of 40 and 59 years.[11]

Ocular rosacea affects both sexes equally, which is different from facial rosacea that has a slight preponderance in women.[11] The incidence of ocular rosacea varies among ophthalmologic and dermatologic studies, ranging from 6% to 72%, being more prevalent in ophthalmology clinics.[3,15]

PATHOPHYSIOLOGY

Ocular rosacea is an inflammatory disorder, although its precise pathophysiology remains poorly understood. Studies have revealed elevated concentrations of interleukin-1α and -β and a greater activity of gelatinase B (metalloproteinase [MMP]-9) and collagenase-2 (MMP-8) in tear fluids of patients with ocular rosacea.[16-19] Further supporting the inflammatory nature of the disease, doxycycline, which decreases both MMP-8 and MMP-9 activity, is successfully used in the treatment of both cutaneous and ocular rosacea.[18,19]

Micro-organisms such as *Helicobacter pylori*, *Demodex folliculorum*, *D brevis*, and *Staphylococcus epidermidis* have been identified as possible causative factors in exacerbation of the disease; however this remains controversial.[7,20-27] *Demodex* is a microscopic mite commonly found in hair and eyelash follicles, as well as in sebaceous glands and meibomian glands.[28] Studies have reported that *Demodex* infestation may lead to eyelid inflammation, trichiasis, madarosis, blepharitis, meibomian gland dysfunction, conjunctivitis, and corneal lesions, all signs of ocular rosacea.[28] *Demodex* counts have been significantly higher in patients with facial rosacea and support the role of *Demodex* in the activation of immune mechanisms in certain subtypes of rosacea, especially papulopustular rosacea.[23] A strong correlation between positive serum immunoreactivity and ocular *Demodex* infestation in facial rosacea and eyelid margin inflammation was demonstrated recently.[7,28,29]

A decreased concentration of group IIA phospholipase A_2, a protein with antimicrobial properties, was observed in tears of patients with ocular rosacea. This phospholipase plays an important role in innate host defense.[30]

CLINICAL PRESENTATION: SIGNS AND SYMPTOMS

Symptoms of ocular rosacea include tearing, redness, foreign body sensation, burning, itching, photophobia, and blurred vision. Patients may report varying degrees of decreased visual acuity when the cornea is involved.[2]

Ocular manifestations are usually bilateral and, as previously mentioned, can be quite nonspecific. Lid disease-related manifestations are most common.[3] Blepharitis and meibomian gland dysfunction are frequently observed. Slit-lamp examination of the eyelid margins reveals telangiectases, posterior displacement of gland orifices, capping of meibomian orifices, dilated meibomian glands, excessive seborrheic secretion, and collarettes around the eyelashes[5] (Fig 1). Recurrent hordeolum and chalazion, as well as tear film insufficiency are commonly observed as a consequence of meibomian gland dysfunction. The inferior tear meniscus may have a soapy or foamy appearance as a result of excess meibomian secretion. Debris may be present in the tear film. Abnormal Schirmer testing was reported in 56% to 62.5% of patients with ocular rosacea.[7,31] Diminished tear break-up time has also been reported in a large majority of patients with ocular rosacea.[7,8,31]