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Ocular Rosacea

Aysun Sanal Dogan

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Abstract

Acne rosacea (AR) is a chronic cutaneous inflammatory disease of the midface. Ocular involvement occurs in 30–70% of patients. Although the incidence of this disease is seen highest between the ages of 30 and 50 years, it can also develop during childhood. The diagnosis depends on clinical findings such as meibomian gland dysfunction (MGD), conjunctival hyperemia, and corneal vascularization, and untreated cases can progress and lead to vision loss. Pathogenetic factors can be the altered the immune system, colonization of microorganisms, inflammation, abnormalities of sebaceous, and meibomian glands, environmental factors, and vascular dysregulation. Differential diagnosis from other ophthalmologic and dermatologic diseases is important. Management requires an interdisciplinary approach with a step-wise treatment algorithm. Patients should be informed about the chronic course of the disease and avoid the exacerbating factors. Caring about the lid hygiene and use of non-preserved artificial eye tears, topical ointments including antibiotics, anti-inflammatory agents are used when necessary. However, the mainstay of the therapy is the use of oral antibiotics for a long period. Surgical interventions may be needed in cases with a vision-threatening condition. During the long-term treatment period and disease course, the complications of medications should also be considered cautiously and patient should be followed up routinely.

Keywords: ocular rosacea, dry eye, meibomian gland, meibomian gland dysfunction, treatment

1. Introduction

Acne rosacea (AR) is the chronic inflammatory disease of skin typically involving the cheeks, nose, chin, and central forehead. The dermatological findings are transient or persistent erythema, papules, pustules, and telangiectasia. During the chronic course, these findings show exacerbations and remissions that may end up with progression. This dermatologic condition has been classified by National Rosacea Society into four subtypes based on the clinical fea-

tures: (1) erythematotelangiectatic rosacea, (2) papulopustular rosacea, (3) phymatous rosacea, and (4) ocular rosacea [1]. Flushing, chronic inflammation, and fibrosis are present in dermatologic course. The presence of one of the findings: flushing, non-transient erythema, plaque, dry appearance, edema, papules-pustules, and telangiectasia on the face with burning sensation, ocular manifestations, and phymatous changes is indicative of rosacea, and these symptoms are graded as mild, moderate, and severe [2]. Ocular manifestations are defined as one of the secondary criteria [1].

Under the circumstances of existing acne rosacea, the diagnosis of ocular rosacea (OR) is made by the presence of inflammation of the ocular surface, accompanying redness, burning, and itching symptoms of the eye. The diagnosis is confirmed by the presence of corneal infiltration with meibomian gland inflammation, and accompanying skin findings of rosacea [3].

2. Epidemiology

AR is usually seen between ages of 30 and 50 years [4, 5]. The prevalence is reported from 4 to 22% that is more frequent in fair-skinned people [5–8]. The OR starts to be detected approximately 10 years after the diagnosis of AR, with an increasing incidence between ages of 40 and 50 years [5]. The ocular involvement occurs in 58–72% and interestingly the ocular signs may precede in 20% of rosacea patients [9, 10]. Because of mild cutaneous manifestations, the ocular findings may be underestimated in children. Therefore, the diagnosis is delayed with more ocular complications. In a case series, it was shown that only two of six children with ocular rosacea demonstrated cutaneous rosacea findings [11].

Although AR affects women more than men, ocular involvement is to be seen in both sexes equally [5, 12]. There is a family history in 15–30% of cases [13, 14]. Hence, with a suspicion of family history, the children should be followed up closely and should be kept in mind that the condition tends to progress in adulthood [15].

3. Pathogenesis

Although AR has no proven cause, scientific studies showed that there is dysregulation of vascular, immunologic, and nervous systems [16, 17]. Ocular surface is the mainly affected area with OR. Ocular surface compromises cellular components of the palpebral and bulbar conjunctiva such as corneoscleral limbus, cornea, eyelid margins, eyelashes, and tear film [18].

3.1. Altered immune system

Altered immune system may be one of the factors. It was postulated that a type IV hypersensitivity reaction may be responsible for the conjunctival inflammation in OR in which the reactant is unknown [19, 20].

3.2. Colonization of microorganism

Demodex folliculorum is a saprophytic mite that is found in normal flora of the skin. There are studies demonstrating that the Demodex density increased in rosacea patients [21, 22].

