

## Corneal ulcers with non-infectious appearance caused by nasolacrimal duct obstruction or canaliculitis

Atsuko Ishimoto<sup>a</sup>, Kaoru Araki-Sasaki<sup>a,\*</sup>, Chieko Shima<sup>a</sup>, Miwako Tajika<sup>b</sup>, Noriko Toyokawa<sup>b</sup>, Kanji Takahashi<sup>a</sup>

<sup>a</sup> Department of Ophthalmology, Kansai Medical University, 2-5-1, Shinmachi, Hirakata City, Osaka, 573-1010, Japan

<sup>b</sup> Nagata Eye Clinic, 1147 Horaicho, Nara City, Nara, 631-0844, Japan

### ARTICLE INFO

#### Keywords:

Corneal ulcer  
Nasolacrimal duct obstruction  
Canaliculitis  
Corneal perforation

### ABSTRACT

**Purpose:** To describe the clinical features of corneal ulcers with non-infectious appearance due to nasolacrimal disease in a retrospective case series.

**Observations:** Eight eyes of 8 patients (aged  $74.4 \pm 11.1$  years) with corneal disease due to nasolacrimal duct obstruction or canaliculitis, who were treated between October 2013 and December 2020 at 3 hospitals were included. Patient background, anterior ocular findings, organisms in secretion, and time course during treatment were retrospectively analyzed. The corneal findings were peripheral ulcers (5 cases), phlyctenular keratitis (1 case), and paracentral perforation with slight cellular infiltration (2 cases). All cases were suspected as autoimmune disease-related-corneal ulcers because of the pathogenic region and clinical appearance and later diagnosed as corneal disorders derived from nasolacrimal duct obstruction or canaliculitis. The autoimmune disease-like appearance and purulent secretion connecting the punctum with/without swelling were characteristic. The most common microorganism detected in the purulent secretions was *Streptococcus* spp.. The resolution of corneal lesions needed steroid eye drops with antibiotic eye drops. Two patients required a superficial corneal transplantation. The extraction of nasolacrimal calculus, punctal tube insertion, or dacryocystorhinostomy was necessary for complete healing of ocular surface disease.

**Conclusions and importance:** Nasolacrimal duct diseases cause corneal disorders without bacterial colonization and growth. When corneal ulcers resemble autoimmune disease in shape and are not accompanied by systemic disease, attention should be paid to nasolacrimal duct obstruction or canaliculitis.

## 1. Introduction

Nasolacrimal duct obstruction (NLDO) can cause corneal disorders. Li et al.<sup>1</sup> reported that 35% of 31 eyes with infectious keratitis suffered from NLDO. Cho et al.<sup>2</sup> and Ishikawa et al.<sup>3</sup> also reported infectious keratitis secondary to canaliculitis and described the difficulty of determining a diagnosis. They speculated that the accumulation of pathogenic microorganisms in the obstructed nasolacrimal duct and conjunctival sac would promote colonization of the organisms in the corneal epithelial layer and evoke infectious keratitis. However, Yokokawa et al.<sup>4</sup> analyzed 31 corneal perforations by classifying them into infectious and noninfectious cases and found 2 interesting cases of non-infectious corneal perforation caused by canaliculitis. Therefore, corneal disease associated with NLDO or canaliculitis can occur both due to an infectious etiology with colonization and non-infectious etiology

due to an inflammatory reaction to the accumulated organisms.

In the past literature, the clinical features of corneal ulcer associated with nasolacrimal disease have not been clarified. When a corneal ulcer has a non-infectious finding, it is easy to overlook nasolacrimal tract disease as a cause of the ulcer. In this report, we describe the characteristics of non-infectious corneal disorders caused by NLDO or canaliculitis.

## 2. Patients and methods

This retrospective, non-invasive study was approved by the Ethical Committee of Kansai Medical University (approval no. 2020299) and followed the tenets of the Declaration of Helsinki.

Eight eyes of 8 patients who were transferred to our hospital with corneal ulcers of unknown cause were included. They were treated at the

\* Corresponding author.

