

# Botulinum Toxin Injection for the Management of Refractory Filamentary Keratitis

Koray Gumus, MD, FEBOphth; Seongmu Lee, MD; Michael T. Yen, MD; Stephen C. Pflugfelder, MD

**Objective:** To evaluate the efficacy of onabotulinumtoxinA injection for the treatment of refractory filamentary keratitis.

**Methods:** A retrospective review of treatment response of 33 eyes of 17 patients with filamentary keratitis resistant to conventional medical therapy who were treated with onabotulinumtoxinA injection was performed. Ocular surface findings, symptom improvement, and the number and location of filaments before and after the injections were recorded. All eyelids were injected subcutaneously with onabotulinumtoxinA (10 U/0.1 mL). All treatments were performed in accordance with an individualized treatment plan using precise localizing treatment maps, with adjustments to dosage based on treatment response.

**Results:** Objective and subjective improvement was noted after the initial onabotulinumtoxinA injection in all patients. Filaments completely resolved after the onabotulinumtoxinA injection in 29 eyes (88%). In 20 of these

eyes, filaments and punctate fluorescein staining resolved, whereas in 9 eyes, filaments resolved but punctate fluorescein staining persisted. Three eyes (9%) had partial improvement: 2 residual microfilaments were noted in one eye and 1 in the other eye. In 1 eye, filaments resolved after initial and subsequent injections but recurred within 8 weeks of each injection. Although 14 treated eyes (42%) showed sustained improvement after 1 onabotulinumtoxinA injection, additional injections were necessary in 19 eyes (58%) during the follow-up period because of the recurrence of symptoms and filaments on the cornea.

**Conclusions:** OnabotulinumtoxinA injection should be considered an effective option for treating refractory filamentary keratitis. Because of the likelihood of recurrence, serial onabotulinumtoxinA injections may be necessary in some cases.

*Arch Ophthalmol.* 2012;130(4):446-450

**F**ILAMENTARY KERATITIS IS A chronic and recurrent disorder of the cornea characterized by the formation of epithelial and mucous filaments on the corneal surface.<sup>1,2</sup> This condition is more common in women and elderly individuals and may be seen either unilaterally or bilaterally, depending on the underlying cause. Patients with filamentary keratitis generally experience foreign-body sensation, chronic pain, tearing, mucoid discharge, photophobia, and blepharospasm.

Even though filamentary keratitis most often accompanies dry eye, especially aqueous tear deficiency, it may also be associated with various other ocular surface diseases, including superior limbic keratoconjunctivitis, viral keratoconjunctivitis, prolonged patching after any ocular surgery, penetrating keratoplasty, ptosis, recurrent corneal erosion, neurotrophic keratitis, and bullous keratopathy.<sup>1,3-5</sup>

Conventional treatment of filamentary keratitis involves mechanical removal of the filaments and therapies to decrease inflammation and lubricate the ocular surface. Unfortunately, conventional treatment modalities may not produce sufficient improvement in some cases, leading ophthalmologists to explore the effectiveness of alternative treatments. The best example of an alternative treatment was the successful use of blepharoptosis surgery to treat filamentary keratitis.<sup>6,7</sup> The purpose of our study was to determine whether injection of onabotulinumtoxinA (BOTOX; Allergan Pharmaceuticals), another alternative treatment modality, might effectively eliminate filaments in cases that are refractory to conventional therapy.

## METHODS

This retrospective medical record review was approved by the Baylor College of Medicine In-

**Author Affiliations:** Cullen Eye Institute, Baylor College of Medicine, Houston, Texas. Dr Gumus is now with the Department of Ophthalmology, Erciyes University Medical Faculty, Kayseri, Turkey.

stitutional Review Board. The research protocol adhered to the tenets of the Declaration of Helsinki for clinical research.

## STUDY POPULATION

The medical records of 17 patients (33 eyes) with a history of filamentary keratitis resistant to conventional medical therapy were reviewed. Information regarding the type of tear dysfunction, previous treatments, number and location of filaments, and type and outcome of therapy were recorded.

