Ocular Rosacea

Patient Characteristics and Follow-up

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Purpose: The purpose of this report is to review the presenting symptoms and signs, treatment regimens used, complications encountered, and outcome in a cohort of patients with ocular rosacea.

Methods: The medical records of 131 patients with a diagnosis of ocular rosacea were reviewed retrospectively. Data were entered in a tabulated form, and a descriptive analysis was performed.

Results: The age range at presentation was between 23 and 85 years (mean, 56 years). Cutaneous manifestations of rosacea were present in 112 of the patients at their first visit. The most common presenting symptoms were foreign body sensation and burning, and the most common signs were telangiectasia and irregularity of lid margins, and meibomian gland dysfunction. Thirteen patients had decreased visual acuity at the time of presentation due to corneal complications. Six of these patients required penetrating keratoplasty during the course of their disease. Seven patients had severe cicatrizing conjunctivitis at the time of referral. One hundred thirteen patients were treated with oral tetracycline derivatives. Seven patients were left with visual acuity less than 20/400, and one patient underwent enucleation for corneal perforation and endophthalmitis.

Conclusions: Ocular rosacea is a common disease involving the skin and the eyes. It is widely underdiagnosed by many ophthalmologists despite the blinding potential. Successful therapy requires a multidisciplinary approach.

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Acne rosacea is a common chronic skin disease characterized by persistent erythema, telangiectases, papules, and pustules in the flush areas of the face and neck. The typical feature of the advanced stage of the disease is the rhinophyma caused by sebaceous gland hypertrophy.[1]

Ocular involvement (ocular rosacea) is reported in 3%[2] to 58%[3] of cases depending on the series. The severity of the ocular signs ranges from mild blepharoconjunctivitis to vision-impairing corneal involvement such as neovascularization, thinning, and, in rare instances, perforation.[4]

The etiopathogenesis of ocular rosacea is not yet clear. Rufli and Büchner[5] attributed the skin lesions to a cell-mediated immune response to *Demodex folliculorum* because inflammatory infiltrates, mainly helper-inducer T cells, were found around these sites. Brown and Shahinian[6] showed immunoglobulin and C3 deposition in the epithelium and the basement membrane of patients with severe ocular rosacea. Hoang–Xuan et al[7] concluded that the mechanism involved in rosacea conjunctival inflammation resembled a type-IV hypersensitivity reaction by studying the histology–immunopathology of conjunctival biopsy specimens from patients with the diagnosis of ocular rosacea.

This report describes the patient demographics, presenting symptoms and signs, treatment regimens used, complications encountered, and outcome in a cohort of patients with ocular rosacea who were treated throughout

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Table 1. Patient Characteristics at the Initial Examination

Patient Characteristic	Value
No. of patients	131
Male/female	75/56
Race	White
Mean age at onset (yrs)	56 (23–85)
No. of patients <30 yrs	10
Facial rosacea	112
Previous diagnosis of rosacea	12

their follow-up at the Massachusetts Eye and Ear Infirmary Immunology Department.

Patients and Methods

The medical records of 131 patients who were admitted to the Immunology Service at the Massachusetts Eye and Ear Infirmary with a diagnosis of ocular rosacea were reviewed. The diagnosis of rosacea was based on the findings of telangiectasia of the nose and face and one or more of the following: hypertrophic sebaceous glands, papules, pustules, and erythema of the flush areas of the face.[8] Records were entered in a tabulated form, and a descriptive analysis was performed to determine the patient characteristics retrospectively.

Results

Fifty-six (43%) of the 131 patients were women and 75 (57%) were men. The age range at presentation was between 23 and 85 years (mean, 56 years). Ten patients were younger than 30 years of age. None of the patients were black (Table 1).

Most patients presented with a chief reported problem of foreign body sensation, pain, burning, or redness. Usually both eyes were affected simultaneously, but occasionally alternate involvement was noted.

Thirteen patients had an initial reported problem of decreased visual acuity due to the corneal complications; 12 were referred due to the cicatrizing conjunctivitis to rule out ocular cicatricial pemphigoid, 5 were referred for further treatment of ocular rosacea, 2 for recurrent chalazia, and 1 for recurrent episcleritis.

Facial skin rosacea was present in 112 of the patients at their first visit. In most of these patients, the dermatologic findings were not so pronounced so as to make the diagnosis obvious to even a casual observer. Indeed, only 12 of the patients were diagnosed previously with acne rosacea. In 11 patients, the skin manifestations developed later, and in 8 patients, only mild skin changes were noted during a follow-up period of 2 to 40 months (mean, 13 months). The age range of these eight patients was 31 to 84 years (mean, 47 years).