E-mail address: [sasakis@sa2.so-net.ne.jp](mailto:sasakis@sa2.so-net.ne.jp) (K. Araki-Sasaki).

<https://doi.org/10.1016/j.ajoc.2022.101651>

Received 6 September 2021; Received in revised form 25 June 2022; Accepted 5 July 2022

Available online 9 July 2022

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Kansai Medical University Ophthalmology, JCHO Hoshigaoka Medical Center, and Nagata Ophthalmology from October 2013 to December 2020. They were diagnosed with corneal disorders caused by NLDO or canaliculitis during the course of treatment.

Patient background, anterior ocular findings, organisms in secretion, and time course during treatment were retrospectively analyzed. The colonizing organisms were confirmed by culture of the purulent discharge or secretions from the punctum during nasolacrimal duct drainage.

#### Case 1. Representative Case 1

An 88-year-old woman had been suffering from conjunctivitis of the right eye and was treated with antibiotic and low-concentration steroid eye drops by a previous doctor. Several months later, she complained of redness, tearing, and sudden vision loss and was referred to our hospital. She had no systemic disease. Medical scrutiny, including blood tests and a physical examination, ruled out rheumatoid arthritis and other collagen diseases (CRP0.83mg/dl, Rheumatoid Factor4U/ml, anti-nuclear antigen<40). A slit lamp examination showed mild hyperemia of the conjunctiva and paracentral corneal perforations on the nasal side (Fig. 1a). Under the slit lamp examination, the corneal stroma around the perforation showed slight or less cellular infiltration. The punctum was slightly swollen without redness, and a massive white purulent discharge was noted from the punctum. There were no notable findings in the left eye. We performed lamellar corneal keratoplasty (LKP) for corneal perforation with a cover of antibiotics and low-grade steroid eye drops. However, white purulent discharge connecting to the nasolacrimal punctum was observed continuously, even after the LKP. *β-hemolytic Streptococcus* was identified from the purulent secretion by blood agar culture (Fig. 1b). The discharge accumulated in the inner canthus, and the perforation was situated on the paracentral lesion in the nasal side of the cornea, which was close to the punctum. The patient was diagnosed with NLDO by endoscopic observation. Endoscopic nasolacrimal duct silicone tube placement was performed 1 month after LKP. Neither hyperemia nor discharge recurred during the placement of the tubing nor after its removal. After lamellar corneal transplantation, the patient wore therapeutic contact lenses for one month. Corneal epithelium healed smoothly and the epithelial erosions did not recur after the

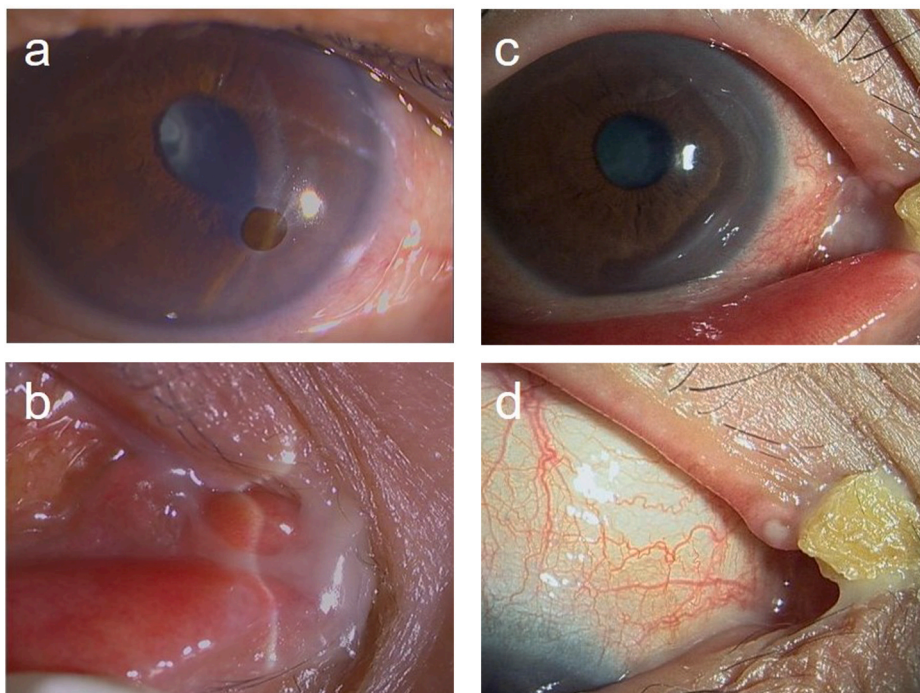
contacts were removed.