## BOTULINUM TOXIN INJECTION

OnabotulinumtoxinA was reconstituted with sterile, nonpreserved normal saline to achieve a concentration of 10 U/0.1 mL. The area to be injected was prepared with isopropyl alcohol. All injections were administered into the pretarsal orbicularis near the eyelid margin of the upper and lower eyelids. Patients were usually given 2 injections into each eyelid with a dosage of 2 to 5 U of onabotulinumtoxinA per eyelid. All treatments were performed in accordance with an individualized treatment plan using precise localizing treatment maps, with adjustments to dosage based on treatment response. Patients were reevaluated at 6- to 12-week intervals, and injections were administered again at these visits, if needed. After the injection, all patients continued with their previous medical treatment during the follow-up period.

## RESULTS

The **Table** summarizes demographic information, clinical features, and prior treatment of patients who received onabotulinumtoxinA injection. The mean (SD) age of the 17 patients treated (13 women and 4 men) was 65.3 (12.5) years (range, 42-89 years). All patients were followed up at regular intervals of 6 to 12 weeks after the injection. Relative to the first injection, mean follow-up duration was 26.8 months per eye (range, 1-45 months).

Objective and subjective improvement was observed after the initial onabotulinumtoxinA injection in all patients. Filaments completely resolved after either single or additional onabotulinumtoxinA injections in 29 eyes (88%). In 20 of these eyes, filaments and punctate epithelial fluorescein staining resolved; however, in 9 eyes, filaments resolved but punctate epithelial fluorescein staining was noted to persist. Only 3 eyes (9%) revealed partial healing; 2 had only 1 tiny filament and 1 had microfilaments. In the left eye of patient 3 (Table), filaments resolved after initial and subsequent injections but recurred within 12 weeks of each injection.

Although 14 treated eyes (42%) showed sustained improvement after 1 onabotulinumtoxinA injection, additional injections were necessary in 19 eyes (58%) during the follow-up period due to the recurrence of symptoms and corneal filaments. The mean (SD) number of injections was 3.9 (2.5) (range, 2-10). No significant adverse effects were found secondary to the injection of onabotulinumtoxinA in any patient during the follow-up period.

No significant correlation was found between the number of injections with age or the underlying cause of filamentary keratitis (Spearman correlation test,  $P = .60$ ).

Images taken before and 6 weeks after the initial onabotulinumtoxinA injection in a 76-year-old woman (patient 3) with filamentary keratitis, who had secondary Sjögren syndrome, are shown in the **Figure**. These images are representative of the outcome achieved with onabotulinumtoxinA injections. Recurrent filaments were noted 12 weeks after the first and second injections in the left eye, which had more severe keratoconjunctivitis sicca and photophobia.

## COMMENT

This study evaluated the efficacy of onabotulinumtoxinA injection in the treatment of refractory filamentary keratitis. Botulinum toxin is a neurotoxin that prevents the release of acetylcholine into the neuromuscular junction, resulting in paralysis of the injected muscle.<sup>8</sup> OnabotulinumtoxinA is a formulation of type A botulinum toxin that has been approved by the US Food and Drug Administration since 1989 for the treatment of essential blepharospasm and hemifacial spasm. We chose to use onabotulinumtoxinA in this study because of our extensive experience with the medication and our familiarity with the dosing, efficacy, and potential complications of the injections.

In our study, objective and subjective improvement was achieved in almost all of the treated patients. Filaments completely resolved after either single or multiple onabotulinumtoxinA injections in 29 eyes (88%). Because of the chronic and recurrent nature of this condition, additional onabotulinumtoxinA injections were necessary to maintain the treatment effect in most cases. Even though adverse events, including lack of effect, injection site reaction, eyelid ptosis, diplopia, or lagophthalmos, have been reported in the literature, no clinically significant adverse events were noted in our case series.<sup>9</sup>

Ideally, treatment of filamentary keratitis should target the underlying pathophysiologic mechanism. However, the exact pathogenesis of filament formation has not been established. Zaidman and colleagues<sup>2</sup> hypothesized that underlying causes lead to focal areas of basement membrane detachment. After this initial step, the shearing force of the eyelids contributes to the elevation of these epithelial foci with time.<sup>2</sup> Finally, the elevated epithelial foci bind with mucin strands and degenerated epithelial cells, forming long filaments.<sup>2</sup> Because the filaments are firmly attached to the underlying epithelium, each blink may result in epithelial tearing, ocular pain, and chronic inflammation, which, in turn, stimulates reflex blinking that leads to a vicious cycle on the ocular surface.<sup>3</sup> Therefore, breaking this vicious cycle is important for managing challenging cases of filamentary keratitis.