Bacillus oleronius serum immunoreactivity was detected in ocular rosacea patients. Its proteins cause high immune reactions [22, 23].

Staphylococcus epidermidis and *Propionibacterium acnes* that are found commonly in lid flora are accused microorganisms for their production of high levels of bacterial lipases [24].

In a study, *Chlamydia pneumoniae* antigen was detected in 40% of skin biopsies patient with rosacea [25].

Moreover, *Helicobacter pylori* IgG antibodies were found in 81% of the acne rosacea patients with dyspepsia, but there is a debate whether this is a coincidence or not [26]. The proteins produced by these pathogens might be responsible for the some aspects of rosacea.

The increased amount of free fatty acids produced by meibomian glands causes tear film instability and irritates the ocular tissues [27]. This increase may be due to biochemical abnormality of the meibomian gland secretions or lipolytic exoenzymes of bacteria which degrade lipids into free fatty acids [28].

3.3. Inflammation

OR was found to be associated with the increased tear fluid levels of several inflammatory mediators such as interleukin-1 (IL-1) and gelatinase B activity [29]. Matrix metalloproteinases (MMP), interferon-alpha (IFN- α), and inflammatory cytokines seem to be an important component of pathophysiology [30].

The meibomian glands of rosacea patients cause keratinization of epithelial cells, end up with thickening of secretions, plugging of the orifices, and trapping of the secretions [31].

3.4. Environmental factors

Many rosacea patients are aware of some factors that exacerbate their symptoms. Although these triggering factors differ for each patient: alcohol, sunlight, wind, temperature extremes, hot, and spicy foods, vigorous exercise, hot baths, medications that dilate blood vessels, menopause, and emotional factors (stress, anger, and embarrassment) can also play role in the pathogenesis [32–34].

3.5. Genetics

Rosacea is associated with familial predisposition [35]. In a study conducted in twin pairs, rosacea contribution has been reported equally by genetic and environmental factors [36]. The genetic predisposition showed single nucleotide polymorphisms in HLA-DRA and BTNL2 genes that support the concept of a genetic component for rosacea [37].

3.6. Vascular dysregulation and neurologic system

There is vascular dilatation and telangiectatic vessels and increased blood flow, causing erythema, flushing, and neovascularization [5, 34, 38], which is probably under control of the sympathetic system [39].

4. Diagnosis

The diagnosis of both dermatological rosacea and ocular rosacea is clinical. There is no single-specific test—even skin biopsy—to confirm the diagnosis.

Ocular involvement is varied and non-specific. Most of the patients refer to ophthalmologist with dry eye symptoms (Table 1). No correlation exists between the severity of the ocular manifestations and that of the skin lesions. However, in patients with increased flushing, ocular rosacea prevalence is higher [40].

Although rosacea is uncommon in pediatric cases, it deserves attention due to undiagnosed ocular rosacea that is common with severe ocular complication [41]. History of triggering factors should be investigated and dermatologist consultation is required.

4.1. Clinical feature

Both eyes are usually affected simultaneously, but unilateral or sequential involvements can also occur.

The primary and the starter of the ocular involvement is the meibomian gland dysfunction (MGD) [42]. Ghanem et al. reported that the most common ocular signs in patients with rosacea from the ophthalmologic clinic were meibomian gland dysfunction (MGD) in 85.2%, lid margin telangiectasias in 53.4%, blepharitis in 44.3%, and interpalpebral hyperemia in 40.9%. Accordingly, patients from the dermatology clinic were reported to exhibit MGD in 27.3%, chalazion/hordeolum, lid margin telangiectasia in 18.2%, anterior blepharitis in 13.6%, and pinguecula in 13.6% [9] Vision loss is a rare but devastating complication [43]. OR has been graded as mild, moderate, and severe (Table 2) [2].

Ocular symptoms
– dryness sensations (burning and stinging, feeling of a having foreign body sensation in the eye)
– irritation
– itching
– redness
– sensitivity to light (photophobia)
– tearing
– red and swollen eyelids
– blurry or decreased vision

Table 1. Ocular symptoms of the ocular rosacea patient.

