



Association Between Skin Findings and Ocular Signs in Rosacea

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Abstract

Objectives: To report the most frequent signs in ocular rosacea and evaluate their association with skin findings.

Materials and Methods: Fifty-one patients diagnosed with rosacea by a trained dermatologist were evaluated by an ocular surface specialist. A complete ophthalmological examination was performed.

Results: In our study, the prevalence of ocular signs in patients with rosacea was 74.5%. The average age at presentation was 50 years and women were more affected than men. The most common findings were lid margin erythema, meibomian gland dysfunction, and blepharitis. Fifteen patients had decreased visual acuity due to complications related to rosacea such as leukoma and corneal neovascularization. Interestingly, patients that had the lowest visual acuity presented with dermatological signs of papules and pustules ($p=0.001$) and rhinophyma ($p=0.023$). Two patients who showed subepithelial fibrosis and fornix foreshortening were diagnosed as having ocular cicatricial pemphigoid (OCP) by immunohistopathological analysis of conjunctival specimens.

Conclusion: Ocular compromise is common in rosacea. Our study shows that there might be a relationship between the severity of ocular involvement and certain subtypes of cutaneous disease. Rosacea and OCP may coexist. In cases that present with conjunctival fibrotic changes, a diagnostic biopsy is mandatory.

Keywords: Rosacea, ocular rosacea, ocular cicatricial pemphigoid, ocular surface disease, dry eye disease

Introduction

Rosacea is a chronic inflammatory skin syndrome that most commonly affects middle-aged, fair-skinned adults. Clinical signs include central face involvement manifesting with erythema, telangiectasias, papules, pustules, and rhinophyma. However, rosacea can also present with ocular morbidity. Recent studies suggest that the worldwide prevalence of rosacea is 5.46% in the adult population.¹ The disease usually follows a pattern of repeated remissions and exacerbations. Although it was historically classified into four major subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) that could overlap and progress from one to another, the classification criteria was recently updated to include only two features that may be

considered diagnostic: Persistent centrofacial erythema showing periodic intensification, and phymatous changes. Even though ocular involvement is not diagnostic of rosacea, it is considered a major phenotype and can also occur in the absence of dermatologic disease in 20% of cases.^{2,3,4} Ocular signs include lid margin erythema and telangiectasias; anterior blepharitis and meibomian gland dysfunction (MGD); styes and chalazia; corneal erosion, vascularization, and thinning; scleritis and sclerokeratitis.^{2,3,4,5} The treatment consists mainly of avoiding the external stimuli that exacerbate the disease and controlling the chronic inflammation. Although ocular involvement may initially respond to warm compresses, lid hygiene, and artificial tears, some patients may require the prescription of oral antibiotics such as tetracyclines;⁶ immunomodulation

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with topical cyclosporine;⁷ topical azithromycin;⁸ or in-office procedures such as intense pulsed light therapy⁹ and meibomian gland probing.¹⁰ Surgical treatment may be necessary in some cases with severe corneal neovascularization, leukoma, progressive corneal thinning, and spontaneous perforation.¹¹

The aim of this study was to report the prevalence, clinical signs, and therapeutic modalities for ocular rosacea in our country and attempt to identify which skin phenotypes are associated with more severe ocular disease. We also report two cases of the coexistence of rosacea and ocular cicatricial pemphigoid (OCP).

Materials and Methods

A descriptive, observational, retrospective, and cross-sectional study was performed. All voluntary adult patients of both sexes who were previously diagnosed with rosacea by a trained dermatologist in our institution and provided informed consent to participate were included consecutively. Patients with ocular or systemic pathology other than rosacea that was associated with diminished visual acuity or dry eye disease and/or had required any ocular surgical treatment were excluded. Contact lens wearers were also excluded from the study. All patients meeting the inclusion criteria were evaluated by a cornea and ocular surface specialist in the Ophthalmology Division of the Hospital de Clínicas "José de San Martín" in Buenos Aires between August 31, 2017 and May 31, 2018. The project was approved by the Ethics Committee of the Hospital de Clínicas of the University of Buenos Aires (date: 16.09.2015) and conducted in accordance with the guidelines of the Declaration of Helsinki (Fortaleza 2013).

