Clinical Manifestation and Risk Factors Associated With Remission in Patients With Filamentary Keratitis

SEUNG MIN LEE, ROO MIN JUN, KYU-RYONG CHOI, AND KYUNG EUN HAN

• PURPOSE: This study investigated the clinical manifestation and risk factors associated with remission in filamentary keratitis.
• DESIGN: Retrospective, interventional, comparative case series.
• METHODS: We retrospectively reviewed the medical records of 116 patients with filamentary keratitis diagnosed and treated between January 2012 and December 2018. We investigated the 5 causative factors including brain lesion, dry eye syndrome, autoimmune disease, ocular surgery or injury, and other conditions; treatment methods and duration; and remission status, and analyzed the risk factors associated with remission.
• RESULTS: The mean age of the patients was 56.9 ± 19.1 years and the mean follow-up duration was 14.9 ± 22.8 months. The most common underlying condition associated with filamentary keratitis was identified as a brain lesion (36.2%), followed by dry eye syndrome (30.2%) and autoimmune disease (24.1%). A comparison of remission rates among the causative factors revealed that cases associated with brain lesions had significantly lower remission rates (33.3%) than those associated with other causative factors (>60%) (P = .001). After adjustment for sex, age, diabetes mellitus, and hypertension, the treatment failure rate in patients affected by brain lesions was 6.602-fold higher than that associated without brain lesion (P = .001). The treatment method–dependent differences in the remission rate were observed in brain lesion and dry eye syndrome (P = .041 and P = .005, respectively).
• CONCLUSIONS: The most common condition leading to filamentary keratitis was a brain lesion, followed by dry eye syndrome and autoimmune disease. The treatment failure rate was statistically significantly low only in patients with filamentary keratitis associated with brain lesions. (Am J Ophthalmol 2020;218:78–83. © 2020 Elsevier Inc. All rights reserved.)

FILAMENTARY KERATITIS IS AN UMBRELLA TERM FOR conditions in which filaments are attached to the cornea and, more rarely, conjunctival surface. Filaments are composed of degenerated epithelial cells and mucus, and they cause pain on eye movement, photophobia, watery eye, foreign body sensation, and blepharospasm.[1] Filamentary keratitis may occur at any time on the ocular surface under an abnormal tear film condition, and known high-risk groups are patients with dry eye syndrome,[2–4] autoimmune disease,[5] exposure keratopathy,[6] ocular surgery or injury,[7,8] prolonged eyelid closure,[9,10] superior limbic keratopathy,[2] and brainstem lesions.[11,12] Filamentary keratitis is a chronic and recurrent disease, and successful treatment that avoids recurrence can be challenging. Conventional treatments include mechanical removal of filaments followed by the correction of underlying ocular diseases using preservative-free artificial tear supplements and punctal occlusion; reduction of inflammation using anti-inflammatory agents including steroids and cyclosporine; reduction of the viscosity of the mucinous component of the tear film using N-acetylcysteine eye drops; and, for mechanical protection, therapeutic contact lens.[13,14]

At present, only limited reports of histologic analyses or treatment methods of filamentary keratitis are available.[13–17] No in-depth research has been conducted to date to investigate etiology-dependent remission rates and factors influencing remission. We have addressed this research gap by investigating in detail the clinical features of patients with filamentary keratitis and remission-related factors.

METHODS

THE RETROSPECTIVE, INTERVENTIONAL, COMPARATIVE case series were carried out following the tenets of the Declaration of Helsinki and was approved by the institutional review board of Ewha Womans University Mokdong Hospital (IRB No.: EUMC 2019-10-010) and registered at

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• **DATA COLLECTION:** We retrospectively reviewed the medical records of 116 outpatients and inpatients with filamentary keratitis diagnosed and treated between January 2012 and December 2018 at Ewha Womans University Mokdong Hospital.

In all patients, slit-lamp microscopy was used for diagnosis after staining the ocular surface with a fluorescein eye stain strip. In cases where a slit-lamp microscope could not be used, a hand-held slit lamp (SL-15, Kowa Ophthalmic & Medical Equipment, Nagoya, Aichi, Japan; SLM-6M, Chongqing Kanghua Ruiming S&T Co, Ltd, Chongqing, China) was used.