Grade	Involved areas	Signs and symptoms	Recommended treatment
Mild	Eyelid margin, meibomian gland	Mild itching and dry eye sensation Fine scaling and erythema of eyelid margins Mild conjunctival hyperemia	Topical treatment only
Moderate	Ocular surface	Moderate burning, tearing, foreign body sensation Eyelid margin irregularities, erythema and telangiectasia Prominent conjunctival hyperemia, ciliary injection Hordeolum and chalazion formation	Topical, systemic treatment
Severe	Corneal involvement and decreased vision	Pain, sensitivity to light, blurred vision Severe conjunctival inflammation, madarosis and trichiasis Corneal involvement	Topical, systemic, surgical treatment

Table 2. Grading of ocular rosacea [2].

4.2. Symptoms

Feeling of dryness, irritation symptoms with burning and stinging and feeling of having foreign body sensation in the eye are common. Blurry vision, redness, sensitivity to light (photophobia), tearing, itching, red, and swollen eyelids are the other encountered symptoms.

4.3. Signs

It is not rare that the symptoms of the patient are not proportional with the ocular findings. Reduced fluorescein tear breakup time, punctate staining on the cornea, and bulbar conjunctiva (**Figure 1**). Superficial punctate keratopathy (due to tear film instability), dry eye disease, blepharitis, styes, MGD, eyelid inflammation-collarettes, telangiectasis, conjunctival hyperemia, conjunctival scarring, punctate epithelial keratitis, corneal infiltrate/vascularization, corneal thinning, corneal astigmatism, corneal ulceration, phlyctenules, phlyctenular keratitis, limbal pannus, episcleritis, scleritis, corneal melting, and perforation, iritis, periorbital edema, recurrent chalazia, pannus, neovascularization, trichiasis (**Figures 1–5**) [43–46].

4.3.1. Eyelid

The lipid layer produced by meibomian glands stabilizes the tear film and prevents evaporation. Abnormality of this function is the primary cause of the blepharitis and evaporative-type dry eye. Dry eye can be detected by decreased tear breakup times. There is inflammation, dilatation, and occlusion of the meibomian glands [31]. With pressure to eyelid margins, there is hardness to express the secretion, and usually occluded by toothpaste-like material namely meibomana. Hordeolum and chalazion are the signs of focal inflamed obstructive MGD. In chronic course, there will be telangiectatic vessels around the orifices of the meibomian glands. At the end, the ducts are fully keratinized and disappears leading the meibomian gland dropout.



Figure 1. Ocular rosacea patient with irregular ocular margin, conjunctival hyperemia and trichiasis.

4.3.2. *conjunctiva*

Conjunctival hyperemia is the common finding. Hyperemia is mostly obvious in interpalpebral area. In 9% of OR, there is also conjunctival scarring [47].

4.3.3. *cornea*

Disease starts with inferior punctate epitheliopathy. Superficial vascularization of the peripheral cornea (especially triangular in shape and extending from inferior cornea) develops in



Figure 2. Ocular rosacea with sterile corneal infiltrate, lid telangiectasia, meibomian gland occlusion and foamy secretion.

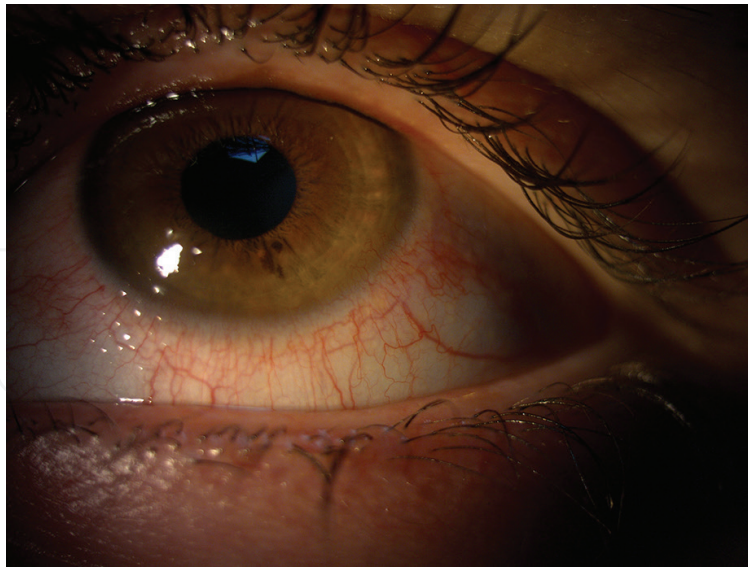


Figure 3. Bulbar interpalpebral conjunctival hyperemia with fine corneal vascularization.

untreated cases. In case of recurrent epithelium defects, one should be suspicious of OR also. Inflammatory episodes will end up with devastating problems, such as corneal scarring, thinning even perforation and sight threatening keratitis [48–51].