A treatment strategy involves eliminating the mucous filaments as thoroughly as possible and improving ocular surface health.<sup>3</sup> Filaments can be eliminated mechanically or pharmaceutically. Mechanical removal can be performed with jeweler's forceps<sup>10</sup> or a cellulose acetate filter.<sup>11</sup> Hypertonic saline<sup>12,13</sup> and mucolytic agents<sup>14</sup> have been successfully used in the treatment of filamentary keratitis.<sup>3</sup> Hypertonic saline is believed to promote

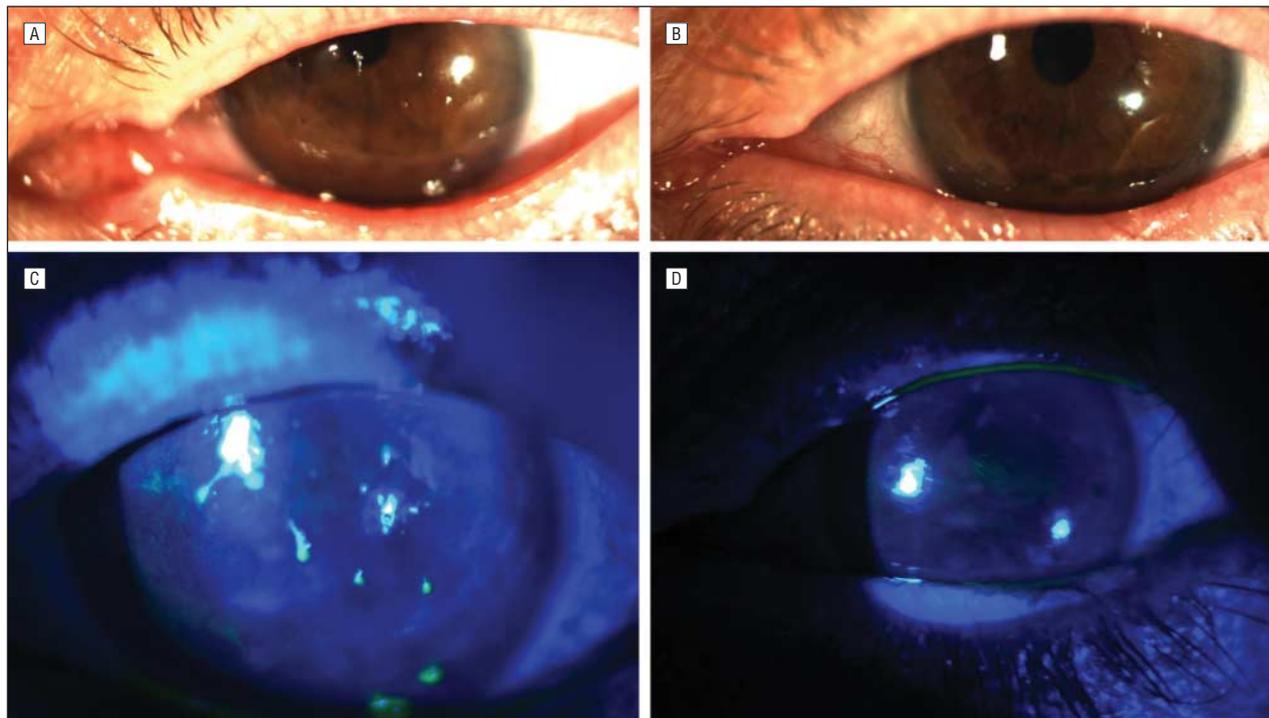
**Table. Demographic and Clinical Characteristics of Patients Who Received OnabotulinumtoxinA Injections**