The patients' ocular findings were confined mainly to the eyelids, conjunctiva, and cornea (Table 2). The most common finding was telangiectasia and irregularity of the lid margins, which occurred in 106 patients (81%). Meibomian gland dysfunction that is stagnation of the expressible sebum from the meibomian duct orifices were encountered in 103 patients (78%), and 86 patients (65%) had blepharitis with varying degrees of erythema, edema, scale, and scurf formation of the eyelid skin along with meibomian gland dysfunction. Fourteen patients were affected by chalazia at the time of the initial examination.

Conjunctival hyperemia, mostly confined to the bulbar conjunctiva, was noted in 59 patients (45%). Seven of the 12 patients having signs of cicatrizing conjunctivitis had either fornix foreshortening, symblepharon, or entropion and trichiasis at the time of their referral. None of the conjunctival biopsy specimens showed immunoreactant deposition at the epithelial basement membrane zone on immunohistochemical analysis. The histopathologic characteristics of the biopsy specimen showed a conjunctival granuloma in one patient who had a bulbar conjunctival mass and chronic diffuse granulomatous inflammation in the others. One patient had phlyctenular conjunctivitis.

Episcleritis was seen in 11 patients, scleritis in 1 patient, and iritis developed in 3 patients sometime during the course of their disease.

Thirty-four patients had keratoconjunctivitis sicca confirmed by Schirmer test with topical anesthesia. After instillation of a drop of topical anesthetic (0.5% proparacaine) and removal of tears in the lower cul-de-sac by tissue paper capillary attraction, aqueous tear production was measured by the extent of wetting the standard Schirmer paper strip at the end of 5 minutes. Less than 5 mm was considered as deficient "basal" aqueous tear production. These patients were treated with preservative-free artificial tears.

Table 2. Ocular Findings of Patients with Rosacea

Sign	No. (%) of Patients
Total no. of patients	131
Telangiectasia and irregularity of lid margins	106 (81)
Meibomian gland dysfunction	103 (78)
Blepharitis	86 (65)
Conjunctival hyperemia	59 (45)
Keratoconjunctivitis sicca	34 (26)
Stromal keratitis with peripheral neovascularization	21 (16)
Superficial punctate keratitis	20 (15)
Chalazia	14 (10)
Cicatrizing conjunctivitis	12 (9)
Episcleritis	11 (8)
Recurrent epithelial erosion	7 (5)
Corneal ulcer	7 (5)
Iritis	3 (2)
Scleritis	1 (0.7)
Conjunctival granuloma	1 (0.7)
Phlyctenular conjunctivitis	1 (0.7)

A spectrum of corneal findings was documented in 54 patients. Superficial punctate keratopathy, usually confined to the inferior half of the cornea, affected 20 patients. Mild-to-severe stromal keratitis with peripheral vascularization was seen in 21 patients. Three of these patients had peripheral corneal thinning in the inferior half of the cornea and one patient had descemetocele formation. One of the patients with stromal keratitis had Salzmann's nodular degeneration develop, and another patient had peripheral corneal thinning. Two patients showed improvement and increased visual acuities after oral tetracycline therapy.

Intermittent pain on awakening with characteristic signs of recurrent erosion, discrete areas of epithelial elevations, epithelial erosions, and subepithelial opacities was present in six patients. Seven patients had a corneal ulcer develop, two of whom had a corneal perforation. Stromal puncture was performed for one patient with recurrent corneal erosion syndrome, and a bandage contact lens was applied to a patient with a corneal ulcer. The vision improved in both patients with these treatment methods.

Thirteen patients with corneal complications had significantly decreased visual acuity at the time of presentation; 6 required penetrating keratoplasty. During a follow-up period of 1 to 8 years (mean, 4 years), three of the grafts remained clear and three failed because of immune rejection. Two patients needed repeat keratoplasties, but those grafts failed as well.

One patient (56-year-old white male) with a history of herpetic keratouveitis had a corneal perforation of the right eye. The patient had no cutaneous manifestations of rosacea at the time of his examination. He underwent penetrating keratoplasty two times and the graft failed each time. A year later, the classical rosacea facies developed and the patient was treated with oral doxycycline. But the patient was an alcohol abuser and he had a compliance problem with treatment and follow-up visits to the clinic. Three years after his initial clinical presentation, the cornea perforated, and the patient underwent enucleation because of endophthalmitis. The left eye of the patient with extreme meibomian gland dysfunction, blepharitis, and superficial punctate keratitis improved and remained stable on doxycycline for a period of 12 years.

