Infectious Keratitis in Patients with Ocular Sjögren’s Syndrome

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Purpose: To investigate the incidence, characteristics, risk factors, and treatment outcomes for infectious keratitis in patients with ocular Sjögren’s syndrome (SS).

Methods: We performed a retrospective chart review of patients who had been followed up for ocular SS in Seoul National University Hospital from 2010 to 2020 and identified cases where infectious keratitis developed. The incidence, demographic and clinical characteristics, risk factors, microbiological profiles, and treatment outcome were investigated, some of which were compared with infectious keratitis cases in the non-SS group.

Results: Out of 929 patients with ocular SS, infectious keratitis occurred in 18 eyes (1.94%). All 18 patients were female in the ocular SS group, while 48 out of 100 infectious keratitis patients (48%) were female in the non-SS group (p < 0.01). The mean age at diagnosis of infectious keratitis was 66.1 years in the ocular SS group, which was not different from the non-SS group (57.2 years, p = 0.12). Of risk factors analyzed, the use of therapeutic contact lens was more frequently used in the ocular SS patients, compared to the non-SS patients (67% vs. 11%, p < 0.01). Culture-positivity rate was 50% in the ocular SS group. All culture-proven cases were bacterial infection, one of which was bacterial-fungal coinfection. Infection resolved in all eyes after the mean 29 days of medical treatment, except one that additionally required penetrating keratoplasty with vitrectomy. The visual acuity improved in 15 eyes (83%) after resolution. Infectious keratitis recurred in three patients (17%) during the mean 55.7 months of follow-up.

Conclusions: The incidence of infectious keratitis was 1.94% in patients with ocular SS. Most were bacterial infections and resolved by medical treatment. Therapeutic and visual outcomes were favorable, but recurrence occurred in 17%.

Key Words: Cornea; Infectious keratoconjunctivitis; Keratitis; Keratoconjunctivitis sicca; Sjögren’s syndrome
In addition to DE, various ocular manifestations have been reported in SS including conjunctivitis, sterile corneal ulcer [5], uveitis [6], scleritis [7], optic neuritis, and retinal vasculitis [8]. However, the incidence and characteristics of infectious keratitis, the fourth-leading cause of blindness globally [9,10], have not been investigated in patients with SS. Given that DE and its associated corneal epithelial defect are one of the main predisposing factors for infectious keratitis [10,11], it can be assumed that SS patients are susceptible to infectious keratitis. Moreover, frequent uses of corticosteroids, immunosuppressants, and therapeutic contact lens in SS patients would further increase the risk of infectious keratitis.

The aims of this study are to investigate the incidence, demographics, clinical and microbiological characteristics, risk factors, treatment methods, and therapeutic outcomes of infectious keratitis in patients with ocular SS over a 10-year period at Seoul National University Hospital, a tertiary referral hospital in South Korea, and to compare them with infectious keratitis patients without ocular SS.

Materials and Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2012-098-1181) and conducted with adherence to Declaration of Helsinki. Due to the retrospective nature of this study, the patient consent was waived under the approval of the Institutional Review Board.

The medical charts and anterior segment photographs were reviewed of patients who had been followed up for ocular SS and/or diagnosed with infectious keratitis at Seoul National University Hospital from 2010 to 2020. The following data were collected: (1) demographical and medical information including age, sex, laterality of the affected eye, immune-compromising disorders such as diabetes mellitus, SS type and status (primary or secondary SS, salivary gland involvement), and the use of systemic immunosuppressants; (2) clinical ocular conditions including the presence of corneal epithelial defect or filaments, ocular staining score (National Eye Institute and Oxford scales), Schirmer test result, contact lens use, history of ocular trauma or surgery, and the use of topical medications (corticosteroids, antibiotics, artificial tears, antiglaucoma medications); (3) ocular findings at diagnosis of infectious keratitis including visual acuity (VA), hypopyon, and epithelial defect size (as measured by corneal photographs with fluorescein staining); (4) results of corneal culture (isolated microorganisms, antibiotic sensitivity, and resistance); and (5) ocular treatment methods and therapeutic outcome including infection resolution (as defined by disappearance of epithelial defect and stromal infiltration), VA, and recurrence.

Statistical analysis was done with the IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). After normality test with Kolmogorov-Smirnov test or Shapiro-Wilk test, Mann-Whitney U-test or Fisher test was used to compare the values between two groups.

Results

Incidence of infectious keratitis

In total, 1,893 patients had been diagnosed with SS at Seoul National University Hospital from 2010 to 2020. Among them, 929 patients had been followed up for ocular SS during the same period. Out of 929 ocular SS patients, infectious keratitis occurred in 18 eyes of 18 patients (1.94%). Meanwhile, 100 infectious keratitis patients were identified among non-SS patients.