We investigated the patient characteristics (sex, age, underlying diseases, history of ophthalmic diseases), causative factors for filamentary keratitis, treatment methods and duration, and remission status. We divided the patients into 3 age groups (<30, 30-59, ≥60 years) and categorized the conditions leading to filamentary keratitis into 5 causative factors, namely, brain lesion, dry eye syndrome, autoimmune disease, ocular surgery or injury, and other ophthalmic conditions. Autoimmune disease included Sjögren syndrome and graft-vs-host disease, and dry eye syndrome included cases not associated with these autoimmune diseases. To focus on the factors associated with recurrence of filaments, we excluded filamentary keratitis occurrence in epidemic keratoconjunctivitis because most of the cases showed episodic filaments on the ocular surface during the disease course and they did not recur. Patients who visited our clinic fewer than 4 times were also excluded.

• **TREATMENT METHODS AND DEFINITION OF REMISSION:** In all patients, treatment was preceded by the removal of filaments with cotton swabs or forceps after using topical anesthetics. The treatment methods were classified into 5 groups: (1) bandage soft contact lens; (2) 5% or 10% N-acetylcysteine drops; (3) autologous serum eye drops; (4) conservative care (eye drops) for each underlying disease; and (5) combination therapy. Remission was defined as the disappearance of filaments after removing the bandage soft contact lens for those treated with the bandage soft contact lens and after ceasing the application of 5% or 10% N-acetylcysteine or autologous serum eye drops for those treated with the application of those eye drops. Treatment failure was defined as persistence of filaments despite treatment.

• **STATISTICAL ANALYSIS:** For statistical analysis, we used SPSS Statistics 25.0 (SPSS Inc, Chicago, Illinois, USA), and Fisher exact test and the χ^2 test were used for comparing remission status among causative factors, locations of brain lesions, and treatment methods. In the event of statistically significant differences in remission status, we calculated the odds ratio using the logistic regression model, and $P < .05$ was set as the threshold for a statistically significant difference.

TABLE 1. Demographics and Clinical Manifestations of the Patients Diagnosed With Filamentary Keratitis (N = 116)

Clinical Characteristics	N (%)
Age (mean ± SD, years)	56.9 ± 19.1
Follow-up duration (mean ± SD, months)	14.9 ± 22.8
Sex	
Female	69 (59.5)
Male	47 (40.5)
DM	
Yes	12 (10.3)
No	104 (89.7)
HTN	
Yes	27 (23.3)
No	89 (76.7)
Causative factors and laterality	Both/Right/Left
Brain lesion (n = 42)	20 (47.6)/5 (11.9)/17 (40.5)
Dry eye syndrome (n = 35)	8 (22.9)/9 (25.7)/18 (51.4)
Autoimmune disease (n = 28)	12 (42.9)/7 (25.0)/9 (32.1)
Ocular surgery or injury (n = 6)	2 (33.3)/2 (33.3)/2 (33.3)
Others (n = 5)	1 (20.0)/2 (40.0)/2 (40.0)

DM = diabetes mellitus; HTN = hypertension.

RESULTS

THE PATIENTS' DEMOGRAPHICS, CAUSATIVE FACTORS, AND laterality are listed in Table 1. The mean age of the patients was 56.9 ± 19.1 years (range: 6-92 years), and the mean follow-up period was 14.9 ± 22.8 months (range, 0-83 months). Analysis of the patients across all age groups revealed brain lesions (n = 42) as the most common cause, followed by dry eye syndrome (n = 35) and autoimmune disease (n = 28).

Patients were divided into 3 age groups: <30 years (n = 8), 30-59 years (n = 54), and ≥60 years (n = 54) (Figure). In the young and mid-aged group (<60 years), brain lesion was the most common; on the other hand, in the old-aged group (≥60 years), dry eye syndrome was the most common.

We also examined the locations of filaments that were available in 103 cases, depending on the causative factor. In all patients with a history of ocular surgery or injury (n = 3), filaments were found at suture sites (100%). For all other causative factors, the most common location of filaments was the interpalpebral zone (Table 2).