Treatment with oral tetracycline derivatives was instituted in 113 patients (86%). The usual starting dose for the tetracycline was 250 mg four times a day, and for the doxycycline, the starting dose was 100 mg once daily. After a period of remission of 3 to 6 months, the antibiotics were tapered and then discontinued. Patients with sight-threatening complications were kept on a low-dose maintenance treatment indefinitely to prevent recurrence. Two patients did not respond to both tetracycline and doxycycline. The remaining patients responded well and showed dramatic improvement in their symptoms or signs or both. The response time varied from 2 to 6 weeks. Thirty-three patients (25%) reported adverse effects; the most common effects were nausea (17/113, 15%) and photosensitivity (8/113, 7%). One patient reported chest pain, and one had difficulty swallowing. Genital yeast infection occurred in only 2 (4%) of the 48 female patients while they still were receiving the antibiotics.

Seven patients who had advanced cicatrizing conjunctivitis findings had no further complications develop and remained stable receiving oral tetracycline without evidence of further conjunctival cicatrization.

Among the 47 patients with a follow-up period of 3 or more years (range, 3–16 years), 6 patients were left with visual acuity of 20/400 or less. This was because of opaque corneal grafts (performed for severe complications due to rosacea itself in three patients and for pseudophakic bullous keratopathy in three patients). One patient was left with no light perception (the patient who underwent enucleation).

Discussion

Duke–Elder[9] described ocular rosacea as a common and frequently undiagnosed disease. Skin involvement in rosacea is characterized by erythema, telangiectasia, papules, pustules, and sebaceous gland hypertrophy. The lesions are reported to be distributed only in the flush areas, including cheeks, forehead, nose, chin, and the ''V'' of the neck. Rosacea is distinguished from acne vulgaris by the absence of comedones and by its confinement to flush areas. Acne vulgaris commonly involves the back and chest as well as the face.[4]

The age range most common for patients with rosacea, as reported in the dermatologic literature, is 40 to 50 years.[2,10] In a series of 47 patients with ocular rosacea, the decade of peak prevalence was 51 to 60 years.[11] In our study, the mean age was 56 years, and only 10 of the 131 patients were younger than 30 years of age; the youngest was 26.

Rosacea without ocular involvement was reported to involve women twice as often as men,[12,13] but cases with ocular manifestations are about evenly divided between the sexes. In our study, there was a small male preponderance (M/F: 1.3/1).

There are no data on the variation in prevalence of rosacea among races. There is a widespread clinical impression that rosacea mainly affects fair-skinned people of northern European descent. Dermatologists, however, accept the existence of rosacea in blacks, although the condition is rare.[3,14] In our study, none of the patients were black.

Facial rosacea was evident at the initial visit in 112 patients (85%). Eleven other patients had obvious rosacea facies develop some time during the course of their disease. Eight patients had only few telangiectasias and mild erythema. We attributed this to the young age range of the patients (mean, 47) and to the relatively short follow-up period (mean, 13 months).

Ocular manifestations of rosacea can be attributed to acne rosacea with certainty when there is simultaneous involvement of the facial skin. Therefore, the ophthalmologist should perform a careful dermatologic inspection of the face and be familiar with the variable presentation of facial rosacea to make the diagnosis. However, the skin

lesions required to confirm a suspicion of ocular rosacea need not be severe.[4] In fact, only 10% (12/112) of our patients with facial rosacea had been diagnosed elsewhere. However, 15% of our patients (19/131) had ocular rosacea without the skin lesions. In such cases, because there is no specific test available to distinguish rosacea from other causes of ocular inflammation, consultation with a dermatologist is invaluable. Browning and Proia[4] suggest that response to a therapeutic trial of oral tetracycline may be helpful in confirming a tentative diagnosis.

The most common symptoms of ocular rosacea are nonspecific and include a foreign body, gritty, or dry sensation, burning, tearing, or redness. Frequently, the symptoms are out of proportion to the minimal eye findings,[8] and this has been our impression as well.

The ocular manifestations of rosacea range from minor to severe. Blepharitis, conjunctival injection, tearing, burning, recurrent chalazia, corneal vascularization and scarring, corneal and scleral perforation, episcleritis, and iritis have been reported to occur in rosacea.[2,3,8,12,15–17] The most common findings in our study were lid margin telangiectasia in 106 patients (81%), meibomian gland dysfunction in 103 patients (78%), and blepharitis in 86 patients (65%).