Patient No./Sex/ Age, y and Eye	Diagnosis	Previous Treatment	No. of Injections	Response to Injection	Findings at Last Visit
1/F/59 Right	SS, SLK	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily)	1	Partial healing	1 Tiny filament
Left	SS, SLK		1	Complete healing	No filaments
2/F/89 Right	KCS, SLK	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily)	1	Complete healing	No filaments
Left	KCS, SLK		1	Complete healing	No filaments
3/F/76 Right	Second SS (RA)	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, PO, PT	2	Complete healing	No filaments
Left	Second SS (RA)		2	Initial healing and recurrence	6 Filaments
4/F/48 Right	KCS, second BS	AT, 0.05% cyclosporine emulsion, PO, oral doxycycline (20 or 50 mg twice daily)	4	Complete healing	No filaments
Left	KCS, second BS		4	Complete healing	No filaments
5/F/63 Right	KCS, second BS	AT, 0.05% cyclosporine emulsion	1	Complete healing	No filaments
Left	KCS, second BS		1	Complete healing	No filaments
6/F/68 Right	KCS, SLK, second BS	AT, oral doxycycline (20 or 50 mg twice daily), PT	2	Complete healing	No filaments
7/F/57 Right	KCS, second BS	AT, 0.05% cyclosporine emulsion	2	Complete healing	No filaments, PES
Left	KCS, second BS		2	Complete healing	No filaments, PES
8/M/67 Right	SLK, second BS	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, PO	2	Complete healing	No filaments
Left	SLK, second BS		2	Complete healing	No filaments
9/M/42 Right	Post-laser eye surgery KCS, second BS	AT, PO	1	Complete healing	No filaments
Left	Post-laser eye surgery KCS, second BS		1	Complete healing	No filaments
10/M/43 Right	KCS, MGD, second BS	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily), CL	10	Complete healing	No filaments, PES
Left	KCS, MGD, second BS		10	Complete healing	No filaments
11/M/79 Right	SS	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, PO, oral doxycycline (20 or 50 mg twice daily)	3	Partial healing	1 Tiny filament
Left eye	SS		2	Complete healing	No filaments
12/F/64 Right	FES, second BS	AT, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily)	6	Complete healing	No filaments, PES
Left	FES, KCS, second BS		6	Complete healing	No filaments, PES
13/F/75 Right	Post-laser eye surgery CED	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, PO, oral doxycycline (20 or 50 mg twice daily)	4	Complete healing	No filaments
Left	BS		4	Complete healing	No filaments
14/F/65 Right	KCS, SLK	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily)	4	Complete healing	No filaments
Left eye	KCS, SLK		4	Complete healing	No filaments
15/F/73 Right	KCS	AT, 0.05% cyclosporine emulsion, PO, oral doxycycline (20 or 50 mg twice daily)	1	Complete healing	No filaments, PES
Left	KCS		1	Complete healing	No filaments, PES
16/F/79 Right	KCS	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, oral doxycycline (20 or 50 mg twice daily)	1	Complete healing	No filaments, PES
Left	KCS		1	Complete healing	No filaments, PES
17/F/64 Right	KCS	AT, 0.05% cyclosporine emulsion, 0.5% loteprednol etabonate, PO, oral doxycycline (20 or 50 mg twice daily), PT	1	Complete healing	No filaments
Left	KCS		1	Partial healing	Microfilaments, PES

Abbreviations: AT, artificial tears; BS, blepharospasm; CED, corneal epithelial defect; CL, contact lens; FES, floppy eyelid syndrome; KCS, keratoconjunctivitis sicca; MGD, meibomian gland disease; PES, punctate epithelial fluorescein staining; PO, punctal occlusion; PT, autologous plasma tears; RA, rheumatoid arthritis; SLK, superior limbic keratoconjunctivitis; SS, Sjögren syndrome.

adherence of the epithelial cells on the corneal surface by extracting fluid from the cornea and preventing formation of new receptor sites for filament formation. N-acetylcysteine, a mucolytic agent, used primarily as an

inhalant for patients with bronchial disease, effectively dissolves corneal filaments when applied topically in a 2% to 10% solution.<sup>3</sup> Additional treatment strategies include the use of preservative-free artificial tears, elimi-



**Figure.** Slitlamp photography of the left eye. Images without (A and B) and with (C and D) fluorescein staining before (A and C) and 6 weeks after (B and D) the initial onabotulinumtoxinA injection in a 76-year-old woman (patient 3) with filamentary keratitis who had secondary Sjögren syndrome. Filaments completely disappeared after the first and second onabotulinumtoxinA injections but were noted to recur by 12 weeks after each injection.

nation of toxic or preserved topical medications, punctal occlusion, and use of anti-inflammatory agents.