The age and gender of every admitted patient were recorded. According to the most prevalent skin signs in each case, the patients were classified as having erythematotelangiectatic, papulopustular, or phymatous rosacea. A complete ophthalmological exam was performed, including best corrected visual acuity and slit-lamp biomicroscopy. A 1% sodium fluorescein solution was used to stain the tear film. First, tear film break-up time (TBUT) was measured. A TBUT longer than 10 seconds was considered normal, less than 10 seconds was noted as diminished TBUT. Each eye was measured three times and the results were averaged. Afterwards, fluorescein corneal staining was assessed with a standardized 4-point scale (0: none, 1: mild, 2: moderate, 3, severe). Meibomian gland function was evaluated in the upper and lower lid based on the expressibility of secretions upon digital compression of an area including five gland orifices. The results were classified on a 4-point scale according to the number of glands expressing meibum (0: all five glands, 1: three to four glands, 2: one to two glands, 3: zero glands).

A decrease in visual acuity due to corneal complications related to rosacea (corneal thinning, scarring, infiltrates, and neovascularization) was considered an indicator of more severe ocular involvement. Patients were divided into those with and without ocular rosacea. All patients who presented with

palpebral erythema and telangiectasias were classified in the ocular rosacea group.

Statistical Analysis

The groups were compared using chi-square or Fisher's t-test for categorical variables and Student's t-test or Mann-Whitney U test for numerical variables. A p value <0.05 was used to evaluate statistical significance.

Results

A total of 102 eyes of 51 patients with a dermatological diagnosis of rosacea were analyzed. The more affected eye of each patient was selected for statistical analysis; in cases where the degree of involvement was the same, the right eye was selected. The study patients were predominantly female (84.2%) and the average age at presentation was 50 years (range: 18-84).

Ocular signs of rosacea were detected in 38 patients (74.5%). Slit-lamp biomicroscopy in these patients showed lid margin erythema and telangiectasia (100%), MGD (94.7%), anterior blepharitis (73.7%), chalazia (23.0%), corneal neovascularization (10.5%), peripheral corneal infiltrates (10.5%), keratitis (7.9%), corneal ulcer (7.9%), and scarring (7.9%) (Table 1). Fifteen patients had decreased visual acuity due to rosacea-related complications such as leukoma and corneal neovascularization; 3 of them (7.9%) required keratoplasty. Interestingly, among these patients, those who had the lowest visual acuity presented with dermatological signs of papules and pustules ($p=0.023$); and rhinophyma ($p=0.017$). Two patients who presented with subepithelial fibrosis and fornix foreshortening were diagnosed as having OCP by immunohistopathological analysis of conjunctival specimens.

The most commonly used treatments were artificial tears (65.8%), oral doxycycline (60.5%), corticosteroid-antibiotic ointment (57.9%), and lid hygiene (39.5%). However, 7.9% of patients with ocular rosacea required a corneal transplant due to decreased visual acuity related to corneal complications.

Case 1

An 18-year-old woman presented with skin rosacea showing papules and pustules (Figure 1). Ophthalmological examination revealed a visual acuity of counting fingers in both eyes due to bilateral corneal neovascularization and leukoma. Slit-lamp biomicroscopy also showed intense blepharitis and MGD. Treatment with oral doxycycline, topical ciprofloxacin/dexamethasone ointment, and artificial tears was initiated. One month later, systemic and local involvement was stabilized and keratoplasty was performed in both eyes. Systemic treatment with oral doxycycline and corticosteroids was maintained for 6 months. Eighteen months after keratoplasty, the right eye developed mild graft rejection that responded well to topical prednisolone.