#### Case 2. Representative Case 2

A 70-year-old woman was referred to our hospital because of an advanced peripheral nasal ulcer in the right eye that did not improve with betamethasone eye drops. She had rheumatoid arthritis, which was well controlled by oral methotrexate and prednisolone. A slit lamp examination showed mild conjunctival hyperemia and a peripheral corneal ulcer from the 1 to 6 o'clock position (Fig. 1c). The ulcer was accompanied with slight cellular infiltration and unremarkable abscess around the ulcer. There were no notable findings in the left eye. The corneal ulcer improved with low-concentration steroids and antibacterial agents. However, white purulent discharge has accumulated in the inner canthus (Fig. 1d). And nasolacrimal tract lavage was performed under the suspicion of NLDO. Finally, a sticky string-like secretion with concretion was extracted by lacrimal duct drainage after incision of the upper punctum. Methicillin-resistant *Staphylococcus aureus* was identified in the secretion by blood agar culture. The patient finally agreed to have dacryocystorhinostomy five months later. The symptom was addressed by repeated nasolacrimal duct flushing until the surgical treatment. After dacryocystorhinostomy for NLDO and canaliculitis, rheum and hyperemia did not recur, and the corneal findings were alleviated.

### 3. Results

Eight patients (8 eyes) with keratitis caused by NLDO or canaliculitis were included in this study (Table 1). These 8 patients (2 males, 6 females) had an age range of 55–89 years (average  $76.9 \pm 11.6$  years). Non-active rheumatoid arthritis was observed in 2 patients. None of them had suffered from diabetes. All patients had received antimicrobial eye drops prior to the visit of our affiliation. All corneal findings were located on the nasal side. These included peripheral ulcers ( $n = 5$ ), phlyctenular keratitis ( $n = 1$ ), and paracentral perforation ( $n = 2$ ) with slight cellular infiltration. The clinical appearances in all cases were similar to corneal diseases caused by an autoimmune reaction such as rheumatic corneal disease. The ulcerative region was not accompanied with severe infiltration of neutrophils nor abscess. White purulent



**Fig. 1.** Representative slit-lamp biomicroscopic photograph of cornea in cases 1 and 2

**Case 1:** (a) Paracentral corneal perforation with slight cellular infiltration is found on the nasal side. (b) String-like mass of white purulent discharge is seen accumulated in the inner canthus.

**Case 2:** (c) Corneal peripheral ulcer extending from 1 to 6 o'clock position is similar to an ulcer due to autoimmune disease. (d) White purulent discharge is noted emerging from the punctum and accumulating in the inner canthus.

**Table 1**  
Clinical data of the patients in all cases.

Case	Age/ Sex	RA	Corneal findings	Culture from purulent secretions	Lacrimal punctum and discharge properties
1	88/F	(-)	Paracentral perforation	<i>β-hemolytic streptococcus</i>	<Lacrimal punctum> Various from severe redness/swelling to normal <Discharge> Lumpy or string-like white purulent secretion from the punctum
2	70/F	(+)	Peripheral ulcer	MRSA	
3	83/F	(-)	Peripheral ulcer Paracentral perforation	<i>Strept. Anginosus</i> , <i>C. acnes</i>	
4	76/F	(-)	Peripheral ulcer	<i>Nocardia</i>	
5	55/F	(+)	Peripheral ulcer	<i>Strept. Intermedius</i>	
6	89/M	(-)	Peripheral ulcer	<i>S. aureus</i> , <i>Peptostreptococcus</i>	
7	66/M	(-)	Phlyctenular infiltration	<i>α-streptococcus</i> , <i>E. faecalis</i>	
8	88/F	(-)	Peripheral ulcer	<i>Trichophyton fungus</i>	