To compare the remission rates among the causative factors, we analyzed 97 patients with available data (Table 3). Brain lesions demonstrated the lowest remission rate

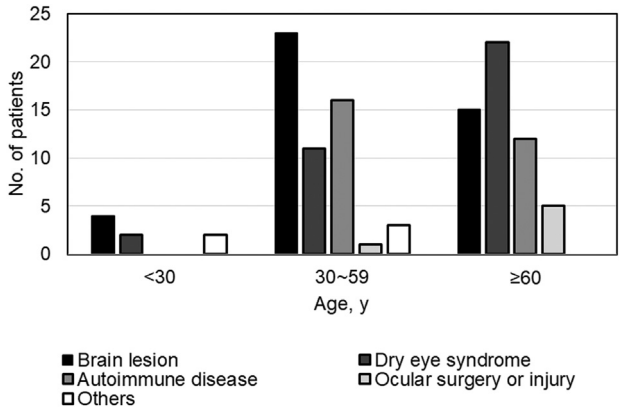

FIGURE. Causative factors of filamentary keratitis among different age groups. Patients were divided into 3 age groups: < 30 years, 30-59 years, and ≥60 years. The number of patients in each age group according to causative factors are as follows: (1) < 30 years group: Brain lesion = 4, Dry eye syndrome = 2, Others 2, Total = 8; (2) 30-59 years group: Brain lesion = 23, Dry eye syndrome = 11, Autoimmune disease = 16, Ocular surgery or injury = 1, Others = 3, Total = 54; (3) ≥60 years group: Brain lesion = 15, Dry eye syndrome group = 22, Autoimmune disease = 12, Ocular surgery or injury 5, Total = 54.

(33.3%) of filamentary keratitis among all causative factors, with statistical significance ($P = .001$). Other factors showed remission rates ranging between 60% and 80%, but differences in the remission rates were not statistically significant (all $P > .05$). After adjustment for sex, age, diabetes mellitus, and hypertension, the treatment failure rate in patients affected by brain lesions was 6.602-fold higher than that associated with no brain lesion ($P = .001$) (Table 4).

To establish whether there were differences in remission status between patients with brain lesions in the brainstem and other brain sites, we evaluated brain image data and compared the brain lesion sites of 31 patients with available brain image data. There was significant difference in remission rates according to the location of the brain lesions ($P = .033$); none of the 7 patients with brainstem lesions showed remission, whereas 11 of 24 patients (45.8%) with lesions in other brain regions, such as the cerebrum and diencephalon, achieved remission. We could check the blinking pattern in 18 of 42 patients with filamentary keratitis caused by brain lesions. Among these, 7 patients had been in a state of prolonged eye closure, 5 patients were in a state of being exposed, and 6 patients were capable of spontaneous blinking. The differences in remission depending on the blinking pattern were not statistically significant ($P = .605$).

To compare the treatment-dependent remission rates, we investigated the remission rates in patients affected by 3 major causative factors (brain lesion, dry eye syndrome, and autoimmune disease). The comparison revealed that statistically significant differences were shown among different treatment methods for brain lesion ($P = .041$) and dry eye syndrome ($P = .005$) (Table 5). For brain lesion, bandage soft contact lens was verified to have achieved the highest remission rate ($P = .022$), and combination therapies resulted in lowest remission rates ($P = .015$) (Supplemental Table, available at AJO.com). For dry eye syndrome, among the 5 treatment methods conservative care was verified to have achieved the highest remission rate, and combination therapies resulted in lowest remission rates ($P = .005$) (Supplemental Table).

DISCUSSION

FILAMENTARY KERATITIS IS A CHRONIC AND REFRACTORY disease related with various ocular diseases. In this study, we evaluated clinical manifestation and remission rates of filamentary keratitis according to the 5 causative factors and found that the most frequent causative factor leading to filamentary keratitis was brain lesions, followed by dry eye syndrome and autoimmune disease. Cases associated with brain lesions and dry eye syndrome had the lowest and highest remission rates, respectively.

Chen and associates recently reported that among 147 patients with filamentary keratitis, the most common cause of filamentary keratitis in all age groups was dry eye syndrome (65 of 162 eyes; 38.27%), followed by autoimmune disease (34 eyes; 20.99%) and viral keratitis (28 eyes; 17.28%).[1] The locations of filaments were mostly observed in the interpalpebral zone in dry eye syndrome and exposure keratopathy (52 of 65 eyes; 80.00%), the corneal limbus in autoimmune and inflammatory diseases (41 of 78 eyes; 52.56%), and corneal damage or suture sites in patients with a history of ocular surgery or injury (8 of 19 eyes; 42.11%).[1] In this study, the most common cause of filamentary keratitis was identified as the presence of brain lesions, followed by dry eye syndrome, even though dry eye syndrome was the most common cause in older patients (≥60 years), in line with previous studies.[1–3,13] Except for ocular surgery or injury, in which case filaments were observed exclusively at suture sites (3/3, 100%), the locations of filaments in this study were mostly observed in the interpalpebral zone in relation to all (for all other causes), which was consistent with the results of the study reported by Chen and associates.