4.4. Ocular tests and imaging

Tests of evaporative dry eye are altered in OR. Tear osmolarity values, Ocular surface disease index (OSDI) questionnaire and corneal staining scores were significantly higher, and

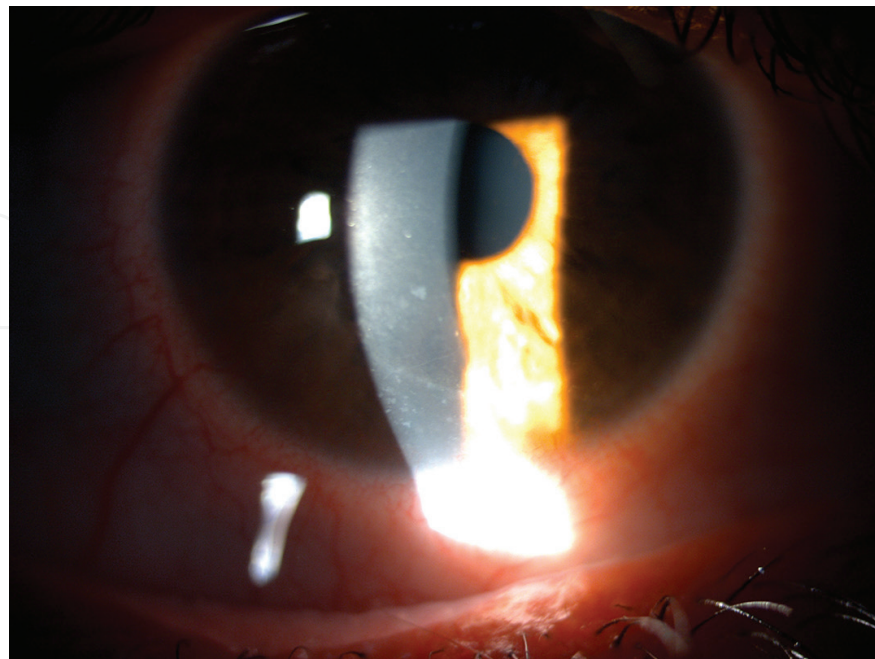


Figure 4. Ocular rosacea with severe dry eye symptoms and inferior punctate epitheliopathy.

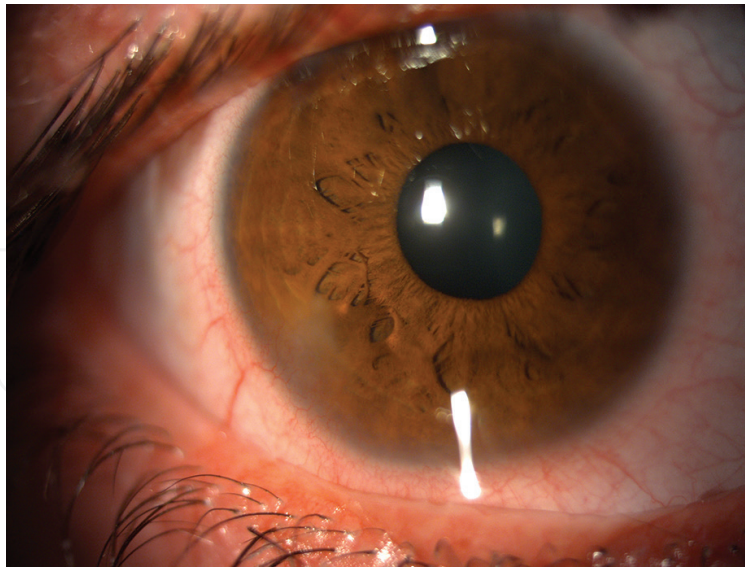


Figure 5. Corneal haze inferotemporally signifying healed corneal involvement of ocular rosacea.

Schirmer-I test and fluorescein tear breakup time were significantly lower, which all confirms tear hyperosmolarity and tear film dysfunction [52].