Case 2

A 22-year-old woman presented with skin rosacea including papules, pustules, and rhinophyma (Figure 2A). Ophthalmological evaluation showed a best corrected visual

Table 1. Comparison between group 1 (with ocular rosacea) and group 2 (rosacea without ocular involvement)			
	Group 1 (n=38)	Group 2 (n=13)	p
Males, n (%)	6 (15.8)	1 (7.7)	0.662
Age (years), mean (range)	50 (18 -84)	41 (19-64)	0.086
Erythema and telangiectasia, n (%)	38 (100)	0 (0)	0
Meibomian gland dysfunction, n (%)	36 (94.7)	11 (84.6)	0.266
Blepharitis, n (%)	28 (73.7)	4 (30.8)	0.008
Chalazia, n (%)	9 (23.7)	6 (15.8)	0.414
Keratitis, n (%)	3 (7.9)	0 (0)	0.405
Peripheral corneal infiltrates, n (%)	4 (10.5)	0 (0)	0.295
Corneal ulcer, n (%)	3 (7.9)	0 (0)	0.405
Neovascularization, n (%)	4 (10.5)	0 (0)	0.295
Corneal scarring, n (%)	3 (7.9)	0 (0)	0.295

acuity of 20/40 in the right eye and 20/60 in the left eye. Slit-lamp biomicroscopy revealed intense MGD and blepharitis, corneal neovascularization, and scarring (Figure 2B, C). Initially, treatment with oral doxycycline, topic ciprofloxacin/dexamethasone ointment, and artificial tears was initiated. Due to a poor response to treatment, a short course of oral corticosteroids was needed to control the disease. The patient now presents periodic relapses that respond well to oral doxycycline 100 mg/day in 30-day courses.

Case 3

A 65-year-old man presented with intense skin rosacea including papules, pustules, and rhinophyma (Figure 3A). Ophthalmological examination revealed a best corrected visual acuity of counting fingers in both eyes. Slit-lamp biomicroscopy showed blepharitis, MGD, fornix foreshortening, conjunctival scarring, corneal neovascularization, and leukoma in both eyes. Conjunctival immunohistochemistry revealed OCP. Systemic immunosuppression with methotrexate was initiated. Rosacea was treated with oral doxycycline, topical antibiotic/dexamethasone ointment, cyclosporine 0.05%, and preservative-free artificial tears. Keratoplasty was performed in the left eye. No graft rejection was observed in the first 5 years of follow-up (Figure 3B).

Discussion

In this study we present a series of 51 patients with a clinical diagnosis of rosacea who were evaluated in the Ophthalmology Department of the Hospital de Clínicas "José de San Martín". Currently, there is no gold standard for the diagnosis of ocular rosacea and every patient with cutaneous rosacea may have some degree of ocular compromise.¹² Because erythema is considered a diagnostic sign of skin disease and it is usually accompanied by telangiectasias in the lid margin, all patients in our study with palpebral erythema and telangiectasias were classified in the ocular rosacea group. We found the prevalence of ocular signs to be 74.5%, similar to that reported in other studies.⁴ The mean age at presentation for rosacea was 50 years, also similar to the literature,¹¹ and most patients were women. The most common

ocular signs were erythema and telangiectasias of the lid margin, MGD, and anterior blepharitis. More serious manifestations of ocular involvement such as keratitis, corneal infiltrates, ulcers, leukomas, and corneal neovascularization occurred with low frequency. These results are consistent with the findings in other series.^{4,5,11}

Severe dry eye can be caused by MGD. Meibomian gland loss in rosacea can be assessed objectively with meibography. Atrophy