Although chronic filamentary keratitis has been reported in case studies of vegetative patients or patients with brainstem lesions,[11,12] no study to date has reported brain lesions as the leading cause of filamentary keratitis. In our study, both inpatients and outpatients were considered (previous studies did not report whether inpatients were included in their analysis)[1]; 14 of 42 patients (33.3%) with brain lesion were inpatients, and different incidence rates may have resulted if only outpatients had been included.

TABLE 2. Locations of Filaments Among Different Groups

Causative Factors	Patients[a]	IP	Inf	Sup	Multi	Sut
Brain lesion	38	26 (68.4)	1 (2.6)	6 (15.8)	5 (13.2)	0 (0.0)
Dry eye syndrome	32	15 (46.9)	8 (25.0)	3 (9.4)	6 (18.8)	0 (0.0)
Autoimmune disease	25	14 (56.0)	9 (36.0)	0 (0.0)	2 (8.0)	0 (0.0)
Ocular surgery or injury	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
Others	5	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	103	58 (56.3)	20 (19.4)	9 (8.7)	13 (12.6)	3 (2.9)

Inf = inferior; IP = interpalpebral zone; Multi = multiple site; Sup = superior; Sut = suture site.

Results are n (%) patients.

[a]Thirteen patients whose filaments could not be located were excluded. The number of patients excluded in each group are as follows: Brain lesion = 4; Dry eye syndrome = 3; Autoimmune disease = 3; Ocular surgery or injury = 3; Others = 0.

TABLE 3. Comparison of Remission Rate of Filamentary Keratitis According to Causative Factors

Causative Factors	Patients[a]	Remission Achieved	Treatment Failed	*P* Value
Brain lesion	33	11 (33.3)	22 (66.7)	.001[b]
Dry eye syndrome	29	20 (69.0)	9 (31.0)	.111[b]
Autoimmune disease	26	17 (65.4)	9 (34.6)	.296[b]
Ocular surgery or injury	5	4 (80.0)	1 (20.0)	.385[c]
Others	4	3 (75.0)	1 (25.0)	.631[c]
Total	97	55 (56.7)	42 (43.3)	

Results are n (%) patients.

[a]Nineteen patients who were lost to follow-up were excluded. The number of patients lost to follow-up in each group were as follows: Brain lesion = 9; Dry eye syndrome = 6; Autoimmune disease = 2; Ocular surgery or injury = 1; Others = 1.

[b]χ^2 test.

[c]Fisher exact test.

Ocular sensory neurons have their cell bodies in the trigeminal ganglion, and the trigeminal ganglion neurons go to the trigeminal brainstem nuclear complex, specifically to the regions between (1) the caudal Vi and Vc and (2) the Vc and upper cervical cord junction.[18] Ocular neurons in these 2 regions project to the facial nucleus and eventually activate the orbicularis oculi along the facial nerve, causing blinking[18,19]; when these neurons project to the thalamus and reach the somatosensory cortex, they are processed into pain.[20–22] Blink reflex and sensitivity impairment can occur when damage occurs at any point in this pathway,[19,23–25] and as a result cause ocular surface disorders.[9] Based on this knowledge, we examined the brain region sites in patients with filamentary keratitis caused by brain lesions, to determine whether brain lesions, especially brainstem lesions, are responsible for the development of filamentary keratitis. The remission rate was statistically significantly different between patients with brainstem lesions and those with other brain lesions (P = .033); none of the patients with brainstem lesions showed remission of filamentary keratitis, as expected.

Lavrijsen and associates stated that conditions in the filamentary keratitis with brainstem lesion are attributed not to dry eye itself, but to prolonged eye closure, and they prevented the recurrence of filamentary keratitis by frequently opening the patient's eyes.[12] The differences in remission depending on the blinking pattern were not statistically significant; however, the blinking pattern of 57.1% (24/42) of patients with brain lesion was not described in the medical chart. Future research would be necessary to conclude associations between the alteration of corneal sense and/or blinking pattern and filamentary keratitis in patients with brain lesion.

In this study, the treatment failure rate in patients affected by brain lesions was 6.602-fold higher than that associated with patients without brain lesion. This can be ascribed to the fact that, in filamentary keratitis cases caused by brain lesions, changes in the state of the underlying disease can

TABLE 4. Logistic Regression Predicting Treatment Failure Risk

	Crude OR			Adjusted OR		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value[a]
Brain lesion	4.400	1.796-10.781	.001	6.602	2.179-20.002	.001
Sex				0.627	0.213-1.851	.398
Age				1.014	0.987-1.041	.320
DM				0.483	0.091-2.558	.392
HTN				2.936	0.905-9.530	.073

CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; OR = odds ratio.
[a]*P* value was calculated by logistic regression model adjusting sex, age, DM, and HTN as covariates.