Abbreviations: F: female, M: male, RA: Rheumatoid arthritis, MRSA: methicillin-resistant *Staphylococcus aureus*.

secretions, which were lumpy or string-like, were characteristic, and the appearance of punctum varied from severe redness/swelling to normal. The most common bacteria detected from the secretion was *Streptococcus* spp., followed by *Staphylococcus aureus* and *Enterococcus faecalis*. In addition, actinomycetes such as *Nocardia*, *Trichophyton fungus*, and anaerobic bacteria such as *Cutibacterium acnes* and *Peptostreptococcus* spp. were detected. All cases of corneal lesions healed with antibacterial and steroid eye drops (2 cases required superficial corneal transplantation). The surgical treatments for NLDO and canaliculitis included concretion removal in 3 cases, endoscopic punctal tube insertion in 3 cases, and dacryocystorhinostomy in 2 cases. As the strategy of the treatment, the administration of antibacterial eye drops and steroid eye drops were given first in all cases. In the two cases with corneal perforation, superficial corneal transplantation was performed after the administration of antibacterial eye drops for few days. The corneal findings improved mildly, but amount of purulent discharge continued. Afterwards, the treatment for NLDO were performed as soon as we confirmed nasolacrimal duct obstruction or when the patient had agreed to have nasolacrimal surgery.

The purulent discharge was completely resolved after the concretion removal or endoscopic tube insertion or dacryocystorhinostomy.

#### 4. Discussion

Corneal disease due to NLDO or canaliculitis can be classified as infectious or non-infectious ones. The latter is difficult to distinguish from corneal diseases caused by auto-immune disease. Because they have some similar characteristics including peripheral ulcers or paracentral perforation with slight cellular infiltration in the nasal region of the cornea. However, one differential characteristic is amount of purulent discharge. Although the redness or swelling of the punctum is also characteristic in NLDO, this is easily missed under the severe conjunctival hyperemia.

In 1977, Kim et al.<sup>5</sup> reported a marginal furrow-like corneal ulcer with chronic nasolacrimal duct obstruction. Although there was a heavy growth of *β-hemolytic streptococci* in culture, they reported this as an unusual feature of *streptococcal* conjunctivitis. They speculated that chronic NLDO may be a pathogenic cause. They mentioned that intense conjunctival chemosis trapped the exudate of NLDO, causing a breakdown of the epithelium and leading to an ulcer. Additionally, Yokokawa et al.<sup>4</sup> reported paracentral corneal perforation with slight cellular infiltration in the NLDO. These previous studies suggested that corneal disorders resulting from NLDO are not caused by bacterial colonization and growth in the cornea.

All of our cases showed characteristic white purulent discharge (mucopurulent mass-like secretion or linear-shaped discharge) connected to the punctum. And cellular infiltration was not remarkable at the pathogenic site of the cornea despite having a lot of rheum (Fig. 1). However, the appearance of the punctum varied from severe redness/

swelling to normal depending on the observation period. Thus, swelling/redness of the punctum is not always a reliable diagnostic indication of NLDO and canaliculitis. It is necessary to confirm the punctal findings at every ophthalmic examination.

We speculate that the changes in humoral factors such as chemokine or proteases caused by NLDO or canaliculitis might be the underlying pathological mechanisms of the corneal disorders. We described corneal disorders caused by NLDO as being similar to non-infectious corneal ulcers observed in rheumatoid arthritis, in which corneal marginal ulcers and paracentral perforations with unremarkable cellular infiltration are well known.