Anti-inflammatory agents, including nonsteroidal anti-inflammatory agents and corticosteroids, may break the vicious cycle in some cases of the filamentary keratitis. In one retrospective study, Marsh and Pflugfelder<sup>15</sup> reported that topical treatment with the preservative-free corticosteroid methylprednisolone improved irritation symptoms and resolved filamentary keratitis in a series of patients with severe keratoconjunctivitis sicca. In addition, some studies<sup>13,16</sup> have reported the successful use of topical nonsteroidal anti-inflammatory agents, such as 0.1% diclofenac sodium, in the treatment of challenging filamentary keratitis. Avisar and colleagues<sup>13</sup> compared the efficacy and short-term safety of 0.1% diclofenac sodium and 5% hypertonic saline ophthalmic solution in the treatment of filamentary keratitis associated with secondary Sjögren syndrome. They concluded that patients treated with this nonsteroidal anti-inflammatory drug had more rapid improvement in clinical symptoms than those treated with 5% hypertonic saline solution.

Although certain contact lenses, particularly conventional hydrogel lenses with low oxygen permeability, have been reported to cause filamentary keratitis,<sup>17</sup> therapeutic bandage contact lenses have been successfully used to treat filamentary keratitis.<sup>18</sup> The Boston Ocular Surface Prosthesis (Boston Foundation for Sight), with its unique fluid-filled reservoir, may also protect the cornea from blink trauma in challenging filamentary cases.

In our case series, as indicated in the Table, the underlying causes of refractory filamentary keratitis included blepharospasm, superior limbic keratoconjunc-

tivitis, and severe keratoconjunctivitis sicca. All these conditions are related in that they are associated with blink-related microtrauma.<sup>4</sup> In superior limbic keratoconjunctivitis, corrugations parallel to the upper eyelid margins can be observed due to redundant superior bulbar conjunctiva; in contrast, horizontal conjunctival folds may occur along the eyelid margins in eyes with severe keratoconjunctivitis sicca.<sup>19-21</sup> In both situations, the eyelid movement during each blink traumatizes the ocular surface, which in turn leads to a vicious frictional cycle on the cornea that may predispose patients to formation of filaments. The frictional component is exacerbated by tear deficiency and accompanying ocular surface epithelial changes, such as conjunctival squamous metaplasia and goblet cell loss. Increased eyelid friction is the most likely mechanism for filaments associated with eyelid ptosis, where the eyelid margin and a portion of the tarsal conjunctiva are in constant contact with the superior cornea. Resolution of filaments after ptosis repair suggests that reducing the extent of eyelid friction can break the cycle.<sup>6,7</sup> This mechanism served as our rationale for using onabotulinumtoxinA to treat filaments. Relaxation of the orbicularis muscle would be expected to decrease eyelid pressure on the cornea and blink frequency and force. The treatment outcomes clearly support this mechanism. However, our findings indicate that filaments are more likely to recur in eyes with more severe tear deficiency as the relaxing effect of onabotulinumtoxinA on eyelid pressure wanes.

In summary, onabotulinumtoxinA injection was performed in challenging cases of filamentary keratitis that did not improve with conventional treatments. Both subjective and objective outcomes were impressive, with reso-

lution of filaments after onabotulinumtoxinA injection in 88% of eyes. No serious clinical events related to onabotulinumtoxinA injections were reported during the follow-up period. Perhaps the biggest deficiency of this novel treatment for filamentary keratitis is the need for additional injections to maintain the therapeutic effect. The mean number of injections per person was almost 4 in this case series. No prospective studies on the effects of onabotulinumtoxinA injections on filamentary keratitis have been reported to date. Larger, prospective, randomized trials are needed to verify our preliminary observations.