Dry eye in rosacea patients can also be diagnosed by tear meniscus measurement with optical coherence tomography (OCT) with considerable sensitivity and specificity [53]. Central corneal thickness, corneal hysteresis and corneal resistance factors were all significantly decreased in OR patients when compared to healthy controls [54]. Patients with OR show significant meibomian gland dropout which can be demonstrated by meibography (**Figure 6**)

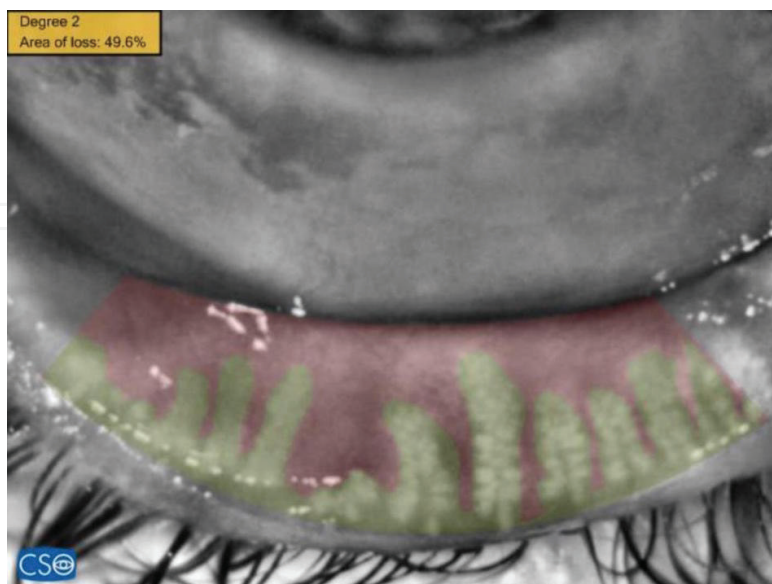


Figure 6. Ocular rosacea. Meibography, meibomian dropout.

[31, 42]. *In vivo* confocal microscopy findings revealed inflammatory changes of ocular surface and even Demodex infestations on eyelids [55, 56].

5. Differential diagnosis

5.1. From dermatological diseases

In patients with suspicion of OR, if facial dermatologic inflammatory changes exist, clinician would be aware of three main differential diagnosis [57]. These are as follows:

Acne vulgaris: The presence of comedones—which does not exist in rosacea—in young patients direct the clinician to diagnosis of acne vulgaris.

Seborrheic dermatitis: In seborrheic dermatitis, facial erythema is accompanied by yellowish scaling and prominent dandruff.

Perioral dermatitis: There is perioral involvement without flushing or telangiectasia.

5.2. From ophthalmological diseases

Ocular findings must be differentiated from the other causes of dry eye.

Corneal involvements must be differentiated from herpetic or bacterial keratitis and recurrent epithelial defects [48, 58, 59].

All forms of conjunctivitis are in differential diagnosis. Due to chronic course and leading to conjunctival scarring, chlamydial conjunctivitis deserves attention.

In severe OR, which ends up with inferior thinning and irregular astigmatism, it may resemble to keratoconus [51].

6. Management

For an effective therapeutic strategy, an interdisciplinary collaboration is needed between ophthalmologist and dermatologist. The stepwise approach is recommended.

- Inform patient about the chronic nature of their disease and requirement for regular follow-up.
- Avoid triggering and exacerbating factors. It might be advised to keep a daily diary to figure out triggering factors.
- Avoid wearing contact lenses and eye makeup when the symptoms are exaggerated.
- Lid hygiene: Hot compressing and MG expressions by mechanical massage to lids, lid hygiene cleaning solutions, eyelid scrubs massage to the tarsal plate [60]. This is the main approach and must be recommended to all OR patients