Kalsow et al.<sup>6</sup> reported that interleukin-6 (IL-6) and tumor necrosis factor – alpha increase in tears with rheumatism, and this change would induce activation of immune cells, trigeminal nerve, and the corneal stroma cells, thus resulting in peripheral corneal ulcers. Ali et al.<sup>7</sup> reported that NLDO caused a change in cytokines in the tear fluid. They showed upregulation of 10 pro-inflammatory cytokines in tears from patients with NLDO. The upregulated cytokines include matrix metalloproteinase 9, serpin E1, IL-6, hepatocyte growth factor, vascular endothelial growth factor-A and R2, platelet-endothelial cell adhesion molecule, c-reactive protein, chemokine ligand 2, and platelet-derived growth factor-AA. Non-infectious corneal disorders caused by NLDO or canaliculitis may occur in the same manner as rheumatoid arthritis-related corneal disorders.

Although 2 out of 8 cases (cases 2 and 5) had rheumatism, general conditions were well controlled and no other cases had a history of autoimmune disease. Oral steroids and immunosuppressants may have effect on the amount of the microorganism. However, all our cases were unilateral, and the corneal disorder did not resolve without treatment for lacrimal duct disease. Thus, we believe that rheumatism is not the primary cause of corneal disorders, although it might accelerate pathogenic mechanisms.

In this study, various kinds of microorganisms were detected (*Streptococcus* spp., followed by *S. aureus* and *E. faecalis*). Among them, we found several organisms, including *Trichophyton fungus* and anaerobic bacteria (*C. acnes* and *Peptostreptococcus*) that do not grow well in conventional cultures. Previous report showed that coagulase-negative *Staphylococci* are the most common isolates from the nasolacrimal sac by conventional culture methods.<sup>8</sup> Other studies reported that in healthy subjects the microbiome in the nasolacrimal sac is usually dominated by *Staphylococci* and *Corynebacterium*. In contrast, a significantly lower relative abundance of *Corynebacterium* was observed in a case of NLDO.<sup>9</sup> Many of our patients had been complaining of discharge for months and were previously receiving antimicrobial medications. Although drug sensitivity was not investigated in the detected microorganism, the detections of MRSA and *Streptococcus* sp. But not Coagulase-negative *Staphylococci* may indicate the dysbiosis of the nasolacrimal duct. Additionally, the presence of oral commensal and anaerobic bacteria of purulent secretions in our cases seemed to be retrograde origin from

nasolacrimal duct. The 16SrRNA gene analysis with next-generation sequencing would be a suitable method to detect the conjunctival microbiome in NLDO and canaliculitis.

Further experiments are necessary to reveal the mechanisms of corneal disease in patients with NLDO and canaliculitis.

## 5. Conclusions

We described characteristics of corneal disorders in NLDO and canaliculitis. One is an autoimmune disease-like appearance, and the second is purulent string-like discharge connecting to the punctum. When corneal ulcers resemble autoimmune disease in shape and are not accompanied by systemic disease, attention should be paid to nasolacrimal duct obstruction or canaliculitis.

## Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

The consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s) by written form or optout.

## Funding

Funding was received for this work.

All of the sources of funding for the work described in this publication are acknowledged below:

This research was funded by Osaka Eye Bank Grant, Katano Grant and Johnson and Johnson Medical Research Grant.

No funding was received for this work.

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Kaoru Araki-Sasaki [sasaki@sa2.so-net.ne.jp](mailto:sasaki@sa2.so-net.ne.jp).

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## CRediT author contribution statement

**Atsuko Ishimoto:** Writing – original draft and Patient treatment. **Kaoru Araki-Sasaki:** Conceptualization, Methodology, Patient treatment and observation, Formal analysis, Writing – original draft, preparation. **Chieko Shima and Miwako Tajika:** Patient observation and treatment. **Noriko Toyokawa:** reviewing draft. **Kanji Takahashi:** Supervision.

## Acknowledgements

We are grateful to Dr. Chika Miyazaki of Hyogo Prefectural Amagasaki General Medical Center for treatment of nasolacrimal duct disease.

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