**Submitted for Publication:** July 26, 2011; final revision received October 21, 2011; accepted October 31, 2011.

**Correspondence:** Stephen C. Pflugfelder, MD, Ocular Surface Center, Cullen Eye Institute, Baylor College of Medicine, 6565 Fannin, NC205, Houston, TX 77030 (stepenvp@bcm.edu).

**Financial Disclosure:** None reported.

## REFERENCES

1. Tanioka H, Yokoi N, Komuro A, et al. Investigation of the corneal filament in filamentary keratitis. *Invest Ophthalmol Vis Sci.* 2009;50(8):3696-3702.
2. Zaidman GW, Geeraets R, Paylor RR, Ferry AP. The histopathology of filamentary keratitis. *Arch Ophthalmol.* 1985;103(8):1178-1181.
3. Albietsz J, Sanfilippo P, Troutbeck R, Lenton LM. Management of filamentary keratitis associated with aqueous-deficient dry eye. *Optom Vis Sci.* 2003;80(6):420-430.
4. Cher I. Blink-related microtrauma: when the ocular surface harms itself. *Clin Experiment Ophthalmol.* 2003;31(3):183-190.
5. Baum JL. The Castroviejo Lecture: prolonged eyelid closure is a risk to the cornea. *Cornea.* 1997;16(6):602-611.
6. Kakizaki H, Zako M, Mito H, Iwaki M. Filamentary keratitis improved by blepharoptosis surgery: two cases. *Acta Ophthalmol Scand.* 2003;81(6):669-671.
7. Kitazawa K, Yokoi N, Watanabe A, et al. Eyelid surgery for refractory filamentary keratitis [in Japanese]. *Nihon Ganka Gakkai Zasshi.* 2011;115(8):693-698.
8. de Paiva A, Meunier FA, Molgó J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A.* 1999;96(6):3200-3205.
9. Coté TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol.* 2005;53(3):407-415.
10. Kowalik BM, Rakes JA. Filamentary keratitis: the clinical challenges. *J Am Optom Assoc.* 1991;62(3):200-204.
11. Arora I, Singhvi S. Impression debridement of corneal lesions. *Ophthalmology.* 1994;101(12):1935-1940.
12. Hamilton W, Wood TO. Filamentary keratitis. *Am J Ophthalmol.* 1982;93(4):466-469.
13. Avisar R, Robinson A, Appel I, Yassur Y, Weinberger D. Diclofenac sodium, 0.1% (Voltaren Ophtha), versus sodium chloride, 5%, in the treatment of filamentary keratitis. *Cornea.* 2000;19(2):145-147.
14. Fraunfelder FT, Wright P, Tripathi RC. Corneal mucus plaques. *Am J Ophthalmol.* 1977;83(2):191-197.
15. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. *Ophthalmology.* 1999;106(4):811-816.
16. Grinbaum A, Yassur I, Avni I. The beneficial effect of diclofenac sodium in the treatment of filamentary keratitis. *Arch Ophthalmol.* 2001;119(6):926-927.
17. Bloomfield SE, Jakobiec FA, Theodore FH. Contact lens induced keratopathy: a severe complication extending the spectrum of keratoconjunctivitis in contact lens wearers. *Ophthalmology.* 1984;91(3):290-294.
18. Bloomfield SE, Gasset AR, Forstot SL, Brown SI. Treatment of filamentary keratitis with the soft contact lens. *Am J Ophthalmol.* 1973;76(6):978-980.
19. Maudgal PC, Missotten L. Superior limbic keratoconjunctivitis. In: Maudgal PC, Missotten L, eds. *Superficial Keratitis.* Holland, the Netherlands: Dr W Junk; 1981:180-185.
20. Höh H, Schirra F, Kienecker C, Ruprecht KW. Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye. *Ophthalmologie.* 1995;92(6):802-808.
21. Veres A, Tapasztó B, Kosina-Hagyó K, Somfai GM, Németh J. Imaging lid-parallel conjunctival folds with OCT and comparing its grading with the slit lamp classification in dry eye patients and normal subjects. *Invest Ophthalmol Vis Sci.* 2011;52(6):2945-2951.