TABLE 5. Comparison of the Remission Rate According to the 3 Major Causative Factors and Treatment Methods

Causative Factors	Treatment Method	Patients	Remission Achieved	Treatment Failed	*P* Value
Brain lesion	Bandage soft contact lens	20	10 (50.0)	10 (50.0)	.041
	5%-10% N-acetylcysteine	2	0 (0)	2 (100.0)	
	Conservative care	2	1 (50.0)	1 (50.0)	
	Combination above	9	0 (0)	9 (100.0)	
	Total	33	11 (33.3)	22 (66.7)	
Dry eye syndrome	Bandage soft contact lens	7	6 (85.7)	1 (14.3)	.005
	5%-10% N-acetylcysteine	3	1 (33.3)	2 (66.7)	
	Autologous serum	3	2 (66.7)	1 (33.3)	
	Conservative care	10	10 (100.0)	0 (0)	
	Combination above	6	1 (16.7)	5 (83.3)	
	Total	29	20 (69.0)	9 (31.0)	
Autoimmune disease	5%-10% N-acetylcysteine	3	2 (66.7)	1 (33.3)	.521
	Autologous serum	5	3 (60.0)	2 (40.0)	
	Conservative care	13	10 (76.9)	3 (23.1)	
	Combination above	5	2 (40.0)	3 (60.0)	
	Total	26	17 (65.4)	9 (34.6)	

Results are n (%) patients.
The number of patients lost to follow-up in each group were as follows: Brain lesion = 9; Dry eye syndrome = 6; Autoimmune disease = 2.
Fisher exact test was used.

hardly be expected, resulting in a low possibility of remission. Actually, 83.3% (35/42) of patients with brain lesion were in a severe condition, such as quadriplegia, to the extent that visual acuity could not be measured.

There are several treatment methods for filamentary keratitis: applying lubricants including artificial tears and punctal occlusion, anti-inflammatory eye drops to reduce inflammation, N-acetylcysteine drops to dissolve mucus plaque, and therapeutic contact lenses for corneal surface protection.[13,14,17] Absolon and Brown reported that topical N-acetylcysteine instillation was more efficient than artificial tears for treating keratoconjunctivitis sicca.[26] In refractory cases with severe ocular discomforts, therapeutic contact lens was recommended to relieve pain.[27] In this study, treatment method–dependent differences in the remission rate were observed in patents with brain lesion and dry eye syndrome patients. As previously mentioned in other studies,[13,17] filamentary keratitis with bandage soft contact lens was effective both in brain lesion and dry eye syndrome groups (for brain lesion, $P = .022$); even though treating with bandage soft contact lens in dry eye syndrome did not reach statistical significance ($P = .382$), the second-greatest number of patients who achieved remission were treated with bandage soft contact lens. Except for treatment with bandage soft contact lens, other treatment methods were not successful in treating filamentary keratitis in patients with brain lesion; combination therapy showed statistically significant treatment failure ($P = .015$). In dry eye syndrome patients, contrary to our expectation, conservative care was most efficient in

obtaining remission, and combination therapy was found to be least efficient. This can be ascribed to the fact that patients affected by dry eye syndrome are heterogeneous in terms of disease severity, and more low-severity patients are included in the conservative care group than in the combination therapy group. In terms of treatment duration, patients that received conservative care mostly showed improvement within 1 month (median: 0 month), whereas the treatment duration for the patients that received combination therapy was much longer (median: 11 months) (Supplemental Figure, available at AJO.com).

This study has some limitations. First, we cannot obtain information regarding the blinking pattern of 57.1% of patients affected by brain lesions. Second, the stability of the tear film and the amount of tear secretion could not be assessed because the tear break-up time, Schirmer test, or corneal sensitivity was not performed in the cases other than in patients with dry eye syndrome or autoimmune disease. In the future, evaluation of corneal sensitivity using a corneal esthesiometer or a cotton-tipped applicator in patients with brain lesions would be necessary to reinforce our findings. Finally, patients from only 1 institution were analyzed. However, despite these limitations, this study is significant in that it has verified that brain lesions are a major cause of refractory filamentary keratitis and can recur more in patients with brain lesions.

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