- Lubricants: Lubricants are used to decrease inflammatory mediators, and to provide symptomatic relief. Non-preserved artificial tears are recommended with a patient-individualized dosage [61]. The initial high dosages might be tapered gradually. OR is usually mild and responds well to lid hygiene and lubricants, but must be advised to do regularly to avoid exacerbations of symptoms.
- Topical antibiotics: Azithromycin 1.5% eye drops are effective for MGD treatment even with phlyctenular keratoconjunctivitis complicating OR [62, 63]. It has an anti-inflammatory effect as well as an antimicrobial effect. Topical antibiotic ointments (fucidic acid and metronidazole gel applied to lid margins), especially in the nighttime, are also effective to restore the flora.
- Mainstay of the treatment is the use of systemic antibiotics. Due to relapses, maintenance treatment may be 6 months. Low doses with longer duration of the antibiotic usage must be preferred to benefit from the anti-inflammatory effect without inducing resistance and other side effects.
 - Systemic tetracycline/doxycycline/minocycline shows the therapeutic effects by decreasing lid flora, inhibiting collagenase activity which prevents corneal thinning, inhibiting inflammatory mediators (i.e. MMP), decreasing concentration of free fatty acids [64–66].
 - Clarithromycin are also effective to *H. pylori* [67].
 - Metronidazole has anti-inflammatory, anti-microbial, anti-parasitic, and immunosuppressive effects [68].
 - Azithromycin 3 times per week for 4 weeks [69].
 - Erythromycin is appropriate for children <8 years old to avoid the untoward effects of tetracycline [70].
- Topical anti-inflammatory agents: Topical corticosteroids suppress the exacerbation episodes and are effective in prevention of the recurrent corneal erosions when used in combination with systemic doxycycline [71]. The application would be tapered and stopped after the symptomatic relief. Topical steroids should be used cautiously, minimal dose with minimal duration, under the supervision of the ophthalmologist. Instead of steroids, topical cyclosporine (with 0.05% concentration) might be the choice for a longer period of treatment [72].
- Dietary intervention with omega-3 fatty acids for 6 months is effective in decreasing the dry eye symptoms and signs in ocular rosacea [73].
- Surgical: Intraductal meibomian gland probing is shown to be a promising technique to improve dry eye symptoms related with OR [74]. Epilation of trichiatric lashes will eliminate the mechanical insult to ocular surface.

In cases of severe corneal involvement, surgical options are indicated [49]. Progressive epitheliopathy unresponsive to topical treatment with hazy epithelium extending centrally,

indicating limbal stem cell insufficiency, is treated with limbal stem cell transplantation [75]. Thinning of the cornea and threatening perforation are treated with conjunctival flaps or amniotic membranes [43]. Little corneal perforations may benefit from cyanoacrylate glues. Minority people with untreated or resistant to treatment may need keratoplasty at the end of long-term OR [49].

Rosacea naturally waxes and wanes. However, because the damage from rosacea can be progressive, the long-lasting use of therapy has advantages. Due to the lack of prospective controlled studies, the optimum modality and duration for treatment and prevention of OR recurrence remain unclear. The duration of the treatment depends on the ophthalmologist's decision and the severity of the ocular involvement. There is a consensus to give treatment for several months, and tapering the doses within follow-ups.

7. Complications

Long-standing OR will end up with irregular eyelid margins and misdirected eyelashes (trichiasis). Untreated corneal involvement will lead to vision loss.

The long-term use of topical steroids may cause increased intraocular pressure, cataract formation, corneal thinning, and exacerbation of underlying herpes. Chronic use of systemic antibiotics makes necessary to control the hepatic functions.

Although it is recommended to use low dose with a long duration, clinician should be cautious about the potential side effects of oral tetracycline as gastrointestinal discomfort, vaginal yeast infections, photosensitivity, and decreased effectiveness of oral contraceptives. It is not appropriate for the children <8 years old, because of its accumulation in bone, color changes in teeth, and interfering enamel development [76].

Oral isotretinoin, which has both anti-inflammatory and immunomodulatory properties, has been used as a treatment for severe rosacea, particularly phymatous presentation by dermatologists [77]. In these cases, routine ophthalmologic follow-up should be recommended since the retinoids may cause blepharoconjunctivitis, worsening telangiectasias and may lead to severe keratitis [78].

8. Conclusion

Rosacea, mainly being a dermatological disease, may show ocular manifestations that sometimes may have severe consequences. The diagnosis mainly depends on the clinical findings and suspicion of the clinician. The evaluation and management should be performed by a collaborative approach by both dermatologist and ophthalmologist. The management should have a stepwise structure. The complications of both the disease and the treatment should be considered during the disease course.

Author details

Aysun Sanal Dogan

Address all correspondence to: asanaldogan@gmail.com

Ophthalmology Department, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

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