Demographics, clinical characteristics, and risk factors

Table 1 summarizes the demographics, general medical and ocular histories, and ocular characteristics at the time of infectious keratitis in ocular SS patients. Infectious keratitis developed at the mean 1,655 ± 1,317 days (range, 0–4,344 days) after SS diagnosis. The mean age at diagnosis of infectious keratitis was 66.1 ± 11.5 years (range, 50–86 years), and all patients were female. When compared with the non-SS group, there was a significant female predominance in infectious keratitis patients in the ocular SS group (100% in the ocular SS group vs. 48% in the non-SS group, p < 0.01); 48 out of 100 infectious keratitis patients were female in the non-SS group. There was, however, no significant difference in the age of infectious keratitis patients between the ocular SS group and the non-SS group (66.1 ± 11.5 years in the ocular SS group vs. 57.2 ± 20.1 years in the non-SS group, p = 0.12).

Among 18 patients, six had secondary SS associated
with one rheumatoid arthritis, two systemic lupus erythematosus, one systemic sclerosis, one Raynaud disease, one mixed connective tissue disease. The use of systemic immunosuppressant, such as methotrexate and hydroxychloroquine, was combined in 12 (67%). The salivary gland involvement was confirmed in three (17%). As for other immune-compromised conditions, diabetes mellitus was present in four patients (22%), and the percentage of diabetes mellitus in the ocular SS group (4 of 18 eyes, 22%) was not different from that in the non-SS group (13 of 100 eyes, 13%; \( p = 0.29 \)).

Before developing infectious keratitis, all 18 eyes had Schirmer test results of <5 mm and nine eyes (50%) had corneal filaments. One (6%) had ocular trauma right before the infection, and four (22%) had a history of ocular surgery: two cataract surgery, one glaucoma surgery, and one laser in situ keratomileusis (LASIK) surgery. The history of ocular surgery was significantly higher in non-SS group (60 of 100 eyes, 60%; \( p < 0.01 \)): 31 had cataract surgery alone or with other surgeries, 30 had penetrating keratoplasty alone or with other surgeries, 10 had glaucoma surgery alone or with other surgeries, four had LASIK and/or laser epithelial keratomileusis (LASEK) surgery, four had vitrectomy with other surgeries, and three had other surgeries. At the time of infection, four eyes (22%) in the ocular SS group had been using topical antiglaucoma medications, six (33%) topical corticosteroids, seven (39%) topical antibiotics, and 13 (72%) topical autologous serum eye drops or artificial tears. There wasn’t significant difference between the ocular SS group and the non-SS group in the use of topical corticosteroid (39% in the non-SS group, \( p = 0.79 \)) or topical antiglaucoma medications (29% in the non-SS group, \( p = 0.78 \)). Notably, 12 eyes (67%) in the ocular SS group had been using topical antiglaucoma medications, six (33%) topical corticosteroids, seven (39%) topical antibiotics, and 13 (72%) topical autologous serum eye drops or artificial tears. There wasn’t significant difference between the ocular SS group and the non-SS group in the use of topical corticosteroid (39% in the non-SS group, \( p = 0.79 \)) or topical antiglaucoma medications (29% in the non-SS group, \( p = 0.78 \)). Notably, 12 eyes (67%) in the ocular

### Table 1. Demographics, clinical characteristics, and ocular manifestations at the time of infectious keratitis in ocular SS patients

| Variable                                      | Value                      |
|-----------------------------------------------|----------------------------|
| Demographical and general medical characteristic |                            |
| No. of patients (eyes)                       | 18                         |
| Age (yr)                                      | 66.1 ± 11.5 (50–86)        |
| Sex (male : female)                           | 0 : 18                     |
| Time after SS diagnosis (day)                 | 1,655 ± 1,317 (0–4,344)    |
| Salivary gland involvement                    | 3 (17)                     |
| Secondary SS                                  | 6 (33)                     |
| Diabetes mellitus                             | 4 (22)                     |
| Systemic immunosuppressant use                | 12 (67)                    |
| Ocular conditions prior to infection          |                            |
| Corneal filaments                             | 9 (50)                     |
| Schirmer test (<5 mm)                         | 18 (100)                   |
| Ocular trauma                                 | 1 (6)                      |
| History of ocular surgery                     | 4 (22)                     |
| Cataract surgery                              | 2 (11)                     |
| Glaucoma surgery                              | 1 (6)                      |
| LASIK surgery                                 | 1 (6)                      |
| Therapeutic contact lens wear                 | 12 (67)                    |
| Topical antiglaucoma medication               | 4 (22)                     |
| Topical corticosteroids                       | 6 (33)                     |
| Topical antibiotics                           | 7 (39)                     |
| Topical autologous serum or artificial tears  | 13 (72)                    |
| Ocular findings at time of infection diagnosis|                            |
| Visual acuity (logMAR)                        | 0.66 ± 0.50 (0–1.6)        |
| Counting fingers                              | 2 (11)                     |
| Light perception                              | 3 (17)                     |
| No light perception                           | 1 (6)                      |
| Hypopyon                                      | 1 (6)                      |
| Epithelial defect size (%)                    | 14.1 ± 19.4 (0–60.0)       |

Values are presented as number (%) or mean ± standard deviation (range).

SS = Sjögren’s syndrome; LASIK = laser in situ keratomileusis; logMAR = logarithm of the minimum angle of resolution.