Conjunctival involvement in ocular rosacea usually is in the form of a mild hyperemia, especially of the bulbar conjunctiva. Although rosacea is listed among the causes of cicatrizing conjunctivitis, it is infrequent. Seven of our patients were referred for diagnosis and further treatment of their advanced cicatrizing conjunctivitis. We also noted conjunctival granuloma (one patient) and phlyctenular conjunctivitis (one patient) among our patients. Conjunctival granuloma in rosacea has been reported previously, and it has been recommended that rosacea be included in the differential diagnosis of conjunctival granulomas.[18]

Lempert et al[19] found that 57% of patients older than 19 years of age scheduled for chalazion excision had rosacea. We found that only 2 of the 14 patients who had recurrent chalazia were taking oral tetracycline for diagnosed rosacea.

Corneal involvement is, of course, the sight-threatening problem in rosacea. The most common manifestation is superficial punctate keratitis, usually in the inferior half of the cornea. Peripheral nodular epithelial elevations, map-like changes, fingerprints, epithelial microcysts, keratitis with neovascularization, and corneal thinning have been described.[8] Corneal involvement in varying degrees was noted in 54 patients (41%) among our study group. Thirteen patients had significantly reduced visual acuity at the time of initial presentation. Six of these patients required penetrating keratoplasty (two of the patients were regrafted) and three did not respond despite aggressive treatment. Patients with rosacea who require penetrating keratoplasty are reported to be more prone to graft rejection than are other patients, because of the corneal vascularization.[4]

Keratoconjunctivitis sicca has been described in patients with acne rosacea,[20,21] but no clear explanation was hypothesized for this association. In the study carried out by Zengin et al,[22] the tear film breakup time in patients with meibomian gland dysfunction was found to be decreased significantly compared with that of those patients without meibomian gland dysfunction (dermatologic rosacea). Because meibomian gland expression did not improve the tear film breakup time, but oral tetracycline did, Zengin et al[22] concluded that the tear film breakup time abnormality in ocular rosacea was caused by an abnormal lipid composition. Because neither meibomian gland dysfunction nor tetracycline therapy had a beneficial effect on decreased tear secretion, they recommended the use of artificial tears in addition to oral tetracycline.[11] We found decreased tear production, confirmed by Schirmer's test with anesthesia, in 34 patients. These patients were provided with lid hygiene, artificial tears, and oral tetracycline. Three patients required inferior punctal plug insertion. All 34 patients improved with these treatment methods.

Episcleritis and scleritis also have been reported to occur in patients with rosacea.[2,16] Episcleritis was quite common (8%) among our patients, and one patient had scleritis.

Because most of the patients with rosacea have meibomian gland dysfunction and blepharitis, a continuing regimen of eyelid hygiene with warm compresses and meibomian gland expression is important. The patient is instructed to warm the eye lids with cloths soaked in warm-to-hot water to liquefy the solidified sebum in the meibomian ducts and to dilate the ducts. The patient then is instructed to massage the lids to mechanically force the sebum and debris from the plugged or stagnant ducts. The patient's goal is to massage down on the upper lid and up on the lower lid to express stagnant sebum from the ducts and to clean the bases of the eyelashes and the lid margins, not just the eyelid skin. Antibiotics effective against staphylococci such as bacitracin and erythromycin may be useful in controlling bacterial overgrowth.

The conventional management of chalazia and sties, including warm compresses and incision with curettage, may help speed the resolution of these lesions while tetracycline is taking effect. Topical steroid therapy can be useful in managing iritis, keratitis, and episcleritis of ocular rosacea. However, close follow-up and the lowest concentration of the steroid that is effective are strongly recommended because patients with rosacea are prone to rapid corneal melting with higher corticosteroid concentrations.[23]

Frucht–Pery et al[24] compared the effects of tetracycline and doxycycline on the subjective symptoms of rosacea. They reported that tetracycline alleviates the symptoms faster, but doxycycline causes less gastrointestinal side effects and is easier with which to comply. In our study, we noted relatively more side effects with doxycycline than with tetracycline. Among 17 patients having nausea, 12 were taking doxycycline, and of the 8 patients with photosensitivity, 6 were taking doxycycline. In addition, two female patients experienced a fungal genital tract infection while taking doxycycline therapy. Two patients did not respond to any of the oral tetracyclines and were advised to continue with aggressive lid hygiene. Topical metronidazole, a broad-spectrum antibiotic and

antiparasitic agent, was reported to be highly effective in treating the facial rosacea.[25] However, it currently is not available in an ophthalmic preparation to be used directly on the lids or in the eye, and whether controlling the facial skin findings has any effects on the ocular manifestations is not certain. Although in vitro evaluation of the effects of metronidazole on rabbit corneal epithelial cells showed that it was quite safe at low doses,[26] clinical safety and efficacy studies need to be done to determine whether topical metronidazole is useful for the treatment of ocular rosacea.