Figure 1. Woman with skin rosacea presenting with papules and pustules

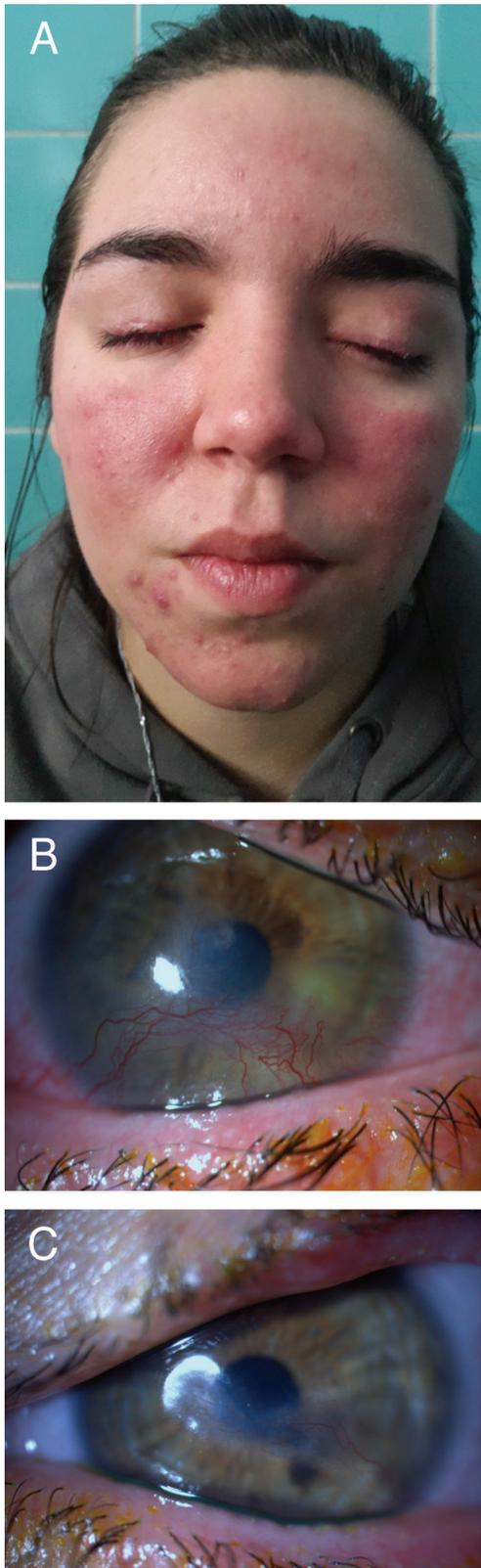


Figure 2. Woman with skin rosacea presenting with papules, pustules, and mild rhinophyma (A). Both the right eye (B) and left eye (C) showed intense blepharitis, meibomian gland dysfunction, corneal scarring, and neovascularization

has been correlated to impaired gland function, including diminished TBUT and an altered tear lipid layer pattern. Meibography using infrared light technology allows for the detection of gland dropout, shortening, dilation, and distortion, and is very important in the diagnosis and follow-up of patients with MGD.^{13,14} Unfortunately, it was not possible in our center.

In cases of severe corneal compromise producing low visual acuity or spontaneous perforation, keratoplasty may be needed. Akpek et al.¹¹ published a series of 131 cases in which 6 patients underwent corneal transplantation (4.6%). In our study, 3 of 38 patients (7.9%) in the ocular rosacea group required keratoplasty. Interestingly, one of those patients also showed signs of cicatricial conjunctivitis and a conjunctival biopsy confirmed OCP. Such an association might have been partly responsible for the need for keratoplasty in that particular patient.

Ocular rosacea can be accompanied by signs of chronic cicatricial conjunctivitis and is a well-known cause of pseudopemphigoid. Several studies describe pseudopemphigoid