### Table 2. The culture results of corneal scrapings (n = 12)

| Variable                                      | No. of eyes (%) |
|-----------------------------------------------|-----------------|
| Culture-positive                              | 6 (50)          |
| Bacteria alone                                | 5 (42)          |
| G (+) coccii                                  | 2 (17)          |
| Coagulase-negative staphylococci              | 1 (8)           |
| *Staphylococcus auricularis*                  |                 |
| G (+) bacilli†                                | 1 (8)           |
| G (-) bacilli†                                | 2 (17)          |
| *Aeromonas hydrophila*                        | 1 (8)           |
| *Pantoea species*                             | 1 (8)           |
| Mixed infection (bacteria and fungus)*        | 1 (8)           |

* Bacillus species; † Candida parapsilosis + Bacillus species.
lar SS group were wearing therapeutic contact lens, while 11 of 100 eyes (11%) in the non-SS group used contact lens ($p < 0.01$).

At first presentation of infectious keratitis in ocular SS patients, the mean logarithm of the minimum angle of resolution VA was $0.66 \pm 0.50$; VA was counting fingers in two eyes (11%), light perception in three (17%), and no light perception in one (6%). Hypopyon was present in one eye (6%). The mean epithelial defect size was 14.1% $\pm$ 19.4% (percentage relative to the corneal whole area).

Microbiological profiles

Out of 18 eyes with infectious keratitis, 12 eyes underwent corneal scrapings for culture. The culture results were shown in Table 2. Six of 12 scrapings (50%) were culture-positive, five yielding bacteria alone and one both bacteria and fungus. The identified microorganisms were diverse including one coagulase-negative staphylococci, one *Staphylococcus aureus*, one *Bacillus*, one *Aeromonas hydrophila*, one *Pantoea* species, and one combined infection of *Candida parapsilosis* and *Bacillus* species.

**Table 3. Therapeutic methods and outcomes (n = 18)**

| Treatment                                    | Value               |
|----------------------------------------------|---------------------|
| **Method**                                   |                     |
| Topical antibiotic                           | 18 (100)            |
| Fourth-generation fluoroquinolones           | 7 (39)              |
| Fortified antibiotics combination            | 11 (61)             |
| Combination with topical 1% voriconazole     | 1 (6)               |
| Systemic antibiotics                         | 10 (56)             |
| Penetrating keratoplasty and vitrectomy      | 1 (6)               |
| Evisceration                                 | 0 (0)               |
| **Total treatment period (day)**             | 29 ± 65 (1–287)     |
| **Outcome**                                  |                     |
| Visual acuity (vs. pretreatment)             |                     |
| Improved                                     | 15 (83)             |
| Stationary                                   | 1 (6)               |
| Worsened                                     | 2 (11)              |
| Recurrence                                   | 3 (17)              |
| **Total follow-up period (day)**             | 1,671 ± 985 (135–3,310) |

Values are presented as number of eyes (%) or mean ± standard deviation (range).
50% of our patients had corneal filaments, the evidence of corneal epithelial disruption, and 67% were wearing therapeutic contact lens at the diagnosis of infectious keratitis. Interestingly, all patients in the ocular SS group were female, whereas 48 out of 100 infectious keratitis patients were female in the non-SS group, which is mainly due to the strong female predominance in SS; SS occurs predominately in women (16:1) [14]. Importantly, all ocular SS patients had DE, the most representative characteristics of SS, as evidenced by the observation that Schirmer test results were <5 mm in all of our patients. Because DE is the predisposing factor for infectious keratitis [11], it can be assumed that ocular SS patients are vulnerable to infectious keratitis as we found in our study.

The culture of corneal scrapings was positive in 50% of our patients. The culture-positivity rates largely vary from studies to studies, ranging from 23.7% to 78.3% [15-19]. Most of culture-proven cases were bacterial infections and resolved by medical treatment, except for one medically uncontrolled case that progressed to endophthalmitis and required both therapeutic penetrating keratoplasty and vitrectomy for infection control. No eye underwent enucleation. Moreover, VA improved in 83% after treatment. These results suggest that the treatment response and outcome of infectious keratitis are excellent in ocular SS patients. Despite the favorable therapeutic outcome, careful follow-up for the possibility of infection recurrence is essential in ocular SS patients because their immunocompromised state associated with topical and systemic immunosuppressant, DE comorbidity and the use of therapeutic contact lens would constantly put the patients at risk of infectious keratitis. In fact, the recurrence of infectious keratitis was observed in 17% of ocular SS patients in this study.

The drawbacks of our study are the small number of patients and the limited data collection. These are inevitable because this was a single hospital-based study, and data were retrospectively collected from a chart review. To generalize our results, a prospective, multicenter-based research would be necessary in the future.

In conclusion, our 10-year analysis showed that the incidence of infectious keratitis was 1.94% in ocular SS patients. Most were bacterial infections and resolved by medical treatment. Therapeutic and visual outcomes were favorable, but recurrence occurred in 17%.

Conflicts of Interest: None.
Acknowledgements: None.
Funding: This work was supported by the National Research Foundation grant funded by the Korean government (No. 2021R1A2C3004532).

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