In summary, acne rosacea is a common disease of unknown cause and protean manifestations. Although the minor manifestations are more prevalent than the major ones, acne rosacea is a potentially blinding disease. There is no specific test for the disease, and none of the findings of ocular rosacea are specific. It is underdiagnosed by ophthalmologists who do not carefully examine the face of the patient, because the skin lesions required to confirm a suspicion of ocular rosacea need not be severe. The treatment of rosacea is multifaceted and prolonged, requiring high patient compliance.

References

1. Tolman EL. Acne and acneiform dermatoses. In: Moschella SL, Hurley HJ, eds. Dermatology, 3rd ed. Vol. 2. Philadelphia: WB Saunders, 1992;58.
2. Borrie P. Rosacea with special reference to its ocular manifestations. Br J Dermatol 1953;65:448–57.
3. Starr PA. Oculocutaneous aspects of rosacea. Proc R Soc Med 1969;62:9–11.
4. Browning DJ, Proia AD. Ocular rosacea. Surv Ophthalmol 1986;31:145–58.
5. Rufli T, Büchner SA. T-cell subsets in acne rosacea lesions and the possible role of Demodex folliculorum. Dermatologica 1984;169:1–5.
6. Brown SI, Shahinian L Jr. Diagnosis and treatment of ocular rosacea. Ophthalmology 1978;85:779–86.
7. Hoang–Xuan T, Rodriguez A, Zaltas MM, et al. Ocular rosacea. A histologic and immunopathologic study. Ophthalmology 1990;97:1468–75.
8. Jenkins MS, Brown SI, Lempert SL, Weinberg RJ. Ocular rosacea. Am J Ophthalmol 1979;88(3 Pt 2):618–22.
9. Duke–Elder S. Diseases of the Outer Eye and Conjunctiva. In: Systems of Ophthalmology, Vol. 8 (Pt 1). St Louis: CV Mosby, 1965;537–46.
10. Marks R. Concepts in the pathogenesis of rosacea. Br J Dermatol 1968;80:170–7.
11. Jenkins MS, Brown SI, Lempert SL, Weinberg RJ. Ocular rosacea. In: Dobl Srinivasan, ed. Ocular Therapeutics. New York: Masson Publishing, 1980;101–6.
12. Rulison RH. Rosacea with a study of accompanying conditions. Am J Med Sci 1927;174:60–9.
13. Wise G. Ocular rosacea. Am J Ophthalmol 1943;26:591–609.
14. Brauner GJ. Cutaneous disease in the black races. In: Moschella SL, Hurley HJ, eds. Dermatology, 2nd ed. Vol. 2. Philadelphia: WB Saunders, 1985;1915.
15. Doggart JH. The ocular complications of acne rosacea. Br J Ophthalmol 1931;15:446–57.
16. Richter S. Skleraperforation bei Rosaceakeratitis. Klin Monatsbl Augenheilkd 1965;146:422–4.
17. Roper–Hall MJ. The ocular aspects of rosacea. Trans Ophthalmol Soc UK 1966;86:727–32.
18. Albert DL, Brownstein S, Jackson WB. Conjunctival granulomas in rosacea [letter]. Am J Ophthalmol 1992;113:108–10.
19. Lempert SL, Jenkins MS, Brown SI. Chalazia and rosacea. Arch Ophthalmol 1979;97:1652–3.
20. Lemp MA, Mahmood MA, Weiler HH. Association of rosacea and keratoconjunctivitis sicca. Arch Ophthalmol 1984;102:556–7.
21. Gudmundsen KJ, O'Donnell BF, Powell FC. Schirmer testing for dry eyes in patients with rosacea. J Am Acad Dermatol 1992;26(2 Pt 1):211–4.
22. Zengin N, Tol H, Gündüz K, et al. Meibomian gland dysfunction and tear film abnormalities in rosacea. Cornea 1995;14:144–6.
23. Hyndiuk RA, Chin GN. Corticosteroid therapy in corneal disease. Int Ophthalmol Clin 1973;13:103–23.
24. Frucht–Pery J, Sagi E, Hemo I, Ever–Hadani P. Efficacy of doxycycline and tetracycline in ocular rosacea. Am J Ophthalmol 1993;116:88–92.
25. Espagne E, Guillaume JC, Archimbaud A, et al. Etude en double insu contre exipient du metronidazole gel 0.75 p 100 dans le traitement de la rosacee. Ann Dermatol Venereol 1993;120:129–33.
26. Hardten DR, Lima PH, Schmidt BJ, Nelson JD. In vitro evaluation of the effects of metranidazole on rabbit corneal epithelial cells. Cornea 1994;13:259–63.