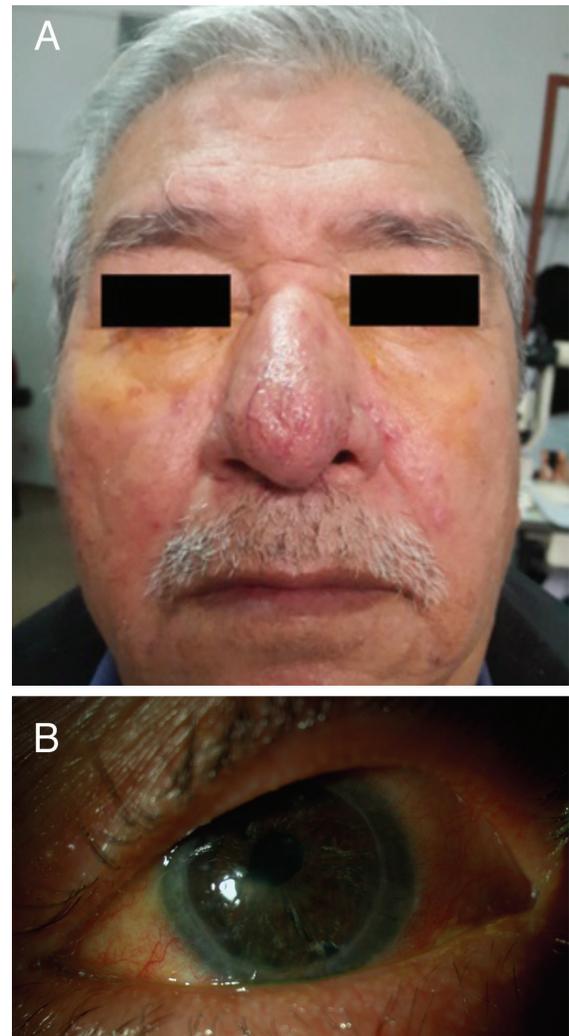


Figure 3. Man showing signs of severe skin rosacea with papules, pustules, and rhinophyma (A). Keratoplasty was performed in the left eye, which shows a paracentral leukoma (B)

associated with rosacea.^{11,15,16} Furthermore, Thorne et al.¹⁷ identified rosacea as responsible for 20% of cases, with immunohistopathological confirmation. We identified two cases of associated OCP in patients with ocular rosacea. This suggests that these two diseases can coexist. OCP is an autoimmune disease that involves a type 2 hypersensitivity reaction. Both environmental factors and genetic susceptibility might be involved in loss of tolerance to the components of the basement membrane zone.¹⁸ As has been proposed for other diseases that may coexist with OCP, ocular surface injuries related to rosacea could expose basement membrane epitopes of damaged conjunctiva, which might act as neoantigens that precipitate the autoimmune response.¹⁹ Although further research is needed, all patients who present with conjunctival fibrotic changes should be thoroughly analyzed to rule out OCP.

To date, a reliable correlation between the severity of skin findings and ocular involvement has not been established.¹² However, Keshtcar-Jafari et al.²⁰ reported an association between facial erythema and ocular involvement. Furthermore, Whitfield et al.²¹ suggested that there would be a correlation between the presence of *Staphylococcus epidermidis* and ocular compromise because the same pathogen was isolated on the lid margin and in the pustules of patients with papulopustular rosacea. We found a significant association between the severity of ocular findings, assessed as a diminished visual acuity due to rosacea corneal involvement, and the presence of rhinophyma, papules, and pustules. As it has been mentioned before, rosacea manifests with relapses and remissions. Special attention should be given to ocular involvement during exacerbations, as progression of skin disease could lead to more severe ocular damage. Early referral to the ophthalmologist in these cases might prevent visual loss.

As in other case series,^{5,7} the most commonly used treatments included artificial tears (65.8%), oral doxycycline (60.5%), and antibiotic ointment combined with topical corticosteroids (57.9%).

Study Limitations

The main limitation of our study is the relatively small number of patients.

Conclusion

Ocular compromise in rosacea is common. Our study shows that there might be a relationship between the severity of ocular involvement and specific cutaneous signs. On the other hand, rosacea and ocular mucous membrane pemphigoid may coexist. In patients presenting with conjunctival fibrotic changes, we believe that a diagnostic biopsy is imperative.

Ethics

Ethics Committee Approval: The project was approved by the Ethics Committee of the Hospital de Clínicas of the University of Buenos Aires (date: 16.09.2015).

Informed Consent: It was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: F.L.S., F.C., P.C., Concept: F.L.S., F.C., P.C., Design: F.L.S., F.C., P.C., Data Collection or Processing: F.L.S., F.C., P.C., Analysis or Interpretation: F.L.S., F.C., P.C., Literature Search: F.L.S., F.C., P.C., Writing: F.L.S., F.C., P.C.

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